Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults[1–3]

Mark A Pereira, David R Jacobs Jr, Joel J Pins, Susan K Raatz, Myron D Gross, Joanne L Slavin, and Elizabeth R Seaquist

ABSTRACT

Background: Epidemiologic studies have found whole-grain intake to be inversely associated with the risk of type 2 diabetes and heart disease.

Objective: We tested the hypothesis that whole-grain consumption improves insulin sensitivity in overweight and obese adults.

Design: This controlled experiment compared insulin sensitivity between diets (55% carbohydrate, 30% fat) including 6–10 servings/d of breakfast cereal, bread, rice, pasta, muffins, cookies, and snacks of either whole or refined grains. Total energy needs were estimated to maintain body weight. Eleven overweight or obese [body mass index (in kg/m^2): 27–36] hyperinsulinemic adults aged 25–56 y participated in a randomized crossover design. At the end of each 6-wk diet period, the subjects consumed 355 mL (12 oz) of a liquid mixed meal, and blood samples were taken over 2 h. The next day a euglycemic hyperinsulinemic clamp test was administered.

Results: Fasting insulin was 10% lower during consumption of the whole-grain than during consumption of the refined-grain diet (mean difference: -15 ± 5.5 pmol/L; $P = 0.03$). After the whole-grain diet, the area under the 2-h insulin curve tended to be lower (-8832 pmol·min/L; 95% CI: -18720, 1062) than after the refined-grain diet. The rate of glucose infusion during the final 30 min of the clamp test was higher after the whole-grain diet (0.07×10^{-4} mmol·kg^{-1}·min^{-1} per pmol/L; 95% CI: 0.003×10^{-4}, 0.144×10^{-4}).

Conclusion: Insulin sensitivity may be an important mechanism whereby whole-grain foods reduce the risk of type 2 diabetes and heart disease. *Am J Clin Nutr* 2002;75:848–855.

KEY WORDS Carbohydrate, diet, whole grains, nutrition, insulin, hyperinsulinemia, type 2 diabetes, insulin response

INTRODUCTION

Grains account for ≈25% of energy consumption in the United States (1); however, an estimated 95% of grain available for human consumption is refined (S Gerrior, personal communication, 1997; 2). During the refining process grains are stripped of their bran and germ, thereby depleting many biologically active nutrients and constituents, including fiber, antioxidants, minerals, and phytoestrogens. When consumed close to their natural form, with the bran and germ present, either intact or pulverized, in breakfast cereals and bread products or as brown rice and other whole grains, their nutrients and other constituents may act synergistically to lower the risk of chronic diseases (3, 4). Although most epidemiologic studies combine grains with other carbohydrates and therefore have not differentiated whole- from refined-grain foods, the observation of an inverse association between fiber from grains (cereal fiber) or whole-grain foods and the risk of developing ischemic heart disease is consistent (2, 5–13), relatively strong (≈20–50% reduction in risk), independent of other lifestyle factors and body weight, and biologically plausible. A few studies observed inverse associations between cereal fiber or whole-grain foods and the risk of type 2 diabetes in men and women (14–17). However, the possibility of residual bias in the epidemiologic data cannot be ruled out. To make the inference that whole-grain intake causally reduces risk, elucidation of biological mechanisms is needed.

Given that insulin resistance increases the risk of type 2 diabetes and cardiovascular disease (18–20), insulin sensitivity may be one important mechanism through which whole-grain consumption confers protection. Studies have reported fasting insulin, a good measure of insulin resistance in epidemiologic studies (21), to be lower in individuals reporting higher dietary fiber intakes, after adjustment for other lifestyle and dietary factors (22–25). Although ingestion of whole- and refined-grain flour results in a similar acute increase in blood glucose (high glycemic index), certain minimally processed whole-grain foods—such as oats, barley, bran-based cereals, and bulgar—have a more favorable, moderate glycemic index (26), owing to factors such as larger particle size, high ratios of bran or germ to endosperm, presence of viscous soluble fibers, and resistant

[1] From the Department of Pediatrics, Harvard Medical School, and the Department of Medicine, Children's Hospital, Boston (MAP); the Division of Epidemiology (DRJ and MDG), the General Clinical Research Center (SKR), and the Departments of Food Science and Nutrition (JLS), Medicine (ERS), and Family Practice (JJP), University of Minnesota, Minneapolis; and the Institute of Nutrition Research, University of Oslo (DRJ).

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[3] Address reprint requests to MA Pereira, Children's Hospital, Division of Endocrinology, 333 Longwood Avenue, 6th floor, Boston, MA 02115. E-mail: mark.pereira@channing.harvard.edu.

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TABLE 1
Subject characteristics[1]

	Women (n = 6)	Men (n = 5)	Total (n = 11)
Age (y)	41.3 ± 3.70	41.8 ± 4.33	41.6 ± 2.67 (26–54)
BMI (kg/m^2)	30.5 ± 1.64	29.9 ± 1.24	30.2 ± 1.01 (27.2–36.2)
Waist-to-hip ratio	0.85 ± 0.009	0.94 ± 0.021	0.89 ± 0.019 (0.82–1.01)
Fasting insulin (pmol/L)	134 ± 12.2	211 ± 23.0	169 ± 16.9 (96–288)
Fasting glucose (mmol/L)	5.1 ± 0.20	5.4 ± 0.20	5.3 ± 0.14 (4.6–5.9)

[1] $\bar{x}$ ± SE; range in parentheses.

starch content. We previously hypothesized that the consumption of whole-grain foods correlates inversely with fasting insulin concentrations, independent of other potential confounding factors. We supported this hypothesis in an observational study of young black and white adults (27).

