ORIGINAL RESEARCH

Dietary Acid Load Is Associated With Serum Bicarbonate but not Insulin Sensitivity in Chronic Kidney Disease

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Objective: In chronic kidney disease (CKD), dietary acid may promote metabolic acidosis and insulin resistance, which in turn may contribute to adverse clinical health outcomes. We examined associations between dietary acid load, serum bicarbonate, and insulin sensitivity in CKD.

Design: In a cross-sectional study, we collected 3-day prospective food diaries to quantify dietary acid load as net endogenous acid production (NEAP, the nonvolatile acid load produced by the diet's acid balance) and potential renal acid load (PRAL). We measured urine net acid excretion (NAE) in 24-hour urine samples. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamp.

Subjects: Forty-two patients with CKD Stages 3 to 5 attending nephrology clinics in the Pacific Northwest and 21 control subjects (estimated glomerular filtration rate [eGFR] ≥ 60 mL/minute/1.73 m^2).

Main Outcome Measures: Serum bicarbonate and insulin sensitivity (SI_{clamp}).

Results: Mean age was 60.8 ± 13.6 years, and 54% of participants were men. Mean eGFR and serum bicarbonate concentrations were 34.4 ± 13.1 mL/minute/1.73 m^2 and 24.1 ± 2.9 mEq/L for participants with CKD and 88.6 ± 14.5 mL/minute/1.73 m^2 and 26.3 ± 1.8 mEq/L for control subjects, respectively. Mean NEAP, PRAL, and NAE were 58.2 ± 24.3, 9.7 ± 18.4, and 32.1 ± 19.8 mEq/day, respectively. Considering all participants, dietary acid load was significantly, inversely associated with serum bicarbonate, adjusting for age, gender, race, eGFR, body mass index, and diuretic use: −1.2 mEq/L per standard deviation (SD) NEAP (95% confidence interval [CI] −1.8 to −0.6, $P < .0001$); −0.9 mEq/L bicarbonate per SD PRAL (95% CI −1.5 to −0.4, $P = .0005$); −0.7 mEq/L bicarbonate per SD NAE (95% CI −1.2 to −0.1, $P = .01$). These associations were similar in participants with and without CKD. However, neither NEAP and PRAL nor NAE was significantly associated with SI_{clamp}. Serum bicarbonate was also not significantly associated with SI_{clamp}.

Conclusions: In CKD, dietary acid load is associated with serum bicarbonate, suggesting that acidosis may be improved by dietary changes, but not with insulin sensitivity.

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Introduction

METABOLIC ACIDOSIS IS a common complication of CKD. Its prevalence is highest among patients who have an estimated glomerular filtration rate (eGFR) of less than 30 mL/minute/1.73 m^2, although mild or subclinical acidosis may develop even in early stages of CKD.[1,2] The decreased ability of the kidney to excrete acid is a major contributor to the development of metabolic acidosis. Impaired acid excretion in CKD occurs even in the setting of clinically normal serum bicarbonate concentration.[3]

Diet may play a role in the development of metabolic acidosis in CKD. Fruits, vegetables, and non-animal protein contribute alkali to the balance, whereas animal protein and grain contribute to acid.[4] Net endogenous acid production (NEAP) is the total nonvolatile acid load produced by consumption of countervailing acid and alkali elements of the diet.[5] In the general population, NEAP is inversely correlated with serum bicarbonate.[6,7] Dietary acid load has also been shown to associate with metabolic acidosis in renal transplant recipients.[8]

Metabolic acidosis may contribute to CKD complications, including insulin resistance. In the general population, metabolic acidosis is associated with greater fasting insulin and triglyceride levels.[9] In observational studies of CKD patients, lower serum bicarbonate concentrations are associated with decreased insulin sensitivity[10]; additionally, patients with end-stage renal disease treated with bicarbonate therapy

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demonstrate improved insulin sensitivity.[11,12] Insulin resistance may promote cardiovascular diseases and the development and progression of CKD.[10,13–17]

Significantly, the introduction of more fruits and vegetables into the diet with the goal of reducing dietary acid load has been shown to reduce kidney injury and slow the decline in glomerular filtration rate in hypertensive nephropathy.[18] Additionally, greater dietary acid load and the development of acidosis itself may contribute to the progression of CKD and other CKD complications, such as muscle wasting and hyperparathyroidism.[19–26] Thus, dietary acid load is a potential intervention to limit metabolic acidosis and its sequelae in CKD.

