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ORIGINAL ARTICLE

High-protein diet with renal hyperfiltration is associated with rapid decline rate of renal function: a community-based prospective cohort study

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ABSTRACT

Background. The effect of a high-protein diet with renal hyperfiltration (RHF) on decline of kidney function has rarely been explored. We investigated the association between a high-protein diet, RHF and declining kidney function.

Methods. A total of 9226 subjects from the Korean Genome and Epidemiology Study, a community-based prospective study (2001–14), were enrolled and classified into quartiles according to daily amount of protein intake based on food frequency questionnaires. RHF was defined as estimated glomerular filtration rate (eGFR) with residuals of >95th percentile after adjustment for age, sex, history of hypertension or diabetes, height and weight. Rapid decline of renal function was defined as decline rate of eGFR >3 mL/min/1.73 m^2/year.

Results. The relative risk of RHF was 3.48-fold higher in the highest than in the lowest protein intake quartile after adjustment for confounding factors [95% confidence interval (CI) 1.39–8.71]. The mean eGFR decline rate was faster as quartiles of protein intake increased. Furthermore, the highest quartile was associated with 1.32-fold increased risk of rapid eGFR decline (95% CI 1.02–1.73). When subjects were divided into two groups with or without RHF, the highest quartile was associated with a rapid decline in renal function only in RHF subjects (odds ratio 3.35; 95% CI 1.07–10.51). The sensitivity analysis using the Korean National Health and Nutrition Examination Survey (2008–15) data with 40 113 subjects showed that higher quartile was associated with increased risk for RHF.

Conclusions. A high-protein diet increases the risk of RHF and a rapid renal function decline in the general population. These findings suggest that a high-protein diet has a deleterious effect on renal function in the general population.

Keywords: estimated glomerular filtration rate, kidney function, protein intake, rapid decline, renal hyperfiltration

INTRODUCTION

A high-protein intake is considered to increase the risk of renal hyperfiltration (RHF) in the general population [1–3]. Furthermore, a high-protein diet can aggravate the progression of chronic kidney disease (CKD) [4–6]. Some experimental studies also showed that a high-protein diet induces glomerular hypertrophy and RHF [7–9]. These processes are suggested to be maladaptive responses to abnormal renal hemodynamics and an antecedent to kidney injury or the consequent progression of kidney disease [10, 11]. Thus, a low-protein diet is suggested for conservative management of CKD [12]. However, several clinical studies have reported inconsistent data about the association between dietary protein intake and estimated glomerular filtration rate (eGFR). The Prevention of Renal and Vascular End stage Disease study, which included subjects aged 28–75 years without kidney disease, showed a lack of association between protein intake and eGFR or eGFR change after a 6-year follow-up [13]. Based on these observations, it remains a major challenge to determine whether a high-protein intake induces worsening renal outcomes in the general population.

Several studies recently reported the clinical consequences of an abnormally high GFR [14, 15]. Park *et al.* [16] demonstrated that RHF is a novel marker of all-cause mortality in the general population. Furthermore, other study groups reported that RHF is associated with a rapid renal function decline in both types I and II diabetes [17, 18]. RHF is caused by various medical conditions, such as diabetes, hypertension and autosomal

dominant polycystic kidney disease as well as physiologic status, such as pregnancy or obesity [2, 19–22]. As mentioned above, a high-protein diet is also considered as one of the causes of RHF. However, the association between high-protein intake with RHF and future kidney function deterioration has yet to be elucidated.

Therefore, here we aimed to investigate the association between a high-protein diet and RHF adjusted for age, sex, history of diabetes and/or hypertension, height, weight and kidney function decline in a healthy adult population. We also examined the effect of time-averaged protein intake on the association between RHF and a decline in kidney function and further validated the association between protein intake and RHF using a different community-based cohort data set.

MATERIALS AND METHODS

Study subjects

Subjects were recruited from the Korean Genome and Epidemiology Study (KoGES), a prospective community-based cohort study. The detailed profile and methods of how the KoGES cohort was built were previously described elsewhere [23]. Briefly, the study cohort consisted of 10 030 subjects aged 40–69 years who were residents of Ansan or Ansung, two cities in South Korea. They underwent government-sponsored medical health checkups and various surveys at baseline. Serial health examinations and surveys were performed biennially from 2001 to 2014. In our study, we selected subjects for whom information including protein intake data were available for the initial survey and subsequently excluded those with an eGFR <60 mL/min/1.73 m^2 or underlying kidney disease at baseline, missing data and missing follow-up creatinine data. A total of 9226 subjects were included in the final analysis. All subjects voluntarily participated in the study and provided informed consent. The study protocol was approved by the Ethics Committee of KoGES at the Korean National Institute of Health. This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (4-2016-0900).

