

Effect of Wheat Bran on Glycemic Control and Risk Factors for Cardiovascular Disease in Type 2 Diabetes

DAVID J. A. JENKINS, MD^{1,2,3,4}
CYRIL W. C. KENDALL, PHD^{1,3}
LIVIA S. A. AUGUSTIN, MSC^{1,3}
MARGARET C. MARTINI, PHD⁵
METTE AXELSEN, PHD⁶
DOROTHEA FAULKNER, RD¹
EDWARD VIDGEN, BSC^{1,3}
TINA PARKER, RD¹

HERB LAU, MD^{7,8}
PHILIP W. CONNELLY, PHD^{2,9,10}
JEROME TEITEL, MD^{7,8}
WILLIAM SINGER, MD²
ARTHUR C. VANDENBROUCKE, PHD^{7,10}
LAWRENCE A. LEITER, MD^{1,2,3,4}
ROBERT G. JOSSE, MD^{1,2,3,4}

OBJECTIVE— Cohort studies indicate that cereal fiber reduces the risk of diabetes and coronary heart disease (CHD). Therefore, we assessed the effect of wheat bran on glycemic control and CHD risk factors in type 2 diabetes.

RESEARCH DESIGN AND METHODS— A total of 23 subjects with type 2 diabetes (16 men and 7 postmenopausal women) completed two 3-month phases of a randomized crossover study. In the test phase, bread and breakfast cereals were provided as products high in cereal fiber (19 g/day additional cereal fiber). In the control phase, supplements were low in fiber (4 g/day additional cereal fiber).

RESULTS— Between the test and control treatments, no differences were seen in body weight, fasting blood glucose, HbA_{1c}, serum lipids, apolipoproteins, blood pressure, serum uric acid, clotting factors, homocysteine, C-reactive protein, magnesium, calcium, iron, or ferritin. LDL oxidation in the test phase was higher than that seen in the control phase ($12.1 \pm 5.4\%$, $P < 0.034$). Of the subjects originally recruited, more dropped out of the study for health and food preference reasons from the control phase (16 subjects) than the test phase (11 subjects).

CONCLUSIONS— High-fiber cereal foods did not improve conventional markers of glycemic control or risk factors for CHD in type 2 diabetes over 3 months. Possibly longer studies are required to demonstrate the benefits of cereal fiber. Alternatively, cereal fiber in the diet may be a marker for another component of whole grains that imparts health advantages or a healthy lifestyle.

Diabetes Care 25:1522–1528, 2002

From the ¹Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital, Toronto, Ontario, Canada; the ²Department of Medicine, Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; the ³Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; the ⁴Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; ⁵Kraft Foods, Glenview, Illinois; the ⁶Lundberg Laboratory for Diabetic Research, Department of Internal Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; the ⁷Department of Laboratory Medicine, Division of Clinical Biochemistry, St. Michael's Hospital, Toronto, Ontario, Canada; the ⁸Department of Hematology, St. Michael's Hospital, Toronto, Ontario, Canada; the ⁹Department of Biochemistry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; and the ¹⁰Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

Address correspondence and reprint requests to David J. A. Jenkins, Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital, 61 Queen St. East, Toronto, Ontario, Canada, M5C 2T2. E-mail: cyril.kendall@utoronto.ca.

Received for publication 12 April 2002 and accepted in revised form 28 May 2002.

Abbreviations: CHD, coronary heart disease; NCEP, National Cholesterol Education Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial on p. 1652.

There is much interest in the possible health benefits of fiber-containing cereals (1–3). The exact component or facet of fiber that is responsible has not been clearly defined, and there are indications that the whole grain confers metabolic benefits (4) and reduces the risk of chronic disease (1,5,6). The results of large cohort studies have suggested that wheat fiber protects against the development of diabetes (1–3). Many diabetes associations advise increased fiber intake, either to improve glycemic control (7) or to confer general health benefits (8). Increases in fiber from a variety of dietary sources have been shown to improve glycemic control in type 2 diabetes (9). Early studies suggested that cereal fiber improved both glycemic control in diabetes (10) and glucose tolerance in nondiabetic subjects (11). The reason for the beneficial effects of nonviscous cereal fiber is not clear. Cereal fibers do not reduce the rate of gastric emptying and small intestinal absorption or flatten the postprandial glycemic response to a high-carbohydrate test meal (12). In contrast, viscous fibers such as guar and pectin have been shown to reduce the rate of gastric emptying (13) and small intestinal absorption (14), thereby providing a mechanism for potential benefits. These fibers have been shown to reduce postprandial glycemia when added to test meals. They also decrease 24-h urinary glucose losses when added to the diets of subjects with type 2 diabetes (15).

