Intestinal phosphate binders to reduce cardiovascular risk in patients with CKD?

Presenter: Nigel Toussaint, Melbourne, Australia
Chairs: Juan Jesus Carrero, Amaryllis van Craenenbroeck
Written by: Jasna Trbojevic-Stankovic

Hyperphosphatemia commonly accompanies end-stage renal disease (ESRD) in the absence of dietary phosphate restriction or the use of phosphate binders. It may lead to the development and progression of secondary hyperparathyroidism and metastatic calcification, contributing to increased morbidity and mortality.

Phosphate and cardiovascular risk

The positive association between elevated serum phosphate levels and risk of death in ESRD patients has been well documented nearly two decades ago in several large studies. This was also observed in chronic kidney disease (CKD) and non-renal patients in whom cardiovascular and all-cause mortality risks increase linearly with serum phosphate rise. Higher serum phosphate is associated with an increased risk of new heart failure, myocardial infarction, and the composite of coronary death or nonfatal myocardial infarction, even when it remains within the normal range. Additionally, a recent study using Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry described an association between high and low serum phosphate and all-cause and cardiovascular mortality in incident hemodialysis and peritoneal dialysis patients.
Several mechanisms have been suggested to elucidate the connection between phosphate levels and cardiovascular disease. Excess phosphate may contribute to cardiovascular calcification, endothelial dysfunction, and hyperparathyroidism, subsequently leading to cardiovascular morbidity and mortality. Furthermore, there is epidemiological evidence and biological plausibility that phosphate has a direct cardiotoxic effect and adds to a higher CKD progression rate.

Phosphate management – a few caveats

The impact of phosphate management on attenuating cardiovascular risk and reducing cardiovascular mortality in CKD patients has been a matter of debate. Meta-analysis suggested a morbidity and mortality benefit associated with lowering serum phosphate levels. Nevertheless, these findings are based on observational studies, and there is still no conclusive evidence from randomized controlled studies to substantiate them. Therefore, continued widespread treatment to lower phosphate and the choice of the optimal therapeutic approach is still controversial. Nevertheless, hyperphosphatemia does pose a risk and should therefore be intensely managed.