Anthropometric and laboratory data

All subjects underwent a comprehensive medical health examination and filled out questionnaires about health and lifestyle factors at the time of study entry. Demographic and socioeconomic data, including age, sex, level of education and income, smoking status, alcohol intake and medical histories, were obtained. Anthropometric parameters such as height and body weight were measured by skilled study workers following standard methods. Blood and urine samples were obtained after an 8-h fast and transported to a central laboratory (Seoul Clinical Laboratories, Seoul, Korea) within 24 h of sampling. Serum concentrations of blood urea nitrogen, creatinine, hemoglobin, albumin, glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HbA1c and C-reactive protein (CRP) were measured. Serum creatinine level was measured by the Jaffé method using ADVIA 1650 (Siemens, Tarrytown, NY, USA). We reduced serum creatinine levels by 5%, which is an often used method for standardization to isotope dilution mass spectrometry reference method [24]. Urine samples were collected in the morning after the first voiding and subjected to dipstick test using URISCAN Pro II (YD Diagnostics Corp., Seoul, Korea).

Assessment of protein intake

At baseline and the second follow-up examination, dietary intake was assessed by trained dietitians with a semiquantitative food frequency questionnaire (FFQ). Details of this questionnaire, including its relative validity, have been published elsewhere [25]. The FFQ was investigated by 13 dietitians who were trained with prepared protocol. The second follow-up was performed at 4-years interval from the baseline. The FFQ was subsequently validated using 12-day diet records as reference method and readministration of the FFQ among 124 cohort participants. The correlation coefficient by these two methods for each dietary component ranged between 0.23 and 0.64, and the proportion of classification into opposite quartiles by nutrient intakes from each method was $<7\%$. Based on the FFQ, the subjects were categorized into four groups according to quartiles of daily amount of protein intake at baseline.

Definition of RHF and kidney function decline

RHF was defined as previously suggested with some modifications [26]. Briefly, the residuals were calculated from a multivariable linear regression analysis in which logarithm-transformed eGFR was a dependent variable and logarithm-transformed age, sex, history of hypertension and/or diabetes, height, and weight were independent variables. A logarithm-transformed eGFR larger than the 95th percentile in the distribution of residuals from the multivariable linear regression after the adjustment for logarithm-transformed age, sex, history of hypertension and/or diabetes, height and weight was defined as RHF. The exact eGFR value for the RHF was 94.4 mL/min/1.73 m^2. The eGFR was calculated using the CKD-Epidemiology Collaboration (CKD-EPI) equation [27]. The rate of decline in eGFR over time was determined using the linear mixed model; fixed effects included quartiles of protein intake and time with random effects for subject and time. The slope was expressed as the estimates from the model. A rapid eGFR decline was defined as an annual eGFR decline rate ≥ 3 mL/min/1.73 m^2/year.

Sensitivity analysis

The impact of mean protein intake over time on RHF and decline of kidney function was further evaluated in subjects for whom dietary intake data were available at the second follow-up. A total of 6906 participants were analyzed, and the time-averaged amount of protein intake was used in the analysis. A total of 41 692 subjects from another independent community-based cohort, the Korean National Health and Nutrition Examination Survey (KNHANES IV, V and VI, 2008–15), were analyzed to validate the association between high daily protein intake and RHF. The KNHANES is a

nationwide, population-based cross-sectional health examination and survey that is regularly conducted by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention of the Ministry of Health and Welfare to monitor the general health and nutrition status of South Koreans [28].

Statistical analysis

All statistical analyses were performed using IBM SPSS software for Windows version 23.0 (IBM Corporation, Armonk, NY, USA), SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) and R software 3.3.1 (http://www.R-project.org). Continuous variables were expressed as mean ± standard deviation and categorical variables as absolute numbers with percentages. All data were tested for normality before the statistical analysis. The Kolmogorov–Smirnov test was performed to determine the normality of the distribution of the parameters. Intergroup comparisons were performed using analysis of variance or Student's *t*-test for normally distributed continuous variables, while categorical variables were examined using the Chi-square test or Fisher's exact test. Data that did not show a normal distribution were presented as median with interquartile range and were compared using the Mann–Whitney U-test or Kruskal–Wallis test. General linear model was used to compare mean adjusted eGFR among quartiles of protein intake. Linear mixed analysis was performed in groups with or without RHF, respectively, to confirm the differences in eGFR change over time among the quartiles of protein intake. Fixed effects included quartiles of protein intake and time, with random effects for subject and time. Logistic regression analysis was performed to evaluate the association between protein intake and RHF or rapid decline of eGFR. Furthermore, multivariable Cox analysis was performed to evaluate the risk of reaching eGFR <60 mL/min/1.73 m^2 during follow-up. Variables that showed statistical significance in the univariate analyses or considered to have clinical significance were included in the multivariable models. For all analyses, two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study subjects