Furthermore, it is wheat fiber, rather than viscous fiber, that for more than two decades has been shown consistently in cohort studies to be associated with a reduced risk of heart disease (5,6,16,17). These effects are seen despite the fact that viscous fibers from oats, barley, psyllium, pectins, and guar gum have been shown to lower serum cholesterol and improve the blood lipid profile, whereas the insoluble fibers were largely without effect (18,19).

In view of the apparent benefits of cereal fiber in preventing diabetes and cardiovascular disease and the lack of an

obvious mechanism in acute or short-term studies, we tested the effect of high-wheat bran breakfast cereals and breads in studies of 3 months' duration. The study was designed to assess the effect of increased wheat fiber consumption rather than a dietary change to whole grain cereal products. We assessed not only glycemic control and conventional risk factors for coronary heart disease (CHD) but also nonlipid risk factors, homocysteine, and inflammatory biomarkers, which have not previously been measured in studies of fiber and diabetes.

RESEARCH DESIGN AND METHODS

Protocol

Subjects with type 2 diabetes undertook two phases of 3-month supplementation with either high or low cereal fiber in a randomized crossover study design with a washout period of ~2 months between phases. In one phase (test), subjects were provided with high-fiber breakfast cereals and bread, which provided an average of 19 g cereal fiber per day, and in the control phase, the supplements were low fiber (4 g fiber per day). Both supplements supplied ~24% of daily energy requirements. Fasting body weight and blood pressure were measured, and blood samples were collected before the start of each phase and at weeks 2, 4, 8, 10, and 12. Seven-day weighed food records were also obtained before the start of each phase and at week 12; three-day food records were collected during weeks 2, 4, 8, and 10 to assist in counseling subjects on weight maintenance to ensure that no changes in body weight occurred.

Subjects

A total of 67 subjects with type 2 diabetes were recruited by newspaper advertisements and from patients attending St. Michael's Hospital and the Clinical Nutrition and Risk Factor Modification Center. Subjects were accepted if they were treated with diet or diet and oral hypoglycemic agents and if BMI was $<32 \text{ kg/m}^2$. Subjects had no clinical evidence of significant autonomic neuropathy, gastroparesis, and were without clinical or biochemical evidence of significant renal or hepatic disease.

Two patients withdrew before randomization after the nature of the study

was explained to them. An additional 15 subjects withdrew after randomization but before beginning the first phase (5 subjects withdrew before the control phase and 10 subjects withdrew before the wheat bran phase). An additional 21 subjects dropped out of the study during (14 subjects) or after (7 subjects) the first phase; 13 of these subjects were in the control phase and 8 subjects were in the bran phase. During the second phase, six more subjects withdrew from the study (three in the control phase and three in the wheat bran phase). Of the 16 subjects who dropped out during a control phase or in the washout following the first control, 8 subjects failed to complete the study for unrelated health reasons, 2 subjects withdrew because of poor compliance, and 1 subject dropped out because of poor glycemic control. The reasons for withdrawal from the study for the 11 subjects who dropped out during the test phase were health reasons (1 subject), supplement-related diarrhea (1 subject), poor glycemic control (3 subjects), and dislike of the supplements (1 subject). The remainder of subjects from both treatments withdrew for work-related reasons (four subjects), unplanned vacations (two subjects), loss of interest (one subject), change in medication (one subject), and personal reasons (two subjects). In 12 of the dropouts who provided 8- to 12-week samples during one phase, HbA_{1c} was also assessed.

A total of 23 subjects with type 2 diabetes (16 men and 7 postmenopausal women) aged 63 ± 1 years (mean BMI $26.7 \pm 1.1 \text{ kg/m}^2$) completed the study. In 16 subjects, diabetes had been diagnosed ≥ 3 years ago, and in 7 subjects, diabetes had been diagnosed 1–3 years ago. These subjects were treated either with diet alone (4 subjects) or with diet and oral agents (19 subjects). Of the subjects taking oral hypoglycemic agents, 7 were taking sulfonylureas alone, 2 were on biguanides alone, and 10 were taking both sulfonylureas and biguanides. A total of 10 men and 5 women were taking one or more medications for hypertension (β -blocking agents in 4 subjects, ACE inhibitors in 11 subjects, and calcium channel blockers in 2 subjects). Three women were on hormone replacement therapy. Eight men and two women were taking cholesterol-lowering medications (statins in six men and two women, fibrates in two men). All medications

were held constant throughout the course of the study and subjects were instructed to maintain the same level of physical activity throughout the study.

