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Effect of a High-Protein Diet on Kidney Function in Healthy Adults: Results From the OmniHeart Trial

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Abstract

Background

Consumption of a diet high in protein can cause glomerular hyperfiltration, a potentially maladaptive response, which may accelerate the progression of kidney disease.

Study Design

An ancillary study of the OmniHeart trial, a randomized 3-period crossover feeding trial testing the effects of partial replacement of carbohydrate with protein on kidney function.

Setting & Participants

Healthy adults (N=164) with prehypertension or stage 1 hypertension at a community-based research clinic with a metabolic kitchen.

Intervention

Participants were fed each of 3 diets for 6 weeks. Feeding periods were separated by a 2- to 4-week washout period. Weight was held constant on each diet. The 3 diets emphasized carbohydrate, protein, or unsaturated fat; dietary protein was either 15% (carbohydrate and unsaturated fat diets) or 25% (protein diet) of energy intake.

Outcomes

Fasting serum creatinine, cystatin C, and β_2 -microglobulin levels, estimated glomerular filtration rate (eGFR).

Measurements

Serum creatinine, cystatin C, and β_2 -microglobulin collected at the end of each feeding period.

Results

Baseline cystatin C-based eGFR was 92.0 ± 16.3 (SD) mL/min/1.73 m². Compared with the carbohydrate and unsaturated fat diets, the protein diet increased cystatin C-based eGFR by ~ 4 mL/min/1.73 m² ($P < 0.001$). The effects of the protein diet on kidney function were independent of changes in blood pressure. There was no significant difference between the carbohydrate and unsaturated fat diets.

Limitations

Participants did not have kidney disease at baseline.

Conclusions

A healthy diet rich in protein increased eGFR. Whether long-term consumption of a high-protein diet leads to kidney disease is uncertain.

Keywords: Diet, macronutrients, randomized controlled trial, glomerular filtration rate, cystatin C, β_2 -microglobulin

In observational studies and clinical trials, the effects of dietary protein on the development or progression of chronic kidney disease (CKD) have been inconsistent.¹⁻⁸ However, in animal models and short-term studies of humans, high-protein diets can induce renal hypertrophy⁹ and glomerular hyperfiltration,¹⁰ which are early maladaptive responses to abnormal renal hemodynamics and an antecedent to kidney injury and kidney disease progression.^{11,12} The impact of increased dietary protein intake on kidney function in those without evidence of kidney disease is less clear: part of the challenge in establishing these effects in trials is the reliance on creatinine-based equations for estimated glomerular filtration rate (eGFR).

Dietary protein consumption increases serum creatinine level through protein catabolism rather than decreased clearance.^{13,14} Hence, serum creatinine may be less reliable for estimating GFR or estimating a glomerular hyperfiltration response in studies that manipulate dietary protein.¹⁵ Alternative biomarkers of kidney function include cystatin C and β_2 -microglobulin (B2M), which are believed to be unaffected by the changes in creatinine level that accompany higher protein intake.

In this ancillary study of the OmniHeart (Optimal Macro-Nutrient Intake) trial, we determined the effects of partial replacement of carbohydrate with protein on kidney function in healthy adults using novel markers (cystatin C and B2M). We also assessed for high-protein diet-induced effects on glomerular filtration using a cystatin C-based estimating equation.

METHODS

OmniHeart Trial Overview

The rationale, design, and main effects of the OmniHeart trial have been published previously.^{16,17} In brief, the OmniHeart trial was a multicenter, large-scale, investigator-initiated, randomized, crossover, feeding study sponsored by the National Heart, Lung and Blood Institute; the effects of 3 diets with different macronutrient profiles on traditional cardiovascular disease risk factors (blood pressure and blood lipids) in the setting of stable weight were tested. All 3 diets differed in macronutrient composition (see [Table 1](#)), but otherwise were similar: a carbohydrate-rich diet (55% of total kilocalories) similar to the DASH (Dietary Approaches to Stop Hypertension) diet,¹⁸ a diet (referred to as the unsaturated fat diet) in which 10% of kilocalories from carbohydrate were replaced with unsaturated fats, and a diet (protein diet) in which 10% of kilocalories from carbohydrates were replaced with protein.

