Effect of a Low–Glycemic Index or a High–Cereal Fiber Diet on Type 2 Diabetes

A Randomized Trial

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Context Clinical trials using antihyperglycemic medications to improve glycemic control have not demonstrated the anticipated cardiovascular benefits. Low–glycemic index diets may improve both glycemic control and cardiovascular risk factors for patients with type 2 diabetes but debate over their effectiveness continues due to trial limitations.

Objective To test the effects of low–glycemic index diets on glycemic control and cardiovascular risk factors in patients with type 2 diabetes.

Design, Setting, and Participants A randomized, parallel study design at a Canadian university hospital research center of 210 participants with type 2 diabetes treated with antihyperglycemic medications who were recruited by newspaper advertisement and randomly assigned to receive 1 of 2 diet treatments each for 6 months between September 16, 2004, and May 22, 2007.

Intervention High–cereal fiber or low–glycemic index dietary advice.

Main Outcome Measures Absolute change in glycated hemoglobin A_{1c} (HbA_{1c}), with fasting blood glucose and cardiovascular disease risk factors as secondary measures.

Results In the intention-to-treat analysis, HbA_{1c} decreased by −0.18% absolute HbA_{1c} units (95% confidence interval [CI], −0.29% to −0.07%) in the high–cereal fiber diet compared with −0.50% absolute HbA_{1c} units (95% CI, −0.61% to −0.39%) in the low–glycemic index diet ($P<.001$). There was also an increase of high-density lipoprotein cholesterol in the low–glycemic index diet by 1.7 mg/dL (95% CI, 0.8-2.6 mg/dL) compared with a decrease of high-density lipoprotein cholesterol by −0.2 mg/dL (95% CI, −0.9 to 0.5 mg/dL) in the high–cereal fiber diet ($P=.005$). The reduction in dietary glycemic index related positively to the reduction in HbA_{1c} concentration ($r=0.35$, $P<.001$) and negatively to the increase in high-density lipoprotein cholesterol ($r=-0.19$, $P=.009$).

Conclusion In patients with type 2 diabetes, 6-month treatment with a low–glycemic index diet resulted in moderately lower HbA_{1c} levels compared with a high–cereal fiber diet.

Trial Registration clinicaltrials.gov identifier: NCT00438698

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THE NEED FOR IMPLEMENTATION of effective dietary strategies in diabetes prevention and management has been emphasized by the success of diet and lifestyle changes in preventing diabetes in high-risk patients.[1] There is also concern that use of antihyperglycemic medications to improve glycemic control in type 2 diabetes may not always significantly improve cardiovascular outcomes.[2-7]

One dietary strategy aimed at improving both diabetes control and cardiovascular risk factors is the use of low–glycemic index diets.[8-10] These diets have been reported to benefit the control of diabetes[11]; increase high-density lipoprotein cholesterol (HDL-C)[12,13]; lower serum triglyceride, plasminogen activator inhibitor 1, and high-sensitivity C-reactive protein (CRP) concentrations[14-16]; and reduce diabetes incidence[8,9] and overall cardiovascular events.[10] Use of the α-glucosidase carbohydrate absorption inhibitor acarbose, which effectively creates a low–glycemic index diet by

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slowing the rate of carbohydrate absorption, similarly reduced not only the rate of progression to diabetes in high-risk individuals but also the incidence of hypertension and the risk of cardiovascular disease.[17,18] Nonetheless, the relevance and practicality of applying the low–glycemic index dietary approach to the treatment of diabetes has been questioned.[19-21] Furthermore, although meta-analyses of clinical studies have indicated a benefit in diabetes in terms of reduced glycated proteins,[11] individual trials have often failed to demonstrate a clear benefit for low–glycemic index diets.[11,22] However, these trials have usually been of short duration with relatively small numbers of participants.[11] An exception is a recent larger and longer trial,[22] but in that study, the mean baseline glycated hemoglobin A_{1c} (HbA_{1c}) concentration was already relatively low at 6.1%, thus making it difficult to demonstrate benefit from the intervention.

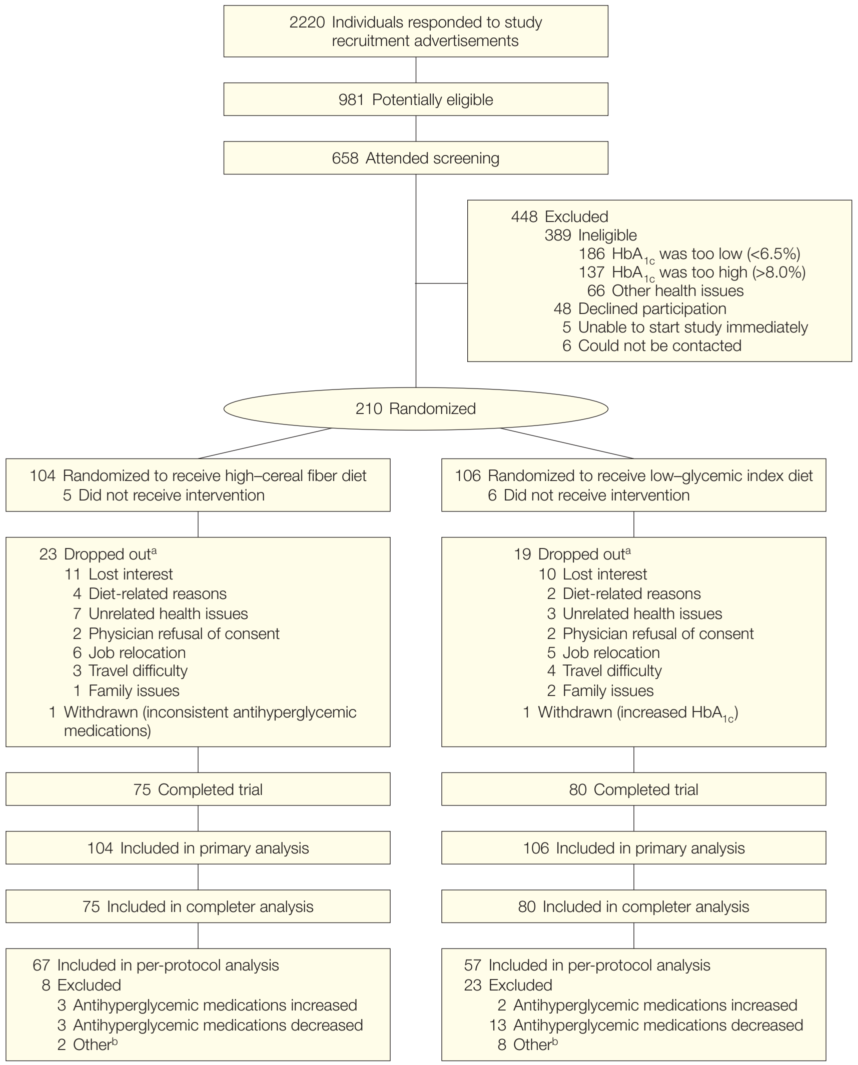
Our goal in this study was to assess the effect of a low–glycemic index diet in an adequately powered study of patients with type 2 diabetes controlled by oral medications with HbA_{1c} concentrations between 6.5% and 8.0%. At these levels, a reduction in glycemia and associated risk factors for diabetes complications are likely to be observed more clearly. We selected a high–cereal fiber diet treatment for its suggested health benefits[8,9,23-25] for the comparison so that the potential value of carbohydrate foods could be emphasized equally for both high–cereal fiber and low–glycemic index interventions.