Diets

Throughout the study period, subjects followed their habitual therapeutic diets. They had been previously instructed, as part of their routine care, to follow diets that conformed to National Cholesterol Education Program (NCEP) guidelines (20) (Table 1). Subjects who had not been instructed previously were instructed before the start of the study by the research staff. Of the 23 subjects, 7 were following saturated fat guidelines for NCEP Step II diets ($<7\%$ saturated fat calories) and 12 subjects were following saturated fat guidelines for NCEP Step I diets ($<10\%$ saturated fat calories), with advice to increase fiber intake as part of their regular clinical management strategy (7). A total of 14 subjects (61%) routinely used high-fiber cereal products rather than their white flour equivalents (in breads, breakfast cereals, muffins, etc.) before the study. On the study, at 2-week intervals in the control phase, subjects were provided with white bread and a low-fiber breakfast cereal, equivalent to ~24% of their total caloric intake based on their 7-day food records, to act as their sole source of bread and breakfast cereal during the 3-month period. The macronutrient profile of the control supplement was 4.2% energy as fat, 18.4% protein, and 77.5% available carbohydrate, with 4 g dietary fiber per day. On the test or cereal fiber phase, high wheat bran bread and breakfast cereal were provided at the same caloric intake as in the control phase, with 5.9% energy as fat, 18.8% protein, and 75.4% available carbohydrate, with 19 g dietary fiber per day. For 11 of the 23 subjects, the wheat bran added to the high-fiber bread was ground ultra-fine (mean particle size $\sim 70 \mu\text{m}$) compared with the conventional wheat bran (mean particle size $\sim 750 \mu\text{m}$) provided to the remaining 12 subjects. All breads were specially prepared by Natural Temptations Bakery (Burlington, Ontario, Canada). Because no difference was seen in glycemic control, blood lipid level, or blood pressure dependent on fiber particle size, data from both fine and coarse wheat bran phases were combined and the mean high-fiber diet results were used in all analyses. It must be noted that

Table 1—Calculated macronutrient intakes on the control and wheat-bran phases (n = 23)

	Control (week 12)	Wheat bran (week 12)
Energy		
(MJ/day)	7.66 ± 0.43	7.50 ± 0.46
(kcal/day)	(1,824.5 ± 102.2)	(1,785.8 ± 110.0)
Total protein		
(g/day)	93.8 ± 5.6	94.1 ± 5.9
(%)	(21.0 ± 0.9)	(21.5 ± 1.0)
Vegetable protein		
(g/day)	30.1 ± 2.5	36.8 ± 2.2*
(%)	(6.6 ± 0.4)	(8.5 ± 0.5)
Available carbohydrate		
(g/day)	239.2 ± 14.2	234.7 ± 14.5
(%)	(52.6 ± 1.3)	(52.9 ± 1.3)
Total dietary fiber		
(g/day)	21.0 ± 1.5	37.1 ± 2.0*
(g/1,000 kcal)	(11.7 ± 0.7)	(21.3 ± 0.8)
Total fat		
(g/day)	50.8 ± 4.3	48.3 ± 5.1
(%)	(24.7 ± 1.3)	(23.9 ± 1.2)
SFA		
(g/day)	15.6 ± 1.6	14.6 ± 1.7
(%)	(7.5 ± 0.6)	(7.1 ± 0.5)
MUFA		
(g/day)	19.2 ± 1.7	18.0 ± 2.2
(%)	(9.3 ± 0.6)	(8.8 ± 0.6)
PUFA		
(g/day)	9.9 ± 1.1	9.1 ± 1.0
(%)	(4.8 ± 0.4)	(4.5 ± 0.4)
Dietary cholesterol (mg/day)	229.4 ± 23.3	210.9 ± 21.0
Alcohol		
(g/day)	5.0 ± 2.0	4.9 ± 2.7
(%)	(1.7 ± 0.7)	(1.7 ± 0.9)

Data are means ± SEM. % = percent of total energy. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. *Significance of the treatment difference between high-fiber and control phases ($P < 0.05$).

the focus of this study was the addition of wheat bran to the diet and not the provision of whole grain (i.e., whole meal) cereal products. Although the test and control breakfast cereals and breads were similar in appearance, they were significantly different in color and texture. The subjects were therefore not blinded to their treatment. However, the investigators interviewing the patients on a regular basis were unaware of the treatment.

Compliance was assessed by the subjects' diet histories and by return of uneaten supplements, which were weighed and recorded.

