Influence of Adiponectin Gene Polymorphisms on Adiponectin Level and Insulin Resistance Index in Response to Dietary Intervention in Overweight-Obese Patients With Impaired Fasting Glucose or Newly Diagnosed Type 2 Diabetes

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OBJECTIVE — The aim of this study was to determine the effect of common adiponectin gene polymorphisms on dietary intervention-mediated changes in adiponectin levels and homeostasis model assessment of insulin resistance (HOMA-IR) indexes.

RESEARCH DESIGN AND METHODS — A total of 363 subjects with impaired fasting glucose (IFG) or newly diagnosed type 2 diabetes followed a dietary intervention (replacement of cooked refined rice with whole grains and an increase in vegetable intake) and regular walking for 12 weeks without any medication. Adiponectin gene single nucleotide polymorphisms (SNPs) (45, 276, and −11377) were examined in these subjects.

RESULTS — After this dietary intervention, fasting glucose levels decreased in all three SNP 45T>G genotype groups. Subjects with the SNP 45TT genotype showed increased adiponectin levels and decreased HOMA-IR indexes. Haplotype analysis revealed that homozygous carriers of the TG haplotype (45TT and 276GG) and heterozygous carriers of the TG haplotype (TG/X) showed a reduction in the HOMA-IR index after adjustment for baseline levels. Significant differences were observed in changes in HOMA-IR indexes and adiponectin concentrations according to the 45-276 TG haplotype in overweight-obese, but not in normal-weight subjects: the greatest decrease in HOMA-IR indexes and the greatest increase in adiponectin levels were shown in overweight-obese subjects with the TG/TG haplotype.

CONCLUSIONS — *ADIPOQ* genetic variants can affect circulating adiponectin levels and insulin resistance indexes in subjects with IFG or newly diagnosed type 2 diabetes in response to dietary intervention.

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Adiponectin is a protein produced and secreted by adipocytes that influences the body's response to insulin. It is encoded by the *ADIPOQ* gene on chromosome 3q27 (1) in a region previously identified through genetic linkage studies as a diabetes susceptibility locus (2). Several single nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene have been shown in Japanese and European populations to be associated with diabetes (3–5) or insulin resistance syndrome (6). However, previous work on *ADIPOQ* SNPs have shown that the SNPs associated with type 2 diabetes or circulating adiponectin levels differ according to both the study cited and the ethnic population studied. Specifically, SNPs 276G>T (intron 2) and 45T>G (exon 2) have been associated with various levels of adiponectin as well as BMI, fasting insulin concentration, and homeostasis model assessment of insulin resistance (HOMA-IR) in nondiabetic Koreans (7).

Circulating levels of adiponectin are unlikely to be affected by acute dietary changes but rather reflect dietary intake over time (8). However, little is known about the dietary modulation of plasma adiponectin levels in humans. Although humans differ in their responses to diet and many of these differences can be due to genetic polymorphisms (9,10), the majority of previous studies have considered the *ADIPOQ* gene only in relation to the degree of insulin resistance syndrome without considering responses to dietary intervention. Recently, a carbohydrate-rich diet with a high glycemic load was found to be associated with lower adiponectin levels (8). According to the 2005 Korean National Health and Nutrition Survey (11), carbohydrate-derived calories account for 64% of total caloric intake, and cooked refined rice is the major source of carbohydrates in middle-aged adults. Because of this high carbohydrate

intake, the replacement of refined rice with whole grains and legumes has been suggested as a way to reduce the risk factors for type 2 diabetes (12). Therefore, we determined the effects of dietary intervention (replacement of refined rice with whole grains, a high intake of vegetables, and regular exercise) on circulating adiponectin levels and insulin resistance indexes in conjunction with common adiponectin gene polymorphisms in Koreans with impaired fasting glucose (IFG) or newly diagnosed type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Study subjects were selected from participants in a nutrition genomic study conducted by the National Research Laboratory of Clinical Nutrigenetics/Nutrigenomics (Program R0A-2005-000-10144-0) at Yonsei University. Study subjects were recruited from the Health Service Center or the outpatient clinics at Yonsei University Severance Hospital in Seoul, Korea, and National Health Insurance Corporation Ilsan Hospital in Goyang, Korea.

