Phosphate absorption occurs in the gastrointestinal tract through paracellular absorption and transcellular transport. The paracellular pathway does not saturate and has a significantly higher absorption capacity than does the transcellular pathway. Evidence indicates that this pathway is the primary mechanism of intestinal phosphate absorption, particularly with Western diets containing high amounts of phosphorus. Elevated serum phosphorus concentrations are associated with cardiovascular morbidity and mortality but serum phosphorus concentrations > 5.5 mg/dL are highly prevalent despite best efforts with dietary phosphate restriction, dialysis, and the use of phosphate binders. The efficacy of phosphate binders may be inherently limited because the mechanism of action does not target any phosphate absorption pathway. Thus, therapeutic innovations are needed to address the limitations of phosphate binders. Novel therapies leveraging new mechanistic understandings of phosphate absorption and the primacy of the paracellular pathway may improve phosphate control. Phosphate absorption inhibitors that target the pathway are a novel therapeutic class. Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that inhibits the sodium-hydrogen exchanger isofrom 3 to reduce paracellular permeability specific to phosphate. Phosphate absorption inhibitors may represent a new mechanistic approach to phosphate management with the potential to improve clinical outcomes.

Systemic phosphate homeostasis is maintained primarily through urinary excretion. As chronic kidney disease (CKD) progresses, kidney function declines, leading to phosphate retention. Elevated serum phosphorus concentrations, or hyperphosphatemia, are seen in most patients with advanced CKD and those receiving dialysis.

NEW UNDERSTANDING OF PHOSPHATE ABSORPTION PATHWAYS

Diet is the primary source of phosphate intake and absorption of dietary phosphate occurs in the gastrointestinal (GI) tract through 2 distinct pathways: paracellular absorption and transcellular transport (Fig 14-14). Paracellular absorption occurs passively along concentration gradients through the tight junction complexes (eg, claudins and occludins) between cell membranes. The paracellular pathway is not limited by a saturation point and has been shown to be responsible for most intestinal phosphate absorption, particularly when luminal phosphate concentrations are high. The transcellular sodium-dependent pathway takes in phosphate primarily through the action of the sodium-dependent phosphate cotransporter 2b (NaPi2b). Evidence suggests that NaPi2b is responsible for phosphate absorption in the presence of low amounts of dietary phosphate, but because this pathway saturates, it is less relevant for people who consume Western diets, which typically have high amounts of phosphorus.

New studies have found that the paracellular pathway is the primary mechanism of phosphate absorption under typical conditions of phosphate availability in individuals consuming standard Western diets, not the transcellular pathway as previously believed. Although transcellular phosphate transport by NaPi2b plays a significant role in rodents, recent clinical evidence shows this pathway to be less physiologically relevant in humans. Furthermore, maximum absorption through the transcellular pathway is reached at a very low luminal concentration of ~ 2 mmol/L. Based on reported gastric volumes of 750 to 1,500 mL, a typical Western diet of ~2,500 mg of phosphate per day translates to luminal concentrations of 18 to 36 mmol/L, far exceeding the maximum concentration that the transcellular pathway can accommodate. Paracellular absorption is biologically favored by the intestinal electrochemical gradient and has much higher capacity for absorption than the transcellular transport system.

CHALLENGES IN ACHIEVING PHOSPHATE GOALS WITH CURRENT THERAPIES

Phosphate is one of the most abundant minerals in the body, and serum phosphorus concentration must be maintained within the normal range (2.5-4.5 mg/dL) for optimal functioning of many biological processes. Elevated serum phosphorus concentrations are associated with significant negative clinical outcomes, and management of phosphate is a guideline-recommended established clinical practice. National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2003 guidelines recommend targeting phosphorus concentrations of 2.7 to 4.6 mg/dL in patients with stages 3 and 4 CKD and 3.5 to 5.5 mg/dL in patients with stage 5 CKD and those receiving dialysis. These recommendations are based on the association between elevated serum phosphorus concentrations and adverse

References

1. KDOQI (Kidney Disease Outcomes Quality Initiative) 2003 guidelines recommend targeting phosphorus concentrations of 2.7 to 4.6 mg/dL in patients with stages 3 and 4 CKD and 3.5 to 5.5 mg/dL in patients with stage 5 CKD and those receiving dialysis.

2. Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that inhibits the sodium-hydrogen exchanger isofrom 3 to reduce paracellular permeability specific to phosphate.

3. Paracellular absorption is biologically favored by the intestinal electrochemical gradient and has much higher capacity for absorption than the transcellular transport system.

4. Elevation of serum phosphorus concentrations is associated with cardiovascular morbidity and mortality.

5. Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that inhibits the sodium-hydrogen exchanger isofrom 3 to reduce paracellular permeability specific to phosphate.

6. Phosphate absorption inhibitors may represent a new mechanistic approach to phosphate management with the potential to improve clinical outcomes.
clinical outcomes, as well as the expert opinion of the KDOQI working group.9 The KDIGO (Kidney Disease: Improving Global Outcomes) 2017 guideline recommends that patients with CKD stages 3A–5D lower elevated phosphate levels toward the normal range.20 Phosphate binders, which reduce the quantity of absorbable phosphate by binding to dietary phosphate to create insoluble compounds, are currently the only US Food and Drug Administration–approved treatment for hyperphosphatemia21 and are prescribed to 80% of US patients receiving dialysis (Table 18,15-18).22 Although phosphate binders are widely used, a disturbingly large proportion of patients are unable to consistently achieve and maintain phosphate levels ≤ 5.5 mg/dL.23 A total of 77% of dialysis patients receiving binders are unable to maintain levels ≤ 5.5 mg/dL over a 6-month period.23 An even greater proportion of patients receiving dialysis are unable to achieve more normal phosphate levels.24-25 Modern diets are high in phosphate, primarily from phosphate additives,26 which makes it challenging for patients to take sufficient binders to consistently maintain target phosphate levels.27,28 As evidenced by these data, current phosphorus management strategies that include phosphate binders, reduction in phosphorus dietary intake, and dialysis are insufficient to achieve and maintain phosphate levels ≤ 5.5 mg/dL (or more normal levels) for most patients. Phosphate binders have a fundamentally inefficient mechanism of action that potentially explains the continuing clinical challenge of consistently achieving and maintaining target serum phosphorus concentrations. Instead of directly acting on phosphate absorption pathways,29-33 either the secondary transcellular pathway or the primary paracellular pathway, phosphate binders "scavenge" particles of dietary phosphate in the GI tract. To scavenge and bind the phosphorus before it is absorbed, the binders must be in the gut

Figure 1. (A) Illustration of the transcellular phosphate absorption pathway.11 The sodium-dependent phosphate cotransporter 2b (NaPi2b) is responsible for transcellular phosphate absorption.6 This phosphate transporter saturates at phosphate concentrations well below those associated with conventional Western diets.4 There is evidence that NaPi2b plays a larger role in intestinal phosphate absorption when luminal phosphate concentrations are low,4 which is likely to occur during dietary privation. (B) Illustration of the paracellular phosphate absorption pathway.5,9-14 Paracellular phosphate absorption is characterized by passive diffusion along concentration gradients through tight junction complexes of claudins and occludins between cell membranes.2 The paracellular route does not saturate2 and is the dominant intestinal phosphate absorption pathway.16 (C) Illustration of the paracellular phosphate absorption pathway with tenapanor. Tenapanor blocks paracellular absorption of phosphate in the GI tract by local inhibition of the sodium/hydrogen exchanger isoform 3 (NHE3).10 NHE3 inhibition directly reduces sodium absorption, leading to modest intracellular proton retention that is proposed to induce conformational changes in tight junction proteins.10 These changes directly reduce permeability specific to phosphate through the paracellular pathway.10
Hyperphosphatemia is associated with numerous negative consequences (eg, vascular calcification, CVD, and secondary hyperparathyroidism) and may be an independent risk factor for progression of CKD. The population-attributable risk percentage for disorders of mineral metabolism was 17.5%, largely due to the high prevalence of hyperphosphatemia. The population-attributable risk for CKD mortality is much higher for elevated phosphate levels (12%) than for hypercalcemia (4%), hyperparathyroidism (2%), low urea reduction ratio (5%), or anemia (6%). Thus, serum phosphorus concentrations are an important remaining modifiable contributor to mortality in patients with CKD.

