Beyond Mineral Metabolism: Vitamin D Signaling, Microbial Metabolites, and Intestinal Barrier Dysfunction in the Gut–Kidney Axis

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Abstract

Background: Chronic kidney disease disrupts excretory, endocrine and immune homeostasis, while intestinal dysbiosis can alter microbial metabolite generation and epithelial barrier integrity. Vitamin D signaling has recognized roles in calcium-phosphate regulation and proposed actions in mucosal defense. Objective: To synthesize physiological links among intestinal microbial metabolism, vitamin D receptor signaling and renal injury, and critically appraise their therapeutic implications. Methods: This narrative review integrates the accompanying thesis literature with peer-reviewed mechanistic investigations, clinical trials, evidence syntheses and kidney-disease practice guidelines. Findings: Declining renal function increases retention of protein-bound microbial products, including indoxyl sulfate and p-cresyl sulfate, and may alter gut luminal chemistry and barrier function. Vitamin D activation becomes impaired as nephron function and mineral hormone regulation change. Experimental work suggests reciprocal interactions between VDR activity, epithelial permeability and inflammatory signaling, but direct evidence that vitamin D treatment beneficially reprograms the human CKD microbiome is limited. Synbiotic therapy has reduced selected circulating toxins in small studies, whereas effects vary across interventions and have not established protection against kidney failure or mortality. Active vitamin D analog trials have improved biochemical secondary hyperparathyroidism without consistently improving cardiac structural outcomes. Conclusion: The gut–kidney–vitamin D network is biologically coherent but clinically heterogeneous. Studies integrating microbial function, free toxin exposure, mineral hormones and meaningful clinical outcomes are needed before combined gut-directed and vitamin D strategies can be recommended for renoprotection.

Keywords: chronic kidney disease; gut–kidney axis; vitamin D receptor; microbiota; uremic toxins

Introduction

Chronic kidney disease (CKD) is frequently described through loss of filtration capacity, yet its systemic phenotype reflects a much wider failure of physiological communication. Impaired nephron function changes the circulating milieu, endocrine signaling, intestinal environment and immune response. In parallel, products of microbial metabolism can influence renal tubular transport, inflammatory pathways and vascular function. The intestine is therefore more than a passive source of absorbed nutrients in CKD. It is an organ whose metabolic and barrier functions may help determine the intensity of uremia. This perspective complements conventional risk stratification by cause, glomerular filtration rate (GFR) and albuminuria; it does not replace these clinically validated measures. [1,2]

Interest in the gut–kidney axis has expanded alongside recognition that vitamin D has actions extending beyond calcium balance. Vitamin D receptor (VDR) signaling participates in epithelial differentiation, innate immunity and inflammatory control, whereas CKD alters substrate handling and endocrine activation. These observations suggest connections among microbial ecology, intestinal permeability and disordered vitamin D metabolism. Their clinical meaning remains uncertain: demonstrating a pathway in cultured cells or animals is not equivalent to showing that supplementation prevents kidney failure. This review examines the underlying physiology, critically compares translational and interventional evidence, and proposes a framework for research that preserves clinically important distinctions among mechanisms, biomarkers and hard outcomes. [3,4]

1. CKD as a disturbance of interorgan homeostasis

The healthy nephron regulates volume, electrolytes and acid–base balance while removing organic solutes and participating in endocrine feedback. Progressive nephron loss increases single-nephron workload and often activates glomerular hypertension and inflammatory repair pathways. The resulting combination of metabolic overload, hypoxia, capillary rarefaction and matrix deposition contributes to glomerulosclerosis and tubulointerstitial fibrosis. Since renal excretion is a major pathway for numerous endogenous and microbially generated molecules, filtration decline also changes the composition of blood delivered to intestinal, immune and cardiovascular tissues. Gut–kidney interactions thus arise within the broader physiology of organ crosstalk rather than as a separate disease process. [5,6]

