Phosphate Binders in CKD: Bad News or Good News?

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Hyperphosphatemia has long been considered an important contributor to the mineral and bone disorder associated with CKD (CKD-MBD). Already 50 years ago, Slatopolsky et al. showed that as GFR decreased, fractional phosphate excretion rose because of inhibition of tubular phosphate reabsorption by parathyroid hormone (PTH), thus preventing serum phosphorus to rise. In the last 10 years, fibroblast growth factor 23 (FGF23) has been progressively recognized as another major regulator, if not the most important factor, in controlling renal phosphate excretion and avoiding phosphate retention in CKD. FGF23 exerts this action by activating its main receptor, FGFR-1, in the proximal tubular epithelium, with Klotho as an obligatory coreceptor. These adaptive mechanisms allow serum phosphorus to stay normal or near normal until CKD stages 4–5.

The contribution of hyperphosphatemia to the pathogenesis of secondary hyperparathyroidism and hence osteitis fibrosa in CKD is well established. Moreover, hyperphosphatemia favors the development of soft tissue calcifications, including vascular calcification. Most importantly, a significant association has been identified between high serum phosphorus levels and mortality, both in CKD patients and in the general population. The associations may be both direct and indirect, through concomitant changes in circulating hormone levels such as PTH and FGF23. It must be pointed out, however, there is no high-quality evidence to date based on randomized controlled trials (RCTs) that normalizing serum phosphorus improves hard patient outcomes.

Available evidence is only circumstantial, mostly based on association studies. The recent Kidney Disease—Improving Global Outcomes guideline on CKD-MBD suggests to reduce elevated phosphorus levels toward the normal range in CKD stage 5D and to keep serum phosphorus normal in CKD stages 3–5. Note, these are suggestions based on weak evidence. Although both extremely high and extremely low serum phosphorus levels clearly are associated with major complications, there is an intermediate gray zone with optimal serum phosphorus targets difficult to define for the different stages of CKD.

Several means are available to reduce high serum phosphorus levels. They include dietary phosphate restriction, use of phosphate binders, and phosphate removal by effective dialysis in patients with ESRD. In general, limiting oral phosphate intake cannot be achieved effectively without reducing protein intake. This may be useful in CKD stages 3–5, but not necessarily in CKD stage 5D, where it could even do more harm than benefit. In any case, efficient long-term dietary phosphate restriction proves to be difficult in the majority of patients. In those on renal replacement therapy, the use of high-efficiency dialysis procedures alone allows optimal hyperphosphatemia control. However, most patients prefer standard dialysis regimens with which phosphate control is generally insufficient.

The prescription of oral phosphate binders therefore remains the principal therapeutic approach. The degree of reduction of hyperphosphatemia that can be achieved with the various types of available binders is comparable. It appears to depend more on patient acceptance and tolerance than on differences in phosphate-binding capacity. It is fair to say that in patients with CKD stage 5D, it is often difficult, if not impossible, to achieve normal or near normal serum phosphorus values.

All this brings us back to the issue of optimal hyperphosphatemia control. Is it useful at all to take phosphate binders? Are some types of binders superior to others in terms of patient outcomes? The authors of two recent observational studies examined the question of whether the prescription of phosphate binders compared with no phosphate binder prescription led to better patient outcomes. Unfortunately, we are left with opposite conclusions. Isakov et al. compared patients who began treatment with phosphate binders during the first 90 days after initiating hemodialysis with those who did not receive binders during that period. They found, using different types of analyses, that treatment with phosphate binders was independently associated with decreased mortality risk compared with no treatment. However, Winkelmayer et al. who compared use versus nonuse of calcium-containing phosphate binders in incident dialysis patients, did not observe any mortality differences, using multivariate and propensity score-matched Cox regression models.

Several RCTs were undertaken to identify possible superiority of one type of phosphate binder to another in terms of
surrogate outcomes, such as vascular calcification or hard outcomes such as cardiovascular events and mortality. Although some RCTs have been performed, they all suffer from important methodological limitations, and none of them has provided convincing evidence that selecting a particular phosphate binder will reduce the risk of clinically relevant outcomes. The critique has also been made that none of these RCTs were placebo controlled. However, from an ethical point of view, it appears impossible to leave dialysis patients with hyperphosphatemia on placebo treatment for prolonged time periods.

One major unsolved issue in CKD-MBD is whether active measures should be taken in early stages of CKD; that is, when serum phosphorus is still in the normal or near normal range, with the goal to prevent phosphate retention and related complications. Block et al. addressed this issue in a pilot clinical trial in the current issue of JASN, with the goal to determine the safety and efficacy of phosphate binders in patients with moderate to advanced CKD. They recruited 148 patients with CKD stages 3b–4 who were randomly allocated to treatment with either calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo in a prospective, blinded fashion for a time period of 9 months. The placebo-controlled approach in these patients was ethically acceptable—and approved by an international review board—because baseline serum phosphorus levels were either normal or only slightly elevated and because it is unknown at present whether the active prevention of phosphate retention in such patients is beneficial or harmful. At inclusion, the patients did not take any phosphate-binding agent, active vitamin D sterol, or calcimimetic compound. Their serum intact PTH was <500 pg/ml. Following inclusion, study medication (phosphate binder or placebo) was progressively increased with the aim to reach serum phosphorus levels ≥3.5 mg/dl. All patients received a daily oral cholecalciferol supplementation of 1000 IU. The primary end point of the trial was change in serum phosphorus from baseline to the mean of months 3, 6, and 9 among all active versus all placebo.

The interpretation of changes in coronary artery, thoracic, and abdominal aorta calcium volume scores is most problematic and should be done with extreme caution because it is in stark contrast to previous experimental findings in animals with chronic kidney failure and the finding of a clinical trial in CKD. Of note, the assessment of changes in arterial calcium scores in the study by Block et al. was possible only in a subset of 90 patients (60 active and 36 placebo) and was effectively performed only in those with non-zero calcium scores at baseline (n=81; 55% of the original cohort). Moreover, the baseline characteristics of this subgroup of 81 patients have not been reported separately in the manuscript, and lack of perfect matching between active treatment and placebo groups therefore remains possible. Moreover, it is worthwhile noting that even in the entire patient cohort there were significant baseline differences between groups for serum bicarbonate, LDL cholesterol, and 1,25-dihydroxy vitamin D, as shown in the Supplemental Table S1 of Block et al. We would also like to point out that the lack of significant differences in arterial calcium scores between individual treatment subgroups (Table 1 of Block et al.), both at baseline and at study end, might mainly be explained by insufficient sample size, with large standard deviations.
Because the results of changes in biochemical parameters other than phosphorus and in imaging findings were secondary end points, they must be considered as hypothesis generating. Thus, only the beneficial effect on phosphate retention is firmly established based on the present pilot study. Clearly, additional RCTs in larger CKD patient cohorts both before and after the initiation of dialysis therapy are required to answer the question of whether phosphate binders should be given early on or only at the stage of ESKD and whether calcium-free binders or calcium- and/or magnesium-containing binders should be the preferred option.12

DISCLOSURES
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