Phosphate REINs in the Renoprotective Benefit of ACE Inhibition

Geoffrey A. Block* and Myles Wolf†
*Denver Nephrologists, PC, Denver, Colorado, and †the Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida

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Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARB) attenuate progression of chronic kidney disease (CKD).1,2 Nevertheless, the incidence and prevalence of end-stage renal disease (ESRD) continue to increase despite widespread use of these agents in patients with CKD.3 Additional therapeutic targets are desperately needed to partner with inhibitors of the renin-angiotensin system to further protect patients with CKD.

Disordered mineral metabolism, especially aberrant phosphate homeostasis, has emerged as a novel and potent risk factor for adverse clinical outcomes in CKD. Set points for serum phosphate in the population depend on a variety of genetic variants for phosphate-related genes,4 and environmental factors, such as socioeconomic status, contribute to serum levels independent of race.5 In addition to numerous reports linking elevated serum phosphate to increased risks of cardiovascular events and mortality among dialysis, CKD, and non-CKD patients,6–8 several studies suggest that elevated levels of serum phosphate are independently associated with more rapid progression of established CKD and perhaps, greater risk of incident disease.9–11 Enthusiasm to target disordered phosphate metabolism in intervention in early stages of CKD, however, has been dampened by the normal serum phosphate levels that are found in the majority of early-stage CKD patients.12 The discovery and characterization of fibroblast growth factor 23 (FGF23) as a key hormonal regulator of phosphate homeostasis that may be a more accurate measure of the phosphate load sensed by osteocytes and a more discriminating predictor of adverse outcomes than the serum phosphate has galvanized renewed interest in targeting this pathway in early CKD.12,13

In this issue of JASN, Zocalli et al. provide the first clinical report of the intersection between the renin-angiotensin system and phosphate metabolism in CKD.14 In a post hoc analysis of 331 of the 352 participants in the randomized Ramipril Efficacy in Nephropathy (REIN) study, the authors investigated whether baseline serum phosphate modified the risk of ESRD or of doubling of serum creatinine in response to ramipril versus placebo in patients with nondiabetic, proteinuric CKD (baseline ioHexol GFR of 44 ± 18 ml/min per 1.73 m²). Although the median serum phosphate was normal (3.5 mg/dl) and only 7% of participants manifested overt hyperphosphatemia (>4.6 mg/dl), higher levels of serum phosphate were independently associated with greater risk of reaching the renal end points even after adjusting for randomization group and baseline ioHexol GFR, proteinuria, systolic BP, and serum albumin. Although these findings are consistent with previous observations, the new and most striking finding of this report is that higher baseline serum phosphate levels progressively attenuated the renoprotective effect of ramipril that was demonstrated in the primary analysis of the parent trial.15 Indeed, participants in the highest serum phosphate quartile derived no demonstrable benefit from ramipril on preventing adverse renal outcomes in unadjusted or adjusted analyses. In support of the study’s main finding, the results were qualitatively identical regardless of whether serum phosphate was analyzed in quartiles or as a continuous variable.

By performing the analysis within a randomized trial, the authors benefitted from its high-quality clinical data and adjudicated end points. Consistent with the randomized design, Table 1 in the article reports well balanced characteristics across the ramipril treatment groups overall but also across the treatment groups within each stratum of serum phosphate. However, it must be emphasized that post hoc analyses across serum phosphate strata are no different from any other observational, nonrandomized cohort study. Consistent with the nonrandomized aspect of the current study are the large and expected differences in baseline characteristics across the phosphate strata that demonstrate that higher serum phosphate is associated with other markers of more severe kidney dysfunction, for example, lower GFR.

Low baseline GFR is the strongest predictor of CKD progression. This is likely due to both biologic phenomena, for example, the vicious cycle of glomerular hyperfiltration in response to injury,16 but also due to study design considerations. Specifically, study participants who are closer to the finish line (ESRD) when a study begins are by definition more likely to cross it sooner during the observation phase. Adjusting for differences in baseline GFR is the statistical equivalent of eliminating the head start of participants with low starting GFR.
Although this technique should theoretically minimize this critical source of bias, most studies use simple linear adjustments for baseline GFR and fail to consider nonlinear relationships that could be addressed by incorporating squared and cubed terms. In addition, most studies adjust for estimated rather than directly measured GFR, which is less precise (this study did adjust for iohexol GFR). Even if measured perfectly, GFR alone is unlikely to fully capture all of the components that constitute healthy renal function, for example, patients with high-grade proteinuria or renal tubular acidosis can manifest normal GFR. These limitations set the stage for other factors that are markers of worse renal function—for example, higher serum phosphate—to emerge as independent predictors of CKD progression, even after adjusting for baseline GFR. Left unanswered by these analyses is whether elevated serum phosphate is a mechanism of CKD progression, as investigators prefer to conclude, or simply a marker that captures the severity of renal dysfunction in combination with GFR more accurately than GFR alone.

