Original Article

Dietary fiber intake is associated with chronic kidney disease (CKD) progression and cardiovascular risk, but not protein nutritional status, in adults with CKD

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Background and Objectives: Evidence suggests that dietary fiber benefits patients with chronic kidney disease (CKD); however, this conclusion requires further validation. In this study, we examined the effects of dietary fiber on kidney function, inflammation, indoxyl sulfate, nutritional status, and cardiovascular risk in patients with advanced CKD. **Methods and Study Design:** We performed linear regressions to assess the association between dietary fiber intake and CKD parameters. The aforementioned parameters were compared over an 18-month follow-up period. Kaplan–Meier analysis was used to investigate the association between fiber intake and Cardiac vascular disease (CVD). **Results:** In total, 157 patients were included in this study. Dietary fiber and inflammatory indices were associated (interleukin [IL]-6: β=−0.024, p=0.035). The differential estimated glomerular filtration rate (ΔeGFR) as well as levels of C-reactive protein, IL-6, indoxyl sulfate, and serum cholesterol in the higher fiber intake (≥25 g/day) group were lower than those in the lower fiber intake (<25 g/day) group (p<0.05). Differences in IL-6 and indoxyl sulfate levels were more significant in patients in the higher protein intake group (p<0.05). Dietary fiber intake may be a protective factor associated with CVD (hazard ratio=0.537 and 0.305–0.947). The protein nutritional status was not different between the two groups (p>0.05). **Conclusions:** Our results suggest that increasing fiber intake can retard the decrease in the eGFR; can reduce the levels of proinflammatory factors, indoxyl sulfate, and serum cholesterol; and is negatively associated with cardiovascular risk, but does not disrupt the nutritional status of patients with CKD.

Key Words: chronic kidney disease, dietary fiber, inflammation, indoxyl sulfate, cardiovascular event

INTRODUCTION

Chronic kidney disease (CKD) is a progressive loss in renal function over several years. It is independently associated with CVD, cardiovascular mortality, and all-cause mortality. Moreover, the prevalence of CKD has been rapidly increasing. According to the 1999–2004 National Health and Nutrition Examination Survey, CKD affected an estimated 16.8% of the US population aged ≥20 years.[1] Therapy for predialysis CKD aims to retard or halt the progression of CKD to stage 5. Dietary nutrients potentially play a major role in the progression and complications of predialysis CKD.[2,3] Dietary strategies for patients with CKD are completely different from those for healthy people. Patients with CKD are generally recommended a restricted intake of dietary salt, phosphorus, potassium, and protein. However, the roles of some nutrients, such as dietary fiber, in CKD progression lack sufficient evidence.[4,5]

Dietary fiber is beneficial in treating various disorders, including persistent inflammation, acidosis, and multiple endocrine disorders. All these disorders are strongly associated with CKD progression and even mortality.[6,7] Krishnamurthy et al conducted a retrospective case–control study with large samples and reported that high dietary fiber intake was associated with a lower risk of inflammation and mortality in patients with CKD.[8] In the Fukuoka

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Manuscript received 14 January 2016. Initial review completed 15 February 2016. Revision accepted 18 March 2016.
doi: 10.6133/apjcn.072016.08

Diabetes Registry, the conclusion was also applicable for patients with diabetic nephropathy.[9] In addition, some gut-derived uremic toxins in particular, indoxyl sulfate and p-cresyl sulfate, have been extensively investigated for their cardiorenal toxicity because they cannot be dialyzable.[10] Indoxyl sulfate derived from colonic bacterial fermentation of protein, could be counteracted by dietary fiber through limiting proteolytic bacterial fermentation.[11] Several studies have reported that dietary fiber may reduce the serum concentration of uremic toxins; however, long-term data are lacking.[11-13] Although dietary fiber intake is a potential simple intervention for improving the prognosis of CKD, some possible limitations were reported in a previous study. In that study, protein intake induced deviation in renal function according to the serum creatinine level; however, the study did not examine an East Asian population, and the follow-up period was excessively short (median follow-up, 4.5 weeks). Therefore, we performed a longitudinal cohort study to examine the association of dietary fiber intake with inflammatory factors, uremic toxins, the estimated glomerular filtration rate (eGFR), and cardiovascular events.

