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Oh, My Gut! New insights on the role of the gastrointestinal tract and the gut microbiome in chronic kidney disease-mineral and bone disorder

Seyedeh Nooshan Mirmohammadali[1], **Kathleen M. Hill Gallant**[2,3], **Annabel Biruete**[1,3]

[1] Department of Nutrition Science, Purdue University, West Lafayette, Indiana, USA

[2] Department of Food Science and Nutrition, University of Minnesota, St. Paul, Minnesota, USA

[3] Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, USA

Abstract

Purpose of the review: The aim of this review is to highlight recent evidence on the role of the gastrointestinal tract and gut microbiome on CKD-MBD outcomes, including intestinal phosphorus absorption and sensing, and the effect of gut-oriented therapies.

Recent findings: Recent evidence has revealed a complex interplay among mineral metabolism and novel gut-related factors, including paracellular intestinal phosphate absorption, the gut microbiome, and the immune system, prompting a reevaluation of treatment approaches for CKD-MBD. The inhibition of NHE3 limits phosphate transport in the intestine and may lead to changes in the gut microbiome. A study in rats with CKD showed that the supplementation of the fermentable dietary inulin delayed CKD-MBD, lowering circulating phosphorus and parathyroid hormone, reducing bone remodeling and improving cortical parameters, and lowering cardiovascular calcifications. In non-CKD preclinical studies, probiotics and prebiotics improved bone formation mediated through the effect of butyrate facilitating the differentiation of T cells into Tregs, and T regs stimulating the osteogenic Wnt10b, and butyrate was also necessary for the PTH bone effects.

Summary: Recent findings support multiple possible roles for gut-oriented therapies in addressing CKD-MBD prevention and management that should be further explored through clinical and translational studies.

Keywords

gut microbiome; dysbiosis; phosphorus; paracellular; chronic kidney disease-mineral and bone disorder

Corresponding Author: Annabel Biruete, PhD, RD, Assistant Professor, Department of Nutrition Science, Purdue University, Phone: (765) 494-0101, abiruete@purdue.edu.

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Introduction

Chronic kidney disease-mineral bone disorder (CKD-MBD) is a highly prevalent systemic disorder of mineral and bone metabolism characterized by biochemical disturbances, bone abnormalities, and extra-skeletal calcifications.(1) Hyperphosphatemia is a key biochemical abnormality driving the pathophysiology of CKD-MBD.(2) Despite phosphorus being a vital nutrient with various important functions, including as a primary component bone mineral, excessive phosphorus intake has detrimental effects on bone health, cardiovascular health, and inflammation.(3–5) Therefore, prevention and management of hyperphosphatemia has been a primary focus of CKD-MBD treatment.

In CKD, therapeutic strategies for reducing hyperphosphatemia have primarily focused on limiting intestinal phosphate absorption by dietary phosphorus restriction and phosphate binder medications.(1, 6) While the current Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD updated guidelines do not have a specific dietary phosphorus recommendation(7), people with kidney disease are often prescribed dietary phosphorus intakes of 800–1000 mg/day.(8) However, limiting dietary phosphorus intake is challenging due to its widespread presence in the food supply.(6) In the United States, estimated daily phosphorus consumption is approximately 1500 mg/day, surpassing the adult Recommended Dietary Allowance of 700 mg/day.(9) Unfortunately, serum phosphorus has been increasing in the last decade in people with kidney failure undergoing dialysis, despite low phosphorus diets, phosphate binders, and dialysis treatment.(10) Ongoing studies are evaluating the effects of strict vs. liberalized approaches to hyperphosphatemia management on hard clinical outcomes (NCT03573089 and NCT04095039).(11) However, even normal range serum phosphorus levels have been associated with increased risk of mortality, (12) and a recent preclinical study supports that excess dietary phosphorus can be detrimental to bone in the absence of hyperphosphatemia.(13) Roberts, et al.(13)* fed mice with normal kidney function a diet with three times the normal phosphorus content (1.8%) for 20 weeks and showed lower bone volume and a higher number of T cells expressing IL-17a, RANKL, and TNF-α, suggesting that a possible inflammation mechanism by which chronic high intake of phosphorus exerts negative effects on bone. Further clinical and translational studies are needed that elucidate the effects of dietary phosphorus intake on CKD-MBD outcomes, as well as the mediating mechanisms.

