

Effect of a High-Fiber Diet vs a Fiber-Supplemented Diet on C-Reactive Protein Level

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Background: Diets high in fiber are associated with lower levels of inflammatory markers. This study examined the reduction in inflammation from a diet supplemented with fiber compared with a diet naturally high in fiber.

Methods: Randomized crossover intervention trial of 2 diets, a high-fiber (30-g/d) Dietary Approaches to Stop Hypertension (DASH) diet or fiber-supplemented diet (30 g/d), after a baseline (regular) diet period of 3 weeks. There were 35 participants (18 lean normotensive and 17 obese hypertensive individuals) aged 18 to 49 years.

Results: The study included 28 women and 7 men; 16 (46%) were black, the remainder white. The mean (SD) fiber intake on baseline diets was 11.9 (0.3) g/d; on the high-fiber DASH diet, 27.7 (0.6) g/d; and on the supplemented diet, 26.3 (0.4) g/d. Overall, the mean C-reactive protein (CRP) level changed from 4.4 to 3.8 mg/L (−13.7%; $P = .046$) in the high-fiber DASH diet group and to 3.6 mg/L (−18.1%) in the fiber-supplemented diet group

($P = .03$). However, CRP levels decreased in the 18 lean normotensive participants in either intervention diet group (2.0 mg/L [baseline] vs 1.4 mg/L [high-fiber DASH] vs 1.2 mg/L [supplemented]); $P < .05$) but did not change significantly (7.1 mg/L [baseline] vs 6.2 mg/L [high-fiber DASH] vs 6.5 mg/L [supplemented]; $P > .05$) in obese hypertensive participants. Neither age nor race influenced the response of CRP levels to the diets. No evidence of a crossover effect was detected.

Conclusions: The results demonstrate that fiber intake of about 30 g/d from a diet naturally rich in fiber or from a supplement can reduce levels of CRP. Further research is needed to more clearly elucidate the differential effect seen in lean vs obese individuals and whether modification of dietary fiber may be helpful in modulating inflammation and its consequent cardiovascular consequences.

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RECENT EVIDENCE SUPPORTS A significant role for inflammation in the development of cardiovascular disease. Elevation of the C-reactive protein (CRP) level, a key inflammatory marker,¹ has been linked to insulin resistance, hypertension, the development of diabetes mellitus, and the metabolic syndrome and other risk factors for cardiovascular diseases.²⁻⁷ In addition, higher levels of inflammatory markers such as CRP are associated with an increased risk of cardiovascular events.⁸⁻¹⁰ A large percentage of the adult population has elevated CRP levels (>25%).⁷ Consequently, the identification of interventions to a lower CRP level is important for public health.¹ One direction for intervention suggested by several epidemiologic studies^{11,12} is diet, and in particular, a high-fiber diet.^{7,13}

Although weight loss and lower body mass index (BMI) (calculated as weight in kilograms divided by height in meters

squared) have been associated with lower CRP levels,¹⁴ to our knowledge, the effects of specific dietary factors such as fiber on CRP levels and other markers of inflammation have not been well elucidated in prospective studies. Esposito et al¹⁵ recently demonstrated a significant lowering of inflammatory markers using a high-fiber Mediterranean diet for 2 years, but information on the specific role of fiber is limited owing to the study's use of multiple lifestyle changes in the intervention and the inclusion of women only.¹⁵ Another study found a significant association between total dietary fiber and the likelihood of elevation of the CRP level that was independent of age, race, sex, BMI, and smoking.¹³ However, these data were cross-sectional; therefore, only general association, not causality, could be tested. Further prospective research is needed to evaluate the relationship between dietary fiber and inflammatory markers to determine whether a high-fiber diet or fiber

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supplementation can achieve a significant reduction in CRP levels.¹²

The purpose of this study was to determine whether a high-fiber diet would reduce inflammatory markers, including CRP, and compare the results obtained using a diet naturally high in fiber with those obtained using a fiber supplement (psyllium) to achieve the same amount of grams per day of fiber.

METHODS

The protocol was reviewed and approved by the institutional review board at Medical University of South Carolina (MUSC), Charleston. The study was a randomized crossover intervention trial of 2 diets, a diet naturally high in fiber diet or fiber-supplemented diet, after a baseline diet period of 3 weeks.

Study volunteers were recruited from the staff and clinics at MUSC using newspaper and internet advertisements. Potential participants were directed to call the study coordinator and undergo a screening evaluation. The principal investigator (D.E.K.) or coinvestigating researcher (Y.A.-S. or A.J.) obtained informed consent from each volunteer in the outpatient unit of the MUSC General Clinical Research Center (GCRC) prior to any study procedures.

