AJKD

Original Investigation

Acid Load and Phosphorus Homeostasis in CKD

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Background: The kidneys maintain acid-base homeostasis through excretion of acid as either ammonium or as titratable acids that primarily use phosphate as a buffer. In chronic kidney disease (CKD), ammoniagenesis is impaired, promoting metabolic acidosis. Metabolic acidosis stimulates phosphaturic hormones, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) in vitro, possibly to increase urine titratable acid buffers, but this has not been confirmed in humans. We hypothesized that higher acid load and acidosis would associate with altered phosphorus homeostasis, including higher urinary phosphorus excretion and serum PTH and FGF-23.

Study Design: Cross-sectional.

Setting & Participants: 980 participants with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Predictors: Net acid excretion as measured in 24-hour urine, potential renal acid load (PRAL) estimated from food frequency questionnaire responses, and serum bicarbonate concentration < 22 mEq/L.

Outcome & Measurements: 24-hour urine phosphorus and calcium excretion and serum phosphorus, FGF-23, and PTH concentrations.

Results: Using linear and log-linear regression adjusted for demographics, kidney function, comorbid conditions, body mass index, diuretic use, and 24-hour urine creatinine excretion, we found that 24-hour urine phosphorus excretion was higher at higher net acid excretion, higher PRAL, and lower serum bicarbonate concentration (each $P < 0.05$). Serum phosphorus concentration was also higher with higher net acid excretion and lower serum bicarbonate concentration (each $P = 0.001$). Only higher net acid excretion associated with higher 24-hour urine calcium excretion ($P < 0.001$). Neither net acid excretion nor PRAL was associated with FGF-23 or PTH concentrations. PTH, but not FGF-23, concentration ($P = 0.2$) was 26% (95% CI, 13%-40%) higher in participants with a serum bicarbonate concentration <22 versus ≥ 22 mEq/L ($P < 0.001$). Primary results were similar if stratified by estimated glomerular filtration rate categories or adjusted for iothalamate glomerular filtration rate (n = 359), total energy intake, dietary phosphorus, or urine urea nitrogen excretion, when available.

Limitations: Possible residual confounding by kidney function or nutrition; urine phosphorus excretion was included in calculation of the titratable acid component of net acid excretion.

Conclusions: In CKD, higher acid load and acidosis associate independently with increased circulating phosphorus concentration and augmented phosphaturia, but not consistently with FGF-23 or PTH concentrations. This may be an adaptation that increases titratable acid excretion and thus helps maintain acid-base homeostasis in CKD. Understanding whether administration of base can lower phosphorus concentrations requires testing in interventional trials.

Am J Kidney Dis. 70(4):541-550.

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Received October 27, 2016. Accepted in revised form April 26, 2017. Originally published online June 21, 2017.

In line with AJKD's procedures for potential conflicts of interest for editors, described in the Information for Authors & Journal policies, an Acting Editor-in-Chief (Editorial Board Member Masafumi Fukagawa, MD, PhD) handled the peer-review and decision-making processes.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2017.04.022

INDEX WORDS: Acid-base; acidosis; phosphorus; fibroblast growth factor 23 (FGF-23); parathyroid hormone (PTH); chronic kidney disease (CKD); phosphorus homeostasis; phosphorus excretion; FE_{Pi}; phosphaturic hormones; acid load; physiology; potential renal acid load (PRAL).

The major role of the kidneys is to maintain the internal milieu, including preserving acid-base and phosphorus homeostasis. In health, the kidney regulates acid-base balance by excreting fixed acids generated from nutrient metabolism[1,2] and phosphorus balance by excreting the absorbed load of ingested phosphorus.[3] As kidney function declines in chronic kidney disease (CKD), both these functions are compromised. To overcome lower acid excretion in the form of ammonium, excretion of titratable acid in the form of monovalent phosphate may be relatively increased through reduction in urine pH or augmented phosphaturia.[4-7] Additionally, to prevent hyperphosphatemia, fractional excretion of phosphorus (FE_{Pi}) may be augmented by the phosphorus-regulatory hormones parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23).[3] Thus, both these processes occur in tandem during progressive kidney disease and may converge on urine phosphorus excretion as a critically regulated parameter (see Fig S1, available as online supplementary material). Nonetheless, few studies have evaluated the relationship between derangements in acid-base and derangements in phosphorus homeostasis in patients with CKD.