We examined dietary acid load measured as NEAP, potential renal acid load (PRAL), and net acid excretion (NAE) in the urine, and their associations with serum bicarbonate and insulin sensitivity, among people with and without moderate to severe CKD. We hypothesized that measures of dietary acid intake, NEAP, PRAL, and NAE would be associated with lower serum bicarbonate concentrations and lesser insulin sensitivity in participants with CKD.

Materials and Methods

Design and Study Population

We performed a cross-sectional study among a subset of participants in the Study of Glucose and Insulin in Renal Disease (SUGAR). In brief, SUGAR recruited nondiabetic patients with CKD Stages 3 to 5 in Seattle, Washington from nephrology clinics at an academic medical center, a county hospital, and a veterans affairs medical center. Exclusion criteria were a clinical diagnosis of diabetes mellitus, fasting glucose $\geq$ 126 mg/dL, use of glucose-lowering medication or insulin; maintenance dialysis, hemodialysis access in place, or kidney transplant; diagnosis of HIV, lipodystrophy, or polycystic ovary syndrome; use of corticosteroids, immunosuppressive agents, antiretrovirals, or certain psychotropic medications; cirrhosis of the liver, or hemoglobin $<$ 10 g/dL. Patients taking calcitriol or calcitriol analogs were asked to hold these medications for 4 weeks before study procedures. Control subjects, classified as eGFR $\geq$ 60 mL/minute/1.73 m^2, were drawn from clinics that refer to the nephrology clinics used to recruit CKD participants. Control subjects were identified through evaluation of electronic medical records or contacted at participating primary care clinics. For the study described herein, we included SUGAR participants enrolled through August, 2014 (N = 70), excluding 1 with previously undiagnosed diabetes mellitus, 5 with insufficient dietary data, and 1 with implausible dietary data, leaving an analytic sample of 63 participants.

The study was reviewed and approved by institutional review boards at the University of Washington and VA Puget Sound Healthcare System. All subjects gave written informed consent before participating in the study.

Dietary Acid Load

Food intake was quantified using 3-day prospective food diaries. Subjects were instructed by a trained dietitian to record all food consumed over 3 days including a weekend day. A dietitian reviewed the food diary for completeness and reconciled inconsistencies with subjects on retrieval. Food intake data from the diary were converted into daily nutrient intake using Nutrition Data System for Research software (Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota, 2013).

PRAL and estimated NEAP describe the acid load of an individual's diet by estimating the production of nonvolatile acids and bases produced during digestion based on known nutritional content. PRAL was calculated by the following formula as described by Remer and Manz[27]:

$$\begin{aligned}\text{PRAL (mEq/day)} = {} & .49 \times \text{protein intake, g/day} \\ & + .037 \times \text{phosphorus intake, mg/day} \\ & - .02 \times \text{potassium intake, mg/day} \\ & - .013 \times \text{calcium intake, mg/day} \\ & - .027 \times \text{magnesium intake, mg/day}\end{aligned}$$

Results were similar when organic acids were included in PRAL.[28]

NEAP was calculated by the formula described by Frassetto et al.[29]:

$$\begin{aligned}\text{NEAP(mEq/day)} = {} & (54.5 \times \text{protein intake, g/day} \\ & / \text{potassium intake, mEq/day}) - 10.2\end{aligned}$$

Collected 24-hour urine was stored at $-80°C$ before analysis. Urinary NAE, the gold standard of measuring metabolic acid load,[5] was determined by urine titratable acid (TA), bicarbonate (HCO_3-), and ammonium (NH_4) using the method described by Chan[30]:

$$\begin{aligned}\text{NAE (mEq/day)} = {} & [(NH_4 + TA) - HCO_3\text{(mEq/L)}] \\ & \times \text{urine volume (L)} \times 24/(\text{urine} \\ & \text{collection time (hours)})\end{aligned}$$

Serum Bicarbonate and Insulin Sensitivity

Serum bicarbonate was measured at the University of Washington Clinical Laboratory using the ion selective electrode method. Insulin sensitivity was determined by the hyperinsulinemic euglycemic clamp method adapted from the study by DeFronzo et al.[31] Clamp procedures were performed after an overnight fast. Insulin was infused as a prime (5 minutes at 160 mU/m^2/minute) followed by a continuous rate (80 mU/m^2/minute). These infusion rates were selected based on preliminary studies demonstrating consistent suppression of endogenous glucose production at 80 mU/m^2/minute. A 20% dextrose solution was titrated to maintain