Recent evidence has revealed a complex interplay among mineral metabolism and novel gut-related factors, including paracellular intestinal phosphate absorption, the gut microbiome, immune cell dysfunction, inflammation, oxidative stress, prompting a reevaluation of treatment approaches.(14) Of particular interest has been the successful targeting of the paracellular phosphate absorption pathway by inhibition of sodium hydrogen exchanger type 3 (NHE3) with tenapanor, which has been shown to be effective as an add-on therapy or a stand-alone therapy for the management of hyperphosphatemia in people with kidney failure undergoing dialysis.(15, 16) Furthermore, preclinical evidence shows that metabolites derived from the gut microbiota may directly or indirectly impact bone and vascular outcomes, promoting renal osteodystrophy and cardiovascular calcification. Therefore, therapies that modulate gut microbial metabolism are of interest. The aim of this

review is to highlight the recent evidence on the role of the gastrointestinal tract and gut microbiome in CKD-MBD.

New insights in intestinal phosphate absorption and sensing

Intestinal phosphate absorption occurs along the small and large intestine by transcellular active transport via brush border membrane sodium-dependent phosphate co-transporters, and paracellular passive transport through intestinal epithelial cell tight junctions.(17) At the intakes observed in the general population and in people with CKD, paracellular absorption is favored.(17) Recently, Stremke et al.(18) demonstrated that fractional intestinal phosphorus absorption in people with moderate CKD was similar to people with normal kidney function (matched for age, sex, and race) when consuming dietary phosphorus at a typical U.S. intake level – despite lower 1,25-dihydroxyvitamin D in people with CKD. Therefore, therapies that reduce paracellular phosphorus absorption may offer a benefit to limiting overall intestinal phosphorus absorption in CKD, especially as intestinal phosphorus absorption efficiency appears to be maintained in CKD.

Tenapanor is an NHE3 inhibitor that alters tight junction permeability to phosphate, thereby limiting paracellular phosphate absorption.(19) Tenapanor has been shown to be effective in lowering serum phosphorus in combination with phosphate binders and as a monotherapy.(15, 16) Tenapanor was approved by the FDA in October of 2023 for use in patients on dialysis for treatment of hyperphosphatemia, and is currently the only phosphate-lowering therapy that directly inhibits intestinal phosphate absorption. In addition to phosphate-lowering effects, tenapanor has been approved since 2019 for treating irritable bowel syndrome (IBS) with constipation by inhibiting intestinal sodium absorption and softening stool.(20) These effects of tenapanor on bowel movements and sodium and phosphorus absorption suggest the possibility for effects of NHE3 inhibition on the gut microbiome. Xue et al.(21) recently explored the impact of intestine-specific NHE3 knockout in mice, and found that α-diversity, or diversity within a sample, was higher in the knockout mice compared with control mice. Furthermore, the overall bacterial composition, or β-diversity, also differed between knockout and control mice. Specific taxonomical changes in the intestine-specific NHE3 knockout mice included a higher relative abundance of *Bacteroides, Enterococcus, Alistipes,* and *Parabacteroides,* and a lower relative abundance of *Robinsoniella, Eubacterium, Kineothrix, Roseburia,* and *Prevotella.* Overall, this study suggests that a complete intestinal deletion drives a substantial change in the gut microbiome. However, this study did not assess changes in the microbial metabolome and was not in the context of CKD. Therefore, future studies should assess the impact of inhibiting intestinal NHE3 on the gut microbiome and microbial metabolome, as well as effects on CKD and CKD-MBD outcomes.

