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Small Intestinal Phosphate Absorption: Novel Therapeutic Implications

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Abstract

Background: Chronic kidney disease (CKD) affects approximately 15% of adults in the USA. As CKD progresses, urinary phosphate excretion decreases and results in phosphate retention and, eventually, hyperphosphatemia. As hyperphosphatemia is associated with numerous adverse outcomes, including increased cardiovascular mortality, reduction in phosphorus concentrations is a guideline-recommended, established clinical practice. Dietary phosphate restriction, dialysis, and phosphate binders are currently the only options for phosphate management. However, many patients with hyperphosphatemia have phosphorus concentrations >5.5 mg/dL, despite treatment. ***Summary:*** This review presents recent advances in the understanding of intestinal phosphate absorption and therapeutic implications. Dietary phosphate is absorbed in the intestine through two distinct pathways, paracellular absorption and transcellular transport. Recent evidence indicates that the paracellular route accounts for 65–80% of total phosphate absorbed. Thus, the paracellular pathway is the dominant mechanism of phosphate absorption. Tenapanor is a first-in-class, non-phosphate binder that inhibits the sodium-hydrogen exchanger 3 or solute carrier family 9 member 3 (SLC9A3) encoded by the SLC9A3 gene, and blocks paracellular phosphate absorption. ***Key Messages:*** Targeted inhibition of sodium-hydrogen exchanger 3 effectively reduces paracellular permeability of phosphate. Novel therapies that target the paracellular pathway may improve phosphate control in chronic kidney disease.

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Biological Role and Sources of Phosphate

Phosphorus is one of the most abundant minerals in the body [1, 2]. Approximately 85% of total body phosphorus is skeletal and the remaining 15% is in soft tissues [1]. Almost all of the phosphorus found in the extracellular fluid space is in the form of inorganic phosphate [1]. Proper functioning of many biological processes, including cellular energy production, release of oxygen to the peripheral tissue by red blood cells, and bone mineralization, requires normal phosphate concentrations [1]. Although orthophosphate primarily circulates in plasma as $H_2PO_4^{2-}$ and HPO_4^- (4:1 ratio) [1], a small proportion forms complexes with calcium and magnesium ions [3].

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Laboratory measurement of orthophosphate is reported as serum phosphorus [4], with a normal range of 2.5–4.5 mg/dL [5].

Dietary phosphate ingestion is the primary source of phosphorus intake [6]. Plant-based phosphate is primarily in the form of phytate (6-fold dihydrogen phosphate ester of inositol) and is concentrated in whole grain cereals and legumes [7, 8]. Because humans lack the enzyme phytase, there is minimal to no phytate degradation in the small intestine, accounting for the low bioavailability of plant-based dietary phosphate [9]. Phytates are considered by some experts to be "anti-nutritional factors" due to their ability to prevent absorption of minerals [10, 11], and the phytase enzyme is sometimes added to processed food products to increase the bioavailability of minerals [12]. There is evidence to suggest that phosphate from animal-based sources such as meat or fish may be more bioavailable than phosphate from plant-based sources [13]. In a 1-week study, a primarily plant-based diet led to lower phosphorus concentrations than a primarily animal-based diet containing the same quantity of phosphate [13]. This may have been due to the lower bioavailability of phytate-bound phosphorus in comparison to animal-based sources and/or the additional strain on the kidney from higher availability of protein in meat-based diets [13]. Therefore, the source of dietary phosphate (animal-based vs. plant-based) influences phosphorus management [13].

Modern food processing has significantly increased the quantity of dietary phosphate intake. The inclusion of processed foods is estimated to increase daily dietary phosphorus intake by approximately 1,000 mg [14, 15]. However, as food manufacturers are not required to list the quantity of phosphorus in their food additives, the actual quantity of dietary phosphorus from food additives may easily supersede the estimated intake of 1,000 mg [16, 17]. In addition, food additives are mostly inorganic phosphate, which are believed to be more readily and completely absorbed in humans compared to organic phosphates [14].

