Randomized, Controlled, Crossover Trial of Oat Bran in Hypercholesterolemic Subjects

Joseph M. Keenan, MD, Joyce B. Wenz, RD, MS, Shepherd Myers, MA, Cynthia Ripsin, MS, and Zhiquan Huang, MD

Minneapolis, Minnesota

Background. Despite animal and metabolic ward studies that support the benefit of oat bran as a useful dietary supplement for the lowering of cholesterol, there have been few controlled studies on free-living subjects that have convincingly demonstrated this benefit.

Methods. This is a report of a randomized, controlled, blinded clinical trial with a crossover design using oat bran (28 g [1 oz] twice daily) vs wheat cereal as a supplement to a fat-modified diet for the reduction of total cholesterol and low-density lipoprotein (LDL) cholesterol. The study included male and female subjects aged 20 to 70 years, with baseline LDL cholesterol in the 50th to 95th percentile. All subjects were instructed in the American Heart Association Step I (AHA-I) diet, and eating behavior was monitored using 4-day food records during each study period.

Results. Eighty-two percent (n = 145) of the total number of subjects who were randomized to treatment groups completed the study. Blood lipid studies demonstrated significantly greater reductions in total cholesterol (average −2.2%) and LDL cholesterol (average −3.9%) in the oat-bran groups than in the wheat-cereal groups (average total cholesterol +3.3%, average LDL cholesterol +4.0%) or in the diet alone group (total cholesterol +6.0%; LDL cholesterol +6.4%). All groups did comparably well at adhering to the AHA-I diet; however, dietary factors alone, when analyzed by the Keys equations, could not explain the group differences in lipid change.

Conclusions. The addition of oat bran (28 g [1 oz] twice daily) to the AHA-I diet provided significant added benefit in lowering total cholesterol and LDL cholesterol in most hypercholesterolemic subjects. Analysis for factors that predict LDL cholesterol response to oat bran revealed a significant age-by-sex interaction ($P < .001$). Women under the age of 50 years, as a group, showed essentially no increased benefit from the addition of oat bran to their diet. Cholesterol levels in older women appear to be significantly more responsive to a modified diet containing oat bran than those of younger women.

Key words. cholesterol; cereals; dietary fiber; glucans. *J Fam Pract 1991; 33:600-608.*

Epidemiologic studies have reported an association of reduced risk of coronary artery disease in populations with increased fiber intake.[1,2] Dietary fiber, specifically soluble fiber, has been shown to have important lipid-lowering effects.[3] Oat bran, a rich source of the soluble fiber β-glucan, has demonstrated significant reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol in both animal and human studies.[4–8] The National Cholesterol Education Program (NCEP), in its dietary recommendations, has pointed out that the addition of soluble fiber, such as that found in beans and oats, has been shown to be a beneficial adjunct to a heart-healthy diet.[9]

The recent publication of a small (20 subjects) but well-controlled study by Swain et al[10] has raised some questions regarding the benefits of oat bran in managing hyperlipidemia. Swain and colleagues concluded that the apparent improvement in blood lipids attributed to oat bran could be explained by the change in dietary fat and cholesterol intake (ie, a substitution effect) rather than by a specific active effect of oat bran per se. In discussing these conflicting results, they discounted the balance of the scientific literature on the subject, which supports a beneficial cholesterol-lowering effect of oat bran, noting that few, if any, studies have included adequate low-fiber controls and dietary analysis of the possible "substitution

Submitted, revised, July 29, 1991.

From the Department of Family Practice and Community Medicine, University of Minnesota, Minneapolis. Requests for reprints should be addressed to Joseph M. Keenan, MD, Department of Family Practice, 825 Washington Ave SE, Box 25, Minneapolis, MN 55414.

ISSN 0094-3509

effect." In an editorial regarding the oat bran controversy, Connor[11] recommended that a larger controlled and randomized study using hypercholesterolemic subjects in a crossover design similar to the Swain study be undertaken to answer these questions more conclusively. This paper reports the results of a randomized, double-blind, low-fiber and diet-controlled crossover trial of oat bran in 209 hypercholesterolemic subjects.

Methods

Subjects

Potential subjects were identified from community-based cholesterol screening programs. Approximately 6000 screening program records were reviewed with respect to age, sex, and cholesterol level of each individual. The 2940 screenees identified were then sent a questionnaire to determine interest in the study and possible exclusionary factors. Of the 951 responding positively to the questionnaire, 302 were considered potential study candidates. These were contacted by phone to discuss the study and to schedule further cholesterol screening. Eligibility criteria were age between 20 and 70 years and a total blood cholesterol level between the 50th and 95th percentiles for the participant's age and sex (based on values from the National Center for Health Statistics [NCHS] tables reprinted in the NCEP expert panel report[9]). Exclusion criteria included a history of diabetes, drug or alcohol abuse, use of medications known to affect blood lipid levels, surgical treatment to lower lipid levels, unusually high-fiber intake (greater than 10 g of soluble fiber per day based on responses given on the questionnaire concerning intake of high soluble fiber foods), lactose intolerance, lower intestinal difficulties, pregnancy, and weight more than 20% above or below ideal weight for height and sex. Subjects with extremes in body weight, especially obese subjects, were excluded because they would have probably lost weight on a fat-modified diet. Weight change, per se, is known to affect cholesterol levels and could have confounded the study results.