METHODS

Participants

Study participants were recruited from local newspaper advertisements. Out of 2220 responses by telephone, 981 participants were considered potentially eligible and were invited to attend an information session at the Risk Factor Modification Center, St Michael's Hospital, Toronto, Ontario, Canada, where all study clinical activity took place. Of those participants invited, 658 attended a screening appointment. A total of 389 participants were ineligible and 269 were eligible; however, 6 participants could not be contacted, 5 were unable to start the study immediately, and 48 declined to continue. The remaining 210 participants were randomized (**FIGURE 1**). Recruitment took place between July 8, 2004, and December 5, 2006, with the last follow-up visit on May 22, 2007. Eligible participants were men or postmenopausal women with type 2 diabetes who were taking oral medications other than acarbose to control their diabetes, with medications stable for the previous 3 months, and who had HbA_{1c} values at screening between 6.5% and 8.0% (to convert to proportion of total hemoglobin, multiply by 0.01). None had clinically significant cardiovascular, renal, or liver

Figure 1. Flow of Participants Through the Trial



HbA_{1c} indicates glycated hemoglobin A_{1c}. The mean time to dropout for those participants who did not complete the end point assessment was 5.9 weeks for the high–cereal fiber diet and 3.4 weeks for the low–glycemic index diet.

[a] Seventeen participants had more than 1 reason for dropping out. One participant who dropped out from the high–cereal fiber diet had an antihyperglycemic medication dosage decrease and 1 participant who dropped out from the low–glycemic index diet had an antihyperglycemic medication dosage increase.

[b] Included not postmenopausal, prestudy oral hypoglycemic medication change, not taking oral hypoglycemic medications, or taking acarbose.

disease (alanine aminotransferase >3 times the upper limit of normal) and none were undergoing treatment for cancer. Participants were accepted after surgery or myocardial infarction providing an event-free, 6-month period had elapsed before the study.

After randomization, it was found that 5 participants had not been excluded who were taking acarbose and had not subsequently been advised to stop taking acarbose, and 2 participants were not taking diabetes medications. In addition, 8 participants had changed their medications within 3 months before the start of the study and 2 women were not postmenopausal. Furthermore, at the start of the trial, 9 participants (6 in the low–glycemic index diet and 3 in the high–cereal fiber diet) did not receive the appropriate dietary advice for the treatment to which they had been randomized. This error was corrected within the first 4 weeks of the study. Nevertheless, all randomized participants were retained both for the intention-to-treat (ITT) and study completion analyses.

Race/ethnicity was determined by a member of the research team (S.M.) and included to allow for future subgroup analyses when genetic data (to be determined) become available. The study was approved by the research ethics board of St Michael's Hospital and the University of Toronto, Toronto, Ontario, Canada, and written consent was obtained from all participants.

Protocol

Our study was a randomized, parallel study with 2 treatments, a low–glycemic index diet and a high–cereal fiber diet, each of 6 months' duration. After stratification by sex and HbA_{1c} ($\leq 7.1\%$), randomization was performed by using participant identification (subject ID) by a statistician (E.V.) who was geographically separated from the center at which participants were observed. Neither the dietitians who were responsible for the day-to-day running of the study nor the participants could be blinded to the treatment allocation. The technical staff involved in the analyses were blinded to treatment, as was the statistician up to and during the preliminary assessment of the primary outcome, HbA_{1c}. In addition, during the study, equally strong emphasis was placed by dietitians on the potential importance of either high–cereal fiber foods or low–glycemic index foods and appropriate weekly checklists were developed for each treatment.

Participants were observed at the Clinical Nutrition and Risk Factor Modification Center at baseline, weeks 2 and 4, and thereafter at monthly intervals until the end of the 6-month period. During the first month, participants received instructions regarding the diet to which they were allocated. Throughout the study, this advice was reinforced by the dietitians. At all center visits, participants were weighed in indoor clothing without shoes and a fasting blood sample was taken. Blood pressure was measured seated on 3 occasions at 1-minute intervals using an Omron automatic sphygmomanometer (OMRON Healthcare Inc, Burlington, Ontario, Canada) and the mean of the 3 measurements was taken. In addition, participants brought with them their 7-day food record covering the week before the visit; this was discussed with the dietitian together with their checklist of low–glycemic index or high–cereal fiber food items recorded on a daily basis throughout the study. Participants noted their overall feeling of satiety or hunger over the previous weeks on a scale of $+4$ to -4, where $+4$ was extremely satiated, 0 was neutral, and -4 was extremely hungry. For the last 114 participants who were enrolled in the study, adherence was rated formally under 1 of 3 categories (good, adequate but may need additional encouragement with a between-visit telephone call, or nonadherent with definite need for a telephone call between scheduled visits).

During the study, participants were asked to maintain their antihyperglycemic medications constant and letters were sent to family physicians for their support in this matter. When patients experienced symptoms of hypoglycemia with blood capillary glucose levels of less than 63.1 mg/dL (to convert to millimoles per liter, multiply by 0.0555) for no obvious reason, study endocrinologists (R.G.J., J.S., G.L.B., and L.A.L.) who were blinded to treatment were consulted. The patients were then referred back to their family physicians so that medications could be reduced according to a predetermined protocol. If HbA_{1c} increased to more than 8.5% on 2 successive occasions, participants were withdrawn from the study and referred back to their own physicians. Only 1 participant was withdrawn due to HbA_{1c} being more than 8.5% on 2 successive occasions. The participant's HbA_{1c} was 7.6% at recruitment, but increased to 8.2% by baseline and was later withdrawn due to readings of more than 8.5% during the study.

