Soluble fiber intake at a dose approved by the US Food and Drug Administration for a claim of health benefits: serum lipid risk factors for cardiovascular disease assessed in a randomized controlled crossover trial[1–3]

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ABSTRACT

Background: The US Food and Drug Administration (FDA) approved health claims for 2 dietary fibers, β-glucan (0.75 g/serving) and psyllium (1.78 g/serving), on the assumption that 4 servings/d would reduce cardiovascular disease risk.

Objective: We assessed the efficacy of this dose of fibers in reducing serum lipid risk factors for cardiovascular disease.

Design: Sixty-eight hyperlipidemic adults consumed a test (high-fiber) and a control low-fat (25% of energy), low-cholesterol (<150 mg/d) diet for 1 mo each in a randomized crossover study. The high-fiber diet included 4 servings/d of foods containing β-glucan or psyllium that delivered 8 g/d more soluble fiber than did similar, unsupplemented foods in the control diet. Fasting blood samples and blood pressure readings were obtained at baseline and weeks 2 and 4, and the subjects' weight was monitored weekly.

Results: Compared with the control diet, the high-fiber diet reduced total cholesterol ($2.1 \pm 0.7\%$; $P = 0.003$), total:HDL cholesterol ($2.9 \pm 0.8\%$; $P = 0.001$), LDL:HDL cholesterol ($2.4 \pm 1.0\%$; $P = 0.015$), and apolipoprotein B:A-I ($1.4 \pm 0.8\%$; $P = 0.076$). Applying the Framingham cardiovascular disease risk equation to the data confirmed a reduction in risk of $4.2 \pm 1.4\%$ ($P = 0.003$). Small reductions in blood pressure were found after both diets. The subjects reported no significant differences in palatability or gastrointestinal symptoms between the diets.

Conclusions: The reduction in serum lipid risk factors for cardiovascular disease supports the FDA's approval of a health claim for a dietary fiber intake of 4 servings/d. Although relatively small in terms of patient treatment, the reduction in cardiovascular disease risk is likely to be significant on a population basis. *Am J Clin Nutr* 2002;75:834–9.

INTRODUCTION

The US Food and Drug Administration (FDA), which assesses health claims for foods, has approved health claims for the viscous fibers oat β-glucan and psyllium as cholesterol-lowering agents that in the context of a good diet may reduce the risk of cardiovascular disease (1, 2). Furthermore, national agencies concerned with cardiovascular health have for the first time recommended viscous fiber intake (3, 4). Much interest has been shown internationally by the general public, the scientific community, and federal regulators in the medical application of these food components in so-called functional foods, foods that favorably modify physiologic function. There is therefore a need to substantiate the validity of current regulations that govern health claims in this area (1, 2, 5, 6). To address this need, we tested the effects of psyllium and β-glucan intake, in the amounts approved by the FDA for a fiber health claim, on serum lipid risk factors for cardiovascular disease (1, 2).

SUBJECTS AND METHODS

Ninety-one hyperlipidemic subjects were recruited and 82 were available for random assignment. Of these, 68 (83%; 37 men and 31 postmenopausal women) completed both 1-mo dietary phases, separated by a 2-wk washout period in a randomized crossover study. The subjects' mean ($\pm$SE) age was 60 ± 1 y (range: 33–82 y) and their mean body mass index (in kg/m²) was 25.6 ± 0.3 (range:

TABLE 1
Calculated macronutrient intakes from week 4 dietary records with the high-fiber and control ad libitum diets[1]

