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Phosphate Binders and Non-Phosphate Effects in the Gastrointestinal Tract

Annabel Biruete, PhD, RD^{1,2}, Kathleen M. Hill Gallant, PhD, RD, CD^{1,3}, Stephen R. Lindemann, PhD^{3,4}, Gretchen Wiese, RD³, Neal Chen, PhD¹, Sharon Moe, MD^{1,2,5}

¹Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

²Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, Indiana, USA

³Department of Nutrition Science, Purdue University, West Lafayette, Indiana, USA

⁴Department of Food Science, Purdue University, West Lafayette, Indiana, USA

⁵Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; Roduebush Veterans Affairs Medical Center, Indianapolis, Indiana, USA

Abstract

Phosphate binders are commonly prescribed in patients with end-stage kidney disease (ESKD) to prevent and treat hyperphosphatemia. These binders are usually associated with gastrointestinal distress, may bind molecules other than phosphate, and may alter the gut microbiota, altogether having systemic effects unrelated to phosphate control. Sevelamer is the most studied of the available binders for non-phosphate-related effects including binding to bile acids, endotoxins, gut microbiota-derived metabolites, and advanced glycation end-products. Other binders (calcium- and non-calcium-based binders) may bind vitamins, such as vitamin K and folic acid. Moreover, the relatively new iron-based phosphate binders may alter the gut microbiota as some of the iron or organic ligands may be utilized by the gastrointestinal bacteria. The objective of this narrative review is to provide the current evidence for the non-phosphate effects of phosphate binders on gastrointestinal function, nutrient and molecule binding, and the gut microbiome.

Introduction

Phosphate binders are commonly prescribed in patients with end-stage kidney disease (ESKD) to prevent and treat hyperphosphatemia (1). Phosphate binders can be classified as calcium and non-calcium-based. Calcium-based phosphate binders use has been decreasing, as they may lead to a positive calcium balance (2) and increased risk of extra-skeletal calcifications and poor outcomes (3). Contrarily, the use of non-calcium-based phosphate

Corresponding Author: Sharon Moe, MD, Stuart A. Kleit Professor of Medicine, Professor of Anatomy & Cell Biology, Director of Division of Nephrology, Indiana University School of Medicine, 950 W Walnut St R2-202, Indianapolis, IN 46202, smoe@iu.edu.

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binders (e.g., sevelamer) has increased and has been associated with improved outcomes and survival compared to calcium-based phosphate binders (4, 5). Besides the phosphate-lowering effects, phosphate binders may have other effects within the gastrointestinal (GI) tract, and these effects may extend systemically.

There are several changes in the function of the GI tract as kidney function declines. These include impaired digestion and absorption of nutrients (6), increased gut permeability (7), increased prevalence of GI symptoms (8), increased risk of upper GI inflammation and bleeding (9), and alterations in the gut microbiome (10). Phosphate binders may have effects in these GI functions as they impair the absorption of nutrients (e.g., vitamins and minerals), may impact gut integrity, and alter the gut microbiome (Table 1). However, these functions are often overlooked and have not been studied extensively.

The gut microbiome is the genomically-diverse community of microorganisms that includes bacteria, archaea, fungi, parasites, and viruses within the GI tract (11). In chronic kidney disease (CKD), the gut microbiota has been described to have lower relative abundance of commensal bacteria thought to perform beneficial functions, such as short-chain fatty acid (SCFA) production by *Bifidobacteria* spp. and *Lactobacillus* spp., and a higher relative abundance of potential pathobionts, such as species within the *Enterobacteriaceae* family and *Clostridium perfringens* (7). In patients with ESKD, bacteria with indole and p-cresol-forming enzymes are increased, while bacteria with enzymes needed for SCFA (i.e., butyrate) production are reduced (12). Subsequently, there is an increase in plasma metabolites originally derived from gut bacterial metabolism, such as p-cresyl sulfate and indoxyl sulfate (13). These metabolites have been associated with the pathogenesis and progression of kidney disease, cardiovascular disease, CKD- mineral and bone disorder (MBD), and vascular calcification (14). Moreover, newer iron-based phosphate binders may have an effect on the gut microbiome, as some of the iron or its associated ligands may be metabolized by the gut microbiota (15). As phosphate binders are one of the most prescribed medications in ESKD, the effects of these medications on the composition and function of the gut microbiome is of interest. The objective of this narrative review is to synthesize the current literature on the non-phosphate binding effects of phosphate binders, including gastrointestinal function, nutrient and molecule binding, and the gut microbiome.

Calcium-based Phosphate Binders

Calcium Carbonate and Calcium Acetate

Calcium carbonate provides ~500mg of elemental calcium per 1250mg tablet and is traditionally used as an antacid or dietary calcium supplement, but also acts as a phosphate binder. Similarly, calcium acetate provides 169mg of elemental calcium per 667mg tablet. When taken with food, calcium and phosphate form an insoluble complex, which is excreted in feces. In an *in vitro* study by Schumacher et al. (16), calcium carbonate bound more phosphate at a pH of 3, while calcium acetate bound more phosphate at pH of 6.

