The Impact of Protein Intake on Renal Function Decline in Women with Normal Renal Function or Mild Renal Insufficiency

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Background: **In individuals with moderate to severe renal insufficiency, low protein intake may slow renal function decline. However, the long-term impact of protein intake on renal function in persons with normal renal function or mild renal insufficiency is unknown.**

Objective: **To determine whether protein intake influences the rate of renal function change in women over an 11-year period.**

Design: **Prospective cohort study.**

Setting: **Nurses' Health Study.**

Participants: **1624 women enrolled in the Nurses' Health Study who were 42 to 68 years of age in 1989 and gave blood samples in 1989 and 2000. Ninety-eight percent of women were white, and 1% were African American.**

Measurements: **Protein intake was measured in 1990 and 1994 by using a semi-quantitative food-frequency questionnaire. Creatinine concentration was used to estimate glomerular filtration rate (GFR) and creatinine clearance.**

Results: **In multivariate linear regression analyses, high protein intake was not significantly associated with change in estimated GFR in women with normal renal function (defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2). Change in estimated GFR in this subgroup over the 11-year period was 0.25 mL/min per 1.73 m^2 (95% CI, −0.78 to 1.28 mL/min per 1.73 m^2) per 10-g increase in protein intake; the change in estimated GFR was 1.14 mL/min per 1.73 m^2 (CI, −3.63 to 5.92 mL/min per 1.73 m^2) after measurement-error adjustment for protein intake. In women with mild renal insufficiency (defined as an estimated GFR > 55 mL/min per 1.73 m^2 but <80 mL/min per 1.73 m^2), protein intake was significantly associated with a change in estimated GFR of −1.69 mL/min per 1.73 m^2 (CI, −2.93 to −0.45 mL/min per 1.73 m^2) per 10-g increase in protein intake. After measurement-error adjustment, the change in estimated GFR was −7.72 mL/min per 1.73 m^2 (CI, −15.52 to 0.08 mL/min per 1.73 m^2) per 10-g increase in protein intake, an association of borderline statistical significance. High intake of nondairy animal protein in women with mild renal insufficiency was associated with a significantly greater change in estimated GFR (−1.21 mL/min per 1.73 m^2 [CI, −2.34 to −0.33 mL/min per 1.73 m^2] per 10-g increase in nondairy animal protein intake).**

Conclusions: **High protein intake was not associated with renal function decline in women with normal renal function. However, high total protein intake, particularly high intake of nondairy animal protein, may accelerate renal function decline in women with mild renal insufficiency.**

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The potential effects of dietary protein consumption on renal function in persons with normal renal function or mild renal insufficiency have important public health implications given the prevalence of high-protein diets and protein supplementation (1–3). The American Heart Association's most recent revised guidelines suggest that a sustained high-protein diet may have adverse effects on renal function (4), but no data support this claim in people with normal renal function or mild renal insufficiency. However, there are theoretical reasons for such concern, including the fact that a high-protein diet may acutely increase the glomerular filtration rate (GFR) (5, 6) and possibly cause intraglomerular hypertension, which may lead to progressive loss of renal function (7).

Many clinical studies have demonstrated that protein restriction may slow renal function decline compared with usual protein intake in patients with moderate renal insufficiency (8–11). However, these results remain controversial because the largest study of protein restriction in patients with moderate renal insufficiency found no significant benefit (12). A recent meta-analysis estimated that among patients with moderate renal insufficiency, GFR decreases by 0.53 mL/min less per year in those who follow a low-protein diet compared with those who do not (13). The authors of this meta-analysis suggested that benefits of a low-protein diet might be more apparent with longer follow-up. Some experimental evidence also suggests that animal proteins may play a greater role in the progression of renal disease than vegetable proteins (14–16), but not all studies have confirmed these results (17). In experiments in humans, meat protein acutely increases GFR compared with dairy protein (18).

The primary purpose of our study was to examine the association between total protein intake and renal function decline over an 11-year period in women with normal renal function or mild renal insufficiency. We also examined the association between intake of different types of protein and renal function decline.

