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Race/Ethnicity, Dietary Acid Load, and Risk of End-Stage Renal Disease among US Adults with Chronic Kidney Disease

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Keywords
Acid-base · Epidemiology · Incidence

Abstract

Background: Dietary acid load (DAL) contributes to the risk of CKD and CKD progression. We sought to determine the relation of DAL to racial/ethnic differences in the risk of end-stage renal disease (ESRD) among persons with CKD. ***Methods:*** Among 1,123 non-Hispanic black (NHB) and non-Hispanic white (NHW) National Health and Nutrition Examination Survey III participants with estimated glomerular filtration rate 15–59 mL/min/1.73 m^2, DAL was estimated using the Remer and Manz net acid excretion (NAE_{es}) formula and 24-h dietary recall. ESRD events were ascertained via linkage with Medicare. A competing risk model (accounting for death) was used to estimate the hazard ratio (HR) for treated ESRD, comparing NHBs with NHWs, adjusting for demographic, clinical and nutritional factors (body surface area, total caloric intake, serum bicarbonate, protein intake), and NAE_{es}. Additionally, whether the relation of NAE_{es} with ESRD risk varied by race/ethnicity was tested. ***Results:*** At baseline, NHBs had greater NAE_{es} (50.9 vs. 44.2 mEq/day) than NHWs. It was found that 22% developed ESRD over a median of 7.5 years. The unadjusted HR comparing NHBs to NHWs was 3.35 (95% CI 2.51–4.48) and adjusted HR (for factors above) was 1.68 (95% CI 1.18–2.38). A stronger association of NAE with risk of ESRD was observed among NHBs (adjusted HR per mEq/day increase in NAE 1.21, 95% CI 1.12–1.31) than that among NHWs (HR 1.08, 95% CI 0.96–1.20), *p*

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interaction for race/ethnicity × NAE_{es} = 0.004. ***Conclusions:*** Among US adults with CKD, the association of DAL with progression to ESRD is stronger among NHBs than NHWs. DAL is worthy of further investigation for its contribution to kidney outcomes across race/ethnic groups.

Introduction

Blacks experience more rapid decline in kidney function than whites [1, 2] and have a greater risk of end-stage renal disease (ESRD) [3, 4]. While the contributions of apolipoprotein L1 (APOL1) risk variants to racial disparities in chronic kidney disease (CKD) have received attention in the recent past [1, 5], focus on the potential role of modifiable risk factors, such as diet, in these disparities is also warranted [6].

High dietary acid load (DAL) is associated with adverse kidney outcomes [7–9]; interventional studies have shown that alkaline diets (e.g., rich in fruits and vegetables) provide benefits to the kidney [10–12]. Explanatory mechanisms underlying the association of DAL and kidney injury may include tubular toxicity of elevated ammonium concentration [13], increased endothelin and aldosterone [14–16], and increased angiotensin II activity [17], with the latter agents yielding the physiologic benefit of increased distal nephron acidification but with the attendant pathophysiologic consequence of long-term kidney injury.

We reported in a nationally representative sample that non-Hispanic black (NHB) race was associated with higher DAL than non-Hispanic white (NHW) race [9] and high DAL was associated with increased risk of ESRD among US adults with CKD [8]. However, the relationship of racial differences in DAL to racial disparities in CKD progression is unknown. Understanding these relationships could inform interventions designed to mitigate disparities in ESRD risk.

The objective of the present study was to determine the contribution of racial differences in DAL, quantified by dietary net acid excretion (NAE_{es}), to the more rapid progression to ESRD observed among NHBs as compared to NHWs [3, 4]. We also sought to determine whether the association of DAL and risk of ESRD varied by race. Our study was conducted among a nationally representative sample of US adults with CKD stages 3 or 4 [18] using data from the National Health and Nutrition Examination Survey (NHANES) III, with follow-up for ESRD outcomes.

