The Influence of Adiponectin Gene Polymorphism on the Rosiglitazone Response in Patients With Type 2 Diabetes

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OBJECTIVE — The aim of this study was to examine the effects of rosiglitazone on adiponectin and plasma glucose levels in relation with common adiponectin gene (*ACDC*) polymorphisms.

RESEARCH DESIGN AND METHODS — A total of 166 patients with type 2 diabetes were treated with rosiglitazone (4 mg/day) for 12 weeks without changing any of their previous medications. In all, single nucleotide polymorphism (SNP)45 and SNP276 of *ACDC* were examined.

RESULTS — Regarding SNP45, there was a smaller reduction in the fasting plasma glucose (FPG) level and the HbA_{1c} value in the carriers of the GG genotype than in the carriers of the other genotypes ($P = 0.031$ and 0.013, respectively). There was a smaller increase in the serum adiponectin concentration for the GG genotype than for the other genotypes ($P = 0.003$). Regarding SNP276, there was less reduction in the FPG level for the GG genotype than for the other genotypes ($P = 0.001$). In the haplotype analysis, the reductions in the FPG and HbA_{1c} levels were smaller for the GG homozygote haplotype than for the other haplotypes ($P = 0.001$ and 0.001, respectively). The increase in the plasma adiponectin concentration for the GG homozygote haplotype was smaller than that of the other haplotypes ($P = 0.003$).

CONCLUSIONS — These data suggest that genetic variations in the adiponectin gene can affect the rosiglitazone treatment response of the circulating adiponectin level and blood glucose control in type 2 diabetic patients.

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Adiponectin is a circulating protein secreted by adipocytes and is associated with the development of insulin resistance and atherosclerosis (1,2). Serum adiponectin concentrations are lower in patients with type 2 diabetes, obesity, and coronary heart disease than in healthy subjects (3,4). This molecule is known to be a potent insulin sensitizer. Thiazolidinediones lower the blood glucose level primarily by activating the peroxisome proliferator–activated receptor (PPAR)-γ, which then improves insulin sensitivity (5). The synthetic PPAR-γ agonist, rosiglitazone, is reported to increase the serum adiponectin level in type 2 diabetes (6).

Adiponectin is encoded by *ACDC*, which is located on chromosome 3q27 (7,8). Studies of *ACDC* mutations have revealed 16 single nucleotide polymorphisms (SNPs) (9). Among them −11377, +45, and +276 have been reported to be associated with type 2 diabetes, circulating adiponectin levels, and insulin resistance in a Japanese population (10,11). However, previous studies on the association between *ACDC* SNPs, type 2 diabetes, and adiponectin levels have shown that the specific SNPs associated with this process differ according to both the study and the ethnic population. The aim of this study was to examine the association between SNPs in *ACDC* and the response to rosiglitazone. In addition, this study also investigated the PPAR responsive element (PPRE) polymorphism in the *ACDC* promoter.

RESEARCH DESIGN AND METHODS

— A total of 166 patients were treated with rosiglitazone (4 mg/day) during a 12-week treatment course without changing previous medications. Type 2 diabetic patients with a HbA_{1c} values of 7.5–11.5% and fasting plasma glucose (FPG) levels of 7.8–14.0 mmol/l; (140–252 mg/dl) were enrolled in this study. The inclusion criteria were *1*) age 35–80 years, *2*) BMI 18.5–30 kg/m^2, *3*)

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Abbreviations: FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; PPAR, peroxisome proliferator–activated receptor; PPRE, PPAR responsive element; SNP, single nucleotide polymorphism.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

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

no history of PPAR agonist use, 4) no medication changes in the previous 3 months, and 5) for women, postmenopausal or using appropriate contraceptive methods. Patients with type 1 diabetes, any history of ketoacidosis, ischemic heart disease, or congestive heart failure (New York Heart Association II–IV) or who were receiving insulin therapy and pregnant or lactating women were excluded from this study. The patients were advised to consume a fixed-calorie diet and maintain a constant level of physical activity throughout the study. The Institutional Review Board of Yonsei University College of Medicine approved the study protocol. All subjects were provided adequate information about this study and gave their informed consent.

