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Original Article

Effects of fermentable dietary fiber supplementation on oxidative and inflammatory status in hemodialysis patients

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Abstract: Background: Increased oxidative stress, inflammation, and malnutrition are important risk factors for cardiovascular disease in hemodialysis patients. High dietary intake in soluble fiber can decrease the elevated level of serum c-reactive protein in patients with chronic kidney disease. The aim of this study was to evaluate the effect of supplementation of dietary water-soluble fiber on oxidative and inflammatory status in hemodialysis patients. Methods: In a randomized placebo-controlled trial, we examined the effects of supplementation of dietary fiber on oxidative and inflammatory status in hemodialysis patients. 124 hemodialysis patients were randomly selected and given either 10 g/d, 20 g/d of fiber or placebo for 6 weeks. Anthropometric indices and 24 h diet recall intake was assessed. The CRP, albumin, triglyceride, total cholesterol, LDL, HDL were measured before and after of the intervention. The malondialdehyde (MDA), total antioxidant capacity (T-AOC), Cu-Zn superoxidase dismutase (SOD), glutathione peroxidase (GSH-Px) high-sensitivity C-Reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) were measured. Results: After 6 weeks of intervention, in 10 g and 20 g/d of fiber supplement groups, TC and LDL level and TC:LDL ratio were significantly decreased, T-AOC was significantly increased, MDA level was significantly deceased, TNF-α, IL-6, IL-8 and CRP level were significantly deceased. TG, HDL, SOD and GSH-Px had no change before and after the intervention. Conclusions: Dietary fermentable fiber supplementation improved lipid profile and oxidative status, decreased systemic inflammatory state of hemodialysis patients. Thus, it may decrease the risk of cardiovascular events in these patients.

Keywords: Dietary fiber, hemodialysis, inflammation, oxidative status, blood lipids, cardiovascular disease

Introduction

Cardiovascular disease is highly prevalent and has a major effect on morbidity and mortality in patients undergoing maintenance hemodialysis (MHD) [1]. Malnutrition and inflammation with hemodialysis were proved to be the common risk factors related to the high morbidity and mortality [2, 3].

Dietary fiber has been shown to have several health benefits related to cardiovascular disease [4, 5]. Evidence suggested that high dietary intake of fiber, specifically soluble fiber, can significantly lower LDL and total cholesterol, improve blood glucose response and lipid profiles [6-8]. Recent research in an analysis of data from 14,533 participants in the third National Health and Nutrition Examination Survey has demonstrated an association between dietary fiber and levels of C-reactive protein (CRP). Each 10 g/day increment in total fiber intake is associated with 38% and 11% decreased likelihood of having elevated C-reactive protein (CRP) in patients with and without CKD, respectively [9]. It is suggested that inflammation may be an important mediator in the association between dietary fiber and cardiovascular disease (CVD) [10].

As to the hemodialysis patients, most of them did not meet the dietary guidelines for reducing the risk of cardiovascular disease. Khoueiry et al [11] found that the mean fiber intake of hemodialysis patients was 10.77 ± 5.87 g/day, and only 2 of 71 (2.9%) were in compliance with the recommended daily intake of > 25 g/day. Kalantar-Zadeh et al [12] also found that