Kidney function cannot be represented completely by a single serum creatinine value. Estimated GFR is affected by creatinine generation and the equation used, while albuminuria provides a distinct indication of glomerular injury and future risk. CKD is classified by cause, GFR and albuminuria, and persistent abnormalities must be confirmed for at least three months. This matters when evaluating microbiome studies: participants labeled with the same CKD stage may differ markedly in residual secretion, protein intake, medication exposure, diabetes, gut motility and dialysis status. Failure to account for these characteristics can produce apparent microbial disease signatures that are partly consequences of treatment or selection. [1,6]

CKD-associated cardiovascular disease reflects pathways beyond conventional atherosclerosis, including vascular stiffness, myocardial remodeling, mineral abnormalities, oxidative stress and inflammation. Protein-bound uremic metabolites have been investigated as contributors to endothelial and cardiac injury, but their circulating concentrations are also markers of impaired renal elimination. Cross-sectional associations cannot distinguish a toxin that drives injury from one that accumulates because injury is already present. Accordingly, causal claims require triangulation using experimental work, longitudinal observation and randomized interventions that alter the proposed mediator. [7,8]

A further physiological issue is that loss of filtration and loss of secretion do not progress identically. Creatinine-based estimates largely track glomerular function, whereas many protein-bound metabolites rely on active basolateral uptake and apical efflux across proximal tubular epithelium. Changes in renal blood flow, transporter abundance, competing organic anions and residual nephron function can therefore alter toxin exposure independently of the estimated GFR. This separation also explains why two patients with similar serum creatinine may display distinct uremic symptoms or metabolite profiles. Studies that recruit by GFR category alone may consequently blend biologically different participants. Measuring secretory clearance in a subgroup, while impractical for routine clinical care, can strengthen

mechanistic interpretation and may reveal why some interventions work only in selected individuals. [9,10]

2. The intestinal ecosystem and its metabolic division of labor

The intestinal microbiota comprises bacteria, archaea, viruses and other microorganisms organized in metabolically cooperative communities. Their functions include fermentation of otherwise indigestible substrates, synthesis and transformation of small molecules, bile acid metabolism and competition against opportunistic organisms. Taxonomic composition is informative, but the physiological relevance of a microbial community often lies in the genes it expresses and the metabolites it produces. Two communities with different bacterial names can carry overlapping functional capacities, while identical taxa may behave differently under distinct dietary conditions. This distinction is particularly important in CKD, where restriction of some nutrients changes substrate availability independently of microbial abundance. [11,12]

Microbial fermentation of nondigestible carbohydrates generates short-chain fatty acids (SCFAs), principally acetate, propionate and butyrate. These compounds participate in epithelial energy metabolism, intestinal barrier regulation and host metabolic signaling. Butyrate is an important substrate for colonocytes, while SCFA-responsive receptors influence immune and vascular pathways. In a 2026 meta-analysis of 21 studies including 9,661 participants, Thakur and Harmer reported reduced circulating acetate and propionate in adults with CKD, with variation by kidney disease stage and treatment modality. These findings support altered SCFA handling in CKD but do not establish whether microbial production, intestinal absorption or host metabolism is primarily responsible. Stool taxonomy alone cannot quantify systemic SCFA availability or prove that deficiency causes progressive renal injury. [13,14]

Protein fermentation follows a different metabolic trajectory. Bacterial enzymes can transform dietary tryptophan, tyrosine and other amino acids into precursors that undergo host modification after absorption. These reactions are not intrinsically harmful: indole metabolites include compounds with differing receptor affinities and biological roles. The balance between potentially protective and harmful products depends on the microbiota, intestinal transit, nutrient supply and host biotransformation. Grouping all products of protein fermentation as toxic obscures this diversity and may lead to oversimplified dietary advice. Better interpretation requires metabolite-specific pathways and measurement of the molecular species actually present in plasma. [11,14]

The distinction between ecosystem composition and function is important when reading intervention trials. A rise in Bifidobacterium after a synbiotic preparation may indicate that the administered substrates favored particular organisms, yet it does not reveal whether those organisms displaced toxin-forming pathways elsewhere in the community. Cross-feeding allows a metabolite released by one taxon to become substrate for another. The same intervention may increase beneficial fermentation while leaving aromatic amino-acid metabolism unchanged. The location of activity also matters: stool reflects the distal intestinal compartment and may not capture conditions in the small intestine, where permeability, bile acids and nutrient absorption differ. Integrating metagenomics with targeted metabolite measurements provides a more discriminating test of a proposed mechanism than counting bacterial taxa alone. [11,12]