Table 1

Nutrient Targets and Macronutrient Content of Diets

Nutrient	Carbohydrate Diet ^a	Unsaturated Fat Diet ^b	Protein Diet ^c
Fat (kcal%)	27	37	27
Saturated (kcal%)	6	6	6
Polyunsaturated (kcal%)	8	10	8
Monounsaturated (kcal%)	13	21	13
Protein (kcal%)	15	15	25
Protein from plant (%)	36	36	48
Carbohydrates (%)	58	48	48
Fiber (g/1,000 kcal)	14.3	14.3	14.3
Cholesterol (mg/1,000 kcal)	71	71	71

Abbreviation: kcal%, percentage of total calories.

Source: Appel et al.¹⁷

^aCarbohydrate diet was similar to the DASH (Dietary Approaches to Stop Hypertension) diet.

^bUnsaturated fat diet emphasized monounsaturated fat in the form of olive oil, canola oil, safflower oil, and a variety of nuts and seeds to meet targeted fatty acid distributions.

^cPlant protein sources included legumes, grains, nuts, and seeds.

All 3 diets were designed to be “healthy” and were low in saturated fat (6% kcal) and cholesterol (150 mg/d). Furthermore, the diets provided other nutrients (calcium, magnesium, potassium, and dietary fiber) at recommended levels and were reduced in sodium (2,300 mg/d). The food sources used for protein replacement primarily were vegetable-based. Institutional review boards at Johns Hopkins University, Brigham & Women’s Hospital, and the Harvard School of Public Health approved the study protocol.

Participant Recruitment

Trial participants were adult men and women residing in and around Boston, MA, and Baltimore, MD, between April 2003 and June 2005. Participants were 30 years and older with systolic (SBP) and diastolic blood pressure (DBP) ranging from 120-159 or 80-99 mm Hg, respectively. Exclusion criteria included a diagnosis of diabetes, kidney disease (eGFR <60 mL/min/1.73 m²), history of cardiovascular disease, more than 2 alcoholic drinks per day for men or 1 alcoholic drink per day for women, or use of medications for the treatment of hypertension or hyperlipidemia.¹⁷

Controlled Feeding

Participants were randomly assigned to 1 of 6 dietary sequences.¹⁷ There was a 2- to 4-week washout period between assigned diets. Each diet was designed using commonly available foods. Calorie targets were determined for each participant based on body size, sex, and physical activity level. The goal was to keep weight within 2% of participants' baseline values. Participants were encouraged to maintain the same activity levels and alcohol consumption throughout the study. Adherence to the feeding protocol was >95% of trial person-days; in other words, all study foods were eaten without the introduction of nonstudy foods.¹⁷ Participants kept a diary in which they listed their consumption of nonprotocol foods; in other words, any foods not given by study staff.

Of the initial 191 participants randomly assigned to 1 of the 6 diet sequences, 164 completed at least 2 feeding periods and were included in analyses: 160 completed all 3 feeding periods and 4 participants completed 2 feeding periods only. There were 4 missed feeding periods in total: unsaturated fat diet (n = 2), carbohydrate diet (n = 1), and protein diet (n = 1). From run-in to the end of the first period, weight decreased by an average of ~1 kg in all 3 diets. However, mean end-of-period weights were similar across the 3 diets.¹⁷

Measurement of Main Outcomes

Fasting serum was collected in 2003-2005 from each participant at baseline and at the completion of each 6-week feeding period. Blood samples were allowed to clot at room temperature for 15 minutes, centrifuged at 2°C, and stored at -70°C. Cystatin C and B2M subsequently were measured with particle-enhanced immunonephelometric assays (N Latex Cystatin C assay and N Latex β_2 -microglobulin assay; Siemens). Both cystatin C and B2M are novel markers of kidney function¹⁹ thought to be influenced less by factors affecting serum creatinine level, such as muscle mass and diet.²⁰ eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) cystatin C equation,²¹ which was chosen because it was developed in a population sample that included individuals who, like participants in the OmniHeart trial, did not have CKD. Serum creatinine also was measured from serum specimens using standardized laboratory assays, and creatinine-based eGFR was calculated using the CKD-EPI creatinine equation.²²

Other Measurements and Variables

Data collected by questionnaire included age, sex, race (white, black, or other), ethnicity (Hispanic or non-Hispanic), current smoking status (yes or no), and education (high school diploma or lower and college education or higher). Laboratory and physical examination variables included body mass index, hypertension status, homeostasis model assessment (HOMA) index, high sensitivity C-reactive protein level, serum triglyceride levels, serum high-density lipoprotein (HDL) cholesterol level, and serum low-density lipoprotein (LDL) cholesterol level.