A total of 9226 subjects were included in this study (Figure 1). The median study follow-up duration was 11.5 (5.2–11.7) years. The baseline characteristics of the 9226 subjects are shown in Table 1. The mean age was 52.0 ± 8.8 years; 4437 (48.1%) were male. The mean eGFR was 93.9 ± 14.1 mL/min/1.73 m^2 and the mean daily protein intake was 1.1 ± 0.5 g/kg/day. The subjects were categorized into four groups according to the quartiles of daily amount of protein intake. The daily amounts of food intake including total energy, carbohydrate, fat and sodium were larger in the higher quartile groups of daily protein intake. The participants in the higher quartile groups in daily protein intake were more likely to be young, male, smokers, taking more alcohol and active, and were more highly educated with a higher income level. Participants in the higher quartile groups tended to have a higher body mass index (BMI), lower systolic blood pressure (SBP) and lower prevalence of hypertension. Hemoglobin, serum albumin and fasting plasma glucose levels were higher in the higher quartile groups. However, the prevalence of diabetes, dyslipidemia, cardiovascular event (CVEs), baseline eGFR, lipid profiles, HbA1c levels and CRP levels did not differ among the four groups. In addition, we depicted baseline characteristics according to quartiles of protein intake with or without RHF in Supplementary data, Table S1.

Association between daily protein intake and RHF

Among the four groups, the prevalence of RHF was significantly higher in the highest quartile group (5.2, 4.0, 5.2 and 6.0% in Q1, 2, 3 and 4, respectively; $P = 0.02$) (Table 2). A logistic regression analysis was performed to evaluate the effect of daily protein intake on RHF. After the full adjustment of confounding factors, the highest quartile group showed higher odds ratios (ORs) than the lowest quartile group [OR = 3.48, 95% confidence interval (CI) 1.39–8.71; $P = 0.01$] (Table 2).

Association between daily protein intake and decline of kidney function

The annual mean decline rate of eGFR was compared among the quartiles of daily protein intake. The model was adjusted for age, sex, baseline eGFR and daily intake of total energy. The numbers of expected and observed numbers of eGFR measurements were 5.5 and 5.0 per subject, respectively. The annual mean decline rate of eGFR was −2.01, −2.05, −2.19 and −2.34 in Q1, 2, 3 and 4, respectively ($P = 0.02$) (Figure 2). Furthermore, we evaluated whether a higher protein intake affected the risk of a rapid annual decline in kidney function, which was defined as an annual eGFR decline rate ≥3 mL/min/1.73 m^2/year. Table 3 shows that the highest quartile group showed a higher OR for rapid decline of eGFR than the lowest quartile group after full adjustment (OR = 1.32, 95% CI 1.02–1.73; $P = 0.03$). Interestingly, RHF *per se* was not associated with increased odds of a rapid eGFR decline in the fully adjusted logistic regression analysis (Supplementary data, Table S2).

Higher risk of rapid decline of kidney function in high-protein intake with RHF group

To test our main hypothesis that high-protein diet-induced RHF is related to a higher risk of kidney function decline, subjects were divided into two groups according to RHF status. Each group was further categorized into four groups according to daily protein intake quartiles. Among groups stratified by protein intake in RHF, there were no significantly different baseline characteristics that could increase the risk of kidney function loss except amount of food intake (Supplementary data, Table S1). The mean amount of daily protein intake was higher in the RHF group compared with the non-RHF group (1.07 g/kg versus 1.02 g/kg, respectively; $P = 0.02$). Furthermore, mean eGFR decline rate was faster in the RHF group than in the non-RHF group (−3.1 versus −2.1 mL/min/1.73 m^2/year, respectively; $P < 0.001$) (Table 4). The difference between the RHF and non-RHF groups in eGFR changes over