Subjects with a diagnosis of type 2 diabetes or IFG who consented to the dietary intervention program were included. Hyperglycemia was defined according to the American Diabetes Association criteria (9), in which diabetes is defined as fasting glucose ≥126 mg/dl, and IFG is defined as fasting glucose between 100 and 125 mg/dl. Exclusion criteria included *1*) previous history of diabetes, *2*) abnormal liver or renal function, *3*) history of cardiovascular disease and cancer, *4*) unstable weight loss/gain (≥2 kg) over the previous 6 months, and *5*) thyroid or pituitary disease. A total of 430 Koreans were recruited, and 67 participants discontinued the study for personal reasons. Finally, 363 subjects completed the study program. All subjects gave their written informed consent for the study, which was approved by the Institutional Review Board of Yonsei University.

Detailed methods for the genotyping of *ADIPOQ* SNPs (−11377, 45, and 276) and clinical laboratory tests were described previously (7).

Dietary intervention program and assessment of dietary intake/physical activity level

A 12-week dietary intervention program was conducted. The subjects' usual diets were assessed using a semiquantitative food frequency questionnaire and a 24-h recall method at baseline. All subjects were given written and verbal instructions by a registered dietitian on how to complete a 3-day dietary record every 4 weeks. Individualized and nutritionally balanced diets were planned for each subject at the initial visit. The dietary intervention program consisted of the replacement of refined rice with whole grains three times a day as a carbohydrate source and an increase in vegetable intake to at least 6 units (30–70 g/unit) per day for sufficient dietary fiber intake. The subjects were told to drink no more than one alcoholic beverage drink (15 g alcohol) per day and were assigned physical activity, comprising a regular 30-min walk after dinner each day.

The energy values and nutrient content of dietary intake were calculated using the Computer Aided Nutritional Analysis Program (CAN-Pro 2.0, Korean Nutrition Society). Total energy expenditures were calculated from activity patterns including basal metabolic rate (by the Harris-Benedict equation), physical activity for 24 h, and the specific dynamic action of food.

Statistical analysis

Hardy-Weinberg equilibrium, linkage disequilibrium (LD), and haplotype frequencies were determined by Haploview (version 3.32; http://www.broad.mit.edu/mpg/haploview/), and subject-specific haplotypes were estimated using the Hap-Analyzer program (http://hap.ngri.go.kr) with the EM algorithm. We also used SPSS (version 12.0 for Windows; SPSS, Chicago, IL). A paired *t* test was used to evaluate the effect of dietary intervention. ANOVA with the Bonfer-roni method or a general linear model was used to test the genotype or haplotype effects. Pearson and partial correlation coefficients were used to examine the relationship between adiponectin levels and other metabolic variables. Finally, a multiple linear regression analysis was performed to find independent effects on changes in adiponectin levels after dietary intervention. Each variable was examined for normal distribution, and the skewed variables were tested after logarithmic transformation. For descriptive purposes, mean values are presented on untransformed and unadjusted variables. $P < 0.05$ was considered statistically significant.

RESULTS

Distribution of *ADIPOQ* SNPs in the study population (n = 363)

All SNPs were in Hardy-Weinberg equilibrium ($P > 0.05$). SNP −11377 contained 56.5% C/C, 36.6% C/G, and 6.9% G/G (C frequency = 0.748). SNP 45 contained 49.3% T/T, 41.9% T/G, and 8.8% G/G (T frequency = 0.703). SNP 276 contained 52.3% G/G, 39.4% G/T, and 8.3% T/T (G frequency = 0.720). LD was calculated between the three SNPs: low LD between SNP +45T>G and SNP −11377C>G ($D' = 0.692$; $P < 0.001$) and between SNP +276G>T and SNP −11377C>G ($D' = 0.003$, $P = 0.092$) and complete, strong LD between SNP +45T>G and SNP +276G>T ($D' = 1$; $P < 0.001$). Accordingly, haplotype analysis was performed for SNP 45T>G combined with SNP 276G>T. Estimated 45–276 haplotype frequencies were 17.8% for TG/TG, 22.8% for TG/TT, 25.7% for TG/GG, 8.1% for TT/TT, 16.3% for TT/GG, and 9.2% for GG/GG. In subsequent statistical analyses, subjects were divided into three haplotype groups: homozygous for the TG haplotype (TG/TG; n = 65) and heterozygous for the TG haplotype (TG/X; n = 177) and non-TG haplotype (X/X; n = 121).

