Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3–5: The Modification of Diet in Renal Disease Study

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KDIGO guidelines recommend dietary phosphate restriction to lower serum phosphate levels in CKD stages 3–5. Recent studies suggest that dietary phosphate intake is only weakly linked to its serum concentration, and the relationship of phosphate intake with adverse outcomes is uncertain. To evaluate this, we used Cox proportional hazards models to assess associations of baseline 24-h urine phosphate excretion with risk of end-stage renal disease (ESRD), all-cause mortality, and mortality subtypes (cardiovascular disease (CVD) and non-CVD) using the Modification of Diet in Renal Disease data. Models were adjusted for demographics, CVD risk factors, iothalamate GFR, and urine protein and nitrogen excretion. Phosphate excretion was modestly inversely correlated with serum phosphate concentrations. There was no association of 24-h urinary phosphate excretion with risk of ESRD, CVD, non-CVD, or all-cause mortality. For comparison, higher serum phosphate concentrations were associated with all-cause mortality (hazard ratio per 0.7 mg/dl higher, 1.15 (95% CI 1.01, 1.30)). Thus, phosphate intake is not tightly linked with serum phosphate concentrations in CKD stages 3–5, and there was no evidence that greater phosphate intake, assessed by 24-h phosphate excretion, is associated with ESRD, CVD, non-CVD, or all-cause mortality in CKD stages 3–5. Hence, factors other than dietary intake may be key determinants of serum phosphate concentrations and require additional investigation.

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In patients with kidney failure receiving maintenance dialysis, higher serum phosphate concentrations are associated with mortality and cardiovascular disease (CVD) events.[1] Experimental studies demonstrate that higher extracellular phosphate induces the transformation of vascular smooth muscle cells into osteoblast-like cells, and promotes deposition of calcium in the vascular wall,[2] potentially exacerbating vascular stiffness and cardiac afterload. In patients on dialysis, dietary phosphate intake is a key determinant of serum phosphate concentrations, and conversely limiting phosphate intake significantly reduces serum phosphate concentrations.[3]

More recently, higher serum phosphate concentrations have been linked with the risk of death, CVD, and progression to end-stage renal disease (ESRD) in patients with earlier stages of chronic kidney disease (CKD),[4] and even among persons with ostensibly normal kidney function.[5,6] In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) international consensus guidelines work-group recommended maintenance of serum phosphate concentrations within the normal laboratory range in persons with CKD stages 3–5. KDIGO recommended the use of intestinal phosphate binders and limiting dietary phosphate intake as methods to accomplish this goal.[7] Thus, a key tenet of the KDIGO recommendations was that intestinal phosphate absorption is a key determinant of serum phosphate concentrations in patients with CKD stages 3–5, similar to dialysis patients, and that the methods used to lower phosphate in dialysis would be effective in CKD stages 3–5. However, in 2009, there were little data demonstrating the effects of alterations in intestinal phosphate absorption on serum phosphate concentrations in earlier stages of CKD. Since that time, several new lines of evidence question that assumption. Several studies have demonstrated only modest or altogether absent correlations between dietary phosphate intake and serum phosphate

concentrations.[8,9] For example, using 24-h urine phosphate excretion (UPE) as the clinical gold standard for assessing intestinal phosphate absorption, randomized clinical trials evaluating high doses of intestinal phosphate binders in CKD stages 3–5 have shown marked reductions in 24-h UPE, but only minimally altered serum phosphate concentrations.[10] Several smaller randomized trials found no effect of binders on serum phosphate concentrations.[9,11,12] In the Modification of Diet in Renal Disease (MDRD) Study, we previously demonstrated that randomization to a low-protein/low-phosphate diet substantially lowered 24-h UPE but had minimal effects on serum phosphate concentrations.[13] These findings suggest that factors other than intestinal phosphate absorption may be the major determinants of serum phosphate concentrations in CKD stages 3–5. If so, then the use of intestinal phosphate binders or dietary phosphate restriction may not significantly lower serum phosphate concentrations, leaving it unclear whether these interventions would translate into improvements in clinical outcomes in CKD stages 3–5. However, data evaluating relationships of dietary phosphate intake with clinically meaningful outcomes in CKD stages 3–5 are lacking.