METHODS

Study Sample

The Nurses' Health Study (NHS) began in 1976, when 121 700 female nurses 30 to 55 years of age completed a detailed questionnaire regarding health-related information (19). Since then, questionnaires have been sent to participants biennially. Information on lifestyle factors and new medical diagnoses is collected every 2 years, and a detailed dietary questionnaire is mailed every 4 years (20).

The creatinine measurements used to estimate renal function were initially obtained as part of a study designed to assess the association between analgesic use and change in renal function. We limited our study sample to the 32 826 participants who provided a blood sample in 1989. Of these, we identified women who reported using acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs 15 or more days per month on both the 1992 and the 1998 biennial questionnaires. For comparison, we also included a group of women who reported no use of any of the three analgesics on the 1990, 1992, and 1998 biennial questionnaires. After we excluded women with a history of cancer (except nonmelanoma skin cancer) or cardiovascular disease (myocardial infarction, angina, stroke, or transient ischemic attack), 4238 women were eligible for inclusion. A supplementary questionnaire was mailed in 1999 to collect detailed information on current and lifetime use of analgesics from these 4238 women, and 3876 women (91%) returned it. A second blood sample was collected in 2000 from women who originally provided a specimen in 1989. From those who returned the supplementary questionnaire and provided a second blood sample, we selected all women with lifetime consumption of at least 1501 tablets of one of the analgesics and a random sample of women who had taken fewer than 1501 tablets. Of the 1769 women selected, 20 were missing a creatinine value from either 1989 or 2000, 4 were excluded because they had a creatinine concentration less than 0.4 mg/dL (<35 μmol/L) in 1989, 33 were excluded because they reported a history of abnormal kidney function, 21 were excluded because they had an estimated baseline GFR less than or equal to 55 mL/min per 1.73 m^2, and 67 were excluded because data were missing for other covariates. Therefore, a total of 1624 women were included in the current study. Of these, 98% were white and 13 (1%) were African American.

Assessment of Dietary Protein Intake and Other Nutritional Variables

In 1990, participants were asked to complete a semiquantitative food-frequency questionnaire that inquired about the average intake of specified foods and beverages during the previous year (coinciding with the first blood specimen). In 1994, the questionnaire was repeated. The reproducibility and validity of this questionnaire have been described in detail elsewhere (20). Nutrient intake, including protein intake, was computed from the reported frequency of consumption of each specified unit of food or beverage by using published data on the nutrient content of the specified portions (20). Using this information, we were able to estimate protein consumption from different sources, as well as intake of phosphorus and animal fat. We examined total protein intake continuously (per 10-g increment) and in quintiles and examined nondairy animal, dairy, and vegetable protein continuously. The Pearson correlation coefficient (r) between total protein intake in 1990 and 1994 was 0.51 ($P < 0.001$). Total protein intake also correlated with phosphorus intake ($r = 0.64$; $P < 0.001$) and animal fat intake ($r = 0.32$; $P < 0.001$).

Nutrient values were adjusted for total energy intake by regressing total caloric intake on absolute nutrient intake (21, 22). Because total energy intake for a given person tends to be fixed within a narrow range, variations in nutrient intake are largely attributable to changes in composition of diet, not the total amount of food consumed. Energy-adjusted values reflect the nutrient composition of the diet independent of the total amount of food consumed. In addition, adjustment for energy reduces any variation introduced by questionnaire responses that underreported or overreported intake, thus improving the accuracy of nutrient measurements (21, 22).

Ascertainment of Other Factors

Age, weight, height, diabetes, hypertension, smoking, alcohol use, hypercholesterolemia, analgesic medication use, and antihypertensive medication use were examined as potentially important confounders. We used 1989 weight to calculate the estimated 1989 creatinine clearance and used 1998 weight to calculate the estimated 2000 creatinine clearance, since a weight from the 2000 questionnaire was not yet available. Diabetes, hypertension, and hypercholesterolemia were recorded if a woman reported any of these diagnoses from 1976 to 1996. Smoking status, alcohol consumption, and analgesic use were obtained from the 1990 questionnaire. Smoking was classified as current smoker, past smoker, or nonsmoker; alcohol intake was classified as none, 0.1 to 14.9 g/d, or at least 15 g/d; and acetaminophen, aspirin, and nonsteroidal anti-inflammatory use was classified according to days of use per month. We used information on use of antihypertensive medica-

Context

Although dietary protein restriction appears to slow the decline in renal function among patients with moderate renal insufficiency, its effect on normal and mildly decreased renal function is unknown.

