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Dietary Protein Intake and Change in Estimated GFR in the Cardiovascular Health Study

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Abstract

Objective—With aging, kidney function declines, as evidenced by reduced glomerular filtration rate. It is controversial whether or not high protein intake accelerates the kidney function decline.

Research Methods & Procedures—We examined whether dietary protein is associated with change in kidney function (mean follow-up 6.4 (SD=1.4, range = 2.5 to 7.9) years in the Cardiovascular Health Study ($n=3,623$). We estimated protein intake using a food frequency questionnaire (FFQ) and estimated glomerular filtration rate (eGFR) from cystatin C. Associations between protein intake and kidney function were determined by linear and logistic regression models.

Results—Average protein intake was 19% of energy intake (SD=5%). Twenty-seven percent ($n=963$) of study participants had rapid decline in kidney function, as defined by ($eGFR_{cysC} > 3$ mL/min per 1.73 m²). Protein intake (characterized as g/day and % energy/day), was not associated with change in eGFR ($P>0.05$ for all comparisons). There were also no significant associations when protein intake was separated by source (animal and vegetable).

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All authors contributed substantively to the conception and design of the study; generation, collection, assembly, analysis and/or interpretation of data; and drafting or revision of the manuscript; approval of the final version of the manuscript.

Conclusion—These data suggest that higher protein intake does not have a major impact on kidney function decline among elderly men and women.

Keywords

kidney; glomerular filtration rate; vegetable protein; animal protein; macronutrients

Introduction

The 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines recommend lowering protein intake to 0.8 g/kg/day among all individuals with chronic kidney disease[1], although the outcomes of such a diet have not been fully explored outside a clinical trial setting. A systematic review recently summarized the evidence from four studies reporting associations between dietary protein intake and renal function as inconclusive.[2]

The recommendation that individuals with chronic kidney disease avoid protein intake is based primarily upon data defining low estimated glomerular filtration rate (eGFR) based upon rises in serum creatinine. [1] However, protein intake is a known confounder that can increase creatinine among patients with normal and stable renal function. Therefore, studies using cystatin C, which is independent of muscle mass[3], as a measure of kidney function are warranted. Data from the Modification in Diet and Renal Disease Trial suggest that creatinine, but not cystatin C, is affected by changes in dietary protein among individuals with moderate to severe kidney disease.[4] Differences in both the magnitude[5, 6] and direction[7] of associations have been reported comparing creatinine and cystatin C as markers of kidney function. Within the Women's Health Initiative, protein intake was not associated with impaired kidney function estimated using cystatin C in cross-sectional, observational analyses[8] among postmenopausal women.

The goal of this study is to examine longitudinal associations between protein intake and kidney function among a cohort of men and women having a wide range of kidney function. Most studies investigating optimal dietary protein intake have been conducted either in healthy individuals or individuals with overt kidney disease, so it would be informative to study the association between protein intake and longitudinal changes in kidney function in a broader population setting. We examined associations between baseline protein intake and change in eGFR within the Cardiovascular Health Study (CHS) of men and women 65 years and older having a wide range of eGFR. We also examined whether associations differed by protein source (i.e. animal versus vegetable).

Materials and Methods

Study Population

The CHS is a community-based longitudinal study of adults who were 65 years of age or older at baseline.[9] A main cohort of 5,201 participants was recruited between 1989 and 1990 from 4 US communities (Sacramento County, Calif., USA; Forsyth County, N.C., USA; Washington County, Md., USA; Allegheny County, Pa., USA). Eligible participants

were sampled from Medicare eligibility lists in each area. Subjects were excluded if they were institutionalized, required a proxy to give consent, were planning to move out of the area within 3 years after recruitment, required a wheelchair in the home, were receiving hospice care, or were undergoing radiation or chemotherapy for cancer. Institutional review board approval for the data collection procedures of the CHS was obtained at each of the 4 clinical sites and at the Data Coordinating Center (University of Washington). This analysis consisted of the 3,623 CHS participants who completed the FFQ at baseline and had cystatin C and creatinine measures from the baseline visit in 1989–1990 and the follow-up visit in 1996–1997. Men and women were excluded for implausible energy intakes per the dietary assessment, defined as <500 kcal or >3500 kcal for women and <600 kcal or >4000 kcal for men (n=87). [10]