	Control diet		High-fiber diet	
	Baseline	Week 4	Baseline	Week 4
Energy				
(MJ/d)	7.05 ± 0.22	7.47 ± 0.21	7.08 ± 0.24	7.42 ± 0.20
(kcal/d)	1686 ± 53	1787 ± 50	1694 ± 57	1774 ± 48
Total protein				
(g/d)	75 ± 3	73 ± 3	77 ± 3	74 ± 3
(% of energy)	17.9 ± 0.3	16.3 ± 0.3	18.3 ± 0.4	16.6 ± 0.3
Available carbohydrate				
(g/d)	230 ± 7	268 ± 7	229 ± 8	258 ± 6[2]
(% of energy)	55.0 ± 0.8	60.7 ± 0.7	54.4 ± 0.9	58.9 ± 0.8[2]
Total dietary fiber (g/d)	23 ± 1	20 ± 1	22 ± 1	30 ± 1[3]
Soluble fiber (g/d)	6 ± 0	4 ± 0	6 ± 0	13 ± 0[3]
Total fat				
(g/d)	52 ± 3	47 ± 2	52 ± 3	50 ± 3
(% of energy)	27.1 ± 0.9	23.1 ± 0.6	27.4 ± 0.8	24.5 ± 0.7[2]
SFA				
(g/d)	16 ± 1	13 ± 1	16 ± 1	15 ± 1[2]
(% of energy)	8.2 ± 0.3	6.5 ± 0.2	8.2 ± 0.4	7.4 ± 0.3[3]
MUFA				
(g/d)	21 ± 1	19 ± 1	21 ± 1	20 ± 1
(% of energy)	10.9 ± 0.4	9.0 ± 0.3	11.1 ± 0.4	9.6 ± 0.4[4]
PUFA				
(g/d)	11 ± 1	10 ± 1	11 ± 1	10 ± 1
(% of energy)	5.5 ± 0.2	5.1 ± 0.2	5.6 ± 0.2	5.0 ± 0.1
Dietary cholesterol				
(mg/d)	179 ± 11	127 ± 9	185 ± 13	144 ± 10
(mg/MJ)	25 ± 2	17 ± 1	26 ± 2	19 ± 1[2]
Alcohol				
(g/d)	8 ± 1	7 ± 1	7 ± 1	7 ± 1
(% of energy)	3.1 ± 0.6	2.5 ± 0.5	2.7 ± 0.5	2.7 ± 0.5

[1] $\bar{x}$ ± SE; $n = 68$. SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

[2–4] Significance of the treatment difference assessed by analysis of covariance with the general linear model procedure in SAS (11): [2] $P < 0.01$, [3] $P < 0.001$, [4] $P < 0.05$.

20.0–33.8). At baseline, all subjects had elevated serum LDL-cholesterol concentrations (>4.1 mmol/L) (7). One subject started with triacylglycerol concentrations >4.0 but <6.0 mmol/L. None had clinical or biochemical evidence of diabetes, liver disease, or renal disease, and none were taking hypolipidemic agents. Dosages of medications and level of physical activity were held constant for both study periods. Blood samples were obtained and blood pressure was measured with the subjects seated after they had fasted 12–14 h overnight before the start and at the end of weeks 2 and 4 of each phase. Serum was stored at −70°C until analyzed. Body weight was measured at the start and during biweekly clinic visits in both phases, and the subjects were also asked to monitor their weight on a home scale weekly.

For the last 7 d of each phase, the subjects recorded their diets after weighing food items on self-tarring electronic scales. During week 4 of each phase the subjects noted their number of bowel movements and rated flatulence, bloating, and abdominal pain on a 9-point bipolar scale. At each biweekly visit, subjects also rated their feelings of satiety with the use of a 9-point scale on which −4 represented extremely hungry, 0 neutral, and +4 completely satiated. The study was approved by the Ethics Committee of the University of Toronto. All the subjects gave informed consent.

Diets

At least 1 mo before the start of the study, the subjects were instructed on the principles of a National Cholesterol Education Program Step II diet (total fat <30% of energy, saturated fat <7% of energy, and dietary cholesterol <200 mg/d) (3). The subjects were instructed to follow these guidelines throughout the course of the study. Test (high-fiber) and control study foods consisted of a variety of breakfast cereals, breads, pasta-based frozen dinners, tea cakes, cookies, potato chips, and smoothie beverages. On average these contributed 36.2% of total daily energy intake. The test foods contained 1.8–2.5 g psyllium or 0.75 g β-glucan/serving (The Kellogg Co, Battle Creek, MI). Each subject selected 4 servings/d from the available foods, with the stipulation that one breakfast cereal and one frozen dinner must be chosen. On average, 7.2 g psyllium and 0.75 g β-glucan were consumed daily from these products (**Table 1**). The control diet provided similar commercial foods without the added fiber. The foods provided replaced similar foods in the subjects' diets such that they maintained their weight. Supplements were recorded when eaten, and any uneaten supplements were returned at the end of the dietary phase.

Analyses

Serum was analyzed in a single batch for total cholesterol, triacylglycerols, and HDL cholesterol after dextran sulfate–magnesium chloride precipitation in accordance with the guidelines of the Lipid Research Clinics Program (8). LDL cholesterol was calculated by using the Friedewald equation. Serum apolipoprotein A-I and B were measured by nephelometry.

