Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia[1–3]

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ABSTRACT

Background: Hypercholesterolemia is a major risk factor for coronary heart disease and nutrition management is the initial therapeutic approach.

Objective: This multicenter study evaluated the long-term effectiveness of psyllium husk fiber as an adjunct to diet in the treatment of persons with primary hypercholesterolemia.

Design: Men and women with hypercholesterolemia were recruited. After following an American Heart Association Step I diet for 8 wk (dietary adaptation phase), eligible subjects with serum LDL-cholesterol concentrations between 3.36 and 4.91 mmol/L were randomly assigned to receive either 5.1 g psyllium or a cellulose placebo twice daily for 26 wk while continuing diet therapy.

Results: Serum total and LDL-cholesterol concentrations were 4.7% and 6.7% lower in the psyllium group than in the placebo group after 24–26 wk ($P < 0.001$). Other outcome measures did not differ significantly between groups.

Conclusions: Treatment with 5.1 g psyllium twice daily produces significant net reductions in serum total and LDL-cholesterol concentrations in men and women with primary hypercholesterolemia. Psyllium therapy is an effective adjunct to diet therapy and may provide an alternative to drug therapy for some patients. *Am J Clin Nutr* 2000;71:1433–8.

KEY WORDS Psyllium, dietary fiber, hypercholesterolemia, total cholesterol, LDL cholesterol, men, women

INTRODUCTION

Despite substantial medical progress in the past 2 decades, coronary heart disease (CHD) remains a major health problem in most industrialized countries (1). Elevated serum total and LDL-cholesterol concentrations are powerful risk factors for CHD (2, 3), with oxidation of LDL potentially playing a major role in atherogenesis and development of CHD (4). Each 1% increase in the serum cholesterol concentration results in a 2–3% increase in CHD risk (5, 6). Furthermore, in primary and secondary prevention trials, a reduction in total and LDL cholesterol concentrations improved the function of the coronary endothelium (7, 8) and decreased the risk of CHD (9).

The second report of the National Cholesterol Education Program Adult Treatment Panel (ATP II) confirms diet therapy as the primary intervention for lowering serum cholesterol concentrations; drug therapy is reserved for persons at high risk of CHD who do not respond adequately to diet (2). On the basis of the ATP II guidelines, almost 30% of American adults require dietary intervention for elevated serum cholesterol concentrations (10).

Consumption of viscous soluble fibers significantly lowers serum total and LDL cholesterol concentrations (11, 12). Such fibers may provide an alternative to drug therapy for some patients (13–15). Of the viscous soluble fibers, psyllium husk fiber appears to be one of the most effective (16, 17) with the least adverse effects (18). Short-term placebo-controlled studies showed that consumption of 7–10 g psyllium/d lowers serum total cholesterol concentrations 4–11% and serum LDL cholesterol concentrations 6–18% below placebo control concentrations (12–16, 19–24). The long-term effects of psyllium on serum lipids have not been reported.

The purpose of this multicenter study was to compare the long-term effectiveness and safety of psyllium husk fiber with that of a cellulose placebo as an adjunct to an American Heart Association (AHA) Step I diet in the treatment of men and women with primary hypercholesterolemia.

SUBJECTS AND METHODS

Subjects

Men and women with hypercholesterolemia were recruited for study. The protocol and consent form for the study were approved by the institutional review boards at each study site and subjects gave written, informed consent after the study procedures had been fully explained to them. Eligible subjects were

[1] From the University of Kentucky and the Veterans Affairs Medical Center, Lexington; the Chicago Center for Clinical Research; the Ochsner Clinic, New Orleans; the Medlantic Research Institute, Washington, DC; the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York; and The Procter & Gamble Company, Cincinnati.

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aged 21–70 y and were free of significant organic disease. Persons who had had a myocardial infarction or major surgery ≤6 mo before the study were excluded, as were those with a history of phenylketonuria or allergies to psyllium or aspartame. Women who became pregnant were excluded or dropped from the study. Persons who had taken corticosteriods, androgens, phenytoin, thyroid hormones, oral contraceptives, antibiotics, fiber supplements, calcium supplements, or oral hypolipidemic agents ≤3 mo before the study were also excluded.

