Phosphate Control: The Next Frontier in Dialysis Cardiovascular Mortality

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Background: Cardiovascular disease (CVD) is a major cause of death in patients with chronic kidney disease (CKD) on dialysis. Mortality rates are still unacceptably high even though they have fallen in the past 2 decades. Hyperphosphatemia (elevated serum phosphate levels) is seen in almost all patients with advanced CKD and is by far the largest remaining modifiable contributor to CKD mortality. Summary: Phosphate retention drives multiple physiological mechanisms linked to increased risk of CVD. Fibroblast growth factor 23 and parathyroid hormone (PTH) levels, both of which have been suggested to have direct pathogenic CV effects, increase in response to phosphate retention. Phosphate, calcium, and PTH levels are linked in a progressively worsening cycle. Maladaptive upregulation of phosphate absorption is also likely to occur further exacerbating hyperphosphatemia. Even higher phosphate levels within the normal range may be a risk factor for vascular calcification and, thus, CV morbidity and mortality. A greater degree of phosphate control is important to reduce the risk of CV morbidity and mortality. Improved phosphate control and regular monitoring of phosphate levels are guideline-recommended, established clinical practices. There are several challenges with the current phosphate management approaches in patients with CKD on dialysis. Dietary restriction of phosphate and thrice-weekly dialysis alone are insufficient/unreliable to reduce phosphate to <5.5 mg/dL. Even with the addition of phosphate binders, the only pharmacological treatment currently indicated for hyperphosphatemia, the majority of patients are unable to achieve and maintain phosphate levels <5.5 mg/dL (or more normal levels). Phosphate binders do not target the primary pathway of phosphate absorption (paracellular), have limited binding capacity, and bind nonspecifically. The recommended phosphate management strategies for patients on dialysis and CKD patients are listed below:

- Dietary phosphate restriction
- Thrice-weekly dialysis
- Phosphate binders

Keywords
Chronic kidney disease · Cardiovascular vascular mortality · Hyperphosphatemia · Fibroblast growth factor 23 · Parathyroid hormone · Vascular calcification · Congestive heart failure · Left ventricular hypertrophy
er carbonate) (prescribing information) 2020. **Key Messages:** Despite current phosphate management strategies, most patients on dialysis are unable to consistently achieve target phosphate levels, indicating a need for therapeutic innovations [RealWorld dynamix. Dialysis US: Sphera Global Insights, 2019]. Given a growing evidence base that the dominant mechanism of phosphate absorption is the intestinal paracellular pathway, new therapies are investigating ways to reduce phosphate levels by blocking absorption through the paracellular pathway.

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**Introduction**

Cardiovascular disease (CVD) is a major cause of death in patients with CKD on dialysis. Mortality rates in patients on dialysis have fallen in the past 2 decades [1]. Changes that may have contributed to this include a decrease in catheter placements and a concurrent rise in fistula placements, an emphasis on lower target hemoglobin levels, and more intensive nutritional support for patients [1–3]. However, mortality and hospitalization data showed little change after 2014, and current rates are still unacceptably high [4, 5]. In the USA, the all-cause-adjusted mortality rate in patients with end-stage renal disease (ESRD) was ∼140 deaths per 1,000 patients-years in 2016 [5]. Patients with ESRD on dialysis have an even higher mortality rate (∼160 deaths per 1,000 patient-years) [4]. These rates are higher than those of some cancers; the unadjusted probability of 5-year survival is ∼50% in patients with dialysis compared to 83% for prostate cancer, 56% for colorectal cancer, and 82% for breast cancer [6]. Novel approaches may be necessary to further improve clinical outcomes and quality of life in patients on dialysis [7].