Analysis

Fasting plasma containing fluorocitrate was stored at -70°C and analyzed for glucose by a glucose oxidase technique using a YSI analyzer (YSI 2300; Yellow

Springs Instruments, Yellow Springs, OH). $\text{HbA}_{1\text{c}}$ was measured using a fresh whole-blood sample collected in Vacutainer tubes containing EDTA by ion-exchange high-performance liquid chromatography technique (TOSHO Medics, Forest City, CA). Serum lipids were analyzed according to the Lipid Research Clinics Protocol for total cholesterol, triglycerides, and HDL cholesterol, after dextran sulfate magnesium chloride precipitation (CH1000; Technicon, Tarrytown, NY). LDL cholesterol was calculated using the Friedewald equation. Serum apolipoproteins A-I and B were measured by nephelometry. Oxidized LDL was measured as conjugated dienes in LDL fatty acids. Details of the measurement of serum lipid, lipoprotein, apolipoprotein, and oxidized LDL levels have been described elsewhere (21).

Serum stored at -70°C was also analyzed for C-reactive protein by end-point nephelometry (Behring BN-100, N high-sensitivity C-reactive protein reagent; Dade-Behring, Mississauga, ON), uric acid (Ektachem analyzer; Eastman Kodak, Rochester, NY), and the minerals calcium, magnesium, sodium, and potassium (Vitros 950; Ortho Clinical Diagnostics, Rochester, NY). Serum iron level was determined colorimetrically (at 560 nm using a Beckman-Coulter Synchron LX20 analyzer; Beckman, Fullerton, CA) and serum ferritin level was measured by chemiluminescent immunometric assay (using a DPC Immulite 2000 analyzer; DPC, Los Angeles, CA). Plasma homocysteine level was measured by fluorescence particle immunoassay (Abbott Imx; Abbott Laboratories Diagnostics Division, Mississauga, ON), and indexes of thrombosis were measured by commercial ELISA assays for tissue plasminogen activator (TintElize; American Diagnostica, Greenwich, CT), plasminogen activator inhibitor-1 (IMUBIND Plasma PAI-1 ELISA; American Diagnostica, Greenwich, CT), and urokinase antigen (22) on citrated plasma stored at -70°C .

The supplements were analyzed for macronutrients and fiber by Association of Official Analytical Chemists (AOAC) methods (23,24) and for minerals, iron, calcium, magnesium, and potassium by induction-coupled plasma (ICP) optical emission spectrometry (Varian Vista-Pro Spectrometer; Varian, Mississauga, Ontario, Canada) with a charge-coupled device (CCD) Detector (Varian).

Dietary histories were assessed using a computer program based on the U.S. Department of Agriculture Data (25), supplemented with data from foods analyzed in the laboratory. The percentage figures for soluble and insoluble fiber were derived from published data (26).

Statistical analysis

The results are expressed as means ± SEM. Absolute differences between treatments were assessed by ANCOVA using the General Linear Model (GLM) procedure in SAS statistical software (SAS Institute, Cary, NC). The response variable was the mean of weeks 8–12 (i.e., measurements made in the last month of each treatment phase). The statistical model included diet, sex, and sequence as main effects, the interaction term diet by sex, a term representing the individual nested

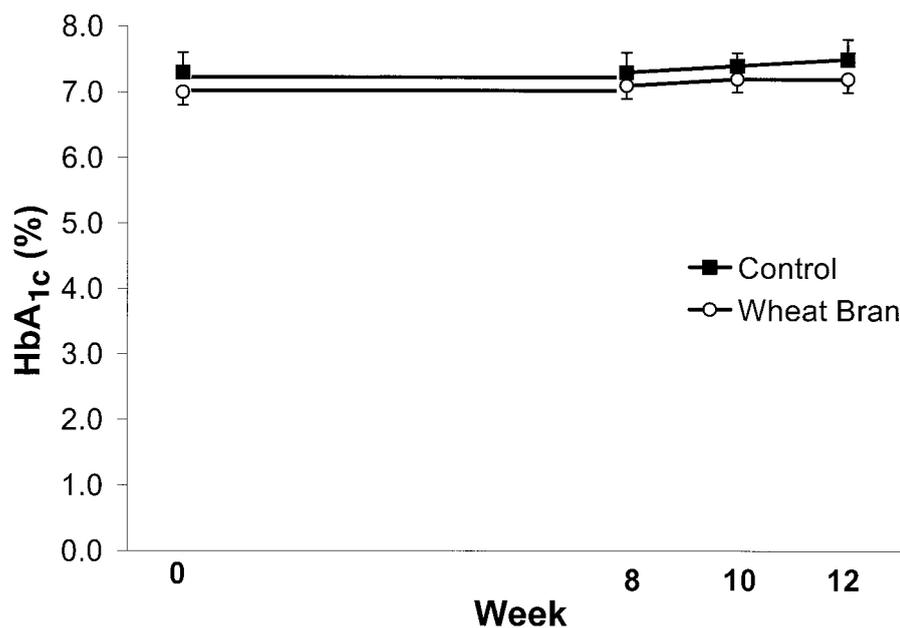


Figure 1—Plasma HbA_{1c} levels across the control and wheat-bran treatment periods.

within sex by sequence, and baseline as a covariate for measurements with baseline values (SAS/STAT User's Guide, ed. 6.12; SAS Institute). Student's *t* test for paired data (two-tailed) was used for end-of-phase differences between treatments. Cardiovascular risk was calculated using systolic blood pressure and the total-to-HDL cholesterol ratio was calculated using the Framingham Cardiovascular Risk Equation (27).