Dietary Interventions

General dietary advice conformed to the National Cholesterol Education Program Adult Treatment Panel III[26] and the American Diabetes Association[27] guidelines to reduce saturated fat and cholesterol intakes. Most of the participants were overweight (179/210 [85.2%], with body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of ≥ 25) or obese (113/210 [53.8%], BMI ≥ 30) and wished to lose weight. They were informed that this was not a weight-loss study but appropriate advice was given on portion size and fat intake to help them meet their body weight objectives. Participants were also provided with a checklist with either low–glycemic index or high–cereal fiber food options from different categories (breakfast cereals, breads, vegetables, fruit) as approximately 15-g carbohydrate servings. The number of carbohydrate servings prescribed covered 42% to 43% of total dietary calories.

In the low–glycemic index diet, the following foods were emphasized: low–glycemic index breads (including pumpernickel, rye pita, and quinoa and flaxseed) and breakfast cereals (including Red River Cereal [hot cereal made of bulgur and flax], large flake oatmeal, oat bran, and Bran Buds [ready-to-eat cereal made of wheat bran and psyllium fiber]), pasta, parboiled rice, beans, peas, lentils, and nuts (TABLE 1). In the high–cereal fiber diet, participants were advised to take the "brown" option (whole grain breads; whole grain breakfast cereals; brown rice; potatoes with skins; and whole wheat bread, crackers, and breakfast cereals) (Table 1). Six servings were prescribed for a 1500-kcal diet, 8 servings for a 2000-kcal diet, and 10 servings for a 2500-kcal diet. Detailed advice was also given to avoid starchy foods not directly recommended as part of the treatment, including those foods advised in the alternative treatment.

In both diets, participants were specifically advised to avoid foods such as pancakes, muffins, donuts, white buns, bagels, rolls, cookies, cakes, popcorn, french fries, and chips. Three servings of fruit and 5 servings of vegetables were encouraged on both treatments. In the low–glycemic index diet, temperate fruit was the focus, including apples, pears, oranges, peaches, cherries, and berries; and in the high–cereal fiber diet, tropical fruit, such as bananas, mangos, guavas, grapes, raisins, watermelon, and cantaloupe, were emphasized. Participants were also advised against eating fruit recommended in the alternative treatment.

Checklists were completed by participants on a daily basis throughout the study and 7-day diet records were completed before each visit. Participants were instructed on how to record using food models as examples of portion size and were asked to give actual weights or to express the amounts in terms of common measures, including cups, teaspoons, and dessert spoons. Adherence was assessed from the 7-day diet records. The daily checklists were of value in alerting the dietitian to problems with adherence to the diet plan over the month before center attendance. The overall goal was to achieve a 10% to 20% reduction in glycemic index on the low–glycemic index diet while keeping dietary fiber similar between treatments.

Analyses

Blood glucose was measured in the hospital routine analytical laboratory by a glucose oxidase method using a Random Access Analyzer and reagents (SYNCHRON LX Systems; Beckman Coulter, Brea, California), with coefficient of variation between assays of 1.9%. HbA_{1c} was analyzed within 2 days of collection on whole blood collected in EDTA Vacutainer tubes and measured by a designated high-performance liquid chromatography method (Tosoh G7 Automated HPLC Analyzer, Grove City, Ohio), with coefficient of variation of 1.7%.

Serum was analyzed for total cholesterol, triglycerides, and HDL-C by using a Random Access Analyzer and reagents (SYNCHRON LX Systems), with coefficient of variation of 1.5% to 2.4%. Low-density lipoprotein cholesterol (LDL-C) was calculated by the method of Friedewald et al[28] [LDL-C = total cholesterol–(triglycerides/5 + HDL-C)] in mg/dL (to convert HDL-C and LDL-C to millimoles per liter, multiply by 0.0259). C-reactive protein was measured by end point nephelometry (Behring BN-100, N high-sensitivity CRP reagent; Dade-Behring, Marburg, Germany), with coefficient of variation of 2.3%. Diets were assessed for macronutrients, fatty acids, cholesterol, fiber, and glycemic index by using a computer program based on US Department of Agriculture data[29] and international glycemic index tables,[30] with white bread as the standard. Additional measurements were made on local foods, especially specialty breads used as part of the low–glycemic index diet. Glycemic load was calculated as the product of the mean daily available carbohydrate and glycemic index divided by 100.

Table 1. Example Diets Based on 2000 Kilocalories[a]

	High–Cereal Fiber Diet		Low–Glycemic Index Diet	
	Meal	**Portion Size**	**Meal**	**Portion Size**
Breakfast	Weetabix[b]	1	Red River Cereal (dry)[b]	2 T
	Milk, skim[c]	1 cup	Milk, skim[c]	1 cup
	Whole wheat toast with margarine with double fruit jam	2 slices 1 T 1 T	Quinoa bread with peanut butter with double fruit jam	2 slices 1 T 1 T
	Cantaloupe	1 cup	Orange	1
Lunch	Entrée[d]		Entrée[d]	
	Vegetables	½ cup	Vegetables	½ cup
	Brown rice	1 cup	Spaghetti, al dente	1 cup
	Tossed salad with vinaigrette (1 T oil, 1 T vinegar)	1 cup 2 T	Tossed salad with vinaigrette (1 T oil, 1 T vinegar)	1 cup 2 T
	Grapes	15	Apple	1
Dinner	Entrée[d]		Entrée[d]	
	Baked potato with margarine	½ 2 t	Lentils with tomato sauce	½ cup 2 T
	Spinach with balsamic vinegar	½ cup	Spinach with balsamic vinegar	½ cup
	Carrot coins	½ cup	Carrot coins	½ cup
	Mango with low-fat yogurt	1 1 cup	Pear with low-fat yogurt	1 1 cup
Snack	Whole wheat toast	1 slice	Finland rye pita	½
	Part skim mozzarella cheese	1.5 oz	Part skim mozzarella cheese	1.5 oz

Abbreviations: T, tablespoon; t, teaspoon.

[a] The high–cereal fiber diet included 35 g of fiber, glycemic index of 86, and glycemic load of 201. The low–glycemic index diet included 42 g of fiber, glycemic index of 62, and glycemic load of 141.

[b] Weetabix is a whole-grain wheat flake cereal shaped into a biscuit and Red River Cereal is a hot cereal made of bulgur and flax.

[c] One cup skim milk can be substituted with 1 cup unsweetened soy beverage.

[d] Entrée options (each choice provides 20-28 g of protein): conventional (3 oz of lean beef, chicken, veal, pork, lamb, or fish) and vegetarian alternatives (1 cup tofu, 2 veggie burgers, or 2 veggie dogs).

Outcome Measures

The primary outcome measure was HbA$_{1c}$, with glucose, HDL-C, triglycerides, CRP, blood pressure, and body weight as secondary outcome measures.