Body mass index was calculated using baseline height and weight measurements and further dichotomized to ≥ 30 kg/m² (obese) or < 30 kg/m² (nonobese). SBP and DBP were based on the average of 3 sets of blood pressure baseline measurements obtained during separate screening visits at least 1 week apart.

Participants were considered hypertensive (yes or no) at baseline if they had an average baseline SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg. Serum insulin concentration, measured at baseline, was used to quantify insulin resistance. The HOMA index was calculated using $\text{HOMA} = [(\text{fasting plasma insulin concentration in } \mu\text{U/mL}) \times (\text{fasting plasma glucose concentration in mmol/L})] / 22.5$. HOMA was dichotomized based on a previously described clinical cutoff of ≥ 2.6 .²³ High-sensitivity C-reactive protein was measured using enzymatic assays in blood samples measured at baseline and dichotomized using a cutoff of 2.0 mg/dL. Similarly, traditional assays were used to measure total triglycerides and HDL cholesterol. LDL cholesterol levels were estimated by the Friedewald equation.²⁴ Triglyceride, HDL cholesterol, and LDL cholesterol levels were categorized using clinical cutoffs: ≥ 150 mg/dL for triglycerides, < 40 mg/dL in men and < 50 mg/dL in women for HDL cholesterol, and ≥ 130 mg/dL for LDL cholesterol.

Statistical Analysis

All analyses were performed using Stata, version 11.1 (Stata-Corp). The main outcomes examined were serum cystatin C, B2M, creatinine, and eGFR levels. The primary comparisons were between-diet contrasts of outcomes measured at the end of each dietary period among the 3 diets. We also compared end-of-period with baseline values for eGFR and kidney markers. Both between-diet and baseline comparisons were performed with generalized estimating equation regression, using robust variance estimation and an exchangeable working correlation. Between-diet differences in eGFR also were examined by strata of factors thought to modify the diets' effects on kidney function; namely race, hypertension status, LDL cholesterol level, serum glucose level, and HOMA index. Sensitivity analyses were performed using independent and unstructured working correlations for all generalized estimating equation analyses and random-effects linear regression.

To assess whether changes in kidney function were independent of dietary effects on blood pressure,¹⁷ we examined the association between baseline change in eGFR and change in SBP or DBP using linear regression. We also performed sensitivity analyses comparing the end-of-period eGFR between diets adjusted for SBP, DBP, or hypertensive status.

Kidney marker correlations were calculated using baseline serum samples with Pearson coefficients and Spearman coefficients and plotted with fitted linear regression curves. We also examined the differences between cystatin C and creatinine levels as markers of eGFR by performing sensitivity analyses of the baseline change and end-of-period comparisons using the CKD-EPI creatinine equation.²² In addition, we examined the baseline change and end-of-period effects on cystatin C level for each diet adjusted for creatinine level. $P < 0.05$ was considered statistically significant for all comparisons.

RESULTS

Participants

[Table 1](#) lists the macronutrient composition of each diet. Characteristics of the study population at baseline are listed in [Table 2](#). Overall, participants had a mean age of 53.5 ± 10.9 years and were 55% African American and 45% women. At baseline, mean cystatin C-based eGFR was 92.0 ± 16.3 (SD) mL/min/1.73 m², mean cystatin C level was 0.89 ± 0.13 mg/dL, mean B2M level was 2.01 ± 0.48 mg/dL, and mean serum creatinine level was 0.78 ± 0.18 mg/dL ([Table 3](#)). At baseline, cystatin C level was correlated highly with B2M level, with Spearman correlation of 0.76 (Pearson $r = 0.80$). In contrast, cystatin C and B2M levels were not

correlated highly with serum creatinine level, with Spearman correlations of 0.24 (Pearson $r = 0.24$) and 0.09 (Pearson $r = 0.14$), respectively. See [Fig S1 \(provided as online supplementary material\)](#) for scatterplots with Spearman correlations between main outcome variables at baseline.