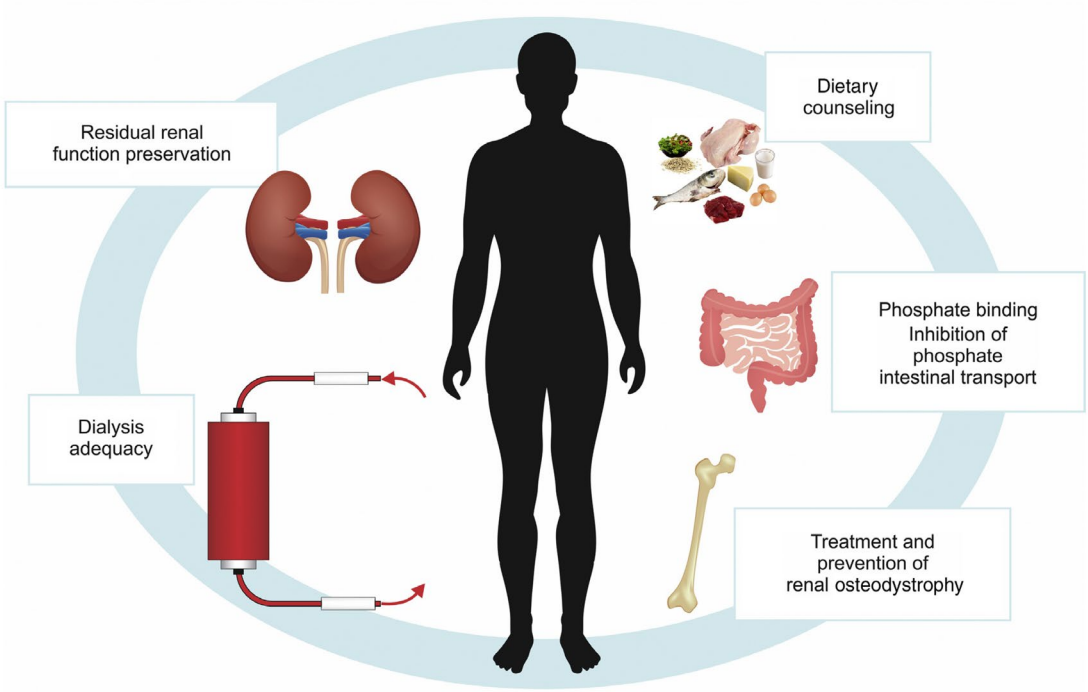


Figure 1. Therapeutic approaches to control serum phosphate in CKD patients

Serum phosphate concentration depends on a complex interplay among the kidneys, intestinal tract, and bone, and is tightly regulated by a complex endocrine system. The management of hyperphosphatemia is thus a major challenge for both nephrologists and patients and requires a multidisciplinary approach. Interventions include: preservation of residual renal function, dietary counseling, pharmacotherapy, renal osteodystrophy treatment, and providing adequate dialysis.
The ideal phosphate binder should effectively lower phosphate, have minimal systemic absorption and side effects, not require too many tablets, be palatable, affordable, and improve clinical outcomes. Currently available binders include calcium-, aluminum-, and magnesium-based binders, and aluminum-free calcium-free binders. A systematic meta-analysis of all trials comparing outcomes between CKD patients taking calcium-based phosphate binders with those on non-calcium-based binders published between 2008 and 2012 concluded that non-calcium-based phosphate binders are associated with a decreased risk of vascular calcification and all-cause mortality compared with calcium-based phosphate binders in patients with CKD. Thus, the 2017 KDIGO guidelines suggested restricting the dose of calcium-based phosphate binders in patients with CKD stages 3a-5D.

Phosphate binders – dialysis patients

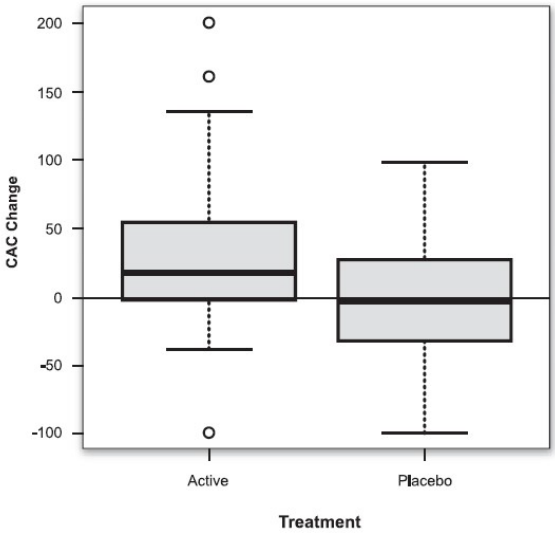
Conventional dialysis removes between 1,800 and 2,500mg per week, representing only a fragment of total phosphate ingestion. Therefore, phosphate binders are the cornerstone of hyperphosphatemia management for patients undergoing dialysis. They effectively reduce the absorption of dietary phosphate through an exchange of anion phosphate with active cation to form a non-absorbable compound that is removed by the feces. Nevertheless, their use is associated with various problems, such as pill burden, tolerability, adherence to therapy, positive calcium balance and consequent vascular calcifications, potential aluminum overload with iron-based binders, and increased costs with non-calcium-based binders. Non-adherence remains the essential obstacle with phosphate binders,

with rates of up to 70%, and only about half of the patients reach serum phosphate levels recommended by the guidelines. Gastrointestinal side effects particularly contribute to low adherence. Binders do not target or directly act on either transcellular or paracellular phosphate absorption pathways, and they bind only a limited amount of phosphate. Furthermore, there is no evidence from randomized controlled trials for the benefits of patient-centered outcomes with their use. However, several prospective cohort studies confirmed that treatment with phosphate binders is independently associated with improved survival among hemodialysis patients. A 3-year-follow-up, multicenter, open-cohort, observational prospective COSMOS study showed a lower all-cause and cardiovascular mortality risk in nearly 7,000 dialysis patients from 227 European dialysis centers, while the DOPPS prospective cohort study observed longer survival and better nutritional status in nearly 24,000 maintenance hemodialysis patients treated with phosphate binders. Interestingly, survival benefit in these studies was independent of serum phosphate as patients treated with phosphate binders even had higher serum phosphate levels.

The ambivalence regarding the effects of strict phosphate control on clinical outcomes in dialysis patients provides clinical equipoise to perform a randomized outcomes trial to compare different strategies for hyperphosphatemia management. Two currently recruiting studies, a Pragmatic randomized trial of High Or Standard PhosphAte Targets in End-stage kidney disease (PHOSPHATE) and a pragmatic cluster-randomized HiLo trial, are aiming to overcome this impediment and provide substantiated data on the impact of targeting a high or low serum phosphate level on vascular complications, rate of hospitalization and cardiovascular and all-cause mortality.

Phosphate binders – non-dialysis patients

Phosphate binders were more extensively investigated in non-dialysis CKD patients, even in several randomized and placebo-controlled trials focusing on biochemical endpoints and surrogate cardiovascular parameters. A decade ago, Block et al. published one of the first studies aiming to determine the effects of phosphate binders on parameters of mineral metabolism and vascular calcification among patients with moderate to advanced CKD. They concluded that calcium acetate, lanthanum carbonate, and sevelamer carbonate significantly lower serum and urinary phosphate compared to placebo, but also promote the progression of vascular calcification, mostly related to the use of calcium-based binders in this study.