Contribution

Among women from the Nurses' Health Study with normal renal function, protein intake was not associated with decline in glomerular filtration rate (GFR). In women with mild renal insufficiency, high protein intake, particularly of nondairy animal origin, was associated with more rapid than expected decline in GFR.

Implications

High protein intake is associated with declining GFR among women with mild renal insufficiency. A causal connection has not been demonstrated. Additional studies are needed to show that reducing protein intake protects the kidney.

–The Editors

Table 1. **Demographic, Laboratory, Dietary, Exposure, and Disease-Specific Information***

Variable	Participants with Normal Renal Function (*n* = 1135)†	Participants with Mild Renal Insufficiency (*n* = 489)‡
Age in 1989 (range), *y*	54.8 ± 6.6 (42–68)	56.8 ± 6.5 (42–68)
Weight in 1989 (range), *kg*	68.9 ± 15.2 (40.8–163.3)	69.8 ± 13.5 (36.3–125.2)
Creatinine concentration in 1989 (range), *mg/dL*	0.68 ± 0.08 (0.40–0.88)	0.88 ± 0.07 (0.77–1.09)
Creatinine concentration in 2000 (range), *mg/dL*	0.76 ± 0.14 (0.44–1.83)	0.89 ± 0.14 (0.50–1.59)
Estimated GFR in 1989 (range), *mL/min per 1.73 m^2*	98.4 ± 15.2 (80.0–187.4)	71.0 ± 6.5 (55.1–79.9)
Estimated GFR in 2000 (range), *mL/min per 1.73 m^2*	84.9 ± 16.6 (29.1–156.2)	69.1 ± 13.4 (35.0–129.2)
Estimated creatinine clearance in 1989 (range), *mL/min*	105.1 ± 19.9 (69.4–243.3)	78.7 ± 11.7 (36.1–114.2)
Estimated creatinine clearance in 2000 (range), *mL/min*	85.7 ± 19.3 (34.1–178.9)	70.7 ± 15.7 (30.9–131.5)
Protein intake (range), *g/d*	76.7 ± 13.6 (19.1–163.7)	76.2 ± 13.3 (37.0–143.0)
Nondairy animal protein intake (range), *g/d*	40.3 ± 14.9 (0–134.0)	40.4 ± 14.2 (0–124.2)
Dairy protein intake (range), *g/d*	15.3 ± 9.0 (0–52.2)	15.3 ± 8.7 (0–64.2)
Vegetable protein intake (range), *g/d*	21.1 ± 4.7 (7.9–53.3)	20.4 ± 4.1 (6.9–33.3)
Animal fat intake (range), *g/d*	29.9 ± 9.1 (0.6–61.3)	30.0 ± 8.1 (6.3–71.8)
Phosphorus intake (range), *g/d*	1215 ± 252 (597–3544)	1208 ± 244 (638–3329)
Alcohol intake 0.1–14.9 g/d, *n (%)*	573 (51)	245 (50)
Alcohol intake ≥15 g/d, *n (%)*	113 (10)	55 (11)
Hypercholesterolemia, *n (%)*	564 (50)	304 (62)
Diabetes, *n (%)*	53 (5)	13 (3)
Hypertension, *n (%)*	403 (36)	204 (42)
Current smoker, *n (%)*	134 (12)	54 (11)
Past smoker, *n (%)*	481 (42)	209 (43)

* Values presented with plus/minus signs are means ± SD. To convert mg/dL to μmol/L, multiply by 88.402; to convert mL/min per 1.73 m^2 to mL · s^{-2} · m^{-2}, multiply by 0.00963; to convert mL/min to mL/s, multiply by 0.0167. GFR = glomerular filtration rate.
† Defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2.
‡ Defined as an estimated GFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2.

tions, including angiotensin-converting enzyme inhibitors, from the 1994 and 1996 questionnaires.