RESULTS — Compliance was good for test and control supplements. Subjects consumed 97 ± 2 and $96 \pm 2\%$ of the total test and control supplements, respectively, assessed as the percentage of energy prescribed. The weight changes on both control and cereal fiber supplements were similar (control 0.0 ± 0.1 kg, cereal fiber 0.1 ± 0.2 kg), and these changes were not significantly different ($P = 0.856$).

No change was seen in mean blood glucose or HbA_{1c} level across either treatment or between treatments (Fig. 1, Table 2). After inclusion in a parallel design of the 12 dropout subjects with data on one phase (6 on control phase and 6 on cereal fiber), the lack of significant difference between control and cereal fiber treatments remained ($P = 0.293$).

No treatment differences were seen in blood lipid, lipoprotein, apolipoprotein, C-reactive protein, homocysteine, or uric

acid concentrations. Similarly, there were no treatment differences in serum ferritin level and the minerals calcium, magnesium, sodium, or potassium (Table 2). Indexes of thrombosis risk, tissue plasminogen activator, plasminogen activator inhibitor-1, and urokinase were unaffected by diet (Table 2). Blood pressure was not different between treatments (Table 2). Unexpectedly, total conjugated dienes in the LDL fraction, as a marker of LDL oxidation, was increased during the wheat bran phase (Table 2).

No treatment differences were seen between the sexes.

CONCLUSIONS — Wheat bran taken in supplements for 3 months, sufficient to double fiber intake and in line with many current recommendations (28), did not seem to improve blood glucose control or lipid and nonlipid risk factors for cardiovascular disease. Included were clotting factors, homocysteine, C-reactive protein, and proinflammatory cytokines, which have not been measured previously after wheat bran feeding.

Epidemiological studies have consistently shown a beneficial effect of fiber, especially wheat fiber, in reducing the risk of diabetes (1–3) and cardiovascular disease (5,6,16,17), and a recent report indicated that total dietary fiber intake was associated with reduced CHD risk factors

in young people (29). The reports of benefits for cereal fiber in reducing CHD risk extend over 25 years to the studies of civil servants by Morris et al. (16). Recent estimates have suggested a reduction in CHD relative risk of 19% for every 10-g increase in cereal fiber intake (17). This estimate requires formal testing. To date, the only large-scale (secondary prevention) prospective study, the Diet and Reinfarction Trial (DART), which increased cereal fiber by 10–12 g/day in the diet, failed to detect a cardiovascular benefit (30). Nevertheless, there are data indicating that in some studies, wheat bran administration improved blood lipid profiles (31) and blood glucose control in people with diabetes (7). Furthermore, 6-month wheat bran administration improved glucose tolerance in nondiabetic subjects (11). It is possible that medication use may have obscured the effect of wheat bran on blood lipids and glucose control. However, tight control of these parameters, as now advocated, will increase medication use in the future and, therefore, the representativeness of our study sample.

Bran is a source of magnesium and has been shown to reduce iron bioavailability and lower serum iron levels (32). Lower serum iron or higher magnesium concentrations may be factors tending to reduce oxidative stress, which in turn may improve carbohydrate tolerance (33). Lower ferritin concentrations as a marker of iron status have been associated with reduced CHD risk (34), and regular blood donors have been reported to be protected from cardiovascular disease (35). In the present study, the tendency of ferritin levels to decrease was not sufficient to alter serum iron concentrations, and oxidized LDL concentrations were unexpectedly higher after wheat bran feeding. Prolonged wheat bran feeding may be required to reduce serum ferritin level and achieve a reduction in serum iron level. In this respect, Brodribb and Humphreys (11) saw an improvement in glucose tolerance after feeding wheat bran for 6 months, but serum iron and ferritin levels were not measured.