Clinical characteristics and nutrient intake both before and after dietary intervention. The 12-week dietary intervention increased HDL cholesterol but significantly decreased blood pressure and serum concentrations of glucose, triglycerides, total cholesterol, and LDL cholesterol (Table 1). Adiponectin levels were slightly but not significantly higher after dietary treatment. There were significant increases from baseline in both fiber intake and the polyunsaturated fatty acids–to–saturated fatty acids ratio and a slight increase in total energy expenditure but a decrease in total energy intake. The mean body weights of the study participants were slightly but significantly reduced after dietary intervention (Table 1).

Baseline characteristics, adiponectin levels, and HOMA-IR indexes according to *ADIPOQ* SNP genotypes

There were no significant differences in terms of sex distribution, age, and BMI associated with SNP 45 (Table 2), SNP 276 (Table 2), and SNP −11377 (data not shown) genotypes. At baseline, we did not observe any significant genotype-related associations between the three SNPs and plasma adiponectin levels.

Table 1—*Effects of a 12-week dietary intervention on anthropometric and biochemical markers*

	Before	After	*P* value*
Weight (kg)	67.5 ± 0.56	67.1 ± 0.54	<0.001
BMI (kg/m^2)	25.3 ± 0.16	25.1 ± 0.15	0.001
Systolic blood pressure (mmHg)	130.5 ± 0.92	126.8 ± 0.92	<0.001
Diastolic blood pressure (mmHg)	79.4 ± 0.58	77.3 ± 0.61	<0.001
Glucose (mg/dl)†	131.2 ± 1.64	123.2 ± 1.83	<0.001
Insulin (μU/ml)†	10.0 ± 0.37	9.50 ± 0.30	0.259
HOMA-IR†‡	3.24 ± 0.13	2.88 ± 0.10	0.001
Triglycerides (mg/dl)†	162.9 ± 5.49	154.8 ± 5.53	0.012
Total cholesterol (mg/dl)	198.7 ± 1.95	191.2 ± 2.03	<0.001
LDL cholesterol (mg/dl)	122.9 ± 1.72	115.1 ± 1.85	<0.001
HDL cholesterol (mg/dl)	45.7 ± 0.65	47.2 ± 0.66	0.001
Adiponectin (μg/ml)†	4.75 ± 0.18	4.98 ± 0.21	0.351
Total energy expenditure (kcal)	2,243 ± 19	2,281 ± 18	<0.001
Estimates of daily nutrient intake			
Energy intake (kcal)	2,342 ± 19	2,264 ± 19	<0.001
Carbohydrate (%)	62 ± 0.43	55 ± 0.41	<0.001
Protein (%)	17 ± 0.15	20 ± 0.16	<0.001
Fat (%)	21 ± 0.30	24 ± 0.39	<0.001
Crude fiber (g)†	11 ± 0.23	15 ± 0.25	<0.001
PUFA/SFA†	1.42 ± 0.05	1.52 ± 0.06	0.019

Data are means ± SE. n = 363. *Tested by paired t test. †Tested by logarithmic transformation. ‡HOMA-IR = (fasting insulin [microunits per milliliter] × fasting glucose [millimoles per liter])/22.5. PUFA/SFA, polyunsaturated fatty acids–to–saturated fatty acids ratio.

However, for SNP 276, baseline serum glucose levels were significantly higher in GG subjects than in TG and TT subjects (Table 2). For the 45T>G/276G>T haplotypes, TG/TG subjects showed higher insulin levels and HOMA-IR indexes than did non-TG subjects (X/X) (Table 2).

Effect of a 12-week dietary intervention on HOMA-IR indexes and adiponectin levels in relation to *ADIPOQ* SNP genotype

Regardless of the SNP 45T>G genotype, the dietary intervention significantly decreased serum glucose levels without any significant increase in insulin levels (Table 2). After the dietary intervention, HOMA-IR indexes were reduced in subjects carrying the SNP 45T allele. SNP 45TT subjects also had a mean adiponectin level increase of 0.48 ± 0.17 μg/ml (10.9%). There was a significant genotype-related difference in insulin levels (P = 0.005), HOMA-IR indexes (P = 0.049), and adiponectin levels (P = 0.037) for SNP 45.

After the 12-week trial, serum glucose levels were reduced in subjects carrying the SNP 276G allele, and HOMA-IR indexes were reduced in SNP 276GG subjects (Table 2). There was initially a significant decrease in HOMA-IR indexes among the genotypes (P = 0.025), but this difference disappeared after adjustment for the baseline levels (P = 0.074).