Table 1. Characteristics of subjects in the study at baseline

Parameters	Group A (n = 41)	Group B (n = 39)	Control (n = 44)
Age (y)	53.7 ± 14.2	51.7 ± 15.7	53.1 ± 13.2
Sex (M/F)	24/17	18/20	26/18
BMI (Kg/m^2)	22.5 ± 2.4	22.1 ± 2.1	22.8 ± 1.8
Dialysis duration (M)	22.7 ± 6.5	22.9 ± 7.1	22.2 ± 7.2
Number of comorbidities			
Chronic glomerulonephritis	23	21	25
Diabetic nephropathy	14	11	14
Hypertensive nephropathy	3	5	3
Polycystic kidney disease	1	2	2
SBP (mmHg)	135.6 ± 16.4	136.7 ± 16.6	136.3 ± 16.1
DBP (mmHg)	77.9± 12.7	79.1±11.5	81.3 ± 11.8
Creatinine (mmol/L)	912.4 ± 268.9	1013.5 ± 284. 1	948.6 ± 272.4
BUN (mmol/L)	23.5 ± 6.9	23.4 ± 6.3	22.7 ± 6.5
Albumin (g/L)	35.6 ± 1.4	34.8 ± 1.2	35.2 ± 1.6
Hemoglobin (g/L)	9.4 ± 3.5	9.1± 2.8	9. 5 ± 3.1
Transferrin (g/L)	48.5 ± 4.0	47.6 ± 5.2	49.2 ± 5.3
Fasting blood glucose (mmol/L)	6.6 ± 0.4	5.5 ± 0.7	6.5 ± 0.6

patients receiving dialysis may consume significantly lower amounts of dietary fibers (12 ± 6 g/d) compared to the non-dialytic individuals (18 ± 11 g/d).

It is important to confirm the relationships among dietary fiber, oxidation and inflammation, and CVD. The purpose of the present study was to prospectively evaluate the effects of dietary fiber supplementation on plasma lipid profiles, oxidative and inflammatory status in patients undergoing maintenance hemodialysis.

Materials and methods

This 6-week randomized controlled trial was conducted at the Dialysis Center from Department of Nephrology, Shanghai East Hospital, Tongji University, Shanghai, and approved by the Ethics Committee of Shanghai East Hospital. Written Informed consent was obtained from each patient and their medical records were studied by anonymous means. A total of 124 maintenance haemodialysis patients (68 males, 56 females, mean age 52.8 ± 13.6 y; range 46 to 71) were recruited between April 2013 and August 2014. The mean duration of haemodialysis in included patients was 22.63 ± 14.25 m. All patients recruited had no complications with acute inflammation, trauma, gastrointestinal disorders, liver diseases, cancers, mental retardation within recent three months, and there were no patients taking supplementation of herbs, antioxidants, vitamins/minerals, and fish oils. All patients received four-hour HD sessions three times a week with a high-flux membrane dialyzer. The dialysate flow rate was 500 mL/min and blood flow 250~300 ml/min, the heparin was used as an anticoagulant. Kt/V > 1.2 (1.46 ± 0.13) was achieved. The other clinical and dialysis characteristics are shown in **Table 1**.

This study consisted of one week on regular diet to establish baseline dietary intake and 6 weeks on regular diet plus dietary fiber supplementation. Each patient was instructed about how to follow a regular diet for dialysis and how to add soluble dietary fiber to rice by dietician during the first week. Water soluble fiber (fermentable rate > 75%) was used as supplement. The total daily dietary intake was estimated for each participant by diet assessment made at the end of the first week and the end of six weeks intervention. The regular diet was prescribed with caloric intake 35 kcal/kg bw, protein intake 1-1.2 g/kg bw, fats < 35%, and with sodium and potassium restriction. During nutrition intervention period, patients maintained their regular diets and add either 10 grams fiber (Group A), 20 grams fiber (Group B) or pla-

Table 2. Estimated dietary intakes anthropometric characteristics of the subjects in the study (Mean ± SD)