Table 2

Baseline Characteristics of Trial Participants

Characteristic	Overall (N = 164) ^a
Age (y)	53.5 ± 10.8
Female sex	73 (45)
Race	
African American	90 (55)
Non-Hispanic white	65 (40)
Other	9 (5)
Body mass index (kg/m ²)	30.2 ± 6.1
Baseline SBP ≥140 or DBP ≥90 mm Hg	32 (19)
Creatinine-based eGFR (mL/min/1.73 m ²)	104.6 ± 16.4
HOMA insulin resistance index ^b	1.79 ± 2.17
Current smoking status	18 (11)
hs-CRP >2.0 mg/dL	79 (51)
Triglycerides ^b	109.1 ± 1.76
HDL cholesterol	50.0 ± 16.1
LDL cholesterol	129.2 ± 32.4
Education ≤HS diploma	33 (20.1)

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HS, high school; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

^aTotal number is not always equal to 164 due to missing data.

^bPresented as the geometric mean due to a non-normal distribution.

Table 3

Baseline and Change From Baseline in Biomarkers of Kidney Function by Diet Assignment

Biomarkers	No.	Baseline Value	Change From Baseline by Diet					
			Carbohydrate		Unsaturated Fat		Protein	
			Mean β (95% CI)	P	Mean β (95% CI)	P	Mean β (95% CI)	P
eGFR (mL/min/1.73 m ²) ^a	156	92.0 ± 16.3	-0.43 (-1.93 to 1.07)	0.6	-0.77 (-2.01 to 0.47)	0.2	3.81 (2.54 to 5.09)	<0.001
SCysC (mg/dL)	157	0.89 ± 0.13	0.00 (-0.01 to 0.01)	0.8	0.01 (-0.01 to 0.02)	0.3	-0.03 (-0.05 to -0.02)	<0.001
B2M (mg/dL)	157	2.01 ± 0.48	0.03 (-0.02 to 0.08)	0.3	0.04 (0.00 to 0.08)	0.04	-0.05 (-0.10 to -0.01)	0.03
SCr (mg/dL)	164	0.78 ± 0.18	0.03 (0.02 to 0.05)	<0.001	0.03 (0.02 to 0.05)	<0.001	0.02 (0.00 to 0.03)	0.04
SBP (mm Hg)	164	131.2 ± 9.4	-8.13 (-9.52 to 6.74)	<0.001	-9.37 (-10.66 to -8.09)	<0.001	-9.51 (-10.85 to -8.17)	<0.001
DBP (mm Hg)	164	77.0 ± 8.2	-4.11 (-4.94 to -3.27)	<0.001	-4.83 (-5.62 to -4.04)	<0.001	-5.23 (-6.05 to -4.42)	<0.001

Note: Baseline values are given mean ± SD. Conversion factor for creatinine in mg/dL to μ mol/L, $\times 88.4$.

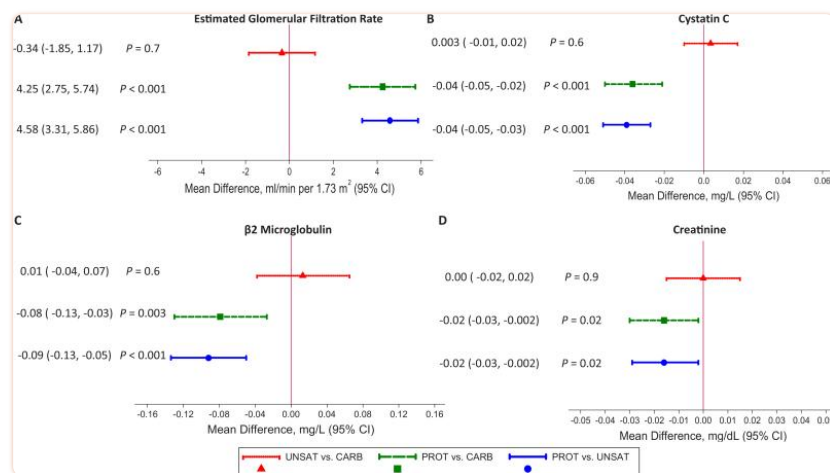
Abbreviations: B2M, β_2 -microglobulin; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SCr, serum creatinine; SCysC, serum cystatin C; SD, standard deviation.