The purpose of the current study was to test the hypothesis that a healthful diet that includes whole-grain rather than refined-grain foods improves insulin sensitivity independent of body weight change in overweight hyperinsulinemic individuals.

SUBJECTS AND METHODS

Study design

We conducted a randomized, nonblinded, crossover controlled feeding trial with two 6-wk feeding periods. During a washout of 6–9 wk the subjects were asked to resume their usual diets. Clinic examinations were conducted at baseline and at 3 follow-up time points—after 2, 4, and 6 wk. The metabolic kitchen of the General Clinical Research Center (GCRC), University of Minnesota, where the study was conducted, prepared and provided all the food. General Mills, Inc (Golden Valley, MN), supplied the kitchen with some of the breakfast cereals and the flour for muffins and cookies for both the whole-grain and refined-grain diets. The participants were asked to consume all of the food provided to them and to consume no other food, except energy-free beverages, during the 2 feeding periods. Each participant was randomly assigned to receive the whole-grain or refined-grain diet during the first feeding period and then was fed the other diet for the second period.

Subject recruitment

The subjects were recruited from the University of Minnesota and its surrounding community. Responders were screened via a telephone interview according to the following inclusion criteria: *1*) age between 21 and 65 y; 2) body mass index (in kg/m^2) 26–36; *3*) body weight fluctuation over the past 6 mo of <10%; *4*) not currently smoking cigarettes; *5*) consuming ≤2 alcoholic beverages/d; *6*) free of diabetes, cancer, cardiovascular disease, and other chronic clinical conditions; *7*) not taking medications that would affect glucose, insulin, lipids, or blood pressure; *8*) not engaging in a high level of physical activity; *9*) not following a special diet (eg, vegetarian); *10*) not allergic to any foods; and *11*) not planning to change dietary habits, increase physical activity, change body weight, move out of town, or take a lengthy vacation during the time of the study. Those satisfying these criteria were invited to visit the GCRC for measurement of height, weight, blood pressure, and fasting glucose and insulin. They were invited to participate in the study if their fasting (≥12 h) blood glucose was normal (<6.1 mmol/L) and their fasting insulin was elevated above the 75th percentile of the distribution on the basis of epidemiologic studies (≥90 pmol/L). Six men and 6 women were enrolled in the study. One man did not complete the study because of an illness (unrelated to diet) that developed during the washout period before the second diet. The recruitment and study procedures were approved by the Institutional Review Board of the Human Subjects Committee at the University of Minnesota. All subjects read and signed consent forms before enrollment in the study, and they were remunerated on completion of the study. *See* **Table 1** for subject characteristics.

Treatment diets

Two 6-d menu rotations were developed. One menu contained refined grains, which contained no bran or germ and little fiber. The refined-grain menus were developed to provide 55% of energy as carbohydrate, 15% of energy as protein, and 30% of energy as fat. The diet was designed to achieve a ratio of saturated to monounsaturated to polyunsaturated fatty acids of 1:1:1. The cholesterol content was controlled at 23.9 mg/MJ. After the refined-grain menus were developed, the whole-grain diet was created by substitution of an equal volume of whole-grain food items for the refined-grain products; the food was otherwise identical in the 2 treatment periods. The second menu contained whole grains, which were unrefined and contained bran, germ, and considerable fiber, but were mostly ground to flour. White bread and refined wheat, rice, and corn products were substituted with commercially available whole-grain items, of which ≈80% were wheat and the remainder oats, rice, corn, barley, and rye. The diets were fed at an energy level to maintain body weight according to the Harris-Benedict prediction equation adjusted for activity level (28). A sample 1-d menu for the refined-grain and whole-grain diets is shown in **Table 2**.

Nutrient calculations were performed by using the NUTRITION DATA SYSTEM FOR RESEARCH (NDS) software version 4.02, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Food and Nutrient Database 30, released November 1999. When an analytic value is not available for a nutrient in a food, the Nutrition Coordinating Center calculates the value on the basis of the nutrient content of other nutrients in the same food, a product ingredient list, or the nutrient content of similar foods. A missing value is allowed only if *1*) the value is believed to be negligible, *2*) the food is usually eaten in very small amounts, *3*) it is unknown whether the nutrient exists in the food at all, or *4*) there is no way to estimate the value because the food is unlike any other (29). The nutrient analysis of each of the 12 menus was computed separately, and the average nutrient composition of the 6 menus for each treatment was computed. The NDS software was also used to determine compliance with the treatment diets by analyzing the energy and nutrient contents of all treatment foods and beverages

TABLE 2
Sample menu from the refined-grain and whole-grain diets[1]