Parameters	Group A		Group B		Group control	
	Before	After	Before	After	Before	After
Energy (Kcal)	1334.5 ± 53.3	1207.5 ± 47.8	137.5 ± 44.6	1380.2 ± 51.6	1259.2 ± 48.2	1206.2 ± 49.3
Protein (%)	13.4 ± 2.4	12.9 ± 2.7	15.1 ± 2.2	13.5 ± 2.0	14.6 ± 2.4	12.7 ± 2.8
Carbohydrate (%)	63.5 ± 11.9	61.7 ± 11.5	67.5 ± 11.1	62.8 ± 13.7	64.3 ± 11.2	64.7 ± 12.4
Fats (%)	24.8 ± 9.6	25.3 ± 7.7	25.6 ± 8.1	24.7 ± 9.2	26.3 ± 11.7	24.5 ± 9.4
Dietary fiber without added (g)	11.4 ± 5.5	10.8 ± 5.1	12.3 ± 6.7	11.6 ± 6.1	10.2 ± 4.7	10.7 ± 6.5
P (mg)	1481.6 ± 314.9	1376.6 ± 331.4	1327.5 ± 368.8	1563.5 ± 432.3	1476.2 ± 457.1	1423.8 ± 456.7
Ca (mg)	544.2 ± 84.4	525.9 ± 77.5	503.2 ± 76.3	568.2 ± 93.6	518.4 ± 88.7	521.6 ± 93.6
Weight (Kg)	58.4 ± 5.5	58.7 ± 6.1	58.6 ± 4.7	57.8 ± 6.2	58.1 ± 5.7	57.4 ± 5.2
AC (cm)	23.2 ± 1.4	22.6 ± 2.1	22.5 ± 1.8	22.6 ± 1.6	23.5 ± 1.4	22.5 ± 2.4
TSF (mm)	10.4 ± 0.9	10.7 ± 0.6	10.1 ± 0.5	10.5 ± 0.5	10.9 ± 0.6	10.2 ± 0.6
BMI (Kg/m^2)	22.5 ± 2.4	22.4 ± 2.2	22.1 ± 2.1	22.7 ± 2.5	22.8 ± 1.8	22.6 ± 2.3

cebo starch (Control group) to their staple food rice.

Five-milliliter blood samples were collected after 12 h of overnight fasting and immediately prior to dialysis before the intervention and after 6 weeks. Plasma was prepared by blood centrifugation (3000 g, 10 minutes) and stored at -70°C until required. Albumin, transferrin, creatinine, urea nitrogen, hemoglobin, triglycerides (TG), total cholesterol (TC), LDL, HDL were tested with Hitachi 7180 Automatic Analyzer. The malondialdehyde (MDA), total antioxidant capacity (T-AOC), glutathione peroxidase (GSH-Px) and Cu, Zn-SOD (SOD) activities were determined with assay kits (Nanjing Jianchen Bio. Co.). High-sensitively C-reactive protein (hs-CRP) concentrations were measured using the hs-CRP ELISA kit, and inflammatory cytokines IL-6, IL-8 and tumor necrosis factor-α (TNF-α) were measured with ABC-ELISA (Shanghai Shenxiong Biotech Co.).

Anthropometric measurements including mid arm circumference (AC), triceps skinfold thickness (TSF), weight and height were done after termination of the hemodialysis sessions at the time before and after intervention. The body mass index (BMI) was calculated according to Weight/(height)^2 formula.

A 3-day diet diary assessed by a trained dietitian was used to estimate daily dietary intake. Dietary intake was recorded over the last hemodialysis treatment day of the week and the two subsequent nondialysis days. The YY Nutrition Analysis software (version 2.05) was used to complete the nutrient analysis.

Statistical analysis

All analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, Ill, USA). The results were expressed as mean ± standard deviation for all continuous data. The normality of data was confirmed by the Shapiro-Wilk test. For comparison of different variables, chi-square test, student's t-test, pair t-test, one-way analysis of variance (ANOVA), or Kruskal-Wallis ANOVA, as appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

There were 124 patients in total participated in this study. The three groups were comparable with respect to sex distribution, age, weight, height, BMI, prevalence of existing comorbidity, hemodialysis duration, nutritional status, fasting blood glucose before supplementation intervention (**Table 1**).

After the 6 weeks dietary fiber supplementation, there were no significant differences in dietary intakes and anthropometric measurements among the three groups (**Table 2**).