^aCKD-EPI cystatin C equation.²¹

Changes From Baseline and End-of-Period Comparisons

When end-of-period measurements were compared with baseline values, the protein diet showed mean increases in eGFR of 3.81 mL/min/1.73 m² ($P < 0.001$) and serum creatinine level of 0.02 mg/dL ($P = 0.04$) and mean changes in cystatin C level of -0.03 mg/dL ($P < 0.001$) and B2M level of -0.05 mg/dL ($P = 0.03$). There was less consistency in changes from baseline when the diets were either carbohydrate or unsaturated fat (Table 3). Although significant increases in creatinine levels from baseline were observed during both the carbohydrate and unsaturated fat diets (both $P < 0.001$), the unsaturated fat but not the carbohydrate diet was associated with a significant increase in B2M level. Baseline changes in eGFR by subgroup resembled the overall effects for each of the 3 diets (Table S1).

There was no difference in between-diet comparisons in eGFR between the carbohydrate and unsaturated fat diets (Fig 1). However, the protein diet was associated with increased eGFR compared with both the carbohydrate and unsaturated fat diets (both $P < 0.001$), and cystatin C, B2M, and creatinine levels were all lower at the end of the protein diet compared with the carbohydrate or unsaturated fat diet.

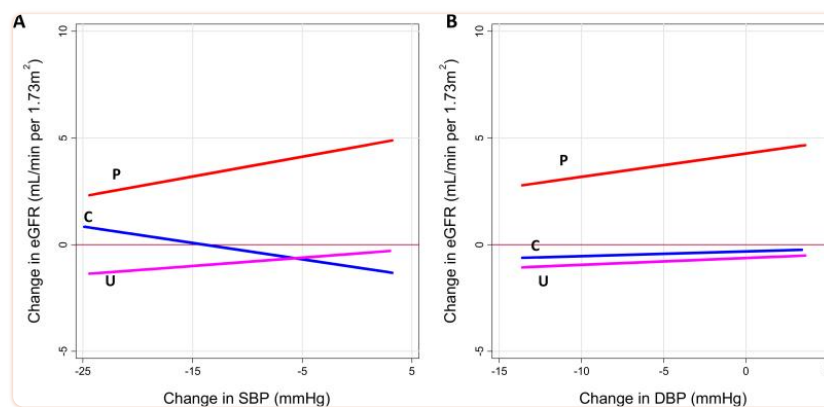


[Figure 1](#)

Between-diet comparisons and 95% confidence intervals (CIs) of (A) estimated glomerular filtration rate (eGFR), (B) cystatin C level, (C) β_2 -microglobulin level, and (D) serum creatinine level measured at the end of each feeding period. The 3 feeding periods were the unsaturated fat diet (UNSAT) versus the carbohydrate diet (CARB; triangle), protein diet (PROT) versus the CARB (square), and PROT versus the UNSAT (circle).

Correlations With Blood Pressure Changes

To understand whether the related change in eGFR was due to changes in blood pressure, we used simple linear regression and plotted the change in eGFR and changes in SBP and DBP ([Fig 2](#)). Regardless of diet, none of the associations between change in eGFR and SBP or DBP were statistically significant. Furthermore, between-diet comparisons of end-of-period eGFR showed that the protein diet was associated with an increased eGFR of about 4-5 mL/min/1.73 m² even after adjusting for concurrent SBP, DBP, or hypertensive status.



[Figure 2](#)

Linear fits of the diet-specific change in estimated glomerular filtration rate (eGFR) and change in (A) systolic (SBP) and (B) diastolic blood pressure (DBP). β coefficients resulting from linear regression between change in eGFR and change in SBP were -0.08 ($P = 0.4$), 0.04 ($P = 0.6$), and 0.09 ($P = 0.2$) for the carbohydrate (C), unsaturated fat (U), and protein diets (P), respectively. With regard to DBP, β coefficients were 0.02 ($P = 0.9$), 0.03 ($P = 0.8$), and 0.11 ($P = 0.4$), respectively. Linear fits were truncated at the 5th and 95th percentiles of change in blood pressure.