Estimation of Renal Function

Renal function was estimated by using creatinine values from blood samples that had been drawn in 1989 and 2000 and stored at −130 °C, as well as self-reported measurements of height and weight. Creatinine values for both years were determined simultaneously at Boston Children's Hospital laboratory in 2001 by using a modified Jaffe method. The coefficient of variation was 10% for the 371 masked samples included with the study sample.

We used two formulas to estimate renal function (23, 24). Our primary estimate of GFR was based on data from the Modification of Diet in Renal Disease (MDRD) Study (24). This formula, 186 × creatinine concentration$^{-1.154}$ × age$^{-0.203}$ × 0.742, was empirically derived from 1070 patients with renal insufficiency by using iothalamate GFR measurements and was subsequently validated in 558 patients in the same study (25). Creatinine is measured in mg/dL, and age is measured in years. Results are multiplied by a factor of 1.212 for African-American women. The second formula was a modification of the Cockcroft–Gault formula for estimating creatinine clearance (26), which Salazar and Corcoran (23) developed to estimate creatinine clearance on the basis of fat-free body mass. The modified formula has the advantage of attenuating the overestimation of creatinine clearance in obese persons that occurs with the Cockcroft–Gault formula and providing similar results in average-weight women. The formula for women is (146 − age) × [(0.287 × weight) + (9.74 × height^2)]/(60 × creatinine concentration), where age is measured in years, weight in kilograms, height in meters, and creatinine in mg/dL. This formula has been validated by comparison with actual measurements of creatinine clearance (23).

Statistical Analyses

For continuous variables, the mean, median, and standard deviation were calculated. We tested the normality assumption for change in estimated GFR and creatinine clearance using the Kolmogorov–Smirnov statistic, and there was no evidence to reject the normality assumption for either. The primary outcomes of interest were defined as absolute change in estimated GFR during the study period or decrease in estimated GFR of at least 15%, 20%, or 25% during the study period. These cut-points were chosen to select participants whose decline in renal function was greater than that expected from normative data (27). We examined these outcomes in women with normal renal function at baseline (defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2) and separately examined a subset of women who had mild renal insufficiency at baseline (defined as an estimated GFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2). In the latter group, because of limited numbers, we were unable to examine a decrease in estimated GFR of 25% or greater. We repeated all of these analyses using estimated creatinine clearance and repeated the linear regression models using change in creatinine concentration.

The following prespecified independent variables were included in all models: age (continuous), weight (continuous), protein intake (continuous and quintiles), animal fat intake (continuous), phosphorus intake (continuous), alcohol intake (three categories), hypercholesterolemia (yes or no), diabetes (yes or no), hypertension (yes or no), and smoking status (current, past, or never). African-American ethnicity was not included as a covariate because only 13 participants were African American. Aspirin, nonsteroidal anti-inflammatory, acetaminophen, and antihypertensive medication use were removed from the final models because they did not affect the point estimates of the main exposures of interest. Baseline protein intake (in 1990) was used for the primary analyses, and mean protein intake from 1990 and 1994 was used for secondary analyses. Multivariate analyses were performed by using linear and logistic regression analyses, and 95% CIs were calculated for each parameter estimate and odds ratio. Interactions between protein intake and age and protein intake and hypertension were examined in women with mild renal insufficiency by adding interaction terms to the model.