Wheat bran is a rich source of potassium, which has been recognized as contributing to reduction of blood pressure (36). Despite positive findings in some previous studies, the increased potassium intake from the bran supplements did not reduce blood pressure. Similarly, no ef-

Table 2—The effects of high-wheat bran diets on body weight, blood pressure, and serum measurements in 23 diabetic subjects

	Control phase		Test phase		End treatment difference		P
	Week 0	Weeks 8–12	Week 0	Weeks 8–12	Absolute	(%)	
Body weight (kg)	74 ± 3	74 ± 3	74 ± 3	74 ± 3	0.1	(0.0)	0.915
Blood pressure (mmHg)							
Systolic	137 ± 5	131 ± 3	131 ± 3	129 ± 3	−2	(−1.5)	0.388
Diastolic	81 ± 2	76 ± 1	77 ± 1	75 ± 1	−1	(−1.0)	0.505
Calculated CHD Risk							
CHD risk (10 years %)	11.8 ± 1.0	11.5 ± 0.9	11.2 ± 1.1	11.3 ± 1.0	−0.3	(−4.1)	0.288
Measures of glycemic control							
Fasting blood glucose (mmol/l)	7.4 ± 0.4	7.9 ± 0.4	7.3 ± 0.3	7.5 ± 0.3	−0.4	(−3.7)	0.154
HbA _{1c} (%)	7.3 ± 0.3	7.4 ± 0.3	7.0 ± 0.2	7.2 ± 0.2	−0.2	(−2.2)	0.263
Lipids and apolipoproteins							
Total cholesterol (mmol/l)	4.97 ± 0.17	4.87 ± 0.15	4.84 ± 0.21	4.97 ± 0.17	0.1	(2.2)	0.169
Triglycerides (mmol/l)	1.59 ± 0.18	1.53 ± 0.18	1.51 ± 0.19	1.63 ± 0.20	0.1	(9.3)	0.098
HDL cholesterol (mmol/l)	1.26 ± 0.05	1.17 ± 0.03	1.23 ± 0.05	1.23 ± 0.05	0.05	(4.9)	0.280
LDL cholesterol (mmol/l)	2.99 ± 0.14	2.99 ± 0.14	2.93 ± 0.18	3.00 ± 0.15	0.01	(0.6)	0.798
Apolipoprotein A-I (mmol/l)	1.57 ± 0.05	1.51 ± 0.04	1.53 ± 0.05	1.55 ± 0.05	0.04	(2.2)	0.064
Apolipoprotein B (mmol/l)	1.03 ± 0.04	1.03 ± 0.04	1.01 ± 0.05	1.04 ± 0.04	0.01	(0.9)	0.595
Total cholesterol/HDL cholesterol	4.04 ± 0.16	4.19 ± 0.13	4.02 ± 0.18	4.16 ± 0.17	−0	(−0.2)	0.942
LDL/HDL cholesterol	2.45 ± 0.14	2.59 ± 0.14	2.44 ± 0.16	2.53 ± 0.15	−0.1	(−1.4)	0.698
Apolipoprotein B/A-I	0.67 ± 0.03	0.69 ± 0.03	0.67 ± 0.03	0.69 ± 0.03	0.00	(−0.9)	0.671
Oxidized LDL cholesterol							
LDL conjugated dienes		44 ± 4		48 ± 3	4	(12.1)	0.034
LDL conjugated dienes/LDL		15.8 ± 1.8		15.9 ± 1.5	0.1	(6.1)	0.300
Clotting factors							
Urokinase (ng/ml)	1.16 ± 0.05	1.11 ± 0.05	1.13 ± 0.05	1.13 ± 0.05	0.02	(3.6)	0.396
PAI-1 (ng/ml)	30.2 ± 3.3	29.5 ± 3.2	30.8 ± 3.0	32.8 ± 3.5	3.3	(26.1)	0.120
tPA (ng/ml)	5.4 ± 0.4	5.3 ± 0.5	5.3 ± 0.4	5.5 ± 0.5	0.2	(9.7)	0.201
PAI/tPA	6.1 ± 0.7	6.5 ± 0.8	6.4 ± 0.6	6.4 ± 0.7	2.8	(30.7)	0.143
Nonlipid CHD risk factors							
C-reactive protein (mg/l)*	4.37 ± 1.91	4.8 ± 2.01	4.61 ± 1.93	3.79 ± 1.56	−3.8	(−7.9)	0.398
Homocysteine (μmol/l)	8.5 ± 0.9	8.7 ± 0.7	8.8 ± 0.8	8.9 ± 0.7	0.22	(5.8)	0.282
Serum uric acid (μmol/l)	294 ± 11	289 ± 12	302 ± 11	302 ± 13	13	(5.9)	0.142
Minerals							
Ferritin (μg/l)*	123 ± 21	120 ± 24	119 ± 18	106 ± 21	−14	(−2.2)	0.732
TIBC (μmol/l)	46 ± 2	48 ± 2	45 ± 2	49 ± 2	1	(2.5)	0.221
Iron (μmol/l)	17 ± 1	15 ± 1	17 ± 1	17 ± 1	2	(13.1)	0.189
Calcium (mmol/l)	2.34 ± 0.04	2.33 ± 0.03	2.35 ± 0.03	2.37 ± 0.06	0.04	(2.1)	0.415
Magnesium (mmol/l)	0.82 ± 0.02	0.84 ± 0.02	0.85 ± 0.02	0.85 ± 0.03	0.01	(1.6)	0.628
Potassium (mmol/l)	4.15 ± 0.08	4.15 ± 0.08	4.09 ± 0.12	4.19 ± 0.13	0.03	(1.0)	0.724
Sodium (mmol/l)	137 ± 1	137 ± 3	139 ± 2	141 ± 3	4	(4.1)	0.214

