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Higher protein intake is associated with increased risk for incident end-stage renal disease among blacks with diabetes in the Southern Community Cohort Study

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Abstract *Background and aims:* Diabetes, a risk factor for end-stage renal disease (ESRD), is associated with impaired protein metabolism. We investigated whether protein intake is associated with ESRD and whether the risk is higher among blacks with diabetes.
Methods and results: We conducted a nested case-control study of ESRD within the Southern Community Cohort Study, a prospective study of low-income blacks and whites in the southeastern US (2002–2009). Through 2012, 1057 incident ESRD cases were identified by linkage with the United States Renal Data System and matched to 3198 controls by age, sex, and race. Dietary intakes were assessed from a validated food frequency questionnaire at baseline. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed from logistic regression models that included matching variables, BMI, education, income, hypertension, total energy intake, and percent energy from saturated and polyunsaturated fatty acids. Mean (±SD) daily energy intake from protein was higher among ESRD cases than controls (15.7 ± 3.3 vs. 15.1 ± 3.1%, $P < 0.0001$). For a 1% increase in percent energy intake from protein, the adjusted ORs (95% CIs) for ESRD were 1.06 (1.02–1.10) for blacks with diabetes, 1.02 (0.98–1.06) for blacks without diabetes, 0.99 (0.90–1.09) for whites with diabetes and 0.94 (0.84–1.06) for whites without diabetes. Protein intake in g/kg/day was also associated with ESRD (4th vs. 1st quartile OR = 1.76; 95% CI: 1.17–2.65).
Conclusion: Our results raise the possibility that among blacks with diabetes, increased dietary protein is associated with increased incidence of ESRD. Studies on how protein intake and metabolism affect ESRD are needed.
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List of abbreviations: ESRD, end-stage renal disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; eGFR, estimated glomerular filtration rate; KDOQI, kidney disease outcomes quality initiative; SCCS, Southern Community Cohort Study; CHC, community health centers; USRDS, united states renal data system; PUFA, polyunsaturated-fatty acids; FFQ, food-frequency questionnaire.

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Introduction

Chronic kidney disease (CKD) is a common public health problem [1,2] that progresses to end-stage renal disease (ESRD), a condition associated with high morbidity and mortality [3–5]. Several studies have consistently demonstrated that blacks have up to 4-fold higher incidence of ESRD than whites [6–8]. While diabetes and hypertension are established as strong risk factors for ESRD among both blacks and whites [9–11], these risk factors do not fully explain the observed racial disparity in ESRD incidence [6]. Dietary factors such as the type and quantity of nutrients consumed could, directly or indirectly through interaction with diabetes [12], contribute to the disparity in ESRD incidence [13].

One particular dietary component that has gained much attention is protein because its metabolism is directly regulated by insulin, and uncontrolled diabetes is associated with impaired protein metabolism [14,15]. While this impairment is more severe in type 1 diabetes, individuals with type 2 diabetes also experience dysregulated protein metabolism, especially in hyperinsulinemic states [16]. It is possible that the resulting protein metabolites could impair kidney function through podocyte injury as shown in animal studies with peptides from diphtheria toxins or high protein diets [17,18]. In addition to kidney damage due to protein metabolites, high protein diets may also damage kidneys through sustained hyperfiltration as previously suggested [19]. Since both high protein consumption and diabetes are known to cause glomerular hyperfiltration and renal hypertrophy [20,21], it is possible that kidney damage due to increased dietary protein could be enhanced in individuals with diabetes.

Indeed, over the past 50 years, several experimental and population-based studies have suggested that increased protein intake may be associated with the development of CKD and its progression to ESRD [19,22,23]. In the Nurses' Health Study, high protein intake was associated with decline in kidney function among patients with reduced kidney function at baseline [24]. The results from observational studies have not been confirmed in a large multiethnic clinical trial. The landmark Modification of Diet in Renal Disease (MDRD) study results were inconclusive, and did not confirm if protein restriction delays or prevents the development of ESRD; importantly, the study was restricted to individuals without diabetes [25]. Meta-analyses examining the effect of dietary protein on kidney function have also been inconclusive [12,26], though some suggest a potential deleterious effect of high protein intake [27]. One major limitation of existing studies is the insufficient number of blacks who could be more susceptible to renal effects of protein because of the high prevalence of insulin resistance and differences in fat-free body composition compared to whites [28,29]. Also, many studies did not include high-risk subgroups (e.g., those with diabetes). When effects of protein were studied among individuals with diabetic kidney disease, reduction in protein intake was associated with a reduction in albumin excretion and in the rate of decline in the estimated glomerular filtration rate (eGFR) [30].