GI symptoms are the most common side effects with the use of calcium-based phosphate binders and a frequent reason for their discontinuation (17). Constipation is commonly reported with calcium carbonate, while nausea (6.1%) and vomiting (4.1%) are common

with calcium acetate (17). The prevalence of constipation has been reported to be as high as 63% in ESKD patients (18). Constipation may be related to factors other than the use of phosphate binders, such as reduced physical activity, low dietary fiber intake, various medications, and other comorbidities (i.e., diabetes) (18). A longer transit time may increase the production and absorption of indoles and phenols derived from the bacterial metabolism of tryptophan and tyrosine, respectively (13). These indoles and phenols can be then absorbed into portal circulation and modified in the liver to the uremic toxins indoxyl sulfate and p-cresyl sulfate, respectively (13). It is unknown, however, if calcium carbonate-induced constipation increases the bacterial fermentation of these amino acids.

Calcium carbonate and calcium acetate may bind other nutrients. Neradova et al. (19) showed *in vitro* that calcium carbonate and calcium acetate bound vitamin K₂ (menaquinone-7; MK₇) in a solution with a pH of 6 with and without phosphate. Vitamin K is needed for the carboxylation of some proteins, including matrix γ -carboxyglutamate (Gla) protein (MGP), which is an inhibitor of vascular calcification (20). Dietary intake of vitamin K and serum concentrations have been reported to be low in CKD and ESKD patients (21). Therefore, based on *in vitro* studies, calcium-based binders may contribute to two risk factors for vascular calcification: positive calcium balance and reduced absorption of vitamin K₂, leading to reduced carboxylation of MGP.

There is limited evidence of the effect of calcium-based phosphate binders on the gut microbiota. In a study that assessed the effects of high dietary phosphorus with or without supplemented calcium (as calcium carbonate) in healthy individuals, Trautvetter et al. (22) found an increase in the fecal excretion of SCFA and increased relative abundance of species from the *Clostridium* cluster XVIII in those supplemented with calcium carbonate. However, the results may not be generalized to the CKD population. Similarly, there are no studies on the effects of calcium acetate on the gut microbiota. In a mouse model for hypertension, Marques et al. (23) showed that the supplementation of acetate, similarly to a high fiber diet, reduced the firmicutes-to-bacteroidetes ratio and attenuated the development of hypertension. However, the effects of calcium acetate in patients with ESKD are unknown.

Non-calcium-based phosphate binders

Lanthanum Carbonate

Lanthanum is a rare earth element that has a high affinity for phosphate. It is minimally absorbed in the GI tract and then excreted through bile (24). Lanthanum binds phosphate and dissociates from carbonate at a pH of 3, forming an insoluble complex that is excreted in feces (24).

The most common GI symptoms associated with lanthanum are nausea (11%), vomiting (9%), and abdominal pain (5%) (17). Some of these symptoms, however, may decrease with the continuous use of the binder. After 52 weeks of substituting sevelamer hydrochloride with lanthanum carbonate, the constipation score was reduced (25). Another consequence of the use of lanthanum is the resistance to dissolution, which can cause GI deposition (26).

Lanthanum has been shown to bind vitamin K *in vitro* in the absence of phosphate, suggesting competitive binding between vitamin K2 and phosphate (19). As mentioned earlier, this may have a detrimental effect on the carboxylation of MGP and increased risk of vascular calcification. However, the *in vivo* effects of lanthanum on vascular calcification are limited. Toussaint et al. (27) showed that aortic calcification progression was lower in hemodialysis patients treated with lanthanum for 18 months, compared with calcium carbonate. Lanthanum may also bind oxalates. In a study in rats that were given oral oxalates, lanthanum prevented their absorption, showing a blunted effect on oxaluria and calcium oxalate crystals (28). Gut bacteria, particularly *Oxalobacter formigenes* can degrade oxalate and decrease urinary oxalate excretion (29). However, the effect of lanthanum on oxalate metabolism and *Oxalobacter formigenes* abundances in the CKD gut remains to be explored.

Sevelamer Hydrochloride/Carbonate

Sevelamer is a non-specific anion exchange resin with a backbone of multiple amines. Once sevelamer binds to an anion, it exchanges it for chloride or carbonate. In an *in vitro* study, sevelamer carbonate was shown to bind more phosphate in a solution with a pH of 3, while sevelamer hydrochloride binds more phosphate at pH of 5.5 (16). Since the use of sevelamer hydrochloride was associated with acidosis in patients with CKD, the use of sevelamer carbonate is now more common (30).

GI symptoms are a common cause for discontinuation of sevelamer, where as much as 55% of patients discontinued sevelamer due to GI upset (17), the highest among phosphate binders. Among the GI symptoms, vomiting (24%), nausea (25%), diarrhea (21%), dyspepsia (16%), and constipation (13%) are common with sevelamer carbonate, while diarrhea (16%), dyspepsia (11%), and vomiting (12%) have been reported with sevelamer hydrochloride (31).