Power Calculations

The original power calculation was based on a predicted HbA$_{1c}$ difference between end of treatments of 0.7 HbA$_{1c}$ units, with an SD of effect of 1.2 HbA$_{1c}$ units, $\alpha = .05$, $1-\beta = .80$, and a dropout rate of 25%. Our participant requirement was 67 for each treatment. However, the preliminary results of a large (but at the time unpublished) study that assessed the diet effect on HbA$_{1c}$ suggested our effect size would be smaller than we had originally predicted.[22] In an unplanned interim analysis, we confirmed a smaller than predicted difference in the change in HbA$_{1c}$ between treatments for the first 58 participants to complete the study. Our revised goal therefore was to detect a difference of half of an SD (0.6%) in the change in HbA$_{1c}$ between treatments (change = 0.3%), with type I error of 2.53% (Bonferroni adjustment to allow for the initial analysis of the preliminary ITT HbA$_{1c}$ data with $\alpha = .05$) and type II error of 20%. Assuming a loss of 25% of participants due to dropouts and medication changes, 104 participants were needed in each treatment group.

Table 2. Baseline Characteristics of Study Participants

Characteristics	No. (%) of Participants High–Cereal Fiber Diet (n = 104)	 Low–Glycemic Index Diet (n = 106)
Age, mean (SD), y	61 (9)	60 (10)
Sex		
Male	63 (60.6)	65 (61.3)
Female	41 (39.4)	41 (38.7)
Race/ethnicity[a]		
European	65 (62.5)	79 (74.5)
Indian	21 (20.2)	14 (13.2)
Far Eastern	6 (5.8)	6 (5.7)
African	9 (8.7)	4 (3.8)
Hispanic	2 (1.9)	3 (2.8)
Native American	1 (1.0)	0 (0.0)
Weight, mean (SD), kg	87.8 (19.4)	87.0 (20.0)
BMI, mean (SD)	31.2 (5.8)	30.6 (6.0)
Current smokers	2 (1.9)	12 (11.3)
Glucose, mg/dL	140 (29)	139 (31)
HbA$_{1c}$, %		
Mean (SD)	7.1 (1.0)	7.1 (1.0)
No. of participants $\leq$7.1%	58 (55.8)	57 (53.8)
No. of participants $>$7.1%	46 (44.2)	49 (46.2)
Lipids, mean (SD), mg/dL		
Total cholesterol	168 (32)	164 (37)
LDL-C	101 (29)	97 (34)
HDL-C	43 (10)	42 (12)
Triglycerides	122 (58)	128 (70)
Blood pressure, mean (SD), mm Hg		
Systolic	128 (14)	127 (16)
Diastolic	75 (9)	74 (10)
Duration of diabetes, mean (SD), y	7.2 (5.9)	8.3 (6.5)
Medication use		
Hypoglycemic medications	104 (100)	104 (98)
Thiazolinedione	34 (33)	36 (34)
Biguanide	83 (80)	86 (81)
Sulfonylurea	46 (44)	61 (58)
Meglitinides (nonsulfonylurea)	3 (3)	3 (3)
α-Glucosidase inhibitors	2 (2)	3 (3)
Cholesterol-lowering medications	62 (60)	71 (67)
Blood pressure medications	68 (65)	70 (66)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. SI conversions: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and HbA$_{1c}$ to proportion of total hemoglobin, multiply by 0.01.

[a] Race/ethnicity was determined by a member of the research team (S.M.) and included to allow for future subgroup analyses.

Statistical Analyses

Results are expressed as means with 95% confidence intervals (CIs). All analyses were performed by using SAS version 9.1.2.[31] Three participant groups were analyzed. The first and primary analysis was an ITT analysis, which included all 210 randomized participants, with the baseline observation carried forward, rather than the last observation, for all those who did not complete the study. This procedure was used to recognize that these individuals would most likely have reverted to their previous diets and behavioral patterns, resulting also in a reversion to their previous level of diabetic control. Participants who were randomized but did not receive intervention (n = 11) had their screening value used as baseline and this value was carried forward. The second analysis included 155 participants who completed the study (completer analysis), and the third analysis involved 124 participants who completed the study according to the protocol but who did not change their antihyperglycemic medications before or during the study period (per-protocol analysis).

The significance of treatment differences was assessed by using an analysis of covariance model (Proc GLM)[31] with change from baseline to end of study as the response variable and diet and sex as main effects, with diet × sex as the interaction term and baseline as a covariate. Additional analyses were also performed to assess the effects of possible factors at baseline associated with diabetes outcome, including adequate glycemic control (HbA_{1c} ≤7.0%), normal BMI (<25), younger age (<60 years), and smoking. The analysis of covariance model for these analyses was the basic model described above together with the main effect of interest and its diet interaction. The time trends were estimated by using Proc GLM in SAS and the repeated statement assuming a spatial power covariance structure to control for unevenly spaced time intervals between measurements. This is an autoregressive test assuming correlations between successive observations. A significant time trend therefore indicates a monotonic relationship between time and change in the study measurement. HbA_{1c}, glucose, HDL-C, and the lipid ratios with HDL-C in the denominator showed significant time trends. No time trend was observed between weeks 2 to 24 for the other measurements.

Additional analyses were performed by using change in fiber, carbohydrate intake, and body weight as covariates in the analysis of covariance model (Proc GLM).[31] For skewed data, the results were confirmed with nonparametric analysis but only parametric analyses are reported. The Mantel-Haenszel, χ^2 test, and Fisher exact tests were used to assess differences in medication changes[31] and baseline comparisons. Pearson product-moment correlations were calculated to examine associations of dietary fiber, glycemic index, and body weight change with other variables of interest. Partial correlations controlling for either change in body weight, fiber, or glycemic index were also undertaken to examine the independent association of fiber and glycemic index with the variables of interest.[31]

RESULTS

The participant flow diagram is shown in Figure 1. Eleven participants dropped out after randomization but before their baseline visit and were therefore unaware of their treatment allocation (5 in the high–cereal fiber diet group and 6 in the low–glycemic index diet group). After starting the high–cereal fiber diet, 23 of 99 participants (23%) dropped out compared with 19 of 100 participants (19%) in the low–glycemic index diet group.

There were no treatment differences at baseline (TABLE 2), with the exception of more carbohydrate and less fat consumed before the high–cereal fiber diet compared with the low–glycemic index diet (TABLE 3). By the end of the study, although carbohydrate intake increased similarly on both treatments, fiber intake increased slightly more with the low–glycemic index diet (18.7 g/1000 kcal at week 24) than with the high–cereal fiber diet (15.7 g/1000 kcal at week 24; *P*<.001). The glycemic index decreased with the low–glycemic index diet (from 80.8 to 69.6 glycemic index units) compared with an increase in the high–cereal fiber diet (from 81.5 to 83.5 glycemic index units), indicating adherence with the low–glycemic index diet (*P*<.001) (Table 3). In the assessment of the last 114 participants enrolled, the dietitians rated adherence similarly and poor in 8 of 58 participants (13.8%) in the high–cereal fiber diet group and in 6 of 56 participants (10.7%) in the low–glycemic index diet group. Satiety ratings (scale, +4 to –4) were also similar in both diets (high–cereal fiber diet [n=94], 0.79; 95% CI, 0.60-0.98; and low–glycemic index diet [n=93], 0.74; 95% CI, 0.57-0.91; *P*=.71).