A conventional Western diet contains a significant proportion of processed foods [15, 18], which often contain unknown quantities of phosphate additives [15, 19]. The normal daily phosphorus intake is estimated at >2,500 mg [14, 20, 21]. This intake is >3-fold greater than the recommended daily allowance of approximately 700 mg [22]. Consequently, although patients with end-stage renal disease (ESRD) should adhere to low phosphorus diets of <1,000 mg daily [23], numerous phosphate additives may lead to an intake of much greater quantities of phosphorus than appreciated [14]. Phosphate excipients (e.g., anhydrous calcium hydrogen phosphate) commonly accompany medications prescribed for dialysis-dependent chronic kidney disease (CKD) patients, and excipients may contribute 100–200 mg of phosphorus to the daily load [24, 25]. Therefore, the daily phosphorus intake may approach 2,500 mg. Of this quantity, approximately 60–80% would be absorbed by the gastrointestinal tract [26].

Phosphate Regulation and Negative Impact of Hyperphosphatemia in CKD

CKD is estimated to affect 15% of adults in the USA [27]. As CKD progresses, urinary phosphate excretion decreases and phosphate retention occurs [28]. Phosphate homeostasis is regulated by 3 hormones: parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23), and active vitamin D in the form of calcitriol (1,25-dihydroxycholecalciferol) [29]. Calcitriol increases active intestinal phosphate transport by increasing expression of the transporters PiT-2 and NaPi2b [30–32], whereas PTH and FGF23 work to decrease phosphate concentrations [29]. In the early stages of CKD, PTH and FGF23 concentrations increase as compensatory mechanisms [33–35]. These mechanisms enhance renal phosphate excretion and decrease intestinal phosphate absorption to maintain serum phosphorus concentrations within the normal range [33–35]. Vitamin D receptor-dependent decreases in intestinal transcellular phosphate transport as a result of compensatory mechanisms have been observed in animal models [35]. Phosphorus concentrations are stable in early CKD stages before increasing in later stages, but FGF23 and PTH increase steadily and significantly as the disease progresses, suggesting that these mechanisms are eventually insufficient to maintain phosphate homeostasis [33]. Consequently, >80% of patients with ESRD require treatment for hyperphosphatemia [36].

Hyperphosphatemia is associated with several adverse outcomes (e.g., vascular calcification, cardiovascular (CVD) disease, and secondary hyperparathyroidism) [37–39]. Phosphate retention is considered the initiating and driving force of the mineral and endocrine disruptions that comprise CKD-mineral bone disorder [40], a common complication in patients with CKD associated with CV morbidity and mortality [41–43]. Phosphate retention also triggers an increase in FGF23 and PTH concentrations, both of which have been suggested to have

Fig. 1. Dietary phosphorus absorption occurs in the small intestine via 2 distinct pathways: transcellular and paracellular. The transcellular pathway is characterized by active intestinal phosphate transport that occurs primarily through the action of the NaPi2b. Maximum absorption via the transcellular pathway is achieved at luminal phosphorus concentrations of approximately 6.0 mg/dL (2 mmol/L). Paracellular phosphate absorption occurs passively along concentration gradients through tight junction complexes (e.g., claudins and occludins) between cell membranes. The mechanism of the paracellular phosphate absorption is consistent with nonsaturable, passive diffusion, which constitutes the majority of intestinal phosphorus absorption in humans. NaPi2b, sodium-dependent phosphate cotransporter 2b.
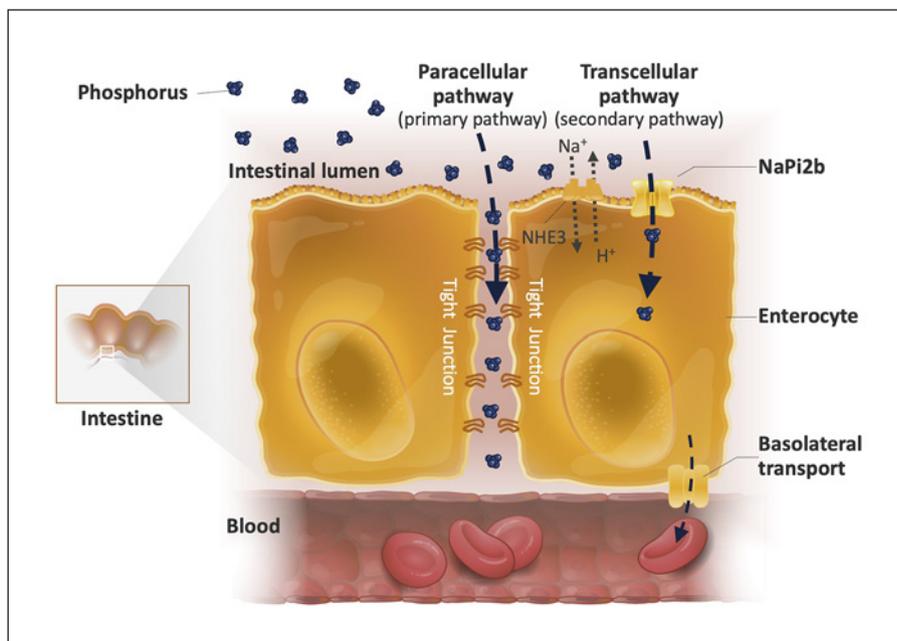
direct pathogenic CV effects [44, 45]. Hyperphosphatemia is also an independent risk factor for CV mortality, the primary cause of death in patients with CKD [27, 46, 47]. Kestenbaum et al. [48] found that each 1 mg/dL increase in serum phosphorus was associated with ~23% increased mortality risk. Phosphorus concentrations of 4.5–4.9 mg/dL were associated with greater hazard ratios than concentrations of 4–4.5 mg/dL (1.93 vs. 1.34) [48]. Phosphorus concentrations greater than 3.5 mg/dL have also been shown to increase mortality risk in both adults with and without CKD [48, 49], confirming that even increases within normal concentrations (2.5–4.5 mg/dL) negatively impact health outcomes. Improved patient survival is associated with serum phosphorus concentrations that do not exceed 4.5 mg/dL [50].