In the 45–276 haplotype analysis (Table 2) after the 12-week trial, serum glucose levels were significantly decreased in all haplotype groups. However, HOMA-IR indexes were reduced only in subjects carrying the TG haplotypes (TG/TG + TG/X) but not in the non-TG subjects (X/X). There were significant differences in insulin levels (P < 0.001) and HOMA-IR indexes (P < 0.001) regarding the 45–276 haplotype, even after adjustment for baseline insulin (P = 0.005) and HOMA-IR (P = 0.008). We also found haplotype-related differences for 45T>G/276G>T regarding the change in adiponectin levels (P = 0.03). TG/TG subjects had a mean adiponectin increase of 0.71 ± 0.35 μg/ml (16.3%) after the 12-week trial, whereas X/X subjects showed a mean adiponectin decrease of −0.19 ± 0.21 μg/ml (3.8%).

Effect of the *ADIPOQ* 45–276 haplotype on HOMA-IR indexes and adiponectin levels in response to the 12-week dietary intervention in relation to BMI

The subjects were divided into two subgroups according to individual BMI values, either <25 kg/m^2 (normal-weight) or >25 kg/m^2 (overweight-obese). We evaluated the effects of BMI on changes in HOMA-IR indexes and plasma adiponectin levels in association with the 45–276 haplotype. As expected, the two BMI subgroups differed significantly in baseline values of adiponectin (5.1 ± 0.26 vs. 4.4 ± 0.25 μg/ml, P < 0.05), insulin (8.2 ± 0.32 vs. 11.4 ± 0.50 μU/ml, P < 0.001), and HOMA-IR (2.67 ± 0.12 vs. 3.65 ± 0.17, P < 0.001); however, no significant difference was found in glucose levels (133 ± 2.2 vs. 130 ± 2.3 mg/dl).

In the normal-weight subgroup, there were no significant differences in either baseline or change values for HOMA-IR and adiponectin after dietary intervention among the three 45–276 haplotype groups (Fig. 1). However, in the overweight-obese group, TG haplotype carriers had significantly higher baseline HOMA-IR values than non-TG carriers (TG/TG 4.2 ± 0.45, TG/X 3.9 ± 0.24, and X/X 2.9 ± 0.27, P = 0.009) (Fig. 1). After dietary intervention, HOMA-IR indexes were significantly reduced in overweight-obese subjects with the TG/TG haplotype, but not with either the TG/X or the X/X haplotype. A significant difference was observed in HOMA-IR indexes according to the 45–276 haplotypes (TG/TG −1.05 ± 0.31, TG/X −0.43 ± 0.19, and X/X 0.46 ± 0.26, P = 0.001), even after adjustment for baseline HOMA-IR (P = 0.017). We also found haplotype-related differences for changes in adiponectin levels (P = 0.017). After dietary intervention, overweight-obese subjects with the TG/TG haplotype had a mean adiponectin increase of 1.09 ± 0.61 μg/ml (26.2%), whereas those with the X/X haplotype had a mean adiponectin decrease of −0.33 ± 0.28 μg/ml (7.9%). In addition, circulating adiponectin levels after the 12-week program in the overweight-obese subjects with the TG haplotype were higher than those in non-TG carriers (X/X) (Fig. 1).

Finally, a multiple linear regression analysis was performed to find the independent effects of the *ADIPOQ* 45–276 haplotype as well as sex, age, BMI, baseline values of glucose, insulin, and adiponectin and change values of glucose, insulin, and adiponectin in the total group and subgroups according to BMI. In the total group, the *ADIPOQ* 45–276 haplotype (standardized β = −0.154, P = 0.025), baseline insulin levels (standardized β = −0.188, P = 0.041), baseline adiponectin levels (standardized β = −0.159, P = 0.034), and changes of in-

sulin levels (standardized $\beta = -0.200$, $P = 0.018$) showed independent effects on adiponectin levels after dietary intervention. In a subgroup analysis, changes in adiponectin levels were affected by only baseline adiponectin levels (standardized $\beta = -0.372$, $P < 0.001$) in the normal-weight group and only the *ADIPOQ* polymorphism (standardized $\beta = -0.214$, $P = 0.033$) in the overweight-obese group.