Table 3. Nutritional Profile of High–Cereal Fiber and Low–Glycemic Index Diets for Intention-to-Treat Population (n = 195)[a]

	Mean (95% Confidence Intervals)			
	Week 0		Week 24	
	High–Cereal Fiber Diet	Low–Glycemic Index Diet	High–Cereal Fiber Diet	Low–Glycemic Index Diet
Energy, kcal	1830 (1720-1940)	1916 (1805-2026)	1690 (1594-1786)	1706 (1607-1805)
Fat, % of energy				
Total	33.0 (31.6-34.3)	36.1 (34.9-37.4)	30.5 (29.0-32.0)	33.3 (31.8-34.8)
Monounsaturated fatty acids	13.2 (12.4-14.0)	14.6 (13.9-15.4)	12.2 (11.3-13.0)	13.3 (12.4-14.1)
Polyunsaturated fatty acids	6.7 (6.3-7.1)	7.4 (6.9-7.8)	6.2 (5.8-6.7)	6.7 (6.2-7.3)
Saturated fatty acids	10.3 (9.7-10.8)	11.2 (10.6-11.7)	9.3 (8.7-9.8)	9.6 (9.0-10.2)
Dietary cholesterol, mg/1000 kcal	150.2 (138.2-162.3)	156.4 (145.6-167.1)	142.9 (130.2-155.6)	142.0 (128.6-155.4)
Protein, % of energy				
Total	20.1 (19.3-20.8)	20.3 (19.6-20.9)	20.7 (20.0-21.5)	21.2 (20.6-21.8)
Plant	6.9 (6.5-7.3)	6.5 (6.2-6.9)	7.1 (6.7-7.5)	7.5 (7.2-7.9)
Available carbohydrate, % of energy	45.4 (43.7-47.0)	42.2 (40.9-43.4)	47.5 (45.8-49.1)	44.0 (42.4-45.6)
Fiber, g/1000 kcal	14.1 (13.1-15.0)	13.9 (12.7-15.0)	15.7 (14.7-16.7)	18.7 (17.3-20.0)
Alcohol, % of energy	1.6 (0.9-2.3)	1.4 (0.9-2.0)	1.3 (0.7-1.9)	1.5 (0.9-2.0)
Glycemic index	81.5 (80.4-82.7)	80.8 (79.6-82.0)	83.5 (82.4-84.7)	69.6 (67.7-71.4)
Glycemic load	169.0 (156.5-181.5)	161.6 (151.8-171.4)	166.0 (155.5-176.4)	128.9 (120.5-137.3)

[a] Eleven participants did not start the study and have no diet records and 4 participants did not have diet records for week 0. The range for glycemic index was 55 to 99 and the range for glycemic load was 46 to 474.

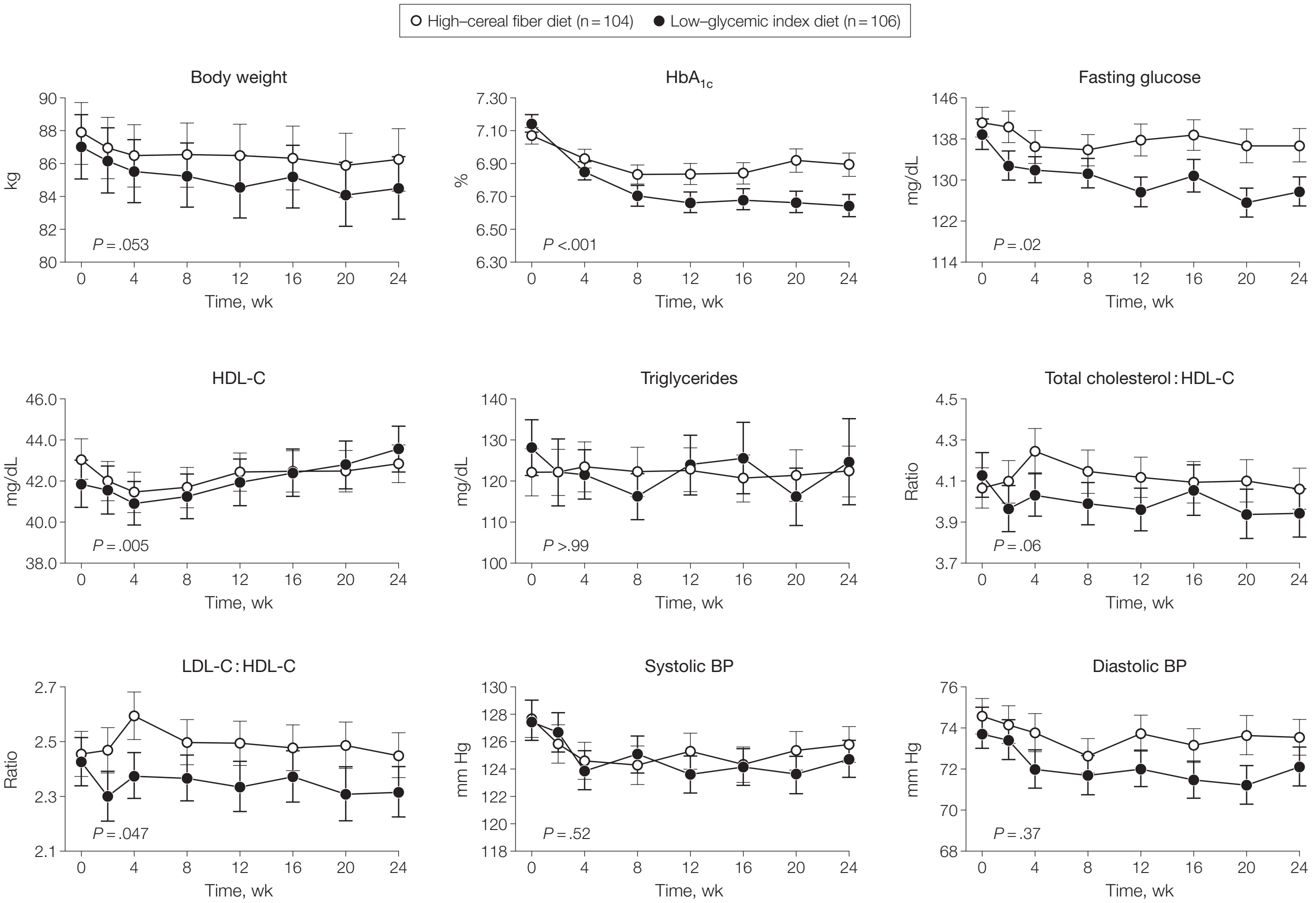
Glycemic Control and Body Weight

In the ITT analysis, antihyperglycemic medication dosages increased similarly in both treatments (3 participants in low–glycemic index diet and 3 participants in high–cereal fiber diet), but dosage reductions were more frequent in the low–glycemic index diet group (13 participants in low–glycemic index diet and 4 participants in high–cereal fiber diet, $P = .06$).

