Dietary Glycemic Index, Glycemic Load, Cereal Fiber, and Plasma Adiponectin Concentration in Diabetic Men

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OBJECTIVE — Adiponectin may improve insulin sensitivity, reduce inflammation, and ameliorate glycemic control. However, few studies have evaluated dietary predictors of plasma adiponectin levels, especially among subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — To examine the associations of dietary glycemic load, glycemic index, and fibers with plasma adiponectin levels, we conducted a cross-sectional analysis in 780 diabetic men from the Health Professionals' Follow-up Study. Dietary information was obtained in 1986, 1990, and 1994 using semiquantitative food-frequency questionnaires.

RESULTS — After adjustment for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, HbA_{1c}, history of hypertension or hypercholesterolemia, and fiber intake, dietary glycemic index and glycemic load were inversely associated with plasma adiponectin in a dose-dependent fashion (P for trend = 0.005 for glycemic index and 0.004 for glycemic load). Adiponectin levels were 13% lower in the highest quintile of dietary glycemic index than in the lowest quintile. For dietary glycemic load, adiponectin levels were 18% lower in the highest quintile than in the lowest. In contrast, high intake of cereal fiber was associated with increased plasma adiponectin levels, adjusting for lifestyle factors and dietary glycemic load (P for trend = 0.003). Adiponectin levels were 19% higher in the highest quintile than in the lowest quintile. Higher magnesium intake was also associated with increased plasma adiponectin.

CONCLUSIONS — Diets low in glycemic load and high in fiber may increase plasma adiponectin concentrations in diabetic patients.

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Dietary glycemic index and load have been shown to predict risk of type 2 diabetes in healthy populations and also play a role in glycemic control among patients with diabetes (1–3). Meanwhile, several clinical studies have documented that a high-fiber diet substantially ameliorated metabolic abnormalities in diabetic patients by lowering fasting and postprandial levels of glucose and insulin and by improving blood lipids (4,5).

The precise mechanism underlying the protective effects of glycemia-related dietary factors is not yet known. The fact that dietary glycemic measures and fiber intake may also affect body fat (6,7) gives rise to a hypothesis that the dietary effects may be in part mediated by adipose-related pathways. It has been recognized that adipose tissue acts as an endocrine organ and plays pivotal roles in regulating whole-body metabolism by releasing bioactive molecules. Adiponectin is a newly identified adipose-secreted cytokine that presents at low plasma level in subjects with type 2 diabetes (8). Experimental and epidemiological studies have provided abundant evidence that adiponectin not only improves insulin sensitivity, but also has potent antiatherosclerotic effects (rev. in 9). Circulating adiponectin levels have been inversely associated with levels of fasting glucose and total–to–LDL cholesterol ratio and have been positively associated with HDL cholesterol in diabetic patients (10,11).

Several short-term human trials indicate that a diet rich in fiber could increase adiponectin concentration (12,13), whereas a diet with high glycemic index might adversely affect plasma adiponectin level in animal models (14). However, no study has investigated the long-term effects of diet on adiponectin levels. Recently, we found adiponectin level was associated with better glycemic control, improved lipid profiles, and reduced inflammation in diabetic subjects (15). In this study we examined the associations of dietary glycemic index, glycemic load, and fiber intakes with plasma adiponectin concentration among diabetic men in the Health Professionals' Follow-up Study (HPFS).

RESEARCH DESIGN AND METHODS

— HPFS is a prospective cohort study of 51,529 American male health professionals aged 40–75 years at study initiation in 1986. Information about health and disease is assessed biennially by self-administered questionnaires. Between 1993 and 1999 (with the majority from 1993 to 1994), 18,159 study participants provided blood samples. Among participants who returned

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Abbreviations: HPFS, Health Professionals' Follow-up Study.

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

blood samples, 999 had a confirmed diagnosis of type 2 diabetes (as reported on a supplementary questionnaire sent to all men who reported a diagnosis of diabetes) at baseline or during follow-up through 1998. Our study included the 780 diabetic men who were free of fatal coronary heart disease, nonfatal myocardial infarcation, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, fatal stroke, and nonfatal stroke at blood draw.