We also developed a formal measurement-error adjustment model for protein intake and applied it to the outcomes of change in estimated GFR and creatinine clearance (22, 28–31). This method is generally applicable only to continuous exposures; thus, we were unable to apply it to quintiles of protein intake. In addition, this method could not be used for these logistic regression analyses because the outcomes must be rare, and the frequency of our outcomes ranged from 14% to 43%. There was no evidence of lack of goodness of fit at the chosen cut-points of estimated GFR, according to the method of Lemeshow and Hosmer (32). All analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

Table 2. **Multivariate Linear Regression Results for Change in Estimated Glomerular Filtration Rate according to Quintile of Total Protein Intake***

Quintile of Total Protein Intake†	Change in Estimated GFR	
	Participants with Normal Renal Function (n = 1135)‡	Participants with Mild Renal Insufficiency (n = 489)§
	mL/min per 1.73 m²	
1	0 (referent)	0 (referent)
2	2.45 (−0.98 to 5.88)	−2.51 (−6.25 to 1.23)
3	1.82 (−1.77 to 5.41)	−0.10 (−4.06 to 3.86)
4	2.23 (−1.66 to 6.12)	−0.32 (−4.50 to 3.86)
5	0.46 (−3.83 to 4.75)	−4.77 (−9.52 to −0.02)

* Adjusted for age, weight, animal fat intake, phosphorus intake, alcohol intake, hypercholesterolemia, diabetes, hypertension, and smoking status. To convert mL/min per 1.73 m^2 to mL · s^{-2} · m^{-2}, multiply by 0.00963. GFR = glomerular filtration rate.
† See Tables 4 and 5 for the specific quintile cut-points in each group of participants.
‡ Defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2.
§ Defined as an estimated GFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2.

Table 3. **Multivariate Linear Regression Results for Change in Estimated Glomerular Filtration Rate per 10-g Increase in Nondairy Animal, Dairy, or Vegetable Protein***

Protein Type	Change in Estimated GFR	
	Participants with Normal Renal Function (n = 1135)†	Participants with Mild Renal Insufficiency (n = 489)‡
	mL/min per 1.73 m²	
Nondairy animal	0.09 (−1.08 to 1.26)	−1.21 (−2.34 to −0.33)
Dairy	1.29 (−0.98 to 3.56)	−0.05 (−1.48 to 1.38)
Vegetable	1.83 (−1.25 to 4.98)	1.03 (−2.08 to 4.14)

* Adjusted for age, weight, animal fat intake, phosphorus intake, alcohol intake, hypercholesterolemia, diabetes, hypertension, and smoking status. To convert mL/min per 1.73 m^2 to mL · s^{-2} · m^{-2}, multiply by 0.00963. GFR = glomerular filtration rate.
† Defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2.
‡ Defined as an estimated GFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2.

RESULTS

Demographic, laboratory, and dietary information are presented in **Table 1** according to baseline estimated GFR. The estimated mean GFR was lower at baseline and changed less during the study period than did the estimated creatinine clearance. Participants in the mild renal insufficiency group were 2 years older than those in the normal renal function group, and both groups had similar total protein intake. Absolute decline in estimated GFR was less pronounced in the renal insufficiency group than in the group with normal renal function.

Women with Normal Renal Function

We performed a multivariate linear regression analysis after adjusting for age; weight; diabetes; hypertension; hypercholesterolemia; smoking status; and animal fat, phosphorus, and alcohol intake. No significant association was seen between total protein intake and change in estimated GFR in women with normal renal function. In this group, estimated GFR changed 0.25 mL/min per 1.73 m^2 (95% CI, −0.78 to 1.28 mL/min per 1.73 m^2) per 10-g increase in protein intake. After we accounted for protein intake measurement error, the change in estimated GFR became more pronounced but the confidence interval widened (1.14 mL/min per 1.73 m^2 [CI, −3.63 to 5.92 mL/min per 1.73 m^2]).

The linear regression results per quintile of protein intake are presented in **Table 2**. Compared with women in the lowest quintile of protein intake, women in the highest quintile had a nonsignificant change in estimated GFR (0.46 mL/min per 1.73 m^2 [CI, −3.83 to 4.75 mL/min per 1.73 m^2]). We also separately examined intake of nondairy animal protein, dairy protein, and vegetable protein (**Table 3**). None of these specific sources of protein were significantly associated with change in estimated GFR. All of these results were similar when we examined change in estimated creatinine clearance and creatinine concentration.

