The 11482G>A Polymorphism in the Perilipin Gene Is Associated With Weight Gain With Rosiglitazone Treatment in Type 2 Diabetes

Eun Seok Kang, md, phd[1,2]
Bong Soo Cha, md, phd[1,2]
Hyeong Jin Kim, md[3]
Hae Jin Kim, md[4]
So Hun Kim, md[1]
Kyu Yeon Hur, md[1]
Hyun Joo Lee, md[1]
Wan Sub Shim, md[1]
Chul Woo Ahn, md, phd[1,2]
Hyun Chul Lee, md, phd[1,2]

OBJECTIVE — The aim of this study was to examine the effects of perilipin gene (*PLIN*) polymorphisms on weight gain with rosiglitazone treatment in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 160 type 2 diabetic patients were treated with rosiglitazone (4 mg/day) for 12 weeks in addition to their previous medications, which were unchanged. Four single nucleotide polymorphisms (SNPs) at the *PLIN* locus were genotyped: *PLIN* 6209T>C, *PLIN* 11482G>A, *PLIN* 13041A>G, and *PLIN* 14995A>T.

RESULTS — Although fasting plasma glucose and HbA_{1c} levels decreased; mean body weight increased significantly after rosiglitazone treatment. Among the four SNPs tested, only the *PLIN* 11482G>A polymorphism was associated with weight gain from rosiglitazone treatment. In addition, there was a significant difference in the increase in the body weight among the genotypes. Patients with the *11482A/A* genotype showed less increase in body weight than those with other genotypes.

CONCLUSIONS — These data suggest that genetic variations in the perilipin gene can affect weight gain associated with rosiglitazone treatment in patients with type 2 diabetes.

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Thiazolidinediones (TZDs) work by enhancing insulin sensitivity in the muscle and adipose tissue. TZDs lower blood glucose and insulin levels and may improve pancreas β-cell function (1). TZDs activate nuclear peroxisome proliferator–activated receptor (PPAR)-γ, which is expressed predominantly in adipose tissue and regulates the transcription of genes involved in adipocyte differentiation, as well as those involved in glucose and lipid metabolism (2,3). Despite normalizing glycemia and hyperinsulinemia, TZDs promote body weight gain in vivo (4–8) and adipogenesis in vitro (9–11). A dose-dependent weight gain of between 2 and 5 kg has been observed with pioglitazone and rosiglitazone (12,13). This is one of the main side effects of TZD treatment. The weight gain associated with the use of TZDs is likely to be due to an increase in adipose tissue (6,14).

Perilipins are phosphoproteins that coat intracellular lipid droplets (15–17). Recent studies have shown that these proteins are essential for the regulation of triglyceride deposition and mobilization (18–24). The perilipin gene (*PLIN*) is located at 15q26.1 (25), in the neighborhood of susceptibility loci for obesity, diabetes, and hypertriglyceridemia (26,27). The *PLIN* gene encodes four different products (Perilipin A, B, C, and D) due to differential splicing (28). Perilipin A is the most common isoform in human adipose tissue (17,23,29). Perilipin is a target of protein kinase A, and nonphosphorylated perilipin may act as a barrier to the hormone-sensitive lipase (HSL)–mediated lipolysis of triglyceride in lipid droplets (18–24). However, following phosphorylation, perilipin may facilitate HSL action (18,22,30,31). Thus, perilipin A functions to increase cellular triglyceride storage by decreasing the rate of triglyceride hydrolysis and serves an additional role in controlling the release of triglycerides in times of need. Regulation of this process may contribute to obesity and alterations in lipid metabolism.

The aim of this study was to examine the effects of *PLIN* polymorphisms on the weight gain associated with rosiglitazone treatment in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— A total of 160 patients with type 2 diabetes were recruited from the outpatient clinics at Severance Hospital Diabetes Center, Youngdong Severance Hospital, and Kwandong University Myoungji Hospital. All patients were treated with rosiglitazone (4 mg/day) during a 12-week treatment course, without changes in their previous medications. Type 2 diabetic patients with an HbA_{1c} (A1C) value ranging from 7.0 to 12.0% and a fasting plasma glucose (FPG) level ranging from 7.8 to 14.0 mmol/l (140–252 mg/dl) were enrolled in this study. The inclusion criteria were as follows: *1*) age between 35 and 80 years, 2) BMI be-

From the [1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; the [2]Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea; the [3]Department of Internal Medicine, Kwandong University College of Medicine, Gangneung, Korea; and the [4]Department of Endocrinology and Metabolism, Ajou University College of Medicine, Suwon, Korea.

Address correspondence and reprint requests to Hyun Chul Lee, MD, PhD, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-Dong Seodaemun-Gu, Seoul, 120-752, Korea. E-mail: endohclee@yumc.yonsei.ac.kr.

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Abbreviations: FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HSL, hormone-sensitive lipase; PPAR, peroxisome proliferator–activated receptor, SNP, single nucleotide polymorphism; TZD, thiazolidinedione.