Sevelamer has been reported to have the most pleiotropic effects; it is also the most studied of the available binders and thus some findings may or may not be true for other binders. Sevelamer can bind molecules that are considered detrimental, such as lipopolysaccharide (LPS)/endotoxin, bile acids, uremic toxins (i.e., indoles and phenols), and advanced glycation end products (AGEs). However, it can also bind beneficial molecules, such as folic acid, and its use has been associated with increased levels of homocysteine (32).

Sevelamer reduces endotoxemia and inflammation—LPS is derived from the outer membrane of Gram-negative bacteria. In CKD and ESKD, circulating LPS may be increased due to the uremia-induced effect on gut barrier integrity, leading to increased bacterial translocation (7). Additionally, in patients with ESKD, intestinal edema and gut ischemia due to the hemodialysis treatment may also lead to bacterial translocation and endotoxemia (33). LPS has immunostimulatory effects as it activates macrophages, neutrophils, and endothelial cells leading to the release of pro-inflammatory cytokines (34). Limiting endotoxemia is important in CKD, as inflammation is associated with increased risk of cardiovascular events, kidney disease progression, protein-energy wasting, and all-cause mortality (35).

A dose-response reduction in LPS with sevelamer has been shown *in vitro* (36). In a rat model of kidney disease (5/6 nephrectomy), the use of sevelamer reduced LPS and inflammatory markers (37). In patients undergoing hemodialysis, sevelamer use was associated with lower plasma LPS (38). In a prospective, randomized controlled study in hemodialysis patients, a 3-month treatment with sevelamer was associated with a reduction of C-reactive protein (CRP), interleukin-6 (IL-6), and LPS compared with calcium acetate (39). The latest meta-analysis revealed that sevelamer reduced all-cause mortality, compared with calcium-based binders (5). However, it is not clear if the reduction on mortality risk is related to the phosphate-lowering effect, a reduction in LPS and inflammation, or a combination of these and other factors.

Sevelamer binds to bile acids and leads to improved metabolic profile—

Sevelamer has been shown to bind bile acids and limit the highly effective enterohepatic recirculation, which recovers ~95% of bile acids (40). In a mouse model of non-alcoholic fatty liver disease (NAFLD), sevelamer improved liver steatosis and inhibited the nuclear farnesoid-X receptor (FXR) (41). FXR induces the ileum transcription of fibroblast-growth factor (FGF) 15/19 and inhibits the transcription of cholesterol 7-hydroxylase (CYP7A1) in the liver, the rate-limiting enzyme for bile acid synthesis. When bile acids are bound to sevelamer, their enterohepatic recirculation is reduced and this inhibits the FXR-negative feedback loop, increasing bile acid synthesis and reducing total cholesterol and low-density lipoprotein (LDL) (41).

Sevelamer has been associated with improved glucose homeostasis, likely mediated by the Takeda G protein receptor 5 (TGR5) located in the L-cells in the colon. When bile acids bind to sevelamer, they reach the L-cells and activate TGR5, which increases glucagon-like peptide-1 (GLP-1) production and secretion. Harach et al. (42) demonstrated that anion-exchanger resins released GLP-1 with glucose-lowering effect mediated by TGR5. A study in patients with diabetes (43) found that sevelamer was associated with reduced fasting plasma glucose, LDL, and unconjugated bile acids, while it increased triglycerides, glucagon, and C4 (a product CYP7A1 conversion from cholesterol to bile acids). Interestingly, these changes were not associated with changes in the gut microbiota, but this was not a primary end-point.

Bile acids may be also related to vascular calcification. Deoxycholic acid has been shown to induce vascular mineralization in experimental models (44). Deoxycholic acid is a secondary bile acid derived from the deconjugated primary bile acid cholic acid through gut microbial metabolism (hydrolysis and dehydroxylation), which is passively diffused to portal circulation (45). Deoxycholic acid may inhibit FXR, and this inhibition has been shown to prevent vascular calcification in a mice model of CKD (46). Jovanovich et al. (44) recently reported a positive association between deoxycholic acid and coronary artery vascular calcification in CKD patients. However, the effect of sevelamer on bile acid metabolism in CKD and the effect through binding of bile acids is unknown.

Finally, due to its binding to bile acids sevelamer may impair the absorption of fat-soluble vitamins. The use of sevelamer has been associated with reductions in serum levels of vitamin D (25-hydroxyvitamin D), compared to lanthanum carbonate (47). Westenfeld et al.

(48) found no association between the use of sevelamer and Vitamin K (menaquinone) levels, despite *in vitro* studies showing affinity of sevelamer for vitamin K; although only a small proportion of patients were prescribed sevelamer. Sevelamer has no effect on absorption of vitamins A and E (49).