The telephone screening evaluation included obtaining information on height, weight, and age and confirmed that subjects were nonsmokers, did not have diabetes mellitus, were not taking any medications, and were not pregnant. The research coordinator then described the protocol, diets, laboratory assessments, total number of visits, and compensation; interested and eligible participants were invited to the initial visit and given directions to the GCRC outpatient center. A pregnancy test was performed to exclude pregnancy at each GCRC visit that included laboratory assessment for CRP. In addition, a physical examination was performed on the screening visit and on each follow-up visit during the study to monitor for any new medical illness that might affect the inflammatory state of the patient.

INCLUSION/EXCLUSION CRITERIA

Lean normotensive volunteers had to be 21 to 49 years old, have BMIs less than 25, waist (abdominal)-to-hip circumference ratios of less than 0.80 for women and less than 0.85 for men; blood pressure consistently lower than 130/85 mm Hg on all 3 visits prior to the first study, fasting glucose level less than 110 mg/dL (<6.1 mmol/L), glycosylated hemoglobin (HbA1c) level less than 5.6%, fasting triglycerides level less than 125 mg/dL (<1.41 mmol/L), high-density lipoprotein cholesterol level greater than 40 mg/dL (>1.04 mmol/L) for men and greater than 45 mg/dL (>1.17 mmol/L) for women, and total cholesterol level less than 200 mg/dL (<5.18 mmol/L).

Obese, hypertensive (high normal, stage 1) volunteers had to be 21 to 49 years old, have BMIs of 27 or greater, and have 3 or more of the following characteristics: a waist circumference greater than 40 in (>101.6 cm) for men and greater than 35 in (>88.9 cm) for women, blood pressure consistently in the range of 130/85 to 159/99 mm Hg on 3 visits prior to the first study day, not taking medications, fasting glucose level less than 126 mg/dL (<7.0 mmol/L) (individuals with diabetes mellitus were excluded, but those with impaired fasting glucose included), HbA1c level less than 7%, and fasting triglyceride levels greater than 150 mg/dL (>1.70 mmol/L) or high-density lipoprotein cholesterol levels less than 50 mg/dL for women (<1.30 mmol/L) and less than 40 mg/dL (<1.04 mmol/L) for men.

Participants were excluded for the presence of diabetes mellitus (fasting blood glucose level ≥ 126 mg/dL [≥ 7.0 mmol/L]), clinically evident target organ damage (more than grade 1 Keith-Wagner-Barker ophthalmic category change), left ventricular hypertrophy as evaluated by electrocardiogram, serum creatinine level of 1.5 mg/dL (133 μ mol/L) or higher, findings from using a urine protein dipstick test of 0.1 g/dL or higher, or history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, congestive heart failure, or pregnancy.

INTERVENTION DIETS

Participants were evaluated first while eating their regular diet and again after randomization to a diet naturally high in fiber (30 g/d; the Dietary Approaches to Stop Hypertension [DASH] diet¹⁶) and a diet supplemented with fiber (psyllium) (hereafter, supplemented diet) to reach 30 g/d, for 3 weeks each. The latter 2 diets were randomized in a 2-period crossover design.¹⁷ The caloric composition of both diets was planned and carefully regulated to achieve a composition of 50% carbohydrate, 34% fat, and 16% protein. The high-fiber DASH diet was also naturally high in antioxidants and thus contained more monosaturated and polyunsaturated fat and less saturated fat than the supplemented diet. For participants in the supplemented diet group, fiber (psyllium) was added to the usual diet to match the fiber content (30 g) of the high-fiber DASH diet. A dietary guideline and sample menus for the high-fiber diets were developed by using minimal modification of the DASH guidelines. The high-fiber DASH diet and the supplemented diet differed in the amount of, respectively, potassium (4100 mg/d vs 1700 mg/d) and magnesium (500 mg/d vs 165 mg/d). Thus, we added appropriate amounts of potassium gluconate (2400 mg/d) and magnesium oxide (335 mg/d) to the supplemented diet to equal the amounts in the high-fiber DASH diet. A licensed dietician designed the diets and instructed each volunteer in the study diet groups.

To ensure dietary compliance, participants were required to photograph all of their food and beverages for 3 days each week of each 3-week diet period. These photographs were reviewed by the licensed dietician. The GCRC dietician carefully estimated diet composition and compliance from the photographs. Weekly urine collections to measure sodium, potassium, calcium, and magnesium levels were also used to confirm compliance. The dietician also met briefly with each participant to answer questions and provide advice to enhance dietary compliance. Weight was measured weekly, and patients were excluded from the study if they lost or gained 1.4 kg (3 lb).