Clinical laboratory tests

Blood samples were collected after an overnight fast. The FPG and total cholesterol and triglyceride levels were determined using an enzymatic colorimetric assay. The HDL cholesterol concentration was measured using lipoprotein electrophoresis. The LDL cholesterol level was calculated using the Friedewald formula (12). The insulin concentration was measured using a radioimmunoassay kit (DAINABOT, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula: (fasting insulin [microunits per milliliter] × fasting glucose [millimoles per liter])/22.5. The HbA_{1c} value was determined using a high-performance liquid chromatography method (Varient II; GREENCROSS, Seoul, Korea). The serum adiponectin concentration was measured using a commercial radioimmunoassay kit (Linco Research, St. Charles, MO).

Genotyping

SNP45 and -276 were chosen because they are common (frequency >20%) in Korean type 2 diabetic patients and have been reported to be associated with type 2 diabetes in other Asian populations (10,11). SNP-11377 was also genotyped. The genomic DNA was extracted from leukocytes in the whole-blood samples using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). PCR amplification was performed in a total volume of 20 μl containing the PCR buffer (10 × Optiperform Buffer III of 40 mmol/l KCl, 10 mmol/l Tris-HCl, 1.5 mmol/l $MgCl_2$), 45 ng/μl genomic DNA, 1 unit of *Taq* DNA polymerase, 250 μM concentrations each dNTPs, and 10 pmol of the sense and antisense primers. The PCR conditions and primer sequences used for *ACDC* PPRE, SNP45 and SNP276 are shown in the online appendix (available at http://care.diabetesjournals.org). The PCR products were genotyped by sequencing with an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

Statistical analysis

Data are shown as means ± SD. All calculations and statistical analyses were performed using the SPSS for Windows software (version 12.0; SPSS, Chicago, IL). A paired *t* test was used to evaluate the effects of rosiglitazone on the metabolic parameters. Comparisons of the continuous variables among the genotypes were assessed using an ANOVA test, and a post hoc Bonferroni correction was made to control the effects of multiple comparisons. The statistical analysis of triglyceride, HDL cholesterol, fasting insulin, and HOMA-IR levels was performed using log-transformed values because the distribution was not normal. *P* values <0.05 were considered significant. The allelic distribution of each SNP was verified using Hardy-Weinberg equilibrium. The haplotypes at locus 45 and locus 276 for each individual were inferred by a maximum likelihood estimation method with the Haplotyper program (http://www.people.fas.harvard.edu/~junliu/Haplo).

Table 1—*Allele, genotype, and haplotype distribution of the SNP*

	n (%)
Allele	
SNP45	
T	228 (68.7)
G	104 (31.3)
SNP276	
G	238 (71.7)
T	94 (28.3)
Genotype	
SNP45	
TT	87 (52.4)
TG	54 (32.5)
GG	25 (15.1)
SNP276	
GG	91 (54.8)
GT	56 (33.7)
TT	19 (11.5)
Haplotype SNP45 and SNP276	
TT/GG	38 (22.9)
TT/TG	31 (18.7)
TT/TT	18 (10.8)
TG/TG	23 (13.9)
TG/TT	32 (19.3)
GG/GG	21 (12.7)

Frequencies of SNP45/276 haplotypes were estimated by using the Haplotyper program.

RESULTS — Table 1 shows the allele, genotype, and haplotype distribution of *ACDC*. No significant deviation from Hardy-Weinberg equilibrium was observed for either locus. Table 2 shows the clinical characteristics of the patients before and after rosiglitazone treatment. The FPG levels and HbA_{1c} values were significantly lower after 12 weeks of treatment compared with the baseline. The serum adiponectin concentration was significantly higher after the rosiglitazone treatment (5.30 ± 4.79 μg/ml vs. 9.92 ± 6.81 μg/ml, $P < 0.001$). No mutation was observed at the PPRE of the adiponectin gene promoter region in any of 166 patients. Tables 3 and 4 show the clinical and biochemical characteristics of the patients according to the SNP45 and SNP276 genotypes. There were no significant differences in terms of age, duration of diabetes, and BMI according to the SNP45, SNP276, and SNP-11377 genotypes. The FPG levels, HbA_{1c} values, and the plasma lipid profiles were not significantly different among the genotypes of SNP45, SNP276, and SNP-11377 at baseline (Tables 3 and 4 and online appendix Table A-3, respectively).