Because of the negative consequences of hyperphosphatemia, reduction in phosphorus, with the goal of maintaining concentrations toward the normal range, is a guideline-recommended, established clinical practice [23, 51]. However, achieving proper phosphorus control remains a clinical challenge, and many patients with CKD have phosphorus concentrations exceeding 5.5 mg/dL [52]. The development of strategies and treatments guided by an understanding of the pathogenesis of hyperphosphatemia and underlying physiology of phosphate absorption can potentially improve our ability to manage phosphorus concentrations and improve clinical outcomes.

Advances in Phosphate Absorption and Regulation Mechanisms

Serum phosphorus concentrations are balanced through intestinal uptake, retention or by release from bone, and regulation of renal phosphate reabsorption [53–55]. Phosphate from dietary sources travels through the gut and becomes available for intestinal absorption [55].

Dietary phosphate absorption occurs in the small intestine via 2 distinct pathways: the saturable transcellular pathway involving specific phosphate transporters and the nonsaturable paracellular pathway driven by the phosphate concentration gradient (Fig. 1) [55–58]. Classically, the transcellular pathway was considered the primary mechanism of phosphate absorption [53]. Animal studies of the transcellular pathway document that active intestinal phosphate transport occurs primarily via the sodium-dependent phosphate cotransporter 2b (NaPi2b) [59]. Maximum absorption via the transcellular pathway is achieved at luminal concentrations of approximately 6.0 mg/dL phosphorus (2 mmol/L) in patients with ESRD [58]. Based on published data describing gastric volume, a typical Western diet containing 2,500 mg of phosphorus per day would produce luminal phosphorus concentrations of approximately 55–110 mg/dL (18–36 mmol/L) [6, 14, 60], which greatly exceeds the transport maximum of the transcellular pathway. Experimental evidence from ESRD patients sug-

gests that NaPi2b is more important for phosphate absorption when luminal phosphate concentrations are low [58], as might occur during dietary privation. The minor role for transcellular absorption in humans is supported by divergent results from NaPi2b inhibitor trials in animals and humans. In animal trials, serum phosphorus concentrations were reduced, consistent with the hypothesis that transcellular transport was the prime mediator of intestinal phosphate absorption [61]. These studies are often performed with diets that favor the transcellular pathway and are not reflective of human phosphorus consumption. In humans, a phase 1 trial of a NaPi2b inhibitor found no changes in phosphorus concentrations of healthy volunteers or hyperphosphatemic patients with ESRD who were administered single (10 or 100 mg) or multiple (10, 30, or 100 mg 3 times per day) doses [62]. The transcellular pathway is not the primary modality of intestinal phosphate absorption in humans [62, 63].