Current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for nutrition in CKD, as well as Institute of Medicine Dietary Reference Intakes, do not endorse prescription of dietary protein restriction among subjects with preexisting kidney disease [31]. Despite American Diabetes Association nutrition guidelines (15%–20% protein intake as percentage of total energy), high protein-low carbohydrate energy–restricted diets (30% protein and 40% carbohydrate) have emerged as an effective weight loss strategy in patients with diabetes [32,33]. Limited literature exists on the effects of protein intake on kidney function in populations that have a high burden of risk factors for kidney disease, including black populations [11], and no study has examined whether racial differences in dietary protein intake contribute to differences in incidence of ESRD. Hence, we sought to evaluate the effect of dietary protein on incidence of ESRD overall and after stratification by race and diabetes. We hypothesized that protein intake is associated with ESRD and that the risk is higher among blacks with diabetes.

Methods

Study population

Participants in the current nested case-control study of ESRD were derived from the SCCS, which enrolled approximately 86,000 black and white men and women, age 40–79, from 12 southeastern states (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia) between 2002 and 2009. Approximately 86% of participants were recruited at community health centers (CHC), which provide primary health and preventive care services for low-income populations [34], while the remaining 14% were recruited via mail-based general population sampling. The study sample for the current study was restricted to CHC-enrollees, which ensured that participants were of similar socioeconomic status and had generally equal access to health care at cohort entry regardless of race. Detailed description of SCCS methods is available on the study website (http://www.southerncommunitystudy.org/) and in previous publications [6,35]. All participants in the SCCS provided written informed consent and the study was approved by Institutional Review Boards of Vanderbilt University Medical Center and Meharry Medical College.

ESRD assessment

Incidence of ESRD was ascertained by linkage of the cohort, using date of birth, Social Security number, and first and last name, with the US Renal Data System (USRDS) from January 1, 2002 to September 1, 2012, the latest date for which data were available. The USRDS registers ESRD cases certified by a physician diagnosis and filed using a medical evidence report form (to the

Medicare ESRD program) or when there is other evidence of chronic dialysis or a kidney transplant irrespective of the GFR [7]. SCCS participants who had a diagnosis of ESRD recorded in the USRDS prior to SCCS enrollment were excluded from our analyses [6]. Three controls were individually matched to each incident ESRD case by age (±5-year categories), sex and race. A total of 4788 participants (1197 cases and 3591 controls) were identified.

Risk factor assessment

At enrollment in SCCS, participant characteristics including demographic variables, socioeconomic status, medical history (e.g., history of diagnosis of hypertension and diabetes), and lifestyle attributes (e.g., smoking and physical activity) were assessed using a standardized computer-assisted personal interview (questionnaire available at http://www.southerncommunitystudy.org/). About half of the participants also provided blood. Dietary intake was assessed using a validated food frequency questionnaire which showed strong agreement (kappa = 0.92) for protein intake estimated from the FFQ and 24 h dietary recalls [36]. Estimates for nutrient intakes were calculated by utilizing sex- and race-specific nutrient databases derived from government food consumption surveys in the southern US [34,35].

Statistical analyses

From the 4788 participants identified by linkage to USRDS, we excluded 327 participants who did not have dietary data from the FFQ. We further excluded 206 participants who were missing data on covariates, leaving a total of 4255 men and women (1057 incident ESRD cases and 3198 matched controls) for the final analyses (Supplemental Fig. 1). Macronutrient (protein, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids (PUFA), and carbohydrate) intakes were expressed as percentages of daily energy intake. For secondary analyses, protein was also expressed in g/kg body weight/day. To test whether the distributions of participant characteristics differed significantly by case-control status, we performed chi-square tests for categorical variables and t-tests for continuous variables. Because of our *a priori* hypothesis that the effect of protein on risk of ESRD may vary by race and diabetes status, we used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for ESRD in relation to protein intake in a model that included matching variables (age, sex and race). This approach allowed us to test whether protein intake interacts with race and diabetes with regard to ESRD. To optimize power, protein intake was modeled as a continuous variable in analyses that tested for interactions. In analyses to assess for confounding and for a dose-response relationship, protein intake variables (% energy or g/kg/day) were modeled as quartiles.

After fitting the basic model (accounting for matching variables), we further adjusted for hypertension (yes vs. no), body mass index (BMI, kg/m^2, continuous), education < high school (yes vs. no), income < $ 15,000 (yes vs. no), smoking status (current and past vs. never), total energy intake and % energy from saturated and polyunsaturated fatty acids as continuous variables. We further investigated whether adjusting for sodium and potassium intake, variables associated with hypertension, significantly altered the associations between protein intake and ESRD. Consistent with our *a priori* hypothesis of different effects of protein on ESRD in diabetes and race strata, we estimated OR (95% CI) for ESRD in different strata from models that included diabetes, race, percent energy from protein and their cross-products.