Sevelamer may bind to gut microbiota-derived metabolites—Metabolites derived from protein fermentation (phenols and indoles) and dietary fiber fermentation (SCFA) by the gut microbiota have been reported to be bound or to be reduced with sevelamer. *In vitro* (50), sevelamer binds to indole, indoxyl sulfate, and p-cresol, but not tryptophan (a precursor of indoles) at different pH solutions. In a study of five patients undergoing hemodialysis, the use of sevelamer reduced serum levels of p-cresyl sulfate, but not indoxyl sulfate (50). Similarly, a cross-sectional study in peritoneal dialysis patients receiving sevelamer had lower plasma p-cresol, a surrogate marker for the p-cresol conjugates p-cresyl sulfate and p-cresyl glucuronide (51). However, the reduction in uremic toxins has been inconsistent *in vivo*. Phan et al. (52) showed no effect on uremic toxins, including indoxyl sulfate, after an 8-week use of sevelamer in apoE^{-/-} uremic female mice; while Brandenburg et al. (53) found no change in indoxyl sulfate and an increase in serum p-cresol after 8 weeks of sevelamer.

SCFA are the predominant anions in the colon, where sevelamer reaches its final equilibrium. Wrong and Harland (54) commented that one mole of SCFA removed by sevelamer hydrochloride was equal to one mole of bicarbonate lost and a gain of chloride; the hypothesized reason of sevelamer hydrochloride-induced acidosis. As sevelamer may bind undesirable microbial metabolites (i.e., indoles and phenols), but also the desirable metabolites (i.e., SCFA), the effects of sevelamer on the microbial metabolome remains to be explored.

Sevelamer reduces advanced glycation end products (AGEs)—AGEs result in part from the non-enzymatic reactions (Maillard reactions) between amine-containing molecules and reducing sugar molecules. AGEs are produced endogenously and are also consumed in the diet. High concentrations of AGEs have been reported to contribute to the progression of kidney disease and are positively associated with vascular calcification (55). Sevelamer has been shown to bind to AGEs and reduce the endothelial expression of the receptor for AGEs (RAGE) *in vitro* (56). In a randomized open-label study in patients with diabetic kidney disease, sevelamer carbonate, compared with calcium carbonate, reduced serum carboxymethyllysine and methylglyoxal, two of the main AGEs, and RAGE in peripheral blood mononuclear cells (57). Similar results were observed in a randomized crossover study in patients with diabetic nephropathy (58). In a randomized clinical trial, the use of sevelamer compared with calcium carbonate reduced coronary artery calcification and maintained plasma pentosidine, an AGE biomarker (59). However, the effect on artery calcification may also be due to the possible positive calcium balance with the use of calcium carbonate.

A diet low in AGEs has been shown to alter the gut microbiota in peritoneal dialysis patients (60). Particularly, there was a reduction in the relative abundance of *Prevotella copri* and *Bifidobacterium animalis*, and an increase in the relative abundance of *Alistipes indistinctus*,

Clostridium citroniae, *Clostridium hathewayi*, and *Ruminococcus gauvreauii*. In this study, 60% and 70% of the patients were prescribed phosphate binders in the high and low AGE diet, respectively, but the authors did not mention what type of binder the patients used.

Ferric Citrate

Ferric citrate is an iron-based phosphate binder that improves markers of CKD-MBD (61) and iron-deficiency anemia (62). Ferric iron dissociates from citrate and a portion of ferric iron binds to phosphate forming ferric phosphate, which is excreted in feces. Yaguchi et al. (63), showed *in vitro* that phosphate binding capacity was across pH levels of 2-8. GI symptoms are a common side effect of the use of ferric citrate including diarrhea (21%), nausea (11%), constipation (8%), and vomiting (7%) (64).

Ferric citrate has not been reported to bind other nutrients. However, of special interest is the iron contained in the compound which may act as an oral iron supplement and may shift the gut microbiota. Iron acts as the catalytic center for redox enzymes in processes such as electron-transport, activation of oxygen, and DNA synthesis and repair (65). Some bacteria, particularly Gram-negative bacteria, increase their relative abundance when the access to iron is increased (66). The utilization of iron by gut bacteria will depend in part on their ability to dissociate the iron from compounds (e.g., phytate, polyphenols, and other minerals), chelate iron through siderophores, internalize the iron, and reduce iron (67). These mechanisms are present in pathogenic bacteria and an increased amount of iron reaching the colon may promote virulence of these bacteria, inducing a pro-inflammatory environment (15). Kortman et al. showed in an *in vitro* kinetic model of the human colon that iron increased protein fermentation metabolites, such as branched-chain fatty acids and ammonia (68). In a recent study of 5/6 nephrectomized rats, Lau et al. (69) showed that a 6-week use of a 4% ferric citrate diet increased fecal α -diversity (species richness), reduced the relative abundance of Firmicutes, and increased the relative abundance of the *Akkermansia* genus and the *Clostridiaceae* and *Enterobacteriaceae* families, compared to the untreated CKD rats. However, as the gut microbiota of rats and humans are different, the effect of ferric citrate in patients with CKD and ESKD remains to be explored.