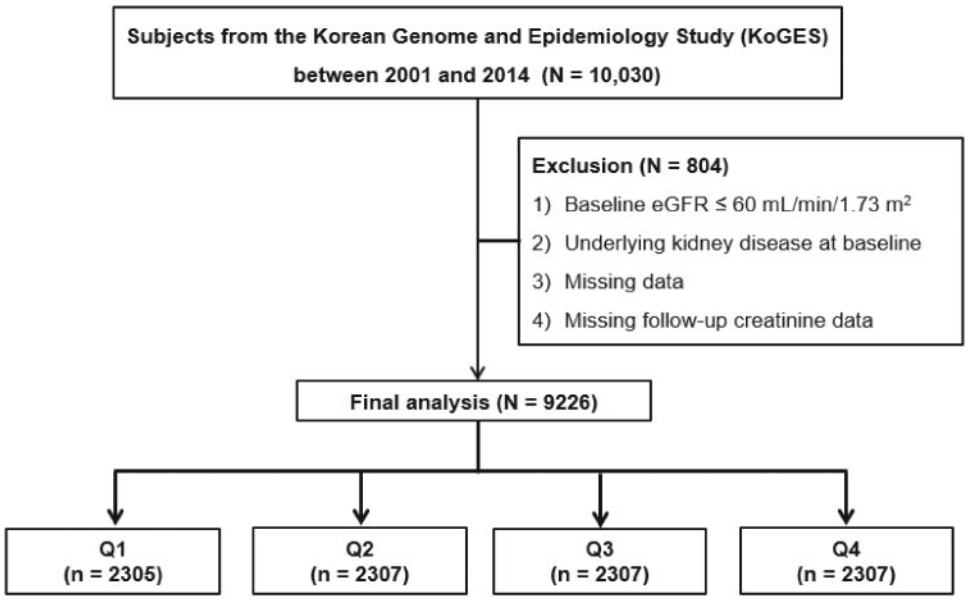

FIGURE 1: Study subjects. Q1–4 represent the quartiles according to daily amount of protein intake based on FFQs. Q1 is the lowest and Q4 is the highest amount of protein intake.

time among quartiles of daily protein intake are shown in Figure 3. Linear mixed model was used after the adjustment for age, sex and daily intake of total energy. The follow-up eGFR level was lowest in the highest protein intake quartile group in the RHF group, whereas the eGFR levels at baseline or follow-up among all quartiles in the non-RHF group were almost equal.

Finally, we performed a logistic regression analysis to confirm that high-protein diet-induced RHF is associated with a higher risk of rapid kidney function decline (P for interaction = 0.01). In the RHF group, the highest quartile of daily protein intake showed a significantly higher OR than the lowest quartile group. However, in the non-RHF group, no statistically significant difference was found among the quartile groups. Table 5 shows the fully adjusted model and the results revealed that the highest quartile groups showed the highest OR for rapid kidney function decline in the RHF group (OR = 3.35, 95% CI 1.07–10.51; P = 0.04). The analysis performed by interaction terms of RHF and protein intake quartiles showed consistent that high-protein intake with RHF showed increased risk for rapid eGFR decline (Supplementary data, Table S3). In addition, we performed multivariable Cox proportional hazard analysis with using the occurrence of eGFR <60 mL/min/1.73 m^2 as outcome. As a result, the highest protein intake group showed increased risk of the occurrence of eGFR <60 mL/min/1.73 m^2 (Supplementary data, Table S4). Moreover, when the subjects were divided into with or without RHF, in the hyperfiltration group there was consistent association that the highest protein intake was related to increased risk for the occurrence of eGFR <60mL/min/1.73 m^2 (Supplementary data, Table S4).

Sensitivity analysis

First, the impact of protein intake on RHF and decline of kidney function was further evaluated in subjects for whom dietary intake data were available at the second follow-up. A total of 6906 participants were analyzed, and the time-averaged amount of protein intake was used for the analysis. Supplementary data, Table S5 shows that the OR of a rapid eGFR decline was significantly higher in the highest quartile group (OR = 2.66, 95% CI 1.37–5.17; P = 0.01). The differential effect between the RHF and non-RHF groups in terms of the risk of a rapid eGFR decline according to quartiles of time-averaged daily protein intake was determined. The results showed that the highest quartile was related to an increased OR compared with the lowest quartile (OR = 1.55, 95% CI 1.14–2.09; P = 0.01) in the RHF group, whereas no statistically significant difference was found in the non-RHF group (Supplementary data, Table S6). In addition, we examined the changing pattern of protein diet using repeated measures of Analysis of Covariance adjusted for age, sex and total intake of energy according to baseline quartiles of protein intake. The result showed that the quartile groups were not changed after follow-up assessments and we assumed that patterns of high or low protein intake may be preserved over time (P = 0.02; Supplementary data, Figure S1). Additionally, because the amount of protein intake could be affected by the meal size, we further evaluated the associations between protein intake and the risks of RHF or rapid decline of eGFR with reclassified protein quartiles, which were calculated by the amount of daily protein intake per individual's body weight. The results showed consistency with the main results (Supplementary data, Tables S8–10)

Next, data from another community-based cohort, the KNHANES (IV, V and VI, 2008–15), were used to validate the relationship between daily protein intake and RHF. A total of 40 113 participants with an eGFR ≥60 mL/min/1.73 m^2 were analyzed, and they were categorized into four groups according to daily protein intake quartiles. A multivariable logistic