Subjects were randomly assigned to the psyllium or placebo group after the dietary adaptation phase if their serum LDL-cholesterol concentrations were between 3.36 and 4.91 mmol/L, if their plasma triacylglycerol concentrations were <4.52 mmol/L, and if their LDL concentrations had stabilized within 0.65 mmol/L ≥2 wk before random assignment. The study protocol specified that subjects maintain a constant body weight (±5%), consume >75% of the test product they received, and comply with the diet throughout the study. As the primary analysis, we analyzed data from all subjects who were randomly assigned to receive either placebo or psyllium (ie, an intention-to-treat analysis). We also analyzed data for just those subjects who completed the study (ie, evaluable subjects) for comparison.

Study design

This double-blind, placebo-controlled, parallel, multicenter study consisted of an 8-wk dietary adaptation phase (weeks −8 to −1) followed by a 26-wk treatment phase (weeks 0–26). During the dietary adaptation phase, subjects with primary hypercholesterolemia received ongoing dietary counseling regarding an AHA Step I diet (25, 26). Subjects who met the entry criteria at the end of the dietary adaptation phase were then stratified by sex and randomly assigned to the treatment or placebo group.

Subjects were randomly assigned to groups independently at each study site in blocks of 5 (4 to the psyllium group and 1 to the placebo group). The study was designed to have 250 subjects complete the protocol, 200 in the psyllium group and 50 in the placebo group. Power calculations were based on a two-sided α risk of 0.05. On the basis of the stated sample sizes and variance estimates from previous studies, this study was designed to have 97% power to detect a 5% difference in serum total cholesterol concentrations and a 7% difference in serum LDL-cholesterol concentrations between groups.

Subjects in the treatment group received 5.1 g psyllium husk twice daily and subjects in the placebo group received 5.1 g microcrystalline cellulose twice daily for 26 wk adjunctive to the AHA Step I diet. Subjects returned at weeks −8, −4, −2, −1, 0, 4, 8, 12, 16, 20, 24, and 26 for serum lipid measurements and dietary counseling.

Diets and test products

All subjects were instructed to consume an AHA Step I diet (26) at enrollment and to continue that diet throughout the dietary adaptation and treatment phases. The Step I diet provided 55% of total energy as carbohydrate, 15% of energy as protein, <30% of energy as fat, <10% of energy as saturated fatty acids, and <300 mg cholesterol daily. Registered dietitians reviewed dietary information and provided dietary counseling.

During the treatment phase, subjects in the psyllium group received orange-flavored, sugar-free Metamucil (Procter & Gamble Co, Cincinnati), whereas subjects in the placebo group received microcrystalline cellulose, an insoluble fiber (Avicel PH-101; FMC Corp, Philadelphia). Both groups received two 6.7-g packets daily; each packet provided 5.1 g psyllium husk fiber or cellulose placebo. The products were packaged in identical foil packets with identical information and instructions. Both products were orange-flavored powders that were similar in taste, texture, and appearance. The subjects were instructed to mix each packet in 240 mL liquid and to drink the mixture immediately before breakfast and dinner. Compliance was monitored by interviewing the subjects and counting unopened packets returned at each follow-up visit.

Variables measured

Subjects underwent a complete physical examination at weeks −4 and 26 of the study and routine clinical chemistry, hematology, and urinalysis evaluations at weeks −4, 0, and 26. At weeks −8, −4, −2, and −1 of the dietary adaptation phase and weeks 0, 4, 8, 12, 16, 20, 24, and 26 of the treatment phase, serum lipids, body weight, blood pressure, and heart rate were measured. Clinic visits occurred in the morning after a minimum 12-h fast and subjects did not consume the test products on these mornings.

Serum lipid profiles included enzymatic measurement of total cholesterol, HDL-cholesterol, and triacylglycerol concentrations (27). LDL-cholesterol concentrations were calculated from total and HDL-cholesterol concentrations by using the Friedewald equation (28). Because the equation has not been validated for triacylglycerol concentrations >4.52 mmol/L, LDL cholesterol was not calculated when triacylglycerol concentrations were >4.52 mmol/L.

Serum concentrations of apolipoproteins A-I (29) and B-100 (30) were measured by radioimmunoassay at weeks 0 and 26. In addition to derived values, serum LDL-cholesterol concentrations were also measured at weeks 0 and 26 by using an ultracentrifugal β-quantition procedure (27). All serum lipid concentrations were determined at PennMed Laboratories, Medlantic Research Institute, Washington, DC.

Adverse events related to the test products were solicited at each clinic visit during the treatment phase. Subjects were asked an open-ended question about the occurrence of any unusual symptoms or events during the previous 4 wk. Subjects were also telephoned by the investigator's staff at 4-wk intervals between clinic visits (weeks 2, 6, 10, 14, 18, and 22) and asked about potential adverse events and study compliance.