Subjects who qualified were further evaluated with two complete lipid profiles. Subjects were accepted if the average of the two baseline measurements for LDL cholesterol was between the 50th and 95th percentile for age and sex (NCHS tables[9]), and if their triglyceride (TG) levels were less than or equal to 4.5 mmol/L (400 mg/dL). Subjects gave written informed consent and indicated, after reading the contents of the test cereals, that they had no known allergies to the ingredients. Two hundred nine subjects entered the study. The study was approved by the Human Subjects Committee of the University of Minnesota.

Study Design

The study design was a stratified, randomized crossover trial with a wheat-based cereal (low in soluble fiber) control group and a control group who remained on dietary intervention alone. Though not a true placebo control, since the cereals were dissimilar in appearance, a double-blind study was accomplished by informing subjects that two cereals were being studied comparatively for their possible cholesterol-lowering effects. Thus, subjects were not aware during the study that investigators expected one cereal to be more effective than the other. Cereals were packaged in plain white boxes, coded, and distributed by support staff so that primary investigators were completely blinded to subjects and treatment groups.

After enrollment, subjects were instructed in the American Heart Association Step I (AHA-I) diet. The study reported here involved free-living subjects; therefore, diet instruction and follow-up were comparable to that offered in a typical clinical setting. Instruction was given during a 2-hour group session (average of 5 to 10 participants per group) conducted by a registered dietitian. Follow-up telephone contact was done within 2 to 4 weeks to reinforce dietary instructions and to respond to subjects' questions regarding the diet. Subjects were asked to follow the AHA-I diet for the study duration and encouraged to make it a lifelong eating pattern.

Encouragement to adhere to the diet was provided by periodic mailing of recipes and brief general dietary information. Subjects were encouraged to phone if they had any dietary questions or concerns. They were also instructed in diet record-keeping and asked to use standard measures or food portion visuals[12] for portion sizes. Food models and charts were employed to demonstrate visually the quantity of food in a typical serving. Subjects were asked to try to maintain baseline weight throughout the study, although a slight weight loss was expected as a result of the anticipated reduction of fat intake.

After the initial 6-week intervention of diet alone, subjects were stratified by sex, age, LDL cholesterol, and baseline estimated fiber intake, and randomized into treatment (oat bran and wheat-based cereal) and control (diet only) groups. Each of two treatment periods was for 6 weeks, with crossover of cereal groups at the midpoint. A washout period between treatments was deemed unnecessary because it was expected that the 6-week duration of the postcrossover treatment period (period 2) would effectively accomplish washout before lipids were retested. The diet control group continued on

the AHA-I diet alone for both treatment periods (periods 1 and 2). The study was conducted during the months of July through December.

At the beginning of the treatment period, the cereal groups received unlabeled, coded packages of ready-to-eat cold cereal,* a measuring cup to measure cereal servings, two cereal bowls, and instructions on measuring and recording the required servings. The treatment subjects were requested to eat 28 g (1 oz) of the cereal twice daily, in the morning and in the evening. They were asked to record the amount and time of daily cereal intake throughout the treatment period, and to measure and report leftover cereal at the end of 6 weeks.

Measurements

DIETARY INTAKE

Dietary intake was measured at baseline by means of a self-administered food-frequency questionnaire.[13] Analysis was done with an optically scanned, computerized, nutrient databank. Four-day food records, including at least 1 weekend day, were assigned in week 5 of each study period. The records were collected and then reviewed by telephone for clarity by registered dietitians in week 6 of each study period; at that time, the dietitians also reviewed with the subjects the elements of the AHA Step I diet. Food records were analyzed by the University of Minnesota Nutrition Coordinating Center's Nutrient Data System (NDS) Version 1.3. Changes in nutrient intake from baseline were examined by comparing data from the food-frequency questionnaires with data from the food records. Comparability of data for dietary fats has been validated in previous studies comparing food-frequency questionnaires with similar dietary food-record collection methods.[13]

BLOOD LIPIDS

Screening and all subsequent fasting blood samples were obtained using a standardized protocol for phlebotomy technique and specimen handling. All lipid testing was performed on plasma samples. Plasma lipid values have been shown to consistently test 4.7% lower than serum values on the same subject.[14] All plasma specimens were frozen until analyzed by the Roche COBAS method at the University of Minnesota Lipid Research Laboratory, a facility certified by the Lipid Standardization Program of the Centers for Disease Control. The baseline cholesterol values were the mean of two plasma sample measurements obtained before entry into the study. The cholesterol values during the study were the mean of three measurements taken during the 6th week of each phase. Whenever possible, plasma samples were collected serially on 3 consecutive days.