Sucroferric Oxyhydroxyde

Sucroferric oxyhydroxyde has been shown to bind more phosphate at pH of 3, compared to pH of 6 *in vitro* (16). The sucrose and starches that are part of the initial chewable tablet are digested and absorbed in the proximal small intestine, exposing the iron-oxyhydroxide core that binds phosphate (70). GI symptoms are the most common side effects: diarrhea (24%), discolored feces (16%), and nausea (10%) (71). Binding of sucroferric oxyhydroxyde to other vitamins or minerals has not been tested (19). Furthermore, to date, there are no studies assessing the effects of this binder on the gut microbiome. However, one can speculate that there may be minor effects as only minimal iron is released from the binder to be utilized by the gut microbiota.

Conclusion

Phosphate binders have effects other than reducing phosphate absorption. These pleiotropic effects may cause physiological changes in the GI tract and alter the gut microbiota and their function. Phosphate binders may bind molecules other than phosphate that are of importance, such as vitamin K, but also others that are detrimental, such as LPS, AGEs, indoles, and phenols, having systemic effects that are often overlooked in CKD. Importantly, these systemic effects may directly affect outcomes in patients with CKD as they impact inflammation, vascular calcifications, and improve the metabolic profile. Studies that assess the changes in the gut microbiome composition and function and their association with outcomes in this clinical population are necessary.

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References

1. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder: Synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. *Ann Intern Med.* 2018;168(6):422–30. [PubMed: 29459980]
2. Hill KM, Martin BR, Wastney ME, McCabe GP, Moe SM, Weaver CM, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease. *Kidney Int.* 2013;83(5):959–66. [PubMed: 23254903]
3. Moe SM, and Chertow GM. The case against calcium-based phosphate binders. *Clin J Am Soc Nephrol.* 2006;1(4):697–703. [PubMed: 17699275]
4. Patel L, Bernard LM, and Elder GJ. Sevelamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials. *Clin J Am Soc Nephrol.* 2016;11(2):232–44. [PubMed: 26668024]
5. Ruospo M, Palmer SC, Natale P, Craig JC, Vecchio M, Elder GJ, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev.* 2018;8:CD006023. [PubMed: 30132304]
6. Grant CJ, Harrison LE, Hoad CL, Marciani L, Gowland PA, and McIntyre CW. Patients with chronic kidney disease have abnormal upper gastro-intestinal tract digestive function: A study of uremic enteropathy. *J Gastroenterol Hepatol.* 2017;32(2):372–7. [PubMed: 27222079]
7. Vaziri ND, Zhao YY, and Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant.* 2016;31(5):737–46. [PubMed: 25883197]
8. Carrera-Jimenez D, Miranda-Alatriste P, Atilano-Carsi X, Correa-Rotter R, and Espinosa-Cuevas A. Relationship between Nutritional Status and Gastrointestinal Symptoms in Geriatric Patients with End-Stage Renal Disease on Dialysis. *Nutrients.* 2018;10(4).
9. Liang CC, Wang SM, Kuo HL, Chang CT, Liu JH, Lin HH, et al. Upper gastrointestinal bleeding in patients with CKD. *Clin J Am Soc Nephrol.* 2014;9(8):1354–9. [PubMed: 24903385]
10. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int.* 2013;83(2):308–15. [PubMed: 22992469]