METHODS

Study participants

Between May 10, 2008 and July 24, 2013, patients aged ≥18 years having stage 3–4 CKD (eGFR, <60 mL/min·1.73m^2 for at least 3 months) who were not undergoing maintenance dialysis were enrolled from the nephrology clinics of TCM-Integrated Hospital and Zhujiang Hospital of Southern Medical University, Guangzhou, China, as part of two randomized clinical trials assessing the nutritional status in CKD (Registration no: ChiCTR-TRC-08000204 and ChiCTR-TRC-12002539). The Institutional Ethics Committee of Southern Medical University approved the study protocol, and written informed consent was obtained from all participants.

The diagnostic criteria were assessed by physicians according to the disease cause and biopsy samples. The GFR was estimated using the Modification of Diet in Renal Disease prediction equation. Protein intake can increase serum creatinine directly as well as indirectly, thereby increasing creatinine-based measures of the eGFR.[14,15] Therefore, the strength of our analysis is the use of cystatin C GFR estimates, which are presumably less influenced by this bias.[16,17] We excluded patients with diseases known to affect the body composition, such as neuromuscular diseases, inflammatory bowel diseases, sickle cell anemia, and malignancy, or a history of liver or cardiac transplantation. Patients with severe cognitive disorders or who chose to not participate were also excluded.

All the study protocols were in accordance with the ethical standards of the Institution of Guangdong Province and 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Dietary assessment

Adequate food intake was estimated using a locally validated FFQ questionnaire (Supplementary FFQ Table), which comprises 15 categories of food and 118 food items and was developed for a dietary survey of the Chinese population. In the cross-sectional study, we asked the participants to write the mean frequency of consumption and average food consumption during the past year. In the longitudinal study, we contacted the participants every 3 months through telephone calls, network communication services, or appointments. The participants were allowed to complete a dietary recall from previous interviews and fill in the FFQ. Dietary fiber was defined as the sum of all cellulosic and non-cellulosic polysaccharides as well as lignin. Data on dietary fiber, protein, and energy intake were assessed using the China Food Composition Survey 2004, which was established by the Chinese Society of Nutrition.

Clinical data measurement

Peripheral blood samples were collected from all participants in the first week of enrollment, and the participants were interviewed every 3 months. The samples were centrifuged at 1200 rpm for 15 min after coagulation, collected, and stored at -80°C until analysis. The blood samples were collected between 7:00 and 7:30 a.m. Serum cystatin C, serum cholesterol, albumin, and bicarbonate levels were measured at local sites by using standard techniques. Furthermore, indoxyl sulfate levels were analyzed using aHigh Performance Liquid Chromatography (HPLC) fluorescence method. Serum prealbumin levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Beckman Coulter, Inc.) with a detection limit of 0.5 ng/mL. Moreover, serum interleukin (IL)-6 levels were determined using an ELISA kit (detection limit, 0.2 pg/mL; Bogoo, Inc.).

The body mass index (BMI) was calculated using the following formula: weight (kg)/height^2 (m^2). The skinfold thickness (TSF) of the biceps and triceps was measured with a conventional skinfold caliper by using standard techniques. The mid-arm circumference was measured with a tape measure, and the mid-arm muscle circumference (MAMC) was calculated using the formula MAMC (cm) = mid-arm circumference (cm) − (3.142×TSF (cm)).

The CVD endpoints included myocardial infarction, atrial fibrillation, heart arrhythmia, congestive heart failure, peripheral arterial disease, and stroke. Follow-up surveys were conducted through telephone calls or network communication services once a month. The CVD endpoints and initiation of chronic dialysis were obtained through participant self-reporting during the follow-up period and were verified by the clinical and hospital records at the local site.

Statistical analysis

Continuous and categorical variables were analyzed using one-way ANOVA and the chi-squared test, respectively. Associations between the variables were assessed using linear regression analysis and multiple linear regressions. The association between dietary fiber and CVD was determined using the Kaplan–Meier method. Two-tailed p values of <0.05 were considered statistically significant. Proportional hazards were generated using MedCalc for Windows, and other statistical analyses were performed using SPSS 18.0.