Regarding SNP45, there was a significant difference in the decrease in the FPG level between the GG genotype and the other genotypes (TT + TG, 1.68 ± 2.40 mmol/l; GG, 0.25 ± 2.95 mmol/l; $P = 0.031$) (Table 5). The degree of the reduction in the HbA_{1c} value was smaller for the GG genotype than for the other genotypes (TT + TG, 0.85 ± 1.05%; GG, 0.05 ± 1.43%; $P = 0.013$) (Table 5). In addition, the degree of the increase in the serum adiponectin concentration was significantly smaller in the subjects with the GG genotype than in the subjects with the other genotypes (TT + TG, 4.81 ± 5.07 μg/ml; GG, 1.67 ± 4.45 μg/ml; $P = 0.003$) (Table 5).

Regarding SNP276, the degree of the decrease in the FPG level was significantly smaller in those patients with the GG ge-

Table 2—*Clinical characteristics of the patients before and after rosiglitazone treatment*

	Before	After	*P* value
Weight (kg)	70.5 ± 10.0	71.2 ± 9.9	<0.001
Waist (cm)	80.2 ± 9.7	81.2 ± 9.7	0.009
FPG (mmol/l)	9.00 ± 2.54	7.77 ± 2.48	<0.001
FPG (mg/dl)	162.13 ± 45.46	139.97 ± 18.01	
HbA_{1c} (%)	8.17 ± 1.52	7.68 ± 1.33	<0.001
Total cholesterol (mmol/l)	4.95 ± 0.94	5.21 ± 0.98	<0.001
Triglyceride (mmol/l)	2.17 ± 1.41	2.17 ± 1.52	0.969
HDL cholesterol (mmol/l)	1.20 ± 0.28	1.23 ± 0.29	0.181
LDL cholesterol (mmol/l)	2.74 ± 0.80	3.01 ± 0.83	<0.001
Fasting insulin (pmol/l)	48.96 ± 32.34	40.08 ± 27.42	<0.001
HOMA-IR	2.97 ± 1.99	2.43 ± 1.75	<0.001
Adiponectin (μg/ml)	5.30 ± 4.79	9.92 ± 6.81	<0.001

Data are means ± SD. *P* values are before vs. after rosiglitazone treatment (paired *t* test).

notype than in those with the other genotypes (GG, 0.86 ± 2.58 mmol/l; GT + TT, 2.23 ± 2.27 mmol/l; $P = 0.001$) (Table 5).

There were no significant differences in terms of insulin resistance, decrease in the FPG, decrease in the HbA_{1c}, and increase in the serum adiponectin levels according to SNP-11377 genotype (data are shown in the online appendix Table A-3).

In the haplotype analysis, the degree of the decrease in the FPG level was smaller in those with the GG homozygote haplotype than in those with the other haplotypes (GG homozygote haplotype, 0.03 ± 3.15 mmol/l; other haplotypes, 1.69 ± 2.40 mmol/l; $P = 0.001$) (Table 5). The patients with the GG homozygote haplotype had a smaller decrease in the HbA_{1c} level than those with the other haplotypes (GG homozygote haplotype, 0.18 ± 1.23%; other haplotypes, 0.85 ± 1.05%; $P = 0.001$) (Table 5). In addition, the degree of the increase in the serum adiponectin level after the rosiglitazone treatment was less in those patients with the GG homozygote haplotype than the subjects with the other haplotype (GG homozygote haplotype, 0.82 ± 3.62 μg/ml; other haplotypes, 4.81 ± 5.07 μg/ml; $P = 0.003$) (Table 5).

CONCLUSIONS — Recently, Iwaki et al. (13) characterized the PPAR-γ binding site, PPRE, in the human adiponectin gene promoter. Although a great deal of effort has been made to identify the mutation in this region, this study could not detect any mutation in the 166 type 2 diabetic patients examined.

Previous studies have shown that thiazolidinediones increase the serum adiponectin concentration by increasing the level of adiponectin transcription (14,15). Also, the association between an adiponectin gene polymorphism and the

Table 3—*Clinical and biochemical characteristics of the subjects according to the adiponectin genotypes at position 45*