No changes in TG levels among the three groups were observed. Total cholesterol was significantly reduced over the 6 weeks dietary fiber intervention in both groups A and B (P < 0.05). There was no significant difference in HDL levels among groups (P > 0.05). LDL was significantly reduced after intervention in both groups A and B (P < 0.05) compared to base-

Table 3. Lipid profiles of the subjects in the study (Mean ± SD)

Parameters	Group A		Group B		Group control	
	Before	After	Before	After	Before	After
TG (mmol/L)	2.6 ± 1.5	2.5 ± 1.4	2.6 ± 1.6	2.6 ± 1.5	2.6 ± 1.5	2.5 ± 1.4
TC (mmol/L)	4.8 ± 1.3	4.3 ± 1.1[a,b]	4.8 ± 1.2	4.2 ± 1.3[a,b]	4.8 ± 1.2	4.8 ± 1.2
LDL (mmol/L)	2.6 ± 0.5	2.1 ± 0.3[a,b]	2.7 ± 0.3	2.2 ± 0.3[a,b]	2.6 ± 0.4	2.5 ± 0.3
HDL (mmol/L)	1.3± 0.4	1.4 ± 0.5	1.4 ± 0.6	1.4 ± 0.7	1.3 ± 0.5	1.3 ± 0.5
TC:HDL ratio	3.6 ± 0.4	3.0 ± 0.3[a,b]	3.4 ± 0.4	2.9 ± 0.4[a,b]	3.3 ± 0.4	3.5 ± 0.4

[a]$P < 0.05$ vs. before value within the group; [b]$P < 0.05$ vs. after value with control group.

Table 4. Oxidative and inflammatory status in the study groups (Mean ± SD)

Parameters	Group A		Group B		Group control	
	Before	After	Before	After	Before	After
SOD (U/ml)	71.7 ± 23.6	73.4 ± 29.4	75.7 ± 27.6	65.2 ± 31.5	67.3 ± 21.3	67.4 ± 22.4
T-AOC (U/ml)	7.3 ± 4.7	16.4 ± 6.8[a,b]	6.4 ± 4.2	15.7 ± 5.4[a,b]	7.0 ± 4.4	8.3 ± 4.6
MDA (nmol/L)	15.4 ± 6.3	6.4 ± 2.1[a,b]	12.5 ± 4.3	5.6 ± 2.8[a,b]	14.6 ± 4.2	15.2 ± 4.5
GSH-Px (U/L)	80.6 ± 21.2	84.4 ± 36.1	86.7 ± 31.4	74.8 ± 26.5	87.2 ± 29.2	71.4 ± 32.5
TNF-α (pg/mL)	13.3 ± 1.8	10.1 ± 1.4[a,b]	12.5 ± 1.8	10.6 ± 1.6[a,b]	13.0 ± 1.6	13.1 ± 2.4
IL-6 (pg/mL)	47.2 ± 7.3	31.8 ± 5.3[a,b]	48.7 ± 9.4	35.2 ± 7.3[a,b]	48.5 ± 9.2	51.5 ± 14.6
IL-8 (pg/mL)	94.8 ± 6.9	22.2 ± 4.8[a,b]	91.4 ± 7.2	34.5 ± 3.7[a,b]	87.6 ± 6.5	96.4 ± 7.2
HsCRP (mg/L)	10.7 ± 4.8	4.8 ± 4.5[a,b]	9.8 ± 4.8	4.7 ± 4.3[a,b]	9.4 ± 4.9	9.5 ± 5.6

[a]$P < 0.05$ vs. before value within the group; [b]$P < 0.05$ vs. after value with control group.

line, however, no significant differences between the two groups were noted at the end of the study ($P > 0.05$). The TC:HDL ratios were significantly improved in both groups A and B compared to baseline ($P < 0.05$). No significant changes in all variables between before and after values in control group ($P > 0.05$) (**Table 3**).