Data are means ± SEM. P represents the significance of the percentage difference between treatments [(test-control/control) × 100] by Student's *t* test (two-tailed). TIBC, total iron binding capacity; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator. **n* = 21; 2 subjects (one on test and one on control) were eliminated as outliers (treatment changes greater than 2 SD); †CHD risk calculated using the Framingham equation (27).

fects on other risk factors for CHD were seen, including clotting factors, homocysteine, and C-reactive protein.

Despite the lack of metabolic differences between high- and low-fiber cereal products in this study, the dropout rate was somewhat higher on the low-fiber supplements than the high-fiber supplements (*n* = 11). Interestingly, dislike of

the supplement accounted for dropout of three subjects from the control phase but only one subject from the test phase.

We conclude that addition of wheat bran to foods did not seem to influence glycemic control or risk factors for CHD in subjects with type 2 diabetes. This study does not address the reported benefits of whole grain cereals, in which ad-

ditional factors such as the germ (37) or larger particle size (38) may be independent factors. Furthermore, high fiber intake from cereals other than wheat, including oats, barley, and rye, may have benefits related to the viscosity of their fiber (18,19). However, in the short term, no major change should be expected in blood lipid levels and glycemic control

from supplementing the diet of diabetic subjects with wheat bran.

Acknowledgments— This study was funded by the University-Industry Research Partnership Program of the Natural Sciences and Engineering Research Council of Canada; Loblaw Brands Limited, Toronto, Ontario, Canada; and Kraft Canada, Don Mills, Ontario, Canada. D.J.A.J. is funded by the Federal Government of Canada as a Canada Research Chair in Nutrition and Metabolism.

We thank Loblaw Brands (Toronto, Ontario, Canada) and Kraft Canada (Don Mills, Ontario, Canada) for the donation of foods used in this study and Parrheim Foods (Saskatoon, Saskatchewan, Canada) for provision of brans. We also thank Robert Chenuaux and Larry C. Griffin of Loblaw Brands, Dr. Steven Hill of Kraft Foods (Glenview, IL), Dr. Ron M. Knight and Dayle Sunohara of Kraft Canada, Kenneth Fulcher of Parrheim Foods, and Kathy Galbraith of Natural Temptations Bakery (Burlington, Ontario, Canada) for their assistance on this project. We also thank Dr. Yu-Min Li and George Koumbridis for their technical assistance.

This study has been published in abstract form: Kendall CW, Augustin LS, Jenkins DJ, Faulkner D, Axelsen M, Martini M: Effect of wheat fiber on glycemic control and CHD risk factors in type 2 diabetes: a randomized controlled crossover trial (Abstract). *Am J Clin Nutr* 75 (Suppl.):401S–402S, 2002 (P201).

