Consumption of Whole Grain and Legume Powder Reduces Insulin Demand, Lipid Peroxidation, and Plasma Homocysteine Concentrations in Patients With Coronary Artery Disease

Randomized Controlled Clinical Trial

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Abstract—Our objective was to evaluate whether isocaloric replacement of refined rice with whole grains and other plant products as a form of powder reduces coronary artery disease (CAD) risk factors, such as insulin demand and lipid peroxidation in CAD patients. Seventy-six male patients with CAD were randomly assigned to either a group ingesting a whole-grain meal daily or a control group for 16 weeks. In the whole-grain group, serum concentrations of glucose and insulin decreased by 24% and 14%, respectively, without altering body weight and energy intake, whereas daily intakes of fiber and vitamin E increased by 25% and 41%, respectively. Consumption of whole grains and legume powder in CAD patients without diabetes decreased fasting levels of glucose and insulin. The areas under the curve for insulin and glucose during the oral glucose tolerance test were also decreased. CAD patients with diabetes in the whole-grain group also showed reductions in fasting glucose and in the area under the curve for glucose. In the whole-grain group, plasma malondialdehyde and homocysteine and urinary 8-epi-prostaglandin $F_{2\alpha}$ concentrations decreased by ≈28%. Also, lipid-corrected concentrations of α-carotene, retinol, tocopherols, and lycopene increased by 11% to 40%, and the percentage composition of n-6 fatty acids of serum phospholipid increased by 14% in the whole-grain group. The replacement of refined rice with whole grain and legume powder as a source of carbohydrate in a meal showed significant beneficial effects on glucose, insulin, and homocysteine concentrations and lipid peroxidation in CAD patients. These effects are likely to substantially reduce the risk factors for CAD and diabetes. **(*Arterioscler Thromb Vasc Biol*. 2001;21:2065-2071.)**

Key Words: whole grain and legume powder ■ insulin demand ■ malondialdehyde ■ homocysteine ■ 8-epi-prostaglandin $F_{2\alpha}$

Hyperinsulinemia, insulin resistance, and abdominal obesity frequently occur in patients with coronary artery disease (CAD). Hyperinsulinemia, a manifestation of insulin resistance, plays a significant role in the development and progression of diabetes.[1] Increased consumption of whole grains has been recommended to improve insulin sensitivity and to lower serum insulin concentrations.[2,3] However, most grain products consumed in developed countries are highly refined.[4] Refined grains are nutritionally inferior to whole grains because they contain lower amounts of fiber, minerals, vitamins, phenols, phytoestrogens, and unsaturated fatty acids.[3]

Higher intake of many constituents of whole grains, including dietary fiber, vitamin E, and polyunsaturated fatty acids, has been independently associated with reduced risk of CAD.[2,5] In addition to reduced insulin resistance, the beneficial effects of whole-grain consumption on lipid peroxidation through antioxidative action may be another possible explanation in the significant inverse relation of whole-grain intake to the risk of CAD. Furthermore, recent reports of an association between insulin resistance and hyperhomocysteinemia may suggest that whole-grain consumption decreased plasma homocysteine (Hcy).[6,7] A review of epidemiological literature found a clear inverse association between whole-grain intake and the risk of ischemic heart disease death.[4] However, surprisingly, only a few prospective studies, such as the Nurses' Health Study, which showed that increased intake of whole grains might protect against cardiovascular disease (CVD)[5] and the research showing that higher intake of whole grain foods was associated with a lower risk of ischemic stroke among women,[8] have examined whether intake of whole grain decreased chronic disease risk.