Diabetes status was confirmed when at least one of the following criteria of the National Diabetes Data Group was met: *1*) fasting plasma glucose ≥7.8, random plasma glucose ≥11.1, and/or plasma glucose ≥11.1 mmol/l after ≥2 h during an oral glucose tolerance test, together with at least one classic symptom (excessive thirst, polyuria, weight loss, or hunger); *2*) no symptoms but at least two elevated plasma glucose concentrations (by the above criteria) on different occasions; or *3*) taking hypoglycemic medication (insulin or oral hypoglycemic agent). Because most of our subjects were diagnosed before the release of the American Diabetes Association criteria in 1997 (16), we used National Diabetes Data Group criteria to define diabetes instead. The validity of self-reported diabetes using the supplementary questionnaire has previously been documented in a subsample (17).

Assessment of dietary factors

Detailed dietary information was obtained in 1986, 1990, and 1994 using semiquantitative food-frequency questionnaires. The questionnaires assess the average frequency of various foods over the previous year. For each man, we calculated energy and nutrient intakes by multiplying the frequency with which each food item was reported by the energy or nutrient content for the specified portion size. The food composition values were obtained from the Harvard University Food Composition Database derived from the U.S. Department of Agriculture sources. The validity of the food-frequency questionnaire was evaluated in a random sample of 127 men from the HPFS living in the Boston area. In that study, nutrient intakes computed from the questionnaire were compared with nutrient intakes from two 1-week diet records 6 months apart. The food-frequency questionnaire was found to be a reasonably accurate measure of intake of carbohydrates ($r = 0.69$), dietary fiber ($r = 0.64$), and magnesium ($r = 0.66$) after within-person variation was taken into account (18). 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 (19). Intake of carbohydrates and fats was expressed as nutrient density (% of total energy intake), while dietary glycemic index, glycemic load, and fiber were energy adjusted using the residual method.

Assessment of plasma adiponectin and covariates

Blood sample collection and treatment were previously described (15). Plasma adiponectin concentrations were measured by competitive radioimunoassay (Linco Research, St. Charles, MO) with a coefficient of variation of 3.4% (20). It has 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 (20). The measurement of other biochemical variables is described in detail elsewhere (21). Anthropometric data and lifestyle factors were derived from the 1986 questionnaire. 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

Linear regression model was used to evaluate associations between dietary intakes and plasma adiponectin concentration, which was logarithmically transformed to achieve a normal distribution. 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 (1986, 1990, and 1994). Dietary intake variables were analyzed in quintiles. Tests for linear trend were calculated by assigning median value for each quintile of intake and treated as continuous variables. We adjusted for the potential confounding variables: age, BMI, smoking, alcohol consumption, physical activity, history of hypertension, history of hypercholesterolemia, and magnesium intake. We also tested for effect modifications by BMI (dichotomized by cutoff 30 kg/m^2), physical activity (dichotomized by median), and alcohol consumption (<5 g/day and ≥5 g/day). 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 by quintiles of plasma adiponectin are shown in Table 1. Compared with men in the lowest quintiles of plasma adiponectin, those in the highest quintile were older and leaner and more likely to consume alcohol, engage in physical activity, and use insulin but less likely to have a history of hypertension, hypercholesterolemia, and family history of myocardial infarction. Participants in the highest quintile of plasma adiponectin tended to have higher intakes of total fiber, cereal fiber, and fruit fiber. The dietary glycemic load did not differ substantially between the lowest and highest adiponectin groups (Table 1).

