

However, this hormonal adaptation may be harmful, due to adverse effects of FGF-23 and PTH on the cardiovascular system, increased renal workload from enhanced phosphate excretion or both [1]. Bellasi clearly distinguishes phosphate balance from circulating phosphate concentrations, which represent a minute fraction of total body phosphate and are subject to circadian fluctuation, and he notes inconsistent associations of serum phosphate concentrations with outcomes in observational studies of pre-dialysis populations. For these and other reasons, Bellasi correctly concludes that serum phosphate is an inaccurate marker of phosphate balance and likely useless as a risk stratification tool in patients with normophosphataemia.

Bellasi's assertion that recent clinical trials focused only on unreliable markers of phosphate balance is not completely accurate. For example, the recent Phosphate Normalization Trial demonstrated that 9 months of phosphate binder therapy lowered 24-h urinary phosphate excretion by an average of 22% [2]. These findings suggest that phosphate binders have moderate beneficial effects on phosphate balance in CKD patients; however, the clinical significance of these actions remains unknown.

Current understanding of phosphate balance in CKD remains tangential to the question of whether to prescribe

phosphate binders to CKD patients. Clinical trials are necessary to determine whether these medications provide any clinically relevant benefits and are reasonably well tolerated over long-term use. Such trials may employ simple or pragmatic designs that omit mechanistic questions that have already been answered by existing studies. Positive results from such trials could reduce the burden of disease among CKD patients whereas negative results would be helpful to re-focus efforts elsewhere. The nephrology community must coalesce to demand the specific evidence needed to answer pressing clinical questions, which include understanding clinically important risks and benefits of commonly prescribed drugs.

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Con: Phosphate binders in chronic kidney disease

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ABSTRACT

Phosphate binders are prescribed to chronic kidney disease (CKD) patients based on associations of serum phosphate concentrations with mortality and calcification, experimental evidence for direct calcifying effects of phosphate on vascular smooth muscle tissue and the central importance of phosphate retention in CKD-mineral and bone disorder (CKD-MBD). Current knowledge regarding phosphate metabolism in CKD provides important insight into disease mechanisms and supports future clinical trials of phosphate binders in CKD patients to determine the impact of these medications on clinically relevant outcomes.

The risks and benefits of phosphate binders cannot be inferred from association studies of serum phosphate

concentrations, which are inconsistent and subject to confounding, animal-experimental data, which are based on conditions that differ from human disease, or physiological arguments, which are limited to known regulatory factors. Many interventions that targeted biochemical pathways suggested by association studies and suspected biological importance have yielded null or harmful results. Clinical trials of phosphate binders are of high clinical and scientific importance to nephrology. Demonstration of reduced rates of clinical disease in such trials could lead to important health benefits for CKD patients, whereas negative results would refocus efforts to understand and treat CKD-MBD. Clinical trials that employ highly practical or 'pragmatic' designs represent an optimal approach for determining the safety and effectiveness of phosphate binders in real-world settings. Absent clinical trial data, observational studies of phosphate binders in large CKD

populations could provide important information regarding the benefits, risks and/or unintended side effects of these medications.

Keywords: binder, chronic kidney disease, dialysis, hyperphosphatemia, mineral and bone disorder, phosphate

INTRODUCTION

Phosphate binders are ubiquitously prescribed to chronic dialysis patients and sporadically prescribed to patients who have chronic kidney disease (CKD). The prescription of phosphate binders is motivated by evidence suggesting potential toxicity of higher serum phosphate concentrations, and by the assumption that phosphate binders can meaningfully reduce serum phosphate levels in CKD. Some, but not all, studies have demonstrated associations of higher circulating phosphate concentrations with mortality and cardiovascular events. Animal models and cell culture data suggest direct calcifying effects of phosphate on vascular smooth muscle tissue. The sum of current evidence suggests an important role for phosphate retention in the pathogenesis and clinical consequences of CKD-mineral and bone disorder (CKD-MBD), a common metabolic complication of kidney disease that affects nearly all patients by the time they reach end-stage renal disease (ESRD). However, knowledge pertaining to serum phosphate concentrations and phosphate metabolism cannot substitute for information regarding the clinical risks and benefits of interventions that are used to reduce phosphate. Many clinical trials in medicine, including nephrology, have found no benefit, or even harm, from treatments that target a single metabolite or metabolic pathway based on biomarker association studies and suspected biological significance to a disease process. Current evidence supports clinical trials of phosphate binders on clinically relevant endpoints as the next appropriate scientific step.