BIOCHEMICAL AND HEMODYNAMIC MEASUREMENT

C-reactive protein levels were measured by high-sensitivity CRP (hs-CRP) assay on a chemistry analyzer (DxC 800; Beckman Coulter Synchron, Fullerton, Calif) using serum from participants. The Beckman Coulter CRP reagent is based on the highly sensitive near-infrared particle immunoassay rate methods. Fibrinogen concentration was determined by the Clauss clotting method, which measures the rate of fibrinogen conversion to fibrin in a diluted sample under the influence of excess thrombin. The white blood cell (WBC) count was measured with the Beckman Coulter MAXM automated hematology instrument.

Data analysis centered on before-and-after comparisons of all participants in each diet group. The principal data of interest included CRP and fibrinogen levels and WBC count. Comparisons were made using paired *t* tests to compare levels of

Table 1. Baseline Descriptive Characteristics of the 35 Patients in the Study Sample

Category	Value
Age, mean (SD), y	38.3 (1.2)
Race, % black	45.8
Sex, % female	80.0
Systolic BP, mean (SD)	121 (2.5)
Diastolic BP, mean (SD)	76 (1.9)
BMI, mean (SD)	28.4 (1.1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure.

Table 2. Average Daily Supplement Intake According to Diet*

Supplement	Baseline Diet	High-Fiber DASH Diet	Supplemented Diet
Fiber intake, g/d	11.9 (0.3)	27.7 (0.06)	26.3 (0.4)
Potassium intake, mg/d	1926 (41.0)	3762 (58.0)	4054 (49.0)
Magnesium intake, mg/d	210 (4.2)	451 (8.1)	400 (7.2)

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.
*Data are given as mean (SD).

CRP. Further analyses included comparisons of fibrinogen levels and WBC count before and after diet intervention, also using paired *t* tests. A 2-period crossover analysis of variance was conducted for the CRP primary dietary analyses. The test for crossover effect was performed prior to assessment of the primary dietary effects on CRP levels, using the Satterthwaite approximation for degrees of freedom. The crossover effect test was performed at the $\alpha = .10$ level. Differences in CRP and fibrinogen levels and WBC count between the normotensive and hypertensive groups after being on the high-fiber DASH diet were assessed using multivariate analysis of variance. Exact *P* values are calculated with statistical significance set at .05.

RESULTS

The study included 35 participants (28 women and 7 men); 16 (45.8%) were black, the remainder white (**Table 1**). The mean (SD) age of participants was 38.3 (1.2) years. There were 18 lean normotensive and 17 obese hypertensive individuals. The mean (SD) fiber intake in the baseline diet was 11.9 (0.3) g/d. The average intake of the study supplements according to diet is shown in **Table 2**. The compliance rates were 89% and 84% in the high-fiber DASH diet and supplemented diet groups, respectively. The mean (SD) CRP level at baseline was 4.4 (0.1) mg/L; the mean (SD) fibrinogen level was 3.11 (0.12) g/dL (91.5 [5.9] $\mu\text{mol/L}$); and the mean (SD) WBC count was $5.4 (0.2) \times 10^3/\mu\text{L}$.

Overall, the mean CRP levels changed from 4.4 to 3.8 mg/L (-13.7% ; $P = .046$) in the high-fiber DASH diet group and from 4.4 to 3.6 mg/L (-18.1%) in the supplemented diet group ($P = .02$) (**Table 3**). Fibrinogen levels and WBC count did not change ($P = .91$) in those in either intervention diet group. Weight, triglycerides level, chole-

sterol level, and insulin resistance status also did not change in either intervention diet group ($P > .05$ for all).

The CRP levels changed to a greater percentage in lean participants than in obese participants (Table 3). The CRP level was 2.0 mg/L in lean participants and decreased by 30% to 1.4 mg/L in the high-fiber DASH diet group and by 40% to 1.2 mg/L in the supplemented diet group ($P < .05$ for both). In obese participants, CRP levels did not change significantly (7.1 mg/L [baseline] vs 6.2 mg/L [high-fiber DASH] vs 6.5 mg/L [supplemented], respectively; $P > .05$). Neither age nor race influenced the response of CRP levels to the diets.

The test for crossover effect was calculated, producing a test statistic of $t = -1.33$ on 17.5 *df*, which has a *P* value of .20. Thus, no evidence of a crossover effect was detected in these data. The 2 treatment diet groups were then compared with each other to detect differences in the treatment effect. The analysis produced a result statistic of 1.76 on 26.5 *df*, which has a *P* value of .09. The mean CRP difference of the supplemented minus the high-fiber DASH diet is 0.051 (95% confidence interval, -0.008 to 0.111). Thus, there was not a statistically significant difference between the CRP measurements of the participants in the supplemented diet and the high-fiber DASH diet groups. Two-period crossover analyses of the CRP levels measured as percentage change from baseline produced similar findings.

