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Dietary acid load is associated with serum bicarbonate but not insulin sensitivity in chronic kidney disease

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Abstract

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—42 patients with CKD stages 3–5 attending nephrology clinics in the Pacific Northwest and 21 control subjects (eGFR ≥ 60 mL/min/1.73m²).

Main outcome measures—Serum bicarbonate and insulin sensitivity (SI_{clamp}).

Results—Mean age was 60.8 $\pm$ 13.6 years and 54% of participants were men. Mean eGFR and serum bicarbonate concentrations were 34.4 $\pm$ 13.1 mL/min/1.73m² and 24.1 $\pm$ 2.9 mEq/L for participants with CKD and 88.6 $\pm$ 14.5 mL/min/1.73m² and 26.3 $\pm$ 1.8 mEq/L for control subjects, respectively. Mean NEAP, PRAL, and NAE were 58.2 $\pm$ 24.3, 9.7 $\pm$ 18.4, and 32.1 $\pm$ 19.8 mEq/day, respectively.

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Considering all participants, dietary acid load was significantly, inversely associated with serum bicarbonate, adjusting for age, sex, race, eGFR, BMI, and diuretic use: -1.2 mEq/L per SD NEAP (95% CI -1.8 , -0.6 , $p<0.0001$); -0.9 mEq/L bicarbonate per SD PRAL (95% CI -1.5 , -0.4 , $p=0.0005$); -0.7 mEq/L bicarbonate per SD NAE (95% CI -1.2 , -0.1 , $p=0.01$). These associations were similar in participants with and without CKD. However, neither NEAP, 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.

Practical application—We observed that a diet with a greater acid load was associated with lower serum bicarbonate but not insulin resistance in patients with chronic kidney disease. It may be beneficial to limit dietary acid in patients with chronic kidney disease to improve metabolic acidosis and its long-term adverse health effects, but additional, experimental studies are needed to establish the safety and usefulness of such interventions.

Introduction

Metabolic acidosis is a common complication of chronic kidney disease (CKD). Its prevalence is highest among patients who have an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/ 1.73m^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 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 sensitivity¹⁰; additionally, patients with end-stage renal disease (ESRD) treated with bicarbonate therapy 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 GFR in hypertensive nephropathy.²⁶ 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^{18–25}. 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 in the urine (NAE), and their associations with serum bicarbonate and insulin sensitivity, among people with and without moderate-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 3–5 in Seattle, WA 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 ≥ 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 analogues were asked to hold these medications for 4 weeks prior to study procedures. Control subjects, classified as eGFR ≥ 60 mL/min/1.73m², 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 prior to participating in the study.

Dietary acid load

Food intake was quantified using 3-day prospective food diaries. Subjects were instructed by a trained dietician to record all food consumed over 3 days including a weekend day. A dietician reviewed the food diary for completeness and reconciled inconsistencies with subjects upon 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, MN, 2013).

Potential renal acid load (PRAL) and estimated net endogenous acid production (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 formula below as described by Remer and Manz ²⁷:

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

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

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

$$\text{NEAP (mEq/d)} = (54.5 \times \text{protein intake, g/d} / \text{potassium intake, mEq/d}) - 10.2$$

Collected 24-hour urine was stored at -80°C prior to analysis. Urinary net acid excretion (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:

$$\text{NAE (mEq/day)} = [(\text{NH}_4 + \text{TA}) - \text{HCO}_3^- \text{ (mEq/L)}] \times \text{urine volume (L)} \times 24 / (\text{urine collection time (hours)})$$

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 DeFronzo et al.³¹ Clamp procedures were performed after an overnight fast. Insulin was infused as a prime (5 minutes at $160 \text{ mU/m}^2/\text{min}$) followed by a continuous rate ($80 \text{ mU/m}^2/\text{min}$). These infusion rates were selected based on preliminary studies demonstrating consistent suppression of endogenous glucose production at $80 \text{ mU/m}^2/\text{min}$. A 20% dextrose solution was titrated to maintain blood glucose concentration at 90 mg/dL by measuring blood glucose every 5 minutes. The steady-state dextrose infusion rate was identified during the first 120–150 minutes of the clamp, after which it was maintained unchanged for an additional 30 minutes. Blood glucose and insulin concentrations were measured three times over the final 30 minutes. The steady-state glucose infusion rate (M, mg/min) was calculated as the final infusion rate (mL/min) multiplied by the glucose concentration measured in the dextrose solution (mg/dL) and adjusted for change in plasma glucose over the last 30 minutes of the clamp.³¹ The insulin sensitivity index, SI_{clamp} , was calculated as M (mg/min), divided by the difference in basal insulin concentration (mean of three measurements) and insulin steady state concentration (mean of three measurements), I ($\mu\text{U/mL}$):