3. Why CKD changes the intestine

Uremia can alter intestinal luminal chemistry before measurable changes in microbial diversity emerge. Urea moves from blood into the gut, where urease-producing organisms generate ammonia and ammonium-related products. Experimental systems indicate that increased luminal urea and its breakdown products can damage epithelial tight-junction architecture. Such effects may coexist with altered intestinal perfusion, constipation, medications, intestinal edema and dietary restrictions. The resulting environment may favor microbial functions that further change the uremic metabolite pool. This is a bidirectional model: kidney dysfunction reshapes gut physiology, and selected gut products may feed back on renal and extra-renal tissues. [15,16]

Microbial functional alterations in CKD may be more informative than a universal claim of reduced

bacterial diversity. Wong et al. identified expansion of intestinal microbial groups with urease, uricase, indole- and p-cresol-forming potential and contraction of groups associated with short-chain fatty acid production in end-stage renal disease. Their observations support a shift in the capacity to generate nitrogenous metabolites, although inferred metabolic capabilities are not identical to directly measured gene expression or metabolite flux. Diet, dialysis exposure, antibiotics and medication use can also influence these patterns. Longitudinal studies combining metagenomics, metabolomics and precise clinical phenotyping are needed to distinguish consequences of kidney failure from pathways that may contribute to its progression. [12,14]

Epithelial integrity is maintained by mucus, antimicrobial peptides, junctional proteins, immune surveillance and continual cell renewal. A leaky barrier may permit increased passage of microbial products such as lipopolysaccharide, with downstream activation of innate immune pathways. Nevertheless, intestinal permeability is not a binary state and circulating endotoxin measurements are technically challenging. Inflammation in CKD also arises from dialysis access, adipose tissue, periodontal disease and underlying comorbidities. Thus, gut permeability is a credible contributor to systemic inflammation, not an established explanation for every elevation of C-reactive protein or interleukin-6 in renal disease. [15,17]

Gastrointestinal symptoms in CKD deserve more attention as measurable modifiers of microbial metabolism. Slow transit extends the opportunity for bacterial transformations of luminal substrates, and constipation is common in populations receiving iron, phosphate binders or other medications. At the same time, nausea, early satiety and dietary monotony can reduce the range of fermentable substrates reaching the colon. These influences may amplify a microbial pattern attributed to CKD severity even when the primary driver is a modifiable treatment-related exposure. Trials should quantify stool frequency, transit-related symptoms, laxative use and antibiotics, not simply classify participants as receiving dialysis or not. Such measurements also offer a clinically meaningful symptom outcome independent of molecular surrogate biomarkers. [17,18]

4. Generation, transport and retention of microbial uremic solutes

Indoxyl sulfate begins with bacterial conversion of tryptophan to indole, followed by hepatic oxidation and sulfation. The resulting solute circulates substantially bound to albumin and is cleared in part through renal proximal-tubule organic anion transport. Because glomerular filtration and tubular secretion decline in CKD, concentrations rise, particularly when residual tubular function is impaired. Indoxyl sulfate can activate oxidative and pro-inflammatory pathways in experimental models, including mechanisms involving aryl hydrocarbon receptor signaling. These biological activities justify mechanistic investigation, but the magnitude of clinically relevant exposure and the direction of cause and effect must be established in humans. [9,10]

The precursor p-cresol is generated through microbial tyrosine and phenylalanine metabolism and undergoes host conjugation, yielding p-cresyl sulfate and related forms. p-Cresyl sulfate is strongly protein-bound, making conventional dialysis relatively inefficient at removing its total circulating pool. Analytical reports must distinguish free from total concentration because the free fraction may be more available for tissue interactions and transport. Albumin concentration, competing ligands and uremic conditions can influence binding, complicating comparisons between patient groups. A fall in total p-cresyl sulfate after an intervention is useful biochemical evidence, but it is not by itself proof of improved survival or kidney function. [19]