Relationship between changes in plasma adiponectin level and metabolic parameters

Overall, changes in adiponectin levels were negatively correlated with changes in both insulin levels ($r = -0.16$, $P = 0.022$) and HOMA-IR ($r = -0.15$, $P = 0.028$) after adjustment for age, sex, and changes in body weight. After adjustments for those, changes in adiponectin levels were negatively correlated with baseline adiponectin levels ($r = -0.32$, $P = 0.001$) in normal-weight subjects and negatively correlated with changes in insulin levels ($r = -0.20$, $P = 0.044$) and changes in HOMA-IR indexes ($r = -0.23$, $P = 0.020$) in overweight-obese subjects.

CONCLUSIONS — The most relevant finding from our study is that the genetic variability at the *ADIPOQ* locus influences the ability of dietary intervention to alter insulin resistance as measured by HOMA-IR indexes in subjects with IFG or newly diagnosed type 2 diabetes. Similarly, Kang et al. (13) reported on the role of specific *ADIPOQ* variants in modulating interindividual differences in the response to drug treatment in type 2 diabetic patients.

We examined three *ADIPOQ* SNPs that had previously been suggested to affect HOMA-IR: 45T>G, 276G>T, and −11377C>G. For the −11377C>G SNP, we found no genotype-dependent differences in HOMA-IR indexes and adiponectin levels in response to dietary intervention. Although previous findings have suggested that SNPs −11391 and −11377 are associated with adiponectin levels and contribute to the development of type 2 diabetes, these studies were performed in Caucasians (3,5). Thus, the discrepancy may be explained by ethnic differences. In fact, the −11391 SNP at the *ADIPOQ* promoter region was monomorphic in this study population (G:A = 1:0), and it is also not found in either the Japanese or Chinese population (4,14).

Fasting serum glucose levels were decreased in all three SNP 45T>G genotypes after dietary intervention. However, subjects with the SNP 45TT genotype had an increase in adiponectin levels and a decrease in HOMA-IR indexes. Similarly, in haplotype analysis for *ADIPOQ* 45T>G/276G>T, subjects with the TG/TG haplotype had a 21% decrease in HOMA-IR indexes and a greater increase in adiponectin levels after dietary intervention. Zacharova et al. (15) also found that the SNP 45G allele predicts the conversion to type 2 diabetes in subjects with impaired glucose tolerance despite regular exercise and either a weight-reducing or a weight-maintaining diet. Furthermore, the combined effects of the 45G allele and the 276T allele on the conversion from impaired glucose tolerance to type 2 diabetes were observed to be stronger than that of each SNP alone (15).

BMI is another factor in the response to dietary intervention. At baseline, the high HOMA-IR index observed among subjects with the TG/TG haplotype was only seen in the overweight-obese subgroup. This result is in accordance with Jang et al. (7) who found an association between the TG haplotype and increased HOMA-IR index in overweight-obese but not in normal-weight nondiabetic Koreans. In response to dietary intervention, overweight-obese subjects carrying the TG/TG haplotype exhibited an increase in adiponectin levels (1.09 μg/ml) and a 25% decrease in HOMA-IR index. This finding might indicate that a genotypic-specific effect is heightened in overweight-obese individuals in terms of altered adiponectin levels and HOMA-IR index after dietary intervention compared with normal-weight individuals. However, these results must be interpreted with caution. They do not mean that normal-weight subjects have a relatively poor outcome after dietary intervention compared with overweight-obese subjects. Moreover, it remains unclear whether adiponectin levels change according to *ADIPOQ* SNPs and whether this change is clinically relevant for long-term dietary intervention programs.

Even though several reports have shown an interaction between *ADIPOQ* SNPs and obesity (5,8,16), the mechanism is not yet known. One possible explanation might be that obesity with increased adipose tissue predispose individuals to altered adipocytokine levels (e.g., decreased adiponectin and increased tumor necrosis factor-α) and, thus, the effect of the adiponectin gene is more exaggerated in obesity. Another possibility is that lower baseline adiponectin levels in obesity might induce additional changes in adiponectin levels and amplify the diet-intervention effect. Indeed, a multiple regression analysis in this study showed that baseline adiponectin levels were independent factors to determine changes in adiponectin levels. Also, there are several reports to suggest the relationship between adiponectin levels and treatment responses (17,18). However, further experimental studies are needed to clarify the mechanism underlying these responses.

