Long-Term Effects of Water-Soluble Dietary Fiber in the Management of Hypercholesterolemia in Healthy Men and Women

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Fifty-one healthy, moderately hypercholesterolemic men and women consuming their usual fat-modified diets completed a 6-month, randomized, double-blind, placebo-controlled, parallel comparison of 15 g/day supplemental water-soluble dietary fiber (WSDF; a mixture of psyllium, pectin, guar gum, and locust bean gum) and an inactive WSDF control (acacia gum). Compliance with the treatments was >95%, adverse effects were minimal, and body weights remained constant. The WSDF mixture yielded 6.4% and 10.5% reductions in mean plasma total and low-density lipoprotein cholesterol concentrations, respectively, after 8 weeks, which were sustained at 16 and 24 weeks. Mean plasma high-density lipoprotein cholesterol and triglyceride concentrations were unchanged. No significant changes in mean plasma lipid or lipoprotein concentrations were observed in the control group. These data demonstrate that a WSDF approach to cholesterol management is effective as an adjunct to a fat-modified diet in healthy, moderately hypercholesterolemic men and women.

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A variety of water-soluble dietary fibers (WSDF) consumed at levels in the range of approximately 5 to 30 g/day have been shown to significantly lower plasma cholesterol concentrations in the short term.[1] In fact, we previously demonstrated in healthy hypercholesterolemic men and women, stabilized on a fat-modified diet, that the addition of 15 g/day of WSDF from a mixture of psyllium, pectin, guar gum, and locust bean gum significantly lowered plasma cholesterol levels in a dose-dependent manner over a 4-week period.[1] Fewer studies have examined cholesterol lowering over a period of ≥6 months,[2–8] and there is some question of whether the cholesterol-lowering effects are sustained over time.[6,9] Consequently, this placebo-controlled study was designed to assess the cholesterol-lowering effects of WSDF administered to healthy hypercholesterolemic men and women over a period of 6 months.

METHODS

Subjects: The study was open to male and female volunteers, 25 to 65 years of age, with plasma total cholesterol concentrations in the range of 200 to 260 mg/dl, plasma triglycerides <350 mg/dl, fasting blood glucose <120 mg/dl, and body weights <130% of ideal body weight according to the 1959 Metropolitan Life Insurance Tables. Subjects were eligible if they were free of lipid-lowering medications and had no history or evidence on medical examination of any disease that might influence lipoprotein metabolism (gastrointestinal, thyroid, cancer, and so forth). Persons were eligible who were receiving antihypertensive medications (blood pressure stable at <160/95 mm Hg), oral contraceptives, or estrogen replacement therapy if they had been on a stable dose for at least 6 months and had no plans to change.

Before the study, all subjects were stabilized on self-selected, low-fat and low-cholesterol diets comparable to the National Cholesterol Education Program (NCEP) Step One diet[10] and were not taking dietary fiber supplements of any kind. The study was approved by Stanford University's committee on the use of human subjects in medical research, and written informed consent was obtained from each subject after the study protocol had been explained.

Design: The study was a 24-week, randomized, double-blind, placebo-controlled, parallel design with 58 subjects. Subjects were randomized to treatment or placebo groups after all baseline data were collected, and were instructed to maintain their typical eating, physical activity, and medication patterns during the study.

Treatments: The WSDF treatment consisted of a mixture of psyllium (2.1 g WSDF/serving), pectin (1.3 g WSDF/serving), guar gum (1.1 g WSDF/serving), and locust bean gum (0.5 g WSDF/serving) prepared as a powder in a carbohydrate base (approximately 15 g of fructose/serving) for palatability. The control mixture consisted of acacia gum (5.0 g WSDF/serving) prepared as a powder in the same fructose base. We have previously demonstrated that acacia gum, despite its WSDF classification, has no significant impact on mean plasma lipid and lipoprotein concentration.[1,11] Subjects were instructed to mix a serving of their respective powders in 8 ounces

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of water and to consume the beverage with each of 3 major meals daily. The WSDF mixture treatment provided 5 g of WSDF/serving for a total of 15 g/day.