There was a trend toward decreasing plasma concentration of adiponectin with increasing quintiles of glycemic index of diet after adjusting for age ($P = 0.046$). Adjustment for BMI, smoking, alcohol consumption, physical activity, aspirin use, HbA_{1c}, and history of hypertension or hypercholesterolemia strengthened this association (P for trend = 0.015), and additional adjustment for the fiber intake further strengthened the association (P for trend = 0.005). Adiponectin levels were 13% lower in the highest quintile of glycemic index than in the lowest quintile. We found a similar positive association between dietary glycemic load and plasma adiponectin levels, which remained significant when potential confounders and fiber intake were included in a multivariate model (P for trend = 0.004). Adiponectin levels were 18% lower in the highest quintile than in the lowest. The associations observed with dietary glycemic index and glycemic load remained significant with further adjustment for intake of magnesium (P for trend = 0.028 for glycemic index and 0.006 for glycemic load) (Table 2). We also found a strong positive association between cereal fiber intake and plasma

Table 1—*Baseline characteristics and dietary intakes according to plasma adiponectin levels*

	Plasma adiponectin quintiles				
	Q1 (n = 162)	Q2 (n = 162)	Q3 (n = 150)	Q4 (n = 160)	Q5 (n = 145)
Adiponectin (μg/ml)	7.2 (<9.3)	10.8 (9.3–12.5)	14.2 (12.5–16.3)	18.5 (16.4–21.3)	26.5 (≥21.5)
Age (years)	53 ± 8	55 ± 8	55 ± 9	57 ± 7	58 ± 8
BMI (kg/m^2)	28.4 ± 4.2	28.5 ± 3.7	28.0 ± 4.2	27.4 ± 4.0	26.1 ± 3.6
Current smoker (%)	7.5	13.5	13.2	13.2	14.0
Alcohol consumption (g/day)	8.2 ± 13.4	11.0 ± 18.9	8.7 ± 14.3	13.8 ± 19.0	12.1 ± 15.9
Physical activity (h/week)	13.7 ± 23.1	14.3 ± 16.5	14.4 ± 21.2	14.5 ± 18.8	14.8 ± 15.8
Family history of myocardial infarction (%)	17.9	14.2	11.3	9.4	8.3
History of hypertension (%)	37.6	37.0	36.7	31.2	27.6
History of hypercholesterolemia (%)	20.4	14.2	12.0	13.7	12.4
Current aspirin use (%)	30.9	29.6	33.3	34.4	31.0
Insulin use (%)	10.5	8.6	17.3	20.0	29.7
HbA_{1c} (%)	7.2	7.4	7.3	7.5	7.2
Diet					
Total fat (% of energy)	32.5 ± 5.1	33.3 ± 5.4	33.4 ± 5.8	33.0 ± 5.0	32.3 ± 5.5
Saturated fat (% of energy)	10.9 ± 2.1	11.3 ± 2.3	11.3 ± 2.4	11.2 ± 2.4	10.9 ± 2.3
Polyunsaturated fat (% of energy)	6.0 ± 1.3	6.0 ± 1.3	6.0 ± 1.3	5.9 ± 1.2	5.8 ± 1.2
Monounsaturated fat (% of energy)	12.6 ± 2.2	12.9 ± 2.3	13.0 ± 2.5	12.9 ± 2.1	12.6 ± 2.5
Trans-fat (% of energy)	1.4 ± 0.5	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4
Cholesterol (mg/day)	301 ± 103	304 ± 111	304 ± 121	318 ± 121	297 ± 141
Total protein (% of energy)	19.4 ± 2.8	19.1 ± 2.6	19.2 ± 2.7	19.2 ± 2.7	19.0 ± 2.6
Carbohydrate (% of energy)	47.3 ± 6.5	46.0 ± 6.3	46.6 ± 7.0	45.4 ± 6.9	47.0 ± 7.0
Total fiber (g/day)	21.7 ± 5.9	21.6 ± 5.9	21.9 ± 6.0	22.2 ± 5.9	23.7 ± 6.4
Cereal fiber (g/day)	6.3 ± 2.6	6.3 ± 2.6	6.4 ± 3.1	6.8 ± 3.4	7.1 ± 3.1
Fruit fiber (g/day)	4.8 ± 2.6	4.7 ± 2.7	4.6 ± 2.6	4.5 ± 2.2	5.5 ± 2.8
Vegetable fiber (g/day)	7.3 ± 2.9	7.4 ± 2.9	7.1 ± 3.1	7.5 ± 2.9	7.6 ± 3.2
Magnesium (mg/day)	373 ± 64	368 ± 69	368 ± 69	385 ± 68	380 ± 37
Glycemic index	53.0 ± 2.8	52.5 ± 2.7	52.6 ± 2.9	52.5 ± 2.5	52.0 ± 2.7
Glycemic load	125 ± 19	121 ± 19	123 ± 21	119 ± 21	122 ± 20