COMMENT

In this study, we tested the hypothesis that providing a diet rich in fiber (25-30 g/d)¹⁸ would significantly reduce inflammation and specifically result in lower CRP levels. The rationale underlying the clinical trial was epidemiologic evidence demonstrating that people with higher fiber intake had a significantly lower likelihood of elevated CRP levels compared with people with lower intake.¹³

In the current study, we found that CRP levels were reduced by 14% in the high-fiber DASH diet and by 18% in the supplemented diet, with no difference between the 2 treatment groups. Reductions in WBC count and fibrinogen levels were not observed. The findings of this study provide new information regarding the relationship between inflammatory markers and dietary fiber and lend support to the fiber intake recommendations in the recently revised American Heart Association guidelines.¹⁹ The reduction in CRP levels was relatively prompt and occurred regardless of whether the fiber was provided by a diet naturally rich in fiber or was provided in the form of a fiber supplement (psyllium) in combination with a lower-fiber diet. The results of this clinical trial provide clinically useful information for formulating dietary advice for people with elevated levels of inflammatory markers.

That lean normotensive participants experienced a greater relative reduction in CRP measurements (40% vs 10%) compared with obese hypertensive persons is both surprising and disconcerting. The result is surprising because many proposed mechanisms for how fiber affects CRP levels, such as modulation of metabolism in ab-

Table 3. Values of Inflammatory Biomarkers According to Diet*

Value	Baseline Diet	High-Fiber DASH Diet	P Value†	Supplemented Diet	P Value†
CRP level, all participants, mg/L	4.4 (1.0)	3.8 (0.98)	.046	3.6 (1.0)	.03
CRP, lean group, mg/L	2.0 (0.6)	1.4 (0.4)	<.05	1.2 (0.4)	<.05
CRP, obese group, mg/L	7.2 (1.8)	6.5 (1.8)	>.05	6.2 (1.8)	>.05
Fibrinogen, g/dL	3.11 (0.12)	3.12 (0.12)	>.05	3.17 (0.12)	>.05
WBC, ×10 ³ /L	5.4 (0.25)	5.5 (0.26)	>.05	5.6 (0.25)	>.05

Abbreviations: CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; WBC, white blood cell count.

SI conversion factor: To convert fibrinogen values to micromoles per liter, multiply by 29.41.

*Data, other than P values, are given as mean (SD).

†Compared with value at baseline.

dominal fat,¹¹ would tend to be more pronounced in the obese participants rather than the lean individuals. However, the absolute reduction in CRP levels was similar in the lean and obese groups (0.6-0.8 mg/L); thus the differences in relative change may be due to the higher baseline CRP levels in the obese participants (7.1 mg/L vs 2.0 mg/L in the lean participants). The finding of less relative effect in obese individuals is somewhat disappointing because one would hope that the intervention would work best in the people who need it most, but this was not the case in the current study. Obese persons, who have higher CRP levels than the general population, did not experience significant reductions in levels of CRP in the study. Obese individuals may not respond as well owing to the presence of insulin resistance or other components of the metabolic syndrome, or they may need higher doses of fiber to see greater change. Thus, obese individuals may need a combination of interventions to reduce their CRP levels to lower risk levels (<3.0 mg/L, per the American Heart Association guidelines).¹

The mechanism of change in CRP levels as a result of dietary intake (and fiber intake in particular) are still a matter for research. Several possibilities have been considered, including fiber causing a slowing of absorption of glucose¹²; meal modulation of cytokines that blunts hyperglycemia, oxidative stress, and inflammation^{11,20}; and gut flora responding favorably to fiber by producing anti-inflammatory cytokines.²¹ Any or all of these mechanisms may play a role.

The study has some limitations worth noting. The duration of each diet was relatively short, only 3 weeks. A longer duration could have resulted in either greater changes or an accommodative effect on CRP levels. Only a longer trial can address this issue. Furthermore, the supplemented group was supplied supplemental magnesium and potassium in addition to fiber to closely match the natural diet group and isolate the effect of fiber. However, the provision of multiple supplements during the trial may complicate replication of these results in practice because of the need to take multiple supplements to match the intervention. The ongoing Trial to Reduce Inflammation (TRIM) trial,²² which is testing the impact of fiber supplementation only in 180 adults, may provide more information.

The results of the current study demonstrate that a diet high in fiber (near 30 g/d), whether achieved natu-

rally or from a supplement, can reduce levels of CRP. The results are modest in their overall impact, owing to no definite impact in obese persons. Nevertheless, the findings indicate that modification of dietary fiber may be helpful in modulating inflammation to a certain degree. It is unclear whether the small effect demonstrated here would be seen over a longer period in the general population, but if so, there would be possible beneficial consequences on cardiovascular risk. Further research is needed to more fully understand which types of fiber work best and which individuals are most susceptible to its anti-inflammatory effect, so that the long-term goal of reducing cardiovascular risks can be realized.

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