CVD accounted for ∼62% of deaths among patients with chronic kidney disease (CKD) on dialysis in 2017 [4]. The majority of patients with CKD die from CVD, not kidney dysfunction, and mortality due to CVD in patients on dialysis is approximately 20 times higher than in a general population [8]. Traditional risk factors for CVD (e.g., hypertension, diabetes, diet, and lifestyle) alone do not explain the high CV morbidity and mortality in patients with CKD [9], and the established treatment strategies for these risk factors have not seen significant recent advancements. CKD-mineral bone disorder (CKD-MBD) is a common complication in patients with CKD known to be associated with CV morbidity and mortality [10]. CKD-MBD is characterized by laboratory abnormalities, bone abnormalities, and vascular calcification, which directly lead to CVD, fractures, and mortality [10]. The initiating and driving force of the mineral and endocrine disruptions that comprise CKD-MBD is phosphate retention [10]. Because CKD-MBD is pathobiologically related to myocardial disease, atherosclerosis, and vascular stiffness, it could be viewed as a treatment target since these mechanisms collectively play a potentially large role in CV outcomes in ESRD. Potential CKD-related therapeutic approaches that may reduce CV mortality include improved dialysis modalities, management of kidney disease-MBD, serum phosphate levels, and inflammation [11–14].

**Phosphate Retention Is a Significant Contributor to CVD**

As CKD progresses, renal function declines and patients experience phosphate retention [15–22]. Although compensatory increases in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) are initially sufficient to offset phosphate retention; these mechanisms are eventually overwhelmed [15–22]. Uncontrolled phosphate retention leads to elevated serum phosphate levels, or hyperphosphatemia, when the glomerular filtration rate falls to <30 mL/min/1.73 m² [23, 24]. This rate corresponds to CKD stages 4 and 5 [25].

Lack of phosphate control is a potential major modifiable risk factor for CV mortality in patients with CKD (Fig. 1) [26, 27]. Elevated phosphate levels are by far the largest remaining modifiable contributor to CKD mortality on a population attributable risk basis, 2–6 fold higher than other top risk factors such as hypercalcemia, hyperparathyroidism, low urea reduction ratio, and anemia (12% vs. 4, 2, 5, and 6%, respectively) [28]. Additionally, ∼70% of patients on dialysis have left ventricular hypertrophy, a known risk factor for CVD and mortality strongly associated with higher phosphate levels [8]. Elevated phosphate is also directly linked to hypertension, a major CVD risk factor that is seen in up to 90% of patients with CKD [8].

Phosphate retention drives multiple physiological mechanisms linked to an increased risk of CVD [29, 30]. Hyperphosphatemia may directly affect vascular health by increasing reactive oxygen species, causing oxidative damage and endothelial dysfunction [29]. Both phosphate and calcium contribute to the development of vascular calcification, but phosphate is the initiating factor [31]. High phosphate conditions also increase vascular...
Fig. 1. Hazard ratio (95% confidence interval) of CV events by CV risk factors. CV, cardiovascular; PTH, parathyroid hormone.

Fig. 2. Mechanism of elevated phosphate concentration causing CV risk. CV, cardiovascular.
calcification by inducing changes in vascular smooth muscle cells [32]. Phosphate directly targets the PiT1 receptor on vascular smooth muscle cells, causing them to transform into osteoblast-like cells permanently [33, 34]. Once this transformation occurs, these osteoblast-like cells begin to produce hydroxyapatite deposits normally found in the bone [35, 36]. Increased calcium-phosphate product may accelerate this mineralization process after initiation [31]. This phosphate-induced calcification of vascular smooth muscle cells increases the risk of coronary artery events, procedural complications, and CV morbidity and mortality, as well as hypertension [37].

Phosphate retention triggers increases in fibroblast growth factor 23 and PTH levels, both of which have been suggested to have direct pathogenic CV effects [38–40]. Increased FGF23 levels directly promote left ventricular hypertrophy and congestive heart failure [38, 39]. Patients with CKD are likely to have experienced long periods of high FGF23 levels by the time they start dialysis; 36% of patients with CKD beginning dialysis already have heart failure [41]. The deleterious CV effects of elevated FGF23 may be exacerbated by common CKD comorbidities such as hypertension and diabetes [38, 42–44]. Increased PTH levels are associated with a pro-inflammatory effect, increased interleukin 6, impaired myocardial energy production, and cardiac fibrosis [45, 46]. Increased serum phosphate levels have also been associated with the inhibition of 1,25-dihydroxy vitamin D synthesis, which is associated with decreased cardiac contractility, coronary artery calcification, myocardial fibrosis, and pro-inflammatory effect [47–51].