RESULTS

Participant characteristics

The mean (±standard deviation) age of the 157 participants included in this analysis was 47.5±13.2 years; 47.1% of the participants were male, and 90.5% were from southern China (mostly Guangdong, Jiangxi, Guangxi, Hunan, and Hubei). The mean eGFR for participants undergoing diet modification was 50.8±17.6mL/min·1.73m^2. The mean fiber intake of the participants was 20.84 g/day (6–56 g/day), and the median was 21.1 g/day. The mean protein intake was 58.81 g/day (19–107 g/day), and the mean energy intake was 2229.10 kcal/day (1120–4450 kcal/day). A higher fiber intake was significantly correlated with a higher protein (r=0.191, p=0.017) and energy (r=0.283, p<0.001) intake. By contrast, a higher fiber intake was associated with lower C-reactive protein (CRP), IL-6, and serum cholesterol levels, as well as higher MAMC (p<0.05; Table 1).

Fiber intake and CKD parameters

As shown in Table 2, linear regression analysis revealed that fiber intake positively correlated with serum albumin (β=−1.348, p=0.001) and prealbumin (β=−1.348, p=0.001) and negatively with CRP (β=−1.348, p=0.001) and IL-6 (β=−1.348, p=0.001). After adjustment for age, sex, protein intake (or total energy intake), diabetes duration, and the smoking status by using multiple regression analysis, the results revealed that the fiber intake still positively correlated with IL-6 levels (β=0.011, p=0.035). No correlations were observed between the fiber intake and the eGFR, indoxyl sulfate, BMI, MAMC, serum cholesterol, and serum bicarbonate either in simple regression analysis or in multiple regression analysis.

Table 1. Characteristics of study participants

Parameter	Lower fiber intake (Fiber intake <21.1 g/d)	Higher fiber intake (Fiber intake ≥21.1 g/d)	p-value
Age (years)	45.9±17.5	49.9±17.7	0.054
Gender (male/female)	(36/42)	(38/41)	0.873
Nephrotic glomerulonephritis (n)	29	33	0.071
Diabetic nephropathy (n)	24	24	0.998
Hypertensive nephropathy (n)	12	10	0.653
Hereditary kidney disease (n)	8	8	0.998
Others (n)	5	4	0.746
eGFR(mL/min·1.73m^2)	49.8±17.5	51.8±17.7	0.463
Serum albumin (g/dL)	37.4±12.8	42.9±13.4	0.087
Serum bicarbonate (mmol/L)	22.4±2.09	22.7±2.22	0.377
Serum prealbumin (mmol/L)	252±50.9	268±52.3	0.061
CRP (mg/mL)	3.90±2.69	2.82±2.25	0.007*
IL-6 (pg/mL)	1.65±0.74	1.40±0.56	0.015*
Serum cholesterol (mmol/L)	5.14±0.93	4.83±0.93	0.038
BMI (kg/m^2)	21.5±3.28	21.3±3.23	0.752
MAMC (cm)	18.0±2.07	18.8±2.10	0.019*
Fiber intake (g/day)†	16.7±2.67	24.5±2.50	<0.001*
Protein intake (g/day)†	57.2±18.0	62.4±16.8	0.063
Energy intake (kcal/day)†	2135±301	2321±308	<0.001*

eGFR: estimated Glomerular filtration rate; CRP: C-reaction protein; IL: interleukin; BMI: body mass index; MAMC: mid-arm muscle circumference.
Continuous variables are presented as mean±SD.
†Fiber intake, protein intake and energy intake are calculated according to data in cohort study.
*p<0.05, lower fiber intake vs higher fiber intake.