Predicted vs Observed Lipid Changes.—As an additional measure of the impact of cereal treatment and diet on lipids, the Keys equations were used to analyze lipid changes by treatment period. The Keys equations were originally developed in the metabolic ward setting. They use the values for dietary changes in saturated fat, polyunsaturated fat, and dietary cholesterol to predict the impact on the cholesterol level in the blood.[15–18] These equations were developed using only male subjects in a strictly controlled metabolic ward setting, so they have limited application to studies of free-living subjects. Nevertheless, some researchers have used the Keys equations to analyze group dietary data and their impact on blood lipid changes. Thus, that analysis was performed on these data and the results reported for completeness and comparison. Body weight was measured in indoor clothing without shoes at baseline and in week 6 of each study period.

Questionnaires

Information on side effects, cereal palatability, and compliance was collected in week 5 of each treatment period. Also, data on physical activity were collected by questionnaire at the beginning and end of the study.

Analytic Methods.—Group and period (baseline, diet only, and treatment periods 1 and 2) differences for lipid variables were assessed by using a 3 (group) × 4 (phase) repeated-measures analysis of variance. Post hoc analyses of group differences at each period (and/or of period differences for each group) were then performed for significant interaction effects using the Tukey's HSD (honestly significant difference) test. For the side effects and palatability data, two-tailed paired *t* tests were computed to assess reported differences between the wheat-cereal and oat-bran periods.

Results

Of the 209 subjects initially accepted into the study, 176 completed the 6-week lead-in diet period to be randomized into cereal treatment groups. One hundred forty-five subjects, 82% of those randomized to treatment groups, completed the entire study. Overall, 64 subjects dropped out. The most common reasons given for discontinuing the study were conflicts with work or family, inconvenience, loss of interest in the study, and nonrelated

**The cereals used in the study were the Quaker Oats Company's Quaker Oat Bran and General Mills' Wheaties.*

Table 1. Lipid Values,* by Study Period and Intervention Sequence (mean ± SD)

Lipid	Preliminary	End of Diet Period (AHA-I Diet, 6 wk)	End of Crossover Period 1 (6 wk)	End of Crossover Period 2 (6 wk)
Cholesterol				
Wheat cereal–oat bran†	6.13 ± 0.77 (237 ± 29.8)	5.98 ± 0.96 (231 ± 37.1)	5.97 ± 0.79 (231 ± 30.5)	5.82 ± 0.83 (225 ± 32.1)
Diet alone	6.15 ± 0.74 (238 ± 28.6)	5.90 ± 0.74 (228 ± 28.6)	6.10 ± 0.78 (236 ± 30.2)	6.25 ± 0.87 (242 ± 33.6)
Oat bran–wheat cereal‡	6.18 ± 0.65 (239 ± 25.1)	5.91 ± 0.81 (229 ± 31.3)	5.80 ± 0.69 (224 ± 26.7)	6.19 ± 0.72 (239 ± 27.8)
LDL cholesterol				
Wheat cereal–oat bran	4.25 ± 0.55 (164 ± 21.3)	4.12 ± 0.73 (159 ± 28.2)	4.09 ± 0.61 (158 ± 23.6)	3.93 ± 0.60 (152 ± 23.2)
Diet alone	4.26 ± 0.64 (165 ± 24.7)	4.04 ± 0.65 (156 ± 25.1)	4.18 ± 0.71 (162 ± 27.5)	4.30 ± 0.76 (166 ± 29.4)
Oat bran–wheat cereal	4.19 ± 0.65 (162 ± 25.1)	4.00 ± 0.78 (155 ± 30.2)	3.84 ± 0.69 (148 ± 26.7)	4.15 ± 0.68 (160 ± 26.3)
HDL cholesterol				
Wheat cereal–oat bran	1.27 ± 0.27 (49.1 ± 10.4)	1.24 ± 0.24 (48.0 ± 9.3)	1.25 ± 0.24 (48.3 ± 9.3)	1.27 ± 0.26 (49.1 ± 10.1)
Diet alone	1.25 ± 0.30 (48.3 ± 11.6)	1.25 ± 0.45 (48.3 ± 17.4)	1.26 ± 0.30 (48.7 ± 11.6)	1.28 ± 0.32 (49.5 ± 12.4)
Oat bran–wheat cereal	1.22 ± 0.31 (47.2 ± 12.0)	1.23 ± 0.30 (47.6 ± 11.6)	1.22 ± 0.31 (47.2 ± 12.0)	1.25 ± 0.33 (48.3 ± 12.8)

Lipid values in mmol/L (mg/dL).
†Subjects ingested wheat cereal for crossover period 1 (6 wk) and oat bran for crossover period 2 (6 wk).
‡Subjects ingested oat bran for crossover period 1 (6 wk) and wheat cereal for crossover period 2 (6 wk).