In the ITT analysis, HbA$_{1c}$ decreased by –0.50% absolute HbA$_{1c}$ units (95% CI, –0.61% to –0.39%) in the low–glycemic index diet compared with –0.18% absolute HbA$_{1c}$ units (95% CI, –0.29% to –0.07%) in the high–cereal fiber diet (**FIGURE 2**). The relative change in absolute HbA$_{1c}$ units in the low–glycemic index diet compared with the high–cereal fiber diet was –0.33% (95% CI, –0.48% to –0.17%) ($P < .001$ and $P = .001$ after Bonferroni correction) (**TABLE 4**). A treatment difference was observed in glucose of –6.8 mg/dL (95% CI, –12.9 to –0.6 mg/dL; $P = .02$). Difference in body weight reduction was not significant (–0.9 kg; 95% CI, –1.71 to –0.04 kg; $P = .053$) (Table 4). An additional assessment determined that the reduction in HbA$_{1c}$ in the low–glycemic index diet was still significant after controlling for changes in body weight ($P = .002$), fiber ($P < .001$), or carbohydrate ($P < .001$) separately as covariates in the analysis of covariance model. No significant interactions were observed between diet and the following factors: sex, baseline glycemic control, age, or BMI in relation to the treatment effect on HbA$_{1c}$.

The diet and smoking interaction approached significance ($P = .06$), although in the low–glycemic index diet group, the HbA$_{1c}$ response was similar in the 12 participants who were smokers (–0.65%) compared with the nonsmokers (–0.48%). However, the smokers were too few to allow meaningful conclusions. Exclusion of the smokers from the analysis of covariance model assessment of the change in HbA$_{1c}$ made no difference to the significance of the treatment effect favoring the low–glycemic index diet (nonsmokers [n=196], –0.33%; $P < .001$; vs including smokers [n=210], –0.32%; $P < .001$).

Figure 2. Mean Study Measurements in Participants With Type 2 Diabetes Following Either a High–Cereal Fiber Diet or a Low–Glycemic Index Diet



HbA$_{1c}$ indicates glycated hemoglobin A$_{1c}$; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure. Error bars indicate SEM. The *P* value at the lower left of each panel indicates the comparison between high–cereal fiber diet vs a low–glycemic index diet as change from week 0 to week 24 for each measurement by intention-to-treat analysis using an analysis of covariance model.

Blood Lipids

No significant treatment differences were observed in lipid medication changes, but significant treatment effects were observed for HDL-C and the LDL-C:HDL-C ratio (Figure 2). In the ITT analysis, HDL-C increased in the low–glycemic index diet group by 1.7 mg/dL (95% CI, 0.8 to 2.6 mg/dL) and decreased by –0.2 mg/dL (95% CI, –0.9 to 0.5 mg/dL) in the high–cereal fiber diet group ($P=.005$) (Table 4). Adjusting for change in body weight, carbohydrate, or fiber intake did not affect the significance of HDL-C in the ITT cohort ($P=.01$, $P=.004$, and $P=.009$, respectively). As a consequence, the LDL-C:HDL-C ratio showed a greater reduction in the low–glycemic index diet group (–0.12; 95% CI, –0.23 to –0.01) compared with the high–cereal fiber diet group (–0.01; 95% CI, –0.09 to 0.08; $P=.047$).

Blood Pressure

The number of participants who changed blood pressure medications was not different between treatments (low–glycemic index diet, 5 increased and 5 decreased; vs high–cereal fiber diet, 3 increased and 8 decreased; $P=.18$). Systolic and diastolic blood pressure dropped slightly in both diets, but the treatment differences did not reach significance (Table 4).

C-Reactive Protein

For the ITT analysis, the reductions from baseline at 24 weeks were −1.6 mg/L (95% CI, −2.9 to −0.3 mg/L; $P=.02$) in the low–glycemic index diet and −1.8 mg/L (95% CI, −3.9 to 0.4 mg/L; $P=.11$) in the high–cereal fiber diet (Table 4). The reductions in both treatments were similar ($P=.78$).

Associations Between Glycemic Index, Fiber, and Body Weight With Outcome Measures

In the ITT analysis (TABLE 5), the reduction in dietary glycemic index was positively associated with the reduction in HbA_{1c} ($n=195$, $r=0.35$, $P<.001$) and negatively associated with HDL-C ($n=195$, $r=–0.19$, $P=.009$).

Table 4. Mean Study Measurements and Significance of Treatment Differences for Intention-to-Treat Analyses (n = 210)

	Mean				
	Week 0		Week 24		
	High–Cereal Fiber Diet (n = 104)	Low–Glycemic Index Diet (n = 106)	High–Cereal Fiber Diet (n = 104)	Low–Glycemic Index Diet (n = 106)	*P* Value Treatment Difference
Body weight, kg	87.8	87.0	86.2	84.5	.053
HbA_{1c}, %	7.07	7.14	6.89	6.64	<.001
Fasting glucose, mg/dL	141.2	138.8	136.8	127.7	.02
Lipids, mg/dL					
Total cholesterol	168.4	164.3	168.4	162.6	.26
LDL-C	101.1	96.9	101.3	95.3	.14
HDL-C	43.1	41.9	42.8	43.6	.005
Triglycerides	122.0	128.1	122.2	124.6	>.99
Total cholesterol: HDL-C ratio	4.07	4.13	4.06	3.94	.06
LDL-C:HDL-C ratio	2.45	2.43	2.45	2.31	.047
C-reactive protein, mg/L	4.59	4.62	2.82	3.02	.78
Blood pressure, mm Hg					
Systolic	127.6	127.4	125.8	124.7	.52
Diastolic	74.5	73.7	73.5	72.1	.37

Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; fasting glucose to mmol/L, multiply by 0.0555; and HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

Change in body weight was significantly related to HbA_{1c} ($n=210$, $r=0.50$, $P<.001$), blood glucose ($n=210$, $r=0.36$, $P<.001$), systolic ($n=209$, $r=0.14$, $P=.04$) and diastolic blood pressure ($n=209$, $r=0.20$, $P=.005$), and negatively associated with HDL-C ($n=210$, $r=–0.19$, $P=.007$). No significant associations were observed with dietary fiber apart from systolic blood pressure ($n=195$, $r=–0.16$, $P=.03$) (Table 5).