$$\text{SI}_{\text{clamp}} = \text{M} / \text{I}$$

Subjects underwent an oral glucose tolerance test (OGTT) approximately one week after the euglycemic clamp. After an overnight fast, subjects were administered a 75-gram glucose drink and their blood glucose and insulin concentrations were measured 10, 5, and 1 minute before glucose administration and 10, 20, 30, 60, 90, and 120 minutes after glucose administration. The Matsuda index, an index of insulin sensitivity, was calculated from the OGTT glucose and insulin concentrations.³²

Statistical analyses

Participants characteristics were summarized by CKD case-control status (eGFR <60 versus 60 mL/min/1.73m²) and by NEAP, divided into tertiles since clinically relevant thresholds are not available. We described correlations of dietary acid measurements (NEAP, PRAL, and NAE) with serum bicarbonate and insulin sensitivity using scatterplots with regression lines, stratified by CKD status. We tested associations of dietary acid measurements (NEAP, PRAL, and NAE, evaluated as parallel exposures) with serum bicarbonate using multivariable linear regression. Next, we tested associations of dietary acid measurements and serum bicarbonate with insulin sensitivity measured as SI_{clamp} or the Matsuda index. Serial multivariable regression models were adjusted for demographic variables (age, gender, and race, Model 1) or for demographic variables and potential confounders (eGFR, body mass index, and use of diuretics), which were selected prior to analyses based on the plausibility that they may confound the associations of interest.

Results

Study population

Of 63 subjects, 42 had eGFR < 60 mL/min/1.73m² and were considered to have CKD, and 21 had eGFR ≥ 60 mL/min/1.73m² and were considered to be controls. Of participants with CKD, eGFR was 45–59 mL/min/1.73m² for 9, 30–44 mL/min/1.73m² for 18, and 8–29 mL/min/1.73m² for 15. Mean subject age was 60.8±13.6; 54% of participants were male. Mean BMI was 29.5±6.3. 76% of subjects were white, 18% black, and 6% Asian or Pacific-Islander. Compared with participants with eGFR ≥ 60 mL/min/1.73m², those with eGFR < 60 mL/min/1.73m² were older and less likely to be white; had higher BMI, systolic and diastolic blood pressures, and PTH concentrations; and were more likely to use diuretics and antihypertensive medications. Mean serum bicarbonate for subjects with and without CKD was 24.1±2.9 mEq/L and 26.3±1.8 mEq/L, respectively (Table 1).

We stratified all participants together by tertiles of NEAP for the purposes of analysis. Compared to participants in the lower tertile of NEAP, those in the higher tertile of NEAP were younger and less likely to be white, had lower eGFR, and more used diuretics and antihypertensive medications. Those in the higher tertile of NEAP also consumed less fiber, potassium, phosphorus, calcium, and magnesium and more protein, which was of a greater proportion from animal sources, than those in the lower tertile of NEAP (Table 2). Food diary measures of dietary acid intake, NEAP and PRAL, correlated positively with NAE (NEAP, $r=0.48$, $p < 0.0001$; PRAL, $r=0.40$, $p = 0.0001$).

Association of dietary acid intake with serum bicarbonate

In unadjusted analysis, both dietary measures of acid intake associated with serum bicarbonate (NEAP, -1.5 (95% CI -2.0, -1.0) mEq/L bicarbonate per SD, $p < 0.0001$; PRAL, -1.3 (-1.7, -0.8) mEq/L bicarbonate per SD, $p < 0.0001$). After adjustment for age, sex, race, eGFR, BMI, and diuretic use, both associations remained significant (NEAP, -1.2 (-1.8, -0.6) mEq/L bicarbonate per SD, $p < 0.0001$; PRAL, -0.9 (-1.5, -0.4) mEq/L bicarbonate per SD, $p = 0.0005$). Urinary net acid excretion, NAE, was similarly associated with serum bicarbonate (adjusted difference -0.7 (-1.2, -0.1) mEq/L bicarbonate per SD NAE, p

= 0.01) (Table 3). Associations were similar when we additionally adjusted for total caloric intake (data not shown). The magnitudes of these associations were not significantly different in subjects with or without CKD (Figure 1, all p-values for interaction by CKD status >0.1).