Methods

Study Population and Baseline Data

NHANES III was a national probability sample of 34,955 US non-institutionalized civilians conducted between 1988 and 1994 by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS). For this analysis, we included NHB and NHW participants ≥20 years of age (n = 14,223) who did not have missing data on dietary intake (n = 12,279), had an estimated glomerular filtration rate (eGFR) ≥15 and <60 mL/min per 1.73 m^2 (n = 1,261), and were not pregnant (final n = 1,123). NHANES III participants provided informed consent.

Sociodemographic and Clinical Measurements

Medical history and demographic data were collected through a standardized survey conducted at participants' homes followed by a medical examination and laboratory testing that occurred in the mobile examination center [19]. Sociodemographic factors were assessed during the interview. Racial/ethnic categories were self-reported by participants. Self-reported information on socioeconomic position (education and income) was obtained during the interview portions of the survey. Income was assessed using the poverty income ratio, a ratio of household income to the household poverty level [19]. Diabetes was defined by self-report or measured hemoglobin A1c ≥6.5% [20]. Hypertension was defined by self-report, a measured average systolic blood pressure ≥140 mm Hg or average diastolic blood pressure ≥90 mm Hg, or reported use of antihypertensive medication [21].

Measurement and Classification of Serum Bicarbonate and Kidney Parameters

Serum bicarbonate was measured by the phosphoenolpyruvate method using the Hitachi 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Serum creatinine measurements that were obtained using a kinetic rate Jaffé method in NHANES III were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH, USA) as standard creatinine = 0.184 + 0.9603 NHANES III-measured serum creatinine [22]. Random spot urine samples were obtained and frozen. Urine albumin was measured using a solid-phase fluorescence immunoassay, and urine creatinine was measured using the modified Jaffé kinetic method in the same laboratory. Estimated GFR was calculated using the isotope dilution mass spectrometry traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for calibrated creatinine [23]. Albuminuria, which was determined by the urinary albumin-to-creatinine ratio, was expressed as milligrams of albumin per gram of creatinine using American Diabetes Association categories: normal (<30 mg/g) and albuminuria (≥30 mg/g) [24].

Dietary Assessment and DAL

Dietary intake data collected in NHANES III were used to estimate the types and amounts of foods and beverages consumed during the 24-h period before the interview (midnight to midnight) and estimate the intake of energy and nutrients from those foods and beverages. The non-bicarbonate anions (protein and phosphorus) intake and the mineral cations (potassium, magnesium, and calcium) intake of foods by participants were derived from the dietary intake data. Potential renal acid load (PRAL) of foods reported by the participants was calculated using the model

by Remer and Manz, (PRAL [mEq/day] = 0.493 protein [g] + 0.0373 phosphorus [mg] 20.0213 potassium [mg] 20.0263 magnesium [mg] 20.01253 calcium [mg]) [25]. DAL was estimated as NAE_{es} (mEq/day) = PRAL + organic acids (OAs), where OA was calculated as OA (mEq/day) = (BSA [m^2] × 41 [mEq/day per 1.73 m^2]/1.73 m^2) [25], as used in our previous work [8, 9, 26].

Outcome Ascertainment

Our primary outcome of interest was progression to ESRD. In NHANES III, ESRD was defined as the initiation of chronic dialysis. ESRD events and mortality follow-up data from the time of the survey (1988–1994) through December 31, 2006, were determined from the Medicare ESRD Registry and National Death Index, which were linked to NHANES III data [27]. ESRD data are available for those NHANES respondents who agreed to provide personal identification data to NCHS and for whom NCHS was able to match with US Renal Data System administrative records.

Statistical Analyses

Baseline characteristics of study participants stratified by NHB and NHW race/ethnicity were compared using chi-square tests for categorical variables. For continuous variables, we checked normality assumptions and used one-way analysis of variance for normally distributed variables. In cases where the assumptions were not met, we used the Kruskal-Wallis test for continuous variables. We investigated the association of race with the development of ESRD while accounting for the competing risk of death prior to ESRD using the method by Fine and Gray [28]. We estimated the hazard ratio (HR) of ESRD with linear and quadratic terms for NAE_{es} in our multivariable Cox regression models to assess the relation between DAL and the rate of ESRD among race groups. We assessed the proportionality of each categorical covariate by plotting log(–log[survival]) versus log of survival time and survival function versus survival time. We tested the proportionality of continuous variables using Schoenfeld residual plots and examined their statistical significance. Product terms were used to examine possible effect modification by race/ethnicity (race/ethnicity × NAE_{es}). All analyses included the NHANES survey sample weights to account for the complex sample design of the survey, and we followed the analytical guidelines for NHANES III data as proposed by the Centers for Disease Control and Prevention [29]. Results were considered statistically significant if $p < 0.05$. All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

