Race/Ethnicity, Dietary Acid Load and Risk of ESRD among U.S. Adults with CKD

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Abstract

Background—Dietary acid load (DAL) confers risk for CKD and CKD progression. We sought to determine the relation of DAL to racial/ethnic differences in risk of ESRD among persons with CKD.

Methods—Among 1123 non-Hispanic black (NHB) and 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-hour 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

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(body surface area, total caloric intake, serum bicarbonate, protein intake), and NAE_{es}. Separately, 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/d) than NHWs. Fully, 22% developed ESRD over a median of 7.5 years. The unadjusted HR comparing NHBs to NHWs was 3.35 [95% confidence interval (CI), 2.51-4.48]; adjusted HR (for factors above): 1.68 (CI 1.18-2.38). A stronger association of NAE with risk of ESRD was observed among NHBs (adjusted HR per mEq/d increase in NAE 1.21, CI 1.12-1.31) than among NHWs (HR 1.08, CI 0.96-1.20), p interaction for race/ethnicity*NAE_{es}=0.004.

Conclusions—Among U.S. 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 recent attention [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]; and interventional studies have shown that alkaline diets (e.g. rich in fruits and vegetables) confer 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 U.S. 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 U.S. 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 United States 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 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 (PIR), a ratio of household income to 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 mmHg or average diastolic blood pressure ≥90 mmHg, 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). Serum creatinine measurements which 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) as standard creatinine=0.184+0.9603NHANES 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 four-variable MDRD Study equation for calibrated creatinine.[23] Albuminuria, which was determined by the urinary albumin-to-creatinine ratio (ACR), was expressed as milligrams of albumin per gram of creatinine using American Diabetes Association categories: normal (<30mg/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-hour period before the interview (midnight to midnight) and estimate 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 consumed 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/d)=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/d) =PRAL+ organic acids (OAs), where OA was calculated as OA (mEq/d)=(BSA (m^2) × 41 (mEq/d 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 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 United States Renal Data System administrative records.

Statistical Analyses

Baseline characteristics of study participants stratified by NHB and NHW race/ethnicity were compared using chi-squared 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 of ESRD with linear and quadratic terms for NAE_{es} in our multivariable Cox regression models to assess relation of 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 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 Prevention and Control.[29] Results were considered statistically significant if $P<0.05$. All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

Sensitivity Analysis

We conducted sensitivity analyses wherein 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 estimated glomerular filtration rate (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 years 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/d [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 Dietary Acid Load with risk of ESRD

A total of 248 (22.1%) participants developed ESRD over a median of 7.5 (IQR 4.5 to 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 [hazard ratio (HR) 3.35, 95% confidence interval (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 ACR) 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 our models using the Modification of Diet in Renal Disease (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.

DISCUSSION

Among a nationally representative sample of NHB and NHW U.S. 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 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 definition of CKD (using MDRD versus CKD-EPI).

This is among the first studies examining 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 (DASH) trial-accordant diet than whites[31, 32], despite there being shown the potential of blacks to derive the greatest blood pressure lowering benefit from the diet.[33] The DASH 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 ($22,350 annually for a family of four), 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 unaccounted for 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 two 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 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 pre-emptive kidney transplantation, which is performed for relatively few U.S. patients each year (2192 patients in 2009) but at unequal rates across race/ethnicities.[48] We do not believe 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 examine 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].