To better understand the shape of the association, we further investigated the relation between protein intake and ESRD using a 4-knot restricted cubic spline that included covariates listed above [37]. We used 15.75% of protein energy intake (US mean protein intake as per CDC estimate) as a reference value [38].

In a subset of the study sample for whom baseline serum creatinine measurements were available, we conducted sensitivity analyses to examine whether baseline kidney function confounded the association between protein intake and ESRD. We performed logistic regression analyses in a subgroup of 1560 participants with eGFR ≥60 mL/min/1.73 m^2 at baseline. These analyses included 179 incident ESRD cases. All analyses were conducted using Statistical Analyses Systems software version 9.4 (Cary, NC, USA). For main effects and interaction terms, *P*-values ≤0.05 and ≤0.10, respectively, were considered statistically significant.

Results

Baseline dietary and non-dietary characteristics of ESRD cases and controls are shown in Table 1. The age, sex and race distributions of cases and controls were similar given the matched design. Participants in the SCCS cohort who subsequently developed ESRD were more likely to have a history of diabetes (64 vs 23%) and hypertension (84 vs 61%) and had higher dietary protein intake as percentage of daily energy intake (15.7 ± 3.3 vs. 15.1 ± 3.1%, $P < 0.0001$). Compared to controls, ESRD cases also had significantly higher mean BMI and were more likely to have annual income below $15,000 ($P < 0.0001$). Cases and controls were similar with regard to dietary intake of carbohydrate, total fat, saturated fatty acids, monounsaturated fatty acids and PUFA.

Since sex, body composition and diabetes, particularly hyperinsulinemia, are known to affect protein metabolism and to vary by race, we investigated the distribution of potential confounders by race, sex and diabetes status among individuals with and without ESRD to explore for reverse causality. Across race and sex-strata of both ESRD cases and controls, individuals with diabetes were significantly different from those without diabetes with regard to age, smoking, history of hypertension, BMI, dietary intake, income and education (Table 2). Individuals with diabetes reported consuming significantly more protein and PUFA as a percent of total energy than those without

Table 1 Baseline characteristics for ESRD cases and matched controls in SCCS.

Variables	Cases n = 1057	Controls n = 3198	*P*
Age, y[a]	54.5 ± 9.1	54.6 ± 8.8	–
Sex, % women[a]	54.4	55.2	–
Race, % black[a]	86.7	86.8	–
BMI, kg/m^2	31.8 ± 8.2	30.3 ± 7.2	<0.0001
Total energy, kcal/d	2454 ± 1440	2563 ± 1449	0.01
Carbohydrate,% energy	49.7 ± 9.1	49.6 ± 9.1	0.90
Protein, % energy	15.7 ± 3.3	15.1 ± 3.1	<0.0001
MUFA, % energy	13.0 ± 2.5	12.9 ± 2.7	0.68
SFA, % energy	10.1 ± 2.2	10.0 ± 2.3	0.46
PUFA, % energy	8.0 ± 1.7	8.0 ± 1.8	0.88
Fiber, g/day	21.5 ± 12.8	21.8 ± 13.1	0.57
Current smokers, %	37.9	41.0	0.08
Income <$15,000, %	68.3	59.6	<0.0001
Education <HS, %	36.8	34.2	0.12
Hypertension, %	84.2	61.4	<0.0001
Diabetes, %	63.7	23.0	<0.0001

Continuous variables are expressed as mean ± SD and categorical variables as percentage (%).
Abbreviations: ESRD = end-stage renal disease; SCCS = Southern Community Cohort Study; BMI = body mass index; MUFA = monounsaturated fatty acids; SFA = saturated fatty acids; PUFA = polyunsaturated fatty acids; HS = high school.
[a] Matching variable.

diabetes ($P < 0.0001$), and compared to whites with diabetes, carbohydrate consumption was significantly higher ($P < 0.001$) among blacks with diabetes (Table 2). Women with diabetes had significantly higher BMIs than men with diabetes regardless of race ($P < 0.05$).