Data are median (range) or means ± SD.

adiponectin levels after adjusting for age, BMI, and lifestyle factors (P for trend = 0.043). Such an association became more significant when dietary glycemic load was added to the model (P for trend = 0.003). Adiponectin levels were 19% higher in the highest quintile than in the lowest quintile of cereal fiber. However, further adjustment for magnesium intake somewhat attenuated the association. There were no significant associations between intakes of total fiber, vegetable fiber, and fruit fiber and plasma adiponectin levels. A significantly positive association was found between magnesium intake and adiponectin after adjusting for nondietary variables (P for trend = 0.011). Such a relation remained significant even when other dietary factors (glycemic load and cereal fiber) were adjusted for (Table 3).

We further examined the joint effects of cereal fiber intake and dietary glycemic load or glycemic index on plasma adiponectin concentration. Individuals with the highest intake of cereal fiber and lowest glycemic load had the highest plasma adiponectin levels, whereas those with the lowest cereal fiber intake and the highest glycemic load had the lowest levels. The difference in plasma adiponectin between these two groups was 3.7 μg/ml (P = 0.0097) (Fig. 1). A similar joint effect was also observed for cereal intake and dietary glycemic index, with a difference of 3.3 μg/ml in adiponectin level between the two extreme groups (P = 0.035).

We also found that the associations of dietary glycemic load and glycemic index with plasma adiponectin were largely consistent across the strata of BMI (30 kg/m^2 as cutoff), physical activity (low and high), and alcohol consumption (5 g/day as cutoff) (data not shown). However, we found that BMI and physical activity modified the effects of cereal fiber intake (P for interactions = 0.047 for BMI and 0.037 for physical activity). The positive association between intake of cereal fiber and plasma adiponectin was stronger in individuals with lower BMI (P for trend = 0.005) or with higher physical activity (P for trend = 0.002) than those with higher BMI or lower physical activity (both were not significant).

CONCLUSIONS — In this cross-sectional analysis of 780 diabetic men, high dietary glycemic index and glycemic load were associated with lower levels of plasma adiponectin in a dose-dependent fashion. In contrast, high intake of cereal fiber and magnesium were associated with higher levels of plasma adiponectin concentration. These associations were independent of age, BMI, smoking, alcohol consumption, physical activity, history of hypertension, and history of hypercholesterolemia. Our results also indicate that the adiponectin-modulation effects of dietary glycemic index and gly-

Table 2—*Plasma adiponectin concentration according to quintiles of carbohydrate intake,* glycemic index, and glycemic load*

	Quintiles					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Carbohydrate	37.9 (163)	43.2 (153)	46.9 (156)	50.3 (147)	55.6 (138)	
Range	<40.6	40.6–45.0	45.1–48.5	48.5–52.6	≥52.6	
Model 1	16.1	15.5	15.0	15.6	15.6	0.231
Model 2	16.1	15.6	15.3	15.6	15.6	0.242
Model 3	15.9	15.3	15.3	15.7	15.9	0.253
Model 4	16.3	15.5	15.2	15.6	15.5	0.613
Glycemic index	49.2 (151)	51.3 (152)	52.5 (157)	54.0 (149)	56.0 (148)	
Range	<50.4	50.4–51.9	51.9–53.3	53.3–54.9	≥54.9	
Model 1	15.9	16.3	15.7	15.5	14.5	0.046
Model 2	16.1	16.7	15.7	15.1	14.4	0.015
Model 3	16.4	16.9	15.7	14.9	14.3	0.005
Model 4	16.2	16.7	15.8	15.0	14.5	0.028
Glycemic load	97 (160)	112 (154)	123 (156)	133 (149)	149 (138)	
Range	<105	105–118	118–128	129–140	≥140	
Model 1	16.1	15.2	15.9	15.2	15.4	0.144
Model 2	16.2	15.3	16.4	15.2	14.9	0.067
Model 3	17.2	15.5	16.2	15.0	14.1	0.004
Model 4	17.2	15.5	16.1	15.1	14.2	0.006