Finally, an additional development in intestinal phosphorus physiology was highlighted by a recent paper on phosphate sensing in enterocytes. Xu et al.(22)* described a phosphate-sensing organelle in absorptive intestinal cells of fruit flies called the Pi-sensitive XPR1 orthologue (PXo). Under a normal phosphorus diet, PXo sensed and transported phosphate to form a phospholipid membrane of PXo bodies. Under a phosphorus-deficient diet, these PXo bodies underwent lysosomal degradation and induced intestinal proliferation, which the

authors speculate was to increase the number of absorptive cells to correct for phosphorus deficiency. While the authors tested the impact of deficiency, they did not test the effects of excess dietary phosphorus, which is relevant in the context of CKD. Therefore, research incorporating this new phosphate sensing mechanism and its impact on CKD-MBD is needed.

The possible contribution of the gut microbiome to CKD-MBD

In CKD, gut dysbiosis is characterized by a shift in microbial metabolism favoring the fermentation of amino acids and other components present primarily in animal-based foods.(23) As a result, there is an increase in the circulating levels of gut-derived uremic toxins, such as p-cresyl sulfate, indoxyl sulfate, and trimethylamine-N-oxide (TMAO).(23) Evidence suggests that accumulation of these toxins results from a lower renal excretion rather than a higher production,(24, 25) but this remains inconclusive. These gut-derived uremic toxins are associated with poor outcomes, likely attributed to their proinflammatory and prooxidant effects.(26) Relevant to CKD-MBD, these gut-derived uremic toxins can impact bone-related outcomes. For example, *in vitro* studies have shown that indoxyl sulfate impairs osteoclastogenesis, having differential effects depending on timing (short-term vs. long-term exposure) and quantity (low-dose vs. high-dose).(27) Indoxyl sulfate also impairs osteoblast differentiation.(28) Furthermore, TMAO has been associated with low bone mineral density,(29) and a mechanistic study suggests that TMAO may lead to an adipogenic rather than osteogenic differentiation of bone marrow mesenchymal stem cells.(30)

Therapies targeting the gut microbiome and their metabolites may represent novel therapies to improve bone-related outcomes in CKD. In the non-CKD literature, probiotic supplementation in animal models and humans has been shown to stimulate bone formation (31–34). In 10-week-old mice, the supplementation of *Lactobacillus rhamnosus GG* (LGG) resulted in an expansion in butyrate-producing bacteria.(35) SCFAs, particularly butyrate, support the differentiation of T cells into Tregs, limiting bone resorption (36–38) augmenting bone formation by facilitating the differentiation of osteoblasts, (39) and playing a pivotal role in mediating PTH-induced bone formation.(40) Mechanistically, LGG and butyrate enhance the differentiation of Tregs independently and increase CD4+/CD8+ T cell ratio through the upregulation of osteogenic Wnt ligand Wnt10b, resulting in enhanced bone formation.(41) Because of these results, probiotic supplementation studies in CKD may be of interest, but caution should be taken as there may be deleterious effects, as seen in a recent study by Wei et al.(42), where the supplementation of LGG in 5/6th nephrectomized rats led to increased vascular calcification.

Another interesting mechanism by which the gut microbiome may impact bone is through the possible mediation of PTH effects on bone. Intermittent PTH treatment enhances bone volume and strength by a butyrate-mediated expansion of Treg cells,(43) and butyrate is crucial for the effects of PTH on conversion of CD4+ T cells into Tregs. Tregs, in turn, stimulate CD8+ T cells to release Wnt10b, serving as a critical signal for osteoblast proliferation, differentiation, and survival. Butyrate expedites this process through dual mechanisms: signaling through GPR43 in dendritic cells and exerting a direct influence on T cells.(44) Notably, germ-free mice and mice treated with antibiotics failed to exhibit

increased osteoblast activity in response to intermittent PTH, primarily due to lower levels of circulating butyrate, which recovered after physiologically-relevant supplementation with butyrate.(45) In contrast, chronically high levels of PTH, as observed in advanced CKD, promote bone loss particularly when segmented filamentous bacteria (SFB) are present in the gut microbiota.(46) SFB expands Th17 and TNF+ T cells within the gut. These immune cells subsequently migrate to the bone marrow and trigger bone resorption, leading to bone loss. Thus, investigation of potential gut-oriented therapies for renal osteodystrophy should include exploration of possible interactions with PTH-lowering therapies.