Except for the protein*race interaction ($P = 0.09$), we did not find evidence of statistically significant interactions between protein and diabetes ($P > 0.10$), but due to our *a priori* hypothesis we present estimates of ESRD risk overall and within race and diabetes strata. The ORs and 95% CIs for the association between protein intake (percentage of daily energy intake) as a continuous variable and ESRD overall and by race and diabetes status are presented in Table 3. In the fully adjusted model, a 1% increase in daily percent energy intake from protein was associated with significantly increased odds of developing ESRD among blacks with diabetes (OR = 1.06; 95% CI: 1.02−1.10) but not among blacks without diabetes (OR = 1.02; 95% CI: 0.98−1.06) or whites with or without diabetes (OR = 0.99; 95% CI: 0.90−1.09 and OR = 0.94; 95% CI: 0.84−1.06, respectively) (Table 3). Further adjustment for sodium and potassium intake did not change the associations appreciably (data not shown). The apparent increased risk of ESRD observed among blacks with diabetes was also evident in analyses in which percent energy from protein was modeled in quartiles to further explore for a dose-response relationship (data not shown). In the total sample and adjusting for confounders listed above, the restricted cubic spline with the US protein intake as the reference (~16% of energy) shows a monotonic increase in the odds of ESRD with increase in dietary protein intake (Fig. 1).

In secondary analyses, we investigated whether protein intake expressed as g/kg/day is associated with ESRD. The median (min, max) protein intake was 0.93 (0.10, 6.46) g/kg/day. Individuals in the highest quartile of protein intake had significantly higher odds of having ESRD than those in the lowest quartile (Table 4). For instance, in the total sample and using the first quartile as the referent (0.47 g/kg/day), the OR (95% CI) for ESRD in the 4th quartile (1.96 g/kg/day) was 1.76 (1.17, 2.65) in the fully adjusted model. As for analyses with percent energy from protein, significant associations were only observed among blacks.

Discussion

In the current prospective study among black and white men and women of generally low socioeconomic status and with a high burden of risk factors for kidney disease, we have demonstrated that higher protein intake is associated with increased incidence of ESRD. Our *a priori* specified subgroup analyses (i.e., by race and diabetes status) revealed that the adverse effect of protein intake on ESRD, albeit statistically significant, was small overall and was restricted to blacks.

A few prior studies have shown a positive correlation between high protein intake and kidney disease [24,39], but these were conducted in predominantly white populations and studied various renal outcomes other than ESRD. In the Nurses' Health Study, Knight et al. showed that increased non-dairy animal protein intake was significantly associated with progressive decline in renal function among women (n = 489) with mild renal insufficiency (i.e., having an eGFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2) [24]. Similarly, in the European Insulin-Dependent Diabetes Mellitus Complications Study of 2696 participants, researchers found direct correlation between dietary animal protein intake and microalbuminuria [40]. Except for blacks in analyses with protein expressed in g/kg/day, we did not find an association between protein intake and ESRD among individuals without diabetes, a finding consistent with results from the 585 kidney disease patients without diabetes enrolled in the MDRD study, in which dietary protein restriction did not delay progression to kidney failure [25]. It is notable that we did not observe an association between protein intake and ESRD among whites with diabetes, possibly due to the small sample size of whites (193 participants with diabetes and 395 without diabetes) in our study. Blacks have more total body protein and fat-free mass when compared to whites of similar BMI [28,29] and blacks are more likely to be obese and have diabetes [41], variables known to predispose to hyperinsulinemia and dysregulated protein metabolism. Thus, our findings are consistent with adverse effects of increased protein intake being more likely to be observed among individuals with deranged metabolism as seen in diabetes and obesity [30].

Consumption of higher amounts of protein has historically been recommended in the setting of obesity and diabetes for weight control [32,42] and is thought to be associated with favorable metabolic adaptations, including

Table 2 Comparison of baseline characteristics of ESRD cases and controls stratified by race, gender and diabetes in SCCS.