	SNP45			
	TT	TG	GG	*P* value
n (male/female)	86 (41/45)	55 (30/25)	25 (18/7)	0.098†
Age (years)	56.3 ± 10.5	57.2 ± 9.3	54.4 ± 7.7	0.500
Duration of diabetes (years)	5.9 ± 5.9	7.3 ± 5.0	6.6 ± 5.3	0.480
BMI (kg/m^2)	25.4 ± 2.4	26.2 ± 3.0	25.5 ± 2.8	0.410
FPG				
Before treatment (mmol/l)	9.45 ± 2.54	9.39 ± 2.35	9.40 ± 2.76	0.990
Before treatment (mg/dl)	170.2 ± 45.8	169.2 ± 42.3	169.3 ± 49.7	
After treatment (mmol/l)	7.78 ± 2.06	7.59 ± 2.48	8.99 ± 3.59	0.061
After treatment (mg/dl)	140.2 ± 37.1	136.7 ± 44.7	161.9 ± 64.7	
Change in FPG (mmol/l)	1.63 ± 2.19 ($P = 0.082$)*	1.79 ± 2.74 ($P = 0.070$)*	0.25 ± 2.95	0.032
Change in FPG (mg/dl)	29.4 ± 39.5	32.2 ± 49.4	4.5 ± 53.1	
HbA_{1c} (%)				
Before treatment	8.55 ± 1.28	8.54 ± 1.49	8.12 ± 1.15	0.388
After treatment	7.69 ± 1.26	7.67 ± 1.36	8.06 ± 1.43	0.413
Change in HbA_{1c}	0.83 ± 1.13 ($P = 0.034$)*	0.87 ± 0.92 ($P = 0.026$)*	0.05 ± 1.43	0.006
Adiponectin (μg/ml)				
Before treatment	4.92 ± 4.12	4.93 ± 5.44	4.65 ± 3.29	0.961
After treatment	10.44 ± 6.79	8.62 ± 7.16	6.32 ± 5.38	0.021
Change in adiponectin	5.52 ± 5.03 ($P = 0.002$)*	3.68 ± 4.98 ($P = 0.154$)*	1.67 ± 4.45	0.002
Total cholesterol (mmol/l)	4.88 ± 0.85	5.05 ± 0.79	5.38 ± 1.46	0.098
Triglyceride (mmol/l)	2.02 ± 1.15	2.18 ± 1.29	2.81 ± 2.04	0.070
HDL cholesterol (mmol/l)	1.23 ± 0.27	1.23 ± 0.32	1.12 ± 0.27	0.285
LDL cholesterol (mmol/l)	2.75 ± 0.78	2.82 ± 0.77	2.85 ± 0.67	0.808
HOMA-IR	3.29 ± 1.93	3.25 ± 2.38	2.86 ± 1.73	0.644

Data are means ± SD. *P* values reflect differences between the three groups and were assessed by ANOVA. **P* value for comparison with GG genotype. Bonferroni correction was made to control the effects of multiple comparisons. †*P* value assessed by χ^2 test.

Table 4—*Clinical and biochemical characteristics of the subjects according to the adiponectin genotypes at position 276*

	SNP276			
	GG	GT	TT	*P* value
n (male/female)	91 (47/44)	56 (31/25)	19 (11/8)	0.899*
Age (year)	56.7 ± 9.4	55.1 ± 10.5	58.3 ± 8.9	0.386
Duration of diabetes (years)	6.1 ± 4.8	6.7 ± 5.5	8.5 ± 9.4	0.438
BMI (kg/m^2)	25.7 ± 2.7	25.7 ± 2.2	25.7 ± 2.6	0.996
FPG				
Before treatment (mmol/l)	9.01 ± 2.46	9.85 ± 2.43	10.14 ± 2.61	0.058
Before treatment (mg/dl)	162.3 ± 44.3	177.4 ± 43.8	182.7 ± 47.0	
After treatment (mmol/l)	8.10 ± 2.82	7.84 ± 2.25	7.12 ± 1.14	0.289
After treatment (mg/dl)	145.9 ± 50.8	141.2 ± 40.5	128.3 ± 20.5	
Change in FPG (mmol/l)	0.86 ± 2.58	1.96 ± 2.18	3.03 ± 2.40	0.001
Change in FPG (mg/dl)	15.5 ± 46.5	35.3 ± 39.3 (P = 0.196)†	54.6 ± 43.2 (P = 0.004)†	
HbA_{1c} (%)				
Before treatment	8.35 ± 1.41	8.59 ± 1.27	8.77 ± 1.14	0.352
After treatment	7.71 ± 1.40	7.90 ± 1.29	7.39 ± 0.83	0.345
Change in HbA_{1c} (%)	0.62 ± 1.09	0.66 ± 1.16 (P = 0.060)†	1.40 ± 1.19 (P = 0.034)†	0.028
Adiponectin (μg/ml)				
Before treatment	5.43 ± 5.17	4.19 ± 3.64	4.37 ± 2.50	0.224
After treatment	9.24 ± 7.36	8.86 ± 6.67	10.22 ± 4.63	0.758
Change in adiponectin (μg/ml)	3.80 ± 5.39	4.68 ± 5.08	5.85 ± 3.07	0.238
Total cholesterol (mmol/l)	5.05 ± 0.99	4.95 ± 0.79	4.96 ± 1.22	0.830
Triglyceride (mmol/l)	2.15 ± 1.48	2.21 ± 1.03	2.26 ± 1.73	0.950
HDL cholesterol (mmol/l)	1.19 ± 0.27	1.23 ± 0.29	1.26 ± 0.37	0.714
LDL cholesterol (mmol/l)	2.82 ± 0.67	2.70 ± 0.76	2.87 ± 1.14	0.659
HOMA-IR	3.37 ± 2.10	2.74 ± 1.92	3.84 ± 1.95	0.103