Trimethylamine N-oxide (TMAO) is a host–microbial co-metabolite formed when intestinal microorganisms convert dietary choline- or carnitine-containing compounds into trimethylamine, which undergoes hepatic oxidation. Circulating TMAO is influenced by dietary intake, microbial activity and renal clearance. In a longitudinal investigation of community-based adults, Wang et al. found that higher serial TMAO measurements were associated with incident CKD and faster subsequent eGFR decline. These observational associations are clinically informative but do not prove that lowering TMAO would preserve kidney function. Reverse causation, changes in diet and comorbidity remain relevant, particularly because impaired renal elimination itself increases TMAO exposure. Interventional studies

are required before TMAO can be treated as an established renoprotective target. [20]

Proximal tubular secretion of uremic solutes is mediated partly by organic anion transporters OAT1 and OAT3 on the basolateral membrane of tubular epithelial cells. Wu et al. demonstrated in vivo that these transporters influence the handling of numerous endogenous and gut-derived solutes, including indoxyl sulfate and p-cresyl sulfate. Because some drugs share transport pathways with retained metabolites, transporter competition may alter solute and medication exposure, although the magnitude of individual drug–toxin interactions in clinical CKD remains insufficiently characterized. Differences in residual secretion and plasma protein binding can therefore produce distinct toxin profiles among patients with similar estimated GFR. Such mechanisms warrant assessment in pharmacokinetic and translational studies, but they do not justify empiric changes in medication dosing without drug-specific clinical evidence. [9,10]

The biochemical sequence from food to circulating toxin contains several potential points of intervention, each with a different risk profile. Dietary modification can change substrate delivery; microbial preparations can influence competing pathways; intestinal adsorbents can reduce precursor uptake; and preservation of renal secretion can affect systemic removal. However, lowering production and increasing removal cannot be assumed equivalent. An intervention might reduce total toxin concentration by altering albumin binding without reducing free tissue exposure, while another could change excretion without affecting intracellular signaling. Future studies need kinetic measurements that distinguish production rate, volume of distribution, free fraction and elimination. Such granularity may explain discordant findings in clinical trials and clarify which biomarker responses are biologically meaningful. [19]

5. Vitamin D physiology across the gut–kidney axis

Vitamin D is obtained through cutaneous production and dietary sources, and it requires metabolic activation. Hepatic 25-hydroxylation yields circulating 25-hydroxyvitamin D [25(OH)D], the principal clinical index of vitamin D status. Renal CYP27B1 then converts 25(OH)D to the hormone calcitriol, or 1,25-dihydroxyvitamin D, under regulation by parathyroid hormone, fibroblast growth factor 23 (FGF23), calcium and phosphate. These pathways establish a feedback network linking kidney, intestine, bone and parathyroid gland. Extrarenal cells can also express CYP27B1, although local generation of active hormone does not substitute for normal systemic endocrine regulation in advanced CKD. [21,22]

Vitamin D metabolites circulate predominantly bound to vitamin D-binding protein and, to a lesser extent, albumin. Nykjaer et al. demonstrated that the endocytic receptor megalin mediates proximal tubular retrieval of filtered vitamin D-binding protein–25-hydroxyvitamin D complexes, helping preserve substrate for activation. In CKD, reduced functioning nephron mass, altered phosphate–FGF23 signaling and abnormalities of tubular handling can limit calcitriol availability. Total circulating 25-hydroxyvitamin D is therefore not interchangeable with endocrine calcitriol production or intestinal VDR activity. Nutritional status, inflammation and urinary protein losses may further influence measured vitamin D indices. [23]

Calcium and phosphate homeostasis remain the most firmly established physiological actions of calcitriol. By binding VDR and altering transcription of transport-related genes, the hormone improves intestinal calcium absorption and contributes to integrated mineral balance. The skeleton, kidney and endocrine organs participate through compensatory feedback, which becomes increasingly strained as GFR decreases. A rise in FGF23 can precede overt hyperphosphatemia, while secondary hyperparathyroidism reflects several interacting abnormalities rather than a single vitamin D deficit. An intervention that changes parathyroid hormone therefore should not automatically be interpreted as correcting the broader pathophysiology of CKD–mineral and bone disorder. [24]