Table 4. **Multivariate Odds Ratios for Decline in Estimated Glomerular Filtration Rate according to Quintile of Total Protein Intake in Women with Normal Renal Function at Baseline (*n* = 1135)***

Quintile of Total Protein Intake	Median Intake (Range), *g/d*	Odds Ratio (95% CI)		
		≥15% Decline in Estimated GFR (*n* = 488)	≥20% Decline in Estimated GFR (*n* = 366)	≥25% Decline in Estimated GFR (*n* = 245)
1	60.4 (19.1–66.2)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	69.8 (66.3–73.1)	0.80 (0.54–1.20)	0.88 (0.57–1.35)	0.71 (0.44–1.17)
3	76.2 (73.2–79.3)	0.79 (0.51–1.22)	1.02 (0.64–1.61)	0.81 (0.48–1.36)
4	82.5 (79.4–86.4)	0.79 (0.50–1.27)	0.91 (0.55–1.49)	0.80 (0.46–1.40)
5	93.0 (86.5–163.7)	0.84 (0.51–1.38)	0.97 (0.57–1.65)	0.89 (0.49–1.62)

* Normal renal function was defined as an estimated GFR ≥ 80 mL/min per 1.73 m^2. Values are adjusted for age, weight, animal fat intake, phosphorus intake, alcohol intake, hypercholesterolemia, diabetes, hypertension, and smoking status. To convert mL/min per 1.73 m^2 to mL · s^{-2} · m^{-2}, multiply by 0.00963. GFR = glomerular filtration rate.

We performed multivariate logistic regression analyses in each study group. In women with normal baseline renal function, no statistically significant association was seen between protein intake and specific cut-points of estimated GFR decline (**Table 4**). These results were confirmed when we used mean protein intake from 1990 and 1994 and when we examined specific cut-points of estimated creatinine clearance.

Women with Mild Renal Insufficiency

We performed separate analyses in women with mild renal insufficiency. In the multivariate linear regression analysis, protein intake was significantly associated with a change in estimated GFR (−1.69 mL/min per 1.73 m^2 [CI, −2.93 to −0.45 mL/min per 1.73 m^2] per 10-g protein increase). The magnitude of the association increased but had borderline statistical significance after we adjusted for protein intake measurement error (change in estimated GFR, −7.72 mL/min per 1.73 m^2 [CI, −15.52 to 0.08 mL/min per 1.73 m^2] per 10-g protein increase). We obtained similar results when we examined change in estimated creatinine clearance and creatinine concentration.

The results of the linear regression analysis for quintile of protein intake are presented in **Table 2**. The highest quintile of protein intake was significantly associated with a larger decline in estimated GFR (−4.77 mL/min per 1.73 m^2 [CI, −9.52 to −0.02 mL/min per 1.73 m^2]). Also, a significant association was seen between estimated GFR change and intake of nondairy animal protein, but not dairy and vegetable protein (**Table 3**). We obtained similar results when we examined change in estimated creatinine clearance and creatinine concentration.

Among women with mild renal insufficiency, the odds ratio for a decrease of at least 15% in estimated GFR was 3.51 (CI, 1.36 to 9.07) for those in the highest quintile of protein intake compared with those in the lowest (**Table 5**). These results were similar when we examined the mean protein intake from 1990 and 1994 (odds ratio, 4.14 [CI, 1.77 to 9.67] for the highest quintile compared with the lowest) and when we examined specific cut-points of estimated creatinine clearance. The interaction terms between protein intake and age and hypertension were not significant.

Table 5. **Multivariate Odds Ratios for Decline in Estimated Glomerular Filtration Rate according to Quintile of Total Protein for Women with Mild Renal Insufficiency at Baseline (*n* = 489)***

Quintile of Protein Intake	Median Intake (Range), *g/d*	Odds Ratio (95% CI)	
		≥15% Decline in Estimated GFR (*n* = 112)	≥20% Decline in Estimated GFR (*n* = 68)
1	61.0 (37–65.5)	1.00 (referent)	1.00 (referent)
2	69.5 (65.6–72.1)	1.87 (0.88–3.99)	2.48 (0.94–6.55)
3	75.7 (72.2–78.4)	1.56 (0.67–3.63)	1.86 (0.64–5.45)
4	81.8 (78.5–85.5)	1.49 (0.59–3.76)	1.60 (0.49–5.19)
5	92.3 (85.6–143)	3.51 (1.36–9.07)	2.85 (0.87–9.36)