References

- Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC: A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 90:1409–1415, 2000
- Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550, 1997
- Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR: Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930, 2000
- Pereira MA, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL, Seaquist ER: Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* 75:848–855, 2002
- Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC: Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr* 70:412–419, 1999
- Jacobs DR, Pereira MA, Meyer KA, Kushi LH: Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study. *J Am Coll Nutr* 19 (Suppl. 3):326S–330S, 2000
- Wolever TM, Barbeau M-C, Charron S, et al: Guidelines for the nutritional management of diabetes mellitus in the new millennium: a position statement by the Canadian Diabetes Association. *Can J Diabetes Care* 23:56–69, 1999
- American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care* (Suppl. 1):S44–S47, 2001
- Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ: Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 342:1392–1398, 2000
- Bosello O, Ostuzzi R, Armellini F, Micciolo R, Scuro LA: Glucose tolerance and blood lipids in bran-fed patients with impaired glucose tolerance. *Diabetes Care* 3:46–49, 1980
- Brodrribb AJ, Humphreys DM: Diverticular disease: three studies. Part III: metabolic effect of bran in patients with diverticular disease. *BMJ* 1:428–430, 1976
- Jenkins DJA, Wolever TM, Jenkins AL, Lee R, Wong GS, Josse R: Glycemic response to wheat products: reduced response to pasta but no effect of fiber. *Diabetes Care* 6:155–159, 1983
- Holt S, Heading RC, Carter DC, Prescott LF, Tothill P: Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol. *Lancet* 1:636–639, 1979
- Jenkins DJ, Wolever TM, Leeds AR, Gassull MA, Dilawari JB, Goff DV, Metz GL, Alberti GM: Dietary fibers, fibre analogues and glucose tolerance: importance of viscosity. *BMJ* 6124:1392–1394, 1978
- Jenkins DJA, Wolever TM, Hockaday TD, Leeds AR, Howarth R, Bacon S, Apling EC, Dilawari J: Treatment of diabetes with guar gum: reduction of urinary glucose loss in diabetics. *Lancet* 2:779–780, 1977
- Morris JN, Marr JW, Clayton DG: Diet and heart: a postscript. *BMJ* 2:1307–1314, 1977
- Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC: Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 281:1998–2004, 1999
- Jenkins DJ: Dietary fibre, diabetes, and hyperlipidaemia: progress and prospects. *Lancet* 2:1287–1290, 1979
- Anderson JW, Gilinsky NH, Deakins DA, Smith SF, O'Neal DS, Dillon DW, Oeltgen PR: Lipid responses of hypercholesterolemic men to oat-bran and wheat-bran intake. *Am J Clin Nutr* 54:678–683, 1991
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
- Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R: The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy, and vegetable protein foods. *Metabolism* 49:67–72, 2000
- Cheung T, Lui AYY, Lau HKF: Characterization of radioimmunoassay for high- and low-molecular weight urokinases and estimation of different molecular forms of urokinase in urine and plasma. *J Lab Clin Med* 121:461–471, 1993
- Association of Official Analytical Chemists: *AOAC Official Methods of Analysis*. Washington, DC, Association of Official Analytical Chemists, 1980
- Proskey L, Asp NG, Furda I, De Vries J, Schweizer TF, Harland BF: Determination of total dietary fiber in foods and food products: collaborative study. *J Assoc Offic Anal Chem* 68:677–679, 1985
- The Agriculture Research Service: *Composition of Foods*. Washington, DC, U.S. Department of Agriculture, 1992 (Agriculture Handbook no. 8)
- Anderson JW, Bridges SR: Dietary fiber content of selected foods. *Am J Clin Nutr* 47:440–447, 1988
- Anderson KM, Wilson PW, Odell PM, Kannel WB: An updated coronary risk profile: a statement for health professionals. *Circulation* 83:356–362, 1991
- FASEB Life Sciences RO: *Physiologic Effects and Health Consequences of Dietary Fiber*. Washington, DC, U.S. Department of Agriculture, Center for Food Safety, 1987
- Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML, Jacobs DR Jr: Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA* 282:1539–1546, 1999
- Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM: Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet* 2:757–761, 1989
- Munoz JM, Sandstead HH, Jacob RA, Logan GM Jr, Reck SJ, Klevay LM, Dintzis FR, Inglett GE, Shuey WC: Effects of some cereal brans and textured vegetable protein on plasma lipids. *Am J Clin Nutr* 32:580–592, 1979

32. Jenkins DJ, Hill MS, Cummings JH: Effect of wheat fiber on blood lipids, fecal steroid excretion and serum iron. *Am J Clin Nutr* 28:1408–1411, 1975
33. Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'Onofrio F: Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. *Am J Clin Nutr* 57:650–656, 1993
34. Tuomainen TP, Punnonen K, Nyysönen K, Salonen JT: Association between body iron stores and the risk of acute myocardial infarction in men. *Circulation* 97:1461–1466, 1998
35. Salonen JT, Tuomainen TP, Salonen R, Lakka TA, Nyysönen K: Donation of blood is associated with reduced risk of myocardial infarction: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Epidemiol* 148:445–451, 1998
36. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ: Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 277:1624–1632, 1997
37. Cara L, Armand M, Borel P, Senft M, Portugal H, Pauli AM, Lafont H, Lairon D: Long-term wheat germ intake beneficially affects plasma lipids and lipoproteins in hypercholesterolemic human subjects. *J Nutr* 122:317–326, 1992
38. Jenkins DJ, Wesson V, Wolever TM, Jenkins AL, Kalmusky J, Guidici S, Csima A, Josse RG, Wong GS: Wholemeal versus wholegrain breads: proportion of whole or cracked grain and the glycaemic response. *BMJ* 297:958–960, 1988