Partial correlations indicated that after controlling for change in body weight the association between change in glycemic index and change in HbA_{1c} remained significant ($r=0.28$, $P<.001$), as it did after controlling for change in fiber ($r=0.33$, $P<.001$). In contrast, the association between change in fiber and change in HbA_{1c} was still nonsignificant after controlling for change in glycemic index ($r=–0.02$, $P=.75$).

Adverse Events

There were no serious adverse events directly related to the study; however, of the 11 participants who reduced their diabetes medications, all 6 who had clear evidence of hypoglycemic symptoms or low blood glucose levels were taking low–glycemic index diets. In addition, 1 participant in the low–glycemic index diet was withdrawn due to high HbA_{1c} (>8.5%) on 2 successive measurements but the HbA_{1c} had increased from 7.6% at screening to 8.2% at the start of the study. The further increase during the study did not therefore appear related to the intervention.

Completer and Per-Protocol Results

In general, the completer and per-protocol analyses confirmed the ITT analysis but showed larger effect sizes and greater significance levels (FIGURE 3). The completer analysis showed a significant reduction in antihyperglycemic medication use in the low–glycemic index diet group (low–glycemic index diet, 13/15 medication changes vs high–cereal fiber diet, 3/6 medication changes; $P=.02$). Greater reductions in HbA_{1c} were observed in the low–glycemic index diet (–0.66%; 95% CI, –0.79% to –0.53%) compared with in the high–cereal fiber diet (–0.24%;

95% CI, –0.40% to –0.09%; $P < .001$), and an increase in HDL-C in the low–glycemic index diet (2.2 mg/dL; 95% CI, 1.0 to 3.5 mg/dL) compared with in the high–cereal fiber diet (–0.3 mg/dL; 95% CI, –1.3 to 0.7 mg/dL; $P = .01$).

The results of the per-protocol analysis were similar except that the reduction in the blood glucose was no longer significant but a significantly greater reduction was observed in body weight in the low–glycemic index diet (–3.6 kg; 95% CI, –4.6 to –2.5 kg) compared with in the high–cereal fiber diet (–2.3 kg; 95% CI, –2.9 to –1.6 kg; $P = .04$).

COMMENT

Lowering the glycemic index of the diet improved glycemic control and risk factors for coronary heart disease (CHD). These data have important implications for the treatment of diabetes where the goal has been tight glycemic control to avoid complications.[32]

The reduction in HbA_{1c} was modest, but we think it has clinical relevance. Reductions in HbA_{1c} of 1% and 0.67%, respectively, in the United Kingdom Prospective Diabetes Study[2] and ADVANCE[6] studies resulted in 37% and 21% reductions in microvascular complications of diabetes. Our 0.33% HbA_{1c} treatment difference might therefore be expected to reduce microvascular complications by 10% to 12% and possibly more in the longer term, because there was a significant time trend for HbA_{1c} with a tendency for separation of low–glycemic index and high–cereal fiber values over time. Furthermore, the US Food and Drug Administration recognizes a 0.3% to 0.4% reduction in HbA_{1c} as clinically meaningful in the development of drugs for diabetes treatment,[33] and the reduction in HbA_{1c} observed in our study was achieved in individuals already treated with 1 or more antihyperglycemic medications, and without weight gain, which often accompanies treatment with glucose-lowering medications.[6,7,23]

Pharmacological interventions to improve glycemic control in type 2 diabetes have often failed to show a significant reduction in cardiovascular events.[2-5] In view of the 2- to 4-fold increase in CHD risk in participants with type 2 diabetes, the ability of a low–glycemic index diet to address both glycemic control and CHD risk factors increases the clinical relevance of this approach for patients with type 2 diabetes, such as those in this study, who are overweight and also taking statins for CHD risk reduction.

Low HDL-C is one of the characteristics of the dyslipidemia associated with type 2 diabetes and may be part of the reason for the increased CHD risk observed in type 2 diabetes.[34] Current data suggest a 1:1 to 1:3 relationship between the percentage increase in HDL-C and the reduction in CHD risk.[35-37] By this reasoning, the 4.7% increase in HDL-C observed in our study in the low–glycemic index treatment group might reduce CHD risk by 4% to 11% in the ITT group and 6% to 19% in the completer group. Previous cross-sectional studies have noted a negative relationship between glycemic index[12,13] or glycemic load[14] and HDL-C. One short-term randomized controlled trial of patients with type 2 diabetes also observed an increase in HDL-C in a low–glycemic index diet,[38] which was also observed in our study.

In our study, the reduction in CRP in the high–cereal fiber diet group was not significant, although significant reductions have been shown previously.[39] The low–glycemic index diet reduced CRP levels similarly but the reduction from baseline was significant. This effect has been reported in earlier studies.[16,22]

Our study has a number of limitations. The dropout rate during the treatment periods was high at 21% (42/199 participants). However, these numbers are in keeping with many nutritional studies.[40] Furthermore, the significance of the data was not materially altered when only the completers were assessed. As observed in other

Table 5. Effect of Body Weight, Fiber, Glycemic Index, and Glycemic Load on Primary and Secondary Outcomes in the Intention-to-Treat Group