* Mild renal insufficiency was defined as an estimated GFR > 55 mL/min per 1.73 m^2 but < 80 mL/min per 1.73 m^2. Values are adjusted for age, weight, animal fat intake, phosphorus intake, alcohol intake, hypercholesterolemia, diabetes, hypertension, and smoking status. To convert mL/min per 1.73 m^2 to mL · s^{-2} · m^{-2}, multiply by 0.00963. GFR = glomerular filtration rate.

DISCUSSION

We observed no significant adverse renal effects of high protein consumption in women who had normal renal function at baseline. In addition, when we separately analyzed nondairy animal, dairy, and vegetable protein intake, we found no evidence of a detrimental effect of animal protein compared with vegetable protein. Since a low-protein diet may slow renal function decline in patients with moderate renal insufficiency, we were also interested in the impact of dietary protein consumption in women with mild renal insufficiency. When we separately examined these women, we found that those who consumed the most protein had the greatest decline in estimated GFR. Small differences in protein intake may not have clinically meaningful implications in women with mild renal insufficiency, but sustained high protein intake may have substantial long-term adverse effects on renal function.

We found evidence of an association between greater consumption of nondairy animal protein and decrease in estimated GFR in women with mild renal insufficiency, indicating that protein source may also be important. The possible adverse effects of nondairy animal protein compared with other sources of protein may relate to differences in plasma levels of amino acids among persons with different diets. For example, Kontessis and colleagues (33) demonstrated that an animal protein diet was associated with higher plasma levels of valine and lysine than a vegetable protein diet, and plasma valine levels were strongly correlated with GFR. Increases in GFR may cause intraglomerular hypertension, which may lead to progressive loss of renal function (7).

Protein intake, as expected, was correlated with phosphorus intake. This relation is important because a high-phosphorus diet has been shown to cause nephrocalcinosis, tubular damage, and interstitial fibrosis in dogs (34). However, studies in humans addressing this concern are limited, and those that have been performed have yielded conflicting results (35, 36). Nonetheless, because of these concerns, we included dietary phosphorus intake in all models to assess the independent effects of protein. The detrimental effect of protein intake observed in studies of patients with renal disease may also be related to the fact that many sources of animal protein are high in cholesterol and saturated fat. High cholesterol levels have also been shown to be a risk factor for progression of renal disease and may adversely affect renal function and renal hemodynamics (37–39). Therefore, since dietary intake of animal fat influences serum cholesterol level, we adjusted for animal fat intake as well as hypercholesterolemia.

There is no clear consensus in the literature about the choice of an appropriate formula to estimate renal function. The primary formula we used was derived from the MDRD Study (12, 24, 25, 40). The major strength of this formula is that it was empirically derived from iothalamate GFR measurements. Limitations include the fact that the MDRD participants were a select sample with renal disease and that the MDRD Study excluded persons with certain chronic medical conditions, including insulin-dependent diabetes and severe obesity (defined as >160% of standard body weight). Traditionally, the Cockcroft–Gault formula has been used to estimate creatinine clearance and, by inference, GFR (26, 41, 42). However, this formula has been shown to overestimate creatinine clearance, especially in obese women (23). Since our cohort included a substantial number of obese women, we chose to use a modified version of the Cockcroft–Gault formula designed to reduce overestimation of creatinine clearance due to obesity. This adjustment minimized estimates of extreme creatinine clearance in obese women.