Phosphate, PTH, and calcium levels are linked in a regulatory cycle in which phosphate is the initiating and driving factor. Increasing phosphate levels trigger not only an increase in PTH but also a decrease in serum calcium [52]. When hypocalcemia develops, PTH levels increase to drive calcium and phosphate to travel out of bone reservoirs [10, 11]. The subsequent increase in phosphate levels starts the cycle again [10, 11]. Without effective phosphate control, this cycle will continue and progressively worsen [10] (Fig. 2).

Absorption of dietary phosphate via the dominant passive paracellular pathway and the active transcellular pathway is not downregulated in patients with CKD [53] (Fig. 3). In fact, a maladaptive upregulation of intestinal phosphate absorption in response to reduced phosphate in the gut due to dietary phosphate restriction and phosphate binding may also occur, further exacerbating phosphate retention [54]. This response may contribute to an explanation for the limited efficacy of dietary restriction and phosphate binders; neither of these phosphate management strategies targets phosphate absorption pathways and are therefore inherently limited [55–59].
The association between increased phosphate levels and CV morbidity/mortality is not limited to hyperphosphatemia or patients with CKD. Phosphate retention, even when phosphate levels are within the normal range, is known to increase the risk of death, CV events, and vascular calcification in both healthy adults and patients with CKD [30]. Phosphate levels of 3.9–4.7 mg/dL were associated with increased CV events in people with normal renal function and CKD stage 1 and 2 patients [60]. In people with normal renal function, the association between phosphate levels and CV risk is linear [60].

Although evidence on the association between phosphate and CV risk is observational, the volume of data that links elevated phosphate levels and increased CV morbidity and mortality in individuals with and without CKD is significant. This connection has been accepted by clinicians and researchers for decades [7, 8, 11, 26, 60–64] (Table 1).

### Phosphate Control Is Associated with a Reduced Risk of CV Morbidity and Mortality

Phosphate levels are an impactful modifiable risk factor for theoretically lowering CV morbidity and mortality in patients with CKD [27, 91]. Abnormal phosphate levels have been shown to be an independent risk factor for CV morbidity and mortality in patients with CKD [60, 92–94], and there is a linear relationship between risk of CVD hospitalizations and mortality and increasing serum phosphate concentrations [65]. Patients with the worst phosphate control (>7.5 mg/dL) had a 25% greater risk of CV events than those with phosphate <4.5 mg/dL [66]. Patients on dialysis with serum phosphate levels >6.5 mg/dL were found to have ~27% greater risk of mortality than those with levels between 2.4 and 6.5 mg/dL [65, 93]. Serum phosphate levels over the reference range of 4.0–5.0 mg/dL resulted in up to 102% increased relative

### Table 1. Multiple observational studies show an association between elevated serum phosphate and mortality in patients with CKD on dialysis [65–90]