Small differences in adiponectin levels can have clinical significance (19). Our findings that a small increase in adiponectin (1.09 μg/ml) along with a decrease in both fasting insulin and glucose levels in overweight-obese subjects carrying the TG/TG haplotype confirm a previous report of the insulin-sensitizing effects of adiponectin (19). In the TG/TG haplotype group, the insulin-sensitizing effects of adiponectin compensate for insulin and result in a decreased demand for insulin and improvement in the insulin resistance index. This hypothesis might be supported by the observation that overweight-obese subjects carrying non-TG alleles showed a decrease in adiponectin levels (0.33 μg/ml) and a slight, although insignificant, increase in HOMA-IR indexes. Thus, we also observed an inverse relationship between changes in HOMA-IR indexes and adiponectin levels similar to previous findings (18,20).

Fumeron et al. (21) found that variations at the adiponectin locus affect body weight gain, onset of hyperglycemia, and adiponectin levels in a 3-year prospective study in French Caucasians. Specifically, GG carriers of SNP 45T>G were found to gain more weight and have a higher risk of hyperglycemia. In this study, however, 45GG subjects or subjects who did not carry the TG haplotype of 45T>G/276G>T showed no significant changes in body weight, fasting glucose and insulin levels, HOMA-IR indexes, or adiponectin levels either before or after dietary intervention. This discrepancy might be due to either the ethnic specificity or the short-term effects of dietary changes.

There is also a conflicting report by Nelson et al. (22) in which adiponectin levels are altered independently of *ADIPOQ* polymorphisms after dietary supplemen-

Table 2—*Effects of ADIPOQ SNP 45 and SNP 276 on insulin resistance indices and plasma adiponectin levels before and after dietary treatment*

	SNP 45T>G				SNP 276 G>T				Haplotype of SNPs 45 and 276			
	TT	TG	GG	P value	GG	GT	TT	P value	TG/TG	TG/nTG	nTG/nTG	P value
n	179	152	32		190	143	30		65	177	121	
Male/female sex (%)	59.2/40.8	50.7/49.3	53.1/46.9	0.288	56.3/43.7	55.2/44.8	46.7/53.3	0.614	61.5/38.5	57.6/42.4	47.9/52.1	0.131
Age (years)	55.1 ± 0.80	57.5 ± 0.86	56.0 ± 1.90	0.143	57.3 ± 0.75	54.7 ± 0.93	56.2 ± 1.73	0.084	55.4 ± 1.37	57.0 ± 0.78	55.5 ± 0.99	0.406
BMI (kg/m^2)	25.4 ± 0.23	25.2 ± 0.23	25.0 ± 0.59	0.714	25.2 ± 0.22	25.4 ± 0.25	24.9 ± 0.49	0.651	25.4 ± 0.43	25.3 ± 0.21	25.1 ± 0.28	0.710
Change in weight	−0.28 ± 0.13	−0.34 ± 0.14	−0.75 ± 0.36	0.379	−0.48 ± 0.13	−0.26 ± 0.15	0.02 ± 0.23	0.259	−0.51 ± 0.23	−0.29 ± 0.13	−0.35 ± 0.16	0.680
Glucose (mg/dl)												
Before*	13 ± 2.41	130 ± 2.34	137 ± 6.62	0.570	135 ± 2.37	127 ± 2.35‡	127 ± 5.84‡	0.038	138 ± 4.25	130 ± 2.22	129 ± 2.87	0.085
After*	126 ± 3.02††††	121 ± 2.27††††	120 ± 5.61†	0.558	124 ± 2.32†††	122 ± 3.33†††	124 ± 6.33	0.848	129 ± 4.77††	123 ± 2.65†††	121 ± 2.91†††	0.414
Change	−5.66 ± 2.41	−8.95 ± 1.83	−16.4 ± 6.69	0.140	−11.3 ± 2.14	−4.23 ± 2.57	−2.48 ± 2.58	0.055[a]	−9.67 ± 4.02	−7.42 ± 2.27	−7.84 ± 2.33	0.862
Insulin (μU/ml)												
Before*	10.0 ± 0.44	9.71 ± 0.48	8.06 ± 0.88	0.218	9.83 ± 0.43	9.96 ± 0.50	7.78 ± 0.69	0.149	10.4 ± 0.76	10.2 ± 0.46	8.51 ± 0.46	0.028
After*	9.41 ± 0.37	9.35 ± 0.48	10.5 ± 1.51	0.889	9.21 ± 0.38	10.2 ± 0.55	8.20 ± 0.83	0.228	9.09 ± 0.49	9.42 ± 0.38	9.81 ± 0.68	0.997
Change	−0.61 ± 0.35	−0.36 ± 0.41	2.45 ± 1.01‡§	0.005								
HOMA-IR												
Before*	3.27 ± 0.16	3.11 ± 0.17	2.69 ± 0.31	0.395	−0.62 ± 0.36	0.21 ± 0.44	0.42 ± 0.66	0.252	−1.33 ± 0.59	−0.79 ± 0.35	1.30 ± 0.48‡§	<0.001[c]
After*	2.90 ± 0.13†	2.81 ± 0.16†	3.11 ± 0.44	0.772	2.81 ± 0.12†††	3.06 ± 0.19	2.52 ± 0.27	0.404	2.87 ± 0.18††	2..85 ± 0.13††	2.93 ± 0.21‡	0.826
Change	−0.37 ± 0.13	−0.30 ± 0.14	0.42 ± 0.29‡	0.049	0.49 ± 0.12	−0.03 ± 0.15‡	0.11 ± 0.20‡	0.025[b]	−0.76 ± 0.22	−0.41 ± 0.12	0.25 ± 0.14‡§	<0.001[d]
Adiponectin (μg/ml)												
n	128	114	21		136	107	20		48	127	88	
Before*	4.40 ± 0.23	4.95 ± 0.31	5.79 ± 0.57	0.138	4.95 ± 0.26	4.51 ± 0.27	4.70 ± 0.65	0.511	4.40 ± 0.42	4.72 ± 0.25	4.99 ± 0.33	0.545
After*	4.88 ± 0.28†	5.08 ± 0.35	5.11 ± 0.61	0.757	5.21 ± 0.32	4.77 ± 0.31	4.62 ± 0.60	0.373	5.10 ± 0.58	5.06 ± 0.29	4.80 ± 0.35	0.331
Change	0.48 ± 0.17	0.13 ± 0.19	−0.68 ± .52‡	0.037	0.26 ± 0.19	0.26 ± 0.17	−0.08 ± 0.27	0.764	0.71 ± 0.36	0.35 ± 0.15	−0.19 ± 0.21‡	0.030