Major previous studies examining the effect of protein intake on renal function have been limited to patients with moderate to severe renal insufficiency. These studies had limitations, including limited power, short follow-up, and a relatively narrow range of protein intake. In 1991, Locatelli and coworkers (10) performed a randomized trial of protein restriction in 456 individuals with a creatinine clearance less than 60 mL/min (<1 mL/s), but follow-up was limited to 2 years. There was a trend toward a difference in the primary end point of doubled creatinine concentration or need for dialysis ($P = 0.06$), but mean creatinine clearance did not change in the intervention group compared with the control group. The MDRD Study, the largest study to date, randomly assigned 585 individuals with moderate renal disease (GFR, 25 to 55 mL/min per 1.73 m^2) to a low-protein or usual-protein diet and randomly assigned 255 individuals with severe disease (GFR, 13 to 24 mL/min per 1.73 m^2) to a low-protein or very low-protein diet for a mean of 2.2 years (12). In individuals with moderate renal disease, GFR did not differ substantially at the end of the study but renal function decline had proceeded at a significantly lower rate from 4 months into the study until the end of the study. In individuals with severe renal disease, the very-low-protein group had a marginally slower GFR decline. A meta-analysis by Kasiske and associates (13) suggested that, overall, protein restriction may confer a small benefit in reducing the rate of renal function decline in patients with renal disease.

Our study has several limitations. Because it was not a randomized trial, we may not have adjusted for all possible confounders. Nonetheless, we had baseline and follow-up data on many potentially important confounders, such as diabetes and hypertension. Also, we did not have an exact measure of average protein intake during the entire study period. To address the issue of whether baseline protein intake reflected protein intake throughout the study, we separately examined multivariate models using mean protein intake from the 1990 and 1994 questionnaires, and the results were similar.

We also addressed the issue of measurement error as a potential limitation of our analyses. To account for measurement error of dietary protein, we performed a measurement-error adjustment of the linear regression parameter estimates using data from a validation study of the dietary questionnaire (22, 28–31). Measurement-error adjustment is designed to account for random and systematic error in data collection (22). For example, omitting a commonly eaten protein source from a standardized questionnaire would reduce the estimated protein intake of all persons eating that food, but the consumption of this food, and the error in estimating protein intake, would differ among individuals. Therefore, to adjust for measurement error, a second, superior measure of exposure, such as dietary validation study, is needed.

After the relevant data are acquired, a two-step process is performed. First, the superior measure (the validation study) is regressed on the surrogate measure (the food-frequency questionnaire). Second, this information is used to adjust the observed regression coefficient for the exposure of interest. When we performed this adjustment for our linear regression results, the observed parameter estimates, as expected, moved farther from the null and the confidence intervals widened. This method, however, has inherent limitations for our analyses, including that the superior measure was not perfect. In addition, this method is not applicable to logistic regression unless the outcome is rare. If this method were applicable to our logistic regression results, we would have expected adjustment for measurement error in protein intake to cause the odds ratios to move farther from the null and the confidence intervals to widen.

Also, if validation data on animal fat and phosphorus intake were available, we could have performed a multivariate measurement-error adjustment (43). It is difficult to predict how this adjustment would have differed from the univariate measurement-error adjustment. Animal fat and phosphorus intake are both correlated with protein intake, so if either or both were measured with more error than protein intake, our univariate measurement-error adjustment may have overestimated the effect of protein intake on renal function decline. Conversely, if either or both were measured with less error than protein intake, our univariate adjustment may have underestimated the effect of protein intake on renal function decline (43). Overall, these results highlight the importance of measuring error magnitude when evaluating the association between an exposure and an outcome (22).

Our use of creatinine concentration to estimate renal function is also a limitation. Creatinine concentration is an imperfect marker of GFR (44). Recent protein ingestion and exercise also influence serum creatinine concentration, but the effect of these factors should be limited by examining change in creatinine concentration over time. Serum creatinine measurements also vary depending on the laboratory assay. Therefore, we measured all of the samples from both blood collections in the same laboratory at the same time.

Despite its limitations, our study has many strengths that made it well suited to address whether protein intake affects renal function in women with normal or mildly reduced renal function. These strengths include a prospective study design, a long follow-up period, a large number of participants, and detailed dietary information.

We conclude that high total protein intake does not seem to be associated with renal function decline in women with normal renal function. However, high total protein intake, particularly high intake of nondairy animal protein, may detrimentally affect renal function in women with mild renal insufficiency. Additional large prospective studies of adequate duration are needed to further address this issue.

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