The subjects provided 3-d food records (2 weekdays and 1 weekend day) at weeks −4, −2, 0, 8, 12, 16, 20, 24, and 26. A registered dietitian reviewed all food records for completeness. Food records from weeks −4, 0, 12, 20, and 24 were analyzed by the Nutrition Coding Center of the University of Minnesota, Minneapolis, by using the Nutrition Coding Center nutrient database for evaluation of total energy, fat, fiber, and cholesterol intakes; the ratio of polyunsaturated to saturated fat; and percentages of energy from fat, protein, and carbohydrate.

Statistical analyses

Comparability of the psyllium and placebo groups at baseline was determined by using a chi-square test for sex distribution and by using analysis of variance and Wilcoxon rank-sum tests for baseline height, weight, and lipid concentrations. Baseline values for serum total, derived LDL, and HDL-cholesterol and plasma triacylglycerol concentrations were defined as the average of values taken at weeks −2, −1, and 0. Posttreatment values for these variables were defined as the average of values taken at weeks 24

TABLE 1
Baseline demographic characteristics of subjects in the psyllium and placebo groups[1]

	Psyllium (n = 105 M, 92 F)	Placebo (n = 25 M, 26 F)
Age (y)	54.5 ± 0.8	52.1 ± 1.8
Height (cm)	170.7 ± 0.8	168.7 ± 1.3
Body weight (kg)	74.2 ± 0.9	73.6 ± 1.7
BMI (kg/m^2)	25.5 ± 0.4	25.8 ± 0.4

[1] $\bar{x}$ ± SEM. Baseline values represent an average of values taken at weeks −2, −1, and 0 during the dietary adaptation phase of the study. Values from all subjects who received a test product are included.

and 26. For serum apolipoproteins and β quantification of LDL cholesterol, values taken at weeks 0 and 26 were compared.

Changes from baseline lipid concentrations and clinical laboratory data, body weight, and dietary data were compared between groups by using one-way analysis of variance. Changes were confirmed by using Wilcoxon rank-sum tests, analysis of covariance with the baseline value as a covariate, and analyses of the percentage change from baseline. Each week in which measurements were taken, comparisons of change from baseline were also made. Paired t tests, Wilcoxon rank-sum tests, or both were used to assess the significance of changes from baseline within groups. All analyses were performed by using SAS (31). Significance was defined as $P \leq 0.05$.

RESULTS

Of the 459 subjects who began the dietary adaptation phase, 248 qualified for assignment to a study group (51 to receive placebo and 197 to receive psyllium). Major reasons for disqualification for random assignment were failure to meet the study's inclusion criteria (n = 152), withdrawal of consent (n = 25), and loss to follow-up (n = 23). Of the randomly assigned subjects, 200 (39 in the placebo group and 161 in the psyllium group) completed the entire study. Of those who completed the entire study, 163 subjects (30 in the placebo group and 133 in the psyllium group) fully complied with the study protocol. Compliance with the regimens was excellent: the subjects consumed 93% of the psyllium and 95% of the placebo.

Baseline characteristics of subjects in the placebo and psyllium groups are shown in **Table 1**. The groups were well-matched for sex, age, height, and weight. Baseline and final dietary intakes of the psyllium and placebo groups are shown in **Table 2**. Subjects in the psyllium group had significantly higher mean cholesterol intakes at baseline than did those in the placebo group. Otherwise, dietary intakes of the groups did not differ significantly throughout the study. Subjects' body weights were also similar between groups; there were no significant differences between groups and no significant change from baseline within groups at any clinic visit.

During the dietary adaptation phase, average serum total and LDL-cholesterol concentrations of the 248 subjects decreased 3.9% and 4.4%, respectively, from study entry (week −8 compared with baseline values). The placebo and psyllium groups had similar baseline lipid concentrations; there were no significant differences in serum total, LDL, or HDL-cholesterol; apolipoprotein; or triacylglycerol concentrations between groups. No significant differences in change from baseline between groups were found for serum HDL-cholesterol, apolipoprotein, or triacylglycerol concentrations at any point during the study.