Table 2. Correlations between dietary fiber and CKD parameters

Parameter	Crude coefficient			Adjusted coefficient†		
	Beta	Std. error	p-value	Beta	Std. error	p-value
eGFR	-0.008	0.302	0.980	-0.225	0.302	0.457
CRP	-0.092	0.043	0.034*	-0.082	0.044	0.066
IL-6	-0.025	0.011	0.027*	-0.024	0.011	0.035*
Indoxyl sulfate	-0.231	0.255	0.365	-0.314	0.262	0.232
Serum albumin	0.405	0.159	0.012*	0.218	0.133	0.103
Serum prealbumin	2.21	0.875	0.013*	1.13	0.734	0.127
MAMC	0.063	0.036	0.079	0.040	0.036	0.268
BMI	-0.004	0.074	0.961	-0.005	0.076	0.948
Serum cholesterol	-0.028	0.016	0.082	-0.024	0.017	0.141
Serum bicarbonate	0.024	0.037	0.514	0.030	0.038	0.434

eGFR: estimated Glomerular filtration rate; CRP: C-reaction protein; IL: interleukin; BMI: body mass index; MAMC: mid-arm muscle circumference.
†Coefficients have been adjusted with age, gender, protein intake, diabetes duration and smoking status.
*p<0.05.

Table 3. Effect of dietary fiber on CKD progression, inflammation, Indoxyl sulfate and other parameters

Group	Parameter	Follow up time (month)						
		Baseline	3	6	9†	12‡	15	18
Lower fiber intake	eGFR (mL/min·1.73m^2)	50.6±17.3	48.0±17.4	45.4±17.5	43.2±16.9	41.3±16.1	38.7±16.3	36.1±16.3
N=127	ΔeGFR (mL/min·1.73m^2)	-	-2.53±1.08	-2.62±1.06	-2.84±1.04*	-2.50±0.99*	-2.60±1.04	-2.62±1.07
(Fiber intake <25 g/d)	CRP (mg/mL)	3.43±2.52	3.68±2.58	3.75±2.66	3.75±2.61	3.98±2.82*	4.30±3.09*	4.16±3.14*
	IL-6 (pg/mL)	1.55±0.66	1.62±0.67	1.69±0.70*	1.72±0.67*	1.78±0.70*	1.85±0.73*	1.95±0.82*
	Indoxyl sulfate (ng/mL)	30.9±14.7*	32.1±15.9*	33.2±17.3*	34.9±18.3*	36.9±20.4*	38.4±21.3	40.1±23.4
	Cholesterol (mmol/L)	5.08±1.02*	5.08±1.13	5.05±1.20	5.09±1.26	5.10±1.39*	5.04±1.44	5.09±1.47*
	Prealbumin (mmol/L)	259±53.2	256±58.2	259±63.6	260±70.9	259±76.5	261±80.4	266±86.5
Higher fiber intake	eGFR (mL/min·1.73m^2)	51.7±19.1	49.3±19.3	46.5±19.7	45.4±19.2	44.5±18.3	41.9±18.3	39.5±18.6
N=30	ΔeGFR (mL/min·1.73m^2)	-	-2.47±1.10	-2.61±1.31	-2.41±1.20*	-2.17±1.23*	-2.68±1.03	-2.36±0.90
(Fiber intake ≥25 g/d)	CRP (mg/mL)	2.63±2.00	2.77±2.17	2.77±2.12	2.85±1.99	2.81±2.05*	2.78±2.05*	2.94±2.02*
	IL-6 (pg/mL)	1.33±0.67	1.38±0.64	1.34±0.67*	1.44±0.70*	1.43±0.67*	1.46±0.65*	1.54±0.67*
	Indoxyl sulfate (ng/mL)	23.6±13.4*	25.2±15.0*	26.1±15.7*	27.1±16.1*	28.4±16.5*	30.9±17.3	31.1±17.1
	Cholesterol (mmol/L)	4.58±1.34*	4.63±1.47	4.74±1.56	4.70±1.67	4.46±1.63*	4.70±1.69	4.34±1.91*
	Prealbumin (mmol/L)	266±47.0	265±61.4	267±67.4	267±67.6	261±68.4	260±77.8	263±84.3

eGFR: estimated glomerular filtration rate; ΔeGFR: differential estimated glomerular filtration rate between the current time-point and the last one; CRP: C-reaction protein; IL: interleukin.
Continuous variables are presented as mean ±SD.
†3 of participants were loss of follow-up (2 in lower fiber intake and 1 in higher fiber intake).
‡3 of participants were loss of follow-up (1 in lower fiber intake and 2 in higher fiber intake).
*p<0.05, lower fiber intake vs higher fiber intake.