Table 1. Baseline characteristics according to quartiles of daily protein intake

Characteristics	Daily protein intake				P-value
	Q1 ($n=2305$)	Q2 ($n=2307$)	Q3 ($n=2307$)	Q4 ($n=2307$)	
Daily amount of food intake (g/kg/day)					
Protein	0.6±0.1	0.9±0.1	1.1±0.2	1.7±0.6	<0.001
Total energy	22.4±5.7	27.8±5.8	32.4±7.1	44.2±15.8	<0.001
Carbohydrate	4.3±1.2	5.1±1.3	5.7±1.5	7.3±2.8	<0.001
Fat	0.2±0.1	0.4±0.1	0.5±0.1	0.9±0.5	<0.001
Sodium (mg/kg/day)	35.9±18.7	44.8±20.0	54.0±22.6	72.4±34.1	<0.001
Demographic data					
Age, years	54.7±8.9	52.2±8.9	50.8±8.5	50.2±8.2	<0.001
Male	841 (36.5)	1099 (47.6)	1199 (52.0)	1298 (56.3)	<0.001
BMI, kg/m^2	24.3±3.3	24.6±3.1	24.6±3.0	24.7±3.1	<0.001
Smoking status	785 (34.1)	950 (41.2)	1026 (44.5)	1142 (49.5)	<0.001
Alcohol status	1011 (43.9)	1242 (53.8)	1326 (57.5)	1446 (62.7)	<0.001
Physical activity	560 (28.1)	756 (38.4)	887 (45.0)	940 (47.5)	<0.001
SBP, mmHg	123.8±19.2	121.5±18.7	121.1±18.6	120.9±17.6	<0.001
Education					<0.001
Low	1152 (50.0)	806 (34.9)	561 (24.3)	512 (22.2)	
Intermediate	1000 (43.4)	1211 (52.5)	1342 (58.2)	1357 (58.8)	
High	153 (6.6)	290 (12.6)	404 (17.5)	438 (19.0)	
Income					<0.001
Low	1204 (52.2)	764 (33.1)	628 (2.2)	578 (25.1)	
Intermediate	873 (37.9)	1135 (49.2)	1168 (50.6)	1148 (49.8)	
High	228 (9.9)	408 (17.7)	511 (22.1)	581 (25.2)	
Comorbidities					
Hypertension	400 (17.4)	319 (13.8)	322 (14.0)	283 (12.3)	<0.001
Diabetes	129 (5.6)	150 (6.5)	154 (6.7)	162 (7.0)	0.05
Dyslipidemia	50 (2.2)	57 (2.5)	57 (2.5)	55 (2.4)	0.65
CVE					
MI	20 (0.9)	16 (0.7)	17 (0.7)	20 (0.9)	0.96
CHF	4 (0.2)	4 (0.2)	2 (0.1)	8 (0.3)	0.29
CAD	20 (0.9)	19 (0.8)	13 (0.6)	14 (0.6)	0.18
Laboratory data					
eGFR, mL/min/1.73 m^2	93.7±13.9	93.9±14.4	94.0±14.3	94.2±14.2	0.72
Hemoglobin, g/dL	13.3±1.5	13.6±1.6	13.7±1.6	13.8±1.5	<0.001
Albumin, g/dL	4.5±0.3	4.5±0.3	4.5±0.2	4.5±0.3	<0.001
Total cholesterol, mg/dL	197.0±37.9	198.1±36.1	199.3±36.5	199.0±36.2	0.14
LDL-C, mg/dL	117.6±34.8	118.3±34.8	119.3±33.8	118.1±34.6	0.38
HDL-C, mg/dL	49.5±11.8	49.4±11.9	49.5±11.7	49.7±11.9	0.84
Fasting glucose, mg/dL	90.2±18.7	92.0±21.8	93.5±22.6	93.7±26.9	<0.001
HbA1c, %	5.7±0.8	5.8.±0.9	5.8±0.9	5.8±1.0	0.11
CRP, mg/dL	0.15 (0.07–0.25)	0.14 (0.07–0.24)	0.14 (0.07–0.25)	0.14 (0.06–0.24)	0.18

Data are presented as mean±SD, median (IQR) or *n* (%).
CAD, coronary artery disease; CHF, congestive heart failure; HDL-C, high-density lipoprotein-cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction.

Table 2. Relative risk of RHF according to quartiles of daily protein intake

Groups		Model 1		Model 2		Model 3	
Daily protein intake	Cases (%)[a]	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Q1	121 (5.2)	Reference		Reference		Reference	
Q2	93 (4.0)	0.94 (0.64–1.39)	0.77	0.98 (0.57–1.69)	0.94	0.4 (0.48–1.48)	0.55
Q3	119 (5.2)	1.51 (1.04–2.19)	0.03	1.63 (0.89–3.00)	0.12	1.57 (0.83–2.97)	0.16
Q4	139 (6.0)	1.84 (1.28–2.65)	0.001	3.52 (1.49–8.31)	0.01	3.48 (1.39–8.71)	0.01

[a]P = 0.02.
Model 1: adjusted for age, sex and eGFR.
Model 2: adjusted for Model 1 + BMI, daily intake of total energy, carbohydrate, fat and sodium.
Model 3: adjusted for Model 2 + smoking status, alcohol status, education and income levels, physical activity, SBP, history of hypertension and diabetes, fasting plasma glucose, serum albumin, total cholesterol and hemoglobin.

regression analysis showed that the higher quartile groups were significantly associated with a higher OR for the prevalence of RHF (Supplementary data, Table S7).