Food	Amount
	g
Breakfast	
Refined rice cereal or whole-oat-flour cereal	30
Blueberry muffin made with white flour or with whole-wheat flour	75
Butter	4
Milk, 2% fat	160
Orange juice	130
Coffee or tea	
Lunch	
Chicken sandwich	
White bread or whole-wheat bread	60
Lettuce	20
Chicken breast	60
Light dressing spread	14
Egg yolk	4
Carrot sticks	30
Celery sticks	30
Potato chips or whole-grain chips	26
Peaches	120
Sugar	4
Coffee or tea	
Dinner	
Spaghetti with meat sauce	
Ground beef, cooked	70
Tomato sauce	120
Safflower oil or butter	11 or 5
Mushrooms	40
Refined-flour spaghetti or whole-wheat spaghetti, cooked	140
Parmesan cheese	10
Green beans	80
Lettuce mix	50
Fat-free dressing	15
Dinner roll or mixed-grain bread	30
Margarine	6
Pears	100
Coffee or tea	
Bedtime snack	
Chocolate chip cookie made with white flour or with whole-wheat flour	25
Milk, 2% fat	170

[1] This is 1 of 6 menus that were rotated over the two 6-wk treatment periods. For grain foods, the item for the refined-grain diet is given first.

not consumed and all extra nontreatment food and liquids consumed. The nutrient contents of the diets from the NDS analysis are shown in **Table 3**. The lower total availability of energy as carbohydrate, owing to the lower ratio of starch to fiber in whole grains than in refined grains, was estimated to result in the provision of ≈250 kJ/d less by the whole-grain than the refined-grain diet. The macronutrient contents of the 2 diets were similar, whereas the total fiber content of the whole-grain diet was ≈1.2 g/MJ higher than that of the refined-grain diet. Of the micronutrients, magnesium and vitamin E were somewhat higher in the whole-grain than in the refined-grain diet.

Clinic measurements

GCRC nurses performed all measurements in the morning after the subjects fasted ≥12 h. The subjects were asked to avoid strenuous exercise for 24 h before each clinic visit. Height to the nearest 0.5 cm and weight to the nearest 0.1 kg were measured with a stadiometer and a digital scale, respectively, with the subjects dressed in light clothes and no shoes. With the subjects seated quietly, blood was drawn from an antecubital vein into evacuated tubes containing a gel serum separator.

At both 6-wk clinic visits, the subjects were administered a nongrain liquid mixed meal (Ensure; Abbott Laboratories, Abbott Park, IL) that provided 50% of energy as carbohydrate, 30% as fat, and 20% as protein. The subjects consumed 355 mL within 5 min after the fasting blood draw, and a butterfly catheter was used to draw a 5-mL blood sample at 15, 30, 60, 90, and 120 min after consumption. The subjects reclined for the duration of the test. The area under the 2-h insulin curve after the liquid mixed meal was computed with the use of the trapezoidal rule for uneven time intervals (30).

On the morning after each 6-wk clinic visit, a 180-min euglycemic hyperinsulinemic clamp test (31) was administered. The subjects were infused with insulin at a rate of 6.0 or 12.0 $pmol \cdot kg^{-1} \cdot min^{-1}$. Euglycemia was maintained by the infusion of 20% dextrose. Samples for glucose (analyzed immediately in whole blood) were taken before, at baseline, and thereafter every 5 min during the clamp. Samples for serum insulin were taken before, at baseline, and every 20 min during the clamp and, as described below, were processed and stored for later analysis. Because of technical difficulties, clamps were not completed for 1 man and 1 woman. Insulin sensitivity was computed as the average rate of glucose infusion over the final 30 min (*M* value = mmol

TABLE 3
Nutrient contents of the foods in the 6-d menus for the whole-grain and refined-grain diets[1]

	Whole-grain diet	Refined-grain diet
Energy (kJ)	8509	8760
Carbohydrate (% of energy)	54.2	54.6
Protein (% of energy)	17.1	15.7
Total fatty acids (% of energy)	31.7	30.7
Saturated fat (g)	19.3	19.3
Polyunsaturated fatty acids (g)	21.7	21.1
Cholesterol (mg)	231.9	235.8
Dietary fiber (g)	28.0	17.8
Insoluble fiber (g)	19.7	10.8
Soluble fiber (g)	7.7	6.7
Starch (g)	137.9	154.7
Sugars (g)	99.2	99.8
Folate (μg)	350.8	353.7
Sodium (mg)	2572.5	2718.9
Potassium (mg)	2690.4	2518.9
Calcium (mg)	892.8	892.1
Iron (mg)	23.4	21.8
Magnesium (mg)	387	259
Copper (mg)	1.5	1.2
Zinc (mg)	11.9	9.6
Vitamin A (μg RE)	1593	1493
Thiamine (mg)	1.9	2.3
Riboflavin (mg)	1.9	2.1
Niacin (mg)	28.1	29.8
Vitamin B-6 (mg)	2.2	2.1
Vitamin B-12 (mg)	3.6	3.4
Vitamin C (mg)	114.2	123.2
Vitamin E (mg)	15.4	13.8

[1] Nutrient contents were determined by using the NUTRITION DATA SYSTEM FOR RESEARCH software (version 4.02; University of Minnesota, Minneapolis). RE, retinol equivalents.

glucose·kg body wt^{-1}·min^{-1}) divided by the average serum insulin concentration (pmol/L) over the final 40 min of the test.