Outcome Measurement

The outcome was seven year change in eGFR. Cystatin C was measured from frozen samples using a BNII nephelometer (Siemens; Deerfield, Ill, USA), and creatinine was assayed from frozen sera by a colorimetric method (Ektachem 700, Eastman Kodak).[11] For the primary analysis, eGFR was estimated from cystatin C using equations based on cystatin C (CKD_cys) alone. As a sensitivity analysis, we repeated models estimating GFR by incorporating creatinine along with cystatin C (CKD_cre-cys). [12]

Exposure Measurement

CHS participants reported dietary intake at the baseline visit using a picture-sort food-frequency questionnaire that demonstrated age and sex-adjusted Pearson correlations of 0.50 (95% CI 0.29 to 0.68) for energy and 0.44 (95% CI 0.14 to 0.67) for protein with six monthly 24-hour dietary recall interviews among a subset of 95 CHS participants. [13] Protein intake was characterized as absolute (g) and relative to energy intake (as a percentage of total energy (% energy)). [14]

Covariate Measurement

Demographic characteristics (age, family, education, race/ethnicity), medical history (prevalent cardiovascular disease [heart failure, coronary heart disease (myocardial infarction, angina, revascularization), stroke and transient ischemic attack, hypertension, diabetes mellitus (defined by use of an oral hypoglycemic agent, insulin or a fasting glucose level ≥ 126 mg/dl), cholesterol (HDL and LDL), lipid lowering medications, and other health-related characteristics (physical activity, smoking, alcohol consumption) were obtained at CHS baseline. BMI was computed using measured height and weight at baseline (weight in kg / height² in m²). All nutrition variables were estimated from the FFQ.

Statistical Analysis

We first described baseline characteristics of the CHS participants by quartiles of protein intake. To evaluate the association between protein intake and kidney function decline, we used linear mixed models with random intercepts and slopes to estimate and compare linear trends in mean eGFR. This approach takes into account the correlation of observations by participant. We further assessed associations of protein intake with rapid decline in kidney

function defined as a dichotomous outcome using logistic regression. Annualized change in $\text{eGFR} < -3 \text{ mL/min/1.73m}^2/\text{year}$ was used to define rapid decline in kidney function, because this threshold has been associated with an increased risk of mortality in this population. [15, 16] Protein (g/day and %energy/day) was evaluated as a continuous predictor per SD and categorized into quartiles. We used nested models with serial adjustment to understand the role of CKD risk factors chosen *a priori* that might explain any observed differences by protein intake. Model 1 adjusted for age, sex, BMI, and energy intake. Model 2 additionally adjusted for Model 1 covariates as well as coronary heart disease, heart failure, stroke, smoking, cholesterol (HDL and LDL), lipid lowering medications, diabetes, hypertension, level of education, physical activity, and alcohol consumption. Effect modification by baseline eGFR was evaluated ($</\geq 60 \text{ mL/min per } 1.73 \text{ m}^2$).

All analyses were performed using Stata (Version 12.1, StataCorp, College Station, TX) and SPSS statistical software (Version 16.0.1, IBM Corporation, Armonk, NY). Two-tailed p-values <0.05 were considered significant.

Results

At CHS baseline, approximately one-quarter (23%, $n=836$) of participants had impaired kidney function, as defined by $\text{eGFR}_{\text{Cys}} < 60$. Mean decline in kidney function was 2.0 (SD=2.3) mL/min/year (Table 1). Over the follow-up period, 27% ($n=963$) of participants had rapid decline in kidney function, as defined by annualized change in estimated GFR $> 3 \text{ mL/min/1.73 m}^2$. Participants consuming greater amounts of protein as a proportion of energy were more likely to be female, completed more formal education, and have a higher BMI compared to participants consuming less protein (Table 1).