Human and animal models have shown that paracellular phosphate absorption occurs passively along concentration gradients through tight junction complexes (e.g., claudins and occludins) between cell membranes [58, 64–66]. The human concentration gradient is subject to dietary intake and the bioavailability of phosphate sources [58, 67]. Under normal dietary conditions, human and animal models have established that the paracellular route is nonsaturable and responsible for the majority of intestinal phosphate absorption, particularly when phosphate concentrations are high [58, 64]. Animal models indicate that paracellular absorption constitutes about 65–80% of intestinal phosphate absorption and transcellular absorption is 20–35% [68, 69]. Because of the relatively high luminal phosphate concentrations associated with modern diets and the lack of a saturation "limit," the paracellular route is responsible for a much greater proportion of phosphate absorption than the transcellular route [58, 65].

Intestinal epithelial permeability of phosphate through the paracellular pathway appears to be influenced by the sodium-hydrogen exchanger 3 (NHE3), which is expressed throughout the human gastrointestinal tract and more highly expressed in the small intestine [66, 70]. Regulation of NHE3 is achieved both acutely and chronically [71]. In animal and in vitro models of human small intestinal enteroids, NHE3 inhibition increases transepithelial electrical resistance [66]. In the absence of an obvious signaling pathway or tight junction protein trafficking, the rapid increase in transepithelial electrical resistance suggests that a direct pH-sensitive conformational change to the tight junction proteins (e.g., claudins) reduces paracellular phosphate permeability [66]. The effects of NHE3 inhibition were evaluated in NHE3-knockout mice, created by disrupting the solute carrier family 9 member 3 gene [72–74], and in animal trials of a targeted NHE3 inhibitor [75]. These studies uniformly demonstrated reduced intestinal phosphate, sodium, and water absorption [72–75]. These results have subsequently been confirmed in clinical trials of an NHE3 inhibitor in healthy volunteers and patients with ESRD. In both groups, a dose-dependent inhibition of intestinal phosphorus absorption was evident, resulting in decreased serum phosphorus in patients with ESRD [66, 76, 77]. Collectively, the paracellular phosphate absorption pathway is diminished by enterocyte inhibition of NHE3.

Challenges of Current Phosphate Management in Patients with CKD

Phosphorus management for patients with CKD currently consists of a three-pronged approach: restricting dietary phosphate intake, reducing intestinal phosphate absorption with phosphate binders, and enhancing phosphate elimination with dialysis [78]. A conventional hemodialysis session can remove up to 1,000 mg of phosphorus [79]. The efficacy of dialysis is limited by the small amount of phosphate present in the readily accessible plasma space [80]. Following removal of plasma phosphate, further removal is regulated by the rate-limiting step of phosphate translocation from the intracellular pool to plasma [80]. While dietary phosphate restriction and phosphate removal by dialysis are important, these maneuvers do not consistently achieve and/or maintain appropriate phosphorus control [81]. For hemodialysis patients with persistent hyperphosphatemia, there is low-quality evidence that monthly dietary therapy represents effective therapy [82].