Sample processing and laboratory procedures

Within 30 min of phlebotomy, whole-blood samples were centrifuged at 2800 × *g* for 10 min at 5°C, and 0.5- to 1.0-mL samples of serum or plasma were pipetted into polyethylene cryovials. Samples were stored at −70°C for ≤7 mo. Laboratory results at all time points for all subjects were performed in batch within the same assay. Serum insulin was measured at the Diabetes Institute for Immunology and Transplantation, University of Minnesota, with a radioimmunoassay specific to human insulin and with <0.2% cross-reactivity with proinsulin and a within-assay CV of 3% (Linco Research, St Louis). Serum glucose was measured at the University Hospital General Chemistry Laboratory with the use of a thin-film adaptation of a glucose oxidase enzymatic, spectrophotometric procedure with a Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc, Rochester, NY) that has a within-assay CV of 1.4%.

Questionnaire

The Health Habits and History Questionnaire (32) was administered before the baseline examination to assess the subjects' usual dietary intake of major food groups and nutrients. A daily log—listing nonprotocol food eaten and protocol food not eaten, unusual symptoms, medication use, satiety, bowel movements, and physical activity—was administered every evening during each treatment period when the subjects arrived at the clinic to eat dinner. The subjects responded on a 5-point Likert scale (with 1 being not hungry at all and 5 being extremely hungry) to the question, "How hungry were you between meals over the past 24 h?," and to a questionnaire about side effects (with 1 being no symptoms and 5 being severe symptoms) for 44 items, including gastrointestinal symptoms and general symptoms of acute or chronic illnesses.

Statistical analysis

The dependent variables were satiety, body weight, fasting insulin, the homeostasis model for insulin resistance, the *M* value from the clamp, and the area under the 2-h curve after the mixed meal. The dependent variable for satiety was the average of each of the three 2-wk intervals, with no baseline satiety score available. The homeostasis model for insulin resistance was computed according to Matthews et al (33), fasting glucose (mmol/L) × fasting insulin (pmol/L)/22.5, as an additional way of estimating insulin sensitivity. SAS software version 6.12 was used for all statistical analyses (34). We first used the PROC MIXED program to perform repeated-measures regression of the baseline value of body weight on period, finding that body weight was 85.4 in period 1 and 86.5 in period 2 (SE for difference: 0.57). Similarly, baseline fasting insulin was 155 in period 1 and 160 in period 2 (SE for difference: 11.5), and the homeostasis model for insulin resistance was 6.1 in period 1 and 6.6 in period 2 (SE for difference: 0.60). Given the within-person variability in starting values before the 2 diet periods, we adjusted the follow-up values by subtracting their period-specific baseline values. We next evaluated treatment differences at baseline, computing similar regressions of baseline body weight, fasting insulin, and the homeostasis model for insulin resistance with treatment (whole-grain compared with refined-grain diet) and period (1 compared with 2).

For the main analyses, we performed repeated-measures regression with the use of follow-up values of several dependent variables to examine the effects of treatment (whole-grain compared with refined-grain diet), time (wk), and treatment × time interaction, adjusting for the baseline value of the dependent variable, period (1 compared with 2), and cohort [the first group of 4 subjects (participated August through mid-December) compared with the second group of 7 subjects (participated October–November and January–February)]. Additional models included period × treatment interaction to assess whether the crossover design assumption was violated. The period × time interaction was not significant in any model; the main effect of period was included in all final models. Sex and cohort had no bearing on the results and were therefore not included in the final models. In the baseline analysis, SEs are computed within person, after removing the overall mean difference between the baseline values of the 2 diet periods. Findings during the active diet periods are presented as the mean (±SE) treatment difference (computed from variation within person) observed over the baseline-adjusted values for the 3 follow-up time points (weeks 2, 4, and 6). The *M* value from the clamp and the area under the 2-h insulin curve after the mixed meal were only measured at the 6-wk time point. For these measures the mean differences between the 2 treatments and their 95% CIs and *P* values were computed. A *P* value <0.05 was considered statistically significant.

RESULTS

All participants were overweight or obese (body mass index: 27–36) and hyperinsulinemic (fasting insulin: 96–288 pmol/L). The habitual diets of the subjects as reported before baseline indicated relatively low median intakes of fruit (1.0 servings/d), vegetables (2.2 servings/d), carbohydrate (40% of energy), and fiber (1.6 g/MJ) and high median intakes of total fat (40% of energy) and saturated fat (40% of fat). Three subjects reported light alcohol consumption (<1 drink/d), and all subjects were either sedentary (no regular leisure-time physical activity and no heavy work on the job) or moderately active during their leisure time. Moderately active individuals were encouraged to maintain steady habits throughout the study.

Treatment compliance

The investigators or research dietitians at the GCRC often joined the participants for dinner to encourage study compliance and good relationships among the participants and research team. As reported on the daily logs and as analyzed by the NDS System, compliance with the diets was very good. The energy content of food not eaten during the two 6-wk diets did not differ significantly between the whole-grain (159 ± 75 kJ/d) and refined-grain (222 ± 126 kJ/d) diets. The same was true of extra (nonprotocol) food from sources other than the treatment diets (whole-grain diet: 46 ± 25 kJ/d; refined-grain diet: 63 ± 33 kJ/d).