Data are means ± SD. *P* values reflect differences between the three groups and were assessed by ANOVA. **P* value assessed by χ^2 test. †*P* value for comparison with GG genotype. Bonferroni correction was made to control the effects of multiple comparisons.

risk of type 2 diabetes has been examined in many studies (9–11,16). SNP45 and SNP276 were reported to be associated with type 2 diabetes in a Japanese population (10), whereas it was reported that SNP-11391 and SNP-11377 were related to type 2 diabetes in a French population (16). Therefore, the SNPs of *ACDC* for type 2 diabetes and insulin resistance appear to be different among different populations. This prospective intervention study was performed to evaluate how rosiglitazone response varies with adiponectin gene polymorphisms.

Our data suggest that there is no association between SNP-11377 genotype and rosiglitazone response, but patients with the GG genotype at SNP45 and/or the GG genotype at SNP276 are unlikely to respond to rosiglitazone. In addition, a smaller increase in the serum adiponectin concentration was observed in patients with the SNP45 GG genotype than for those with the other genotypes. It was also observed that the degree of the decrease in the FPG level and HbA_{1c} value was smaller in the patients with the GG homozygote haplotype than in those with the other haplotypes. In addition, patients with the GG homozygote haplotype had a smaller degree of increase in the serum adiponectin levels than in those with the other haplotypes. Patients with the GG homozygote haplotype are unlikely to respond to rosiglitazone.

The *ACDC* SNP45 is located in exon 2 and is a silent mutation for Gly15 (GGT to GGG). However, it might inactivate the gene or affect the adiponectin concentration by influencing the pre-mRNA splicing or the stability of the mRNA (17). Alternatively, it may be related to another functional locus via a linkage disequilibrium not yet identified. SNP276 is located in intron two of *ACDC*. The intronic SNP can affect the expression level of the gene via an unknown mechanism. There may be a specific linkage structure or gene-environmental interaction.

Although baseline and posttreatment FPG, HbA_{1c}, and serum adiponectin levels were not significantly different between the GG homozygote haplotype and the other haplotypes, there were significant differences in the changes of the FPG, HbA_{1c}, and serum adiponectin levels. The difference in either the adiponectin transcription activity or the adiponectin mRNA stability according to the *ACDC* genotypes could be responsible for the reduced serum adiponectin concentration in the GG homozygote haplotype compared with the other haplotypes. A low adiponectin level in patients with the GG homozygote haplotype may result in increased insulin resistance, which in turn contributes to a smaller decrease in the FPG levels and HbA_{1c} values by several mechanisms (18,19). Multiple regression tests were performed and revealed that age, sex, and BMI were not found to be major confounding factors of serum adiponectin levels according to the *ACDC* genotypes (data shown in online appendix).

Our findings are in contrast to those reported by Yang et al. (20), who found that subjects with the TT genotype at SNP45 are associated with insulin resistance. This discrepancy could be due to the different study population. Yang et al.

