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Net endogenous acid production is associated with a faster decline in GFR in African Americans

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Increased acid excretion may promote renal injury. To evaluate this in African Americans with hypertensive nephrosclerosis, we studied the association between the net endogenous acid production and progression of kidney disease in 632 patients in the AASK trial. Protein and potassium intakes were estimated from 24 h urea nitrogen and potassium excretion, and used to estimate net endogenous acid production, averaged over 2 years, approximating routine intake. The link between net endogenous acid production and the I^{125}iothalamate glomerular filtration rate (iGFR) and time to end-stage renal disease or doubling of serum creatinine was analyzed using mixed models and Cox proportional hazards regressions. The trend in higher net endogenous acid production was significantly associated with a faster decline in iGFR over a median of 3.2 years. After adjustment for age, body mass index, baseline iGFR, urine protein-to-creatinine ratio, and randomized treatment group, the trend in higher net endogenous acid production remained significantly associated with a faster decline in iGFR at a rate of 1.01 ml/min per 1.73 m^2 per year faster in the highest compared to the lowest quartile. However, in time-to-event analyses over a median of 7.7 years, the adjusted hazard ratio (1.10) for composite renal events per 25 mEq/day higher net endogenous acid production was not significant. Hence, our findings implicate endogenous acid production as a potential modifiable risk factor for progressive kidney disease.

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Chronic kidney disease (CKD) is a major public health problem affecting 13% of the US population.[1] Increased risks of morbidity and mortality are evident even among those with only mild decreases in kidney function.[2] Preventive strategies that are low cost, low risk, and scalable are needed to address the epidemic of kidney disease.

Metabolic acidosis, a consequence of decreased renal acid excretion, is a modifiable risk factor for CKD progression.[3–5] In CKD, overall acid excretion is impaired with increased per nephron acid excretion to compensate for nephron loss.[6,7] In turn, increased acid excretion by the nephron may promote tubulointerstitial injury and contribute to disease progression.[8,9] Alkali supplements can lower acid excretion and slow disease progression.[4,10] Manipulation of the net endogenous acid production through diet may be an additional strategy to decrease renal acid excretion that may be more amenable to wide implementation as a public health initiative.

Net endogenous acid production is determined by the balance of fixed acid and alkali precursors in the diet. Fixed acid in the diet is derived largely from protein intake and alkali from organic anions such as citrate and acetate, which are naturally bound to cations, such as potassium.[11] For this reason, net endogenous acid production can be estimated from the ratio of protein and potassium in the diet.[12–14] In this study, we estimate net endogenous acid production in this manner and evaluate its association with CKD progression in a cohort of African Americans with CKD.

RESULTS

A total of 632 participants from the African American Study of Kidney Disease and Hypertension (AASK) trial and cohort study were included in this analysis. The reasons for exclusion are summarized in Figure 1. Median age was

55 years (range 22–70 years). Median I^{125}iothalamate glomerular filtration rate (iGFR) was 48.6 ml/min per 1.73 m^2 (interquartile range 36.6–58.5 ml/min per 1.73 m^2). Median estimated net endogenous acid production was 72.8 mEq/day (interquartile range 57.2–89.5 mEq/day). Median estimated protein intake was 64.9 g/day (interquartile range 53.1–76.3 g/day) and median estimated potassium intake was 43.5 mEq/day (interquartile range 33.8–55.9 mEq/day). The baseline characteristics of the study population stratified by quartiles of net endogenous acid production are presented in Table 1. Higher net endogenous acid production was associated with current smoking, lower income, and lower serum bicarbonate. Differences in protein intake across categories of NEAP were smaller than differences in potassium intake.

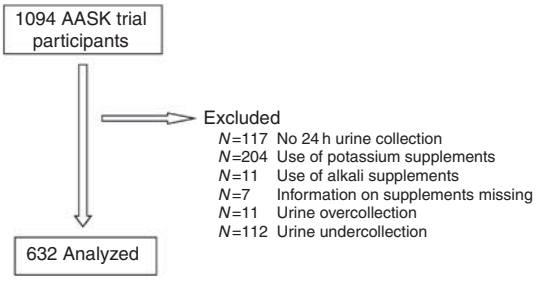

Figure 1 | Summary of reasons for participant exclusion from study population.