Measurements: All subjects completed a screening medical history, including medications, and if their plasma total cholesterol and triglyceride concentrations were not known, a screening lipid panel was performed. Eligible subjects underwent a cardiovascular-oriented physical examination, with measurement of blood pressure and body height and weight. Venous blood samples were obtained after a 12- to 14-hour fast on 2 separate days within a period of 8 days for analysis of plasma lipid and lipoprotein concentrations. The values obtained were then averaged and used as the baseline for each subject. Fasting blood samples were obtained by venipuncture. Plasma lipid and lipoprotein concentrations were measured in the Stanford University Lipid Research Laboratory. Laboratory methods were those of the Lipid Research Clinics and were standardized through the Centers for Disease Control and Prevention lipoprotein standardization program.[12] Total cholesterol and triglyceride concentrations were measured with enzymatic techniques,[13,14] and high-density lipoprotein (HDL) cholesterol concentrations were determined on the remaining plasma after precipitation of very low density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol with dextran sulfate.[15] LDL cholesterol was determined by the calculation method of Friedewald et al.[16]

Adherence to treatments and adverse effects were monitored using diaries that were completed daily and returned every 2 weeks for review by the project staff. At 8, 16, and 24 weeks, subjects completed a follow-up medical history and examination, and fasting blood samples were obtained for measurement of plasma lipid and lipoprotein concentrations. In addition, at baseline and 8 and 24 weeks, each subject completed a self-administered, computer-scannable food-frequency questionnaire.[17] Questionnaires were reviewed by the study dietitian and then sent to the Fred Hutchison Cancer Research Center (Seattle, Washington) for analysis.

Data analysis: Two-sample *t* tests were used to determine whether differences between groups at baseline were significant. Significance was set up at $p < 0.05$. The changes in variables between baseline and 16 and 24 weeks were tested for significance using analysis of variance.

RESULTS

Adherence and adverse effects: Of the 58 subjects (31 men, 27 women) who began the study, 51 completed the entire 24-week protocol (Table I). There were 2 dropouts from the control group (1 man and 1 woman, both because of scheduling conflicts) and 5 dropouts from the treatment group (3 men and 2 women, 3 because of dislike of the WSDF treatment, 1 for medical reasons unrelated to the study protocol, and 1 because of scheduling conflicts). According to subject diaries, adherence to the treatments was 96.4% in the control group and 98.2% in the treatment group. Adherence was calculated as a percentage by dividing the number of servings consumed by the number of servings prescribed and then multiplying by 100. No major adverse effects were noted. Adverse effects reported were generally related to minor and transient gastrointestinal discomfort such as gas, bloating, and loose stools at the beginning of the study.

TABLE I Baseline Characteristics of Subjects Who Completed the Study

Parameter	WSDF Mixture	Control
Male/female ratio	14/10	13/14
Age (yr)	50.0 ± 9.5	54.0 ± 8.1
Body height (m)	1.62 ± 0.13	1.66 ± 0.17
Body weight (kg)	73.8 ± 14.4	74.5 ± 17.6
Body mass index (kg/m^2)	25.8 ± 3.5	25.7 ± 6.17
Fasting blood glucose (mg/dl)	102.5 ± 12.5	103.4 ± 13.6

Values are given as mean ± SD.
WSDF = water-soluble dietary fiber.

Diets and body weights: Analysis of the food-frequency questionnaires indicated similarity at baseline between groups in consumption of calories, percentage of calories from fat and saturated fat, cholesterol, and dietary fiber (Table II). There was also consistency of intake relative to baseline throughout the treatment period for both groups. No significant differences in mean body weights were noted at baseline and between or within treatment groups during the treatment period (Table III).

Plasma lipid and lipoprotein concentrations: There were no differences between groups at baseline for any of the plasma lipid and lipoprotein measures (Table III). Changes in mean plasma lipids and lipoproteins were not significant from baseline to each of the follow-up periods for the control group (Table III). For the treatment group, the mean plasma total cholesterol concentration declined significantly by week 8 (−6.4%, −15 mg/dl), and this reduction was sustained throughout the 24-week study. The decline was largely due to a reduction in the mean plasma LDL cholesterol concentration, which was apparent at week 8 (−10.5%, −16 mg/dl) and was also sustained throughout the study period. Mean plasma HDL cholesterol and triglyceride concentrations did not change significantly over the course of the study. However, triglycerides were quite variable and tended to be higher over the course of study in the treatment group.

