Dual Inhibition of Gastrointestinal Phosphate Absorption: More Questions Than Answers

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Serum levels of fibroblast growth factor 23 (FGF23), a potent phosphaturic hormone, are increased in patients with CKD due to a homeostatic response to restore serum phosphate levels.[1] Serum FGF23 levels are increased even in people with modest decreases in eGFR (60–89 ml/min per 1.73 m^2), whereas hyperphosphatemia generally manifests in advanced stages of CKD (eGFR$<$20 ml/min per 1.73 m^2).[2] Modestly elevated or even upper normal levels of serum phosphate are associated with cardiovascular disease and associated mortality in individuals with normal kidney function and CKD.[1] Increased serum FGF23 concentration is also associated with endothelial dysfunction, vascular calcification, arterial stiffness, left ventricular hypertrophy, cardiovascular events, and mortality in CKD.[3] Thus, FGF23 could be a potential therapeutic target to reduce cardiovascular mortality in early stages of CKD when serum phosphate levels are still in the normal range. However, the hypothesis that phosphate binders may reduce serum FGF23 levels by decreasing gastrointestinal phosphate absorption in patients with nondialysis CKD is not supported by randomized, controlled trials published to date.[4–6]

Currently available calcium-based and noncalcium phosphate binders are limited by gastrointestinal side effects, increased pill burden, poor adherence, and possible maladaptive increase in intestinal phosphate absorption through the sodium-dependent phosphate cotransporter. Nicotinamide, a derivative of vitamin B3, is a novel therapy shown to reduce hyperphosphatemia by inhibiting sodium-dependent phosphate cotransport in the renal proximal tubule and intestine.[7] Thus, the combination of a phosphate binder and nicotinamide could result in greater reductions in serum levels of phosphate and FGF23.

In this issue of *JASN*, Ix *et al.*[8] report the results of the CKD Optimal Management with Binders and Nicotinamide (COMBINE) trial, a double-blind, randomized, placebo-controlled trial to assess the efficacy and safety of nicotinamide and lanthanum carbonate in participants with CKD stages 3b and 4 (eGFR=20–45 ml/min per 1.73 m^2). A total of 205 participants were randomized to four treatment arms: (*1*) active nicotinamide and lanthanum carbonate placebo, (*2*) active lanthanum carbonate and nicotinamide placebo, (*3*) active nicotinamide and active lanthanum carbonate, or (*4*) nicotinamide placebo and lanthanum carbonate placebo. Thus, all participants received a combination therapy. Interestingly, this was not designed as a 2×2 factorial trial but a four-arm trial. This design enabled evaluation of each of the three active arms to the double-placebo group. The coprimary efficacy end points were rates (slope) of change per 12 months in serum phosphate and FGF23. Thus, there were a total of six comparisons. The starting dose of nicotinamide or placebo was 750 mg once daily, which was titrated up to 750 mg twice daily. The starting dose of lanthanum carbonate or placebo was 500 mg thrice daily, which was titrated up to 1000 mg thrice daily.

Mean baseline eGFR was 32±7 ml/min per 1.73 m^2. It should be noted that the mean serum phosphate was in the normal range (3.7±0.6 mg/dl). Consistent with previous trials of phosphate binders in the nondialysis CKD population, there were no significant differences in the rate of change in serum phosphate or FGF23 in any of the three active treatment arms compared with the double-placebo group. Although biochemical or laboratory adverse events were rare, gastrointestinal adverse events were very common in the three active arms. The rate of discontinuation of study medications was highest in the double-active group (42%) followed by the lanthanum carbonate active (30%) and nicotinamide active (25%) groups, whereas the discontinuation rate in the double-placebo group was 14%. The most common reasons for discontinuation were gastrointestinal symptoms and pill burden. A *post hoc* per protocol analysis of patients who remained on medication found no significant changes in serum phosphate, but it did find an 8% reduction in FGF23 in the active lanthanum group compared with a 14% increase in the double-placebo group.

The COMBINE trial is the first randomized, controlled trial of nicotinamide in patients with nondialysis CKD, and Ix *et al.*[8] should be commended for conducting a well designed trial. Although the results of this trial are not practice changing, the trial has advanced our understanding of newer phosphate-lowering strategies, especially combination therapy, in patients with moderately advanced stages of CKD and normal serum phosphate levels. Theoretically, the combination of nicotinamide and lanthanum carbonate should work synergistically, with both gastrointestinal transport

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inhibition of sodium-dependent phosphate cotransport and phosphate binding within the gastrointestinal lumen. Trial participants had normal serum phosphate levels at baseline, and adaptive mechanisms that maintain phosphate homeostasis are still largely present at this level of kidney function. This may explain the lack of reduction in serum phosphate levels in all three active treatment groups, including the combined group. The reasons for the lack of active treatments on serum FGF23 are less clear. Nicotinamide did not reduce urine phosphate excretion either alone or in combination with lanthanum carbonate, but lanthanum carbonate did. On the basis of this finding, Ix *et al.*[8] postulate that nicotinamide had little or no effect on phosphate absorption in patients with nondialysis CKD. Despite the best efforts of investigators, the rates of discontinuation of study medications were very high in all three active groups, which may have reduced statistical power to detect meaningful reduction in serum levels of both phosphate and FGF23. It is not known whether factor or factors other than phosphate may influence FGF23 secretion.

Despite the lack of response on biochemical markers, the COMBINE trial has a clear take-home message that all phosphate-lowering medications are poorly tolerated. Because of their adverse gastrointestinal effects and substantial pill burden, patient adherence to these medications is generally low. We need convincing evidence of reduction in cardiovascular events and mortality with phosphate-lowering therapies to support their widespread use in populations of both patients with nondialysis-dependent CKD and patients with dialysis-dependent CKD. The COMBINE trial was not powered to detect an effect on clinical end points, and the 12-month follow-up period was too short to determine any meaningful difference. The COMBINE trial also evaluated several surrogate markers, such as cardiac magnetic resonance assessment of left ventricular mass, bone turnover markers, and other surrogate measures of CKD progression and inflammation (changes in intrarenal oxygenation and fibrosis). However, results of these investigations were not reported in this manuscript. It would be interesting to see if phosphate-lowering strategies have any effect on these markers, even in the absence of a significant effect on serum levels of phosphate and FGF23. Results of the Impact of Phosphate Reduction on Vascular Endpoints in Chronic Kidney Disease study, a placebo-controlled, randomized trial evaluating the effect of lanthanum carbonate on surrogate markers of cardiovascular disease (pulse wave velocity, aortic calcification, and left ventricular mass) in patients with CKD stages 3b and 4 (eGFR=15–45 ml/min per 1.73 m^2), are expected in late 2019.[9] These studies may pave the way for adequately powered randomized, controlled trials of phosphate-lowering medication with clinical end points.

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See related article, "Effects of Nicotinamide and Lanthanum Carbonate on Serum Phosphate and Fibroblast Growth Factor-23 in CKD: The COMBINE Trial," on pages 1096–1108.