Controlling serum phosphorus through dietary interventions (low phosphorus diet) is a key component of hyperphosphatemia management but brings challenges with adherence as well as maintaining adequate nutrition. For example, there is a strong correlation between dietary phosphate and protein intake [83]. As a corollary, dietary phosphate restriction may place patients at risk for inadequate protein intake [84]. Patients with advanced CKD are at substantial risk for malnutrition, characterized by protein-energy wasting and low energy intake, that increases risk of morbidity and mortality [85, 86].
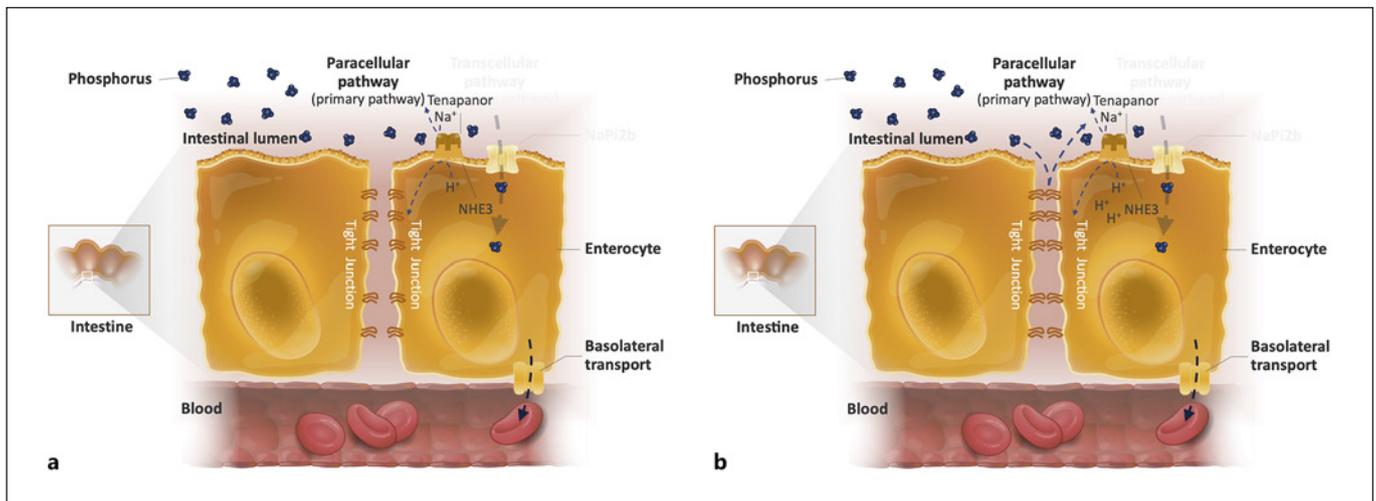
Fig. 2. Tenapanor, a specific, investigational NHE3 inhibitor, produces a modest intracellular proton retention that is proposed to induce conformational change(s) in claudin proteins present in tight junctions, thereby reducing paracellular phosphate transport. NHE3, sodium-hydrogen exchanger 3.

Phosphate binders are prescribed to >80% of patients on dialysis and are the only pharmacological treatment currently indicated for hyperphosphatemia [36]. These agents form complex dietary phosphates in the intestinal lumen and form insoluble complexes that are excreted [87–91]. However, the administration of phosphate binders as a class generally does not achieve and maintain phosphorus concentrations <5.5 mg/dL [92]. The mechanism of action of phosphate binders is inherently inefficient and provides a potential explanation for the challenges that patients and clinicians face in achieving target serum phosphorus concentrations. Nonspecific binding to ligands other than phosphate results in suboptimal efficacy and drug-drug interactions with medications commonly prescribed to patients on dialysis [87–91, 93]. Also, the short duration of action of phosphate binders require binders to be taken with meals and snacks [87–91]. The limited per pill phosphate binding capacity mandates the ingestion of multiple pills, many that are large in size [26, 94–101]. Despite phosphate binder therapy, recent data demonstrate that 42% of patients on dialysis had phosphorus concentrations >5.5 mg/dL, 77% were >4.5 mg/dL in the most recent month, and 77% were unable to consistently maintain phosphorus concentrations <5.5 mg/dL over a 6-month period [92], reinforcing the notion that current therapies, even when properly implemented, are insufficient to manage hyperphosphatemia.

New Targeted Therapies for Hyperphosphatemia

Given the growing evidence that the principal mode of small intestinal phosphate absorption takes place via the paracellular pathway, new therapies targeting this pathway have been investigated. Tenapanor, an investigational, first-in-class non-phosphate absorption inhibitor, targets the paracellular pathway via inhibition of enteric NHE3 (Fig. 2) [66]. In rodents and in experiments using human stem cell-derived enteroid monolayers, inhibition of NHE3 produces intracellular acidification. This change in pH is proposed to produce a subsequent conformational change in tight junction proteins, such as claudins or occludins, which limit paracellular phosphate transit from lumen-to-plasma [66]. By interrupting phosphate absorption, tenapanor directly and efficiently reduces serum phosphorus concentrations [77].

Tenapanor was initially approved for treatment of irritable bowel syndrome with constipation (IBS-C) in 2019, and trial safety data for this indication adds support to the safety data generated in patients with hyperphosphatemia. In phase 1 trials of healthy volunteers, reduced intestinal phosphate and sodium absorption and enhanced intestinal fluid volume were documented without deleterious effect on serum potassium concentrations [76, 102]. Likewise, there were no clinically significant alterations of serum sodium concentrations from baseline in a phase 2 study of IBS-C [103]. Diarrhea was the most common adverse event in the phase 2 (9%)

and phase 3 IBS-C trials (16%) [103, 104]. Most cases of diarrhea were transient and mild to moderate in severity [103, 104].

