DISCLOSURES

None.

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See related article, "Plasmin in Nephrotic Urine Activates the Epithelial Sodium Channel," on pages 299–310.

Phosphorus and Survival: Key Questions That Need Answers

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For more than forty years now, high serum phosphate levels, a highly prevalent condition in patients with chronic kidney disease (CKD), have been associated with the pathogenesis of secondary hyperparathyroidism, a common mineral and bone disorder (MBD).[1] Recent epidemiologic and experimental studies have further amplified the role this condition plays in the larger story of CKD-MBD. Experimental studies have demonstrated that high phosphorus plays a key role in the development of vascular calcification[2] and impairment of bone mass and strength, induces changes in the expression pattern of muscle and bone-related genes,[3,4] and may also act as a pro-aging factor.[5] In addition, clinical studies have demonstrated an association among hyperphosphatemia, vascular stiffness, and left ventricular hypertrophy.[6] Taking all of the aforementioned findings together, it is reasonable to hypothesize all these untoward actions of phosphorus may ultimately affect mortality, as it has been suggested by several studies carried out in different dialysis cohorts.[7,8]

The increase in the importance of phosphorus in the spectrum of CKD-MBD also coincides with the description of the multiple actions of a new modulator, fibroblast growth factor 23 (FGF-23). This phosphatonin carries out some effects independent of phosphorus, such as its inhibitory effect on parathyroid hormone synthesis,[9] but, so far, most of the biologic actions of FGF-23, including its recently described association with mortality,[10] seem to be highly interdependent and related to phosphorus, parathyroid hormone, and vitamin D metabolism.[11,12]

In this issue of *JASN*, Isakova *et al.*[13] investigate in a prospective cohort of incident hemodialysis patients the hypothesis that therapy with any type of phosphate binder *versus* no phosphate binder offers survival benefit. To mimic a randomized trial, they used an interesting approach, performing multivariate-adjusted "intention to treat" analysis and multivariate-adjusted "as treated" analysis in which the analyses started at the time the therapy began.

In the intention-to-treat analysis, the phosphate binders group offered a 30% lower mortality compared with the untreated group. The results were less beneficial (18% lower

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mortality) when survival was calculated with the as-treated approach, in which the phosphorus binder treatment was analyzed as a time-dependent exposure. In addition, the authors examined the outcomes of the cohort of patients excluded from the study because they had already begun treatment with phosphorus binders before the initiation of hemodialysis. In this excluded but treated group, they found a significant survival advantage compared with all groups included in the study; also the advantages persisted in the analysis that excluded deaths during the first 90 d of hemodialysis. In summary, the whole set of analyses performed in this study demonstrate coherent and uniform results on both early and 1-yr mortality in hemodialysis patients.

In this interesting study, there are somewhat expected but also unexpected findings. First, the results were partly independent of baseline and follow-up serum phosphate levels, but the effect of phosphorus binders was particularly effective in patients without severe hyperphosphatemia. These two findings suggest the benefit of phosphorus binders imply actions even beyond the control of serum phosphate, thus opening other challenging areas for future research. Second, the benefit of phosphorus binders was observed regardless and independent of other concomitant medications known to have a likely impact on morbidity and mortality. This was the case with Angiotensin-converting enzyme inhibitors, aspirin, and particularly active vitamin D treatments, which have been associated with lower mortality, not only cardiovascular-related deaths but also those caused by cancer and infections.[14] In the study by Isakova *et al.*,[13] contrary to what might be expected, the treatment with active vitamin D did not seem to add any benefit to that obtained from treatment with phosphorus binders. Unfortunately, during the follow-up period, the authors adjusted for the use of active vitamin D in a time-dependent manner; only the initial low percentage of patients who received active vitamin D in both groups ($<$12%) is quoted. To strengthen the value of this finding, it would have been helpful to know more precisely the figures related to percentage of active vitamin D use throughout the whole study, because potentially both low and high percentage use makes it more difficult to assess the contribution of this use. Third, the authors found a differential positive benefit in Hispanic patients. These findings are in partial agreement with a study related to the use of active vitamin D, which described better survival than previous studies[15] in a Latin American dialysis cohort in which approximately 25% of dialysis patients were Hispanic.[14] Further studies are needed to determine whether the "Hispanic influence" is true or just the result of unknown bias. Finally, a likely effect of phosphate binders' decreasing the levels FGF-23 may have accounted for part of the benefit in survival observed in patients who received phosphorus binders. This may be particularly relevant in patients with mild or moderate hyperphosphatemia, who, unexpectedly, showed great benefits with the use of binders independent of their serum phosphate levels.