In our opinion, the single most important contribution of this study is the new light it shines on this previously gridlocked issue. Table 2 of the article shows substantial attenuation of the point estimates for serum phosphate in the multivariable compared with the crude analyses, consistent with confounding by other factors included in the model. Like previous studies, this raises the concern that other confounders may not have been considered or that the adjustment for those that were may have been incomplete, most notably GFR, as may not have been considered or that the adjustment for those that were may have been incomplete, most notably GFR, as described above. However, another post hoc analysis of the REIN trial demonstrated that participants with the lowest GFR derived the most benefit from ramipril in preventing progression to ESRD.17 Similarly, participants with the highest serum phosphate also had the lowest levels of urinary sodium excretion. Because the renoprotective effects of ACEI are potentiated by a low sodium intake,18 the high-phosphate group would have a priori been expected to derive greater rather than diminished benefit from ramipril. The divergence of effect modification by baseline serum phosphate relative to comparable analyses of baseline GFR and estimated salt intake suggest that the attenuation of the ramipril benefit observed in those with the highest serum phosphate levels is supportive of a mechanistic effect of the phosphate pathway.

Whether this is due to higher serum phosphate per se, elevated FGF23 levels, or reduced klotho expression is a question for future studies to address. Regardless of which of these ultimately proves to be actual villains in the progression of CKD, the possibility that disordered phosphate metabolism interferes with the modern cornerstone of renal protection presents the nephrology community with an opportunity to design and conduct innovative randomized trials dually targeting the renin-angiotensin system and phosphate homeostasis.

REFERENCES

15. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in protein-
Is There Something Better than the Best Marker of Kidney Function?

Brad C. Astor* and Nrupen A. Bhavsar†‡

*Departments of Medicine and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; †Section of Value and Comparative Effectiveness, Division of General Internal Medicine, Department of Medicine, New York University School of Medicine, New York, New York; and ‡Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Measurement of kidney function is critical both for clinical decision-making and research. Direct measurement of GFR using urinary or plasma clearance of exogenously administered markers, such as $^{125}$I-iothalamate, is considered the gold standard method to assess kidney function. These procedures, however, are burdensome and impractical in many settings. Using endogenous markers to estimate GFR is an attractive alternative, and serum creatinine-based estimates are widely reported by clinical laboratories.

The potential biases and inaccuracies of serum creatinine-based GFR estimates are widely known and include variations in creatinine generation as a result of differences in muscle mass or diet and variations in tubular secretion or extrarenal elimination of creatinine. Although serum levels of cystatin C are less affected by muscle mass, other nonrenal determinants of serum cystatin C have been identified. The limitations of directly measured GFR are less well studied but are significant and include substantial measurement error, dietary protein intake, and day-to-day and diurnal variations. The inaccuracies and biases of the different methods to assess GFR have specific implications relevant to each of its uses.

Hsu et al. compared the cross-sectional associations between GFR measured with $^{125}$I-iothalamate (iGFR) and estimated GFR based on serum creatinine (eGFR-Cr) or cystatin C (eGFR-cysC) with chronic kidney disease (CKD)-associated complications in a subset of 1214 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Inclusion criteria were an eGFR-Cr between 20 and 70 ml/min per 1.73 m$^2$ for those aged 21 to 44 years, 20 and 60 ml/min per 1.73 m$^2$ for those aged 45 to 64 years, and 20 and 50 ml/min per 1.73 m$^2$ for those aged 65 to 74 years. Individuals with polycystic kidney disease, kidney transplant recipients, and those with severe comorbid conditions, such as advanced heart failure, were excluded. The authors assessed the linear associations of iGFR, eGFR-Cr, and eGFR-cysC with levels of hemoglobin, potassium, bicarbonate, and phosphate, as well as with dichotomized outcomes based on these values.

As expected, lower iGFR or eGFR was associated with lower levels of hemoglobin and bicarbonate and higher levels of potassium and phosphorus. The correlations, however, were relatively weak, with $R^2$ values ranging from 0.07 to 0.13. Similarly, logistic regression analyses of dichotomized outcomes resulted in C statistics ranging from 0.67 to 0.73, indicating only moderate ability to discriminate between participants with and without each complication. The authors point out that iGFR resulted in slightly better discrimination than eGFR-Cr or eGFR-cysC for anemia but slightly poorer discrimination for hyperphosphatemia, although these differences were not tested statistically. Discrimination for metabolic acidosis and hyperkalemia were similarly weak across all three GFR measures.

The CRIC Study used rigorous data collection methods, including a detailed protocol for iGFR measurements and high-quality laboratory methods. The subset of study participants included in these analyses, consisting of approximately one third of all CRIC Study participants, is representative of the overall CRIC Study population. The results presented provide important information with implications relevant to both clinical treatment and research.

There are several elements of the study that warrant discussion. All three GFR measures were poorly correlated with all four CKD complications. Although few studies have reported $R^2$ or C statistics from linear or logistic regression models, as was done here, the correlations observed by Hsu et al. are somewhat lower than those found in similar populations in several previous studies, although the reasons for these differences are unknown. Although one would not expect a linear relationship between GFR and complications in stages 2 through 4 CKD, the authors found that nonlinear models, including splines, did not substantially improve the fit of the models in this study. Such nonlinearities would be difficult to detect statistically in the presence of such weak associations.