During the treatment phase, mean serum total cholesterol concentrations decreased an additional 2.1% in the psyllium group but increased 2.6% in the placebo group compared with baseline concentrations (**Table 3**). Mean serum LDL-cholesterol concentrations decreased an additional 2.9% with psyllium but increased 3.9% with placebo. Thus, the change in serum total and LDL-cholesterol concentrations (baseline compared with

TABLE 2
Daily dietary intakes of subjects in the psyllium and placebo groups[1]

	Psyllium (n = 197)		Placebo (n = 51)	
Nutrient[2]	Baseline	Final	Baseline	Final
Total energy				
(kJ)	7109 ± 168	6724 ± 173	6852 ± 290	6847 ± 333
(kcal)	1692 ± 40	1601 ± 41	1631 ± 69	1630 ± 79
Protein				
(g)	73.9 ± 1.6	71.8 ± 1.7	71.7 ± 2.9	74.7 ± 4.2
(% of total energy)	18.3	18.7	18.1	18.6
Carbohydrate				
(g)	227.4 ± 6.0	208.6 ± 5.7	225.9 ± 10.1	224.0 ± 13.2
(% of total energy)	54.8	53.7	55.2	54.4
Fiber				
Total (g)	18.2 ± 0.5	17.4 ± 0.5	18.3 ± 0.9	18.5 ± 1.0
Water-soluble (g)	1 ± 0.2	6.0 ± 0	5.9 ± 0.3	6.3 ± 0.4
Fat				
(g)	52.1 ± 1.9	51.2 ± 2.0	49.1 ± 3.2	48.9 ± 3.1
(% of total energy)	26.9	27.6	26.7	27.0
P:S	0.91 ± 0.03	0.91 ± 0.03	0.99 ± 0.05	0.90 ± 0.05
Cholesterol (mg)	182.6 ± 6.4	171.9 ± 7.1	148.8 ± 8.0[3]	173.1 ± 23.4

[1] $\bar{x}$ ± SEM. Baseline and final values were taken at weeks 0 and 24, respectively. Values from all subjects who received a test product are included.
[2] Dietary data from 3-d food records were analyzed by the Nutrition Coding Center of the University of Minnesota, Minneapolis, by using the Nutrition Coding Center nutrient database.
[3] Significantly different from psyllium, $P < 0.001$.

TABLE 3
Serum lipid responses of subjects in the psyllium and placebo groups

	Psyllium (n = 197)			Placebo (n = 51)		
	Baseline	Final	% Change	Baseline	Final	% Change
Total cholesterol (mmol/L)[2]	5.93 ± 0.04	5.08 ± 0.05	−2.1 ± 0.6	5.84 ± 0.08	5.98 ± 0.11[3]	2.6 ± 1.4[4]
LDL cholesterol (mmol/L)[2]	3.99 ± 0.03	3.86 ± 0.04	−2.9 ± 0.7	3.97 ± 0.07	4.11 ± 0.10[3]	3.9 ± 2.0[4]
HDL cholesterol (mmol/L)[2]	1.29 ± 0.02	1.29 ± 0.02	−0.3 ± 0.7	1.19 ± 0.03	1.20 ± 0.03	1.0 ± 1.4
Apolipoprotein A-I (g/L)[5]	1.57 ± 0.03	1.56 ± 0.03	0.4 ± 1.3	1.51 ± 0.04	1.52 ± 0.04	1.3 ± 2.1
Apolipoprotein B-100 (g/L)[5]	1.35 ± 0.02	1.32 ± 0.02	−1.0 ± 1.3	1.39 ± 0.04	1.39 ± 0.04	1.5 ± 2.8
Triacylglycerols (mmol/L)[2]	1.42 ± 0.05	1.43 ± 0.05	3.2 ± 2.3	1.49 ± 0.09	1.51 ± 0.11	2.8 ± 3.7

[1] $\bar{x}$ ± SEM. Values from all subjects who received a test product are included.
[2] Baseline values represent an average of values taken at weeks −2, −1 and 0 of the study; final values represent an average of values taken at weeks 24 and 26.
[3] Absolute change was significantly different from psyllium, $P < 0.001$.
[4] Significantly different from psyllium, $P < 0.001$.
[5] Baseline and final values were taken at weeks 0 and 26, respectively.

final) was significantly different between groups. Serum total and LDL-cholesterol concentrations were 4.7% and 6.7% ($P < 0.001$) lower, respectively, in the psyllium group than in the placebo group after 6 mo of treatment.

The importance of diet therapy during the initial dietary adaptation phase and the additional hypolipidemic effects of psyllium compared with placebo during the treatment phase are shown in **Figure 1**. The greatest reductions in serum total and LDL-cholesterol concentrations occurred at week 4 of the study in both the psyllium and placebo groups. Significant differences between groups in percentage change from baseline in serum total cholesterol concentrations occurred at weeks 8, 12, 20, 24, and 26 of the study. Significant differences in percentage change from baseline in serum LDL cholesterol occurred at weeks 4, 8, 16, 20, 24, and 26.