Associations of dietary acid load and serum bicarbonate with insulin sensitivity

Neither measure of dietary acid intake, nor urinary acid excretion, was significantly associated with SI_{clamp} in unadjusted or adjusted analyses (Table 4). Likewise, serum bicarbonate concentration did not associate with SI_{clamp} . These associations did not differ between subjects with CKD and healthy controls (Figure 2, all p-values for interaction by CKD status >0.1). Similarly, neither NEAP, PRAL, NAE, nor serum bicarbonate was associated with insulin sensitivity measured during the OGTT as the Matsuda index (data not shown).

Discussion

We found that dietary acid load was associated with urinary acid excretion and varied inversely with serum bicarbonate. Magnitudes of association were similar among individuals with and without CKD. Subjects' urinary acid excretion, considered the gold standard of dietary acid load assessment, exhibited the same associations as dietary measures of acid load, confirming the validity of measuring NEAP and PRAL by prospective 3-day food diary. However, we did not observe an association between NEAP, PRAL, NAE, or serum bicarbonate with insulin sensitivity as measured by SI_{clamp} or the Matsuda index.

Our study is particularly advantaged by our use of gold-standard measurements for dietary acid load, urinary acid excretion, and insulin sensitivity. Measurement of urinary acid excretion also enabled us to validate our measurements of NEAP and PRAL by food diary. Limitations of our study include the observational nature, which prohibits conclusions of causality; lack of blood gas measurements to better determine acid state; and lack of chloride data with which to calculate NEAP in the "direct" manner.³³ Associations of dietary acid load with serum bicarbonate concentration may be confounded by comorbidities, medication use, family history, and other characteristics not fully accounted for in our analysis, and dietary acid load may be correlated with intake of other foods that affect serum bicarbonate or insulin sensitivity. The modest study size and the distribution of serum bicarbonate predominantly in the normal range may have limited our ability to detect small associations with insulin sensitivity.

Our findings confirm previous reports that dietary acid load may be a modifiable risk factor for metabolic acidosis.^{23,26} In our study, mean serum bicarbonate concentrations were 3.1mEq/L lower comparing CKD patients in the highest *versus* lowest tertile of NEAP, a magnitude of association greater than reported in other studies of the effect of NEAP on serum bicarbonate in CKD.²⁴ The larger magnitude of association may be attributable to use of 3-day food diaries, which are more precise than 24-hour recall. This difference may also be a result of limiting participants with CKD to those with more severe disease (stages 3–5), though the association of dietary acid load with serum bicarbonate was similar comparing participants with and without CKD. This suggests that dietary acid intake is a

contributor to acidosis across the whole spectrum of renal function, including healthy individuals, consistent with findings that dietary acid intake and serum bicarbonate are associated among the general population⁶.

A search of the literature suggests that greater dietary acid load and metabolic acidosis are associated with insulin resistance. In a classic study, DeFronzo and Beckles acutely induced metabolic acidosis in 16 healthy individuals and demonstrated that their glucose disposal rates diminished ($-15 \pm 5\%$, $P = 0.01$).³⁴ Mak corrected the metabolic acidosis of 8 young patients on dialysis and reported that their insulin sensitivity improved after 2 weeks of bicarbonate treatment.¹¹ Kobayashi et al reported that, in a study of 29 patients with CKD or ESRD whose insulin sensitivity was measured by hyperinsulinemic euglycemic clamp, serum bicarbonate was highly predictive of insulin resistance ($r = 0.611$; $P < 0.0005$).¹⁰ Likewise, in epidemiologic studies of populations with predominantly normal GFR, serum bicarbonate was positively associated with insulin sensitivity and lower risk of incident diabetes, and greater dietary acid intake (quantified as NEAP and PRAL) was associated with higher homeostasis model of assessment insulin resistance score and increased risk of incident diabetes.^{9,35–37}

However, a firm conclusion on the relationship between metabolic acidosis and insulin resistance is difficult to draw due to contradictory reports. In contrast to the above, Harris and Hughes studied the insulin sensitivity of 153 nondiabetic adults over 50 years of age randomized to receive potassium bicarbonate, sodium bicarbonate, potassium chloride, or placebo for 3 months.³⁸ No effects of treatment on HOMA-IR were observed, though the trial was not designed to examine changes in insulin sensitivity, and participants were generally insulin sensitive at baseline. In addition, Xu et al reported in an observational study of 911 community-dwelling Swedish men aged 70–71 that NEAP and PRAL did not associate with incidence of diabetes over 18 years of follow-up.³⁹ Our findings that dietary acid load and metabolic acidosis are not associated with gold-standard insulin resistance more closely mirror these reports.