11. Sommer F, and Backhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol.* 2013;11(4):227–38. [PubMed: 23435359]
12. Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL, and Vaziri ND. Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. *Am J Nephrol.* 2014;39(3):230–7. [PubMed: 24643131]
13. Evenepoel P, Meijers BK, Bammens BR, and Verbeke K. Uremic toxins originating from colonic microbial metabolism. *Kidney Int Suppl.* 2009(114):S12–9. [PubMed: 19946322]
14. Ramezani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R, and Raj DS. Role of the Gut Microbiome in Uremia: A Potential Therapeutic Target. *Am J Kidney Dis.* 2016;67(3):483–98. [PubMed: 26590448]
15. Kortman GAM, Reijnders D, and Swinkels DW. Oral iron supplementation: Potential implications for the gut microbiome and metabolome in patients with CKD. *Hemodial Int.* 2017;21:S28–S36. [PubMed: 28328083]
16. Schumacher SP, Schurgers LI, Vervloet MG, and Neradova A. Influence of pH and phosphate concentration on the phosphate binding capacity of five contemporary binders. *An in vitro study. Nephrology (Carlton).* 2018.
17. Wang S, Anum EA, Ramakrishnan K, Alfieri T, Braunhofer P, and Newsome B. Reasons for phosphate binder discontinuation vary by binder type. *J Ren Nutr.* 2014;24(2):105–9. [PubMed: 24462496]
18. Shirazian S, and Radhakrishnan J. Gastrointestinal disorders and renal failure: exploring the connection. *Nat Rev Nephrol.* 2010;6(8):480–92. [PubMed: 20606629]
19. Neradova A, Schumacher SP, Hubeek I, Lux P, Schurgers LI, and Vervloet MG. Phosphate binders affect vitamin K concentration by undesired binding, an in vitro study. *BMC Nephrol.* 2017;18(1):149. [PubMed: 28464802]
20. Danziger J Vitamin K-dependent proteins, warfarin, and vascular calcification. *Clin J Am Soc Nephrol.* 2008;3(5):1504–10. [PubMed: 18495950]
21. Holden RM, Morton AR, Garland JS, Pavlov A, Day AG, and Booth SL. Vitamins K and D status in stages 3-5 chronic kidney disease. *Clin J Am Soc Nephrol.* 2010;5(4):590–7. [PubMed: 20167683]
22. Trautvetter U, Camarinha-Silva A, Jahreis G, Lorkowski S, and Gleit M. High phosphorus intake and gut-related parameters - results of a randomized placebo-controlled human intervention study. *Nutr J.* 2018;17(1):23. [PubMed: 29452584]
23. Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, et al. High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice. *Circulation.* 2017;135(10):964–77. [PubMed: 27927713]
24. Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. *Curr Med Res Opin.* 2007;23(12):3167–75. [PubMed: 17991307]
25. Suzuki D, Ichie T, Hayashi H, Sugiura Y, and Sugiyama T. Gastrointestinal symptoms after the substitution of sevelamer hydrochloride with lanthanum carbonate in Japanese patients undergoing hemodialysis. *Pharmazie.* 2015;70(8):522–6. [PubMed: 26380521]
26. Hattori K, Maeda T, Nishida S, Imanishi M, Sakaguchi M, Amari Y, et al. Correlation of lanthanum dosage with lanthanum deposition in the gastroduodenal mucosa of dialysis patients. *Pathol Int.* 2017;67(9):447–52. [PubMed: 28799264]
27. Toussaint ND, Lau KK, Polkinghorne KR, and Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: A pilot randomized controlled trial. *Nephrology (Carlton).* 2011;16(3):290–8. [PubMed: 21342323]
28. Robijn S, Vervaeke BA, Hoppe B, D'Haese PC, and Verhulst A. Lanthanum carbonate inhibits intestinal oxalate absorption and prevents nephrocalcinosis after oxalate loading in rats. *J Urol.* 2013;189(5):1960–6. [PubMed: 23228382]
29. Mehta M, Goldfarb DS, and Nazzari L. The role of the microbiome in kidney stone formation. *Int J Surg.* 2016;36(Pt D):607–12. [PubMed: 27847292]

30. Brezina B, Qunibi WY, and Nolan CR. Acid loading during treatment with sevelamer hydrochloride: mechanisms and clinical implications. *Kidney Int Suppl.* 2004;(90):S39–45. [PubMed: 15296506]
31. Locatelli F, Del Vecchio L, Violo L, and Pontoriero G. Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles. *Expert Opin Drug Saf.* 2014;13(5):551–61. [PubMed: 24702470]
32. Goto S, Fujii H, Kim JI, and Fukagawa M. Homocysteine and folic acid levels in hemodialysis patients treated with sevelamer hydrochloride. *Clin Nephrol.* 2010;73(6):420–5. [PubMed: 20497753]
33. McIntyre CW, Harrison LE, Eldehni MT, Jefferies HJ, Szeto CC, John SG, et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin J Am Soc Nephrol.* 2011;6(1):133–41. [PubMed: 20876680]
34. Wong J, Vilar E, and Farrington K. Endotoxemia in end-stage kidney disease. *Semin Dial.* 2015;28(1):59–67. [PubMed: 25040340]
35. Nowak KL, and Chonchol M. Does inflammation affect outcomes in dialysis patients? *Semin Dial.* 2018.
36. Perianayagam MC, and Jaber BL. Endotoxin-binding affinity of sevelamer hydrochloride. *Am J Nephrol.* 2008;28(5):802–7. [PubMed: 18506105]
37. Hauser AB, Azevedo IR, Goncalves S, Stinghen A, Aita C, and Pecoits-Filho R. Sevelamer carbonate reduces inflammation and endotoxemia in an animal model of uremia. *Blood Purif.* 2010;30(3):153–8. [PubMed: 20861617]
38. Sun PP, Perianayagam MC, and Jaber BL. Sevelamer hydrochloride use and circulating endotoxin in hemodialysis patients: a pilot cross-sectional study. *J Ren Nutr.* 2009;19(5):432–8. [PubMed: 19464926]
39. Navarro-Gonzalez JF, Mora-Fernandez C, de Fuentes M Muros, Donate-Correa J, Cazana-Perez V, and Garcia-Perez J. Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. *Clin J Am Soc Nephrol.* 2011;6(9):2272–9. [PubMed: 21784820]
40. Braunlin W, Zhorov E, Guo A, Apruzzese W, Xu Q, Hook P, et al. Bile acid binding to sevelamer HCl. *Kidney Int.* 2002;62(2):611–9. [PubMed: 12110025]
41. McGettigan BM, McMahan RH, Luo Y, Wang XX, Orlicky DJ, Porsche C, et al. Sevelamer Improves Steatohepatitis, Inhibits Liver and Intestinal Farnesoid X Receptor (FXR), and Reverses Innate Immune Dysregulation in a Mouse Model of Non-alcoholic Fatty Liver Disease. *J Biol Chem.* 2016;291(44):23058–67. [PubMed: 27605663]
42. Harach T, Pols TWH, Nomura M, Maida A, Watanabe M, Auwerx J, et al. TGR5 potentiates GLP-1 secretion in response to anionic exchange resins. *Sci Rep-Uk.* 2012;2.
43. Bronden A, Mikkelsen K, Sonne DP, Hansen M, Vaben C, Gabe MN, et al. Glucose-lowering effects and mechanisms of the bile acid-sequestering resin sevelamer. *Diabetes Obes Metab.* 2018.
44. Jovanovich A, Isakova T, Block G, Stubbs J, Smits G, Chonchol M, et al. Deoxycholic Acid, a Metabolite of Circulating Bile Acids, and Coronary Artery Vascular Calcification in CKD. *Am J Kidney Dis.* 2018;71(1):27–34. [PubMed: 28801122]
45. Hylemon PB, Harris SC, and Ridlon JM. Metabolism of hydrogen gases and bile acids in the gut microbiome. *FEBS Lett.* 2018.
46. Miyazaki-Anzai S, Levi M, Kratzer A, Ting TC, Lewis LB, and Miyazaki M. Farnesoid X receptor activation prevents the development of vascular calcification in ApoE^{-/-} mice with chronic kidney disease. *Circ Res.* 2010;106(12):1807–17. [PubMed: 20431060]
47. Pierce D, Hossack S, Poole L, Robinson A, Van Heusen H, Martin P, et al. The effect of sevelamer carbonate and lanthanum carbonate on the pharmacokinetics of oral calcitriol. *Nephrol Dial Transplant.* 2011;26(5):1615–21. [PubMed: 20921291]
48. Westenfeld R, Krueger T, Schlieper G, Cranenburg EC, Magdeleyns EJ, Heidenreich S, et al. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. *Am J Kidney Dis.* 2012;59(2):186–95. [PubMed: 22169620]