Preclinical data from an animal model revealed that tenapanor effectively reduced phosphate absorption and facilitated a 50% reduction in phosphate binder dose [105]. In clinical trials, tenapanor has been evaluated for efficacy as monotherapy (vs. placebo) in separate trials of 12 and 52 weeks. At 12 weeks, tenapanor administration lowered serum phosphorus in subjects from baseline concentrations of 8.1 mg/dL to 5.5 mg/dL in the efficacy analysis set [77]. This phase 3, double-blinded, placebo-controlled randomized trial of tenapanor showed no clinically significant changes of sodium or potassium concentrations from baseline in patients on dialysis in the USA. [77]. Diarrhea, the most common adverse event, was observed in 30%, 41%, and 48% of subjects receiving 3 mg, 10 mg, and 30 mg of tenapanor, respectively [77]. Softened stool and a modest increase in bowel movement frequency may be anticipated with tenapanor administration [77]. In the long-term phase 3 study, at 26 weeks, tenapanor administration lowered serum phosphorus in subjects from baseline concentrations of 7.7 mg/dL to 5.1 mg/dL in the efficacy analysis set [106].

Tenapanor has also been investigated with phosphate binders as part of a dual mechanism approach to phosphorus lowering in a 4-week human study [107]. A significantly larger proportion of subjects treated with tenapanor and binders achieved serum phosphorus concentrations of <5.5 mg/dL at week 1 (49% vs. 21%; $p < 0.001$), week 2 (41% vs. 24%; $p = 0.003$), week 3 (47% vs. 18%; $p < 0.001$), and week 4 (37% vs. 22%; $p = 0.01$) compared to those who only received binders [107]. An extension study evaluating the capacity of tenapanor to reduce serum phosphorus to within the normal range (<4.5 mg/dL) is ongoing (ClinicalTrials.gov: NCT03988920).

Nicotinamide is another potential treatment of hyperphosphatemia. This compound appears to inhibit gut Na-Pi2b cotransporters, thereby reducing phosphate-specific transcellular permeability [108]. Although intestinal Na-Pi2b-mediated cotransport of sodium and phosphate is responsible for >90% of transcellular or active phosphate absorption in rats [59], the bulk of human phosphate absorption is passively mediated by the nonsaturable paracellular route [58]. Consequently, one could surmise that nicotinamide would be less efficacious than tenapanor as a treatment of hyperphosphatemia due to its lack of effect on paracellular phosphate absorption. This hypothesis is supported by the lack of significant reductions in phos-

phorus or FGF23 in nondialysis CKD patients treated by lanthanum carbonate and/or nicotinamide during a 12-month trial [109].

Future Studies

Novel strategies that minimize the detrimental effects of hyperphosphatemia must also be explored in parallel. For example, it is possible that the harmful effects of high phosphorus concentrations are attributable to abnormalities in phosphate-sensing mechanisms [110]. Therefore, a greater understanding of phosphate regulatory and sensing mechanisms may provide insights into future methodologies that reduce the harmful effects of phosphorus overload [110].

Conclusion

Hyperphosphatemia in patients with CKD and ESRD remains a clinical challenge. Current therapeutic options are inadequate. Treatment choices beyond the dietary restriction of phosphate and phosphate binding are urgently needed. Innovations that directly inhibit phosphate absorption represent an advancement over conventional intestinal phosphate-binding strategies. Lowering paracellular phosphate absorption via intestinal NHE3 inhibition represents a novel mechanism that may have a greater quantitative effect on lowering serum phosphorus concentrations. Concomitant with a primary strategy of blocking phosphate absorption via the paracellular pathway, phosphate binders may be considered adjunctive therapy. Additional clinical trials in patients with CKD and ESRD assessing the efficacy of hyperphosphatemia treatments using both surrogate and hard patient-centered outcomes would be beneficial.

Statement of Ethics

For this review article, no new research study was conducted that prospectively assigns human participants or groups of humans to one or more health-related interventions, and therefore, no patients were enrolled or subjected to therapies. Thus, there are no requirements for any ethical approval or informed consent. The process of developing this article complies with internationally accepted standards for research practice and reporting.

Conflict of Interest Statement

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Author Contributions

All authors participated in the review and screening of literature, conceptualization, writing, and revising of this review article.

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