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In addition to whole grains, other plant products, such as vegetables and legumes, also have various kinds of phytochemicals and antioxidants. A higher intake of fruits and vegetables has been found to be protective against CVD, and an increase in their intake has been emphasized.[9] Two hundred fifty observational studies on cancer and CVD have also shown that the increasing consumption of fruits and vegetables carries a large public health benefit.[10] In a randomized cross-design study, phytochemicals in soybeans were found to reduce lipid peroxidation in vivo and to increase the resistance of LDL to oxidation.[11] Therefore, to test the hypothesis that a higher intake of whole grain with vegetables and legumes reduces diabetes and cardiovascular risk factors in CAD patients, we specifically examined the effect of the isocaloric replacement of refined rice (220 kcal) with whole grain and legume powder (66.6% whole grains, 22.2% legumes, 5.6% seeds, and 5.6% vegetables) in CAD patients.

Methods

Subjects and Study Design

Seventy-eight male patients with CAD were referred by the Division of Cardiology of Yonsei Cardiovascular Center, Yonsei Severance Hospital, Seoul, Korea. About a month before the start of the study, they were all recruited concomitantly from participants in a prospective human genetic study, supported by The Brain Korea 21 Project and R&D Promotion Center, Ministry of Health and Welfare, and they all met the inclusion criteria according to the latest laboratory data. The inclusion criteria required angiographic evidence with ≥50% occlusion of ≥1 major coronary artery, old myocardial infarction, or angina pectoris, but any possible nonatherogenic occlusions, such as osteal stenosis and spasm, were excluded. Subjects with baseline lipid profiles with LDL cholesterol levels ≥3.36 mmol/L or triglyceride levels ≥1.81 mmol/L or total cholesterol levels ≥5.17 mmol/L were selected. For patients taking cholesterol-lowering medications, those with total cholesterol ≥3.88 mmol/L were included. All subjects were of stable weight for 1 year before the study. The macronutrient composition of each subject's usual diet was that of a typical diet with cooked refined rice, which is consumed by a substantial number of Koreans; this diet derives about 64% of energy from carbohydrates, 19% from fat, and 17% from protein. Of the CAD subjects, those with a diagnosis of diabetes, renal disease, liver disease, or thyroid disease were excluded. Subjects on vitamin supplements were also excluded. All subjects were outpatients; they underwent a clinical examination and interview and gave their written informed consent to participate in the study, which was approved by the Medical Ethics Committee of Yonsei Medical University.

The present study was carried out in 2 phases: a 4-week run-in phase consisting of the usual diet with cooked refined rice and a 16-week intervention phase consisting of the usual diet or consumption of whole grain and legume powder. During the run-in period, 2 subjects, having maintained neither energy intake nor <1% variation in mean body weight, dropped out. The remaining 76 were randomly subdivided into 2 groups and were assigned to consume either their usual diet (cooked refined rice) or the whole grain and legume powder for breakfast during the 16-week intervention.

Dietary Education and Nutrient Composition of Whole Grain and Legume Powder

All subjects were given written and verbal instructions by a dietitian on how to complete 3-day (2 weekdays and 1 weekend) dietary records every 2 weeks throughout the whole study period. On the sheet, subjects were instructed to record the amount of foods before ingestion and any remaining after ingestion by weighing the foods. During the 4-week run-in period, all participants were advised to continue their usual diet of cooked refined rice. Baseline measurements were also performed at the start of the run-in phase. After the run-in period, the subjects in the control group maintained their usual diet of cooked refined rice, and the subjects in the whole-grain group consumed 70 g of whole grain and legume powder, replacing cooked refined rice as a carbohydrate source for breakfast for 16 weeks. All subjects in the whole-grain group consumed this powder by dissolving it in a glass of water. To check participants' compliance during the whole study period, the dietitian interviewed them during weekly visits. They were interviewed to discern whether they were following the program well, including dietary intake and weight changes. During the study period, all participants were also encouraged to maintain their usual lifestyle and were reminded not to make any changes to their usual dietary habits, except for the whole-grain powder substitution in whole-grain group.