Several animal and in vitro models suggest that changes in acid-base status and acid load may affect phosphorus homeostasis.[7-12] For instance, acid loading in rats increases urine phosphorus excretion, presumably to augment titratable acid excretion.[11] However, study conclusions differ about whether this phenomenon is the result of indirect effects of the phosphaturic hormones PTH and FGF-23[8,9,12] or direct effects on sodium-phosphate transporters.[7,11] Furthermore, in studies documenting increased PTH and FGF-23 transcription, the pH used to elicit these changes was below the typical systemic pH of patients with early to moderate CKD.[8,12] Thus, few studies in animals or humans have evaluated integrated acid-base and phosphorus physiology relevant to early or moderate CKD, when overt metabolic acidosis is uncommon, but adaptations to increase titratable acidity may already be occurring.[7,13] Due to well-documented risks associated with even minor changes in FGF-23 concentrations and other aspects of mineral metabolism,[14] acidosis and acid load may represent additional targets to prevent early derangements in the phosphorus axis. In this study, we used comprehensive data from a prospective cohort of patients with CKD to test the hypothesis that acid load and acidosis are associated with phosphorus homeostasis and phosphaturic hormones.

METHODS

Study Population

The Chronic Renal Insufficiency Cohort (CRIC) Study is an observational cohort study of 3,939 individuals with CKD recruited in 2003 to 2008 at multiple centers in the United States. All participants were aged 21 to 74 years with estimated glomerular filtration rates (eGFRs) within 20 to 70 mL/min/1.73 m^2 at enrollment. By design, ~50% of participants had diabetes mellitus. Participants with multiple myeloma, polycystic kidney disease, or requiring active immunosuppressive therapy were excluded. Detailed inclusion and exclusion criteria have been previously reported.[15,16] The current report includes 980 CRIC participants who were randomly selected to have net acid excretion measurements performed in 24-hour urine collections from baseline (n = 1,000) and who had urine pH of 4.0 to 7.4 (n = 20 excluded). All participants provided written informed consent for participation in the CRIC Study. The CRIC Study was approved by the institutional review boards (IRBs) at all clinical centers, and the net acid excretion ancillary study was deemed exempt by the Duke University Health System IRB under protocol number Pro00056642.

Measurements and Data Collection

We quantified acid load as net acid excretion and potential renal acid load (PRAL) and acidosis based on serum bicarbonate concentration, each as exposure variables. Outcomes include urine and serum phosphorus, urine calcium, FGF-23, and PTH concentrations. Net acid excretion was calculated from urine ammonium, pH, phosphorus, and creatinine values, as described in detail below. Other urine measurements were used as dietary biomarkers, such as urine urea nitrogen and urine sulfate, or outcome measurements (eg, urine calcium and phosphorus). Urine ammonium, pH, and sulfate were measured in baseline 24-hour urine collections that had been stored at −80°C since collection. Urine pH was measured using an electrode, urine ammonium was measured using enzymatic assays, and urine sulfate was measured using turbidometric assay, each by Litholink Corp. Other clinical urine variables (eg, urine phosphorus, calcium, creatinine, and nitrogen) were measured in the central CRIC laboratory in baseline 24-hour urine samples that had been stored at −20°C. Titratable acidity was calculated using the Henderson Hasselbalch equation, urine pH, phosphorus, and creatinine and the pK_a values of the relevant reactions, as previously described by our group[13] and others.[17-19] Net acid excretion was calculated as the sum of titratable acidity and urine ammonium excretion, with urine bicarbonate excretion assumed negligible in a urine pH range of 4.0 to 7.4.[13]

Bicarbonate, phosphorus, intact PTH (Scantibodies), and carboxy-terminal FGF-23 (Immutopics) were measured in baseline serum samples at the CRIC central laboratory. Dietary intake was assessed using the National Cancer Institute Diet History Questionnaire.[20] PRAL estimates the contribution of the diet to fixed acid production as follows: PRAL = 0.49 × protein (g) + 0.037 × P (mg) − 0.021 × K (mg) − 0.026 × Mg (mg) − 0.013 × Ca (mg).[21] PRAL was set to missing for individuals using alkali supplements (n = 23).

Additional covariates were measured per CRIC protocol. Demographics and medical history were assessed by self-reported