There were no significant associations between eGFR and protein intake, irrespective of whether it was characterized as g/day or %energy/day (Table 2). Likewise, there were no significant associations between eGFR and protein intake whether eGFR was expressed as a continuous variable or as a categorical variable (Tables 2 and 3) after accounting for potential confounding factors. Irrespective of whether protein intake was characterized as g/day or %energy, there were no significant associations between protein intake and rapid kidney function decline in the series of models (Table 3). Models evaluating protein source (animal/vegetable) as the exposure were also null in fully adjusted models (Table 4). There was no evidence for effect modification by baseline eGFR ($</\geq 60 \text{ mL/min per } 1.73 \text{ m}^2$) (Table 5). Sensitivity analyses using both creatinine and cystatin C to estimate GFR corroborated with results using cystatin C alone (data not shown).

Discussion

Within a cohort of men and women aged 65 and older, there was little evidence for an association with changes in kidney function when protein intake was expressed in absolute terms or relative to energy intake. Though evidence from long-term intervention studies would be needed to draw causal inferences, these data suggest that higher protein intake

does not adversely impact kidney function among older adults with normal or slightly impaired kidney function, estimated by both cystatin C and creatinine.

A major contribution of the current analysis was using cystatin C to evaluate longitudinal relationships between protein intake and kidney function. Previous studies used serum creatinine to estimate kidney function, but creatinine excretion is positively associated with muscle mass. Higher protein intake may result in changes in serum creatinine concentration that indicate changes in muscle mass rather than kidney function. Cystatin C may be a better biomarker of impaired kidney function and mortality compared to serum creatinine, but its concentration is positively associated with adiposity. [17] [18]

Our findings are consistent with recent literature suggesting that dietary protein is not harmful for kidney function. [19] Two weight loss trials comparing changes in eGFR based on creatinine reported no significant differences between participants randomized to dietary regimens assigned to low-carbohydrate, high protein (>20% energy from protein) compared to comparison diets after one (n=118)[20] and two (n=318)[21] years. Evidence from short-term intervention and observational studies among older adults without overt kidney disease is also emerging. The OMNI-Heart Trial, a randomized 3-period crossover feeding trial, reported a diet comprised of 25% energy from protein (predominantly vegetable protein) improved eGFR after six weeks, as estimated using cystatin C, by 3.8 (95% CI 2.5 to 5.1) mL/min/1.73m² compared to diets comprised of 15% energy from protein[23]. A community-based, short-term (12-week) randomized, controlled combined resistance exercise and supplementation trial (n=237) among older adults (mean age 73.6 ± 5.7 years) reported a 4.4 mL/min/1.73 m² increase in eGFR, as estimated by creatinine, irrespective of whether participants were assigned to a milk, whey, or carbohydrate supplement. [22]

The Nurses' Health Study (NHS) reported no associations between higher protein intake and kidney function decline over an 11-year follow-up period among women (0.25 mL/min. 1.73m², 95% CI = -0.78 to 1.28) change in GFR estimated using creatinine per 10-g increase in protein intake. [24] In subgroup analyses, investigators reported an adverse association between protein intake derived from nondairy animal sources, and change in eGFR (-1.21 mL/min.1.73m², 95% CI= -2.34 to -0.33) per 10-g increase in non-dairy animal protein intake among women with mild impairment in kidney function (defined as eGFR < 80 mL/min per 1.73 m²). [25]

Research examining whether restricting protein intake leads to preservation of kidney function has been conducted predominantly in patients with moderate to severe kidney insufficiency. [26] Most evidence supports moderate restriction of protein intake, but follow-up has typically been short. [27–29] The largest trial, the Modification of Diet in Renal Disease trial (MDRD) demonstrated no effect of protein restriction on kidney function. [30, 31] Long-term follow up of study participants from the MDRD trial reported those assigned to the restricted protein intake group had an increased risk of mortality (adjusted hazard ratio=1.92, 95% CI = 1.15 to 3.20). [32]

Proteins from plant sources deliver lower nonvolatile acid load and have decreased bioavailability of phosphorous suggesting they are better protein sources for patients with

CKD. We considered protein source (animal/vegetable) in our analysis using separate regression models characterizing the exposure of interest as animal protein, vegetable protein, and proportion of total protein from animal sources. These models provided no evidence for a difference in the association between protein intake and kidney function by protein source. However, lack of a biomarker for protein source limits our ability to make inferences related to this question.