Whole grains and legume powder were composed of 66.6% whole grains, 22.2% legumes, 5.6% seeds, and 5.6% vegetables. The diet consisted of brown rice (22.2%), glutinous brown rice (11.1%), barley (22.2%), black beans (22.2%), sesame (5.6%), and Job's tears (11.1%), which were all roasted and coarsely ground. Little amounts of pumpkin, onion, kale, crown daisy, chestnuts, dried sea mustard, and mushroom were also added to the powder. These were added not only for a coloring effect but also for enrichment of phytochemicals and antioxidants. This was in response to consumers' concerns about their health. When compared with 150 g of cooked refined rice, 70 g of whole grain and legume powder was as isocaloric as 220 kcal, but it contained a different composition of nutrients. Cooked refined rice (150 g) provided 46.6 g carbohydrate, 3.8 g protein, 0.73 g fat, 0.15 g fiber, 0.42 mg vitamin E, 0.05 mg vitamin B_1, 0.02 mg vitamin B_2, 0.5 mg niacin, 0.09 mg vitamin B_6, 4.62 μg folate, 0.63 g saturated fatty acid, 0.84 g monounsaturated fatty acid, and 0.90 g polyunsaturated fatty acid, whereas 70 g of whole grain and legume powder provided 35.6 g carbohydrate, 9.2 g protein, 5.0 g fat, 4.2 g fiber, 28.4 retinol equivalent vitamin A, 41.0 μg β-carotene, 0.62 mg vitamin E, 0.2 mg vitamin B_1, 0.1 mg vitamin B_2, 2.0 mg niacin, 0.6 mg vitamin B_6, 7.1 μg folate, 0.76 g saturated fatty acid, 1.27 g monounsaturated fatty acid, and 2.39 g polyunsaturated fatty acid. Nutrient intake data were calculated as mean values from a 3-day food record with use of the database of the computerized Korean food code, which is based on food composition tables for the year 2000 by the National Rural Living Science Institute in Korea. For more information about usual intake, a semiquantitative food frequency questionnaire was used together with a 3-day dietary record.

BMI, Blood Collection, Blood Pressure Measurement, and Lipid Profile

Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Venous blood specimens were collected after a 12-hour fast in EDTA-treated or plain tubes. The tubes were immediately covered with aluminum foil and placed on ice in the dark until they arrived at the laboratory room. Blood pressure was read from the left arm while the subjects remained seated. An average of 3 measurements was recorded for each subject. The fasting total serum cholesterol and serum triglyceride levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of LDL and VLDL with dextran sulfate–magnesium. LDL cholesterol was estimated indirectly by using the Friedewald formula, ie, LDL=total cholesterol−[HDL+(triglycerides/5)], for subjects with serum triglyceride levels <4.52 mmol/L.

OGTT and HOMA

Subjects received a 75 g glucose solution after an overnight fast to investigate the effect of whole grain and legume powder on glucose and insulin responses. Venous specimens were collected before and 30, 60, 90, and 120 minutes after loading. The glucose criteria, newly developed and modified by the National Diabetes Data Group and the World Health Organization Expert Committee on Diabetes Mellitus, were used to categorize subjects as diabetic: symptoms with a casual plasma glucose >11.1 mmol/L or fasting glucose ≥7.0 mmol/L and oral glucose tolerance test (OGTT) with a 2-hour postload value ≥11.1 mmol/L.[12] Glucose was measured by a glucose oxidase method with use of the Beckman Glucose Analyzer (Beckman Instruments). Insulin was measured by radioimmunoassays with

commercial kits from Immuno Nucleo Corp. Each response of glucose and insulin was calculated with the area under each response curve. Insulin resistance and β-cell function were also calculated with the homeostasis model assessment (HOMA).[13] The formulas are as follows: insulin resistance=[fasting insulin (μU/mL)×fasting glucose (mmol/L)]/22.5, and β-cell function=20×fasting insulin (μU/mL)/[fasting glucose (mmol/L)−3.5].