Fiber intake and CKD progression

Table 3 shows the demographic and clinical characteristics at the baseline and 18-month follow-up. A total 6 participants were lost to follow-up during the experiment. Of them, 3 dropped out during 6 mouths follow-up, and 3 dropped out during 9 months follow-up. The cut-off value of higher and lower dietary fiber intakes was 25 g/day, which is the threshold recommended by the Chinese Society of Nutrition (2007). Although no consistent differences were observed in the eGFR among the fiber intake groups, the differential eGFR (ΔeGFR) interval was significantly different between the groups. Participants in the higher fiber intake group showed a retarded decrease of ΔeGFR at 9 and 12 months (p=0.049–0.032). In addition, the higher fiber intake group showed lower serum CRP (p=0.040–0.014), IL-6 (p=0.047–0.011), and cholesterol levels throughout the follow-up period. The indoxyl sulfate levels were higher in the lower fiber intake group at 3 to 15 months compared with those in the higher fiber intake group (p=0.041–0.015). No differences were observed in serum prealbumin between the two groups during the study (p=0.940–0.471).

To adjust the protein intake data, we compared participants in the higher and lower protein intake groups. The cutoff values of higher and lower nutrient intake were based on the medians of dietary protein (61 g/day) and fiber (21.1 g/day) intake (Table 4). Regarding the ΔeGFR interval, CRP, and serum cholesterol, the effect of fiber intake was consistent between the higher and lower protein intake groups. However, IL-6 (p=0.073–0.021) and indoxyl sulfate levels (p=0.047–0.002) decreased in the higher protein intake group, but not in the lower fiber protein group (p=0.677–0.077). The serum prealbumin level showed no statistical differences between four subgroups during the study (p=0.955–0.195).

Fiber intake and CVD risk

We conducted a cohort study that included 157 patients to investigate the association between fiber intake and CVD; 6 participants were lost to follow-up because they developed end-stage renal disease (ESRD) or died. A total of 48 CVD events occurred over a median follow-up period of 15.3 months. The crude rates for CVD events were 21 and 12 per 100 person-years for the lower and higher fiber intake groups, respectively. In the unadjusted analysis, the participants in the lower fiber intake group were more likely to experience any of the cardiovascular composite events than were those in the higher fiber intake group (Table 5; p=0.033). The relative risk (95% confidence interval) of CVD in the higher fiber intake group was 0.537 (0.305–0.947). This association was consistent in all subgroups (Table 3). Cox regression was not performed because the study sample size was inadequate.

DISCUSSION

Evidence shows that patients with CKD may benefit from higher fiber intake; however, most studies have focused on peripheral indices, such as blood pressure, obesity, the lipid profile, and other blood biochemical parameters. Several studies have reported that dietary fiber can reduce serum concentrations of urea and creatinine; however, this result is unreliable because of small sample sizes.[12,13] Xu et al conducted a cross-sectional study to prove the positive association of dietary fiber with kidney function in an elderly population.[18] They reported that a higher fiber intake (per 10 g/day) was associated with a higher eGFR (1.5–2.9 mL/min·1.73m^2), regardless of various confounders. Chiavaroli et al observed a dose-dependent response of serum creatinine to dietary fiber in a meta-analysis; however, most included trials were of a short duration (median follow-up, 4.5 weeks; range, 1.4–20 weeks).[7] Until now, no long-term effects of dietary fiber on kidney function have been reported. In this study, we investigated the association between dietary fiber and CKD function by conducting cross-sectional and longitudinal studies. Although dietary fiber intake was not associated with the eGRF in regression analysis, the longitudinal study revealed that a higher fiber intake retarded the decrease in the eGFR over the 18-month follow-up period, and the results remained statistically significant even after adjustment for protein intake. The inconsistent results may have been obtained because no healthy people were included in the cross-sectional study, thus causing selection bias. Nonetheless, our study confirmed the protective effect of dietary fiber on CKD function.