medical problems. Ten percent of the dropout subjects were unable to be contacted to determine the reason for discontinuing participation. Of those subjects who entered the cereal-treatment periods, one discontinued because of frequent loose stools, presumed to be a side effect of the increased consumption of oat bran; this subject represents the only dropout believed to be due to treatment side effects. Analysis of the dropout group when compared with the subjects who completed the study indicated no significant differences in preliminary variables, including age, sex, baseline lipids, and baseline fiber intake. Of the dropouts leaving the study after randomization, 5 who left were from the group eating oat bran, 11 were from the group eating wheat cereal, and 15 were from the diet control group.

Lipoprotein Responses

Group mean values of the lipid profiles obtained at baseline, at the end of initial diet period, and after each of the cereal treatment periods (1 and 2) are displayed in Table 1. These results for total cholesterol and LDL cholesterol are graphically shown by period in Figures 1 and 2. All groups showed a significant ($P < .05$) reduction in total cholesterol and LDL cholesterol after the initial diet period.

Analysis of lipid response during the cereal treatment periods 1 and 2 is complicated by an order or period effect, which overlays the treatment effect. The expected response to the AHA-I dietary intervention is consistent with that observed for all groups during the initial diet period (approximately 4.4% reduction in LDL cholesterol). The maintenance of that improvement in LDL cholesterol throughout the cereal treatment periods in the diet and wheat-cereal control groups, however, was not observed. Rather, the diet and wheat-cereal groups demonstrated a tendency to return to baseline levels of LDL cholesterol over the subsequent periods of the study. As discussed below, these changes by period are not fully explained by dietary differences between groups or evidence of dietary recidivism during the study. Not only did the oat-bran groups maintain their original diet period improvement in lipids, but post hoc analysis demonstrated evidence of additional significant reductions in total cholesterol and LDL cholesterol when compared with diet and wheat-cereal groups ($P < .01$). The individual range in LDL cholesterol response during oat-bran treatment was from −27.4% to +26.5%. There was no significant change in high-density lipoprotein cholesterol in any treatment group during any study period.

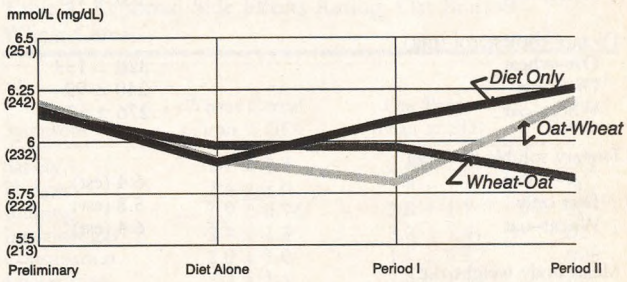

Figure 1. Mean total cholesterol levels of participants, by study period and dietary group. Diet Only denotes AHA-I diet with no cereal at any period; Oat-Wheat indicates oat bran during period 1, wheat cereal during period 2; Wheat-Oat denotes wheat cereal during period 1, oat bran during period 2.

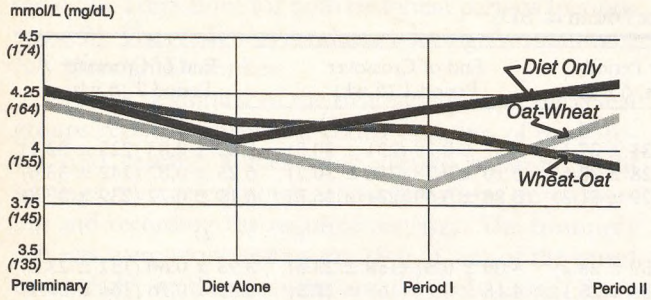

Figure 2. Mean low-density lipoprotein cholesterol levels of participants, by study period and dietary group. Diet Only denotes AHA-I diet with no cereal at any period; Oat-Wheat indicates oat bran during period 1, wheat cereal during period 2; Wheat-Oat denotes wheat cereal during period 1, oat bran during period 2.

Dietary Adherence

Analysis of the baseline semiquantitative food frequency questionnaires indicated that the overall group had a prestudy consumption of 32.8% of their calories from fat; proportionately 11.2% came from saturated fat, 12.0% from monounsaturated fat, and 6.8% from polyunsaturated fat. Mean daily cholesterol intake for the group was 271 mg. There were no significant differences between diet control and cereal-treatment groups on any of the baseline dietary variables. Estimated total daily soluble fiber intake for the overall group during the initial diet period was 6.4 g per day. Table 2 shows dietary variables for each group by period, including mean soluble fiber, energy consumption, and weight.