Hyperphosphatemia is linked to an increased risk for CVD through multiple physiologic mechanisms. First, high phosphate concentrations may increase vascular calcification by inducing the permanent transformation of vascular smooth muscle cells into osteoblast-like cells. Furthermore, as a class, phosphate binders have been associated with clinically significant GI tolerability issues, including abdominal pain, constipation, diarrhea, nausea, and vomiting (Table 1). In clinical trials with phosphate binders, between 14% and 27% of patients discontinued treatment due to adverse reactions, with GI events being the most common reason. Furthermore, serious cases of GI obstruction, some requiring surgery or hospitalization, were identified in postmarketing reports of patients taking lanthanum carbonate. Together, these factors likely contribute to the inability of most dialysis patients to achieve and maintain serum phosphorus concentrations ≤ 5.5 mg/dL, indicating an opportunity for therapeutic innovations, particularly given the association between elevated phosphorus levels and cardiovascular (CV) mortality.

### ASSOCIATION OF PHOSPHATE WITH CV DISEASE IN CKD

Mortality rates in patients receiving dialysis are unacceptably high (~160 deaths/1,000 patient-years) and have not improved in the last 5 years. The 5-year survival probability of patients receiving dialysis (~50%) is lower than those of some cancers (prostate cancer, 83%; colorectal cancer, 56%; and breast cancer, 82%). CV disease (CVD) is the primary cause of death in patients receiving dialysis. In 2017, CVD was the cause of death for ~62% of patients with CKD receiving dialysis, and CV mortality in patients receiving dialysis is approximately 20 times higher than that in a general population. Novel approaches may provide a much-needed avenue to further improve clinical outcomes and quality of life in patients receiving dialysis, especially considering that mortality and hospitalization data have changed very little since 2014.

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growth factor 23 (FGF-23) and parathyroid hormone (PTH) concentrations, which have been associated with direct pathogenic CV effects, increase in response to elevated phosphate or phosphate retention. Increased FGF-23 levels directly target the heart to promote left ventricular hypertrophy, a condition observed in ~70% of patients receiving dialysis, and congestive heart failure. Excess PTH is associated with proinflammatory effects, hyper-tension, impaired myocardial energy production, cardiac fibrosis, left ventricular hypertrophy, and heart failure. Poor phosphate control over a 6-month period was strongly associated with CV mortality but not all-cause mortality, and more normal phosphate levels were correlated with improved survival.

Declining kidney function causes disruptions in mineral homeostasis (eg, calcium and phosphate) in addition to changes in hormone concentrations (eg, PTH and FGF-23). Phosphate retention is an initiating factor and driving force for CKD mineral and bone disorder. CKD mineral and bone disorder is a broad clinical syndrome that describes systemic laboratory abnormalities, bone abnormality, and vascular calcification, which are directly associated with increased risk for CVD, fractures, and mortality. Interactions between increasing phosphate, increasing PTH, and decreasing calcium concentrations drive feedback loops that create a worsening cycle, causing mineral and hormone homeostasis to deteriorate as CKD progresses.
media of the arterial wall leads to increased media thickness and vascular stiffening, and high serum phosphorus concentrations induce calcification of vascular smooth muscle cells. Serum phosphorus concentration increases, even within the normal range, are known to be associated with the risk for death, CV events, and vascular calcification even in individuals without CKD.