We also detected the levels of proinflammatory factors, indoxyl sulfate, serum cholesterol, and protein nutritional parameters, which are associated with morbidity and mortality during CKD progression. A chronic proinflammatory state exists in patients with CKD. Compared with their healthy counterparts, patients with CKD exhibited increased serum levels of CRP, IL-6, interferon-γ, and tumor necrosis factor-α, following altered renal cell dynamics and changed plasma flow.[19] Therefore, it is imperative to identify potential interventions that can reduce proinflammatory levels in the CKD population. Indoxyl sulfate is a gut-derived uremic acid, with strong biological nephrovascular toxicity. Indoxyl sulfate is the by product of dietary protein bacterial fermentation in the colon; therefore, lower protein or higher fiber consumption can reduce its levels.[11] However, evidence on the effects of long-term dietary fiber consumption on patients with CKD is rare. In this study, we demonstrated that a higher fiber intake reduced the levels of serum CRP, IL-6, and indoxyl sulfate during the follow-up period, thus supporting the results of previous studies. Notably, statistical differences in the levels of proinflammatory factors and indoxyl sulfate were observed only in the higher protein intake group. A higher protein intake can reduce the eGFR, consequently increasing indoles and phenols in patients with CKD. However, the association between higher protein intake and CKD-induced inflammation remains controversial.[20,21] In our study, patients with a higher protein intake were associated with higher proinflammatory levels, possibly because of the cumulative photolytic product. Dietary fiber can shift the colonic microbial activity from a proteolytic to a saccharolytic fermentation pattern. This results in the decreased generation of indoles and phenols and may further relieve inflammation.[22,23] However, some studies have reported that high dietary fiber suppresses appetite and energy intake.[24,25] It may promote malnutrition, which always occurs in CKD progression.[26] However, our results did not reveal an association between fiber intake and energy

Table 4. Effect of dietary fiber on CKD progression and other parameters in protein intake subgroups