The iGFR analysis

The slope of iGFR was estimated from all available iGFR measurements performed every 6 months during the AASK

Table 1 | Baseline characteristics of the study population by quartiles of net endogenous acid production (NEAP)

	Quartiles of NEAP (mEq/day)				
Characteristic: mean ± s.d. or *n* (%)	1 (18.2–57.1) (*n*=158)	2 (57.2–72.8) (*n*=158)	3 (72.9–89.5) (*n*=158)	4 (89.6–232.5) (*n*=158)	*P*-value[a]
Age (years)	55 ± 10	56 ± 10	54 ± 11	54 ± 11	0.41
Female sex (%)	63 (39.9)	56 (35.4)	69 (43.7)	51 (32.3)	0.17
History of heart disease (%)	84 (53.2)	75 (47.5)	79 (50.0)	87 (55.1)	0.54
Smoking (%)					0.01
Never	73 (46.2)	63 (39.9)	62 (39.2)	66 (41.8)	
Former	55 (34.8)	55 (34.8)	43 (27.2)	35 (22.2)	
Current	30 (19.0)	40 (25.3)	53 (33.5)	57 (36.1)	
Total income (%)[b]					0.01
<$15,000	65 (41.1)	66 (41.8)	74 (46.8)	84 (53.2)	
⩾$15,000	68 (43.0)	72 (45.6)	50 (31.7)	42 (26.6)	
Body mass index (kg/m^2)	30.3 ± 6.4	30.3 ± 6.2	29.3 ± 5.5	29.5 ± 6.4	0.10
Body mass index (%)					0.07
<25 kg/m^2	25 (15.8)	34 (21.5)	36 (22.8)	45 (28.5)	
25–30 kg/m^2	67 (42.4)	52 (32.9)	61 (38.6)	45 (28.5)	
>30 kg/m^2	66 (41.8)	72 (45.6)	61 (38.6)	68 (43.0)	
Randomized to low BP goal (%)	80 (50.6)	86 (54.4)	72 (45.6)	69 (43.7)	0.21
Randomized drug (%)					0.58
Ramipril	57 (36.1)	68 (43.0)	64 (40.5)	61 (38.6)	
Metoprolol	65 (41.1)	55 (34.8)	68 (43.0)	67 (42.4)	
Amlodipine	36 (22.8)	35 (22.2)	26 (16.5)	30 (19.0)	
Serum phosphorus (mg/dl)	3.5 ± 0.6	3.5 ± 0.6	3.6 ± 0.7	3.5 ± 0.6	0.55
Serum bicarbonate (mEq/l)	25.7 ± 2.9	25.7 ± 2.8	25.0 ± 2.9	24.6 ± 3.3	<0.001
Serum potassium (mEq/l)	4.1 ± 0.5	4.1 ± 0.6	4.1 ± 0.5	4.2 ± 0.5	0.07
Serum potassium >5.0 mEq/l	7 (4.4)	6 (3.8)	9 (5.7)	7 (4.4)	0.88
Urine protein/creatinine (%)[b]					0.29
<0.22	104 (65.8)	118 (74.7)	108 (68.4)	116 (73.4)	
0.22-0.99	37 (23.4)	27 (17.1)	27 (17.1)	29 (18.4)	
⩾1.00	15 (9.4)	13 (9.4)	22 (13.9)	12 (7.6)	
iGFR (ml/min per 1.73 m^2)	46.5 ± 13.4	48.1 ± 13.7	46.4 ± 13.9	48.1 ± 13.1	0.52
Estimated protein intake (g/day)[c]	64.6 ± 19.1	64.6 ± 16.4	66.3 ± 16.6	68.4 ± 20.4	0.04
Estimated potassium intake (mEq/day)[c]	65.4 ± 20.3	47.8 ± 12.8	40.5 ± 10.2	32.4 ± 10.7	<0.001

Abbreviations: BP, blood pressure; iGFR, I^{125}iothalamate glomerular filtration rate.
[a]*P*-value is *P*-trend by univariate linear regression (continuous variables) or Pearson's χ^2 (categorical variables).
[b]Column % do not total 100 because of missing data.
[c]Estimated from 24 h urine collections between 12 and 36 months after randomization in the African American Study of Kidney Disease and Hypertension (AASK) trial phase.