Whole-Grain, Bran, and Cereal Fiber Intakes and Markers of Systemic Inflammation in Diabetic Women

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OBJECTIVE — To evaluate the dietary predictors for the markers of systemic inflammation and endothelial dysfunction in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We examined whether intakes of whole grains and dietary fiber were associated with inflammatory indicators among 902 diabetic women in the Nurses' Health Study.

RESULTS — After adjustment for age, BMI, lifestyle, and dietary covariates, intakes of whole grains and bran were both associated with significantly decreasing trends of C-reactive protein (CRP) (*P* for trend = 0.03 and 0.007, respectively) and tumor necrosis factor-α receptor 2 (TNF-R2) (*P* for trend = 0.017 and 0.06). High intake of cereal fiber was also inversely associated with the lower levels of CRP (*P* for trend = 0.03) and TNF-R2 (*P* for trend = 0.01). The concentrations of CRP and TNF-R2 were 18 and 8% lower in the highest quintile of cereal fiber as compared with the lowest quintile. Dietary glycemic index was positively associated with CRP (*P* for trend = 0.04) and TNF-R2 (*P* for trend = 0.0008) levels. The concentrations of CRP and TNF-R2 were 32 and 11% higher, respectively, in the highest quintile of dietary glycemic index as compared with the lowest quintile.

CONCLUSIONS — Our data indicate that whole grains and a low–glycemic index diet may reduce systemic inflammation among women with type 2 diabetes.

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Consumption of whole grains and dietary fiber have been associated with a lower risk of cardiovascular disease in epidemiological studies (1,2). The biologic mechanisms underlying the effect are not well understood. Previous studies have suggested that fiber may lower serum cholesterol, inhibit lipid peroxidation, increase insulin sensitivity, and improve homocysteine levels (3–6), but the results are not entirely consistent (7).

Type 2 diabetes is associated with low-grade systemic inflammation and accelerated rates of atherosclerosis (8). The inflammatory process plays a pivotal role in the pathogenesis of atherosclerosis and is believed to be responsible for the increased cardiovascular complications among diabetic patients (9,10). Dietary fiber intake was recently associated with serum inflammatory markers in the general population (11,12). However, little is known about the effect of whole grains and fiber on inflammatory markers among diabetic patients.

To address this issue, we examined the associations of long-term intake of whole grains, the grain subcomponents bran and germ, and dietary fibers with markers of inflammation and endothelial function in diabetic women from the Nurses' Health Study. The relation of dietary glycemic index and glycemic load with the inflammatory markers was also examined.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study began in 1976 with the recruitment of 121,700 female registered nurses (>95% Caucasian) between the ages of 30 and 55 years. A total of 32,826 women provided blood between 1989 and 1990. Cases were defined as self-reported diabetes confirmed by supplementary questionnaire. We used National Diabetes Data Group criteria to define diabetes because our subjects were diagnosed before the release of the American Diabetes Association criteria in 1997 (13). The validity of this method has been confirmed (14). A case of diabetes was considered if at least one of the following was reported on the supplementary questionnaire: *1*) classic symptoms plus elevated fasting plasma glucose ≥7.8 mmol/l, random plasma glucose ≥11.1 mmol/l, and/or plasma glucose ≥11.1 mmol/l after ≥2 h during an oral glucose tolerance test; *2*) no symptoms but at least two elevated plasma glucose concentrations (by the above criteria) on different occasions; or *3*) treatment with oral hypoglycemic agents or insulin. We excluded those who had myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty or stroke at blood draw, and 902 diabetic women were included in this study.

Assessment of dietary intakes and covariates

Measurements of dietary intake were repeated in 1986 and 1990 by using semiquantitative food-frequency questionnaires. Participants were asked to report their average frequency of consumption of selected foods and beverages with a

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Abbreviations: CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ICAM, intracellular cell adhesion molecule; TNF-R2, tumor necrosis factor-α receptor 2.

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

Table 1—*Age-standardized characteristics according to quintiles of total fiber and whole-grain intakes (in grams per day)

	Whole grain, quintiles			Total fiber, quintiles		
Variables	Q1	Q3	Q5	Q1	Q3	Q5
n	173	174	172	183	181	172
Age (years)	57	59	60	57	58	60
BMI (kg/m^2)	30.9	29.8	28.4	31	30.1	28.8
Current smoker (%)	18.5	10.7	7.1	16.8	12.4	6.4
Alcohol consumption (g/day)	4.3	2.6	1.1	5.4	1.5	1.4
Physical activity (MET/week)	17.6	39.5	21.1	10.4	26.7	29.2
Family history of coronary heart disease (%)	23.5	20.1	23.2	22.4	24.8	26.7
History of hypertension (%)	45.1	41.5	43.2	49.7	41.6	36.9
History of hypercholesterolemia (%)	42.0	42.8	40.0	42.9	41.0	46.5
Oral diabetes medication (%)	16.3	24.3	26.4	22.1	25.4	26.9
Insulin use (%)	15.5	18.7	23.3	12.5	20.1	20.9
Postmenopausal status (%)	75.9	84.3	84.5	76.4	82.6	83.4
Current hormone use among postmenopausal women (%)	25.2	36.7	35.2	24.1	27.6	36.0
Duration of diabetes (years)	5.0	6.1	7.7	5.1	5.7	7.9
A1C (%)	7.0	7.1	6.7	7.0	6.9	6.7