| Study               | Year | Study design      | Sample   | Geography       |
|---------------------|------|-------------------|----------|-----------------|
| Block et al. [68]   | 1998 | Retrospective cohort* | 6,407    | USA             |
| Coco et al. [69]    | 2000 | Retrospective cohort* | 1,272    | USA             |
| Ganesh et al. [70]  | 2001 | Retrospective cohort* , § | 12,833   | USA             |
| Saran et al. [71]   | 2003 | Retrospective cohort* | 14,930   | USA and Europe and Japan |
| Rubel et al. [72]   | 2003 | Retrospective cohort* | 12,509   | USA             |
| Port et al. [73]    | 2004 | Retrospective cohort* | 17,245   | USA             |
| Block et al. [65]   | 2004 | Prospective cohort* | 40,538   | USA             |
| Slinin et al. [66]  | 2005 | Retrospective cohort* , § | 14,829   | USA             |
| Young et al. [74]   | 2005 | Prospective cohort* | 17,326   | US and Europe and Japan |
| Menon et al. [75]   | 2005 | Prospective cohort* | 840      | USA             |
| Rodriguez-Benot et al. [76] | 2005 | Prospective cohort* | 385      | Europe          |
| Kestenbaum et al. [67] | 2005 | Prospective cohort* | 3,490    | USA             |
| Kalantar-Zadeh et al. [77] | 2006 | Prospective cohort* | 58,058   | USA             |
| Melamed et al. [78] | 2006 | Prospective cohort* | 1,007    | USA             |
| Kimata et al. [79]  | 2007 | Prospective observational* , § | 5,041    | Japan           |
| Kovesdy et al. [80] | 2008 | Retrospective cohort* | 515      | USA             |
| Wald et al. [81]    | 2008 | Retrospective cohort* | 1,846    | USA             |
| Tentori et al. [82] | 2008 | Prospective cohort* | 25,588   | US and Europe and Japan |
| Lacson et al. [83]  | 2009 | Retrospective cohort* | 78,420   | USA             |
| Smith et al. [84]   | 2010 | Retrospective cohort* , § | 930      | USA             |
| Kovesdy et al. [85] | 2010 | Retrospective cohort* | 714      | USA             |
| Tangri et al. [86]  | 2011 | Retrospective cohort* | 7,076    | Europe          |
| Floge et al. [87]   | 2011 | Retrospective cohort* | 7,970    | Europe          |
| Sakaguchi et al. [88] | 2014 | Retrospective cohort* | 142,069  | Japan           |
| Fernandez-Martin et al. [89] | 2015 | Prospective cohort* | 6,307    | Europe          |
| Garagarza et al. [90] | 2017 | Prospective cohort* | 3,552    | Europe          |

CKD, chronic kidney disease; CV, cardiovascular. * All-cause mortality. † CV mortality. ‡ Nonfatal CV event. ‣ Nondialysis-dependent moderate-severe CKD. † Nondialysis-dependent CKD.

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risk of death (relative risk of 1.07, 1.25, 1.43, 1.67, and 2.02 for serum phosphorus 5.0–6.0, 6.0–7.0, 7.0–8.0, 8.0–9.0, and ≥9.0 mg/dL, respectively) [65].

In addition to the degree of phosphate increase, time spent with elevated phosphate levels also increases CV mortality risk. A large multinational study of patients on dialysis found that the more time patients spent with phosphate >4.5 mg/dL over a 6-month period, the greater their risk of CV mortality [26].

Even in patients with CKD in early, pre-dialysis stage, an increase in phosphate within the normal range was predictive of CV morbidity and mortality. So, improved phosphate control and regular monitoring of phosphate levels are beneficial for all patients with CKD (Fig. 4) [67, 95]. Thus, reduction of phosphate to more normal levels is a guideline-recommended, established clinical practice [10, 96].

**Challenges of Current Phosphate Management in Patients with CKD**

Current phosphate management strategies are composed of dietary phosphate restriction, dialysis, and phosphate binders [97]. Dietary restriction of phosphate and dialysis are insufficient/unreliable alone to reduce phosphate to <5.5 mg/dL [98]. Phosphate binders, which work by binding to dietary phosphate to create insoluble complexes that are then excreted, are the only pharmacological treatment currently indicated for hyperphosphatemia [10, 55–59]. As a class, binders are insufficient to achieve and maintain phosphate levels <5.5 mg/dL (or more normal levels) for the majority of patients on dialysis [99]. Binders do not target any phosphate absorption pathway, let alone the primary paracellular pathway, severely limiting their ability to impact absorption [55–59]. Nonspecific binding contributes to suboptimal efficacy and drug-drug interactions. A short duration of actions requires that binders be taken with each meal or snack. And a limited binding capacity per pill requires many large pills (pill requirements increase as phosphate intake increases) [100].

The insufficiency of current phosphate management strategies to consistently achieve and maintain target phosphate levels is well documented [99]. In the USA, an average of 40% of patients on dialysis had serum phosphate levels >5.5 mg/dL in the most recent months [101]. Based on a chart audit, 42% of patients on dialysis treated with phosphate binders continue to have phosphate >5.5 mg/dL in any given month and 77% are unable to consistently maintain phosphate levels ≤5.5 mg/dL over a 6-month period [99]. Therapeutic innovations to reduce the negative clinical outcomes of poorly controlled phosphate levels are needed.