Body weight and satiety

Body weight was not significantly different during the follow-up periods with the whole-grain (84.8 ± 0.29 kg) compared with the refined-grain (85.1 ± 0.29 kg) diet (**Figure 1**). The diets were not hypoenergenic; therefore, subjects were not very hungry between meals. However, in comparison with the refined-grain diet, there was a tendency for the subjects to be less hungry between meals with the whole-grain diet (*P* = 0.08; data not

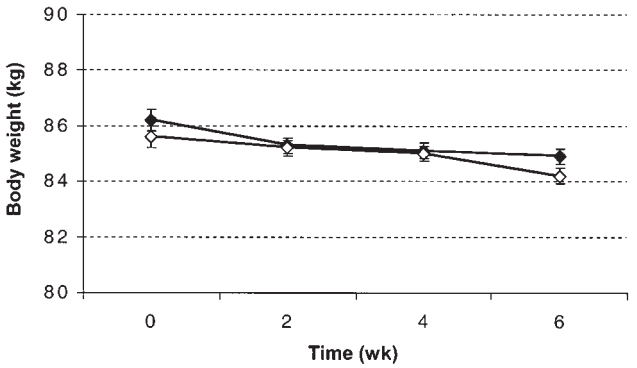

FIGURE 1. Mean (±SE) body weights of overweight or obese adults (n = 11) during consumption of a refined-grain (◆) or whole-grain (◇) diet. There were no significant differences between treatment groups by repeated-measures regression.

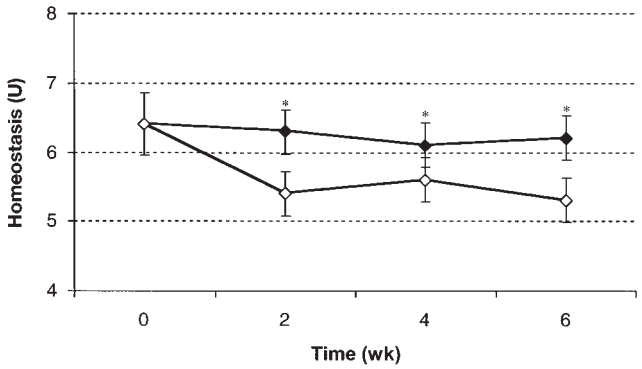

FIGURE 3. Mean (±SE) homeostasis model in overweight or obese adults (n = 11) after consumption of a refined-grain (◆) or whole-grain (◇) diet.*The pooled mean of weeks 2, 4, and 6 was significantly different from the whole-grain diet, $P < 0.01$ (repeated-measures regression). The homeostasis model (HOMA) for insulin resistance was calculated as follows: fasting glucose (mmol/L) × fasting insulin (μmol/L)/22.5.

shown). Self-reported physical activity was similar during the 2 diets (data not shown).

Fasting insulin and homeostasis model

Fasting insulin was significantly lower during the follow-up periods with the whole-grain (141 ± 3.9 pmol/L) than with the refined-grain (156 ± 3.9 pmol/L) diet (**Figure 2**). Adjustment for the change in body weight (mean difference in insulin concentration: −13 ± 5.5 pmol/L; P = 0.02) and physical activity (mean difference in insulin concentration: −14.0 ± 5.5 pmol/L; P = 0.01) did not explain this significant difference in fasting insulin between the 2 diets. There was a tendency for fasting glucose to be lower with the whole-grain diet (5.2 ± 0.08 mmol/L) than with the refined-grain diet (5.3 ± 0.08 mmol/L), although the difference was not significant. The homeostasis model also showed that insulin resistance was lower with the whole-grain (5.4 ± 0.18 U) than with the refined-grain (6.2 ± 0.18 U) diet (**Figure 3**).

Postprandial insulin

The area under the 2-h insulin concentration curve after ingestion of the 355-mL liquid nongrain mixed meal tended to be lower after 6 wk of the whole-grain diet than after 6 wk of the refined-grain diet, although not significantly so (**Figure 4**).

Insulin clamp

After the whole-grain diet, the M value was higher than after the refined-grain diet for 7 of the 9 individuals with complete clamp data. The mean difference in the M value between diets suggested a greater rate of glucose infusion and therefore greater insulin sensitivity with the whole-grain diet (mean difference: 0.07×10^{-4} mmol·kg^{-1}·min^{-1} per pmol/L; 95% CI: 0.003×10^{-4}, 0.144×10^{-4}; $P < 0.05$).

Side effects

Unusual symptoms were reported more often on the daily questionnaire during the refined-grain than during the whole-grain diet period, and the difference appeared to be primarily due to common upper respiratory illnesses in 2 individuals and to chronic low-grade abdominal pain in another subject. Therefore, the incidence of prescription medication use was higher with the refined-grain than with the whole-grain diet. Dry cough (1.4 ± 0.13 compared with 1.1 ± 0.13) and sweating (1.3 ± 0.13 compared with

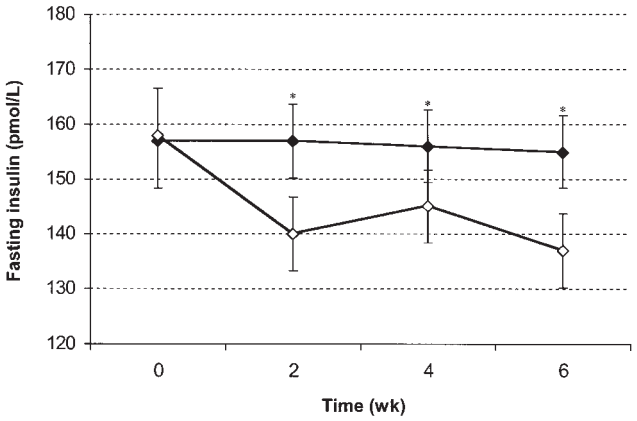

FIGURE 2. Mean (±SE) fasting insulin concentrations in overweight or obese adults (n = 11) during a refined-grain (◆) or whole-grain (◇) diet. *The pooled mean of weeks 2, 4, and 6 was significantly different from the whole-grain diet, $P < 0.01$ (repeated-measures regression).