ASSOCIATIONS OF SERUM PHOSPHATE WITH DISEASE IN DIALYSIS POPULATIONS

Block *et al.* first demonstrated greater risks of mortality among chronic dialysis patients who had serum phosphate concentrations >6.5 compared with <6.5 mg/dL [1]. Subsequently, observational cohort studies of hemodialysis and peritoneal patients consistently observed associations of higher serum phosphate concentrations with all-cause and cardiovascular mortality [2–7]. In general, these studies demonstrated progressively greater risks associated with sequentially higher serum phosphate concentrations; however, heterogeneity in analytic approaches across studies precludes definitive knowledge of the functional pattern of this relationship. Complementary studies of chronic dialysis patients observed associations of higher serum phosphate concentrations with coronary artery calcification [8–10], suggesting a potential mechanism for associations with clinical outcomes.

ASSOCIATIONS OF SERUM PHOSPHATE WITH DISEASE IN CKD AND GENERAL POPULATIONS

Studies of serum phosphate concentrations with disease in non-dialysis-requiring CKD populations have yielded mixed results [11–16]. For example, we demonstrated a graded association of higher serum phosphate concentrations with mortality and incident myocardial infarction among 3490 male US veterans with stage III–IV CKD [11]. On the other hand, Mehrotra *et al.* [16] found no adjusted association of serum phosphate concentrations with all-cause mortality or ESRD among 10 672 individuals who had CKD in the community-based Kidney Early Evaluation Program (KEEP) [16]. Several studies have also demonstrated associations of higher serum phosphate concentrations and with coronary artery calcification, cardiac valve calcification and rapid progression to dialysis in CKD populations [17, 18]. Differences in demographics, CKD etiologies, comorbidity assessment and the timing of serum phosphate measurements, which may vary by as much as 1.0 mg/dL throughout the day [19], may have contributed to heterogeneous associations. Intriguingly, a number of studies have observed associations of serum phosphate with cardiovascular events, vascular calcification and cardiac valve calcification in the general population [20–24]. For example, Foley *et al.* [23] found that relatively high serum phosphate concentrations (>3.9 mg/dL) among young men and women (mean age 25 years) were associated with a greater prevalence of coronary artery calcification 15 years later [23].

Several caveats apply to studies of serum phosphate concentrations in CKD and normal populations. First, steady-state serum phosphate levels reflect the complex interplay of regulatory hormones, cellular receptors and bone metabolic factors that serve to maintain phosphate homeostasis [25–27]. We identified common genetic variants located within or near multiple mineral metabolism genes that associated with serum phosphate concentrations among 16 264 individuals without apparent kidney disease [28]. It is possible that one or more phosphate regulatory factors, and not phosphate directly, is responsible for observed associations with calcification and cardiovascular events in non-dialysis populations. Second, the distribution of serum phosphate concentrations in CKD and general populations is typically within or just above the normal laboratory range. Such concentrations are far lower than those used to induce calcification in experimental models, precluding a plausible mechanism for observed associations. Third, coronary artery calcium detected by computed tomography is far more likely to represent calcified atherosclerosis than medial arterial calcification in non-dialysis populations [29].

EXPERIMENTAL MODELS OF VASCULAR CALCIFICATION

The addition of exogenous phosphate to cultured vascular smooth muscle cells and isolated aortic rings causes loss of the smooth muscle phenotype, expression of bone-specific

markers and mineralization of the extracellular matrix [30–32]. These processes collectively result in calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis) with resultant loss of normal vessel compliance. Moe *et al.* [33] directly demonstrated a 44% prevalence of medial arterial calcification, an otherwise rare finding, in inferior epigastric arteries removed from ESRD patients undergoing renal transplantation. Animal models provide further evidence linking phosphate overload with medial arterial calcification in kidney failure. Dietary phosphate loading in mouse and rat models of kidney disease leads to medial arterial calcification across multiple vascular beds [34, 35]. However, certain aspects of experimental models temper direct application to human calcification. First, the initiation of calcification in cell culture models typically requires substantially high concentrations of phosphate (3.0 mmol = 9.3 mg/dL) under stringent conditions. Second, animal models of phosphate loading utilize diets that contain far greater relative amounts of phosphate than a typical Western diet.

ROLE OF PHOSPHATE RETENTION IN THE PATHOGENESIS OF CKD-MBD

CKD-MBD, defined by disturbances in mineral metabolism hormones and associated bone disease, is one of the most common recognized metabolic complications of CKD [36]. An intriguing and potentially unifying hypothesis suggests that phosphate retention plays a central role in the development of CKD-MBD. Specifically, this theory posits that the loss of filtering nephrons leads to subtle phosphate retention, which subsequently signals the phosphaturic hormones parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) to increase proportionate phosphate excretion through the kidneys [27, 37]. In parallel, phosphate retention directly and indirectly inhibits the synthesis of 1,25-dihydroxyvitamin D (1,25(OH)₂D), the biologically important form of vitamin D, and klotho, a co-factor for FGF-23 with important implications for aging and disease [26, 38]. The result is maintenance of serum phosphate concentrations within the normal laboratory range throughout most of the course of CKD at the expense of chronic disturbances in mineral metabolism hormones.