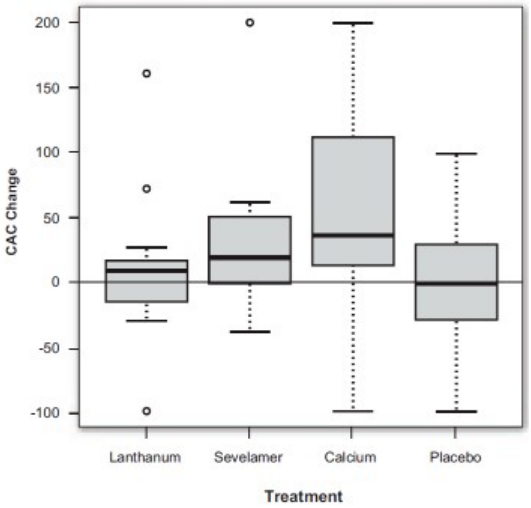


Figure 2. Effects of phosphate binders on coronary artery calcification (CAC) in non-dialysis dependent CKD patients

A year later, Chue et al. published results from a randomized controlled trial that did not support the association between sevelamer use and left ventricular mass, left ventricular function, or arterial stiffness in stage 3 CKD patients. Treatment adherence was rather low, but even compliant patients did not exhibit significantly lower serum phosphate levels. The largest and longest placebo-controlled trial of phosphate binders in non-dialysis CKD patients, the IMPROVE-CKD trial, randomized participants to lanthanum carbonate or placebo to assess the effects of phosphate binding on cardiovascular markers. After 96 weeks of follow-up carotid-femoral pulse wave velocity did not differ significantly between groups, nor did abdominal aortic calcification, serum phosphate, parathyroid hormone, and urinary phosphate. Patients in both groups experienced similar rates of adverse events with prescribed therapies.

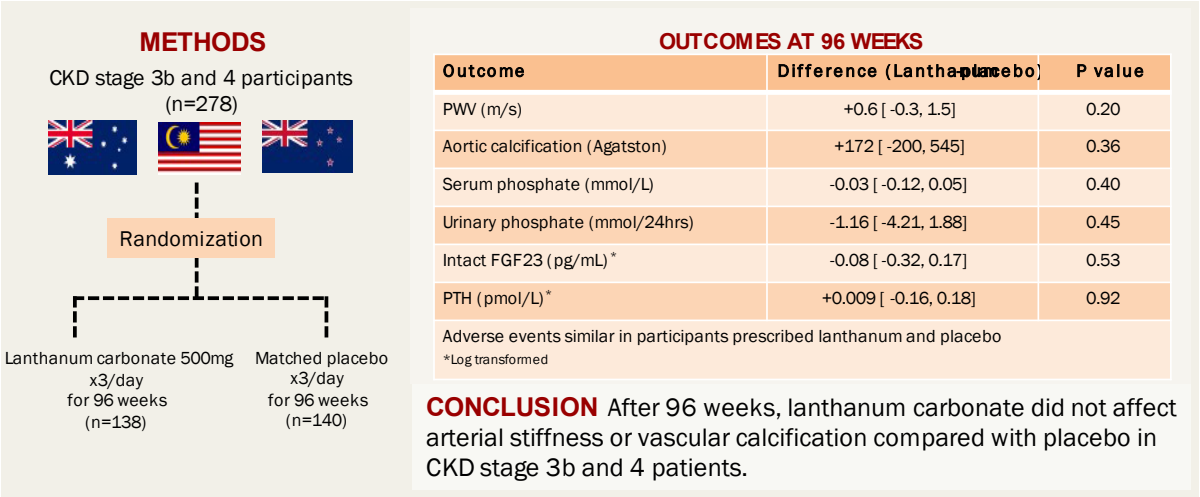


Figure 3. The Impact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease (IMPROVE-CKD) trial

Phosphate and vascular calcification

Vascular calcification is common in CKD patients and is associated with cardiovascular disease and increased mortality. Positive net calcium and phosphate balance and calcium phosphate vascular deposition are the hallmarks of vascular calcification, suggesting that adequate phosphate control might hamper these events. A recently published systematic review and meta-analysis by Lioufas et al. focused on randomized controlled trials involving noncalcium-based phosphate-lowering therapies compared with placebo, calcium-based binders, or no study medication in non-dialyzed or post-transplant CKD patients. Compared with placebo, noncalcium-based phosphate binders reduced serum and urinary phosphate but resulted in increased constipation and greater vascular calcification score. Data for effects on cardiovascular events and mortality were scarce and unconvincing. Another recent systematic review of clinical trials examining interventions to attenuate vascular calcification progression in CKD by Xu et al. was also unable to find plausible evidence that any intestinal phosphate binder mitigates vascular calcification in CKD patients. Therapy involving magnesium or sodium

thiosulfate appears most promising in this area, but larger studies with longer follow-ups are needed to corroborate these findings.

Key points

1. Phosphate binders seem effective in attenuating hyperphosphatemia and should be used to achieve recommended serum phosphate targets.
2. Pill burden and gastrointestinal side effects are significant impediments to patient adherence.
3. Evidence of potential cardiovascular benefits from phosphate binders is still lacking, especially in the dialysis population.
4. Currently recruiting PHOSPHATE and HiLo trials are expected to provide substantiated data on the effects of targeting high or low serum phosphate levels on vascular complications, rate of hospitalization, and cardiovascular and all-cause mortality.

Further reading

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