Variable	ESRD	Whites (n = 562)				Blacks (n = 3693)			
		Men (n = 238)		Women (n = 324)		Men (n = 1678)		Women (n = 2015)	
		Diabetes (n = 66)	No diabetes (n = 172)	Diabetes (n = 114)	No diabetes (n = 210)	Diabetes (n = 456)	No diabetes (n = 1222)	Diabetes (n = 773)	No diabetes (n = 1242)
Age, y	Cases	55.9 ± 6.9	55.9 ± 9.0	57.3 ± 7.5	55.7 ± 7.5	53.3 ± 8.4	52.0 ± 9.3	55.8 ± 8.9	55.0 ± 10.3
	Controls	58.0 ± 6.5	56.0 ± 7.9	58.0 ± 5.8	57.0 ± 8.0	55.5 ± 8.7	52.8 ± 8.2	58.4 ± 8.9	53.9 ± 9.0
BMI, kg/m^2	Cases	32.9 ± 7.0	28.0 ± 6.2	34.7 ± 8.9	28.3 ± 7.1	30.2 ± 6.6	28.2 ± 6.5	34.6 ± 8.5	31.6 ± 9.2
	Controls	32.5 ± 7.4	28.2 ± 5.5	35.1 ± 7.8	29.1 ± 6.4	30.4 ± 6.1	27.0 ± 5.5	34.5 ± 6.9	31.8 ± 7.6
Total energy, kcal/d	Cases	2268 ± 1127	2627 ± 942	1835 ± 912	1945 ± 840	2794 ± 1528	3265 ± 1691	1930 ± 1104	2454 ± 1383
	Controls	2744 ± 1398	2739 ± 1281	1891 ± 885	1833 ± 772	2732 ± 1502	3211 ± 1624	2041 ± 1202	2253 ± 1226
CHO, % energy	Cases	45.6 ± 7.3	50.0 ± 8.3	49.7 ± 8.0	52.8 ± 9.7	48.7 ± 8.6	47.5 ± 9.7	50.8 ± 8.7	52.0 ± 9.4
	Controls	43.9 ± 6.8	47.8 ± 8.3	48.1 ± 9.3	52.1 ± 8.7	48.1 ± 8.8	47.9 ± 9.1	51.5 ± 8.9	50.8 ± 9.0
Protein, g/kg/d	Cases	1.0 ± 0.5	1.2 ± 0.5	0.9 ± 0.6	1.0 ± 0.7	1.2 ± 0.8	1.4 ± 0.9	0.9 ± 0.6	1.1 ± 0.8
	Controls	1.2 ± 0.8	1.2 ± 0.7	1.0 ± 0.8	0.9 ± 0.6	1.1 ± 0.7	1.4 ± 0.8	0.9 ± 0.6	1.0 ± 0.7
Protein, % energy	Cases	17.3 ± 3.2	15.2 ± 2.5	16.5 ± 3.4	14.6 ± 2.8	15.9 ± 3.2	14.7 ± 3.2	16.2 ± 3.2	14.9 ± 3.3
	Controls	17.3 ± 2.9	15.4 ± 2.7	16.7 ± 3.2	15.5 ± 2.9	15.6 ± 3.4	14.6 ± 3.2	15.7 ± 3.1	14.9 ± 2.9
MUFA, % energy	Cases	13.7 ± 2.7	13.1 ± 2.2	13.1 ± 2.3	11.9 ± 3.0	13.1 ± 2.6	13.0 ± 2.7	12.9 ± 2.5	12.8 ± 2.5
	Controls	14.6 ± 2.5	13.5 ± 2.6	13.6 ± 2.7	12.5 ± 2.5	13.1 ± 3.0	12.8 ± 2.8	12.9 ± 2.6	12.8 ± 2.6
SFA, % energy	Cases	8.1 ± 2.0	7.9 ± 1.8	8.5 ± 1.7	7.6 ± 2.0	7.8 ± 1.5	7.5 ± 1.7	8.3 ± 1.7	8.1 ± 1.5
	Controls	12.1 ± 2.3	11.1 ± 2.5	11.0 ± 2.6	10.4 ± 2.4	10.0 ± 2.4	9.8 ± 2.2	9.8 ± 2.1	9.9 ± 2.2
PUFA, % energy	Cases	8.1 ± 2.0	7.9 ± 1.8	8.5 ± 1.7	7.6 ± 2.0	7.8 ± 1.5	7.5 ± 1.7	8.3 ± 1.7	8.1 ± 1.5
	Controls	8.8 ± 1.5	8.1 ± 1.8	8.6 ± 1.8	8.0 ± 1.8	7.7 ± 1.9	7.5 ± 1.7	8.5 ± 1.8	8.2 ± 1.8
Fiber, g/day	Cases	21.2 ± 12.2	20.4 ± 8.3	18.8 ± 10.4	17.0 ± 7.9	24.2 ± 14.0	24.7 ± 15.0	18.8 ± 10.8	21.6 ± 12.2
	Controls	25.2 ± 14.0	22.3 ± 10.9	18.1 ± 8.7	18.2 ± 9.9	23.6 ± 14.4	24.6 ± 14.8	20.7 ± 11.9	19.9 ± 11.8
Current smokers, %	Cases	26.5	63.0	32.2	61.9	39.0	61.6	21.6	41.3
	Controls	34.4	46.2	34.6	41.8	36.5	59.3	19.7	32.6
Income <$15,000, %	Cases	64.7	48.2	79.7	71.4	64.6	66.2	68.9	75.4
	Controls	56.3	46.9	67.3	62.4	56.7	60.2	69.5	56.9
Education <HS, %	Cases	26.5	29.6	37.3	23.8	35.9	33.8	40.3	39.1
	Controls	46.9	22.8	29.1	25.4	40.3	36.5	42.6	30.4
Hypertension, %	Cases	94.1	74.1	84.8	57.1	89.2	74.2	88.2	83.3
	Controls	68.8	49.0	85.5	51.9	77.3	49.7	83.9	62.1

Abbreviations: BMI = body mass index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; SFA = saturated fatty acids; PUFA = polyunsaturated fatty acid; HS = high school. Continuous variables are expressed as mean ± SD and categorical variables as percentage (%).