DISCUSSION

The present study demonstrated that a high-protein intake was associated with a higher OR of both RHF and a rapid eGFR decline. In RHF subjects but not non-RHF subjects, a higher intake of daily protein was significantly associated with an increased risk of a rapid eGFR decline. This positive relationship between a high-protein diet and the prevalence of RHF was confirmed using another large cross-sectional cohort data set. These findings support the role of high-protein intake-induced RHF in progressive kidney function deterioration.

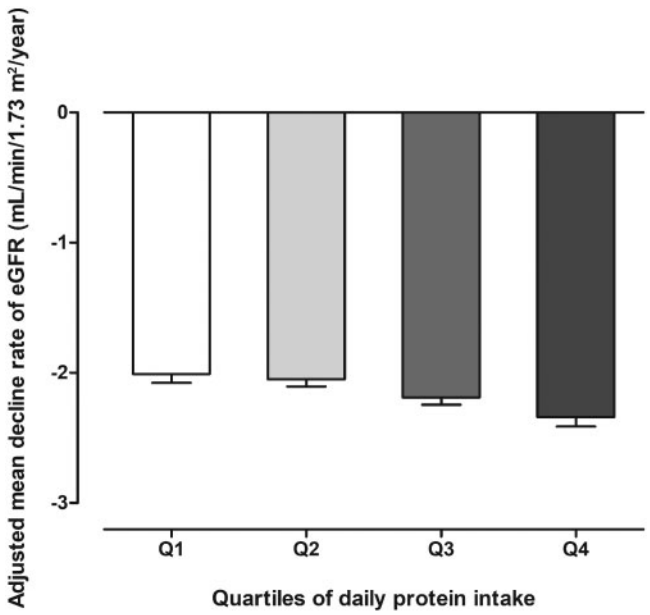

FIGURE 2: Adjusted mean eGFR decline rate according to quartiles of daily protein intake (P = 0.02). Mean eGFR decline rate was adjusted for age, sex, baseline eGFR and daily intake of total energy. The model was adjusted for age, sex, baseline eGFR and daily intake of total energy.

Persistent RHF is a known independent risk factor of accelerated renal function loss, especially in diabetes patients [29]. Bjornstad *et al.* [17] reported that baseline RHF was associated with incident GFR impairments in 646 Type 1 diabetic subjects. Ruggenenti *et al.* [30] longitudinally studied 600 hypertensive Type 2 diabetic patients and showed that RHF affected a fast GFR decline. The interesting finding of this study is that subjects in whom hyperfiltration at inclusion was ameliorated after follow-up were associated with a slower GFR decline than those with persistent hyperfiltration. Furthermore, the RHF groups showed poorly controlled BP and metabolic status including blood glucose level or glucose disposal rate despite intensive treatment. Such a relationship between RHF and deterioration of renal function is primarily explained by glomerular structural damage due to persistent changed glomerular hemodynamics. Ruggenenti *et al.* [30] also addressed that RHF status alone predisposes individuals to the risk of kidney disease because lack of responses to treatment for BP or metabolic factors was seen in RHF patients. In any case, several efforts have been made to demonstrate the association between hyperfiltration status and its effect on future kidney function among diabetics, but no study to date has evaluated this relationship in the general population.

This study is the first to evaluate RHF and decline of renal function in the general population using the commonly acceptable definition of RHF. Furthermore, we used time-averaged amount of protein intake to assess the effect of protein intake on renal health. In this study, the effect of a high-protein diet on a rapid decline of eGFR was obvious in the RHF group compared with the non-RHF group. Additionally, RHF itself was not revealed as an independent risk factor for a rapid eGFR decline. Among groups stratified by protein intake in RHF, there were no significantly different characteristics, such as BP and blood glucose level, that could increase the risk of kidney function loss except amount of food intake. These findings lead us to infer that a higher intake of protein may be an independent risk factor for RHF that can accelerate deterioration of kidney function, especially in the presence of RHF. Possible mechanisms for this can be deduced as follows. Several experimental studies have demonstrated that the infusion of amino acids leads to glomerular hyperfiltration and increased renal plasma flow caused by renal arteriolar vasodilation in humans and

Table 3. Relative risk of rapid eGFR decline[a] according to quartiles of daily protein intake

		Model 1		Model 2		Model 3	
Groups	Case/total number	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Daily protein intake							
Q1	407/2305	Reference		Reference		Reference	
Q2	349/2307	1.02 (0.85–1.21)	0.86	1.02 (0.86–1.22)	0.78	1.01 (0.84–1.21)	0.91
Q3	355/2307	1.14 (0.95–1.38)	0.16	1.21 (1.00–1.46)	0.05	1.15 (0.94–1.41)	0.16
Q4	361/2307	1.31 (1.02–1.69)	0.03	1.44 (1.12–1.85)	0.001	1.32 (1.02–1.73)	0.03

[a]Rapid eGFR decline was defined as annual eGFR decline rate ≥3 mL/min/1.73 m^2/year.
Model 1: adjusted for age, sex, eGFR and daily intake of total energy.
Model 2: adjusted for Model 1 + daily intake of carbohydrate, fat and sodium, smoking status, alcohol status education and income levels and physical activity.
Model 3: adjusted for Model 2 + BMI, SBP, history of hypertension and diabetes, fasting plasma glucose, serum albumin, total cholesterol and hemoglobin.