Data are means ± SEM. n = 363. *Tested by logarithmic transformation. †$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$ compared with baseline values in each genotype or haplotype group tested by paired t test; ‡$P < 0.05$ compared with wild-type and §$P < 0.05$ compared with heterozygotes tested by ANOVA with the Bonferroni method. [a]$P = 0.239$ after adjustment for baseline glucose; [b]$P = 0.074$ after adjustment for baseline HOMA-IR; [c]$P = 0.005$ after adjustment for baseline insulin; [d]$P = 0.008$ after adjustment for baseline HOMA-IR.

tation with α-linolenic acid. Because small sample size (n = 57) in the previous study cannot allow interpretation of the genetic effect, a possible assumption can be made that specific effects of dietary factors (i.e., high ω-3 fatty acids) can mask the genetic effects in relatively insulin-sensitive healthy subjects. In addition, direct comparisons between studies are difficult, considering the differences in the characteristics of the subjects studied (healthy, young, primarily female, and Caucasian versus hyperglycemic patients, middle-aged, fewer female, and Korean) and study intervention program.

There are several limitations in our study design that should be mentioned. First, dietary intake was based on self-reports obtained from weighed food. However, measurement errors from self-reported dietary intake and lifestyle variables have been shown to be relatively small (23). In this study, well-controlled, fasting glucose concentrations reflected the compliance of the subjects to dietary intervention. Second, because of the small sample size, the results of genetic analyses should be interpreted with caution. Finally, heterogeneity in the causes of predisposition to diabetes and diabetes itself must be considered because metabolic differences can be present between subjects with IFG and type 2 diabetes. However, our patients with newly diagnosed type 2 diabetes did not show different metabolic characteristics, including plasma adiponectin levels, compared with those in subjects with IFG (data not shown). Further additional studies with a larger sample size are needed to confirm our findings.

Despite these limitations, we showed that *ADIPOQ* genetic variants can be factors in the interindividual differences in adiponectin levels and insulin resistance indexes after dietary intervention in hyperglycemic patients. We found the greatest decrease in HOMA-IR indexes and greatest increase in adiponectin levels in overweight-obese subjects with IFG or newly diagnosed type 2 diabetes who carry the TG/TG haplotype of *ADIPOQ* 45T>G/276G>T. However, long-term prospective studies are needed to examine the relationship between adiponectin levels and clinical outcomes in these subjects. With a more complete understanding of these factors, our results provide good evidence for tailoring of dietary intervention programs to individuals on the basis of their genetic patterns.