Plasma Total Hcy and Serum Retinol, Carotenoids, and Tocopherols

Plasma total Hcy was analyzed with a Bio20 Autoloader Amino Acid Analyzer (Pharmacia Biotech), including a postcolumn ninhydrin reaction system according to the modified method of Anderson, Ueland, and colleagues.[14,15] Reversed-phase high-performance liquid chromatography (HPLC) was used to determine retinol, carotenoids, and tocopherols in serum simultaneously, as described by Yeum et al,[16] Vogel et al,[17] and Fotouchi et al.[18] The HPLC system consisted of an Alliance Waters 2690 separation module, Waters 996 photodiode array detector, Waters 474 scanning fluorescence detector, C_{18} Symmetry 3.9×15-cm column, and PDA Millennium for version 2.15 data station (Waters). The Waters 474 scanning fluorescence detector was set at 294 nm for the detection of tocopherols. Levels of retinol, carotenoids, and tocopherols in serum were reported as corrected levels and expressed as the sum of the serum lipid (in millimoles per liter).[19]

Plasma Malondialdehyde and Folate

Plasma malondialdehyde (MDA) was assayed according to the fluorometric method described by Buckingham.[20] Plasma folate level was analyzed with the kit from Immuno Nucleo Corp Pharmaceuticals.[21]

Urine Collection and 8-Epi-$PGF_{2\alpha}$

Urine was collected after a 12-hour fast in polyethylene bottles containing 1% butylated hydroxytoluene before blood collection. The tubes were immediately covered with aluminum foil and stored at −70°C until extraction. Urinary 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) was quantified with gas chromatography (Hewlett Packard 6890) and mass selective detector (Hewlett Packard 3973), according to the modified method of Pratico et al[22] and Mori et al.[23] For gas chromatography/mass spectrometry, pentafluorobenzyl derivatives, as opposed to the pentafluorobenzyl ester, were used; after which, trimethylsilyl derivative, as opposed to bis-trimethylsilyl ester, was used. The gas chromatography/mass spectrometry was programmed to go from 190°C to 310°C at 10°C/min; retention time was 8.5 minutes. Quantification of 8-epi-$PGF_{2\alpha}$ was performed by using the peak area ratio. Urinary creatinines were determined by the alkaline picrate (Jaffe) reaction,[24] and urinary 8-epi-$PGF_{2\alpha}$ levels were expressed as picomoles per millimole creatinine.

Serum Phospholipid Fatty Acid Composition

Serum phospholipid composition was analyzed with the modified method of Folch et al,[25] with the use of gas chromatography (Hewlett Packard 6890). The temperatures of injection and detector ports were set at 280°C/min, and retention time was 40 minutes. A flame ionization detector was used, and helium was used as the carrier gas at 0.7 mL/min. Peaks were identified by comparison with a known standard mixture (Supelco). Individual fatty acids were calculated as a relative percentage with the elevated fatty acids set at 100% with Chemstation software. Total n-3 (18:3 n-3, 20:3 n-3, 20:5 n-3, 22:5 n-3, and 22:6 n-3) and n-6 (18:2 n-6, 18:3 n-6, 20:3 n-6, 20:4 n-6, 22:4 n-6, and 22:5 n-6) fatty acids were measured in plasma phospholipids.

Statistical Analysis

Statistical analysis was performed with Win SPSS (Statistical Package for the Social Science, SPSS Inc). For descriptive purposes, mean values were presented on untransformed and unadjusted variables. Results were expressed as mean±SE. Effects of the diet on end points were tested by a paired *t* test in each group before and after consumption. According to whether the subject turns out to have new-onset diabetes, fasting levels of glucose and insulin, their response areas, and insulin resistances were tested by using the Wilcoxon signed rank sum test in each group or by using the Wilcoxon rank sum test between the 2 groups. To determine a more accurate effect of whole grain and legume powder, net differences (change in whole-grain group versus change in control group) were evaluated. To compare differences in frequencies, χ^2 tests were used. A value of $P<0.05$ was considered statistically significant.

Results

Basic Characteristics at Start of 16-Week Intervention

After the run-in period, of 78 subjects, only 76, who had maintained their energy intake and had <1% variation in mean body weight, were selected to participate in the intervention program and were randomly subdivided into the control group or the whole-grain group. There were no significant differences in baseline characteristics, such as age, BMI, lipid profile, medications, and education level between the 2 groups at the start of the 16-week intervention (Table 1). Dosages of antihypertensive and lipid-lowering drugs were not changed during the intervention period.

