Dietary Fibers and Glycemic Load, Obesity, and Plasma Adiponectin Levels in Women With Type 2 Diabetes

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OBJECTIVE — The purpose of this study was to examine the associations of dietary fibers and glycemic load with plasma adiponectin in diabetic women and investigate the modification effect of obesity.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional analysis in 902 women with type 2 diabetes from the Nurses' Health Study. Dietary information was obtained using semiquantitative food frequency questionnaires.

RESULTS — After adjustment for age, smoking, alcohol consumption, physical activity, aspirin use, HbA_{1c}, history of hypertension and hypercholesterolemia, and postmenopausal hormone use, intakes of cereal fiber and fruit fiber (*P* for trend = 0.002 and 0.036, respectively) were significantly associated with an increasing trend of plasma adiponectin concentrations. Further adjustment for BMI did not appreciably change the associations for cereal fiber but attenuated the associations for fruit fiber. Adiponectin concentrations were 24% higher in the highest compared with the lowest quintile of cereal fiber. Dietary glycemic load and glycemic index were significantly associated with lower plasma adiponectin levels, after adjustment for BMI and other covariates (*P* for trend = 0.01 and 0.03, respectively). The percent differences in adiponectin concentration between the highest and the lowest quintiles of dietary glycemic load and glycemic index were 17 and 18%, respectively. The associations between dietary factors and plasma adiponectin were consistent across lean (BMI <25 kg/m^2), overweight ($25 \leq$ BMI <30 kg/m^2), and obese subjects (BMI ≥ 30 kg/m^2).

CONCLUSIONS — Our data indicate that dietary cereal fiber and glycemic load/index are associated with the circulating adiponectin concentration. Such associations were not modified by obesity status.

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Adiponectin is an adipose-secreted cytokine that circulates at a high concentration in blood (1). It is well documented that adiponectin improves insulin sensitivity through reducing blood free fatty acids, enhancing insulin action, stimulating glucose utilization, increasing hepatic fatty acid oxidation, and decreasing hepatic fatty acid synthesis (2–5). Plasma adiponectin concentrations have been inversely associated with the risks of diabetes and cardiovascular diseases in the general population (6,7). Circulating adiponectin was found to be associated with a better lipid profile, better glycemic control, and reduced inflammation in diabetic patients from our cohorts (8,9) and another population (10). Furthermore, we have found that both blood adiponectin concentrations and the variability in the adiponectin gene might affect the risk of diabetes-related cardiovascular diseases (11,12). These data together suggest that adiponectin is an important target for management of diabetes, especially in regard to cardiovascular complications.

Recently, we found that dietary cereal fiber and glycemic load were associated with plasma adiponectin in diabetic men (13). A previous study had documented that blood adiponectin levels were different in women and men (14). We sought to investigate whether the same dietary factors influencing plasma adiponectin in men also affect women. In addition, plasma adiponectin is negatively associated with obesity (15). We suspect the obesity status may modulate the relations between dietary factors and adiponectin levels.

To address these issues, we examined the associations of dietary fibers, glycemic load, and glycemic index with plasma adiponectin concentration among diabetic women from the Nurses' Health Study (NHS). The modulation effects of obesity status on these associations were particularly investigated.

RESEARCH DESIGN AND METHODS

— The NHS began in 1976 with the recruitment of 121,700 female registered nurses between the ages of 30 and 55 years. Between 1989 and 1990, 32,826 women provided blood. The cases of type 2 diabetes were defined as self-reported diabetes confirmed by a supplementary questionnaire. We used National Diabetes Data Group criteria to define diabetes because diabetes in our subjects was diagnosed before the release of the American Diabetes Association criteria in 1997 (16). The validity of this method has been confirmed (17). A case of diabetes was considered if at least one

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Abbreviations: FFQ, food frequency questionnaire; NHS, Nurses' Health Study.