Our findings may contradict studies that suggest that acidosis is associated with insulin resistance for several reasons. Our measurements of participants' dietary acid load and serum bicarbonate concentrations reflect free-living states rather than an experimentally-induced state. Our study population is also relatively larger and older and excludes patients with severe kidney disease. Our data are also advantaged by precise measurements of dietary acid load and insulin sensitivity. Definitive conclusions cannot be reached without well-controlled randomized trials that reflect the chronic disease state.

Evidence continues to suggest that acid-base status and dietary acid load are important factors in the health of patients with CKD. Lower serum bicarbonate is associated with the progression of disease and increased mortality in patients with CKD.^{18,21,40} Sodium bicarbonate treatment in CKD may slow the progression of disease.²⁰ Greater NEAP is associated with the progression of CKD^{23,25} and in the general population, greater NEAP may also be associated with increased risk of developing hypertension.^{41,42} As such, the adjustment of dietary acid load may be beneficial in slowing the progression of CKD.^{8,33} In particular, the restriction of animal protein from the diet may capture both the benefits of

reduction of dietary acid load as well as other health benefits that accrue from promoting greater inclusion of fruits and vegetables – foods that help to reduce dietary acid load and are associated with increased serum bicarbonate.^{43,44} Therefore, our null results examining associations of dietary acid load and serum bicarbonate with insulin resistance do not preclude an impact of dietary acid intake and bicarbonate on other CKD complications.

In conclusion, dietary acid load and net acid excretion were associated with serum bicarbonate concentration in the setting of CKD, suggesting that modification of dietary acid intake may improve metabolic acidosis and potentially prevent some of the downstream adverse consequences of metabolic acidosis in CKD. However, our results do not support the concept that insulin resistance is a CKD complication that is substantially affected by dietary acid load.

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Figure 1.

Associations of dietary acid load with serum bicarbonate concentrations displayed using scatterplots with linear regressions. Circles represent individuals with CKD; triangles represent control individuals. NEAP = net endogenous acid production; PRAL = potential renal acid load; NAE = net acid excretion.

Figure 2.

a. Associations of dietary acid load intake and serum bicarbonate with insulin sensitivity measured by hyperinsulinemic euglycemic clamp displayed using scatterplots with linear regressions. Circles represent individuals with CKD; triangles represent control individuals. NEAP = net endogenous acid production; PRAL = potential renal acid load; NAE = net acid excretion.