49. Wilkes BM, Reiner D, Kern M, and Burke S. Simultaneous lowering of serum phosphate and LDL-cholesterol by sevelamer hydrochloride (RenaGel) in dialysis patients. *Clin Nephrol.* 1998;50(6):381–6. [PubMed: 9877112]
50. Lin CJ, Pan CF, Chuang CK, Liu HL, Huang SF, Chen HH, et al. Effects of Sevelamer Hydrochloride on Uremic Toxins Serum Indoxyl Sulfate and P-Cresyl Sulfate in Hemodialysis Patients. *J Clin Med Res.* 2017;9(9):765–70. [PubMed: 28811853]
51. Guida B, Cataldi M, Riccio E, Grumetto L, Pota A, Borrelli S, et al. Plasma p-cresol lowering effect of sevelamer in peritoneal dialysis patients: evidence from a Cross-Sectional Observational Study. *PLoS One.* 2013;8(8):e73558. [PubMed: 24015307]
52. Phan O, Ivanovski O, Nguyen-Khoa T, Mothu N, Angulo J, Westenfeld R, et al. Sevelamer prevents uremia-enhanced atherosclerosis progression in apolipoprotein E-deficient mice. *Circulation.* 2005;112(18):2875–82. [PubMed: 16267260]
53. Brandenburg VM, Schlieper G, Heussen N, Holzmann S, Busch B, Evenepoel P, et al. Serological cardiovascular and mortality risk predictors in dialysis patients receiving sevelamer: a prospective study. *Nephrol Dial Transplant.* 2010;25(8):2672–9. [PubMed: 20172849]
54. Wrong OM, and Harland CE. Sevelamer-induced acidosis. *Kidney Int.* 2005;67(2):776–7; author reply 7.
55. Rabbani N, and Thornalley PJ. Advanced glycation end products in the pathogenesis of chronic kidney disease. *Kidney Int.* 2018;93(4):803–13. [PubMed: 29477239]
56. Gregorio PC, Favretto G, Sasaki GL, Cunha RS, Becker-Finco A, Pecoits-Filho R, et al. Sevelamer reduces endothelial inflammatory response to advanced glycation end products. *Clin Kidney J.* 2018;11(1):89–98. [PubMed: 29423208]
57. Yubero-Serrano EM, Woodward M, Poretsky L, Vlassara H, Striker GE, and Group AG-IS. Effects of sevelamer carbonate on advanced glycation end products and antioxidant/pro-oxidant status in patients with diabetic kidney disease. *Clin J Am Soc Nephrol.* 2015;10(5):759–66. [PubMed: 25710801]
58. Vlassara H, Uribarri J, Cai WJ, Goodman S, Pyzik R, Post J, et al. Effects of Sevelamer on HbA1c, Inflammation, and Advanced Glycation End Products in Diabetic Kidney Disease. *Clin J Am Soc Nephro.* 2012;7(6):934–42.
59. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. *Am J Kidney Dis.* 2011;57(3):422–31. [PubMed: 21239096]
60. Yacoub R, Nugent M, Cai W, Nadkarni GN, Chaves LD, Abyad S, et al. Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; a randomized open label controlled trial. *PLoS One.* 2017;12(9):e0184789. [PubMed: 28931089]
61. Van Buren PN, Lewis JB, Dwyer JP, Greene T, Middleton J, Sika M, et al. The Phosphate Binder Ferric Citrate and Mineral Metabolism and Inflammatory Markers in Maintenance Dialysis Patients: Results From Prespecified Analyses of a Randomized Clinical Trial. *Am J Kidney Dis.* 2015;66(3):479–88. [PubMed: 25958079]
62. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol.* 2015;26(2):493–503. [PubMed: 25060056]
63. Yaguchi A, Yonekubo S, Maruyama I, Tatemichi S, Maruyama K, and Kobayashi M. Comparison of Phosphate Binding Capacities of PA21, A Novel Phosphate Binder, with those of other Phosphate Binders in vitro and in vivo. *Drug Res (Stuttg).* 2016;66(5):262–9. [PubMed: 26761712]
64. Yokoyama K, Akiba T, Fukagawa M, Nakayama M, Sawada K, Kumagai Y, et al. Long-term safety and efficacy of a novel iron-containing phosphate binder, JTT-751, in patients receiving hemodialysis. *J Ren Nutr.* 2014;24(4):261–7. [PubMed: 24836401]
65. Muckenthaler MU, Rivella S, Hentze MW, and Galy B. A Red Carpet for Iron Metabolism. *Cell.* 2017;168(3):344–61. [PubMed: 28129536]