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

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Table 1—*Characteristics according to the quintiles of plasma adiponectin concentration (μg/ml)*

Variables	Plasma adiponectin quintiles					*P* value*
	Q1	Q2	Q3	Q4	Q5	
n	173	180	185	179		
Adiponectin	2.3 (<3.2)	3.9 (3.2–4.6)	5.6 (4.7–6.3)	8.1 (6.4–10.1)	16.9 (≥10.2)	
Age (years)	56	59	60	58	58	0.08
BMI (kg/m^2)	31.9	31.3	30.6	29.9	26.3	<0.001
Alcohol consumption (g/day)	3.2	2.4	2.3	3.4	2.4	0.79
Physical activity (MET/week)	10.2	12.6	12.6	14.1	16.1	<0.001
A1C (%)	7.0	7.0	6.9	6.6	7.1	0.91
Current smoker (%)	17.3	13.3	14.0	8.9	11.3	0.36
Family history of coronary heart disease (%)	23.7	22.8	25.4	20.1	23.8	0.80
History of hypertension (%)	46.8	45.0	49.1	40.2	34.6	0.03
History of hypercholesterolemia (%)	38.7	37.8	46.5	38.5	39.5	0.39
Postmenopausal (%)	66.9	84.2	86.0	78.7	79.2	0.004

Data are median (range) or mean. Data are from the 1990 questionnaire; physical activity data are from 1988 questionnaire. *Linear regression model was used to test trend for continuous variables; χ^2 test was used for the categorical variables.

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. This cross-sectional analysis included the 902 diabetic women who were free of cardiovascular diseases at blood draw and were measured for plasma adiponectin.

Assessment of dietary intakes

Detailed dietary information was obtained through the use of semiquantitative food frequency questionnaires (FFQ). Participants were asked to report their average frequency of consumption of selected foods and beverages with a specified commonly used unit or portion size during the previous year. The reproducibility and validity of the dietary questionnaires were described previously (18,19). Briefly, the FFQ was administered twice to 173 nurses aged 34–59 years at an interval of ~1 year (1980–1981), and four 1-week diet records for each subject were collected during that period. High correlation coefficients between the FFQ and multiple 7-day diet records were observed for carbohydrate-rich food items and foods with high as well as low glycemic indexes including white bread (0.71), dark bread (0.77), potatoes (0.66), cold breakfast cereal (0.79), cola beverages (0.84), apples (0.80), orange juice (0.84), yogurt (0.94), broccoli (0.69), peanut butter (0.75), and fiber (0.56). We calculated glycemic load by multiplying the carbohydrate content of each food by its glycemic index (the blood glucose response to glucose was used as a standard 100) and 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 (20). Dietary fibers, glycemic index, and glycemic load were energy-adjusted using the residual method (21). To reduce within-subject variation and more accurately represent long-term diet, we used the cumulative average of nutrients from all available questionnaires up to blood draw.

Assessment of plasma adiponectin and covariates

Plasma adiponectin concentrations were measured by competitive radioimmunoassay (Linco Research, St. Charles, MO) with a coefficient of variation of 3.4%. It had previously been demonstrated that adiponectin measurement has excellent intraclass correlation coefficients (as measured in participants over a 1-year period) that were not substantially affected by transport conditions (22). Anthropometric data and lifestyle factors were derived from the 1990 questionnaire that was most close to blood collection. BMI was calculated as weight in kilograms divided by the square of height in meters. Physical activity was expressed as metabolic equivalent task hours based on self-reported types and durations of activities over the previous year.

Statistical analyses

Dietary intake variables were analyzed in quintiles. A linear regression model was used to evaluate associations between dietary intakes and plasma adiponectin concentration. Tests for linear trend were calculated by assigning a median value for each quintile of intake and treated as continuous variables. Plasma adiponectin was logarithmically transformed to achieve a normal distribution. We adjusted for the potential confounding variables: age, BMI, smoking, alcohol consumption, physical activity, HbA_{1c} (A1C), history of hypertension, history of hypercholesterolemia, and postmenopausal hormone use. The effect modifications of obesity status (lean, BMI <25 kg/m^2; overweight, 25 ≤ BMI <30 kg/m^2; and obese, BMI ≥30 kg/m^2) on dietary factors were tested by introduction of a cross-product term into the model. 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 — The participant characteristics at blood collection by the quintiles of plasma adiponectin are shown in Table 1. Women in the highest quintile were leaner, engaged in more physical activity, and were less likely to have had a history of hypertension at baseline than those in the lowest quintile of plasma adiponectin.