Group	Parameter	Follow-up time (month)						
		Baseline	3	6	9[†]	12[‡]	15	18
LPLF N=45	eGFR (mL/min·1.73m^2)	48.4±15.3	45.9±15.3	43.6±15.4	40.9±15.7	38.3±15.6	35.7±15.7	33.0±15.9
(Protein intake <61 g/d, fiber intake <21.1 g/d)	ΔeGFR (mL/min·1.73m^2)	-	-2.51±1.07	-2.31±0.99	-2.75±1.09	-2.52±0.92	-2.66±0.88**	-2.66±1.08
	CRP (mg/mL)	4.08±2.86	3.98±2.70	4.08±2.77	4.09±2.92	4.37±2.97	4.96±3.41*	4.69±3.44
	IL-6 (pg/mL)	1.56±0.55	1.61±0.60	1.69±0.62	1.78±0.70	1.86±0.71	1.93±0.74	2.06±0.83
	Indoxyl sulfate (ng/mL)	27.9±15.1	29.9±16.7	31.7±18.3	33.9±19.4	34.9±21.1	36.1±22.3	37.4±24.5
	Cholesterol (mmol/L)	5.06±0.95	5.09±1.05	5.15±1.20	5.29±1.28*	5.19±1.42*	5.16±1.50	5.01±1.55
	Prealbumin (mmol/L)	227±37.5	221±38.0	223±43.8	223±51.1	225±55.6	231±64.3	235±70.3
LPHF N=33	eGFR (mL/min·1.73m^2)	52.1±17.7	49.8±17.9	47.2±18.0	46.0±17.4	43.9±17.4	41.9±17.6	39.6±18.0
(Protein intake <61 g/d, fiber intake ≥21.1 g/d)	ΔeGFR (mL/min·1.73m^2)	-	-2.29±1.01	-2.59±1.07	-2.31±1.11	-2.09±1.24	-2.01±1.08**	-2.28±0.88
	CRP (mg/mL)	2.97±2.46	3.01±2.40	3.03±2.33	2.99±2.15	3.23±2.40	3.38±2.53*	3.52±2.75
	IL-6 (pg/mL)	1.42±0.51	1.47±0.51	1.49±0.51	1.59±0.60	1.64±0.60	1.71±0.65	1.78±0.75
	Indoxyl sulfate (ng/mL)	26.2±15.2	27.1±15.8	27.3±16.3	29.3±17.4	31.3±19.5	33.0±20.4	35.1±21.9
	Cholesterol (mmol/L)	4.84±0.89	4.83±1.05	4.73±1.11	4.70±0.97*	4.70±0.97*	4.66±1.10	4.66±1.16
	Prealbumin (mmol/L)	225±38.1	221±42.4	224±47.6	223±53.4	228±70.6	225±76.4	228±79.0
HPLF N=33	eGFR (mL/min·1.73m^2)	51.5±20.3	48.5±20.2	45.9±20.6	45.0±18.2	43.6±16.9	40.5±16.7	37.3±16.5
(Protein intake ≥61 g/d, fiber intake <21.1 g/d)	ΔeGFR (mL/min·1.73m^2)	-	-2.98±0.93*	-2.71±1.10	-3.34±0.95**	-2.76±1.06	-3.09±1.00	-3.22±0.96**
	CRP (mg/mL)	3.67±2.48	4.20±2.79*	4.05±2.78	4.01±2.52	4.31±2.86	4.57±3.11*	4.21±2.96
	IL-6 (pg/mL)	1.78±0.92*	1.82±0.91*	1.91±0.95*	1.82±0.72*	1.90±0.85	1.95±0.87*	2.07±0.98*
	Indoxyl sulfate (ng/mL)	35.5±16.5*	37.2±18.1*	38.9±20.4*	41.7±20.9**	45.7±24.1**	47.7±25.5**	50.6±27.6**
	Cholesterol (mmol/L)	5.24±0.91	5.26±1.16	5.36±1.23*	5.31±1.35*	5.35±1.48*	5.38±1.61	5.53±2.08
	Prealbumin (mmol/L)	286±46.9	288±53.7	293±56.8	293±61.2	292±66.5	291±77.6	296±84.7
HPHF N=46	eGFR (mL/min·1.73m^2)	51.6±17.9	49.3±18.4	46.3±18.3	43.6±18.3	43.0±16.6	40.3±16.8	38.0±16.8
(Protein intake ≥61 g/d, fiber intake ≥21.1 g/d)	ΔeGFR (mL/min·1.73m^2)	-	-2.37±1.17*	-2.93±1.20	-2.70±0.98**	-2.40±0.94	-2.68±1.01	-2.27±0.98**
	CRP (mg/mL)	2.71±2.11	2.89±2.34*	3.08±2.59	3.17±2.55	3.17±2.79	3.17±2.72*	3.28±2.94
	IL-6 (pg/mL)	1.38±0.60*	1.43±0.62*	1.47±0.64*	1.52±0.69*	1.51±0.63*	1.57±0.65*	1.63±0.69*
	Indoxyl sulfate (ng/mL)	29.0±12.3*	29.7±12.9*	30.1±14.0*	30.4±14.3**	31.6±14.7**	33.6±15.8**	33.7±16.7**
	Cholesterol (mmol/L)	4.82±0.97	4.82±1.02	4.76±1.09*	4.77±1.18*	4.71±1.13*	4.75±1.18	4.78±1.29
	Prealbumin (mmol/L)	299±36.8	299±49.6	300±61.7	304±68.3	298±74.6	297±76.2	304±84.5

LPLF: lower protein intake with lower fiber intake; LPHF: lower protein intake with higher fiber intake; HPLF: higher protein intake with lower fiber intake; HPHF: higher protein intake with higher fiber intake; eGFR: estimated glomerular filtration rate; ΔeGFR: differential estimated glomerular filtration rate between the current time-point and the last one; CRP-C: reaction protein; IL-interleukin.
Continuous variables are presented as mean±SD.
[†]3 of participants were loss of follow-up (1 in LPHF and 2 in HPLF).
[‡]3 of participants were loss of follow-up (1 in HPLF and 2 in HPHF).
$^{*}p<0.05$, LPLF vs LPHF or HPLF vs HPHF;
$^{**}p<0.01$, LPLF vs LPHF or HPLF vs HPHF.