Sensitivity Analyses

Sensitivity analyses using a creatinine-based eGFR equation showed a significant increase in eGFR of 1.7 mL/min/ 1.73 m² ($P = 0.02$) for the protein diet versus the carbohydrate diet and 1.5 mL/min/ 1.73 m² ($P = 0.03$) versus the unsaturated fat diet. Hence, the creatinine-based equation showed similar relative differences in eGFR effects using B2M or cystatin C level and between the protein and other diets. However, the magnitudes of eGFR effects were less, and notably, creatinine-based eGFR decreased in all 3 diets, but less so in the protein diet, which likely was a result of the relatively higher eGFR in the protein diet group. There was no significant difference between the unsaturated fat and carbohydrate diets ($P = 0.8$). Similarly, a sensitivity analysis examining baseline change and between-diet differences in cystatin C levels after adjusting for creatinine level showed that there was a significant change of about -0.04 to -0.03 (both $P < 0.001$) during the protein diet compared with baseline values as well as compared with the carbohydrate and unsaturated fat diets.

DISCUSSION

This trial found that a high-protein diet increased eGFR. In contrast to diets that were high in carbohydrate or unsaturated fat, the high-protein diet decreased serum B2M and serum cystatin C levels, reflecting a significant increase in eGFR of ~ 4 mL/min/ 1.73 m². These findings suggest that a higher proportion of calories from protein in healthy adults increases eGFR, but whether long-term consumption of a high-protein diet leads to kidney injury is uncertain.

Compared with contemporary high-protein diets, the protein diet is similar or higher in protein content. The carbohydrate diet (55% of kilocalories from carbohydrates) is similar to the DASH diet (58% of kilocalories from carbohydrates), a healthy diet that emphasizes fruits, vegetables, and low-fat dairy products and was low in saturated fat, total fat, and cholesterol.¹⁸ In the carbohydrate diet, 15% of total kilocalories were de-

rived from protein, whereas in the protein diet, 25% of total kilocalories were from protein. Compared with other common diets, this percentage of total kilocalories from protein is greater than in the Mediterranean-style diets and the Ornish diet (both <20%), similar to the South Beach and Atkins diets (about 27%-30%), and less than the Zone diet (35%).²⁵ However, it should be noted that replacement of carbohydrate with protein in the protein diet was accomplished using ~50% vegetable-based protein from minimally processed high-quality food sources. As a result, the findings presented in this study may not directly correspond to these popular diets.

Several biological mechanisms could explain higher eGFRs with consumption of a higher protein diet. Laboratory studies in rats have shown that amino acid infusions increase nephron plasma flow by decreasing afferent arteriole resistance.²⁶ This effect may be mediated through reductions in signaling molecules of the tubuloglomerular feedback system, mitigating arteriolar constriction,²⁷⁻²⁹ or through increases in neuronal nitric oxide synthase in the kidney cortex, reducing afferent arteriolar tone.^{30,31} Also, high-protein diets lead to an increase in size and volume of glomeruli, a process mediated by vascular endothelial growth factor in some animal models.³²

Our results may have been influenced by biological factors that affect biomarker production or elimination. However, we believe the increase in eGFR during the protein diet likely was real as opposed to an artifact from protein-induced effects on cystatin C.³³ Although adjustment for serum creatinine level attenuated the end-of-study decreases in cystatin C level compared to baseline that were observed during the protein diet, the decrease in cystatin C level remained significant. This could be interpreted as a GFR-independent effect of protein on cystatin C. However, during the protein diet, decreases also were observed in levels of B2M, a distinct biomarker with an independent biosynthetic mechanism, suggesting that the protein diet is affecting a common pathway between the 2 markers, namely GFR.