Among the types of dietary fiber, we found that the intakes of cereal fiber (*P* for trend = 0.002) and fruit fiber (*P* for trend = 0.036) were significantly associated with an increasing trend of plasma adiponectin concentrations, adjusting for age, smoking, alcohol consumption,

Table 2—*Adjusted associations between dietary fibers (g/day) and plasma adiponectin

	Quintiles*					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total fiber	15.6 (166)	18.9 (158)	21.6 (139)	24.8 (156)	30.9 (138)	
Range	<17.6	17.6–20.3	20.3–23.1	23.2–27.1	≥27.2	
Without BMI	6.9	7.3	7.3	8.0	7.7	0.15
With BMI	7.0	7.5	7.5	7.6	7.6	0.34
Cereal fiber	3.5 (159)	5.0 (148)	6.2 (162)	7.5 (143)	10.0 (142)	
Range	<4.4	4.4–5.6	5.6–6.9	6.9–8.6	≥8.6	
Without BMI	6.7	7.1	7.1	8.1	8.3	0.002
With BMI	6.9	7.3	7.2	8.0	7.9	0.01
Vegetable fiber	4.1 (160)	5.8 (151)	6.9 (151)	8.5 (151)	11.6 (144)	
Range	<5.1	5.1–6.3	6.3–7.7	7.7–9.6	≥9.6	
Without BMI	7.6	7.9	7.5	7.2	7.0	0.12
With BMI	7.6	8.0	7.5	7.1	7.2	0.16
Fruit fiber	1.8 (160)	3.3 (160)	4.7 (153)	6.0 (144)	8.5 (140)	
Range	<2.6	2.6–4.0	4.0–5.3	5.3–6.9	≥6.9	
Without BMI	6.7	7.5	6.8	8.0	8.3	0.036
With BMI	6.8	7.5	6.9	8.0	8.2	0.06

Data are median (*n*) unless otherwise indicated. *Adjusted for age, smoking, alcohol consumption, physical activity, A1C, history of hypertension or hypercholesterolemia, and postmenopausal hormone use.

physical activity, aspirin use, A1C, history of hypertension and hypercholesterolemia, and postmenopausal hormone use (Table 2). Further adjustment for BMI did not appreciably change the associations for cereal fiber but attenuated the associations for fruit fiber to be nonsignificant. Adiponectin concentrations were 24% higher in the highest compared with the lowest quintile of cereal fiber. The intakes of total fiber and vegetable fiber were not significantly associated with adiponectin concentrations.

In the models without adjustment for BMI, dietary glycemic load and glycemic index were not significantly associated with plasma adiponectin (*P* for trend = 0.06 and 0.12, respectively). After further adjustment for BMI, both dietary glycemic load (*P* for trend = 0.01) and glycemic index ($P = 0.03$) were associated with a significantly decreasing trend of plasma adiponectin (Fig. 1). The percent differences in adiponectin concentrations between the highest and the lowest quintiles of dietary glycemic load and glycemic index were 17 and 18%, respectively.

There was no significant effect modification by obesity status (lean, BMI <25 kg/m^2; overweight, 25 ≤ BMI <30 kg/m^2; and obese, BMI ≥30 kg/m^2) on the associations between dietary factors and plasma adiponectin levels ($P > 0.05$). When the joint effects of dietary factors and adiposity were examined (Fig. 2), we found that individuals who were lean and had either the highest intake of cereal fiber or the lowest glycemic load had the highest plasma adiponectin levels, whereas those who were obese and had either the lowest cereal fiber intake or the highest glycemic load had the lowest