No significant interactions of sex and treatment were found for any of the lipid variables measured. Mean serum total and LDL-cholesterol concentrations decreased in men and women in response to psyllium treatment and increased in response to placebo.

Data from the 163 subjects who completed the entire study in full compliance with all study protocol criteria (ie, evaluable subjects) were also analyzed. Results in this more strictly controlled sample closely paralleled the results that included all treated subjects. For these 163 fully compliant subjects, serum total and LDL-cholesterol concentrations were 4.6% ($P < 0.02$) and 6.2% ($P < 0.02$) lower, respectively, in the psyllium group than in the placebo group. No other significant differences between groups were noted for any of the variables measured.

There were no significant differences in the incidence of adverse events between groups. No serious adverse events

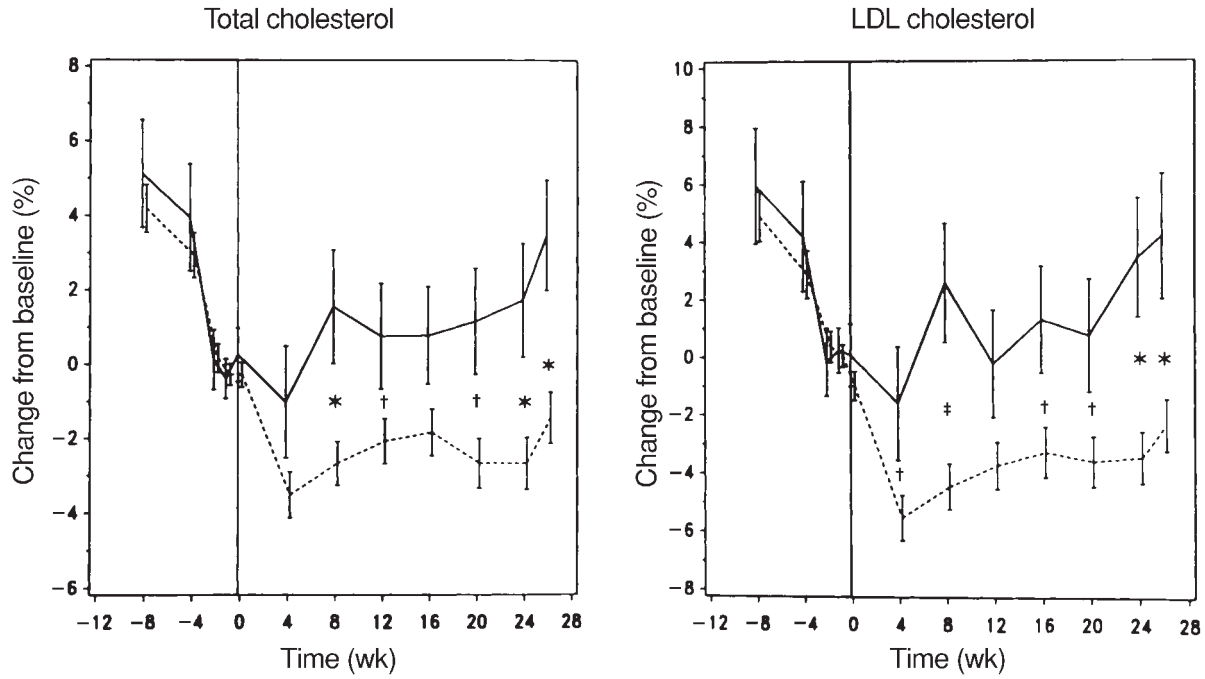

FIGURE 1. Mean (±SEM) percentage change from baseline (weeks −2, −1, and 0) in serum lipid concentrations during treatment with diet alone (weeks −8 to −1) followed by diet plus placebo (·····) or psyllium (————) (weeks 0–26) in all subjects who received a test product. *, †, ‡ Significantly different from placebo group: *$P < 0.01$, †$P < 0.05$, ‡$P < 0.001$.

related to treatment were reported in either group. Mild gastrointestinal effects, such as flatus, bloating, indigestion, nausea, heartburn, diarrhea, and constipation, were reported by 26% of subjects taking psyllium and 31% of subjects taking placebo.