Intestinal vitamin D receptor (VDR) signaling provides a plausible interface between mineral metabolism, epithelial differentiation and mucosal immune defense. VDR-dependent pathways participate in antimicrobial peptide regulation and other host responses that may alter microbial ecology. Jin et al. demonstrated that deletion of VDR in mice changed intestinal microbial community

composition and predicted function, supplying direct experimental evidence for a host receptor–microbiome relationship. However, findings from VDR-deficient animals cannot be equated with clinical effects of vitamin D supplementation in patients with CKD. It remains uncertain whether nutritional correction of vitamin D deficiency restores intestinal barrier integrity or lowers microbial uremic toxin production in this population. [25]

The FGF23–klotho endocrine network helps explain why vitamin D activation changes early in renal disease. Osteocytes respond to altered phosphate balance by releasing FGF23, which acts at the kidney to promote phosphaturia and restrain calcitriol synthesis. Reduced functioning nephron mass limits the ability to excrete phosphate despite hormonal adaptation. As CKD advances, this can produce a state in which circulating FGF23 is elevated and active vitamin D remains relatively low even before marked hyperphosphatemia develops. The compensatory network should not be interpreted as wholly pathological: some early hormonal changes preserve phosphate balance. Treatments designed to correct one component must consider consequences for calcium absorption, parathyroid function and vascular mineral exposure across the full feedback loop. [24]

The term vitamin D deficiency also requires analytical precision. Most clinical laboratories measure total 25(OH)D, which reflects the bound and unbound pool, rather than local VDR activation. Assay methods vary, binding protein concentrations can change in proteinuric states, and inflammation may affect circulating measures. Calcitriol has a shorter circulating half-life and is regulated by endocrine feedback; it is not an interchangeable nutritional status marker. Trials that classify participants using total 25(OH)D alone should therefore avoid claims that they identified impaired gut VDR signaling. Tissue response is influenced by receptor expression, co-regulators and local enzyme activity. No routinely validated clinical assay currently captures that entire pathway in the intestinal mucosa of CKD patients. [22]

6. Immune signaling, inflammation and fibrosis

Chronic kidney disease is commonly accompanied by innate immune activation, oxidative stress and persistent low-grade inflammation. Microbial components crossing a compromised epithelial barrier may stimulate pattern-recognition receptors, while retained solutes can exert direct effects on endothelium and tubular cells. Vitamin D signaling in immune cells has been linked experimentally to modulation of inflammatory mediators and antimicrobial responses. Rather than treating these pathways as independent, a systems perspective considers how an altered lumen, impaired barrier, deficient solute clearance and endocrine dysregulation might reinforce one another. Their relative contribution likely differs in diabetic kidney disease, immune-mediated nephritis and advanced dialysis-dependent disease. [17]

Oxidative stress participates in renal injury through mitochondrial and enzymatic pathways that alter redox balance, disrupt vascular signaling and favor extracellular matrix accumulation. Some uremic metabolites increase reactive oxygen species in experimental systems; others influence aryl hydrocarbon receptor and inflammatory transcription networks. Sustained activation may promote fibroblast responses, epithelial stress and vascular dysfunction, although molecular concentrations used in vitro sometimes exceed free exposures encountered clinically. Histological fibrosis also reflects ischemia, hemodynamic injury and the original kidney disorder. Accordingly, microbial metabolites should be viewed as possible modifiers of a multifactorial process rather than as solitary causes of scarring. [8]

The cardiovascular implications of this network are prominent because CKD combines conventional cardiometabolic risk with vascular calcification, left ventricular remodeling and altered mineral hormone profiles. FGF23, phosphate imbalance, vascular inflammation and circulating toxins may contribute through partly overlapping mechanisms. Observational links between vitamin D status and cardiovascular events cannot, on their own, demonstrate that correcting vitamin D prevents vascular disease. This distinction became clearer in randomized studies: improvements in biochemical indicators of VDR activation did not reliably translate into improvements in left ventricular structure. Translational reasoning should therefore retain both the physiological plausibility and the constraints imposed by clinical trials. [26]