Participants in the MDRD study provided 24-h urine collections at baseline before randomization, which were measured for phosphate content, providing a reliable marker of intestinal phosphate absorption. Iothalamate measures of glomerular filtration rate (GFR), proteinuria, and 24-h urine urea nitrogen excretion (a marker of dietary protein intake) were measured concurrently. Long-term follow-up is available in MDRD to evaluate associations with ESRD, cardiovascular, noncardiovascular, and all-cause mortality. As prior studies in CKD stages 3–5 evaluating the strength of association of intestinal phosphate absorption with serum phosphate and the association of intestinal phosphate absorption with clinical end points are lacking, we set forth to assess the relationship of 24-h UPE with ESRD, cardiovascular mortality, noncardiovascular mortality, and all-cause mortality in patients with CKD stages 3–5 in the MDRD Study.

RESULTS

Participant characteristics

Among the 795 participants in this study, the mean age ± s.d. was 52 ± 12 years, 60% were male, and 15% were nonwhite. The mean iothalamate GFR ± s.d. was 33 ± 12 ml/min per 1.73 m^2, mean serum phosphate ± s.d. was 3.8 ± 0.7 mg/dl, and mean 24-h UPE ± s.d. was 821 ± 285 mg/day. Baseline characteristics by quartiles of 24-h UPE are shown in Table 1 (Data stratified by MDRD Study A and Study B are provided in Supplementary Table S1 online). Compared with those with lower UPE, participants in higher UPE quartiles were more frequently male and white, were more likely to be in the usual protein arm, had higher body mass index, GFR, serum albumin, total caloric intake, and urine creatinine, and urea nitrogen excretion rates, and lower serum phosphorus and high-density lipoprotein concentrations. Participants with higher UPE were also less likely to be taking intestinal phosphate binders. When evaluated as continuous variables, the Pearson's correlation of 24-h UPE with serum phosphate was inverse and statistically significant, but quite modest ($\rho = -0.12$ (95% confidence interval −0.18, −0.05)). When this association was adjusted for iothalamate GFR, the inverse association was attenuated and rendered no longer statistically significant (Figure 1).

Associations of 24-h UPE with risk of ESRD, cardiovascular mortality, noncardiovascular mortality, and all-cause mortality

The mean follow-up was 16 years (range 0.25–22), during which 589 of the 795 participants progressed to ESRD (incidence rate 9.04 per 100 person-years), 191 participants died because of CVD (1.55 per 100 person-years), and 228 participants died because of non-CVD causes (1.85 per 100 person-years), constituting 419 deaths from all causes (3.40 per 100 person-years). Table 2 shows the relationships of 24-h UPE with each of these outcomes. An initial model adjusted for demographics, a second added measured GFR, proteinuria, and urea nitrogen excretion, and a final model additionally added CVD risk factors, total caloric intake, phosphate binder use, and randomized diet and blood pressure strata. When evaluated by UPE quartiles, we observed fairly linear relationships with each outcome, and therefore we focused on the continuous analysis evaluating associations per 1 s.d. unit (285 mg/dl) higher 24-h UPE. We observed no statistically significant associations of 24-h UPE with any of the four outcomes, in either minimally adjusted or fully adjusted models. There were no interactions by randomized treatment arm for any of the 4 outcomes in the fully adjusted model (P interactions all >0.05). Similar results were observed when we evaluated individuals in Study A and Study B separately (Supplementary Table S2 online).

To evaluate the possibility that undercollection or overcollection of urines may have influenced our results, we conducted a sensitivity analysis in which we limited the study sample to those individuals who had measured creatinine excretion rates within 30% of that expected by a validated creatinine excretion rate prediction equation. This resulted in exclusion of 8% ($n = 63$) of individuals. Among the remaining 732 participants, results were similar. We again observed no association of 24-h UPE with any of the outcomes in the fully adjusted model (Supplementary Table S3 online).

We also evaluated the association of dietary phosphate intake measured by 3-day dietary recall rather than 24-h UPE. The Pearson's correlation between 24-h UPE and dietary phosphate intake based on the 3-day dietary recall was weak ($\rho = 0.25$). We observed no association of dietary phosphate intake by 3-day dietary recall with any of the outcomes in models adjusted for demographics or kidney function. In the fully adjusted model, a modest direct association emerged for all-cause mortality (HR per s.d. higher 1.19 (95% confidence interval 1.03, 1.37), $P = 0.02$) but not for the other outcomes (Supplementary Table S4 online).