*Data were from 1990 questionnaire; medication status and physical activity was from 1988 questionnaire. Dietary intakes were the average of 1986 and 1990.

specified commonly used unit or portion size during the previous year. Type and brand of breakfast cereal were also assessed. The correlations coefficients between semiquantitative food-frequency questionnaires and multiple dietary records were 0.75 for cold breakfast cereal, 0.71 for white bread, and 0.77 for dark bread. The correlation for fiber was 0.56 (15,16). Whole grains were defined as previously described (17). Intakes of bran and germ (in grams per day) from both added-to foods and naturally occurring in whole grains were also calculated in a similar manner. Intakes of whole grains and fiber were energy adjusted using the residual method. We calculated glycemic load by multiplying the carbohydrate content of each food by its glycemic index then multiplied this value by the frequency of consumption and summed the values from all foods. The overall dietary glycemic index was calculated by dividing the average daily glycemic load by the average daily carbohydrate intake (18).

Anthropometric data and lifestyle factors were derived from the 1990 questionnaire. BMI was calculated as weight in kilograms divided by the square of height in meters. Physical activity was expressed as MET-hours based on self-reported types and durations of activities over the previous year.

Assessment of markers of inflammation and endothelial function

Blood was collected between 1989 and 1990. Markers of inflammation (C-reactive protein [CRP] and tumor necrosis factor-α receptor 2 [TNF-R2]) and endothelial function (soluble intracellular cell adhesion molecule [ICAM]-1 and E-selectin) were assessed. CRP was measured by using the U.S. CRP enzyme-linked immunosorbent assay (ELISA) kit (DSL, Webster, TX) with a coefficient of variation (CV) range of 2.8–5.1%. TNF-R2 was measured using the human soluble TNF-R2 ELISA kit (R&D Systems, Minneapolis, MN) with a CV range of 2.6–4.8%. ICAM-1 concentration was assayed using the Human soluble ICAM-1 ELISA kit (R&D Systems) with a CV range of 3.3–4.8%. E-selectin was measured using human sE-selectin ELISA kit (R&D Systems) with a CV range of 5.7–8.8%. Plasma adiponectin concentrations were measured by competitive radioimunoassay (Linco Research, St. Charles, MO) with CV of 3.4%. Concentrations of HbA_{1c} (A1C) were based on turbidimetric immunoinhibition with hemolyzed whole blood or packed red cells with a CV of <3.0%.

Statistical analyses

A linear regression model was used to evaluate associations between dietary variables and plasma concentrations of inflammatory markers. To reduce within-subject variation and more accurately represent long-term diet, we used the average intake of nutrients from questionnaires collected close to blood draw (1986 and 1990). Dietary variables were analyzed in quintiles. Inflammatory markers were logarithmically transformed to achieve a normal distribution. Tests for linear trend were calculated by assigning median value for each quintile of intake and modeling this as a continuous variable. We adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, A1C, history of hypertension, history of hypercholesterolemia, postmenopausal hormone use, duration of diabetes, and medication use (oral antidiabetes medications and insulin use). We used the SAS statistical package for all analyses (SAS, Version 8.2 for UNIX; SAS Institute, Cary, NC). All *P* values are two sided.

RESULTS — Table 1 shows the age-adjusted characteristics at blood collection according to the intakes of whole grains and total fiber. Among 902 diabetic women, those in the highest quintiles of whole grains and total fiber had lower BMI, consumed less alcohol, engaged in more physical activity, and were less likely to be smokers than women in the lowest quintiles.

In multivariate analysis, we found a significant trend toward decreasing levels of CRP with increasing quintiles of both whole-grain (*P* for trend = 0.03) and bran intakes (*P* for trend = 0.007) (Table 2). In addition, high intake of whole grain was associated with a significantly decreasing trend of TNF-R2 levels (*P* for trend = 0.017). Women with high bran intake also tended to have lower TNF-R2 (*P* for trend = 0.06). Further adjustment for the duration of diabetes and medication use (oral antidiabetic medications and insulin use) did not appreciably change the associations.