The plasma concentration of T-AOC after six weeks of dietary fiber supplementation in both group A and group B were significantly increased compared to the before values ($P < 0.05$), respectively. The after values of T-AOC in group A and group B were both significantly higher than the after value in control group ($P < 0.05$). There was no significant difference between the after values of T-AOC in group A and group B ($P > 0.05$). The after values of blood MDA content in group A and group B were both significantly lower than the baseline values ($P < 0.05$), respectively, but not statistically different between group A and group B ($P > 0.05$). There were no significant changes between before and after values MDA in group control ($P > 0.05$). No significant differences in both blood levels of SOD and GSH-Px among the three groups ($P > 0.05$) were observed.

HD patients had very high plasma concentration of TNF-α, IL-6, IL-8 and CRP (**Table 4**). After six weeks of dietary fiber intervention, the plasma concentration of IL-6, IL-8 and Hs-CRP in the Group A and Group B significantly decreased compared to the baseline value ($P < 0.05$), respectively, and significantly lower than the after value in control group ($P < 0.05$). The after values between Group A and Group B were not significantly different ($P > 0.05$). There was no statistical difference between the before and after values in control group ($P > 0.05$). No significant changes in the concentration of TNF-α were observed among the three groups ($P > 0.05$).

Discussion

Patients receiving dialysis may consume significantly lower amounts of dietary fibers. Bossola M et al [13] assessed daily dietary intake in 128 hemodialysis patients by a three day diary and found mean daily dietary fiber intake of these patients was 11.8 ± 6.1 g. Kalantar-Zadeh [12] also found that the amount of daily intake in 102 maintenance hemodialysis patients was 12 ± 6 g/d. In this study, a 3-day diary was used and data of 124 patients on

chronic hemodialysis were assessed. We found that the mean dietary fiber intakes in group A from their background diet were 11.4 ± 5.5 g/d before intervention and 10.8 ± 5.1 g/d after intervention, 12.3 ± 6.7 g/d, 11.6 ± 6.1 g/d in group B, and 10.2 ± 4.7 g/d, 10.7 ± 6.5 g/d in control group, respectively. There were no statistical differences among the three groups ($P > 0.05$). The amount of dietary fiber in the diet in our patients was likely lower than that in the studies mentioned above, though the dietary pattern for Chinese is mainly the food from plant origin. Results [14] from National Nutrition and Health Survey 2002 showed that the total and insoluble dietary fiber intake per reference man per day were 18.7 g/d and 12.0 g/d respectively. Wang ZH et al [15] reported that data from China Health and Nutrition Survey showed that dietary fiber intake among Chinese aged 18~45 were 15.7 g/d in 1989, 17.0 g/d in 2000, 16.4 g/d in 2004, and 17.6 g/d in 2006. Compared to healthy Chinese population, the dietary intake in hemodialysis population is much lower. Poor appetite and diet restriction during hemodialysis treatment may negatively impact their dietary fiber intake. Patients in group A and group B were instructed to add 10 g/d and 20 g/d of soluble fiber to their staple food rice, respectively. So the amount of daily dietary fiber intake in group A was about 20.8 g/d, and group 31.6 g/d respectively in total. In control group, starch was added as placebo.