Table 3 Odds ratios and 95% confidence intervals for the association between protein intake (percentage of daily energy intake) and ESRD in SCCS.

	Overall (n = 4255)	Blacks		Whites	
		Diabetes (n = 1229)	No diabetes (n = 2464)	Diabetes (n = 180)	No diabetes (n = 382)
Model 1[a]	1.07 (1.04, 1.09)	1.04 (1.01, 1.08)	1.01 (0.97, 1.05)	0.98 (0.89, 1.07)	0.94 (0.84, 1.05)
Model 2[b,c]	1.03 (1.00, 1.06)	1.06 (1.02, 1.10)	1.02 (0.98, 1.06)	0.99 (0.90, 1.09)	0.94 (0.84, 1.06)

Abbreviations: ESRD = End-stage renal disease; SCCS = Southern Community Cohort Study; BMI = Body mass index; SFA = Saturated fatty acids; PUFA = Polyunsaturated fatty acids.

[a] From unconditional logistic regression models adjusted for matching variables (age, sex and race) and showing the odds ratio per 1% increase in energy from protein intake.

[b] Additionally adjusted for: hypertension, BMI, education, household income, smoking, total energy, SFA, PUFA. When conditional logistic regression is used instead, the inferences are similar to those from unconditional logistic regression. For instance, using conditional logistic regression the OR (95% CIs) for ESRD associated with a 1% increase in energy from protein intake was 1.05 (1.01–1.09) for those with diabetes and 1.01 (0.97–1.06) for those without diabetes; the corresponding estimates using ULR were 1.05 (1.01–1.09) and 1.01 (0.97–1.05).

[c] Further adjusting for eGFR in a subset with eGFR ≥60 mL/min/day (n = 1560), did not change the association appreciably. The OR (95% CI) for ESRD associated with a 1% increase in energy from protein intake was 1.09 (1.00, 1.19) among blacks with diabetes, 1.00 (0.90, 1.11) among blacks without diabetes, 0.93 (0.77, 1.12) among whites with diabetes, and 1.09 (0.81, 1.46) among whites without diabetes.

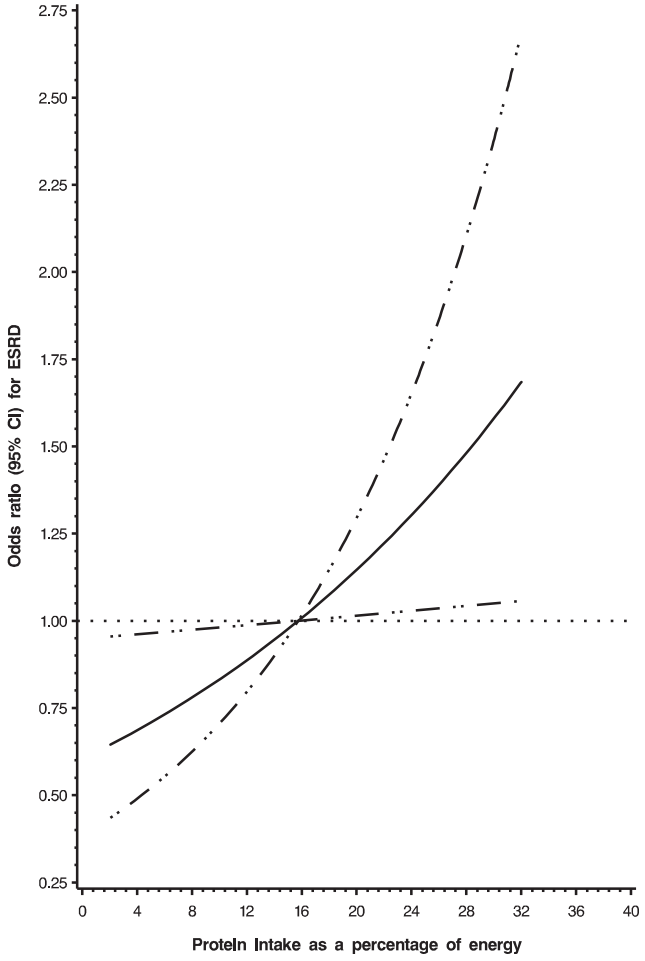

Figure 1 Protein intake and incidence of ESRD in SCCS. Graph showing the relation between percentage protein intake and ESRD in SCCS. The solid line indicates the odds ratio and dashed lines represent the 95% CIs obtained from a restricted cubic spline regression model. The value of 15.75% of protein energy intake (US mean protein intake as per CDC estimate) served as reference value [38].

diet-induced thermogenesis, preservation of lean body mass and improved glycemic control by upregulation of hepatic gluconeogenesis [43,44]. Despite these metabolic advantages, there remains concern that long term high protein consumption may contribute to the development of kidney disease. Our observed association between higher protein intake and ESRD in blacks may have important implications for targeting protein restriction for improved renal outcomes to this population subgroup. If confirmed by additional studies, these findings in blacks have important clinical management implications with widespread applicability.