Predicted vs Observed Changes in Plasma Cholesterol Using the Keys Equations

The overall contribution of diet to change in plasma cholesterol by period was analyzed using the Keys equations.[15–18] Cholesterol change during the initial diet period predicted by the Keys equation was −4.2% as compared with the observed change of −3.6%. During the initial cereal treatment (period 1), predicted changes in plasma cholesterol as determined from records of fat and cholesterol consumption were −0.6%, +1.2%, and −0.5% for diet, wheat, and oat-bran groups, respectively. In comparison, the observed changes in cholesterol during period 1 for diet, wheat, and oat-bran groups were +3.5%, −0.2%, and −1.9%, respectively. For the crossover treatment (period 2), predicted choles-

Table 2. Nutritional Variables, by Study Period and Intervention Sequence (mean ± SD)

Nutritional Variable	Preliminary	End of Diet Period (AHA-I, 6 wk)	End of Crossover Period 1 (6 wk)	End of Crossover Period 2 (6 wk)
Total kilocalories				
Oat–wheat*	2281 ± 764	1858 ± 527	1759 ± 426	1878 ± 439
Diet only	1981 ± 589	1898 ± 661	1836 ± 580	1814 ± 595
Wheat–oat†	2198 ± 715	1684 ± 577	1810 ± 566	1762 ± 459
Kilocalories from saturated fat (%)				
Oat–wheat	11.8 ± 2.3	8.9 ± 2.6	8.8 ± 2.0	9.5 ± 2.9
Diet only	10.7 ± 2.4	8.7 ± 2.3	8.8 ± 2.3	9.2 ± 2.5
Wheat–oat	11.4 ± 2.8	8.6 ± 2.3	8.8 ± 2.4	9.4 ± 2.5
Kilocalories from polyunsaturated fat (%)				
Oat–wheat	7.1 ± 1.8	7.1 ± 1.9	7.0 ± 2.0	6.3 ± 2.0
Diet only	6.8 ± 1.5	6.6 ± 1.8	7.0 ± 2.4	7.0 ± 2.4
Wheat–oat	6.6 ± 1.5	6.9 ± 1.9	6.4 ± 1.9	7.1 ± 2.0
Dietary cholesterol (mg)				
Oat–wheat	320 ± 153	193 ± 86	176 ± 92	199 ± 92
Diet only	240 ± 99	218 ± 211	179 ± 92	190 ± 100
Wheat–oat	276 ± 127	173 ± 80	197 ± 106	182 ± 86
Dietary soluble fiber (g)				
Oat–wheat	6.4 (est)	6.7 ± 1.9	7.7 ± 2.4	6.1 ± 2.1
Diet only	5.8 (est)	6.8 ± 3.3	6.2 ± 2.2	6.0 ± 2.1
Wheat–oat	6.4 (est)	5.8 ± 2.5	6.0 ± 1.9	7.4 ± 1.9
Mean body weight (kg)				
Oat–wheat	75.6 ± 11.9	75.0 ± 11.2	74.6 ± 11.6	74.4 ± 12.3
Diet only	73.5 ± 11.7	73.3 ± 11.3	72.9 ± 11.3	72.0 ± 11.6
Wheat–oat	76.7 ± 10.6	75.8 ± 11.1	75.5 ± 11.2	75.5 ± 11.0

**Subjects ingested oat bran for crossover period 1 (6 wk) and wheat cereal for crossover period 2 (6 wk).*
†Subjects ingested wheat cereal for crossover period 1 (6 wk) and oat bran for crossover period 2 (6 wk).
AHA-I denotes American Heart Association Step I diet.

terol changes were +0.8%, +1.8%, and −0.2% for diet, wheat, and oat-bran groups, respectively, as compared with observed cholesterol changes during period 2 of +2.5%, +7.0%, and −2.5% for these same groups.

Analysis of compliance with cereal doses revealed that, overall, 90.6% of the servings of wheat cereal and 92.1% of the oat-bran servings were consumed. Subjects were comparably compliant in period 1 (90.8% of servings) and in the crossover period 2 (91.8% of servings).

Comparison of estimated total soluble fiber intake during the initial diet period with the total during the oat-bran treatment period (1 or 2) indicated a mean average increase in soluble fiber of 1.4 g (18.7%) for the group eating oat bran in period 1, and 1.6 g (21.6%) for the group eating oat bran in period 2. The wheat-cereal group consumed 3.8% more soluble fiber in period 1 as compared with the diet period, and 8.3% less soluble fiber in period 2 as compared with the diet period. The diet control group consumed progressively less soluble fiber by period: 6.8 g in the initial diet period, 6.2 g in period 1, and 6.0 g in period 2. The calculated soluble fiber contributed by oat bran for the groups eating it was 2.8 g in period 1 and 2.9 g in period 2.

Patterns of Response to Oat-Bran Treatment

The data were analyzed by age, sex, baseline lipid levels, and total soluble fiber intake with respect to change in LDL cholesterol to determine whether there was evidence of any unique groups of responders or nonresponders to oat-bran treatment. Single variables failed to demonstrate significant correlation with reduction in LDL cholesterol except for a correlation with higher baseline LDL cholesterol levels (Pearson's $r = .34$, $P < .001$).