TABLE 2
Body weight, serum lipid, and blood pressure data for the high-fiber and control ad libitum diet periods[1]

	Control diet		High-fiber diet		Mean treatment difference[2]	P^3
	Baseline	Mean treatment	Baseline	Mean treatment		
					%	
Body weight (kg)[4]	71.7 ± 1.5	71.6 ± 1.4	71.7 ± 1.5	71.6 ± 1.4	0.1 ± 0.1	0.494
Cholesterol (mmol/L)						
Total	6.90 ± 0.10	6.78 ± 0.09	6.78 ± 0.10	6.63 ± 0.09	−2.1 ± 0.7[5]	0.001
LDL	4.75 ± 0.09	4.57 ± 0.08	4.67 ± 0.09	4.48 ± 0.08	−1.7 ± 0.9	0.064
HDL	1.30 ± 0.04	1.25 ± 0.03	1.26 ± 0.03	1.26 ± 0.03	1.3 ± 0.9	0.304
Triacylglycerols (mmol/L)	1.96 ± 0.11	2.15 ± 0.11	1.88 ± 0.09	2.00 ± 0.10	−5.2 ± 2.4[6]	0.005
Apo A-I (g/L)	1.64 ± 0.03	1.60 ± 0.03	1.60 ± 0.03	1.58 ± 0.03	−1.3 ± 0.6	0.033
Apo B (g/L)	1.70 ± 0.03	1.69 ± 0.03	1.69 ± 0.03	1.64 ± 0.03	−2.9 ± 0.8[5]	0.001
Total-C:HDL-C	5.53 ± 0.15	5.66 ± 0.15	5.58 ± 0.15	5.47 ± 0.14	−2.9 ± 0.8[5]	0.000
LDL-C:HDL-C	3.79 ± 0.12	3.81 ± 0.11	3.86 ± 0.13	3.70 ± 0.11	−2.4 ± 1.0[6]	0.003
Apo B:apo A-I	1.06 ± 0.03	1.07 ± 0.03	1.08 ± 0.03	1.06 ± 0.03	−1.4 ± 0.8	0.016
Blood pressure (mm Hg)						
Systolic	124 ± 2	122 ± 1	124 ± 2	121 ± 1	−0.7 ± 0.4	0.061
Diastolic	80 ± 2	76 ± 1	79 ± 2	77 ± 2	−0.3 ± 0.6	0.406
CAD risk (%)[7]	11.6 ± 0.7	11.7 ± 0.7	11.7 ± 0.7	11.1 ± 0.7	−4.2 ± 1.4	0.003

[1] $\bar{x}$ ± SE; n = 68. Apo, apolipoprotein; C, cholesterol; CAD, coronary artery disease. To convert cholesterol and triacylglycerols to mg/dL, multiply by 38.67 and 88.57, respectively. To convert apo A-I and apo B values to mg/dL, multiply by 100.

[2] Treatment difference (%) = [(high-fiber − control) × 100/control], where high-fiber and control represent the mean of the absolute values from weeks 2 and 4.

[3] Calculated from the absolute means of the values from weeks 2 and 4 with the general linear model procedure in SAS (11).

[4] Mean treatment data are week 4 values.

[5] $P < 0.01$.

[6] $P < 0.05$.

[7] The Framingham predictive equation for cardiovascular disease risk was used to assess the likelihood of angina, myocardial infarction, or death during a 10-y period.

Macronutrient intakes were assessed from the 7-d dietary records with the use of a database derived from food-composition tables of the US Department of Agriculture (9) and with food labels for the few foods that were not analyzed directly. The supplements used in the study were analyzed with the use of Association of Official Analytical Chemists methods for fat, protein, and fiber, with available carbohydrate determined by difference (10). The fatty acid composition was determined by gas chromatography.

Statistical analysis

The results are expressed as means ± SEs. The mean of weeks 2 and 4 for each phase was used in calculating treatment differences because no significant differences were found between weeks 2 and 4 in any measurement except LDL cholesterol, for which a significant treatment effect was seen only at 2 wk. Furthermore, this difference was not reflected in a corresponding difference in non-HDL cholesterol; the mean of the LDL-cholesterol values from weeks 2 and 4 was therefore used in analysis of the data. The significance of the percentage difference between treatments was assessed by two-tailed Student's t test for paired data. The absolute difference between treatments was assessed by analysis of covariance with the use of the general linear model procedure and SAS software (PROC GLM/SAS) (11), with the response variable as the mean of the measurements from weeks 2 and 4 and the main effects of diet, sex × sequence interaction, and a random term representing the subject nested within the sex × sequence interaction and the baseline value as a covariate. Analysis with an alternative statistical model, with diet, sex, diet × sex, and the random term described above as

main effects and dietary cholesterol and starting value as covariates, yielded similar results.