Sensitivity Analysis

We conducted sensitivity analyses in which we defined CKD stages 3 and 4 using eGFR calculated from the creatinine-based CKD-EPI equation [30] and repeated our primary analyses.

Results

Participant Characteristics

A total of 1,123 NHB and NHW NHANES III participants with an eGFR between 15 and 59 mL/min/1.73 m^2 were included in our study. There were no major differences in the sociodemographic and clinical characteristics of the participants who were included and those who were excluded, except age – those included had a mean age of 69.5 compared to 75.4 years for those excluded.

NHBs and NHWs differed on several characteristics examined (Table 1). NHBs were younger, more likely to live in poverty, less likely to have completed more than high school and more likely to have diabetes and/or hypertension than were NHWs. Compared with NHWs, NHBs had a greater baseline prevalence of albuminuria and a slightly lower median eGFR. The median estimated DAL, calculated as NAE_{es}, was 46.3 mEq/day (interquartile range [IQR] 34.6–58.4 mEq/day) for the full sample, and NHBs had higher PRAL and NAE_{es} than NHWs.

Associations of Race and DAL with Risk of ESRD

A total of 248 (22.1%) participants developed ESRD over a median of 7.5 (IQR 4.5–12.4) years of follow-up, including 154 (43.9%) NHBs and 94 (12.2%) NHWs. In unadjusted Cox regression models accounting for the competing risk of death, NHBs had greater risk of ESRD than NHWs (HR 3.35, 95% CI 2.51–4.48; Table 2). Subsequent models adjusting for covariates yielded an attenuated association of NHB race with risk of ESRD, with a HR of 1.68, 95% CI 1.18–2.38 in our final model, which was adjusted for socio-demographic (age, sex, and poverty income ratio), clinical (diabetes, hypertension, eGFR and albumin-to-creatinine ratio), and nutritional (body surface area, total caloric intake, serum bicarbonate, protein intake, and NAE_{es}) factors. Effect modification by race/ethnicity × NAE_{es} was observed, with a p value of 0.004 for the interaction in our final model. We proceeded by fitting separate models for NHBs and NHWs (Table 3). The estimated adjusted HR of ESRD for each 1 mEq/day increase in NAE_{es} was 1.21 (95% CI 1.12–1.31) among NHBs and 1.08 (95% CI 0.96–1.20) among NHWs.

Sensitivity Analyses

When we defined CKD stages 3 and 4 using GFR estimated from the CKD Epidemiology Collaboration (CKD-EPI) equation (n = 991; Table 4), results were similar to those of our models using the MDRD Study equation. In unadjusted Cox regression models accounting for the competing risk of death, NHBs had greater risk of ESRD than NHWs (HR 2.48, 95% CI 1.81–3.39). In our fully adjusted model, the HR was 1.91, 95% CI 1.28–2.84, and effect modification by race/ethnicity × NAE_{es} was observed (p interaction 0.03). In race-/ethnicity-specific models, the adjusted HR for ESRD associated with NAE_{es} was 1.28 (95% CI 1.17–1.40) among NHBs and 1.10 (95% CI 0.90–1.28) among NHWs.