![Fig. 4. Hazard ratio (95% confidence interval) for mortality by serum phosphate levels in patients with CKD.](image-url)
Phosphate Control Therapies Are Needed to Reduce the Risk of CV Morbidity and Mortality

Phosphate binders act by “scavenging” dietary phosphate to prevent intestinal absorption and do not target or interact with phosphate absorption pathways [55–59]. Given the insufficiency of current phosphate management strategies to achieve and maintain phosphate concentrations <5.5 mg/dL and the understanding that maladaptive hyperabsorption of phosphate limits the efficacy of low-phosphate diets and phosphate binders, there is a need for novel hyperphosphatemia therapies [54, 99]. Several novel therapies that target the active transcellular phosphate pathway have been developed. The sodium-dependent phosphate co-transporter type 2b (NaPi-2b) inhibitor ASP3325 did not reduce serum phosphorus concentrations in patients with ESRD [102]. The novel inhibitor EOS789, which interacts with several sodium-dependent phosphate transporters, decreased serum phosphorus concentrations in animal models [103] but results of a phase 1 clinical study of EOS789 in patients with CKD and hyperphosphatemia have not yet been published. Nicotinamide reduced phosphate concentrations in patients undergoing dialysis [104, 105], but a large proportion of study participants discontinued treatment due to adverse events [104]. Novel therapies targeting the paracellular pathway are logical, given a growing evidence base that the dominant mechanism of intestinal phosphate absorption is the paracellular pathway [23, 53, 106]. One such therapy is tenapanor, an investigational first-in-class nonbinder phosphate absorption inhibitor that targets the primary absorption pathway and provides a novel approach to treating hyperphosphatemia [106]. 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 (NHE3) [106]. NHE3 inhibition directly reduces sodium absorption, leading to modest intracellular proton retention [106, 107]. This induces a conformational change in tight junction proteins, directly reducing permeability specific to phosphate through the paracellular pathway [106]. By blocking the primary pathway for phosphate absorption, tenapanor acts directly, efficiently, and comprehensively to reduce serum phosphate concentrations. Tenapanor effectively reduced phosphate levels in multiple clinical trials and is under FDA review as a hyperphosphatemia therapy [108–110].

To reflect the latest understandings of phosphate absorption, clinicians should consider implementing new hyperphosphatemia treatment paradigms to better achieve phosphate levels <5.5 mg/dL (or closer to normal levels). One option could be to use targeted paracellular phosphate absorption blockers as an initial, foundational treatment. If needed, adjunctive binders could be added as part of a dual mechanism approach for patients with difficulty to control phosphate. In CKD, maladaptive phosphate retention is associated with and predictive of negative clinical consequences, even before a patient develops hyperphosphatemia [54, 111]. Novel therapies may enhance phosphate elimination and improve patient outcomes [112–116].

Conclusion

Clinical guidelines recommend regular monitoring of phosphate levels to reduce the risk of CV morbidity and mortality [10, 96]. Despite dietary phosphate restrictions, thrice-weekly dialysis, and phosphate binders use, management of hyperphosphatemia in patients with CKD on dialysis remain a clinical challenge as these approaches do not help achieve and maintain phosphate levels <5.5 mg/dL (or more normal levels) [10, 55–59, 98, 101]. Phosphate binders do not target the dominant paracellular pathway of phosphate absorption, have limited binding capacity, and bind nonspecifically [55–59]. Considering high mortality rates in patients with CKD, particularly from CV causes, novel therapeutic innovations are necessary [4]. Given a growing evidence base that the dominant mechanism of phosphate absorption is the intestinal paracellular pathway [23, 53, 106], new therapies are investigating ways to reduce phosphate levels by blocking absorption through the paracellular pathway.

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

Dr. McCullough is a paid consultant for Ardelyx, Inc. Writing support provided by Xelay Acumen Group and funded by Ardelyx, Inc. Dr. McCullough has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
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