**PHOSPHATE ABSORPTION PATHWAYS: A MORE TARGETED THERAPEUTIC APPROACH**

The goal of hyperphosphatemia treatment should be to reduce serum phosphorus concentrations to ≤5.5 mg/dL (or closer to normal levels) and alleviate negative clinical outcomes for patients with CKD, especially CV mortality. To reflect the latest understanding of phosphate absorption, clinicians could consider implementing new hyperphosphatemia treatment paradigms to achieve phosphate goals, incorporating targeted phosphate absorption inhibitors.

Several inhibitors of the sodium-dependent transcellular pathway have been developed (Fig 4). The novel compound EOS789 interacts with sodium-dependent phosphate transporters (NaPi2b, PiT-1, and PiT-2) and effectively reduced serum phosphate, FGF-23, and PTH concentrations in rats with hyperphosphatemia. A phase 1 study of EOS789 in patients receiving intermittent dialysis found no significant difference in serum phosphate concentrations between patients treated with EOS789 and patients who received a placebo. To our knowledge, no phase 2 or 3 trials have been conducted for this therapy. The NaPi2b inhibitor ASP3325 reduced serum phosphate concentrations in an animal model but had no effect in healthy volunteers or patients with end-stage kidney disease. Nicotinamide suppresses sodium-dependent phosphate transporter activity and effectively reduced phosphate concentrations in animal models. In a trial of patients receiving maintenance dialysis, the mean reduction in phosphate concentrations from baseline was smaller in patients treated with nicotinamide sevelamer (0.25 vs 0.40 mmol/L), and noninferiority was not established. Patients’ tolerance of nicotinamide was much lower than that of sevelamer; treatment discontinuation due to adverse events in patients who received nicotinamide was 160% higher than for patients who received sevelamer.

Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that targets the primary paracellular absorption pathway, providing a novel approach to treating hyperphosphatemia (Fig 1). Tenapanor has a unique mechanism of action that blocks paracellular absorption of phosphate in the GI tract by local inhibition of the sodium/hydrogen exchanger isoform 3. Sodium/hydrogen exchanger isoform 3 inhibition has the effect of directly blocking sodium absorption, triggering an intracellular signaling cascade that induces conformational changes in tight junction proteins and directly reducing the permeability of the paracellular pathway specifically to phosphate. By blocking the primary pathway for phosphate absorption, tenapanor acts more directly to reduce serum phosphorus concentrations.

High pill burdens are common in dialysis patients and paracellular phosphate absorption inhibitors may improve
patients’ quality of life by reducing the total number of pills needed each day. Akizawa et al.77 investigated tenapanor’s potential for reducing pill burden in dialysis patients with hyperphosphatemia. Patients who were taking at least 2 phosphate-binder pills 3 times per day received treatment with 30 mg of tenapanor twice daily, and 71.6% of patients achieved a 30% decrease in the total number of phosphate-binder and tenapanor pills \((P < 0.001)\). Of those, 52.2% achieved a 50% decrease in total pill burden and 26.9% no longer required any phosphate binders at week 26.77

Tenapanor effectively reduced phosphate levels in multiple clinical trials with a dosing regimen of 1 pill twice daily and was generally well tolerated. Tenapanor has been evaluated for efficacy as monotherapy (vs placebo) in separate 12- and 52-week trials. At 12 weeks, tenapanor administration lowered serum phosphorus concentrations in patients from baseline of 8.1 to 5.5 mg/dL in the efficacy analysis set.78 In the long-term phase 3 study, at 26 weeks, tenapanor administration lowered serum phosphorus concentrations in patients from baseline concentrations of 7.7 to 5.1 mg/dL in the efficacy analysis set.79 A recent trial that compared the effectiveness of a combination of tenapanor and binder versus placebo and binder showed that tenapanor plus binder resulted in more significant serum phosphate concentration reduction from baseline compared with placebo plus binder (0.84–1.21 vs 0.14–0.21 mg/dL; \(P < 0.001\)).80 Additionally, almost twice as many patients treated with tenapanor and binder achieved phosphate concentrations < 5.5 mg/dL compared with patients treated with placebo and binder (37%–50% vs 18%–24%; \(P < 0.05\)).80

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