Table 5. Association of dietary fiber with cardiovascular risk in subgroups

Crude coefficient and subgroups	Hazard ratio	95% confidence interval	Chi-square	*p*-value
Crude coefficient	0.538	0.305 to 0.947	4.53	0.033*
Men	0.572	0.265 to 1.23	2.00	0.158
Women	0.501	0.217 to 1.16	2.55	0.110
Age <50 yr	0.720	0.327 to 1.59	0.631	0.427
Age ≥50 yr	0.404	0.175 to 0.936	4.87	0.027*
CRP <3.1 (mg/mL)	0.766	0.324 to 1.81	0.356	0.551
CRP ≥3.1 (mg/mL)	0.375	0.173 to 0.812	6.10	0.010*
Baseline eGFR >50 mL/min·1.73m^2	0.548	0.245 to 1.23	2.21	0.138
Baseline eGFR ≤50 mL/min·1.73m^2	0.556	0.250 to 1.24	1.90	0.168
Diabetes	0.321	0.114 to 0.905	4.86	0.028*
No-diabetes	0.670	0.357 to 1.26	1.48	0.223
BMI <20.2 kg/m^2	0.655	0.294 to 1.46	1.07	0.302
BMI ≥20.2 kg/m^2	0.441	0.198 to 0.983	3.84	0.050
Serum albumin <38.5 g/L	0.740	0.353 to 1.55	0.629	0.428
Serum albumin ≥38.5g/L	0.364	0.142 to 0.827	5.36	0.021*

eGFR: estimated glomerular filtration rate; BMI: body mass index.
*p<0.05

intake, protein accumulation, or nutritional parameters. Thus, our results suggest that higher fiber intake may compensate for the detrimental effects of dietary protein in CKD progression, but does not disrupt the nutritional status of patients, as reported by a previous study.[6]

Cardiovascular benefits may be one of the most desirable effects of dietary fiber and these have been extensively studied. The effects of CVD on health improvement involve multiple mechanisms, including lipid profile regulation, body weight regulation, improved insulin resistance, blood pressure control, and the reduction of chronic inflammation.[27] However, evidence on CKD is inadequate. Moreover, most studies were conducted in the United States and Europe, primarily among Caucasians of a relatively high socioeconomic status. It is unclear whether this association can be generalized to other ethnic groups, particularly in Eastern Asia where sources and ranges of fiber intake are considerably different. In this study, we observed a strong negative correlation between fiber intake and CVD; this result is in accordance with those reported by previous studies.[8,9] However, in a recent cohort study, Huang et al determined that high dietary fiber was associated with a lower mortality risk but could not determine the benefits of dietary fiber on CVD mortality.[18]This conflicting finding may be attributed to differences between the two studies. Huang et al adjusted the hazard ratio for hyperlipidemia, hypertension, and CRP, which were direct targets of fiber intake. Multicollinearity may yield an invalid result on fiber intake. In addition, the included participants were community-dwelling elderly men (age, 70–71 years) from Sweden, and half of them had a normal eGFR. Differences among the included participants may also cause inconsistencies. Nonetheless, our results are in concordance with those of a cross-sectional study conducted in the Japanese population,[9] and they may add to the existing evidence on the East Asian population.

In conclusion, our results suggest that increasing fiber intake retarded the decrease in the eGFR; reduced the levels of proinflammatory factors, indoxyl sulfate, and serum cholesterol; and was negatively associated with cardiovascular risk. However, the fiber intake did not disrupt the nutritional status in patients with CKD. The effects were stronger in patients with a higher protein intake than in those with a lower protein intake. The study has possible limitations. First, some fiber-rich foods, such as fruits and green vegetables containing potassium, may be harmful in the advanced stage of CKD. Therefore, it is imperative to investigate the food sources of fiber for patients with CKD. In addition, because of the low incidence of crucial endpoints such as stroke, ESRD, and death, their associations with dietary fiber were not assessed. Future research will focus on addressing the aforementioned limitations.

ACKNOWLEDGEMENTS

This research was supported by the National Science Foundation of China (No. 81573729 and No. 81373808), Southern Medical University scientific research Foundation (No. CX2015N003) and Traditional Chinese Medicine Project of Guangdong Province (No. 20151300).

AUTHOR DISCLOSURES

Lu Lu, Yan-Feng Huang and Ming-Qing Wang contrubute equally to the work. All of the authors had full access to the data and participated in the concept, design, and drafting of this manuscript. The authors declare that they have no conflicts of interest. This work has not been published elsewhere.

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