The Framingham predictive equation for cardiovascular disease risk was also applied to the data by using the total:HDL cholesterol and systolic blood pressure results. The equation also includes age, sex, the presence or absence of left ventricular hypertrophy, and whether the individual is a smoker or has diabetes (12). Our subjects did not have diabetes and were non-smokers. Left ventricular hypertrophy was not assessed. Cardiovascular disease risk is expressed in the text as the percentage of individuals who would be predicted to have angina, have a myocardial infarction, or die during a 10-y period (12).

RESULTS

The diets were well accepted and compliance was good. With both the control and high-fiber diets, subjects consumed 96 ± 1% of the supplements provided. Both diets had high and similar palatability scores (high-fiber diet: 3.4 ± 0.1; control diet: 3.2 ± 0.1) and satiety scores (high-fiber diet: 0.6 ± 0.1; control diet: 0.5 ± 0.1). There was no significant body weight change with either the high-fiber diet (−0.1 ± 0.1 kg) or the control diet (−0.1 ± 0.1 kg; **Table 2**).

Blood lipids and apolipoproteins

Significant reductions from pretreatment values were seen in blood lipids after both diets (Table 2). There were no significant differences in pretreatment values between the high-fiber and control diets (Table 2). Mean values were significantly lower after the high-fiber diet than after the control diet for total cholesterol [percentage difference between treatments: 2.1 ± 0.7%;
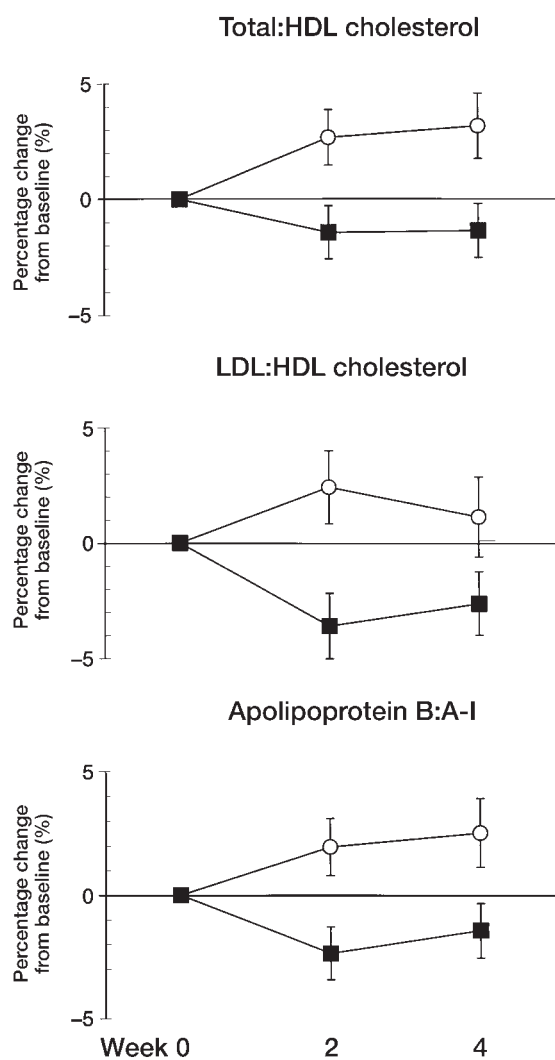
FIGURE 1. Percentage change in blood lipid, lipoprotein, and apolipoprotein ratios from week 0 to weeks 2 and 4 of the high-fiber (■) and control (○) diets.

$P = 0.003$ (Students's t test)]; triacylglycerols ($5.2 \pm 2.4\%$; $P = 0.037$); apolipoprotein B ($2.9 \pm 0.8\%$; $P < 0.001$); total:HDL cholesterol ($2.9 \pm 0.8\%$; $P = 0.001$); and LDL:HDL cholesterol ($2.4 \pm 1.0\%$; $P = 0.015$), with a nonsignificant reduction in apolipoprotein B:A-I of $1.4 \pm 0.8\%$ ($P = 0.076$). There were no other significant differences. The percentage treatment differences in the lipid and lipoprotein ratios at week 2 were similar to the respective values at week 4. The percentage changes from baseline for the high-fiber and control treatments are shown in **Figure 1**. The significance of the effect of diet on serum lipids was confirmed by using the mean of the lipid values from weeks 2 and 4 and the general linear model procedure (for total cholesterol, triacylglycerol, apolipoprotein B, total:HDL cholesterol, LDL:HDL cholesterol, and apolipoprotein B:A-I; Table 2).

There were no significant differences between the sexes in response to diet. In addition, neither age nor body mass index influenced the treatment effect. Controlling for weight change or differences in dietary carbohydrate, saturated or polyunsaturated fat, the ratio of polyunsaturated to saturated fatty acids, or dietary cholesterol in the general linear model procedure did not alter the pattern of significance in treatment differences of blood lipids.