This study[13] has great value; in fact, it is the first prospective observational study to show the advantages of serum phosphorus binders compared with no treatment. The biggest limitation is its observational nature. Even though the investigators provided a rigorous approach by designing multiple analytical strategies aiming to imitate best a randomized trial, including a propensity score–matched analysis to minimize selection bias and confounding by indication, no single analysis could eliminate all potential sources of bias as a trial would.

In addition, the duration of the follow-up was relatively short and does not allow us to know the clinical outcomes beyond that time. Despite that several phosphorus binders were used, the study did not permit one to analyze differences between them or use any sample measurement of compliance, such as pill counts. Like other large dialysis cohort studies, the authors also did not provide any information on dietary phosphorus intake or vitamin D levels.

In summary, the study of Isakova *et al.*[13] has made a relevant contribution to understanding the effect of phosphorus binders on mortality. Because high serum phosphate levels have been systematically associated with increased mortality, the benefits in outcomes were expected to be associated mainly with the control of high serum phosphorus, but the benefits in survival were also obtained at lower serum phosphorus levels. As a result, the study poses new and challenging questions beyond the effects of high serum phosphorus, switching the focus of attention from serum phosphate itself to other contributing factors, such as FGF-23 or other possible pleiotropic effects of phosphorus binder therapy. These new findings offer a powerful argument highlighting the need to conduct long-term placebo-controlled trials designed to investigate the advantages of intervening early in CKD using different drugs and strategies to reduce various levels of serum phosphate, even within the normal range.

DISCLOSURES

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See related article, "Phosphorus Binders and Survival on Hemodialysis," on pages 388–396.

Proteomic Portrayal of Transplant Pathologies

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Despite recent improvements in 1-yr outcomes for kidney transplantation, long-term allograft survival has not changed significantly in the past several decades.[1] The survival half-life for kidneys from deceased donors is approximately 11 yr, and the pathogenesis of these late graft losses is multifactorial.[2] Analyses of graft histology reflected in the revised Banff criteria indicate chronic allograft injury can be subcategorized, in part, on the basis of evidence of local inflammation and the presence or absence of interstitial fibrosis and tubular atrophy (IF/TA).[3] Although specific inciting factors are difficult to define in each situation, distinct histopathologic entities often correlate with likely causes. For example, calcineurin inhibitor toxicity frequently manifests as IF/TA without inflammation; ongoing cellular alloimmunity presents histologically with tubulitis with or without IF/TA; C4d staining suggests transplant glomerulopathy with or without IF/TA; and detectable, donor-specific serum antibodies underlie antibody-mediated allograft injury.[3]

Because only a subset of patients develop chronic injury and because at present physicians do not have the ability to reverse chronic fibrotic kidney damage, it is essential that the transplant community develop reliable and noninvasive approaches to predict which patients are most likely to develop graft failure so that appropriate interventions can be instituted before graft failure becomes clinically apparent. At present, protocol biopsies of well-functioning grafts provide the best assessment tool to predict risk for subsequent graft failure (*e.g.*, the presence of subclinical acute rejection, IF/TA, transplant glomerulopathy).[4–6] Defining likely causes of an ongoing pathologic process is similarly important because this information guides subsequent treatment regimens. For example, calcineurin inhibitors are withdrawn from patients at risk for calcineurin inhibitor–induced toxicity, whereas individuals at risk for cellular and/or antibody-mediated immune injury are candidates for altered immunosuppression aimed at inhibiting the relevant component of the immune system.

A significant worldwide research effort is now focused on delineating assays and approaches to meet the laudatory goal of predicting outcomes after transplantation. These endeavors include detailed characterizations of serum alloantibody levels,[7] measurements of individual soluble or cell-surface markers (proteins or genes) in peripheral blood and/or urine,[8] and evaluations of peripheral cellular alloimmunity,[9] among others. Additional unbiased approaches being used by numerous research groups include profiling gene expression[10] and/or proteome expression patterns[11,12] in patient cohorts to assess the utility of these profiles as surrogate markers of injury.

In this issue of *JASN*, Quintana *et al.*[13] provide new evidence that assessment of the urine proteome can noninvasively distinguish two types of chronic allograft pathology. The authors performed urine proteomic analysis using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in 32 patients with biopsy-proven chronic allograft injury (GFR <35 ml/min, proteinuria, >3 yr after transplantation). These patients had either chronic active an-

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