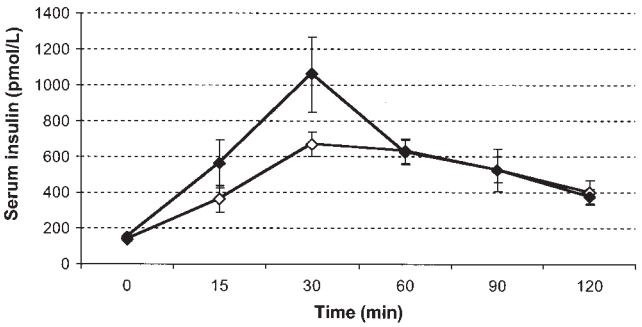

FIGURE 4. Mean (±SE serum insulin concentrations in overweight or obese adults (n = 11) after consumption of a nongrain liquid meal after the consumption for 6 wk of a refined-grain (◆) or whole-grain (◇) diet. There were no significant differences in the area under the curve between treatment groups.

1.0 ± 0.13) tended to be scored significantly higher on the Likert scale with the refined-grain diet. Bowel movements were more frequent with the whole-grain than with the refined-grain diet (1.8 ± 0.17 compared with 1.4 ± 0.17 movements/d; $P < 0.001$). No significant differences between treatments were apparent for heartburn, indigestion, diarrhea, or loose stools.

DISCUSSION

This study showed that dietary whole grains may have important effects on insulin sensitivity. In overweight hyperinsulinemic nondiabetic adults, insulin sensitivity improved over baseline during a 6-wk feeding of many different types of whole-grain foods compared with no change during a 6-wk feeding of refined grains. Body weight was relatively stable in this study; some of the nonsignificant 0.7-kg decrease in weight with the whole-grain diet may have been attributable to a small reduction in energy intake owing to the isovolumic exchange of whole-grain for refined-grain foods. Although body weight is a strong determinant of insulin sensitivity (35), the subtle decline in weight over time did not appear to explain the suppressed fasting insulin concentration and homeostasis model for insulin resistance observed with the whole-grain diet. Furthermore, the rate of glucose infusion/kg body weight during the insulin clamp showed that insulin sensitivity was greater after 6 wk of eating the whole-grain diet than after the refined-grain diet. The diets were well tolerated, with no apparent side effects. Nine of the 11 subjects preferred the whole-grain diet, which could be easily incorporated into their habitual lifestyle because the grain products were either purchased at local stores or prepared by replacing white flour with whole-wheat flour.

Diet composition has a major influence on insulin secretion (36, 37). Although the postprandial rise in serum insulin is greater after carbohydrate ingestion than it is after ingestion of fat or protein, there is a broad range in the glycemic and insulinemic responses to ingested carbohydrate, depending on such factors as the source, structure, composition, processing, and preparation of the foods (38–40). Fiber may attenuate the glycemic response to ingested carbohydrate through its physical action in the gut, where it tends to slow the absorption of nutrients (41, 42). Reduced serum glucose concentrations decrease the amount of insulin needed to clear the glucose load; over time, the reduced ambient insulin concentrations may result in an up-regulation of cell surface insulin receptors, thereby increasing insulin sensitivity (43). Although most whole-grain flours have glycemic indexes that are similar to those of refined-grain flours (26), because of their small particle size, we previously observed that habitual consumers of primarily whole-grain flour products had lower fasting insulin concentrations than did habitual consumers of refined-grain flour (27). The high concentration of fiber and indigestible carbohydrate in many whole-grain foods may be fermented by indigenous bacteria in the large intestine, thereby producing short-chain fatty acids that may enter the portal circulation (3, 4, 44, 45). There is evidence that hepatocytes may, when exposed to an increase in short-chain fatty acids, increase glucose oxidation, decrease fatty acid release, and increase insulin clearance—an environment conducive to enhanced insulin sensitivity (44, 46, 47). A whole-grain, high-fiber diet could therefore enhance insulin receptor sensitivity through a chronic lowering of the overall dietary glycemic index and related insulin secretion (40, 48–50) as well as through short-chain fatty acid production, leading to enhanced hepatic glucose oxidation and insulin clearance (43, 44, 46).

Other suspected mechanisms that might explain the effect of whole grains on insulin sensitivity include the metabolic effects of certain micronutrients, such as magnesium and vitamin E (24, 51–55). Our previous observation of an inverse dose-response association between self-reported whole-grain consumption and fasting insulin was found to be partially explained by body mass index, dietary magnesium, and dietary fiber, although no single mediator accounted for all of the association (27). In addition to these nutrients, whole grains contain a plethora of other nutrients and constituents (eg, antioxidants, phenolic compounds, and phytoestrogens), which have potential independent or synergistic biological effects (3, 4) that need to be elucidated in future studies.