Body Weight, Energy and Nutrient Intake, and Lipid Profile

There was <1% variation in mean body weight between week 0 and 16 in the 2 groups that maintained their usual energy intake. Frequent interviews with the subjects did not suggest any important changes in the physical activity patterns of the individual subjects during the study. As expected, BMI and total energy intake were similar before and after treatment in both groups. However, diastolic blood pressure decreased and energy percentage of protein intake increased significantly in the whole-grain group (Tables 1 and 2). Concentration of HDL cholesterol increased significantly in the whole-grain group. However, there were no significant differences in other lipid profiles (Table 1). With the substitution of whole grain and legume powder for refined rice, estimates of fiber and vitamin E intake increased significantly (Table 2). Compared with net differences of these parameters, percent energy intake of protein, vitamin E intake, and HDL cholesterol level in the whole-grain group showed significant increases. However, percent energy intake of carbohydrate significantly decreased in this group. There were no significant differences in net differences of the other parameters.

Glucose and Insulin

Glucose and insulin concentrations of the control group did not change significantly between 0 and 16 weeks, whereas serum glucose concentrations of the whole-grain group significantly decreased (Table 2). To investigate the effect of whole-grain powder on glucose and insulin response, OGTT was examined, and 9 of the subjects in the control group and 12 of the subjects in the whole-grain group were found to have new-onset diabetes. However, there was no significant difference in diabetic proportion between the 2 groups.

The effects of whole-grain and legume consumption on serum concentrations of insulin and glucose are shown in Table 3. All subjects were subdivided into 2 categories: nondiabetic subjects and subjects with new-onset diabetes according to OGTT. In the nondiabetic category, the whole-grain group showed significant decreases in fasting glucose level, response areas of glucose and insulin, and insulin

TABLE 1. Baseline Characteristics, BMI, and Serum Lipid Profiles in CAD Male Patients

	Control (n=38)		Whole Grain (n=38)		
	0 wk	16 wk	0 wk	16 wk	P*
Age, y	58.4±1.53	...	54.8±1.20	...	...
Consumption of medication†, n	34	...	28	...	...
Antihypertensive agent	15	...	12	...	...
Lipid-lowering agent	20	...	26	...	...
Education level†, n					
University	18	...	12	...	...
High school	9	...	12	...	...
BMI, kg/m^2	24.3±0.34	24.6±0.34	25.1±0.35	24.9±0.35	0.071
Triglycerides, mmol/L	1.74±0.20	1.66±0.14	1.84±0.17	1.63±0.13	0.158
Total cholesterol, mmol/L	5.25±0.13	5.23±0.13	4.91±0.12	4.82±0.13	0.343
LDL cholesterol, mmol/L	3.43±0.13	3.39±0.13	3.06±0.13	2.91±0.13	0.192
HDL cholesterol, mmol/L	1.11±0.03	1.10±0.04	1.03±0.04	1.19±0.06‡	0.001

Values are mean±SE. Age was tested by independent *t* test.
*Comparison of net differences between 2 groups.
†By χ^2 tests to compare differences in frequencies.
‡$P<0.001$ compared with initial value in each group.

resistances and a significant increase in the percentage of β-cell function from the HOMA equation compared with the values in the control group. Net differences of these values also showed a similar pattern with results above. In the group with new-onset diabetes, the fasting level and response area of glucose in the whole-grain group significantly decreased, and net differences of these values also showed significance (Table 3).

MDA, 8-Epi-PGF$_{2\alpha}$, Total Hcy, Vitamins, and Carotenoids

Plasma MDA and urinary 8-epi-PGF$_{2\alpha}$ concentrations decreased by ≈28% in the whole-grain group, but there was no significant change in the control group (Table 4). With whole-grain and legume consumption, plasma Hcy concentration decreased by 32%, and unlike the usual case, plasma folate concentration merely showed a tendency to decrease. Net differences of these values also showed significant decreases in the whole-grain group.