However, when groups were analyzed by sex and age, with age divided into younger (< 50 years) and older subjects (≥50 years), a highly significant age-by-sex interaction was revealed ($P < .001$), and subgroups of responders and nonresponders to oat bran emerged. Younger women demonstrated a poorer lipid response to oat-bran treatment than younger men and older women. Older women as a group appeared to demonstrate the best response to oat bran (Table 3).

Side Effects

Subjects completed a questionnaire at the end of each study period to determine cereal tolerance and side effects, especially the incidence of new gastrointestinal symptoms. The summary of responses to specific questions is included in Table 4. One subject consuming oat bran dropped out of the cereal treatment phase because of increasingly loose stools. In general, the ratings on the cereals were quite similar. However, intestinal gas and looser stools were reported at a significantly higher frequency in the oat-bran treatment periods, and constipation was significantly greater in the wheat-cereal periods.

Table 3. Change in LDL-Cholesterol Level from Baseline Oat Bran Phase, by Sex and Age*

Sex and Age	Mean ± SD mmol/L	Mean ± SD (mg/dL)
Men		
<50 y (n = 22)	−0.24 ± 0.40	(−9.3 ± 15.5)
≥50 y (n = 27)	−0.08 ± 0.37	(−3.1 ± 14.3)
Women		
<50 y (n = 10)	+0.17 ± 0.48	(+6.6 ± 18.6)
≥50 y (n = 16)	−0.37 ± 0.44	(−14.3 ± 17.0)

**Age × sex interaction, P = .001.*
LDL denotes low-density lipoprotein.

Discussion

This study was designed to provide a controlled clinical trial of oat bran as an adjunct to a fat-modified diet for the management of hypercholesterolemia. Male and female subjects from a broad age range with elevated blood cholesterol were selected to enhance the generalizability of the results to populations at risk for cardiovascular disease. Diet and low-fiber controls provided appropriate group comparison, and the crossover design allowed for the internal control of the same subject on comparative treatments. The study was conducted successfully in three cohorts over approximately 26 weeks. The 82% completion rate of all subjects randomized into treatment groups and the overall adherence of subjects to treatment, with greater than 90% of both oat-bran and wheat-cereal servings consumed, demonstrated good

Table 4. Reported Side Effects Rating, Oat Bran vs Wheat Cereal

Symptom	Wheat Cereal (mean ± SD)	Oat Bran (mean ± SD)	Paired *t* Test *P* Value
Satiety	2.7 ± 1.2	2.8 ± 1.3	NS
Hunger	2.4 ± 1.0	2.3 ± 1.1	NS
Burping	1.9 ± 0.94	2.0 ± 1.1	NS
Intestinal gas	2.8 ± 1.3	3.3 ± 1.4	.01
Constipation	2.0 ± 1.0	1.7 ± 0.87	.005
Looser stool	2.2 ± 1.1	2.6 ± 1.2	.05
Bulkier stool	2.6 ± 1.2	2.3 ± 1.2	NS

Scale values: 1 = Never *or* No change *since beginning the study period; 2* = Rarely *or only once or twice in the study period; 3* = Occasionally *or three to six times in the study period; 4* = Frequently *or two to three times per week; 5* = Very frequently *or once per day or more.*
NS denotes not significant.

cooperation of study subjects. Analysis of dropout subjects, including baseline characteristics, reasons for dropout, and their treatment group, did not appear to indicate any bias that would compromise the conclusions of the study.

Lipid Effects

The oat bran effect on total cholesterol and LDL cholesterol is graphically shown in Figures 1 and 2. The initial impact of diet alone was significant, but the addition of oat bran clearly improves and sustains the reduction in total cholesterol and LDL cholesterol. The similarity in the total cholesterol and LDL cholesterol graphs demonstrates that the majority of reduction in total cholesterol produced by oat bran is in the LDL cholesterol fraction. Although the mean LDL cholesterol reduction averaged 3.9% for the oat-bran treatment groups, the range of response (−27.4% to +26.5%) is quite wide and suggests considerable individual variability in response. The complete explanation for this discrepancy is unclear. The diet records, which are a useful approximation of dietary behavior for the study periods, indicate that dietary compliance with the AHA-I diet was good and essentially comparable in all groups. Minor intergroup differences did not, by period, explain the resultant lipid changes.

Although seasonal variation in cholesterol may be an explanation,[19,20] the return of the diet control group to baseline lipid levels despite apparent good dietary adherence leads to questioning and speculation on the accuracy and validity of the 4-day food-record method of dietary monitoring. Recent studies using more objective measures of total energy consumption suggest that subjects may have a tendency to underreport food intake on dietary records.[21,22] However, when diet records are validated using these more accurate techniques (doubly labeled water method), groups of subjects such as those participating in this study, namely, nonobese persons from industrialized countries, are among the most reliable in the recording of dietary intake using food records.[22] Further, a very gross estimate of accuracy of dietary reporting can be made by calculating expected weight changes given the reported total daily calorie intake. Indeed, all groups demonstrated a slight weight loss (Table 3) over the course of the study, and each was within 1 kg of the weight predicted based on caloric intake.