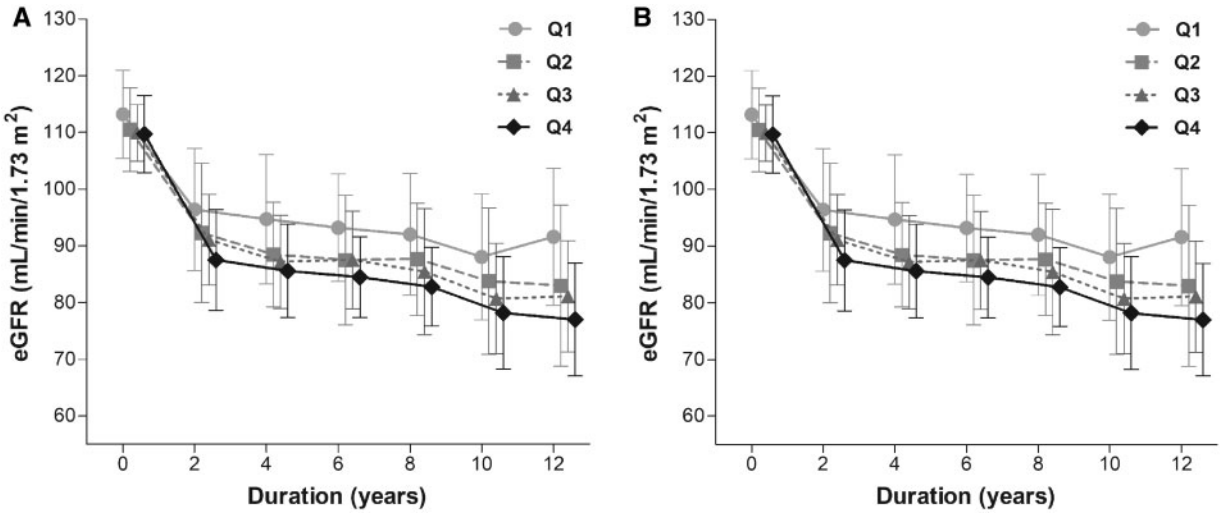

FIGURE 3: The association between daily protein intake and changes in eGFR over time according to RHF. (**A**) RHF group (P = 0.01); (**B**) non-RHF group (P = 0.26).

Table 4. Differences of daily protein intake and mean eGFR decline rate according to RHF

Variables	RHF group ($n = 472$)	Non-RHF group ($n = 8754$)	P-value
Daily protein intake (g/kg/day)	1.07±0.50	1.02±0.49	0.02
Mean eGFR decline rate (mL/min/1.73 m^2/year)	−3.1±2.8	−2.1±2.6	<0.001

Data are presented as mean±SD.

Table 5. Relative risk of rapid eGFR decline according to quartiles of daily protein intake in subgroups with or without RHF

	RHF group		Non-RHF group	
Groups	OR (95% CI)[a]	P-value	OR (95% CI)[a]	P-value
Daily protein intake				
Q1	Reference		Reference	
Q2	2.16 (0.86–4.19)	0.11	0.92 (0.78–1.08)	0.31
Q3	3.31 (1.44–7.64)	0.01	0.95 (0.79–1.14)	0.56
Q4	3.35 (1.07–10.51)	0.04	1.04 (0.81–1.34)	0.75

P for interaction between RHF and protein intake categories = 0.01.
[a]ORs were adjusted for age, sex, eGFR, BMI, SBP, daily intake of total energy, carbohydrate, fat, sodium, smoking status, alcohol status, education and income levels, physical activity, history of hypertension and diabetes, fasting plasma glucose, total cholesterol and hemoglobin.