Limitations must be considered when interpreting these results. Since this was a prospective observational study rather than a randomized trial, this study informed whether higher protein intake is associated with rate of kidney function decline as estimated by cystatin C and creatinine, but measurement error or bias may have led to an attenuation of associations. If women with reduced kidney function were advised by their physicians to limit protein intake, this could partially explain observed associations. Dietary protein intake was assessed using a food frequency questionnaire at a single time point and kidney function was estimated using biomarkers, so measurement error may be obscuring the ability to detect significant associations between protein intake and kidney function. [33]

In conclusion, these data suggest no adverse association between protein intake and kidney function among older adults without overt CKD. We examined associations independent of demographic and lifestyle characteristics and comorbidities. Emerging evidence that higher protein intake may contribute to reduced risk of frailty[34] and protein supplementation may facilitate recovery from illness[35] among older adults; however, it is important to evaluate long-term potential health risks and benefits before recommending changes to protein recommendations for older adults.

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Table 1

Participant Characteristics by Quartile of protein, %kcal

Range	Total	Q1 < 16.5	Q2 16.5 – 19.0	Q3 19.1 – 21.1	Q4 21.2
N	3623	894	902	912	915
Age *	72 (5)	73 (5)	72 (5)	72 (5)	72 (5)
Female	2226 (61%)	506 (57%)	531 (59%)	567 (62%)	622 (68%)
African American	153 (4%)	33 (4%)	46 (5%)	41 (5%)	33 (4%)
Education *					
None-grade 9	543 (15%)	173 (19%)	128 (14%)	136 (15%)	106 (12%)
HS graduate	1375 (38%)	357 (40%)	351 (39%)	324 (36%)	343 (38%)
Professional	1699 (47%)	362 (41%)	422 (47%)	450 (50%)	465 (51%)
Smoking					
Former	1549 (43%)	355 (40%)	382 (42%)	399 (44%)	413 (45%)
Current	383 (11%)	108 (12%)	78 (9%)	98 (11%)	99 (11%)
Alcohol, >3 drinks/wk *	680 (19%)	134 (15%)	159 (18%)	198 (22%)	189 (21%)
BMI, kg/m ² *	26.5 (4.5)	26.1 (4.4)	26.4 (4.3)	26.6 (4.4)	27.0 (4.8)
Physical activity, kcal/wk	1215[475,2565]	1118[465,2520]	1230[485,2679]	1294[479,2599]	1196[475,2430]
Hypertension	1988 (55%)	496 (56%)	468 (52%)	496 (54%)	528 (58%)
Diabetes *	488 (14%)	97 (11%)	117 (13%)	127 (14%)	147 (16%)
Prevalent disease					
Coronary Heart Disease	653 (18%)	170 (19%)	146 (16%)	166 (18%)	171 (19%)
Heart Failure	102 (3%)	36 (4%)	14 (2%)	30 (3%)	22 (2%)
Stroke	122 (3%)	35 (4%)	28 (3%)	33 (4%)	26 (3%)
eGFR _{Cys-CKDEPI} *, ml/min	73 (18)	71 (17)	73 (18)	74 (18)	74 (18)
eGFR _{Cys-CKDEPI} < 60 *, ml/min	836 (23%)	230 (26%)	217 (24%)	197 (22%)	192 (21%)
eGFR _{Cys-CKDEPI} *, ml/min/yr	-2.0 (2.3)	-1.9 (2.3)	-1.91 (2.1)	-2.0 (2.6)	-2.1 (2.3)
HDL, mg/dL *	54 (16)	53 (15)	54 (15)	55 (16)	56 (18)
LDL, mg/dL *	131 (36)	128 (36)	130 (35)	131 (35)	133 (36)
Daily Intake					