If underreporting occurred in this study, all groups might be expected to show a tendency to do less well than predicted by the Keys formulas. Interestingly, that did not occur in the treatment groups supplemented with 56 g (2 oz) of oat-bran cereal. Rather, oat-bran groups demonstrated further reductions in total cholesterol and LDL cholesterol beyond those predicted by the Keys formulas. This phenomenon of maintenance of dietary gains plus additional cholesterol reduction was clearly demonstrated by oat-bran groups in both periods of the crossover, arguing in support of an active oat-bran effect on cholesterol.

Mechanism of Action of Oat Bran

Oat bran is known to enhance bile-acid excretion through biliary-fecal elimination.[23] Thus, diversion of hepatic sterol metabolism to increase bile acid production rather than lipoprotein synthesis may, in part, explain oat bran's effect on total cholesterol and LDL cholesterol. Anderson and Gustafson,[24] however, have demonstrated that this mechanism is not consistent with the studies of the lipid effects of soluble fiber from other sources nor sufficient to explain the full impact of oat bran on blood lipids.[24] They and others have postulated that fermentation in the colon of soluble fiber produces short-chain fatty acids, primarily acetate, proprionate, and butyrate, that, in turn, are absorbed through the portal venous system and appear to inhibit hepatic cholesterol synthesis.[24]

Kelly and Story[25] demonstrated a decreased activity of the HMG-CoA reductase system in rats that were fed oat bran, thus implying a direct effect of oat bran in the lowering of total cholesterol and LDL cholesterol. Soluble fiber may also have an indirect influence on HMG-CoA reductase mediated through a delay in carbohydrate absorption (flattening of the glycemic curve) that slows and decreases the release of insulin after a meal.[26] Insulin appears to directly stimulate sterol synthesis by the HMG-CoA pathway.[27] Thus, indirectly, the oat-bran effect on insulin reduction may be another pathway to lowering cholesterol.

A post hoc discovery in this study of an age-by-sex interaction ($P < .001$) on the pattern of lipid response raises new questions regarding the mechanism of action of oat bran. Although there were individual exceptions, women under the age of 50 years were essentially unresponsive to the lipid-lowering effect of oat bran, and men over the age of 50 years had only a modest response. In contrast, younger men and women over the age of 50 years showed considerable reductions in total cholesterol and LDL cholesterol. The group of female subjects was divided at age 50 years as a proxy for a premenopausal and postmenopausal division. The male group was also divided at age 50 years to make the comparisons symmetrical by age. The interaction findings raise the possibility that estrogen may negatively interact with the lipid-lowering benefits of oat bran in women, or that lack of

estrogen potentiates its benefit. No explanation for the differences in male response by age is yet evident, and further research is needed on the mechanism of oat bran in both sexes.

Conclusions

This study demonstrated significant lipid improvements in oat-bran–treated subjects, but the length of treatment was relatively short: only 6 weeks. In practice, patients are asked to make lifelong changes in eating patterns and lifestyle in an effort to reduce cardiovascular risk, and it appears that the addition of soluble fiber in the form of oat bran may be a useful adjunct to this risk reduction. However, longer term studies of lipid changes and patient acceptability are needed to convincingly demonstrate that the oat bran benefits can, indeed, be sustained.

This study is consistent with the preponderance of research on oat bran and blood lipids. It demonstrates that oat bran, used as a dietary supplement with a fat-modified diet, contributes significantly to the reduction of total cholesterol and LDL cholesterol. Furthermore, oat bran is most effective in those groups generally at higher risk for a cardiovascular disease, namely men and older women with hypercholesterolemia. An unanticipated study finding was the discovery of apparent resistance to the lipid-lowering benefits of oat bran in hypercholesterolemic women under the age of 50 years.

This finding could perhaps explain the apparent lack of superior benefit from oat bran as compared with a low-fiber cereal reported by Swain et al,[10] whose 20 subjects (age range 23 to 49 years; mean 30 years) were almost all (80%) young, normocholesterolemic women. It is unfortunate that the generalizations regarding the efficacy of oat bran from this small and unrepresentative group of subjects received such widespread attention. The controversial report by Swain et al and the resulting publicity in the lay press effectively undermined years of public education on the value of soluble fiber such as oat bran as a dietary supplement, and has confused both physicians and the public.