Lipid-corrected concentrations of α-carotene, retinol, α-tocopherol, γ-tocopherol, and lycopene increased by 11% to 40% in the whole-grain group but did not change significantly in the control group (Table 4). Lipid-corrected concentrations of β-carotene and cryptoxanthin did not change significantly in either group. Only in the case of retinol and α-carotene did net differences show a significant increase in the whole-grain group.

Serum Phospholipid Fatty Acids

The fatty composition of serum phospholipids at baseline was not significantly different between the 2 groups (Table 4). In

TABLE 2. Effects of Whole-Grain Consumption on Blood Pressure, Glucose, and Insulin Levels and Estimates of Daily Nutrient Intakes in CAD Male Patients

	Control (n=38)		Whole Grain (n=38)		
	0 wk	16 wk	0 wk	16 wk	P*
Systolic BP, mm Hg	131.2±2.01	129.7±2.56	131.8±2.81	129.1±2.73	0.722
Diastolic BP, mm Hg	82.2±1.52	81.9±1.04	85.2±1.24	81.3±1.12‡	0.112
Glucose, mmol/L	4.71±0.22	4.90±0.24	6.23±0.19	4.73±0.17§	0.000
Insulin, pmol/L	68.4±5.16	68.4±9.72	75.0±3.66	64.2±3.78‡	0.195
Estimates of daily nutrient intakes†					
Energy intake, kJ/d	8518±237	8665±268	9160±210	9034±139	0.328
Carbohydrate, %	68.3±1.02	69.3±0.95	64.2±1.63	61.0±1.38	0.032
Protein, %	15.3±0.40	14.8±0.40	17.3±0.71	19.4±0.51‖	0.001
Fat, %	16.1±0.82	15.9±0.75	18.6±1.29	19.5±1.11	0.455
Vitamin E, mg/d	11.1±1.89	9.2±0.91	6.73±0.82	9.48±0.92‖	0.034
Fiber, g/d	23.1±2.91	23.2±1.73	20.8±1.81	26.0±1.25‖	0.128

BP indicates blood pressure. Values are mean±SE.
*Comparison of net differences between 2 groups.
†Nutrient intakes, obtained from weighed food records and calculated by using the database of the computerized Korean food code.
‡$P<0.05$, §$P<0.001$, and ‖$P<0.01$ compared with the initial value in each group.

TABLE 3. Glucose and Insulin Responses on 75-g Oral Glucose Tolerance Test Between Control and Whole-Grain Group According to Presence or Absence of Diabetes Identified During the Study

	Nondiabetic CAD (n=55)					New-Onset Diabetic CAD (n=21)				
	Control (n=29)		Whole Grain (n=26)			Control (n=9)		Whole Grain (n=12)		
	0 wk	16 wk	0 wk	16 wk	P*	0 wk	16 wk	0 wk	16 wk	P*
Fasting level										
Glucose, mmol/L	4.31±0.15	4.45±0.16	5.75±0.15	4.46±0.17†	0.000	6.06±0.62‖	6.32±0.68	7.29±0.38¶	5.30±0.31§	0.023
Insulin, pmol/L	64.8±5.52	58.2±5.70	78.6±4.44	66.0±4.50‡	0.304	71.4±11.4	102.0±37.3	67.2±6.24‖	61.8±7.08	0.792
Response area										
Glucose, (mmol/L)×h	18.0±0.56	17.2±0.47	17.0±0.59	13.8±0.45†	0.000	26.8±1.52¶	26.1±1.38	23.2±1.13¶	17.9±1.18‡	0.021
Insulin, (pmol/L)×h	644.7±80.2	637.3±73.0	751.2±87.0	567.0±72.0§	0.022	547.8±99.6	430.8±47.8	426.6±63.6‖	377.4±62.4	0.135
HOMA equation										
β-Cell function, %	217.2±140.0	185.4±151	137.5±18.8	333.6±42.8†	0.003	184.2±56.4	120.6±18.0	63.2±6.00¶	140.0±18.5§	0.135
Insulin resistance	2.05±0.19	1.87±0.17	3.44±0.21	2.16±0.17†	0.001	3.17±0.49	6.21±3.41	3.71±0.48	2.58±0.45	0.157