Immune regulation at the intestinal surface must balance antimicrobial defense with tolerance of commensal organisms and dietary antigens. Epithelial cells, resident macrophages, dendritic cells and lymphocytes interact with microbial molecules within a tightly regulated tissue context. Experimental VDR signaling has been connected to antimicrobial peptide responses and epithelial differentiation, but immune stimulation is not uniformly beneficial. A response that enhances pathogen control in one setting may increase inflammation in another. CKD adds the separate effects of uremia-associated immune dysfunction, including reduced host defense and abnormal inflammatory activation. Mechanistic research should therefore distinguish antimicrobial protection from nonspecific increases or decreases in cytokines and should test function at the tissue level whenever ethically and technically feasible. [25]

7. Microbiome-directed therapeutic approaches

Microbiome-directed treatments include prebiotics, probiotics and synbiotics, each defined by different biological requirements. According to international expert consensus, prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit, whereas probiotics are live microorganisms conferring a health benefit when administered in adequate amounts. Synbiotics combine live microorganisms with selectively utilized substrates in complementary or synergistic formulations. These definitions exclude assuming that every fermented food or mixed microbial preparation has demonstrated therapeutic benefit. Effects depend on formulation, strain, dose, background diet and host characteristics. In CKD, an improvement in microbial composition or an isolated uremic toxin measurement cannot substitute for demonstrated kidney or patient-centered benefit. [27,28,29]

In the randomized SYNERGY crossover trial, six weeks of synbiotic treatment in predialysis CKD reduced serum p-cresyl sulfate but did not significantly lower the primary endpoint, indoxyl sulfate, in the full trial population. Microbial community changes accompanied treatment, and antibiotic exposure appeared to influence response. These data support a mechanism-sensitive intervention rather than a broad assertion of renal protection. The study was relatively small and brief, and it was not powered to establish effects on kidney failure, hospitalization or mortality. Its informative feature is precisely the mismatch between modification of a microbial metabolite and absence of demonstrated improvement in clinical endpoints. [30]

Evidence syntheses indicate heterogeneous biochemical effects of microbiota-directed interventions in CKD. In a 2022 systematic review and meta-analysis of randomized controlled trials, Chen et al. assessed changes in circulating indoxyl sulfate and p-cresyl sulfate following microbial therapies. Pooled results suggested greater consistency for reductions in p-cresyl sulfate than for indoxyl sulfate, although interpretation was limited by differences in participant populations, dialysis status, treatment composition and study duration. These studies primarily measured short-term intermediate outcomes; they did not establish that a particular formulation prevents kidney failure or reduces mortality. Reported benefits should therefore be interpreted as candidate mechanisms rather than proof of renoprotection. [31]

Diet is inseparable from microbial physiology because fermentable fiber and amino-acid supply determine available substrates. Higher intake of plant-derived fermentable material may favor saccharolytic metabolism and SCFA production, whereas very restrictive renal diets sometimes reduce fiber diversity. However, dietary advice must be individualized to potassium burden, hyperkalemia risk, nutritional status and concurrent therapy. Lowering protein intake solely to suppress gut toxins can worsen protein-energy wasting, especially in frail or dialysis-dependent patients. Future trials should compare microbiome interventions against appropriately matched diets, document nutrient intake and avoid interpreting taxonomic changes as a substitute for nutritional safety. [18]

Adsorbents that bind intestinal toxin precursors offer a distinct strategy. The multinational EPPIC randomized trials tested AST-120 in over two thousand participants with moderate-to-severe CKD but did not demonstrate improvement in their primary composite endpoint of kidney disease progression. This negative clinical result is instructive: lowering a mechanistically relevant molecule may be

insufficient if the pathway contributes only a modest fraction of overall risk, treatment starts too late, or off-target processes remain dominant. Post hoc signals can inform new hypotheses but should not displace the neutral prespecified results. [32]