Fukagawa et al (56) reported significant decreases in fasting insulin and glucose and increases in the rate of glucose disposal in healthy adults after a high-carbohydrate, high-fiber diet. However, because 60% of the fiber-rich foods in this diet came from nongrain foods, it was not possible to determine how much of the effect was due to whole grains. A supplement study performed by Keenan et al (50) in a clinical outpatient population of subjects with hypertension, impaired fasting glucose, or both showed beneficial effects on postload insulin and blood pressure with whole-oat cereal but not with a refined rice cereal. Chandalia et al (57) found significant beneficial effects on glucose and insulin in a diabetic population who increased their dietary fiber intake to 25 g soluble and 25 g insoluble fiber daily. In this population, reductions were observed in mean daily blood glucose (0.7 mmol/L) and urinary glucose (0.007 mmol) and in 24-h glucose (10%) and insulin (12%) areas under the curve. However, in the current study, most of the fiber in the whole-grain foods was insoluble, suggesting that soluble fiber may not be necessary to improve insulin sensitivity and raising the possibility that other nutrients and compounds in whole-grain foods may have important biological effects.

Although there was a suggestion of higher satiety between meals with the whole-grain diet than with the refined-grain diet, the subjects rarely reported feeling hungry with either of these euenergetic diets, and our analysis of the daily logs showed no indication of differential compliance. Note that the data in these logs were self-reported and may have masked true differences. Studies have generally provided support for an inverse association between whole grains and body weight (5, 13, 27, 58, 59). In the Coronary Artery Risk Development in Young Adults Study, we found inverse associations between dietary fiber and 10-y body weight gain in young black and white adults (22). The difference in 10-y weight gain was ≈3.6 kg (8 lb) for low compared with high quintiles of dietary fiber intake, and it was independent of dietary fat, total energy intake, physical activity, and many other possibly confounding factors. Although this study did not include sources of fiber in its analysis, whole-grain intake made an important contribution to dietary fiber (60).

Taken together, the findings from the current study are consistent with, and supportive of, epidemiologic evidence showing inverse associations between consumption of cereal fiber or whole grains and type 2 diabetes (14–17), cardiovascular disease (2, 5, 6, 8–13, 61), and total mortality (2, 5). Insulin resistance may be a common antecedent to each of these chronic diseases, because it is known to markedly increase the risk of type 2 diabetes (62, 63) and may be the cornerstone of a metabolic syndrome involving impaired fasting glucose, obesity, hypertension, dyslipidemia, and hypofibrinolysis (64).

In conclusion, whole-grain foods may have favorable effects on insulin sensitivity over a period of 6 wk in overweight and obese adults. These effects may reduce the risk of type 2 diabetes and ischemic heart disease. Although larger and longer controlled trials are needed to confirm these findings and elucidate the mechanisms involved, the epidemiologic and clinical evidence is sufficient to encourage increased consumption of whole-grain foods.

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REFERENCES

1. Putnam JJ, Allshouse JE. Food consumption, prices, and expenditures, 1996. Annual data, 1970–94. Washington, DC: USDA Economic Services Report. (Statistical Bulletin no. 928.)
2. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. Am J Public Health 1999;89:322–9.
3. Slavin J, Jacobs D, Marquart L. Whole grain consumption and chronic disease: protective mechanisms. Nutr Cancer 1997;27:14–21.
4. Slavin JL, Martini MC, Jacobs DR Jr, Marquart L. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr 1999;70(suppl):459S–63S.
5. Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. Am J Clin Nutr 1998;68:248–57.
6. Khaw K-T, Barrett-Connor. Dietary fiber and reduced ischemic heart disease mortality rates in men and women: a 12-year prospective study. Am J Epidemiol 1987;126:1093–102.
7. Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventists Health Study. Arch Intern Med 1992;152:1416–24.
8. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: The Ireland-Boston Diet-Heart Study. N Engl J Med 1985;312:811–8.
9. Morris JN, Marr JW, Clayton DJ. Diet and heart: a postscript. Br Med J 1977;2:1307–14.
10. Pietinen P, Rimm EB, Korhonen P, et al. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Circulation 1996;94:2720–7.
11. Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. JAMA 1996;275:447–51.
12. Wolk A, Manson JE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. JAMA 1999;281:1998–2004.
13. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999;70:412–9.
14. 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 2000;71:921–30.
15. Liu S, Manson JE, Stampfer MJ, et al. A prospective study of whole grain intake and risk of type 2 diabetes mellitus in US women. Am J Public Health 2000;90:1409–15.
16. Salmerón J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545–50.
17. Salmerón J, Manson JE, Stampfer MJ, et al. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;277:472–7.
18. Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995;75:473–86.
19. Hsueh WA, Law RE. Cardiovascular risk continuum: implications of insulin resistance and diabetes. Am J Med 1998;105(suppl):4S–14S.
20. Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 1998;97:996–1001.
21. Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993;137:959–65.
22. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. JAMA 1999;282:1539–46.
23. Vitelli LL, Folsom AE, Shahar E, et al. Association of dietary composition with fasting serum insulin level: The ARIC Study. Nutr Metab Cardiovasc Dis 1996;6:194–202.
24. Marshall JA, Bessesen DH, Hamman RF. High saturated fat and low starch and fibre are associated with hyperinsulinemia in a non-diabetic population: The San Luis Valley Diabetes Study. Diabetologia 1997;40:430–8.
25. Lovejoy J, DiGiroloama M. Habitual dietary intake and insulin sensitivity in lean and obese adults. Am J Clin Nutr 1992;55:1174–9.
26. Foster-Powell K, Brand Miller J. International tables of glycemic index. Am J Clin Nutr 1995;62(suppl):871S–93S.
27. Pereira MA, Jacobs DJ, Slattery ML, et al. The association between whole grain intake and fasting insulin in a bi-racial cohort of young adults: The CARDIA study. CVD Prev 1998;1:231–42.
28. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institute of Washington, 1919.
29. Schakel, SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc 1988;88:1268–71.
30. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5.
31. Defronzo RA, Tobin JD, Andre R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214–23.
32. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
33. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
34. SAS Institute Inc. SAS/STAT user's guide, version 6. 4th ed. Vols 1 and 2. Cary, NC: SAS Institute Inc, 1989.
35. Bogardus C, Lillioja S, Mott DM, Holleneck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol 1985;248:E286–91.
36. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics [serial online] 1999;103:e26. Internet: http//www.pediatrics.org/ (accessed 19 February 2002).
37. Holt SHA, Brand Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr 1997;66:1264–76.
38. Jenkins DJA, Ghafari H, Wolever TMS, et al. Relationship between rate of digestion of foods and post-prandial glycaemia. Diabetologia 1982;22:450–5.
39. Trout DL, Behall KM, Osilesi O. Prediction of glycemic index for starchy foods. Am J Clin Nutr 1993;58:873–8.
40. Jarvi AE, Karlström BE, Granfeldt YE, Björck IE, Asp N-GL, Vessby BOH. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. Diabetes Care 1999;22:10–8.