Acknowledgments

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Table 1

Baseline Characteristics of National Health and Nutrition Examination Survey (NHANES) III Participants with Chronic Kidney Disease Stages 3 or 4, Overall and by Race/Ethnicity

Characteristic	All (n=1123) %	Non-Hispanic Blacks (n=351) %	Non-Hispanic Whites (n=772) %	P-value
Mean age in years (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	
Male sex	42.9	47.5	41.8	0.15
*Poverty Income Ratio				<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
Estimated GFR, median in ml/min per 1.73m² (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 >2000 Kilocalories/day	20.8%	15.3%	22.2%	0.06
Potential Renal Acid Load, median in mEq/day (IQR)	46.3 (34.7-58.4)	50.4 (39.7-66.8)	43.9 (32.3-56.0)	0.001
Body Mass Index, median in kg/m² (IQR)	27.4 (24.1-30.9)	27.8 (25.2-31.6)	26.8 (23.9-30.4)	0.05
Body Surface Area, median in m² (IQR)	1.86 (1.69-2.04)	1.95 (1.71-2.07)	1.83 (1.67-1.99)	0.05
Net Acid Excretion, median in mEq/day (IQR)	46.3 (34.6-58.4)	50.9 (40.4-66.8)	44.2 (31.9-56.9)	0.007

*
Chronic kidney disease defined using Modification of Diet in Renal Disease study equation to estimate glomerular filtration rate. Poverty income ratio 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 mmHg, or use of medications. Diabetes was defined by self-report or measured hemoglobin A1c 6.5%.

Abbreviations: SD, standard deviation; GFR, glomerular filtration rate; IQR, interquartile range

Table 2

Hazard Ratios for Chronic Kidney Disease Progression to End Stage Renal Disease (ESRD) Comparing Non-Hispanic Blacks to Non-Hispanic Whites in the National Health and Nutrition Examination Survey (NHANES) III

Models	Baseline Variables Included	Hazard Ratio (95% Confidence Interval) for ESRD accounting for the competing risk of death n=1123, ESRD events=248
1	Non-Hispanic Blacks versus Non-Hispanic Whites, unadjusted	3.35 (2.51-4.48)
2	Model 1 + net acid excretion*	3.21 (2.40-4.30)
3	Model 2 + age, sex	3.25 (2.41-4.39)
4	Model 3 + poverty income ratio	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 + estimated GFR, urinary albumin-to-creatinine ratio	1.68 (1.18-2.38)

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

Abbreviations: GFR, glomerular filtration rate.

Table 3

Race/Ethnicity Stratified Hazard Ratios for the Association of Net Acid Excretion with Risk of Chronic Kidney Disease Progression to End Stage Renal Disease in the National Health and Nutrition Examination Survey III

	Non-Hispanic Blacks n=351, ESRD events=154 Hazard Ratio (95% Confidence Interval) per unit (mEq/d) increase in Net Acid Excretion	Non-Hispanic Whites n=772, ESRD events=94 Hazard Ratio (95% Confidence Interval) per unit (mEq/d) increase in Net Acid Excretion
Net Acid Excretion [*] (unadjusted)	1.31 (1.20-1.44)	1.02 (0.97-1.06)
+ age, sex	1.26 (1.16-1.38)	1.03 (0.98-1.08)
+poverty income ratio	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)
+estimated GFR, urinary albumin-to-creatinine ratio	1.21 (1.12-1.31)	1.08 (0.96-1.20)

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

Abbreviations: GFR, glomerular filtration rate

Table 4

Baseline Characteristics of National Health and Nutrition Examination Survey (NHANES) III Participants with Chronic Kidney Disease Stages 3 or 4 [Defined using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation], Overall and by Race/Ethnicity

Characteristic	All (n=991) %	Non-Hispanic Blacks (n=309) %	Non-Hispanic Whites (n=682) %	P-value
Mean age in years (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	
Male sex	42.9	46.3	42.0	0.27
Poverty Income Ratio				<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
Estimated GFR, median in ml/min per 1.73m^2 (IQR)	47.3 (41.6-55.5)	50.2 (41.1-55.2)	50.8 (44.5-55.6)	0.04
Albuminuria (>30 mg/gm)	29.9	45.1	26.1	<0.0001
Total Calories >2000 Kcal/day	21.7	16.5	23.1	0.09
Net Acid Excretion, median in mEq/day (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 Modification of Diet in Renal Disease study equations[51]. Poverty income ratio 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 mmHg, or use of medication.