Data are median (*n*). Model 1: adjusted for age; model 2: adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, HbA_{1c}, and history of hypertension or hypercholesterolemia; model 3: in addition to the variables adjusted in model 2, further adjusted for the dietary factors (total energy intake, glycemic load, and fibers) that were not examined as the primary independent variable; model 4: in addition to variables adjusted in model 3, further adjusted for magnesium.*Presented as percent of total energy.

cemic load were independent of fiber and magnesium intakes, and vice versa. Because cereal fiber and magnesium share similar food sources such as whole grains, it is difficult to tease out the independent effects of these nutrients on adiponectin levels. In addition, lower BMI and higher physical activity levels appeared to enhance the beneficial effects of cereal fiber on plasma adiponectin.

Adiponectin is a cytokine secreted by adipose tissue that is abundant in the circulation (9). Humans with insulin-resistant diabetes have lower adiponectin levels (8). It has been found that adiponectin might enhance insulin action, improve glucose metabolism and lipid profile (22,23), and modulate vascular functions (24). Therefore, adiponectin provides an important target for treating cardiovascular complications in diabetic patients.

There are few data available on the long-term effects of dietary factors on circulating adiponectin levels in humans. Our findings of inverse associations of dietary glycemic index and glycemic load with plasma adiponectin and a positive association between cereal fiber intake and adiponectin level are in line with the limited prior evidence from an animal study (14) and short-term trials in humans (12,13). Pawlak et al. (14) fed rats with either high–glycemic index or low–glycemic index diets for 18 weeks while maintaining the same mean body weight. They found that animals given high–glycemic index food tended to have lower plasma adiponectin and more body fat than their low–glycemic index counterparts. In a controlled randomized study with an intervention period of 1 year, consumption of a diet higher in fiber and lower in saturated fat improved blood levels of adiponectin in women with moderately elevated cardiovascular risk (12). In another study with 30 newly diagnosed type 2 diabetic patients and 30 matched control subjects, 1 serving of high-carbohydrate/low-fiber meal was found to decrease serum adiponectin in diabetic patients (13).

Both dietary glycemic index and glycemic load are used to characterize the capability of diet to induce glycemic response. The observed associations between dietary glycemic index, glycemic load, and adiponectin are likely to be mediated through glucose levels. Regular consumption of meals higher in glycemic index was found to increase 24-h blood glucose and insulin levels (25,26). Similarly, increases in dietary glycemic load induced both hyperglycemia and hyperinsulinemia (27). It has been noted that adipose expression of adiponectin is inversely correlated with fasting plasma glucose in humans (28) and that a glucose-enriched diet markedly attenuated adiponectin expression in adipose tissue in an animal model (29). We found that the effects of dietary glycemic load were stronger than glycemic index, because dietary glycemic load takes into account both quality and quantity of carbohydrates.

High intake of fiber may attenuate the glycemic effect of a mixed meal (30). In addition, cereal fiber may also affect adiponectin level through a fatty acid–mediated pathway. Dietary fiber may promote the clearance of lipids (31) and thus reduce free fatty acids available for storage in adipose tissue. Free fatty acids act as ligands to activate the upstream regulation of adiponectin expression, e.g., through peroxisome proliferator–activated receptor-γ (32). It is unclear why the inverse association was observed only with cereal fiber but not fibers from other sources. However, this finding appears to be consistent with results from epidemiologic studies showing a stronger inverse association of cereal fiber with