66. Paganini D, and Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. *Am J Clin Nutr.* 2017;106(Suppl 6): 1688S–93S. [PubMed: 29070552]
67. Kortman GA, Raffatellu M, Swinkels DW, and Tjalsma H. Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. *FEMS Microbiol Rev.* 2014;38(6):1202–34. [PubMed: 25205464]
68. Kortman GA, Dutilh BE, Maathuis AJ, Engelke UF, Boekhorst J, Keegan KP, et al. Microbial Metabolism Shifts Towards an Adverse Profile with Supplementary Iron in the TIM-2 In vitro Model of the Human Colon. *Front Microbiol.* 2015;6:1481. [PubMed: 26779139]
69. Lau WL, Vaziri ND, Nunes AC, Comeau AM, Langille MG, England W, et al. The phosphate binder ferric citrate alters the gut microbiome in rats with chronic kidney disease. *J Pharmacol Exp Ther.* 2018.
70. Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A, et al. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. *Int J Nephrol Renovasc Dis.* 2016;9:11–9. [PubMed: 26893577]
71. Floege J, Covic AC, Ketteler M, Mann JF, Rastogi A, Spinowitz B, et al. Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. *Nephrol Dial Transplant.* 2015;30(6):1037–46. [PubMed: 25691681]

Table 1.
Effects of phosphate binders on nutrient and molecule absorption, gastrointestinal function, and the gut microbiota

Type of phosphate binder	Best pH for binding	Nutrient absorption impairment	Gastrointestinal effects	Gut microbiota and metabolites	Other
Calcium carbonate	3	- Binds to vitamin K2 (MK7) in the presence of phosphate	- Constipation	- ↑ <i>Clostridium spp.</i> * - ↑ SCFA *	- N.A.
Calcium Acetate	6	- Binds to vitamin K2 (MK7) in the presence and absence of phosphate	- Nausea - Vomiting	- ↓ Firmicutes-to-Bacteroidetes (?)	- N.A.
Lanthanum Carbonate	3	- Binds to oxalate - Binds to vitamin K2 (MK7) in the absence of phosphate	- Nausea - Vomiting - Abdominal Pain - If not chewed completely, possible GI accumulation	- <i>Oxalobacter formigenes</i> (?)	- N.A.
Sevelamer Hydrochloride/Carbonate	5.5/3	- Binds to bile acids; ↓ absorption of fat-soluble vitamins (vitamins D and K) - Binds to folic acid	- Nausea - Vomiting - Diarrhea - Dyspepsia - Abdominal pain - Flatulence - Constipation	- Binds to indole, indoxyl sulfate, p-cresol, and SCFA -	- Binds AGEs - Binds LPS - ↓ CRP, TNFα, IL6 - ↓ LDL due to binding to bile acids - Improved glucose homeostasis - N.A.
Sucroferric Oxhydroxyde	3	- ?	- Diarrhea - Discolored feces - Nausea	- ?	- ?
Ferric Citrate	2-8	- ?	- Diarrhea - Nausea - Constipation - Vomiting	- Non-absorbed iron (?)	- Improves markers of iron-deficiency anemia.

* Study in healthy adults (22).

22. Trautvetter U, Camarinha-Silva A, Jahreis G, Lorkowski S, and Gleis M. High phosphorus intake and gut-related parameters - results of a randomized placebo-controlled human intervention study. *Nutr J.* 2018;17(1):23.