Cardiovascular risk estimation

Application of the Framingham cardiovascular disease risk equation to the data confirmed a $4.2 \pm 1.4\%$ treatment difference in cardiovascular disease risk ($P = 0.003$) (12).

Blood pressure

Systolic and diastolic blood pressures tended to be reduced after both dietary phases but were not significantly different between treatments (Table 2).

Gastrointestinal symptoms

No significant differences were seen between the high-fiber and control diets in bloating, flatulence, or abdominal pain. Bowel movements were more frequent during the high-fiber than during the control diet (9.6 ± 0.5 compared with 8.6 ± 0.5 movements/wk; $P = 0.005$).

DISCUSSION

Our data show that incorporation of viscous fibers into a wide range of foods resulted in small but significant reductions in total cholesterol and in the ratio of LDL to HDL cholesterol. These data add support to the FDA-approved health claim that in the context of a low-fat, low-cholesterol diet, 4 servings/d of foods containing the viscous fibers psyllium and oat β-glucan can be expected to reduce serum lipids and the risk of cardiovascular disease.

The FDA was one of the first national agencies to recognize a role for fiber in cardiovascular disease risk reduction. Products that contain 0.75 g β-glucan or 1.78 g psyllium/serving are permitted to carry a health claim stating that the product "will reduce the risk of coronary heart disease" (1, 2). The FDA further determined that 4 servings of these foods is likely to provide the effective daily dose (1, 2).

There is considerable international interest in health claims, both to encourage industry to produce foods with specific health benefits (functional foods) and to ensure efficacy of action (1, 2, 5, 6, 13). Validation of health claims is therefore important, especially in the case of soluble fiber, because national agencies concerned with cardiovascular health have only recently acknowledged a role for fiber in cholesterol reduction (4, 14). The ability of viscous soluble fibers to lower serum cholesterol has been recognized for more than a quarter of a century (15, 16). At first the dietary fibers of interest were pectin and guar (15, 17); later attention focused on oat β-glucan and psyllium, which in most but not all studies were shown to reduce serum cholesterol concentrations (15, 16, 18–20).

The present study assessed the effects of consuming 8 g/d of a combination of the viscous fibers psyllium and β-glucan, an amount that meets the FDA requirements for a health claim for cardiovascular disease risk reduction. Although the cholesterol reduction was modest, estimated cardiovascular disease risk was reduced. In addition, the ratios of total to HDL cholesterol and of LDL to HDL cholesterol were also reduced in our study, which was not previously reported with the consumption of fiber in studies achieving these modest levels of cholesterol reduction. Although glycemic index data are not available on the foods used in the present study, it is possible that part of the beneficial effect on the lipid and lipoprotein ratios was caused by a general

lowering of the glycemic index of the diet. Incorporation of viscous fibers into a range of carbohydrate foods eaten over the day would tend to reduce the dietary glycemic index, as has been shown for individual foods and meals (21). Studies of low–glycemic index diets reported varied effects on serum cholesterol: some showed reductions (22–24) and others did not (25, 26). On the other hand, low-glycemic-index diets appear to lower serum triacylglycerols in subjects with raised triacylglycerol concentrations (27, 28).

In cohort studies, low-glycemic-index diets were associated with higher HDL-cholesterol concentrations (29, 30) and reduced risk of cardiovascular disease (31). The changes in lipoprotein ratios observed in the present study are considered key indicators of cardiovascular disease risk reduction and are central to equations predicting coronary artery disease risk (12). In this respect our data suggest a potential advantage of distributing fiber over the day in a range of carbohydrate foods.

The viscous nature of the types of dietary fiber that are most effective in reducing serum lipids has been a major barrier to their use in foods. Their clinical relevance has been questioned because of the extreme unpalatability of some of the products tested (32). The finding that palatable diets can be produced by incorporating lower amounts of fiber into more foods while retaining effectiveness is therefore important.

Foods containing sufficient psyllium and oat β-glucan per serving to justify a health claim for cardiovascular disease risk reduction reduce serum lipids and are as palatable as their low-fiber counterparts. Spreading the fiber intake over the day may be responsible for reducing the ratio of total to HDL cholesterol and of LDL to HDL cholesterol, through lowering of the glycemic index of the carbohydrate portion of the diet. The palatability of and lack of side effects from these foods suggest that consumption of more servings of fiber-supplemented foods will also prove acceptable in clinical situations where larger reductions in lipid risk factors for cardiovascular disease are required. The present level of supplementation is likely to be of benefit on a population basis as one of several dietary strategies to reduce lipid risk factors for cardiovascular disease (33).

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