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

LU QI, MD, PHD1,2
ROB M. VAN DAM, PHD1
SIMIN LIU, MD, PHD3

MARY FRANZ, MS1
CHRISTOS MANTZOROS, MD, PHD4
FRANK B. HU, MD, PHD1,2,3

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 = 0.17 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 compared with the lowest quintile. Dietary glycemic index was positively associated with CRP (P for trend = 0.04) and TNF-R2 (P for trend = 0.008) levels. The concentrations of CRP and TNF-R2 were 32% and 11% higher, respectively, in the highest quintile of dietary glycemic index 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.

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 diabetestes 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 semi-quantitative food-frequency questionnaires. Participants were asked to report their average frequency of consumption of selected foods and beverages with a...
specifed 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. In addition, high intake of whole grain was associated with a significantly decreasing trend of TNF-R2 levels (P for trend = 0.007) (Table 2). In 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)

### Fiber intakes, glycemic index, and inflammation

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole grain, quintiles</th>
<th>Total fiber, quintiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q3</td>
</tr>
<tr>
<td>n</td>
<td>173</td>
<td>174</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.9</td>
<td>29.8</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>18.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>4.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Physical activity (MET/week)</td>
<td>17.6</td>
<td>39.5</td>
</tr>
<tr>
<td>Family history of coronary heart disease (%)</td>
<td>23.5</td>
<td>20.1</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>45.1</td>
<td>41.5</td>
</tr>
<tr>
<td>History of hypercholesterolemia (%)</td>
<td>42.0</td>
<td>42.8</td>
</tr>
<tr>
<td>Oral diabetes medication (%)</td>
<td>16.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Insulin use (%)</td>
<td>15.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Postmenopausal status (%)</td>
<td>75.9</td>
<td>84.3</td>
</tr>
<tr>
<td>Current hormone use among postmenopausal women (%)</td>
<td>25.2</td>
<td>36.7</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5.0</td>
<td>6.1</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.0</td>
<td>7.1</td>
</tr>
</tbody>
</table>

*Data were from 1990 questionnaire; medication status and physical activity was from 1988 questionnaire.

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)
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
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 glycaemia. 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.

Acknowledgments—This study was supported by research grants (HL65582, HL34594, DK38845, and CA87969) from the National Institutes of Health. Dr. Hu is partially supported by an American Heart Association Established Investigator Award.

References

7. Jenkins DJ, Kendall CW, Augustin LS,