animals [31]. Zager *et al.* [32] suggested that amino acid infusion might affect ischemic renal injury. They performed an experimental study with amino acid infusion into rats and demonstrated that low GFR and morphologically more damaged tubular features were shown in rats with amino acid infusion than in those without infusion treatment. They also explained that continuous exposure to amino acids might induce a combination of increased afferent and decreased efferent arteriolar resistance. In this context, it can be postulated that cumulative exposure to amino acids could instigate a vasodilated status of the renal arterioles, which consequently results in an ischemic injury-prone condition. In fact, a recent study reported that a low-protein diet combined with using renin–angiotensin–aldosterone system inhibitors slowed progression of CKD [33]. Thus, a higher protein load can accelerate kidney injury, especially in the presence of RHF. Second, recent studies performed in diabetic patients suggested that hyperfiltration status was more closely related to a poor BP or metabolic controls, which predisposes patients to a higher risk of kidney disease [17, 30]. These findings indicated that the mechanism is not appreciably affected by available treatments and that other factors likely play a role in decline of kidney function in patients with RHF, even prior to the onset of overt nephropathy [34]. They assumed that these effects might have been caused by intrinsic patient characteristics or acquired/environmental factors. This postulation can be also applied to the general population, suggesting that RHF status itself is related to lower responsiveness to the treatment of risk factors for kidney disease, resulting in the eventual deterioration of kidney function.

Several limitations to the present study are worth mentioning, including the absence of a direct measurement of GFR. GFR was estimated using the serum creatinine-based CKD-EPI equation rather than direct measurements. However, the CKD-EPI equation used in this study is a standard method of estimating GFR, especially in an epidemiologic setting, which outperforms other equations in subjects with normal or above-normal renal function. To this end, the lack of direct GFR measurement data represents only a minor limitation considering that serum creatinine-based eGFR is still the reference point for kidney function assessments in almost all epidemiologic studies [35]. In addition, we included in the definition of RHF not only eGFR itself but also adjusted eGFR from linear regression methods, to overcome the above limitation and clearly demonstrate hyperfiltration status. In the present study, as history of hypertension or diabetes is crucial risk factor for decline of kidney

function, we included this in multivariable linear regression for calculating RHF. In addition, anthropometric measures such as height and weight can confound the association between protein intake and RHF as well as decline of renal function. Thus, we further used height and weight as adjustment factors for defining RHF. Second, animal and plant protein sources can differently affect RHF and adverse clinical outcomes [36–38]. The lack of data on dietary protein sources in this study limits the ability to demonstrate this different effect, so further studies are warranted. Third, the clear-cut causal relationship between the high-protein diet and RHF or decline of kidney function could not be tested due to the observational nature of this study. Fourth, this study included a single ethnic group, which limits the generalizability of our findings.

Despite these limitations, this study has several strengths. First, this is the first study to report an association between high-protein diet and RHF and a decline of renal function among healthy adults with normal renal function, especially using an RHF definition with linear regression methods. Second, in this study, it was observed that the association between RHF and rapid decline of kidney function was independent of other known risk factors for kidney disease except amount of daily protein intake. Finally, we confirmed the association between protein intake and RHF or kidney function using another large-scale community-based cohort dataset.

In conclusion, high-protein diet-induced RHF was significantly associated with a rapid decline of eGFR in apparently healthy adults with normal renal function. Modulating a high-protein diet can be used in subjects with normal renal function, especially those with hyperfiltration status. Future interventional studies must confirm these study findings.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.H.J. and T.-H.Y. contributed to the research idea and study design; J.H.J. is responsible for data acquisition; Y.K.K., S.P. and H.K. contributed to data analysis/interpretation; J.H.J. and Y.K.K. performed statistical analysis; J.T.P., S.H.H., S.-W.K. and T.-H.Y. are responsible for supervision or mentorship; T.-H.Y. is the guarantor. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

(See related articles by Esmeijer *et al.* Dietary protein intake and kidney function decline after myocardial infarction: the Alpha Omega Cohort. *Nephrol Dial Transplant* 2020; 35: 106–115 and Kalantar-Zadeh *et al.* High-protein diet is bad for kidney health: unleashing the taboo. *Nephrol Dial Transplant* 2020; 35: 1–4)

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Dietary protein intake and kidney function decline after myocardial infarction: the Alpha Omega Cohort

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ABSTRACT

Background. Post-myocardial infarction (MI) patients have a doubled rate of kidney function decline compared with the general population. We investigated the extent to which high intake of total, animal and plant protein are risk factors for accelerated kidney function decline in older stable post-MI patients.

Methods. We analysed 2255 post-MI patients (aged 60–80 years, 80% men) of the Alpha Omega Cohort. Dietary data were collected with a biomarker-validated 203-item food frequency questionnaire. At baseline and 41 months, we estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equations for serum cystatin C [estimated glomerular filtration rate ($eGFR_{cysC}$)] alone and both creatinine and cystatin C ($eGFR_{cr-cysC}$).

Results. Mean [standard deviation (SD)] baseline $eGFR_{cysC}$ and $eGFR_{cr-cysC}$ were 82 (20) and 79 (19) mL/min/1.73 m^2. Of all patients, 16% were current smokers and 19% had diabetes. Mean (SD) total protein intake was 71 (19) g/day, of which two-