Table 1. Baseline characteristics of NHANES III participants with CKD stages 3 or 4, overall and by race/ethnicity

Characteristic	All (n = 1,123), %	Non-Hispanic blacks (n = 351), %	Non-Hispanic whites (n = 772), %	p value
Age, years, mean (SD)	73.3 (11.8)	68.01 (10.2)	74.7 (11.2)	0.04
20–49	3.9	6.2	3.4	
50–70	27.4	48.0	22.0	
>70	68.7	45.8	74.6	
Gender, male	42.9	47.5	41.8	0.15
PIR				<0.0001
≤1	18.1	40.7	12.3	
>1 to ≤2	32.3	29.9	32.8	
>2 to ≤3	19.7	14.7	21.0	
>3 to ≤4	13.7	9.0	14.9	
>4	16.2	5.6	19.0	
Level of education				<0.0001
High school or less	50.9	68.8	46.4	
Some college	37.1	26.6	39.8	
College or greater	11.9	4.6	13.8	
Diabetes, yes	18.4	33.3	14.6	0.0001
Hypertension, yes	80.4	89.3	78.1	0.001
eGFR, mL/min/1.73 m^2, median (IQR)	50.6 (43.9–55.5)	50.1 (41.0–55.3)	50.8 (44.6–55.5)	0.02
Albuminuria (≥30 mg/g), %	30.4	46.3	26.3	0.03
Total calories >2,000 kcal/day, %	20.8	15.3	22.2	0.06
PRAL, mEq/day, median (IQR)	46.3 (34.7–58.4)	50.4 (39.7–66.8)	43.9 (32.3–56.0)	0.001
Body mass index, kg/m^2, median (IQR)	27.4 (24.1–30.9)	27.8 (25.2–31.6)	26.8 (23.9–30.4)	0.05
Body surface area, m^2, median (IQR)	1.86 (1.69–2.04)	1.95 (1.71–2.07)	1.83 (1.67–1.99)	0.05
NAE_{es}, mEq/day, median (IQR)	46.3 (34.6–58.4)	50.9 (40.4–66.8)	44.2 (31.9–56.9)	0.007

CKD defined using MDRD study equation for eGFR.

PIR is the ratio of family income to federal poverty threshold. Hypertension was defined by self-report, average systolic blood pressure ≥140 or average diastolic blood pressure ≥90 mm Hg, or use of medications. Diabetes was defined by self-report or measured hemoglobin A1c ≥6.5%.

NHANES, National Health and Nutrition Examination Survey; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PIR, poverty income ratio; PRAL, potential renal acid load; NAE_{es}, net acid excretion; MDRD, modification of diet in renal disease.

Table 2. HRs for CKD progression to ESRD comparing non-Hispanic blacks to non-Hispanic whites in the NHANES III

Models	Baseline variables included	HR (95% CI) for ESRD accounting for the competing risk of death (n = 1,123, ESRD events = 248)
1	Non-Hispanic blacks versus non-Hispanic whites, unadjusted	3.35 (2.51–4.48)
2	Model 1 + NAE_{es}*	3.21 (2.40–4.30)
3	Model 2 + age, gender	3.25 (2.41–4.39)
4	Model 3 + PIR	2.62 (1.92–3.58)
5	Model 4 + body surface area, total caloric intake, serum bicarbonate, protein intake	3.52 (2.55–4.85)
6	Model 5 + diabetes, hypertension	2.64 (1.90–3.65)
7	Model 6 + eGFR, urinary ACR	1.68 (1.18–2.38)

* Model includes both linear and quadratic terms for NAE_{es}.

HR, hazard ratio; CKD, chronic kidney disease; ESRD, end stage renal disease; NHANES, National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; PIR, poverty income ratio; NAE_{es}, net acid excretion; ACR, albumin-to-creatinine ratio.

Table 3. Race/ethnicity stratified HRs for the association of NAE_{es} with risk of CKD progression to ESRD in the NHNES III

	Non-Hispanic blacks (n = 351, ESRD events = 154) HR (95% CI) per unit (mEq/day) increase in NAE_{es}	Non-Hispanic whites (n = 772, ESRD events = 94) HR (95% CI) per unit (mEq/day) increase in NAE_{es}
NAE_{es}* (unadjusted)	1.31 (1.20–1.44)	1.02 (0.97–1.06)
+ Age, gender	1.26 (1.16–1.38)	1.03 (0.98–1.08)
+ PIR	1.24 (1.17–1.35)	1.03 (0.98–1.08)
+ Body surface area, total caloric intake, serum bicarbonate, protein intake	1.20 (1.11–1.30)	1.06 (0.99–1.13)
+ Diabetes, hypertension	1.17 (1.09–1.26)	1.04 (0.97–1.12)
+ eGFR, urinary ACR	1.21 (1.12–1.31)	1.08 (0.96–1.20)

* Model includes both linear and quadratic terms for net acid excretion.