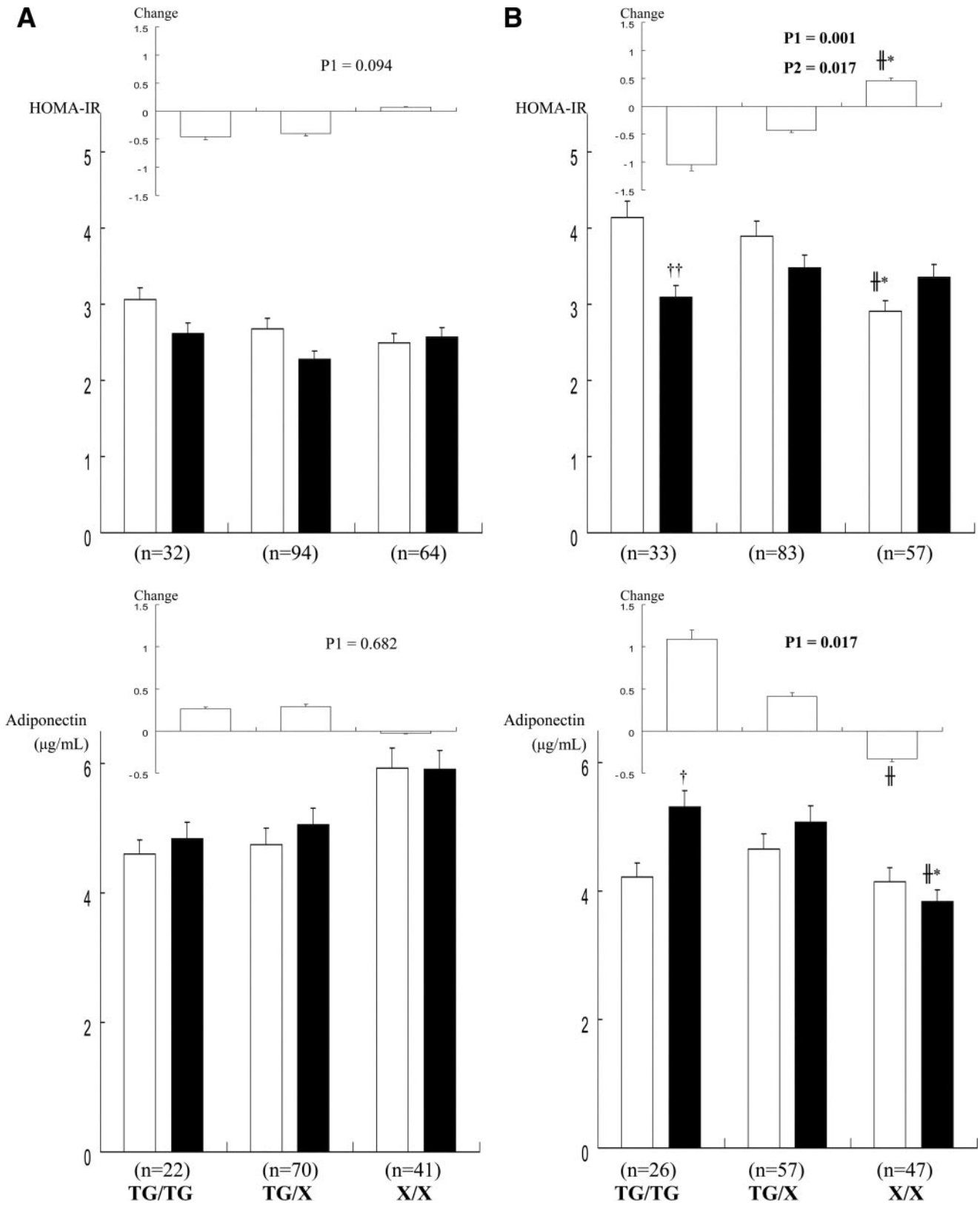

Figure 1—*HOMA-IR indexes and circulating adiponectin levels before (□) and after (■) dietary treatment and mean changes sorted by* ADIPOQ *45T>G/276G>T haplotype according to BMI (*A*: normal-weight;* B*: overweight-obese). P1, unadjusted* P *value; P2, baseline-adjusted* P *value. †*P *< 0.05 and ††*P *< 0.01 compared with baseline values in each haplotype group tested by paired* t *test. ǂ*P *< 0.05 compared with the TG/TG haplotype and **P *< 0.05 compared with the TG/X haplotype tested by ANOVA with the Bonferroni method.*

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