41. Jenkins DJ, Jenkins AL. Dietary fiber and the glycemic response. Proc Soc Exp Biol Med 1985;180:422–31.
42. Potter JG, Coffman KP, Reid RL, Krall JM, Albrink MJ. Effect of test meals of varying dietary fiber content on plasma insulin and glucose response. Am J Clin Nutr 1981;34:328–34.
43. Song YJ, Sawamura M, Ikeda K, Igawa S, Yamori Y. Soluble dietary fibre improves insulin sensitivity by increasing muscle GLUT-4 content in stroke-prone spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 2000;27:41–5.
44. Thorburn A, Muir J, Proietto J. Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. Metabolism 1993;42: 780–5.
45. Lu ZX, Gibson PR, Muir JG, Fielding M, O'Dea K. Arabinoxylan fiber from a by-product of wheat flour processing behaves physiologically like a soluble, fermentable fiber in the large bowel of rats. J Nutr 2000;130:1984–90.
46. Venter CS, Vorster HH, Cummings JH. Effects of dietary propionate on carbohydrate and lipid metabolism in healthy volunteers. Am J Gastroenterol 1990;85:549–53.
47. Frayn KN, Williams CM, Arner P. Are increased plasma non-esterified fatty acid concentrations a risk marker for coronary heart disease and other chronic diseases? Clin Sci 1996;90:243–53.
48. Frost G, Keogh B, Smith D, Akinsanya K, Leeds A. The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary heart disease. Metabolism 1996;45:669–72.
49. Frost G, Leeds A, Trew G, Margara R, Dornhorst A. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic index diet. Metabolism 1998;47:1245–51.
50. Keenan JM, Pins JJ, Frazel C, Moran A, Turnquist L. Oat ingestion reduces systolic and diastolic blood pressure among moderate hypertensives: a pilot trial. J Fam Pract (in press).
51. McCarty MF. Exploiting complementary therapeutic strategies for the treatment of type II diabetes and prevention of its complications. Med Hypotheses 1997;49:143–52.
52. 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 1993;57:650–6.
53. Paolisso G, Sgambato S, Pizza G, et al. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. Diabetes Care 1989;12:265–9.
54. Salonen JT, Nyyssonen K, Tuomainen TP, et al. Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a four year follow up study in men. BMJ 1995;311:1124–7.
55. Sanchez-Lugo L, Mayer-Davis EJ, Howard G, et al. Insulin sensitivity and intake of vitamins E and C in African American, Hispanic, and non-Hispanic white men and women: the Insulin Resistance and Atherosclerosis Study (IRAS). Am J Clin Nutr 1997;66:1224–31.
56. Fukagawa NK, Anderson JW, Hageman G, et al. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr 1990;52:524–8.
57. Chandalia M, Garg A, Lutjohann D, Bergmann KV, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. N Engl J Med 2000;342:1392–8.
58. Miller WC, Niederpruem MG, Wallace JP, Lindeman AK. Dietary fat, sugar, and fiber predict body fat content. J Am Diet Assoc 1994;94:612–5.
59. Nelson LH, Tucker LA. Diet composition related to body fat in a multivariate study of 293 men. J Am Diet Assoc 1996;96:771–7.
60. Ludwig DS, Pereira MA, Jacobs DR Jr. JAMA 2000;283: 1821–2 (letter).
61. Liu S, Manson JE, Stampfer MJ, et al. Whole grain consumption and risk of ischemic stroke in women: a prospective study. JAMA 2000;284:1534–40.
62. Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin dependent diabetes mellitus: prospective studies of Pima Indians. N Engl J Med 1993;329:1988–92.
63. Charles MA, Fontbonne A, Thibult N, Warret JM, Rosselin GE, Eschwege E. Risk factors for NIDDM in white population. Paris prospective study. Diabetes 1991;40:796–9.
64. Reaven G. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.