DISCUSSION

The lipid reductions observed over 24–26 wk in this multicenter study were similar to those in previous, smaller, placebo-controlled studies of shorter duration. Sprecher et al (13) reported that total and LDL-cholesterol concentrations were lower (net differences of 3.5% and 5.1%, respectively) in the psyllium group than in the placebo group after 8 wk of treatment (5.1 g twice daily) in subjects consuming a low-fat diet. In other studies with an 8-wk AHA Step I diet lead-in phase, total and LDL-cholesterol concentrations were 4.8% and 8.2% lower, respectively (15), and 4.3% and 8.8% lower, respectively (19), in subjects who received psyllium (10.2 g/d) for an additional 8 wk than in subjects who received placebo. In a similar study with the longest treatment period reported in the literature thus far (16 wk of psyllium therapy after an 8-wk AHA Step I diet lead-in phase), net decreases in total and LDL-cholesterol concentrations of 5.6% and 8.6% were reported (14). Similar to the results of other studies (19, 32), no significant interactions of sex and treatment were found in the present study for any of the lipid variables measured. Thus, psyllium use by men and women can sustain serum lipid benefits for up to 6 mo.

The low energy intakes reported by subjects in both the psyllium and placebo groups in this study suggest that subjects in both groups underreported food intakes. Underreporting of food intakes was documented in previous clinical studies (33). Because mean energy intakes of the groups did not differ significantly at any time during the study, the reporting bias was probably similar in both groups.

The mechanism of action of psyllium's hypocholesterolemic effects has not been fully elucidated. Psyllium was shown to stimulate bile acid synthesis (7 α-hydroxylase activity) in animal models (34, 35) and in humans (20). The diversion of hepatic cholesterol for bile acid production has long been established as a mechanism for reducing serum cholesterol. Psyllium's effect on the absorption of cholesterol (20, 36) and fat (37) appears minimal but may make a small contribution to cholesterol lowering. Additional mechanisms, such as inhibition of hepatic cholesterol synthesis by propionate (38) and secondary effects of slowing glucose absorption (39), may also play a role.

Other soluble fiber sources, such as guar gum (40), locust bean gum (41), pectin (42), oat bran (43), and legumes (44), have also been reported to decrease serum total and LDL-cholesterol concentrations. However, the practical uses for many of these fibers are limited by a lack of palatable forms (21). In a study in which the effects of 10 different fibers were compared in rats, psyllium-fed rats had the lowest serum and liver cholesterol concentrations (17).

Psyllium has long been used as a bulk laxative with a good safety record. Although rare, allergic reactions to psyllium have been reported in persons with prior exposure to psyllium from manufacturing or bulk dispensing (45). The lack of significant effects of long-term psyllium treatment on hematology, serum chemistry, urinalysis, and routine clinical laboratory results; on coagulation; or on vitamin and mineral status in the present study and in another long-term study indicates the safety of this fiber source (46).

On the basis of ATP II guidelines (2), 32% of men and 27% of women in the United States have undesirably high serum cholesterol concentrations (10). The ATP II guidelines advocate stepwise reductions in fat, saturated fat, and cholesterol as the primary therapy for high total and LDL-cholesterol concentrations; drug therapy is reserved for persons at high risk of CHD or for those who do not respond adequately to diet (2).

Although psyllium therapy does not replace diet therapy for persons with high serum cholesterol concentrations, it offers an additional dietary tool. The results of this study show that psyllium can play an important role in maintaining diet-induced reductions in serum total and LDL-cholesterol concentrations. For some people, psyllium therapy may also be a safe, acceptable, and effective alternative to drug therapy. For example, if a person is trying to reduce his or her LDL-cholesterol concentration to 3.36 mmol/L through dietary modification but can achieve a reduction to only 3.62 mmol/L, the addition of psyllium to the regimen could help the person to attain his or her goal and eliminate the need for drug therapy.

In this study, dietary change and long-term use of a standard dose of psyllium (5.1 g twice daily) resulted in ≈5% lower serum total cholesterol concentrations and 7% lower LDL-cholesterol concentrations than did dietary changes and placebo. Because every 1% reduction in serum total cholesterol concentration results in a 2–3% reduction in risk of CHD, dietary change plus psyllium therapy could potentially reduce CHD risk 10–15% more than diet therapy alone in people with hypercholesterolemia (6).

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Erratum

Anderson JW, Davidson MH, Blonde L, et al. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. Am J Clin Nutr 2000;71:1433–8. In Figure 1, the solid upper lines represent placebo and the dashed lower lines represent psyllium. In Table 3, mean final total cholesterol in the psyllium group should be 5.80 not 5.08.

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