A post hoc analysis of response to the treatments by gender was performed. Sample sizes were relatively small in each group, and there was significant between-visit variability in plasma lipid and lipoprotein measures. Nonetheless, no significant changes from baseline were observed for men or women in the control group, and the maximum cholesterol-lowering effects of the WSDF treatment were similar for men and women. The maximum reductions in

TABLE II Reported Daily Intake of Selected Nutrients at Baseline and at Follow-Up at 8 and 24 Weeks

Time	Calories (kcal)	Fat (%)*	Saturated Fat (%)†	Cholesterol (mg)‡	Fiber (g)§
			Water Soluble Dietary Fiber mixture		
Baseline	1,842 ± 627	31.6 ± 12.7	11.4 ± 6.2	209 ± 146	14.5 ± 9.3
8 wk	1,748 ± 586	30.3 ± 13.4	12.0 ± 5.7	248 ± 163	15.4 ± 10.1
24 wk	1,827 ± 613	29.9 ± 14.2	10.9 ± 6.0	197 ± 151	15.0 ± 10.3
			Control group		
Baseline	1,902 ± 708	33.2 ± 14.8	11.7 ± 6.8	227 ± 164	16.1 ± 11.3
8 wk	1,878 ± 742	34.0 ± 15.1	12.3 ± 5.3	216 ± 132	16.8 ± 12.9
24 wk	1,840 ± 696	31.3 ± 14.3	11.8 ± 5.8	241 ± 176	15.8 ± 11.9

*Percentage of calories from total fat.
†Percentage of calories from saturated fat.
‡Cholesterol intake per day.
§Dietary fiber intake per day, excluding treatments.
Values are given as mean ± SD.

TABLE III Effects of Treatments on Mean Plasma Lipid and Lipoprotein Concentrations and Body Weights

Time	Total C (mg/dl)	LDL C (mg/dl)	HDL C (mg/dl)	TG (mg/dl)	Body Weight (kg)
			Water Soluble Dietary Fiber mixture		
Baseline	235 ± 19	152 ± 22	54 ± 15	142 ± 64	73.8 ± 14.4
8 wk	220 ± 18*†	136 ± 20*†	51 ± 15	200 ± 207	73.8 ± 13.9
16 wk	220 ± 19*†	142 ± 21*†	52 ± 17	153 ± 108	73.4 ± 13.6
24 wk	219 ± 26*†	137 ± 25*†	51 ± 14	166 ± 86	72.8 ± 13.5
			Control group		
Baseline	232 ± 22	144 ± 23	60 ± 21	137 ± 70	74.5 ± 17.7
8 wk	235 ± 28	142 ± 27	63 ± 22	149 ± 118	74.7 ± 17.5
16 wk	234 ± 22	145 ± 27	62 ± 22	133 ± 85	75.0 ± 17.8
24 wk	242 ± 31	152 ± 31	62 ± 20	140 ± 70	74.8 ± 17.6

*Within-group changes from baseline are significant at $p < 0.05$.
†Between-group changes from baseline are significant at $p < 0.05$.
Values are given as mean ± SD.
C = cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

mean plasma total cholesterol concentrations for men were seen at 24 weeks (−7.7%, −18 mg/dl) and for women at 16 weeks (−8.9%, −21 mg/dl). Maximum reductions in mean plasma LDL cholesterol concentrations for men were seen at 8 weeks (−14.9%, −23 mg/dl) and for women at 16 weeks (−12.2%, −18 mg/dl).

DISCUSSION

Compliance with the WSDF supplementation protocol was excellent (>95%), and adverse effects were minimal according to subject diaries. These results suggest that WSDF supplementation is feasible as an adjunct to managing hypercholesterolemia in otherwise healthy subjects.