HRs, hazard ratios; NAE_{es}, net acid excretion; CKD, chronic kidney disease; ESRD, end stage renal disease; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.

Table 4. Baseline characteristics of NHANES III participants with CKD stages 3 or 4 (defined using CKD-EPI equation), overall and by race/ethnicity

Characteristic	All (n = 991), %	Non-Hispanic blacks (n = 309), %	Non-Hispanic whites (n = 682), %	p value
Age, years, mean (SD)	73.2 (11.8)	67.7 (12.7)	74.5 (11.2)	0.03
20–50	4.0	6.7	3.3	
50–70	27.5	48.8	22.2	
>70	68.5	44.5	74.5	
Gender, male	42.9	46.3	42.0	0.27
PIR				<0.0001
≤1	17.1	39.6	11.5	
1–2	32.2	29.3	32.9	
2–3	19.8	15.2	20.9	
3–4	14.0	9.8	15.0	
>4	16.9	6.1	19.6	
Education				<0.0001
<High school	50.6	67.8	46.4	
Some college	37.4	27.3	39.9	
>College	12.0	5.0	13.7	
Diabetes, yes	18.0	32.9	14.3	0.0001
Hypertension, yes	80.4	88.4	78.5	0.003
eGFR, mL/min/1.73 m^2, median (IQR)	47.3 (41.6–55.5)	50.2 (41.1–55.2)	50.8 (44.5–55.6)	0.04
Albuminuria (>30 mg/g)	29.9	45.1	26.1	<0.0001
Total calories >2,000 kcal/day	21.7	16.5	23.1	0.09
NAE_{es}, mEq/day, median (IQR)	47.3 (41.6–53.6)	47.4 (41.2–52.9)	47.2 (41.7–53.8)	0.67

* CKD-EPI equation was used in sensitivity analysis to define chronic kidney disease, given its reported greater precision over the MDRD study equations [51]. PIR is the ratio of family income to poverty threshold. Hypertension was defined by self-report, average systolic blood pressure >140 or average diastolic blood pressure >90 mm Hg, or use of medication.

NHANES, National Health and Nutrition Examination Survey; CKD, chronic kidney disease; CKD-EPI, CKD epidemiology collaboration; PIR, poverty income ratio; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NAE_{es}, net acid excretion; MDRD, modification of diet in renal disease.

Discussion

Among a nationally representative sample of NHB and NHW US adults with CKD, we found that NHBs had greater DAL than NHWs. DAL contributed little to explaining NHBs greater risk of progression to ESRD beyond traditional risk factors, although the association of DAL with the risk of ESRD was stronger among NHBs than among NHWs. Our findings were robust to adjustment for multiple potential confounders of the associations of race/ethnicity, diet, and CKD progression, including albuminuria and total caloric intake, and to the definition of CKD (using MDRD versus CKD-EPI).

This is among the first studies to examine the role of diet in racial disparities in CKD progression. Our work advances the findings of prior studies documenting poorer diet quality among blacks, including their lower likelihood of following a Dietary Approaches to Stop Hypertension trial-accordant diet than whites [31, 32], although it has been shown that blacks have the potential to derive the greatest blood-pressure-lowering benefit from the diet [33]. The Dietary Approaches to Stop Hypertension diet, which is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein, but with substantial amounts of plant protein from legumes and nuts [34], is low in DAL [35] and is associated with lower risk of CKD [32] and kidney function decline [36]. Lower rates of blacks, as compared to whites, following diets low in DAL may be, in part, due to their greater socioeconomic barriers to healthful eating. For example, in 2011, 35% of African Americans lived below the US federal poverty threshold (USD 22,350 annually for a family of 4), compared to 13% of whites [37]. Other potential reasons for poorer diet quality among African Americans compared to whites include African Americans' perceptions of healthful dietary practices, cultural and familial norms, and preferences [38–40].