Safety evidence deserves equal weight to biochemical efficacy. Probiotic organisms are often considered low-risk in healthy populations, but advanced CKD can coexist with malnutrition, immunosuppression, central venous devices, recent surgery or impaired intestinal barrier integrity. Cases of infection related to probiotic organisms are uncommon yet clinically relevant in vulnerable hosts. Species designation is insufficient for evaluating a commercial mixture; genomic strain identity, manufacturing quality and antibiotic resistance characteristics matter. Trials should document contamination testing, viability through the stated shelf life and serious infections, along with gastrointestinal tolerability. A favorable metabolite signal does not justify indiscriminate use of live microbial preparations in patients at elevated infection risk. [27,29]

Indirect comparisons of probiotics and related formulations have been proposed as a way to rank microbiome-directed interventions, but such rankings are highly sensitive to heterogeneity in the underlying trials. Differences in dialysis exposure, diet, administered strains, follow-up and toxin assays can violate assumptions needed for meaningful comparison. The available randomized evidence summarized by Chen et al. supports caution: biochemical signals may differ by toxin and intervention, and adequate direct head-to-head trials with prespecified clinical endpoints remain necessary before a specific formulation can be considered superior. [31]

8. Vitamin D treatment: physiological rationale and clinical limits

Correcting nutritional vitamin D deficiency and treating secondary hyperparathyroidism are different clinical decisions. In CKD, 25(OH)D can be assessed when clinically indicated, with attention to phosphate, calcium, parathyroid hormone and trends over time. Current mineral-and-bone guidance discourages routine calcitriol or active analog use in non-dialysis CKD G3a–G5, reserving such agents for selected patients with severe and progressive hyperparathyroidism. Hypercalcemia, altered phosphate balance and vascular mineral deposition are important potential harms. The presence of VDR in the gut does not independently establish an indication for supraphysiological dosing or routine active vitamin D therapy. [24]

The PRIMO randomized trial enrolled 227 patients with CKD and left ventricular hypertrophy and found that paricalcitol lowered parathyroid hormone without improving left ventricular mass over 48 weeks; hypercalcemia was more frequent with treatment. The smaller OPERA trial likewise showed improvements in biochemical parameters but no significant change in cardiac structural outcomes. These studies challenge an overly direct inference from cardiac VDR biology to patient benefit. They do not negate all tissue-level actions of vitamin D, but they define an evidentiary boundary: biological activity is not proof of cardiovascular protection, and choice of formulation and dose has consequences. [26,33]

Population-level trials of vitamin D supplementation and analyses by renal function have not provided strong support for universal cardiovascular prevention through vitamin D in CKD. Results must be interpreted according to baseline deficiency, kidney disease stage, treatment type and outcome. A nutritional supplement that raises 25(OH)D is not pharmacologically equivalent to an active VDR agonist. Similarly, reduction in albuminuria or inflammation is an intermediate endpoint that may not predict survival or long-term GFR preservation. Studies intended to test the gut–kidney–vitamin D hypothesis should enroll participants based on explicit physiological deficits rather than using a single vitamin D threshold as a proxy for pathway activation. [22,26]

A common interpretive error is to combine nutritional cholecalciferol studies with trials of calcitriol or paricalcitol as if they represent one intervention. Their pharmacological exposure, biochemical targets and risks differ substantially. Nutritional preparations replenish substrate for regulated activation where capacity remains; active analogs bypass parts of that pathway and can suppress parathyroid hormone even when endogenous calcitriol production is impaired. They may also raise serum calcium and phosphate through intestinal absorption. Therefore, a pooled estimate across formulations can conceal

clinically meaningful heterogeneity. For a microbiome hypothesis, the critical question is not simply whether vitamin D concentration rises, but whether the intervention produces demonstrable mucosal pathway changes without mineral-related harm. [22,24]