The food-frequency data indicated that the subjects were consuming a fat-modified, NCEP Step One–type diet, and that regular intake of WSDF in beverage form did not significantly alter their usual dietary patterns or lead to significant changes in body weight for the groups overall. Because exercise patterns and medications were also held constant, it is reasonable to ascribe changes in plasma lipoproteins to the added WSDF mixture.

The 6.4% and 10.5% reductions from baseline in mean plasma total and LDL cholesterol concentrations observed in the treatment group after 8 weeks are within a range typical of various WSDF preparations fed in the short term.[1] The fact that these reductions were sustained over the 6-month study period (−6.8% and −9.9%, respectively) is consistent with studies that have examined WSDF supplementation for ≥6 months in diabetics,[2,5] hypercholesterolemic adults,[3,8] and children[4] (Table IV).

There are 2 published long-term studies that suggest a diminishing effect over time, or no effect of WSDF on plasma total cholesterol concentrations (Table IV). Guar gum administered at 15 to 30 g/day to severely hypercholesterolemic men and women produced an 18% reduction in mean plasma total cholesterol after 8 weeks, but the effect was attenuated thereafter. At 14, 18, 30, and 50 weeks, the reductions were approximately 15%, 14%, 9%, and 11% below baseline, re-

TABLE IV Effects of Long-Term Water-Soluble Dietary Fiber Supplementation on Mean Plasma Total Cholesterol Concentrations

Reference	WSDF Source and Dose	Subjects	DM	Duration (mo)	Change (%)	Tcb (mg/dl)	Tcf (mg/dl)
2	Guar gum (14–26 g/d)	8	+	6	−8	193	178
3	Guar gum (12 g/d)	13	0	12	−13	302	263
4	Psyllium (5–10 g/d)	36	0	8	−17	249	207
5	Food fiber (>40 g/d)	6	+	15	−9	200	183
6	Guar gum (15–30 g/d)	23	0	12	−11	388	347
7	Guar gum (31 g/d)	16	+	6	0	NA	NA
8	Mixture of WSDF (20 g/d)	59	0	12	−5	234	223
Current study	Mixture of WSDF (15 g/d)	51	0	6	−7	235	219

DM = diabetes mellitus; NA = no information available; Tcb = baseline mean plasma total cholesterol concentration; Tcf = final mean plasma total cholesterol concentration; WSDF = water-soluble dietary fiber.

spectively.[6] In addition to the possibility that WSDF has a diminishing cholesterol-lowering effect over time, the investigators suggested that variations in the daily fiber dose and/or diminished subject compliance may have contributed to the attenuated response. In the second study, guar gum administered at approximately 30 g/day to 16 men and women with non–insulin-dependent diabetes mellitus elicited no effect on mean serum total and LDL cholesterol concentrations after 6 months.[7] Measures were taken only at baseline and after treatment, so it is not possible to determine whether a cholesterol-lowering effect might have occurred within the first 2 or 3 months. In addition, the guar gum was fed in the form of a bar, presumably taken all at once and not necessarily with meals. This contrasts with other fiber studies in which significant cholesterol lowering was observed and in which the fiber was consumed with each meal. Consumption of WSDF with meals may be important for cholesterol-lowering efficacy. Although the mechanisms by which WSDF lowers plasma cholesterol are unknown, one proposed mechanism involves binding of WSDF to bile acids secreted in response to food intake, resulting in increased fecal absorption of bile acids, which may affect hepatic cholesterol synthesis.[18]

Previously published long-term WSDF studies have not examined cholesterol-lowering response by gender. Post hoc analysis of mean plasma lipid and lipoprotein responses to the WSDF treatments in this study showed similar effects in men and women. However, the sample sizes were small and reductions were not consistent across all follow-up periods, so these trends should be confirmed in larger studies.

Finally, men and women with moderately elevated LDL cholesterol who go on the NCEP Step One diet generally achieve a 5% to 10% reduction in LDL cholesterol.[19] Going from the NCEP Step One to the Step Two diet usually produces a 3% to 7% reduction in LDL cholesterol.[20,21] Thus, the decrease in LDL cholesterol obtained with WSDF in this study and in other studies testing WSDF in hypercholesterolemic men or women (Table IV) is of the magnitude achieved when such persons go on a reduced-fat diet as recommended by the NCEP.[20]

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