Table 5—*Clinical and biochemical characteristics of the subjects according to the adiponectin genotypes at positions 45 and 276 and the carrying status of the SNP45/276 haplotype*

	SNP45			SNP276			Haplotype		
	TT + TG	GG	*P* value	GT + TT	GG	*P* value	Others	GG/GG	*P* value
n (male/female)	141 (71/70)	25 (18/7)		75 (42/33)	91 (47/44)		142 (71/71)	21 (14/7)	
Age (years)	56.7 ± 10.0	54.4 ± 7.7	0.213	55.9 ± 10.2	56.7 ± 9.4	0.576	56.7 ± 10.0	55.2 ± 7.3	0.839
Diabetes duration (years)	6.4 ± 5.4	6.6 ± 5.3	0.907	7.0 ± 6.4	6.1 ± 4.8	0.383	6.4 ± 5.5	6.2 ± 5.0	0.427
BMI (kg/m^2)	25.7 ± 2.7	25.5 ± 2.8	0.495	25.7 ± 2.3	25.7 ± 2.7	0.941	25.7 ± 2.7	25.7 ± 3.0	0.814
FPG									
Before treatment (mmol/l)	9.43 ± 2.46	9.40 ± 2.76	0.966	9.39 ± 2.46	9.01 ± 2.46	0.019	9.43 ± 2.46	9.41 ± 2.83	0.192
Before treatment (mg/dl)	169.9 ± 44.3	169.3 ± 49.7		178.8 ± 44.3	162.3 ± 44.3		169.9 ± 44.3	169.5 ± 50.9	
After treatment (mmol/l)	7.71 ± 2.23	8.99 ± 3.59	0.020	7.65 ± 2.04	8.10 ± 2.82	0.253	7.72 ± 2.23	9.19 ± 3.75	0.060
After treatment (mg/dl)	138.9 ± 40.1	161.9 ± 64.7		137.9 ± 36.8	145.9 ± 50.8		139.0 ± 40.1	165.5 ± 67.6	
Change in FPG (mmol/l)	1.68 ± 2.40	0.25 ± 2.95	**0.031**	2.23 ± 2.27	0.86 ± 2.58	**0.001**	1.69 ± 2.40	0.03 ± 3.15	**0.001**
Change in FPG (mg/dl)	30.5 ± 43.3	4.5 ± 53.1		40.2 ± 40.9	15.5 ± 46.5		30.5 ± 43.3	0.5 ± 56.7	
HbA_{1c} (%)									
Before treatment	8.54 ± 1.36	8.12 ± 1.15	0.104	8.64 ± 1.23	8.35 ± 1.41	0.170	8.54 ± 1.36	8.0 ± 1.2	0.575
After treatment	7.68 ± 1.30	8.06 ± 1.43	0.223	7.78 ± 1.21	7.71 ± 1.40	0.769	7.68 ± 1.30	8.2 ± 1.4	0.210
Change in HbA_{1c} (%)	0.85 ± 1.05	0.05 ± 1.43	**0.013**	0.85 ± 1.20	0.62 ± 1.09	0.222	0.85 ± 1.05	0.18 ± 1.23	**0.001**
Adiponectin (μg/ml)									
Before treatment	4.93 ± 4.66	4.65 ± 3.29	0.722	4.23 ± 3.38	5.43 ± 5.17	0.074	4.93 ± 4.66	4.49 ± 3.48	0.214
After treatment	9.73 ± 6.97	6.32 ± 5.38	0.008	9.20 ± 6.22	9.24 ± 7.36	0.975	9.73 ± 6.97	5.31 ± 4.50	0.026
Change in adiponectin (μg/ml)	4.81 ± 5.07	1.67 ± 4.45	**0.003**	4.97 ± 4.67	3.80 ± 5.39	0.136	4.81 ± 5.07	0.82 ± 3.62	**0.003**

Data are means ± SD. *P* values assessed by *t* test; values in bold are statistically significant. The GG/GT (two cases) and GG/TT (one case) haplotype were excluded from the statistical analysis due to their low incidence.

(20) examined nondiabetic subjects, which is in contrast to the diabetic patients in this study. Moreover, they used HOMA-IR as an index of insulin resistance, which is not believed to be an accurate indicator for insulin resistance in patients with a low BMI and insulin secretory defect (21). Menzaghi et al. (22) reported that subjects with the TT genotype at SNP276 had a higher serum adiponectin level than the other genotypes. However, no difference was observed in the serum adiponectin level at the baseline among the SNP276 genotypes in this study. This discordance could be explained by differences in the ethnicity or specific study population.

In conclusion, this study suggests that patients with G allele homozygosity at locus 45 and locus 276 are unlikely to respond to rosiglitazone. It was found that variations in the adiponectin gene could affect the rosiglitazone treatment response to the serum adiponectin level and blood glucose control. These findings may be clinically relevant in the prediction of patients who will best respond to rosiglitazone treatment. However, further investigations will be needed to elucidate the functional mechanism of these polymorphisms.

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