Several findings suggest that the phosphocentric hypothesis for CKD-MBD is incomplete. First, reduction of gastrointestinal phosphate absorption using phosphate binders failed to meaningfully change PTH, FGF-23 or 1,25(OH)₂D among stage III–IV CKD patients [39, 40]. Null effects of phosphate binders on these hormones may reflect insufficient blockade of gastrointestinal phosphate absorption, in part due to compensatory up-regulation of sodium–phosphate channels in the gut [41]. This possibility will be addressed by the COMBINE study, which will incorporate phosphate binders plus nicotinamide in an attempt to achieve more potent reduction in phosphate absorption. Second, disturbances in FGF-23, PTH, 1,25(OH)₂D and klotho are detectable at the earliest stages of CKD, when filtration is theoretically sufficient to excrete the daily phosphate load without compensation [42, 43]. Third, direct mechanisms by which phosphate excess stimulates the FGF-23–klotho axis remain incompletely understood. Finally, from a clinical perspective, extreme

dietary protein restriction, and by extension phosphate restriction, failed to impact clinical outcomes in the Modification of Diet in Renal Disease study [44].

STUDIES OF PHOSPHATE BINDERS

Reliable data regarding the risks and benefits of phosphate binders must derive from studies that specifically focus on these medications, not serum phosphate concentrations or phosphate metabolism. There are no definitive clinical trials that compare phosphate binders versus no treatment on clinically relevant outcomes. Current evidence is limited to short-term clinical trials using biochemical and subclinical endpoints, pharmacoepidemiologic studies and head-to-head studies that compare different classes of phosphate binders.

SHORT-TERM CLINICAL TRIALS USING BIOCHEMICAL AND SUBCLINICAL ENDPOINTS

Three recent studies compared the impact of phosphate binders versus placebo on serum phosphate concentrations, mineral metabolism hormones and subclinical cardiovascular disease measurements. The Phosphate Normalization Trial randomized 148 CKD patients (estimated GFR 20–45 mL/min/1.73 m²) to one of three phosphate binders (calcium acetate, sevelamer or lanthanum) versus matching placebos [39]. Over 9 months of follow-up, phosphate binder treatment reduced 24-h urinary phosphate excretion by a mean of 22%, demonstrating reasonable compliance and expected efficacy. However, phosphate binders only minimally impacted the serum phosphate concentration (0.3 mg/dL reduction versus no change in placebo group) or serum concentrations of PTH, FGF-23 or 1,25(OH)₂D. Surprisingly, active therapy with phosphate binders modestly increased coronary artery and aortic calcification scores compared with placebo, with the largest increases observed in the calcium acetate group.

The Chronic Renal Impairment in Birmingham Phosphate study randomized 109 stage III CKD patients to sevelamer 1600 mg three times per day versus placebo [40]. After 40 weeks of follow-up, there were no differences between the treatment and placebo groups with respect to serum phosphate concentrations or phosphate regulatory hormones. Moreover, there were also no differences with respect to change in left ventricular mass, diastolic function, carotid-femoral pulse wave velocity or lumbar spine bone mineral density. Finally, Seifert *et al.* randomized 38 stage III CKD patients to lanthanum carbonate versus placebo for 12 months [45]. No significant between-group differences were observed with respect to changes in serum phosphate, PTH or FGF-23 concentrations, and no differences were observed with respect to changes in carotid artery, coronary artery or aortic calcification.

In summary, existing placebo-controlled trials of phosphate binders in CKD patients, albeit small, demonstrate null effects on serum phosphate concentrations, mineral metabolism hormones and subclinical cardiovascular disease measurements over relatively short-term follow-up. However, selected cardiovascular imaging

modalities in these studies are subject to measurement error, require longer time periods to capture meaningful biological changes and have uncertain relationships with clinical disease in CKD populations. Null findings from these studies should not discourage subsequent trials using clinical endpoints.

PHARMACOEPIDEMOLOGICAL STUDIES

Several studies have found relatively lower risks of mortality comparing chronic dialysis patients treated with phosphate binders to similar untreated patients [46–49]. For example, Isakova *et al.* observed an estimated 22% lower risk of death over 1 year of follow-up among 3186 new phosphate binder users compared with a matched group of non-users [46]. Few observational studies of phosphate binders have been conducted in non-dialysis CKD populations [50, 51]. These studies utilized non-standard methodologies, obscuring the interpretation of results.