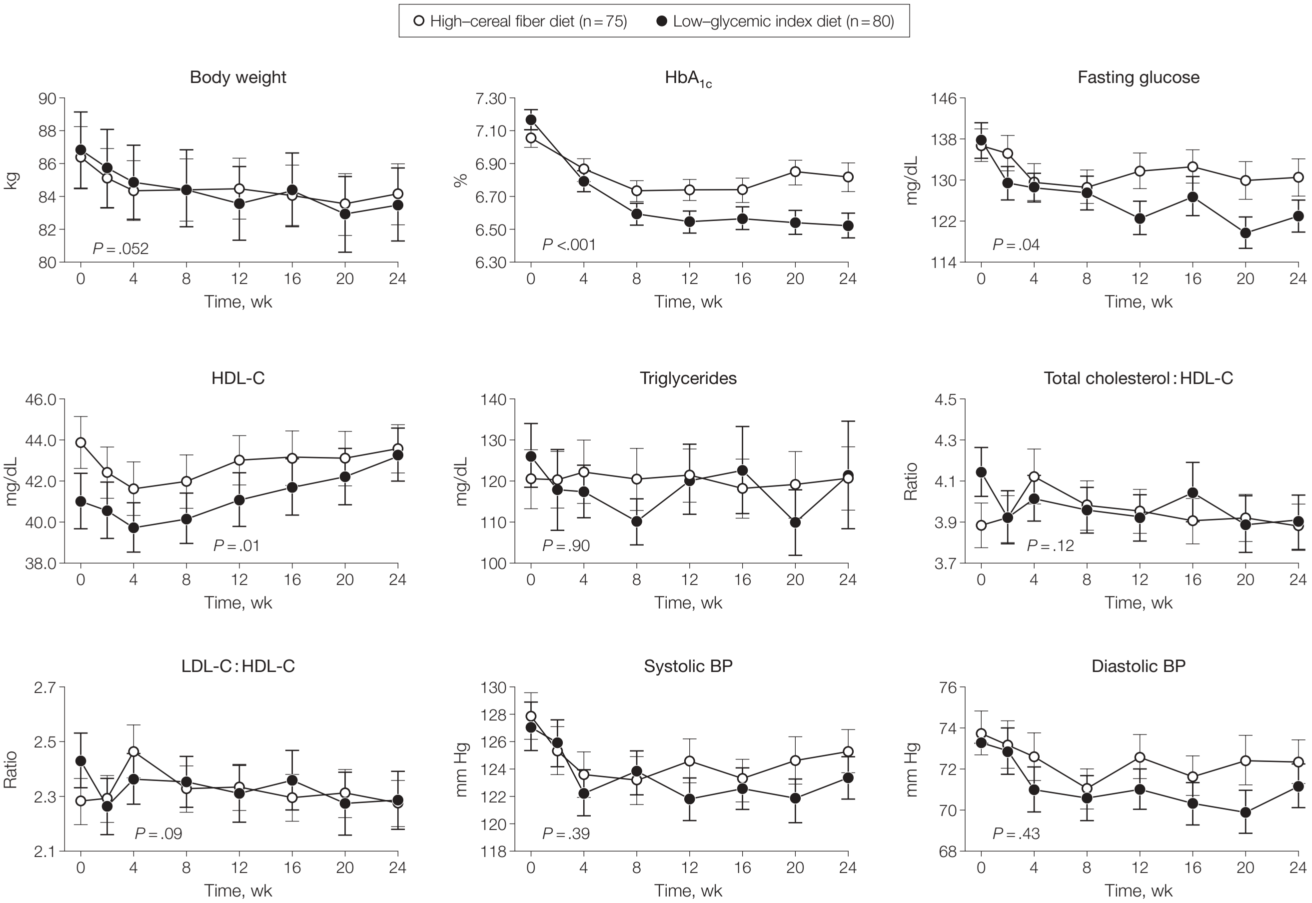
	HbA_{1c}	HDL-C	C-Reactive Protein	Blood Glucose	Systolic Blood Pressure	Diastolic Blood Pressure	Body Weight
Body weight							
No. of patients	210	210	202	210	209	209	210
r (correlation coefficient)	0.50	–0.19	–0.02	0.36	0.14	0.20	1.00
P value	<.001	.007	.78	<.001	.04	.005	NA
Fiber							
No. of patients	195	195	193	195	195	195	195
r (correlation coefficient)	–0.12	0.08	–0.07	0.04	–0.16	–0.10	–0.02
P value	.09	.27	.33	.62	.03	.17	.74
Glycemic index							
No. of patients	195	195	193	195	195	195	195
r (correlation coefficient)	0.35	–0.19	0.01	0.21	0.10	0.10	0.24
P value	<.001	.009	.87	.004	.17	.17	<.001
Glycemic load							
No. of patients	195	195	193	195	195	195	195
r (correlation coefficient)	0.24	–0.12	0.06	0.29	–0.08	–0.02	0.22
P value	.001	.10	.38	<.001	.28	.76	.002

Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol.

studies,[41] a substantial number of participants (11%, n=23) had antihyperglycemic medication changes during the study. Only 6 participants had clear evidence of repeated hypoglycemic episodes or low blood glucose levels, but all of these occurred in the low–glycemic index diet group. Furthermore, retention of participants with medication changes in the analysis did not result in loss of significance in established treatment differences. Dietary fiber intakes were not completely balanced between treatments with an approximately 4.6 g/d higher fiber intake in the low–glycemic index diet than in the high–cereal fiber diet at week 24. Viscous fibers or diets high in fiber from a variety of sources have been shown to improve blood lipids and markers of glycemic control.[24,42] However, with the exception of oat and barley fiber, cereal fibers are largely without metabolic effect. Increasing dietary intake of wheat fiber, even by as much as 20 g/d, has been shown not to influence HbA_{1c} or other biomarkers of chronic disease in patients with type 2 diabetes.[43] In addition, controlling for fiber intake as a covariate in the analysis of covariance analysis did not alter the significance of the results. Similarly, controlling for fiber in the partial regression analysis did not alter the significance of the association of the change in glycemic index with change in HbA_{1c}. A further potential weakness was that our study was a single-site study, which may be seen as a limitation to its generalizability.

Study strengths include the independence of the effect of glycemic index on HbA_{1c} from the fiber or carbohydrate intake and the similarity of the observed HbA_{1c} effect with the magnitude of reduction in glycated proteins observed in a meta-analysis.[11] Another strength of our study was the comparison of the low–glycemic index diet with a high–cereal fiber diet representing another treatment rather than simply a control. Increased cereal fiber intakes have been associated with reduced incidence of diabetes and CHD in the longer

Figure 3. Mean Study Measurements in Participants With Type 2 Diabetes Completing Either a High–Cereal Fiber Diet or a Low–Glycemic Index Diet



HbA_{1c} indicates glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure. Error bars indicate SEM. The *P* value at the lower left of each panel indicates the comparison between high–cereal fiber diet vs a low–glycemic index diet as change from week 0 to week 24 for each measurement by intention-to-treat analysis using an analysis of covariance model.

term[8,9,23-25] and so provided a reason for dietary adherence.

Body weight is recognized as a major determinant of glycemic control.[27,44] However, in our study, the treatment difference in HbA_{1c} remained even after controlling for body weight. Neither the effect of overweight nor the interaction of diet with overweight was significant. Low–glycemic index or low–glycemic load diets have been associated with weight loss,[45,46] although the weight loss was not significant ($P=.053$) in the ITT analysis of our study. At the same time, weight loss resulting from altered insulin economy may be one of the mechanisms through which low–glycemic index diets improve glycemic control.[47] Furthermore, interventions that improve glycemic control without increasing body weight confer an additional benefit in diabetes management by avoiding the macrovascular complications that may be associated with weight gain.[7]

In conclusion, in this study of patients with type 2 diabetes, 6-month treatment with a low–glycemic index diet resulted in moderately lower HbA_{1c} levels compared with a high–cereal fiber diet. Low–glycemic index diets may be useful as part of the strategy to improve glycemic control in patients with type 2 diabetes taking antihyperglycemic medications.[27,48]

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