Our finding of a stronger association between DAL and risk of ESRD among NHBs could be due to the unaccounted differences between NHBs and NHWs with CKD in the United States – including cause of CKD. In our study, NHBs with CKD were about 7 years younger, were more likely to have diabetes and/or hypertension, and were substantially more likely to have albuminuria than NHWs. It is therefore very likely that the causes of CKD differed between the 2 race groups. We would expect, for example, given the estimated prevalence of high risk *APOL1* alleles among persons with CKD who are African American (19%) [5], that a substantial proportion of our NHB study population had high-risk *APOL1* alleles and therefore a greater prevalence of focal segmental glomerulosclerosis [41] than NHWs. In a study examining the potential modifiers of the association of high-risk *APOL1* variants with CKD progression among African Americans with hypertension-attributed kidney disease, high-risk *APOL1* variant status was associated with a 2.3 times greater hazard of CKD progression among individuals with lower DAL (as estimated by net endogenous acid production). In contrast, among individuals with higher DAL, high-risk *APOL1* variant status was minimally associated with CKD progression (HR 1.41, 95% CI 0.97–2.07) [42], suggesting that in the setting of poor diet quality, CKD progression is less attributable to this genetic risk factor. Based upon this study and ours, the relation of dietary factors to the *APOL1*-associated risk of CKD progression among African Americans may warrant further study.

Another potential explanation for our findings is related to the potential effects of DAL on blood pressure. Based upon data from animal models [15, 43, 44], high DAL is postulated to lead to increases in angiotensin II, endothelin-1, and aldosterone, which can ultimately lead to blood pressure elevation as well as kidney fibrosis. NHBs with CKD and hypertension have poorer blood pressure control than NHWs with the same conditions [45], which in part, might be mediated by dietary factors, among other factors.

The limitations of our study warrant consideration. First, error in measuring diet in NHANES could have biased our findings, particularly if it varied by race/ethnicity. Second, we lacked longitudinal measures of dietary patterns and other potential time-varying mediators of the association of diet with CKD progression, including blood pressure and glycemic control. Third, we lacked several measures that may have differentially influenced NHBs and NHWs risk of progression to ESRD. These include constitutional factors such as the aforementioned genetic risk factors, as well as social determinants of health closely linked to diet and/or race that were not examined in our study, such as residential segregation [46] and discrimination [47]. Fourth, we were unable to account for differences in rates of preemptive kidney transplantation, which is performed for relatively few US patients each year (2,192 patients in 2009) but at unequal rates across race/ethnicities [48]. We do not believe that this substantially influenced our results, however, as we observed similar racial differences in progression to ESRD (defined by dialysis initiation) as have been previously reported [3, 49, 50]. Fifth, our study only included NHBs and NHWs. Future studies with greater representation of multiple race/ethnicity groups might further ex-

amine this question. The strengths of our study included its longitudinal design; the examination of a potentially modifiable contributor to racial disparities in CKD progression and a potential pathophysiologic mechanism to account for DAL and progression to ESRD; and the consideration of mortality during follow-up.

Dietary approaches may warrant further consideration as therapeutic targets for CKD patients, including those at high risk for progression. Together with other interventions, such as blood pressure control, DAL may be an important target for addressing the greater risk of CKD progression among NHBs. Evidence pointing to the potential benefits of healthful diets in slowing CKD progression is mounting; however, many individuals face barriers to following such dietary patterns, including food insecurity [51] and a lack of healthful foods in neighborhood stores [46]. Thus, dietary interventions targeting populations at high risk of CKD progression, such as NHBs, might better serve these populations if contextual factors posing challenges to making lifestyle modifications are addressed [38].

Disclosure Statement

The authors report no conflicts of interest relative to this manuscript.

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