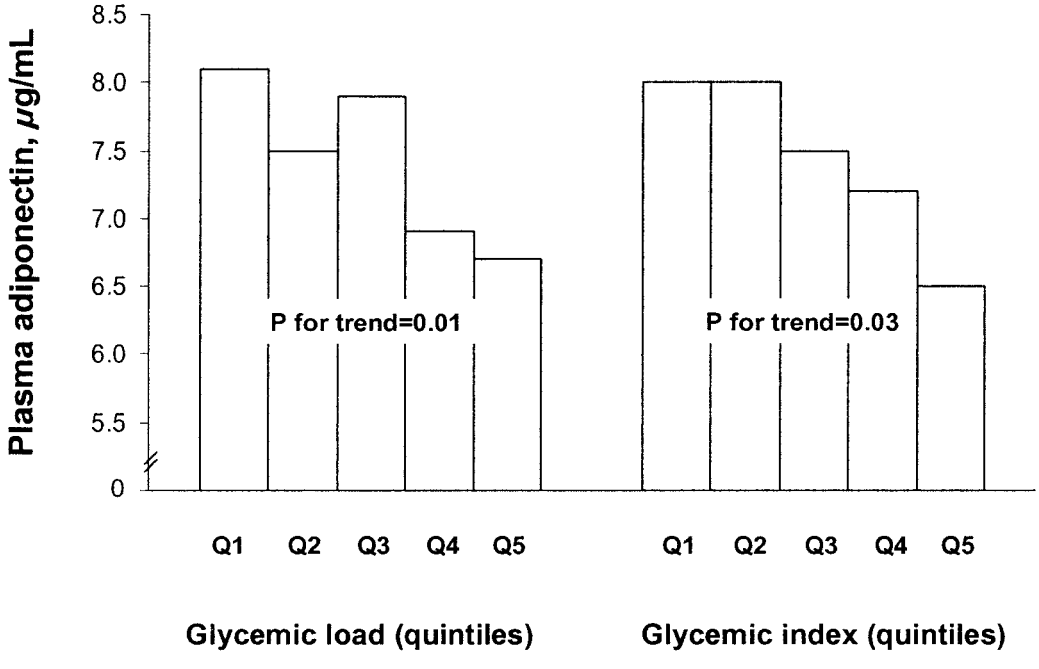

Figure 1—*Geometric means of plasma adiponectin concentration by quintiles of dietary glycemic load and glycemic index. The analyses were adjusted for age, smoking, alcohol consumption, physical activity, aspirin use, A1C, history of hypertension and hypercholesterolemia, postmenopausal hormone use, and BMI.*