Table 1

Characteristics of study population by estimated GFR

Covariate	All participants (N=63)	Estimated GFR	
		< 60 mL/min/1.73m ² (N=42)	60 mL/min/1.73m ² (N=21)
<u>Demographic characteristics</u>			
Age (years)	60.8 (13.6)	62 (14.5)	58.5 (11.8)
Male gender	34 (54)	23 (54.8)	11 (52.4)
Race			
White	48 (76.2)	29 (69)	19 (90.5)
Black	11 (17.5)	9 (21.4)	2 (9.5)
Asian/Pacific Islander	4 (6.3)	4 (9.5)	0 (0)
Highest level of education completed ³			
High school	12 (19)	10 (23.8)	2 (9.5)
Trade school	9 (14.3)	8 (19)	1 (4.8)
College	27 (42.9)	17 (40.5)	10 (47.6)
Graduate school	12 (19)	4 (9.5)	8 (38.1)
Missing	3 (4.8)	3 (7.1)	0 (0)
<u>Medications and lifestyle</u>			
Antihypertensive medication	47 (74.6)	38 (90.5)	9 (42.9)
Diuretics	20 (31.7)	18 (42.9)	2 (9.5)
Current smoking	7 (11.1)	6 (14.3)	1 (4.8)
<u>Physical measurements</u>			
BMI (kg/m ²)	29.5 (6.3)	30 (6.1)	28.3 (6.7)
Systolic blood pressure (mmHg)	130.8 (16.6)	134.4 (16)	123.7 (15.8)
Diastolic blood pressure (mmHg)	79 (10.8)	80 (10.2)	77.1 (12)
<u>Laboratory measurements</u>			
Serum creatinine (mg/dL), median	1.6 (0.9–2)	1.8 (1.6–2.5)	0.9 (0.7–0.9)
Estimated GFR (mL/min/1.73m ²)	52.4 (29.1)	34.4 (13.1)	88.6 (14.5)
Urine AER (mg/24 hours), median ^I	18.1 (6.6–179.9)	117.9 (14.8–280)	4.9 (3.2–7.9)
Urine AER category (mg/24 hours) ^I			
< 30	35 (55.6)	16 (38.1)	19 (90.5)
30–299	17 (27)	16 (38.1)	1 (4.8)
300	10 (15.9)	10 (23.8)	0 (0)
Serum bicarbonate (mEq/L)	24.8 (2.8)	24.1 (2.9)	26.3 (1.8)
Serum phosphorus (mg/dL)	3.9 (0.6)	3.8 (0.7)	4 (0.4)
Serum PTH (pg/mL), median	64.0 (38.5–81.5)	67.5 (50.5–94.2)	53 (35–63)
Fasting plasma glucose (mg/dL)	101.2 (9.6)	102.4 (9.2)	98.9 (10.2)
Fasting plasma insulin (uU/mL)	9.2 (5.1)	9.9 (4.9)	7.9 (5.4)
2-hour OGTT glucose (mg/dL) ²			
< 140	22 (34.9)	11 (26.2)	11 (52.4)

Covariate	All participants (N=63)	Estimated GFR	
		< 60 mL/min/1.73m ² (N=42)	60 mL/min/1.73m ² (N=21)
140–199	31 (49.2)	23 (54.8)	8 (38.1)
200	8 (12.7)	6 (14.3)	2 (9.5)
Hemoglobin A1c	5.5 (0.4)	5.5 (0.4)	5.6 (0.4)
Hemoglobin (g/dL)	13.2 (1.4)	13.1 (1.4)	13.4 (1.4)

Mean (SE) for continuous variables; N (%) for categorical variables; median (IQR) where noted GFR = glomerular filtration rate; BMI = body mass index; AER = albumin excretion rate; PTH = parathyroid hormone; OGTT = oral glucose tolerance test

¹ one missing value omitted;

² two missing values omitted

Table 2

Characteristics and dietary intake of study population by net endogenous acid production