The effect of dietary soluble fiber on serum cholesterol levels has been extensively documented. The result from a meta analysis [16] of 67 controlled trials showed that 2-10 g/d supplementation of dietary soluble fiber such as pectin, oat bran, gum and psyllium was associated with significant decreases in total cholesterol and LDL cholesterol. Knopp RH et al [17] reported that 87 subjects with mild to moderate hypercholesterolemia (LDL cholesterol 3.37-4.92 mmol/L) were given 20 g/d of water-soluble fiber supplement for 36 weeks and significant and sustained reduction in LDL without reducing HDL or increasing triglycerides were observed. Hunninghake et al [18] conducted a clinical trial in which patients with mild to moderate hypercholesterolemia were treated with 10 or 20 g/d of the fiber supplement for 15 weeks, and found that total cholesterol, LDL cholesterol, and the ratio of LDL to HDL were significantly reduced compared with the placebo group. Katie M Queenan et al [19] reported that 75 healthy hypercholesterolemic men and women were given either 6 g/d concentrated oat beta-glucan for 6 weeks and found total and LDL cholesterol were significantly reduced. In this study, hemodialysis patients were treated with 10 g/d (n = 41) or 20 g/d (n = 39) of fermentable dietary fiber for 6 weeks, and the effects of the fiber supplement on cholesterol are consistent with those of other studies evaluating the effects of various water-soluble dietary fiber. We found that treatment with the fiber supplement to hemodialysis patients significantly decreased TC, LDL and TC:LDL ratio, but there were no significant differences among the treatment groups over time in the changes from baseline in HDL and triglycerides. Compared to the control group, there was a significantly greater decrease in TC, LDL and TC: LDL ratio in dietary fiber treatment groups. It was assumed that soluble fibers can bind with bile acids in the small intestine, thereby removing them from the body and stop the bile acid recycling. As a result, total and LDL cholesterol in blood are reduced, while HDL cholesterol and triglycerides are generally unaffected [20, 21]. In addition, soluble fibers are fermented in the lower gut into short-chain fatty acids (SCFAs) and gases. When SCFAs enter the circulatory system, they may regulate gut hormones, inhibit the liver from producing cholesterol and consequently have a direct cholesterol-lowering effect [22, 23].

The role of dietary fiber in the prevention of cardiovascular disease has received increasing attention as data have accumulated. It was believed that fiber may promote cardiovascular health by inhibiting vascular inflammatory processes. C-reactive protein (CRP) is one of several inflammatory compounds formed during atherogenesis. Research has demonstrated an association between dietary fiber and levels of CRP [10, 24]. Numerous studies [25, 26] have revealed positive correlations between dietary fiber intake and levels of circulating CRP. In addition to CRP, research also found that dietary fiber was inversely related to other inflammatory biomarkers, mainly cytokins such as IL-6, IL-8 and TNF-α, etc [27, 28]. Hemodialiysis patients at the end stage of chronic kidney disease is considered on an inflammatory state, and the causes of inflammation are multifactorial including exposure of blood to dialyzer membranes or tubing, infection on vascular access, reduced antioxidants,

and increased oxidative stress [29, 30]. Krishnamurthy et al [9] analyzed data from 14,543 participants in the National Health and Nutrition Examination Survey III and found that for each 10g/day increase in total fiber intake, the odds of elevated serum C-reactive protein levels were decreased by 11% and 38% in those without and with kidney disease, respectively. We conducted an interventional trial in order to establish the effects of fiber intake on inflammation status in patients undergoing hemodialysis. The results showed that after 10 g and 20 g/d dietary fiber supplementation for 6 weeks, CRP, IL-6, IL-8 and TNF-α were significantly decreased. We also evaluated the effects of dietary supplementation of soluble fiber on the oxidative status in hemodialysis patients, and it was found that the plasma concentration of T-AOC after six weeks of dietary fiber supplementation in both 10 and 20 g/d groups were significantly increased compare to the baseline values, respectively ($P < 0.05$). The after values of blood MDA content in groups of 10 and 20 g/d dietary fiber supplement were both significantly lower than the baseline values, respectively ($P < 0.05$). There were no significant differences in blood levels of SOD and GSH-Px among the three groups ($P > 0.05$), respectively. For the interpretation of these results, there should be mentioned that we had some limitations such as small sample size and short period of intervention.

In conclusion, the results of this study revealed that supplementation of dietary soluble fiber can improve inflammatory and malnutrition status in hemodialysis patients. Dietary fiber supplementation might be one of important therapeutic strategies to prevent CVD mortality and morbidity for these patients. However, further investigations will be required in this regard and also we suggest study the effect of dietary fiber supplements on uremic solutes which are derived from the action of colon microbes and on the micronutrients status.

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Disclosure of conflict of interest

None.

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