9. An integrated model and priorities for future research

A coherent working model begins with nephron dysfunction, which increases intestinal urea exposure and retention of microbial co-metabolites. The altered intestinal environment may change community functions and weaken epithelial barrier defenses, facilitating inflammatory signaling. At the same time, reduced renal calcitriol production and altered VDR signaling can modify mineral regulation and potentially epithelial immune homeostasis. Inflammatory and toxin-related signals may then aggravate vascular and renal injury. Several links in this loop are strongly supported physiologically, while others rest mainly on animal experiments or observational human data. Presenting them as a graded causal network is more accurate than depicting a fully proven self-perpetuating cycle. [25]

Research should integrate repeated measures of dietary intake, 25(OH)D and calcitriol, FGF23, phosphate, intestinal permeability markers, stool metagenomic function and targeted circulating metabolites. Free and total protein-bound toxin concentrations should be specified, alongside residual kidney function and transporter-active medications. Paired sampling across CKD stages and well-phenotyped control groups could help separate the influence of diabetes, constipation, antibiotics and dialysis. Controlled mechanistic studies are particularly valuable when they demonstrate concordant changes in microbial capacity, toxin precursor generation, free plasma exposure and downstream biological effects. Without such concordance, a change in one biomarker can be misleading. [9,23]

Future randomized trials should target an explicit biological phenotype, such as high circulating p-cresyl sulfate with low fermentative capacity, instead of enrolling all patients with CKD as a uniform group. Factorial designs could explore diet and a defined microbial preparation, with vitamin D correction performed according to standard care rather than as an unproven universal intervention. Prespecified outcomes should include safety, albuminuria, eGFR slope, patient-reported symptoms and clinically relevant events when sample size permits. Microbial products require rigorous strain identification, viability testing and infection surveillance, particularly in immunocompromised participants or those with vascular access. [31,30]

An additional priority is methodological transparency. Stool composition should not be called a direct measure of permeability, and a concentration of one toxin should not represent the entire uremic metabolome. Functional metagenomics, metabolomics and transport studies can reveal complementary signals, yet high-dimensional datasets invite false discovery without replication and external validation. Trial protocols should register primary endpoints, publish negative results and account for antibiotic exposure, dietary adherence and rescue therapies. A physiologically useful intervention must ultimately improve outcomes that matter to patients without increasing the burden of treatment, mineral derangement or infection. [27,32]

An important source of bias in this field is reverse causation. Poor kidney function raises the concentration of solutes that rely on renal elimination; inflammation changes eating patterns and gut physiology; and severe illness can lower measured vitamin D status. A cross-sectional correlation among these variables may emerge even when no single pathway initiates the others. Prospective repeated-measures cohorts can clarify temporal sequence, while randomized manipulation of a defined mechanism offers stronger causal evidence. Multi-omics platforms will be most useful when nested inside designs that also record simple determinants such as medication changes, weight loss, serum albumin and bowel habit. Sophisticated molecular detail cannot compensate for an inadequately controlled clinical comparison. [17]

A staged translational program may offer better efficiency than immediately mounting a large outcomes trial. The first stage should demonstrate that a defined intervention reaches its intended biological target, for example by changing microbial gene expression and precursor production. The second should determine whether that change produces a reproducible reduction in the free circulating toxin pool or improves a validated barrier measure. Only after these steps should longer trials seek slower GFR

decline, fewer complications or better quality of life. This structure also provides stopping rules for plausible interventions that fail to modify the proposed pathway. Negative mechanistic findings are scientifically valuable because they prevent exposure of large patient populations to costly or ineffective strategies. [30,32]

Conclusion

The gut–kidney axis links renal solute handling, intestinal barrier biology, microbial metabolism and vitamin D-dependent endocrine regulation. Evidence supports substantial physiological interaction among these systems, but clinical translation is uneven. Microbiome-directed interventions can modify selected uremic solutes, while the clearest vitamin D benefits in CKD remain tied to recognized mineral and bone indications rather than proven gut or cardiovascular protection. Future research should prioritize functionally defined patient groups, integrated biomarkers, appropriate safety monitoring and sufficiently powered clinical outcomes. Such an approach offers a credible path from mechanistic insight to treatments that improve kidney and whole-body health.

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