Covariate	All participants	Net endogenous acid production (NEAP)		
		45.3 mEq/day (N=21)	>45.3 to 63.3 mEq/day (N=21)	> 63.3 mEq/day (N=21)
<u>Demographic characteristics</u>				
Age (years)	60.8 (13.6)	68.7 (9.5)	58.6 (10.6)	55.1 (16.4)
Male gender	34 (54)	12 (57.1)	10 (47.6)	12 (57.1)
Race				
White	48 (76.2)	18 (85.7)	18 (85.7)	12 (57.1)
Black	11 (17.5)	3 (14.3)	1 (4.8)	7 (33.3)
Asian/Pacific Islander	4 (6.3)	0 (0)	2 (9.5)	2 (9.5)
<u>Medications and lifestyle</u>				
Antihypertensive medication	47 (74.6)	13 (61.9)	17 (81)	17 (81)
Diuretics (%)	20 (31.7)	3 (14.3)	8 (38.1)	9 (42.9)
<u>Physical measurements</u>				
BMI (kg/m ²)	29.5 (6.3)	28.4 (6.4)	29.5 (6.4)	30.4 (6.3)
Systolic blood pressure (mmHg)	130.8 (16.6)	131 (16.8)	128.5 (13.9)	133 (19.2)
Diastolic blood pressure (mmHg)	79 (10.8)	78.5 (12)	78.5 (9.4)	80.1 (11.2)
<u>Laboratory measurements</u>				
Serum creatinine (mg/dL), median	1.6 (0.9–2)	1.1 (0.7–1.6)	1.9 (0.9–2.5)	1.7 (1.4–2)
Estimated GFR (mL/min/1.73m ²)	52.4 (29.1)	63.8 (26.3)	48.7 (34.2)	44.9 (23.4)
Urine AER (mg/24 hours), median ^I	18.1 (6.6–179.9)	12.2 (5.2–20.3)	17.2 (8.1–566.2)	98.4 (14.7–210.6)
Serum bicarbonate (mEq/L)	24.8 (2.8)	26.4 (1.7)	24.7 (2.6)	23.3 (3)
Serum PTH (pg/mL), median	64.0 (38.2–81.5)	61.0 (44.0–68.0)	63 (37–104)	66 (38–79)
Fasting plasma glucose (mg/dL)	101.2 (9.6)	101.3 (9.6)	101 (9)	101.4 (10.8)
Fasting plasma insulin (uU/mL)	9.2 (5.1)	7.6 (5)	9.8 (4.6)	10.2 (5.6)
2-hour OGTT glucose (mg/dL) ²				
< 140	22 (34.9)	7 (33.3)	6 (28.6)	9 (42.9)
140–199	31 (49.2)	12 (57.1)	11 (52.4)	8 (38.1)
200	8 (12.7)	2 (9.5)	2 (9.5)	4 (19)
<u>Dietary intake</u>				
Total energy intake (kcal/day)	1897.5 (563.4)	1868.1 (511)	2002.8 (669.4)	1821.5 (506.1)
NEAP (mEq/day)	58.2 (24.3)	35.1 (7.2)	53.2 (5.6)	86.3 (18.1)
PRAL (mEq/day)	9.7 (18.4)	–8.5 (10.1)	9 (8.3)	28.7 (12.5)
NAE (mEq/day) ^I	32.1 (19.8)	25.8 (16.8)	28.9 (21.5)	41.3 (18.1)
Percent of energy as protein	16.3 (5)	14.2 (2.7)	15.4 (3.9)	19.4 (6.3)
Percent from animal sources	61.1 (16.1)	53.4 (15.5)	58.9 (16.6)	71 (10.6)
Fiber (g/day)	19.7 (9.8)	25.8 (10.1)	20 (9.6)	13.4 (5.1)
Sodium (mg/day)	3154.1 (1246.2)	2797.6 (1033.5)	3289.4 (1287.5)	3375.2 (1372.7)
Potassium (mg/day)	2547.8 (1068.8)	3145.9 (1115.6)	2556.8 (964.6)	1940.7 (776.8)

Covariate	All participants	Net endogenous acid production (NEAP)		
		45.3 mEq/day (N=21)	>45.3 to 63.3 mEq/day (N=21)	> 63.3 mEq/day (N=21)
Phosphorus (mg/day)	1202.1 (453)	1229.7 (453.5)	1203.7 (468.8)	1172.9 (457.3)
Calcium (mg/day)	812.3 (485.9)	857.8 (368.9)	847.2 (619.8)	732 (449)
Magnesium (mg/day)	287.5 (128.2)	330.3 (133.5)	299.5 (144.5)	232.6 (83.9)

Mean (SE) for continuous variables; N (%) for categorical variables; median (IQR) where noted GFR = glomerular filtration rate; BMI = body mass index; AER = albumin excretion rate; PTH = parathyroid hormone; OGTT = oral glucose tolerance test

¹ one missing value omitted;