The results of the present study and another recently published controlled study[8] support the use of oat bran as a beneficial supplement in a heart-healthy eating plan for most persons with hypercholesterolemia. Although the clinical benefits are modest from the standpoint of coronary risk reduction of the overall group (mean reduction LDL cholesterol −3.9%), certain individuals may experience considerable benefit (up to −27.4% reduction in LDL cholesterol). This study raises the possibility that younger women and older men may be less likely to benefit than younger men and older women. An additional study of larger numbers of subjects is needed to better understand response patterns, and long-term studies are needed to determine whether oat bran benefits can be maintained over time. Research on the oat-bran mechanism of action is also needed, especially in light of selective responder groups.

Acknowledgment

This study was supported by a grant from the Quaker Oats Company, Barrington, Illinois.

References

1. Stamler J. Population studies. In: Levy R, Rifkind B, Dennis B, Ernst N, eds. Nutrition, lipids, and coronary heart disease. New York: Raven Press, 1979:25–88.
2. Kromhout D, Bosschieter EB, DeLezenne Coulander C. Dietary fibre and 10-year mortality from coronary heart disease, cancer, and all causes. The Zutphen study. Lancet 1982; 1:518–22.
3. Anderson JW. Dietary fiber, lipids and atherosclerosis. Am J Cardiol 1987; 60:17G–22G.
4. Shinnick FL, Longacre MJ, Ink SL, Marlett JA. Oat fiber: composition versus physiological function in rats. J Nutr 1988; 118: 144–51.
5. Kirby RW, Anderson JW, Sieling B, et al. Oat-bran intake selectively lowers serum low-density lipoprotein cholesterol concentrations of hypercholesterolemic men. Am J Clin Nutr 1981; 34: 824–9.
6. Kestin M, Moss R, Clifton PM, Nestel PJ. Comparative effects of three cereal brans on plasma lipids, blood pressure and glucose metabolism in mildly hypercholesterolemic men. Am J Clin Nutr 1990; 52:61–6.
7. Gold KV, Davidson DM. Oat bran as a cholesterol-reducing dietary adjunct in a young, healthy population. West J Med 1988; 148:299–302.
8. Davidson MH, Dugan LD, Burns JH, et al. The hypocholesterolemic effects of β-glucan in oatmeal and oat bran. JAMA 1991; 265:1833–9.
9. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1989. NIH publication no. 89-2925.
10. Swain JF, Rouse IL, Curley CB, Sacks FM. Comparison of the effects of oat bran and low-fiber wheat on serum lipoprotein levels and blood pressure. N Engl J Med 1990; 322:147–52.
11. Connor WE. Dietary fiber—nostrum or critical nutrient? N Engl J Med 1990; 322:193–5.
12. Posner BM, Borman CL, Morgan JL, et al. The validity of a telephone-administered 24-hour dietary recall methodology. Am J Clin Nutr 1982; 36:546–53.
13. Willett WC, Reynolds RD, Cottrell-Hoehner S, et al. Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc 1987; 87:43–7.
14. Cloey T, Bachorik PS, Becker D, et al. Reevaluation of serum-plasma differences in total cholesterol concentrations. JAMA 1990; 263:2788–9.
15. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. I. Iodine value of dietary fat versus 2S-P. Metabolism 1965; 14:747–58.
16. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. II. The effect of cholesterol in the diet. Metabolism 1965; 14:759–65.
17. Keys A, Anderson JT, Grande F. Serum cholesterol response to

changes in the diet. III. Differences among individuals. Metabolism 1965; 14:766–75.
18. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. Metabolism 1965; 14:776–87.
19. Thomas CB, Holljes HW, Eisenberg FF. Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. Ann Intern Med 1961; 54:413–30.
20. Gordon DJ, Trost DC, Hyde J, et al. Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial placebo group. Circulation 1987; 76:1224–31.
21. Livingstone MBE, Prentice AM, Strain JJ, et al. Accuracy of weighed dietary records in studies of diet and health. Br Med J 1990; 300:708–12.
22. Schoeller DA. How accurate is self-reported dietary energy intake? Nutr Rev 1990; 48:373–9.
23. Anderson JW, Story L, Sieling B, et al. Hypocholesterolemic effects of oat-bran or bean intake for hypercholesterolemic men. Am J Clin Nutr 1984; 40:1146–55.
24. Anderson JW, Gustafson NJ. Hypocholesterolemic effects of oat and bean products. Am J Clin Nutr 1988; 48:749–53.
25. Kelley MJ, Story JA. Short-term changes in hepatic HMG-CoA reductase in rats fed diets containing cholesterol or oat bran. Lipids 1987; 22:1057–9.
26. Lembcke B, Ebert R, Ptok M, et al. Role of gastrointestinal transit in the delay of absorption by viscous fibre (guar). Hepatogastroenterology 1984; 31:183–6.
27. Bhathena SJ, Avigan J, Schreiner ME. Effect of insulin on sterol and fatty acid synthesis and hydroxymethylglutaryl CoA reductase activity in mammalian cells grown in culture. Proc Natl Acad Sci USA 1974; 71:2174–8.