Range	Total	Q1 <16.5	Q2 16.5–19.0	Q3 19.1–21.1	Q4 21.2
N	3623	894	902	912	915
Energy intake, kcal*	1927[1551,2355]	1750[1446,2147]	1952[1559,2409]	2050[1685,2476]	1925[1547,2335]
Protein, %kcal*	19 (5)	15 (1)	18 (1)	20 (1)	24 (6)
Protein, g/kg body wt*	1.36 (0.54)	1.00 (0.37)	1.31 (0.48)	1.52 (0.49)	1.63 (0.56)
Carbohydrate, %kcal*	48 (9)	50 (9)	48 (8)	46 (8)	45 (8)
Fat, %kcal*	34 (7)	35 (8)	33 (7)	33 (7)	33 (7)
Animal protein, g*	66 (27)	43 (16)	61 (22)	75 (23)	86 (26)
Vegetable protein, g*	29 (11)	26 (10)	30 (10)	31 (10)	28 (11)
Lipid lowering meds	200 (6%)	42 (5%)	40 (4%)	68 (8%)	50 (6%)

Estimates are Mean (SD) or Mean [Inter-quartile range]. HS=high school; BMI=body mass index; eGFR=estimated glomerular filtration rate; HDL=high density lipoprotein; LDL=low density lipoprotein

* p-value for linear trend < 0.05

Table 2

Association between baseline total protein intake and change in kidney function ($eGFR_{cysC}/year$) using linear regression.

	<i>N</i>	Model 1[*] β (95% CI)	Model 2^{**} β (95% CI)
Protein, %energy/day			
Continuous (per SD =5 increase)	3623	-0.003 (-0.07, 0.07)	0.003 (-0.08, 0.08)
Quartiles of protein			
< 16.5	894	0 (ref)	0 (ref)
16.5 --- 19.0	902	-0.04 (-0.22, 0.13)	-0.04 (-0.21, 0.14)
19.1 – 21.1	912	-0.07 (-0.25, 0.11)	-0.05 (-0.23, 0.13)
21.2	915	-0.14 (-0.32, 0.04)	-0.09 (-0.27, 0.09)
Protein (g/day)			
Continuous (per SD =33 increase)	3623	-0.05 (-0.17, 0.06)	-0.03 (-0.15, 0.09)
Quartiles of protein			
< 71	963	0 (ref)	0 (ref)
71 – 92	928	0.07 (-0.12, 0.26)	0.08 (-0.12, 0.28)
93 – 119	951	0.11 (-0.12, 0.34)	0.14 (-0.10, 0.37)
120	808	0.07 (-0.23, 0.36)	0.10 (-0.20, 0.41)

* Model 1 adjusts for age, gender, race, BMI, total energy intake

** Model 2 adjusts for Model 1 covariates plus prevalent CHD, prevalent HF, prevalent stroke, smoking, HDL, LDL, lipid lowering medications, HTN, DM, level of education, physical activity, alcohol consumption

Table 3

Association between baseline total protein intake and rapid kidney function decline ($eGFR_{cysC_CKDEPI} > 3$) using linear regression.

	Total N	Rapid decline N	Model 1* OR (95% CI)	Model 2** OR (95% CI)
Protein, %energy/day				
Continuous (per SD =5 increase)	3623	963	1.04 (0.95, 1.14)	1.03 (0.94, 1.13)
Quartiles of protein				
< 16.5	894	239	1.00 (ref)	1.00 (ref)
16.5 – 19.0	902	228	1.00 (0.79, 1.25)	1.01 (0.80, 1.28)
19.1 – 21.1	912	249	1.17 (0.93, 1.47)	1.16 (0.92, 1.46)
21.2	915	247	1.08 (0.86, 1.36)	1.06 (0.85, 1.34)
Protein, g/day				
Continuous (per SD =33 increase)	3623	963	1.10 (0.95, 1.28)	1.09 (0.94, 1.26)
Quartiles of protein				
< 71	963	267	1.00 (ref)	1.00 (ref)
71 – 92	928	239	0.93 (0.73, 1.18)	0.91 (0.72, 1.17)
93 – 119	951	251	1.03 (0.77, 1.37)	0.99 (0.74, 1.32)
120	808	206	1.08 (0.75, 1.55)	1.03 (0.71, 1.49)

* Model 1 adjusts for age, gender, race, BMI, total energy intake

** Model 2 adjusts for Model 1 covariates plus prevalent CHD, prevalent HF, prevalent stroke, smoking, HDL, LDL, lipid lowering medications, HTN, DM, level of education, physical activity, alcohol consumption