² two missing values omitted

Table 3

Associations of dietary acid load with serum bicarbonate concentration

		Difference in bicarbonate (95% CI), mg/dL		
	Unadjusted mean (SD) bicarbonate mg/dL	Model 0	Model 1	Model 2
NEAP (mEq/day)				
45.3	26.4 (1.7)	0 (Ref)	0 (Ref)	0 (Ref)
> 45.3 to 63.3	24.7 (2.6)	-1.7 (-3, -0.4)	-1.6 (-2.9, -0.2)	-0.7 (-2.1, 0.6)
> 63.3	23.3 (3.0)	-3.1 (-4.5, -1.6)	-2.7 (-4.3, -1.2)	-1.9 (-3.3, -0.5)
Per 1 SD higher		-1.5 (-2.0, -1.0)	-1.5 (-2.1, -0.8)	-1.2 (-1.8, -0.6)
p-value *		< 0.0001	< 0.0001	< 0.0001
PRAL (mEq/day)				
1.95	26.1 (1.7)	0 (Ref)	0 (Ref)	0 (Ref)
>1.95 to 19.1	24.8 (3.4)	-1.4 (-2.9, 0.2)	-1.2 (-2.6, 0.2)	-0.5 (-1.7, 0.7)
> 19.1	23.6 (2.5)	-2.6 (-3.8, -1.3)	-2.2 (-3.7, -0.8)	-1.5 (-2.8, -0.2)
Per 1 SD higher		-1.3 (-1.7, -0.8)	-1.1 (-1.6, -0.6)	-0.9 (-1.5, -0.4)
p-value *		< 0.0001	< 0.0001	0.0005
NAE (mEq/day)				
24.2	26.0 (2.1)	Ref	Ref	Ref
>24.2 to 40.6	24.7 (3.1)	-1.3 (-2.9, 0.2)	-1.3 (-2.9, 0.2)	-1.2 (-2.6, 0.1)
> 40.6	23.6 (2.7)	-2.4 (-3.9, -1.0)	-2.3 (-3.6, -1.1)	-1.7 (-2.8, -0.6)
Per 1 SD higher		-0.9 (-1.5, -0.3)	-0.8 (-1.4, -0.3)	-0.7 (-1.2, -0.1)
p-value *		0.003	0.003	0.01

* p-value is for continuous acid intake exposure

M0: unadjusted, M1: M0 + age, race, and sex, M2: M1 + BMI, eGFR, use of diuretics NEAP = net endogenous acid production; PRAL = potential renal acid load; NAE = net acid excretion.

Table 4

Associations of dietary acid load and serum bicarbonate with insulin resistance measured by hyperinsulinemic euglycemic clamp

		Difference (95% CI)		
	Unadjusted mean (SD)	Model 0	Model 1	Model 2
NEAP (mEq/day)				
45.3	4.2 (1.4)	0 (Ref)	0 (Ref)	0 (Ref)
> 45.3 to 63.3	4.8 (2.7)	0.6 (−0.7, 1.8)	0.1 (−1.1, 1.3)	0.2 (−1.1, 1.4)
> 63.3	4.3 (2.2)	0.1 (−1.0, 1.1)	−0.5 (−1.7, 0.8)	−0.3 (−1.6, 1.1)
Per 1 SD higher		−0.1 (−0.6, 0.4)	−0.3 (−0.9, 0.2)	−0.3 (−0.9, 0.3)
p-value*		0.72	0.23	0.31
PRAL (mEq/day)				
1.95	4.0 (1.3)	0 (Ref)	0 (Ref)	0 (Ref)
>1.95 to 19.1	4.7 (2.8)	0.7 (−0.6, 2.0)	0.5 (−0.7, 1.7)	0.6 (−0.6, 1.9)
> 19.1	4.5 (2.1)	0.4 (−0.6, 1.5)	0.1 (−1.0, 1.2)	0.3 (−0.9, 1.6)
Per 1 SD higher		0.1 (−0.3, 0.6)	−0.1 (−0.6, 0.4)	0 (−0.5, 0.6)
p-value*		0.60	0.82	0.88
NAE (mEq/day)				
24.2	4.6 (2.5)	0 (Ref)	0 (Ref)	0 (Ref)
>24.2 to 40.6	4.4 (1.7)	−0.3 (−1.5, 1.0)	−0.4 (−1.6, 0.8)	−0.3 (−1.6, 0.9)
> 40.6	4.2 (2.3)	−0.4 (−1.8, 1.0)	−0.7 (−2.0, 0.6)	−0.6 (−2.1, 0.9)
Per 1 SD higher		−0.3 (−0.9, 0.4)	−0.3 (−0.9, 0.3)	−0.3 (−0.9, 0.3)
p-value*		0.77	0.65	0.96
Serum bicarbonate (mEq/L)				
22	4.7 (3.0)	0 (Ref)	0 (Ref)	0 (Ref)
> 22	4.4 (1.9)	−0.3 (−2.0, 1.4)	−0.2 (−1.8, 1.4)	−0.1 (−1.6, 1.4)
Per 1 SD higher		0.2 (−0.4, 0.7)	0.3 (−0.2, 0.8)	0.4 (−0.1, 1.0)
p-value*		0.58	0.28	0.09

* p-value is for continuous acid intake/bicarb exposure

M0: unadjusted, M1: M0 + age, race, and sex, M2: M1 + BMI, eGFR, use of diuretics NEAP = net endogenous acid production; PRAL = potential renal acid load; NAE = net acid excretion.