The diet-induced changes in eGFR observed in this trial were independent of effects of the diet on blood pressure, supporting the existing literature.¹² As described previously, baseline reductions in SBP and DBP were similar among the 3 dietary arms and were greater at the end of the protein diet compared to the carbohydrate diet (SBP/DBP, -1.4/-1.2 mm Hg; $P < 0.001$).¹⁷ Despite these decreases in blood pressure, eGFR increased during the protein feeding period. A plot of the change in eGFR versus SBP (Fig 2) showed that although most participants on the protein diet experienced SBP changes of 0 to -15 mm Hg, eGFR was higher (about 5-7 mL/min/1.73 m²) across all diet-related changes in blood pressure. These results suggest that protein affects eGFR independently of changes in blood pressure. However, we did not measure the effects of macronutrients on renal hemodynamics or renal vascular autoregulation.

The eGFR changes during the protein diet calculated using a cystatin C-based equation²¹ differed quantitatively from corresponding eGFR changes calculated using a creatinine-based equation²²; specifically, +3.8 mL/min/1.73 m² (cystatin C) versus -0.8 mL/min/1.73 m² (creatinine). This difference in eGFR is reflected by serum cystatin C level having decreased during the protein diet, whereas serum creatinine level increased during the protein diet. Higher protein diets may increase serum creatinine levels,³³ which would mask the underlying changes in GFR. These observations illustrate the clinical utility of cystatin C level as a more sensitive marker of kidney function in the context of higher protein consumption.

To further corroborate our findings of a relationship between the protein diet and markers of kidney function, we examined effects on B2M, another small freely filtered protein in which serum levels can be used to evaluate kidney function.³⁴ A subunit of the major histocompatibility class I molecule, B2M is metabolized and reabsorbed solely by the proximal tubule.³⁵ As a result, alterations in glomerular filtration influence serum concentrations. At baseline in this trial, we observed a high Spearman correlation (r) of -0.78 between

eGFR and B2M level. Similarly, Spearman correlation between cystatin C and B2M levels was 0.76. This suggests that both B2M and cystatin C level may be effective biomarkers of kidney function in adults with kidney function in the normal range.

Our analysis has a number of strengths. The OmniHeart trial had a large size and was diverse; >50% were African American. Its crossover design permits examination of changes caused by diets within the same individuals. In addition, high adherence and follow-up in each dietary period reduce the risk of bias. OmniHeart also is an isocaloric feeding study in which participant weight was maintained, minimizing confounding due to weight change. Recently, a randomized trial that compared a low-carbohydrate high-protein diet with a low-fat weight-loss diet in generally healthy overweight and obese adults reported no effects of the high-protein diet on eGFR or urine albumin excretion at 2 years.³⁶ However, both groups were assigned to behavior modification therapy, which resulted in significant weight loss (6.6 vs 7.8 kg, respectively). In contrast, by design, our participants were not allowed to lose weight and were provided all their food by the study. Hence, our results are unique in addressing macronutrient effects on eGFR in the setting of isocaloric nutrient intake. Finally, the diets are plausible, with a macronutrient distribution that could be achieved in the general population.¹⁷

This analysis also has limitations. Feeding periods were only 6 weeks and outcomes were surrogate markers of disease rather than clinical events. This limits our ability to speculate regarding the long-term consequences of a high-protein diet on the development of CKD. With regard to kidney function, GFR was not measured directly. As a result, GFR estimates may not reflect actual change in kidney function if diet independently alters the serum concentration of an estimating equation-associated biomarker, for example, serum creatinine. Despite this, there was no apparent effect on cystatin C level. Another limitation pertains to non-standard cystatin C measurements. Although this does not affect the relative comparisons of cystatin C levels between dietary periods, it may reduce the comparability of the absolute estimates with other studies. Finally, the protein diet differed from the unsaturated fat and carbohydrate diets not only by the proportion of total protein, but also by the proportion of vegetable protein as well as vegetable to animal protein ratio. The effects of these differences in protein type cannot be determined in this trial.

In conclusion, a diet with a higher proportion of calories from protein increased eGFR. These findings suggest that increased protein intake might have adverse consequences on kidney function in the long term.

Supplementary Material

Supplementary Figure

[Click here to view.](#) ^(220K, docx)

Supplementary Table

[Click here to view.](#) ^(16K, docx)

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Footnotes

Financial Disclosure: The authors declare that they have no other relevant financial interests.

SUPPLEMENTARY MATERIAL

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2012.10.017>) is available at www.ajkd.org

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