In accordance with the association between whole grains and the inflammatory markers, increasing cereal fiber intake was also significantly associated with decreased plasma CRP (*P* for trend = 0.03) and TNF-R2 (*P* for trend = 0.01)

Table 2—*Inflammatory markers according to the quintiles of whole-grain, germ, and bran intakes

Variables	Quintiles					*P* for trend
	Q1	Q2	Q3	Q4	Q5	
Whole grain (*n*)	173	179	174	175	172	
Median (range)	4.75 (<7.3)	9.82 (7.3–12.5)	15.3 (12.7–17.9)	22.8 (18.0–27.6)	35.4 (>27.9)	
CRP (mg/l)	6.60	5.28	5.76	5.59	5.52	0.03
ICAM-1 (ng/ml)	316	317	314	312	306	0.19
E-selectin (ng/ml)	65.6	67.8	62.6	67.4	65.4	0.96
TNF-R2 (pg/ml)	2,647	2,552	2,571	2,439	2,435	0.017
Germ (*n*)	171	178	176	181	167	
Median (range)	1.15 (<1.3)	1.37 (1.3–1.47)	1.6 (1.5–1.7)	1.9 (1.72–2.1)	2.6 (>2.2)	
CRP (mg/l)	5.96	5.14	6.28	5.62	5.74	0.50
ICAM-1 (ng/ml)	305	318	315	316	311	0.66
E-selectin (ng/ml)	66.0	64.4	64.7	66.3	67.5	0.80
TNF-R2 (pg/ml)	2,559	2,573	2,530	2,492	2,498	0.28
Bran (*n*)	183	166	177	176	171	
Median (range)	1.6 (<2.2)	2.65 (2.2–3.27)	4.07 (3.3–4.87)	6.1 (4.9–7.97)	10.9 (>8.0)	
CRP (mg/l)	6.29	5.61	6.33	5.48	4.96	0.007
ICAM-1 (ng/ml)	319	316	323	304	303	0.11
E-selectin (ng/ml)	67.2	62.7	69.4	61.1	68.1	0.86
TNF-R2 (pg/ml)	2,603	2,597	2,491	2,495	2,462	0.06

*Associations were adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, A1C, history of hypertension or hypercholesterolemia, postmenopausal hormone use, glycemic index, and magnesium.

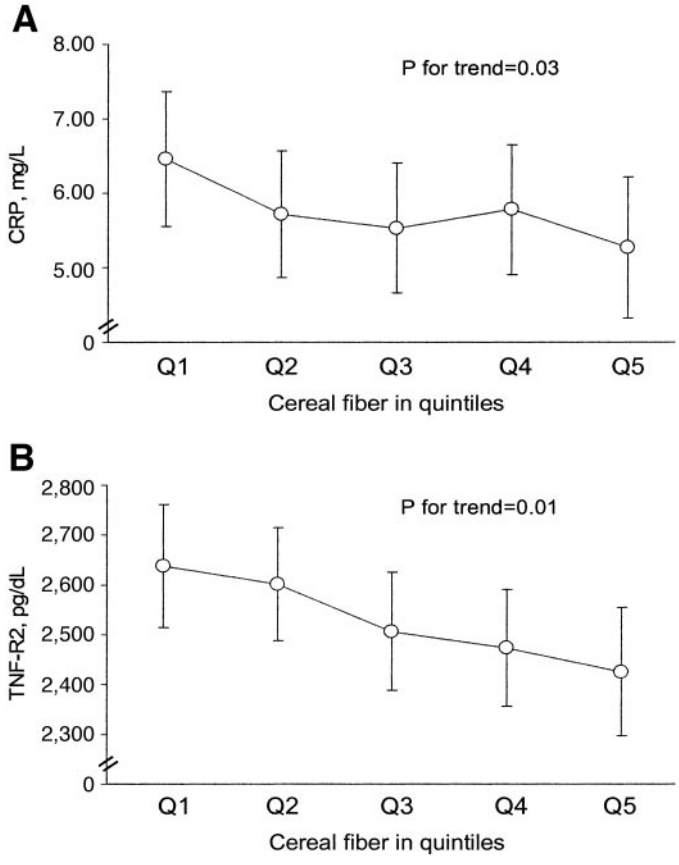

Figure 1—*The association of cereal fiber intake (in quintiles) with plasma concentrations of CRP (A) and TNF-R2 (B) among women with type 2 diabetes. The geometric means and SEs are presented.*

(Fig. 1). The concentrations of CRP and TNF-R2 were 18 and 8% lower, respectively, in the highest quintile of cereal fiber as compared with the lowest quintile. Intakes of total fiber and fiber from other foods including vegetable and fruit were not associated with CRP or TNF-R2 levels (data not shown). We did not find significant associations between whole grain, bran, and dietary fiber intakes with markers of endothelial dysfunction (ICAM-1 and E-selectin).