A widely accepted explanation for the observed adverse effects of protein is hyperfiltration leading to subsequent renal damage, as postulated by Brenner et al. [45] and demonstrated in the recently completed ancillary study to the OmniHeart trial in which high protein intake increased eGFR by about 4 mL/min/1.73 m^2 over a 6-week period [21]. This mechanism may still be valid and partly explain the racial disparity, provided effects of protein on hyperfiltration and subsequently ESRD are modified by other factors such as diabetes and body composition which differ by race. Another plausible explanation is that there are inherent racial differences in protein metabolism which result in alteration of homeostasis of vasoactive compounds and hormones [46] and finally lead to ESRD. It may also be possible that by-products of excess protein metabolism could cause injury to podocytes and other kidney cells resulting in impaired kidney function and subsequent ESRD [17,18]. High protein diet may further lead to downregulation of fibroblast growth factor 21 (FGF-21) resulting in alteration of insulin sensitivity and metabolic responses especially in blacks [47].

Current nutritional guidelines are equivocal regarding the effect of high protein diet on progression of kidney disease and reaching ESRD. While KDOQI guidelines recommend dietary allowance for protein of 0.75 g/kg/d in patients with GFR >30 mL/min/1.73 m^2 (CKD stages 1–3) and 0.6 g/kg/d for patients with GFR <30 mL/min/1.73 m^2 (CKD stage 4–5), UK, Australian, Canadian and European

Table 4 Odds ratios and 95% confidence intervals for the association between protein intake (g/kg body weight/day) and end-stage renal disease in SCCS.

	Odds ratios (95% confidence intervals) by quartiles of protein intake in g/kg/day			
	1 (n = 1063)	2 (n = 1064)	3 (n = 1064)	4 (n = 1064)
Median protein intake, g/kg/d[a]	0.47 [0.38, 0.54]	0.76 [0.68, 0.84]	1.13 [1.03, 1.27]	1.96 [1.65, 2.46]
Overall				
Model 1[b]	1.00	1.04 (0.84, 1.28)	1.01 (0.82, 1.26)	1.11 (0.89, 1.38)
Model 2[c]	1.00	1.15 (0.92, 1.43)	1.21 (0.94, 1.56)	1.62 (1.13, 2.32)
Model 3[d]	1.00	1.18 (0.93, 1.48)	1.27 (0.96, 1.67)	1.76 (1.17, 2.65)
Blacks with diabetes				
Model 1[b]	1.00	1.07 (0.80, 1.44)	0.91 (0.67, 1.23)	1.12 (0.80, 1.57)
Model 2[c]	1.00	1.13 (0.83, 1.53)	1.05 (0.75, 1.47)	1.55 (0.99, 2.43)
Model 3[d]	1.00	1.16 (0.85, 1.59)	1.11 (0.78, 1.57)	1.70 (1.04, 2.77)
Blacks without diabetes				
Model 1[b]	1.00	0.94 (0.66, 1.36)	1.12 (0.79, 1.58)	1.13 (0.81, 1.57)
Model 2[c]	1.00	1.09 (0.75, 1.59)	1.40 (0.96, 2.03)	1.75 (1.13, 2.73)
Model 3[d]	1.00	1.12 (0.77, 1.64)	1.47 (0.99, 2.18)	1.92 (1.18, 3.10)
Whites with diabetes				
Model 1[b]	1.00	1.45 (0.68, 3.06)	0.95 (0.41, 2.22)	0.72 (0.31, 1.70)
Model 2[c]	1.00	1.69 (0.79, 3.63)	1.17 (0.49, 2.81)	1.14 (0.46, 2.82)
Model 3[d]	1.00	1.77 (0.82, 3.82)	1.24 (0.51, 2.99)	1.24 (0.49, 3.14)
Whites without diabetes				
Model 1[b]	1.00	1.08 (0.43, 2.75)	1.27 (0.51, 3.13)	1.46 (0.55, 3.88)
Model 2[c]	1.00	1.29 (0.50, 3.32)	1.55 (0.62, 3.90)	2.25 (0.81, 6.22)
Model 3[d]	1.00	1.32 (0.51, 3.42)	1.62 (0.64, 4.09)	2.44 (0.87, 6.87)

Abbreviations: eGFR = estimated glomerular filtration rate; SCCS = Southern Community Cohort Study; BMI = body mass index; SFA = Saturated fatty acids; PUFA = Polyunsaturated fatty acids.