Values are mean±SE.
*Comparison of net differences between 2 groups in either nondiabetic or diabetic CAD by the Wilcoxon rank sum test.
†$P<0.001$, ‡$P<0.05$, and §$P<0.01$ compared with initial value in each group; ‖$P<0.01$ and ¶$P<0.001$ compared with nondiabetic CAD in each group.

the whole-grain group, the percent composition of n-6 fatty acids of serum phospholipid increased significantly; however, there was no significance in the net difference between the 2 groups.

Discussion

The isocaloric replacement of refined rice with whole-grain powder resulted in substantial improvement in glucose and insulin metabolism as well as reduction in lipid peroxidation and plasma Hcy concentration in CAD patients. Current dietary guidelines for CAD patients recommend increased intake of whole-grain products, legumes, and vegetables, but the amount that is to be consumed is not specified. The present study shows that replacing refined grains with whole grains and other plant products as a form of coarse powder in 1 meal for 16 weeks may reduce the risk factors for CAD and diabetes.

Whole-grain products, because of their physical form and high content of fiber, tend to be slowly digested and absorbed and, thus, have relatively low glycemic indexes.[5] In diabetic and nondiabetic subjects, higher intakes of foods with a low glycemic index have been reported to have an association

TABLE 4. Effects of Whole-Grain Consumption on Plasma MDA, Hcy, and Urinary 8-Epi-$PGF_{2\alpha}$ Serum Vitamins and Carotenoids, and Fatty Acids of Serum Phospholipid in CAD Patients

	Control (n=38)		Whole Grain (n=38)		
	0 wk	16 wk	0 wk	16 wk	P*
MDA, nmol/mL	3.33±0.25	3.26±0.31	4.65±0.32	3.46±0.29‖	0.028
8-Epi-$PGF_{2\alpha}$ pmol/mmol creatinine	579.9±55.8	493.9±44.2	526.8±65.1	384.0±51.5¶	0.003
Hcy, μmol/L	12.9±1.03	12.0±1.21	12.8±0.53	8.75±0.44¶	0.032
Folate, nmol/L	12.4±0.73	13.4±0.75	10.4±0.81	9.61±0.63	0.335
Lipid-corrected levels†					
α-Carotene, μg/mmol	4.47±0.52	4.10±0.74	4.79±0.51	6.00±0.55‖	0.058
β-Carotene, μg/mmol	42.7±5.59	44.1±5.40	32.7±5.20	37.2±4.96	0.667
Retinol, μg/mmol	205.4±15.1	204.6±21.9	190.1±15.7	229.1±17.7‖	0.008
α-Tocopherol, μg/mmol	0.50±0.04	0.49±0.04	0.49±0.05	0.68±0.05#	0.006
γ-Tocopherol, μg/mmol	0.10±0.00	0.10±0.00	0.18±0.02	0.20±0.02‖	0.105
Cryptoxanthin, μg/mmol	68.0±10.8	83.7±7.90	73.6±8.54	67.5±8.58	0.059
Lycopene, μg/mmol	51.9±6.71	51.5±8.77	39.4±4.01	55.1±6.14‖	0.148
Serum phospholipid fatty acids					
n-6‡, % of total fatty acids	19.5±0.97	19.6±1.06	18.1±0.61	20.7±0.77‖	0.083
n-3§, % of total fatty acids	5.22±0.39	4.78±0.22	5.80±0.38	5.77±0.34	0.523