A central goal of pharmacoepidemiologic studies is to estimate results that would be found in randomized clinical trials of similar individuals [52]. To achieve this objective, such studies must first account for potential differences in characteristics between treated and untreated individuals. There is a misconception that complex methodologies (propensity scores, inverse probability weighting and instrumental variables) are mandatory for this purpose; however, standard adjustment methods yield similar validity in most situations and produce results that are easier to interpret and have greater generalizability [53, 54]. Observational studies of medication use should further utilize complementary methods to those employed in clinical trials, specifically, commencing follow-up when patients first initiate therapy (incident users) and performing primary analyses according to initial treatment assignment (intention-to-treat). Well-conducted observational studies of phosphate binder use in large CKD populations could provide welcome new knowledge regarding the real-world safety and effectiveness of these medications.

HEAD-TO-HEAD STUDIES OF DIFFERENT PHOSPHATE BINDER CLASSES

Several studies have compared calcium versus non-calcium-based phosphate binders using a variety of endpoints [55–58]. Unfortunately, head-to-head studies that compare different medications within the same class provide no meaningful information regarding the safety or efficacy of the drug class. An untreated or placebo group is mandatory for determining the risks and benefits of phosphate binders and is ethical in CKD patients given the true uncertainty as to the clinical effects of treatment. Some, but not all, head-to-head comparison studies have suggested greater calcification potential for calcium-based phosphate binders [55, 56]. This topic is beyond the scope this review.

PRAGMATIC CLINICAL TRIALS

Pragmatic clinical trials are designed to directly inform clinical decision-making by evaluating the effectiveness and safety of

treatments in real-world clinical settings [59, 60]. Key characteristics of pragmatic trial designs include the selection of broadly inclusive study populations with minimal exclusion criteria, a focus on clinically relevant outcomes and avoidance of frequent, intense laboratory monitoring and subclinical disease measurements that may discourage retention. Such trials typically avoid hypervigilant procedures for ensuring compliance with treatment, which are clinically unrealistic, may utilize a no-treatment group in place of a formal placebo and can be completed at relatively lower costs. Pragmatic clinical trials of phosphate binders are conspicuously lacking from the current pool of evidence and represent an optimal approach for evaluating the clinical risks and benefits of these medications in CKD populations.

PILL BURDEN

Adherence to phosphate binders requires the consumption of multiple pills per day timed with meals and often snacks. Such a regimen is disruptive to the already reduced quality of life of CKD patients. In a cross-sectional study of 233 prevalent US dialysis patients, the average daily pill burden was 11, of which 49% were phosphate binders [61]. Greater total pill burden in this study was associated with lower physical component scores on the Kidney Disease Quality of Life (KDQOL) instrument. Adherence to phosphate binders is variable across patients and decreases in association with a greater number of prescribed pills [62].

CONCLUSION

The rationales for prescribing phosphate binders to CKD patients derive from studies of serum phosphate concentrations and phosphate metabolism, not phosphate binders. Associations of serum phosphate concentrations with disease, experimental evidence for the calcifying effects of phosphate and the hypothesized central role of phosphate retention in the development of CKD-MBD collectively motivate clinical trials of phosphate binders using clinically relevant outcomes. Complementary laboratory work is vital for disentangling the complex pathophysiology of CKD-MBD and for suggesting new treatments for this disorder. Current evidence does not support the general prescription of phosphate binders to CKD patients. Moreover, current knowledge is insufficient to support guidelines regarding ‘optimal’ serum phosphate concentrations in CKD. Such recommendations necessarily imply some intervention (phosphate binders, dietary modification) for patients whose serum phosphate concentrations fall outside the recommended range, yet clinical evidence for such interventions is absent. Moreover, guidelines for ‘recommended’ values are a recognized strategy of the pharmaceutical industry used to promote more frequent laboratory testing, thereby increasing the number of ‘abnormal’ values to be considered for treatment.

CKD alters the serum concentration of thousands of metabolites, many of which are plausibly related to disease outcomes. Interventions that correct these metabolic disturbances are typically more complex than initially understood. Interventions to correct dyslipidemia, anemia and homocysteine

elevation in kidney disease populations have resulted in either no benefit or unintended harm [63–65]. No intervention to lower serum phosphate concentrations in CKD should be approved without evidence that the intervention provides at least some clinical benefit, is generally acceptable to patients and is relatively safe over long-term use.

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CONFLICT OF INTEREST STATEMENT

B.K. has received honoraria from Keryx Biopharmaceuticals over the past 12 months.

(See related article by Bellasi. Pro: Should phosphate binders be used in chronic kidney disease stage 3–4? *Nephrol Dial Transplant* 2016; 31: 184–188; See related article by Zoccali and Mallamaci. Moderator's view: Phosphate binders in chronic kidney disease patients: a clear 'No' at the moment, but stay tuned. *Nephrol Dial Transplant* 2016; 31: 196–199.)

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Opponent's comments

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Dr Kestenbaum's conclusions are reasonable and in line with a very conservative evidence-based (EBM) approach. However, a

few points raised by his nicely written article deserve further elaboration.