Table 3—*Intakes of dietary fibers (g/day), magnesium (mg/day), and plasma adiponectin concentration*

	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	
Model 1	14.6	15.5	15.3	16.1	16.5	0.320
Model 2	14.5	15.6	15.8	16.1	16.3	0.483
Model 3	14.4	15.5	15.4	16.5	16.6	0.122
Model 4	15.2	15.9	15.5	16.0	15.7	0.866
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	
Model 1	14.2	15.0	15.7	15.8	17.3	0.006
Model 2	14.5	14.8	16.1	15.9	16.8	0.043
Model 3	14.0	14.6	16.2	16.2	17.3	0.003
Model 4	14.5	14.8	16.3	16.0	16.7	0.063
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	
Model 1	15.3	15.4	16.3	15.3	15.4	0.673
Model 2	15.4	15.0	16.7	15.4	15.6	0.663
Model 3	15.6	15.2	16.4	15.4	15.6	0.417
Model 4	16.0	15.3	16.5	15.2	15.1	0.193
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	
Model 1	14.4	16.0	16.0	15.4	16.0	0.979
Model 2	14.7	15.4	16.4	15.9	15.8	0.849
Model 3	14.6	15.4	16.3	15.7	16.4	0.280
Model 4	14.8	15.5	16.2	15.6	16.1	0.888
Magnesium	299 (158)	343 (152)	376 (153)	411 (152)	471 (142)	
Range	<326	327–357	358–391	391–436	≥437	
Model 1	13.9	14.8	16.2	15.8	17.2	0.003
Model 2	14.2	14.9	16.1	16.2	16.8	0.011
Model 3	14.5	14.9	16.3	16.1	16.4	0.042

Data are median (*n*). Model 1: adjusted for age; model 2: adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, HbA_{1c}, and history of hypertension or hypercholesterolemia; model 3: in addition to the variables adjusted in model 2, further adjusted for the dietary factors (total energy intake, glycemic load and fibers) that were not examined as the primary independent variable; model 4: in addition to variables adjusted in model 3, further adjusted for magnesium.*Fibers in g/day and magnesium in mg/day.

type 2 diabetes and coronary heart disease than other types of fiber (1,2). Since major food sources of cereal fiber such as whole grains also contribute greatly to the intakes of magnesium, it is difficult to tease out the independent effects of cereal fiber and magnesium. Magnesium plays important roles in regulation of insulin action and carbohydrate metabolism (33). The insulin-sensitizing effect of magnesium has been observed in diabetic patients and may partly account for the observed association between the nutrient and adiponectin levels (34).

As a major strength of our study, the diet was measured several times and therefore provides the unique opportunity to evaluate long-term intake and reduce measurement error. However, the cross-sectional nature of our study does not allow us to make inference about cause and effect.

In conclusion, we found that higher dietary glycemic index and glycemic load were associated with lower plasma adiponectin concentration. In contrast, intakes of cereal fiber and magnesium were associated with increased circulating adi-

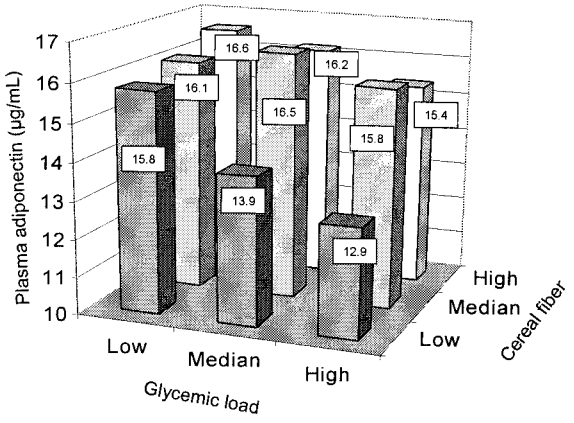

Figure 1—*Geometric means of plasma adiponectin concentration by different levels of dietary glycemic load and cereal fiber intake.*

ponectin level. The results from this study lend support to the recommendation of a diet high in fiber and low in glycemic load for diabetic patients.

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