Values are mean±SE.
*Comparison of net differences between 2 groups.
†Each level of vitamins and carotenoids is divided by sum of cholesterol and triacylglyerol (mmol/L).
‡Sum of 18:2 n-6, 18:3 n-6, 20:3 n-6, 20:4 n-6, 22:4 n-6, and 22:5 n-6.
§Sum of 18:3 n-3, 20:3 n-3, 20:5 n-3, 22:5 n-3, and 22:6 n-3.
‖$P<0.01$, ¶$P<0.001$, and #$P<0.05$ compared with initial value in each group.

with lower concentrations of insulin. Reduced insulin demand, representing improvement of insulin sensitivity, may be 1 of the protective mechanisms for CAD and diabetes in association with a higher intake of whole grain.[1,5] The present study also shows that consumption of whole grain and legume powder reduces insulin demand and hyperinsulinemia in CAD patients with and without diabetes. In fact, an epidemiological study reported that every 6-g increase in daily fiber consumption was associated with a 25% reduction in ischemic heart disease mortality.[2] In addition, reduced risk for CAD has been reported in people who consumed a diet containing at least 37 g of dietary fiber per day.[2]

Whole-grain and legume consumption that decreases insulin resistance or insulin demand, over a long term, may reduce plasma Hcy concentration. This suggestion is related to the report of an association between insulin resistance and hyperhomocysteinemia.[7] Recently, elevated total Hcy concentration, an independent risk factor for atherosclerosis,[26] has also been suggested to be a possible biological link between insulin resistance and atherothrombosis.[6] Although serum concentration of folate did not change significantly, plasma Hcy concentration decreased in the whole-grain group. It might be related to the improvement of insulin resistance, according to decrease in fasting glucose and decreased tendencies of fasting insulin and their respective response.

In addition to being a good source of dietary fiber, whole grains may have beneficial combinations of many micronutrients, antioxidants, and phytochemicals.[4,5] Whole grains, legumes, and vegetables are important dietary sources of antioxidant vitamins and unsaturated fatty acids. The intake of polyunsaturated fatty acids and vitamin E is associated with protection from CAD, and carotenoids may also have such protective effects.[2] A tendency toward an increase in the percent composition of n-6 fatty acids and in serum concentrations of lipid-corrected carotenoids, especially, α-tocopherol and retinol, in the whole-grain group of the present study may result from an increased intake of these nutrients from whole grains. In addition, other antioxidant intakes from whole grain and legume powder and reduced oxidative stress, such as decreased plasma Hcy concentration, could also spare serum tocopherols and some carotenoids.

Whole grains, legumes, and vegetables contain many antioxidants, including vitamins, trace minerals, and nonnutrients, such as phenolic acids, lignans, and phytoestrogens, and antinutrients, such as phytic acid.[4,9,13] Antioxidants in whole grains can slow the rate of oxidation of oxidizable substrates.[3,4] Measurement of products of lipid peroxidation, such as plasma MDA[27] and urinary 8-epi-$PGF_{2\alpha}$,[28,29] may offer a noninvasive approach to the assessment of oxidative stress and the efficacy of antioxidant therapies. The decrease of plasma MDA and urinary 8-epi-$PGF_{2\alpha}$ concentrations in the whole-grain group might be due to the antioxidative effects of many antioxidants in whole grains and other plant products. In addition, reduced plasma Hcy concentration in the whole-grain group might contribute to the decrease in lipid peroxidation. Recently, Voutilainen et al[26] published a study about an enhancement of in vivo lipid peroxidation at elevated fasting plasma total Hcy concentration.

In summary, the present study showed significant beneficial effects of consumption of whole grains and other plant products as a form of coarse powder on glucose, insulin, and Hcy concentrations and lipid peroxidation in CAD patients. These effects are likely to substantially reduce the risk factors of CAD and diabetes in CAD patients. The biological mechanism, whereby whole grain and legume powder may exert their protective effect is not clear in the present study, but it is likely to be due to multiple mechanisms, such as fiber, antioxidants, and many constituents of whole grain and legume powder. Therefore, grains should be consumed in a minimally refined form, and frequent consumption of vegetables and legumes should be recommended to reduce cardiovascular risk factors and the incidence of diabetes in CAD patients.

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