[a] Values are medians [25th, 75th percentile].

[b] Model 1 is an unconditional logistic regression model that included matching variables (age, sex and race) and diabetes.

[c] Model 2 is additionally adjusted for hypertension, education, household income, smoking, total energy, SFA and PUFA.

[d] Model 3: Additionally adjusted for BMI. When analyses were further adjusted for eGFR at baseline among 1560 participants with eGFR $\geq$60 mL/min/1.73 m^2, the odds ratios in the total sample were attenuated but a monotonic positive association between protein intake and ESRD was retained. For instance, the OR (95% CIs) for the 1st, 2nd, 3rd and 4th quartiles of protein intake (g/kg/d) were 1.00, 0.78 (0.43, 1.44), 1.40 (0.73, 2.67) and 1.95 (0.77, 4.97), respectively.

guidelines have no dietary protein restriction in patients with early stage CKD (stages 1–3) and are in line with recommended daily intake for the general population (0.75–1.0 g/kg/day or 15%–20% of their total energy) [48,49]. A protective role for low protein diet has been suggested in patients with diabetic kidney disease [15]; however, no nutritional recommendations are made for individuals who are obese, or pre-diabetic. In addition, race- and sex-specific recommendations remain elusive [31]. It is notable that low protein intake (<16% of energy) in our study may be associated with a lower incidence of ESRD. This result is interesting in that low protein intake, especially when used to replace some carbohydrate, may be beneficial especially among particular subgroups such as those with diabetes. This notion is supported by a meta-analysis showing that moderate protein intake improves blood pressure, a risk factor for CKD and ESRD [48], and by results from the Framingham Heart Study that showed protein intake is inversely associated with blood pressure [50]. In view of recent studies [32,51] showing that regardless of the macronutrient targeted, various popular diets are equivalent in achieving weight loss, our results support avoidance of high protein intake when macronutrients are considered for weight loss in blacks. On the other hand, it is imperative to avoid excessive carbohydrate or solid fat intake in order to replace the limited protein intake in these patients, especially ones with diabetes mellitus.

Our study has several strengths. The SCCS is a large population-based unique cohort comprising black and white participants of comparable generally low socioeconomic status. Detailed information on ESRD risk factors and confounders were obtained at baseline, and ESRD was ascertained for the entire cohort in a complete and systematic manner. There are, however, some limitations to our study. First, FFQ data were self-reported and no updated dietary intakes were obtained so as to study effects of long-term, sustained protein intake. Our FFQ collected dietary history for the previous 12 months and it is possible that a participant's diet at baseline may change during follow-up. Secondly, the small number of white participants in our cohort limited the range of protein intake and precluded detailed analyses in this group. The limited range of protein intake (5th percentile was 10.3% and 95% percentile 20.6% of energy) in our cohort also limits the interpretation of the odds ratios estimated at the extremes of the distribution of protein intake shown in Fig. 1. Finally, levels of serum creatinine as a marker of kidney function at baseline and/or follow up are only available for less than half of the study participants, making it impossible to fully account for baseline differences in kidney function. Nonetheless, the positive

monotonic association between protein intake and ESRD remained after adjusting for eGFR in a subgroup with eGFR $\geq$60 mL/min/1.73 m^2.

In summary, this study demonstrated that increased protein intake in blacks is associated with ESRD, a finding consistent with metabolic studies suggesting that diabetes and obesity (which are common among blacks) alter protein metabolism. Improved understanding of the relationship between dietary protein intake and renal function may help identify population subgroups at high risk for ESRD that could benefit from interventions such as avoidance of excessive protein consumption.

Authors' contributions

Study concept and design: Malhotra, Ikizler, Lipworth, Kabagambe.

Acquisition, analysis, or interpretation of data: Malhotra, Ikizler, Lipworth, Kabagambe.

Drafting of the manuscript: Malhotra, Ikizler, Lipworth, Kabagambe.

Critical revision of the manuscript for important intellectual content: Cavanaugh, Ikizler, Lipworth, Kabagambe, Blot.

Statistical analysis: Malhotra, Lipworth, Kabagambe.

Obtained funding: Ikizler, Blot.

Study supervision: Ikizler, Lipworth, Kabagambe.

Conflict of interest

All authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2016.07.009.

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