Table 4

Association between baseline animal and vegetable protein intake and rapid kidney function decline
($eGFR_{cysC_CKDEPI} > 3$) using linear mixed models regression

	Total N	Rapid decline N	Model 1* OR (95% CI)	Model 2** OR (95% CI)
Animal protein (%energy) per SD =5.0 increase	3623	963	1.03 (0.95, 1.11)	1.02 (0.94, 1.10)
Vegetable protein (%energy) per SD =1.5 increase	3623	963	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)
Animal Protein (%energy) Quartiles				
< 10.9	918	246	1.00 (ref)	1.00 (ref)
10.9 – 13.1	913	225	0.93 (0.75, 1.15)	0.93 (0.75, 1.16)
13.2 – 15.5	901	253	1.13 (0.92, 1.41)	1.12 (0.90, 1.39)
15.6	891	239	1.03 (0.83, 1.27)	1.00 (0.80, 1.24)
Vegetable Protein (%energy) Quartiles				
< 4.8	831	231	1.00 (ref)	1.00 (ref)
4.8 – 5.7	889	221	0.90 (0.72, 1.12)	0.90 (0.72, 1.12)
5.8 – 6.6	947	259	1.06 (0.85, 1.31)	1.05 (0.84, 1.30)
6.7	956	252	1.00 (0.81, 1.24)	1.00 (0.80, 1.25)
Animal protein (g/day) per SD =27 increase	3623	963	1.08 (0.96, 1.21)	1.07 (0.95, 1.20)
Vegetable protein (g/day) per SD =11 increase	3623	963	1.00 (0.88, 1.14)	1.01 (0.88, 1.15)
Animal Protein (g/day) Quartiles				
< 46	925	255	1.00 (ref)	1.00 (ref)
46 – 65	969	259	1.05 (0.84, 1.33)	1.03 (0.82, 1.31)
66 – 86	921	238	1.00 (0.77, 1.29)	0.97 (0.75, 1.26)
87	808	211	1.14 (0.84, 1.56)	1.10 (0.80, 1.52)
Vegetable Protein (g/day) Quartiles				
< 21	901	262	1.00 (ref)	1.00 (ref)
21 – 28	926	241	0.84 (0.66, 1.06)	0.82 (0.64, 1.05)
29 – 36	940	245	0.94 (0.72, 1.23)	0.94 (0.71, 1.12)
37	856	215	0.83 (0.60, 1.15)	0.83 (0.60, 1.16)

* Model 1 adjusts for age, gender, race, BMI, total energy intake

** Model 2 adjusts for Model 1 covariates plus prevalent CHD, prevalent HF, prevalent stroke, smoking, HDL, LDL, lipid lowering medications, HTN, DM, level of education, physical activity, alcohol consumption

Table 5

Association between baseline total protein intake and rapid kidney function decline ($eGFR_{cysC_CKDEPI} > 3$) stratified by baseline eGFR status.

	Total N	Rapid decline N	Model 1* OR (95% CI)	Model 2** OR (95% CI)
Protein (g/day) Quartiles				
p-value for interaction = 0.194				
eGFR ≥ 60				
Continuous protein (g/day) per SD =33 increase	2787	783	1.06 (0.91, 1.24)	1.05 (0.89, 1.23)
eGFR < 60				
Continuous protein (g/day) per SD =33 increase	836	180	1.02 (0.73, 1.42)	1.00 (0.71, 1.41)
Protein (%energy/day) Quartiles				
p-value for interaction = 0.68				
eGFR ≥ 60				
Continuous protein (%energy) per SD =5 increase	2787	783	1.02 (0.93, 1.13)	1.02 (0.92, 1.12)
eGFR < 60				
Continuous protein (%energy) per SD =5 increase	836	180	0.98 (0.77, 1.23)	0.97 (0.76, 1.24)

* Model 1 adjusts for age, gender, race, BMI, total energy intake

** Model 2 adjusts for Model 1 covariates plus prevalent CHD, prevalent HF, prevalent stroke, smoking, HDL, LDL, lipid lowering medications, HTN, DM, level of education, physical activity, alcohol consumption