CKD may also alter changes in the composition and function of the microbiota leading to a lower production of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. While some studies suggest that CKD leads to a lower capacity for producing SCFA,(47, 48) others suggest that it may be due to a lower dietary fiber intake rather than blunted capacity.(49, 50) Dietary fiber intake in people with CKD has been reported to be lower than the recommended amount of 14g per 1000 kcal. (23, 51) Low fiber intake may be secondary to dietary potassium and phosphorus restrictions leading to lower consumption of plant-based fiber-rich foods.(52) Diet is a primary determinant of the gut microbiome, and dietary fiber, particularly fermentable dietary fiber, may aid in shifting microbial metabolism towards higher production of SCFA and lower production of gut-derived uremic toxins.(23)

Our group recently showed that supplementing the fermentable fiber inulin alters the gut microbiota, lowers indoxyl sulfate and p-cresyl sulfate, and improves CKD-MBD outcomes in a rat model of progressive CKD.(53)** Rats with mild-to-moderate CKD were fed a 10% inulin diet for 8–10 weeks until they reached stage 4 and 5 CKD. In addition to lowering gut-derived uremic toxins, inulin supplementation improved the three hallmarks of CKD-MBD: biochemical abnormalities, bone abnormalities, and extra-skeletal calcifications. Specifically, inulin treatment lowered serum phosphorus and PTH, reduced bone remodeling, improved cortical parameters without altering trabecular bone or mechanics, and reduced aorta and heart calcification and left ventricular mass index. Thus, inulin may be a novel, low-cost intervention for preventing CKD-MBD progression, but clinical trials are needed to confirm these effects. Gut-oriented therapies may also act as phosphate-binding agents. Moon et al.(54) screened 30 lactic acid bacteria in Korean fermented foods and found that *Lactobacillus paraplantarum* KCCM 11826P absorbed phosphorus *in vitro*, which was due to a polyphosphate gene cluster. Then, when 5/6th nephrectomized rats were supplemented with this strain, serum phosphorus was lower after six weeks compared with 5/6th nephrectomized rats supplemented with a placebo. Overall, these studies support the possible roles for prebiotic and probiotic (or synbiotic) supplements for improving CKD-MBD-related outcomes.

Conclusion

Recent preclinical and clinical studies suggest that focusing on gut-oriented therapies, such as prebiotics, probiotics, and by inhibiting the intestinal NHE3 may offer a new venue for the prevention and treatment of CKD-MBD. These approaches should be further explored through future clinical and translational studies.

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Key points:

- Intestine-specific NHE3 knockout mice exhibit substantial changes in the gut microbiome including increased bacterial diversity, which may have implications for the impacts of the newly approved Tenapanor.
- Based on CKD rat data, fermentable dietary fiber may represent an innovative, low-cost intervention to improve CKD-MBD outcomes, but clinical trials are needed to confirm.
- *Lactobacillus paraplantarum* KCCM 11826P, a probiotic strain from fermented foods, may have phosphate-binding capacity and potential for lowering serum phosphorus, as shown in CKD rats.
- The short-chain fatty acid butyrate mediates intermittent and chronic effects of high PTH on bone, but this mechanism has not been tested in CKD.
- Phosphorus-sensitive XPR1 orthologue (PXo) was recently described as a sensing mechanism in intestinal absorptive cells of fruit flies, particularly in the context of normal and phosphorus-deficient diets.