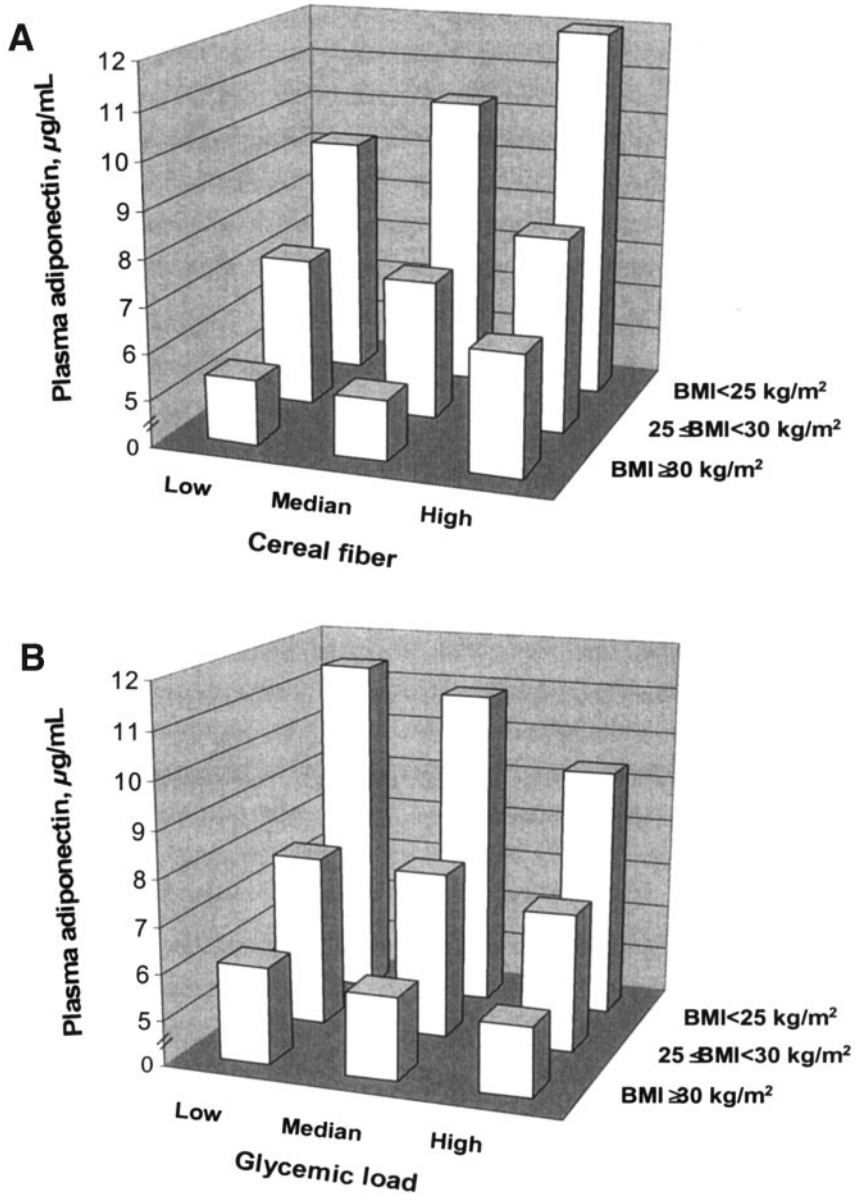

Figure 2—*Adjusted plasma adiponectin according to joint classifications of dietary cereal fiber* (A)*, glycemic load* (B)*, and obesity status in lean (BMI <25 kg/m^2), overweight (25 ≤ BMI <30 kg/m^2), and obese subjects (BMI ≥30 kg/m^2). The analyses were adjusted for age, smoking, alcohol consumption, physical activity, aspirin use, A1C, history of hypertension and hypercholesterolemia, and postmenopausal hormone use.*

plasma adiponectin. It appears that the increment of adiponectin levels associated with higher cereal fiber intake or lower glycemic load cannot counteract the reduction in plasma adiponectin caused by excess weight and obesity.

CONCLUSIONS — In this cross-sectional analysis of 902 diabetic women, intake of cereal fiber was associated with significantly higher plasma adiponectin levels. Dietary glycemic load and glycemic index were inversely associated with adiponectin concentrations. These associations were independent of BMI and other covariates. The obesity status did not modify the relations between dietary factors and plasma adiponectin. In addition, higher intake of cereal fiber and lower glycemic load did not counteract the increase in adiponectin levels conferred by excess weight and obesity.

Little is known about the effects of habitual intake of specific dietary components on blood adiponectin in humans. Recently, Pischon et al. (23) examined the predictive roles of dietary components on plasma adiponectin among healthy men in the Health Professional Follow-up Study (HPFS) cohort. They found that a carbohydrate-rich diet with a high glycemic load was associated with lower adiponectin concentrations. In an earlier analysis, we found that intake of dietary cereal fiber was associated with a higher concentration of plasma adiponectin whereas dietary glycemic load and glycemic index were inversely associated with adiponectin concentration in men with type 2 diabetes (13). The associations observed in diabetic women are highly consistent with those we found in diabetic men.

The dietary factors (fibers and glycemic load/index) may affect plasma adiponectin through modulation of blood glucose, because a diet rich in some types of fiber could lower glucose concentrations (24), whereas a diet high in glycemic load/index may increase blood glucose (25,26). Blood glucose has been inversely correlated with the expression of adiponectin in adipose tissue (27). By contrast, a glucose-enriched diet markedly reduces adiponectin expression in adipose tissue (28). Of note, a recent study suggested that glycemic index and glycemic load may not reflect the glycemic response to food adequately because numerous factors influencing the effect of a food on blood glucose levels may not be captured by these measures (29). This suggests that other mechanisms may also underlie the observed associations between dietary glycemic load/index and adiponectin levels.

Circulating adiponectin concentrations are reduced in obese individuals (15). Adjustment for BMI slightly attenuated the associations between dietary fibers (cereal fiber and fruit fiber) and plasma adiponectin but somewhat improved the associations between dietary glycemic load/index and adiponectin levels. These observations suggest that the change in adiposity or related factors may partly mediate the effects of dietary fibers on plasma adiponectin but not the effects of glycemic load/index. In addition, our data indicate that obesity status did not modify the associations between dietary factors and plasma adiponectin.

We used multiple measurements for dietary intakes that not only reduce measurement error but also provide the unique opportunity to evaluate the effects of long-term intake. However, the cross-

sectional nature of our study does not allow us to make a causal inference.

In summary, we found that intake of cereal fiber was associated with higher adiponectin concentrations in diabetic women. In contrast, dietary glycemic load and glycemic index were inversely associated with plasma adiponectin concentrations. The results, together with our earlier findings in diabetic men (13), strongly indicate that dietary cereal fiber and glycemic load/index may be important determinants for the blood concentrations of adiponectin in patients with type 2 diabetes. Further studies, especially controlled clinical trials and experimental studies, are warranted to confirm our findings as well as to elucidate the underlying mechanisms.

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