We also examined the associations of dietary glycemic load and glycemic index with inflammatory markers. High dietary glycemic index was associated with significantly increasing trend of CRP and TNF-R2 levels (*P* for trend = 0.04 and 0.0008, respectively) (Table 3). The concentrations of CRP and TNF-R2 were 32 and 11%, respectively, higher in the highest quintile of dietary glycemic index as compared with the lowest quintile. Although women with high glycemic load also tended to have higher concentrations of CRP and TNF-R2, the tests for trend were not significant. Dietary glycemic index and glycemic load were not associated with the levels of ICAM-1 and E-selectin.

CONCLUSIONS — We found that among women with type 2 diabetes, intakes of whole grains, bran, and cereal fiber were associated with significantly

Table 3—*Inflammatory markers according to the quintiles of dietary glycemic load and glycemic index**

Variables	Quintiles					*P* for trend
	Q1	Q2	Q3	Q4	Q5	
Glycemic load (*n*)	181	184	182	171	173	
Median (range)	77 (<84)	89 (84–92)	96 (93–99)	104 (100–108)	114 (>108)	
CRP (mg/l)	5.02	6.20	5.57	5.84	6.15	0.17
ICAM-1 (ng/ml)	301	307	314	316	327	0.13
E-selectin (ng/ml)	65.6	63.4	64.8	65	70.1	0.18
TNF-R2 (pg/ml)	2,417	2,573	2,446	2,627	2,594	0.08
Glycemic index (*n*)	179	176	179	172	185	
Median (range)	48.8 (<50.2)	51.2 (50.3–51.8)	52.5 (51.9–53.1)	53.9 (53.2–54.6)	55.7 (>54.7)	
CRP (mg/l)	5.05	5.25	6.55	5.15	6.68	0.04
ICAM-1 (ng/ml)	307	296	310	322	331	0.07
E-selectin (ng/ml)	64	65.4	68.1	65.7	65.5	0.66
TNF-R2 (pg/ml)	2,387	2,397	2,620	2,583	2,660	0.0008

*Associations were adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, A1C, history of hypertension or hypercholesterolemia, postmenopausal hormone use, dietary fibers, and magnesium.

lower levels of CRP and TNF-R2, after adjusting for age, BMI, lifestyle, and dietary covariates. In contrast, dietary glycemic index was associated with significantly higher CRP and TNF-R2 levels.

Little data are available about the effects of whole grain and dietary fiber on systemic inflammation among diabetic patients. Our finding that cereal fiber intake was associated with lower inflammatory markers is in line with recent observations among nondiabetic subjects, in whom dietary fiber intake was inversely associated with serum CRP concentration (11,12). The inverse association between dietary fiber and CRP was also observed among patients with multiple metabolic conditions (19). Our results indicate that cereal fiber may confer stronger effects than fibers from other food sources such as fruit and vegetable. Whole grain, especially bran, is the major source of cereal fiber. Therefore, the inverse association of whole grain and bran with the inflammatory markers is likely in part attributed to their fiber components.

Type 2 diabetes is associated with an accelerated rate of atherosclerosis and heightened systemic inflammation (8). The inflammatory process plays a pivotal role in the pathogenesis of atherosclerosis and is believed to be partly responsible for the increased cardiovascular diseases among diabetic patients (9,10). Elevated CRP concentrations independently predict cardiovascular disease in the general population (20) and among diabetic patients (21). TNF-R2, which reflects TNF system activation, is significantly elevated among patients with coronary heart disease (22) and type 2 diabetes (23). TNF-R2 has been significantly associated with coronary heart disease risk in this cohort of diabetic women (24).

It is possible that the inhibition of inflammation by whole grain and cereal fiber may be secondary to their effects on lowering glycemia. Such a postulation is partly supported by the observations that dietary glycemic index was positively related to the inflammatory markers. A similar effect of dietary glycemic index was also noted in a previous study among nondiabetic subjects (25). It has been suggested that hyperglycemia may modulate the release of proinflammatory cytokines (26,27). However, the observed effects of whole grain, bran, and cereal fiber were independent of dietary glycemic index, suggesting that additional mechanisms may be involved. We recently found that cereal fiber intake, dietary glycemic index, and glycemic load were associated with the levels of blood adiponectin in diabetic patients (28). It has been documented that adiponectin has profound anti-inflammatory effects (29). Nevertheless, further adjustment for adiponectin did not significantly change the association (data not shown).

In conclusion, we found that consumption of whole grains and cereal fiber was associated with lower inflammatory markers among diabetic patients. In contrast, high dietary glycemic index was associated with higher inflammatory markers. Our results support the recommendation that patients with type 2 diabetes should increase intake of whole grain products and maintain a diet low in glycemic index. Because of the observational nature of this study, we cannot claim causality. Further clinical trials are needed to test the potential benefits of these dietary factors among patients with type 2 diabetes.

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