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—*Primer and probe sequences for the amplification of* PLIN *SNPs*

SNP			Primers and probes
11482G/A	rs 894160	Sense	AATAGAGTGGCATCCCCAA
Intron 6		Antisense	AAGAAATTGACTGAGCAAGGG
		Probe	AAGAAATTGACTGAGCAAGGG
14995A/T	rs 1052700	Sense	TCCTCTGTGATCTAGGATGATCT
Exon 9		Antisense	TCCTCTGTGATCTAGGATGATCT
		Probe	CTCTGATGAACATCCTCTGATGATC
6209G/A	rs 2289487	Sense	AGAGTCTTGAAGGAATGGCAT
Intron 2		Antisense	AAACATTTTTCTGGTCTTTCTGG
		Probe	AAGGGCTGTGGGAGGGAAGGTGAGC
13041A>G	rs 2304795	Sense	CTGTGCTGGGCATGGCAG
Exon 8		Antisense	CATCTGATAGGGACATGGC
		Probe	TGCTGCACCTCACACCAGCCCC

tween 18.5 and 30 kg/m^2, 3) no history of PPAR agonist or statin use, 4) no medication changes in the previous 3 months, and 5) for women, postmenopause or using the appropriate contraceptive methods. Patients with type 1 diabetes; those receiving insulin therapy; those with any history of ketoacidosis, ischemic heart disease, or congestive heart failure (New York Heart Association II-IV); and pregnant or lactating women were excluded from this study.

The patients were educated to eat a stable-calorie diet and were instructed to maintain the same level of physical activity throughout this study. The institutional review board of Yonsei University College of Medicine approved the study protocol. Adequate information about this study was provided to the subjects, and all patients provided informed consent.

Anthropometric measurements were taken using standard techniques. All patients were weighed when they visited the diabetes center at the baseline time point and 3 months after rosiglitazone treatment. All measurements were done on the same equipment and by the same personnel. Venous blood was collected into EDTA-containing glass tubes. Plasma total cholesterol, fasting triglyceride, HDL cholesterol, FPG, and 2-h postprandial plasma glucose levels were measured. The A1C values were determined by high-performance liquid chromatography (Variant II; Greencross, Seoul, Korea). Insulin concentration was measured using a radioimmunoassay kit (Dainabot, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula to estimate the level of insulin sensitivity: fasting insulin [(μU/ml) × fasting glucose (mmol/l)]/22.5 (32). A BN II nephelometer analyzer (Dade Behring, Newark, DE) was used to measure serum high-sensitivity C-reactive protein levels using a latex-enhanced, immunonephelometric assay method as previously described (33,34). Serum adiponectin concentrations were measured using a commercial radioimmunoassay kit (Linco Research, St. Charles, MO).

PLIN genotyping

DNA was extracted from blood as described (35,36). The size of the Perilipin gene is 164.07 kilobases. Several single nucleotide polymorphisms (SNPs) have been reported. Four polymorphisms at the *PLIN* locus were genotyped: *PLIN* 6209T>C (intron 2), *PLIN* 11482G>A (intron 6), *PLIN* 13041A>G (exon 8), and *PLIN* 14995A>T (exon 9). We selected these four SNPs because they were reported to be associated with obesity in previous studies (37,38). We initially screened the *PLIN* SNPs in a Korean population and selected SNPs whose mutation rate was >25%. The genotyping was analyzed by single-base primer extension assays using a SNaPShot assay kit according to manufacturer's recommendations (ABI, Foster City, CA). Briefly, the genomic DNA region containing the SNP was amplified with PCR. Each PCR contained 10.0 ng DNA, 1× PCR buffer, 0.125 units of *AmpliTaq Gold* DNA polymerase (ABI), 3.0 mmol/l $MgCl_2$, 0.25 mmol/l of each dNTP, and 0.5 pmol of each primer in a 10-μl reaction volume. Reactions were incubated at 95°C for 10 min, then cycled 30 times at 95°C for 30 s, 60°C for 1 min, and 72°C for 1 min followed by 72°C for 5 min. The primer sequences are shown in Table 1. After amplification, the PCR products were treated with 1 unit each of shrimp alkaline phosphatase (Roche Diagnostics, Indianapolis, IN) and exonuclease I (USB, Cleveland, OH) at 37°C for 60 min and 72°C for 15 min to purify the amplified products. One microliter of the purified amplification products was added to a SNaPshot Multiplex Ready reaction mixture containing 0.15 pmol of genotyping primer. The primer extension reaction was carried out for 25 cycles of 96°C for 10 s, 50°C for 5 s, and 60°C for 30 s. The reaction products were then treated with 1 unit of shrimp alkaline phosphatase at 37°C for 1 h and 72°C for 15 min to remove excess fluorescent dye terminators.

Table 2—*Allele and genotype distribution of the* PLIN *SNPs*

Allele	*n* (%)	Genotype	*n* (%)	*P* value
6209 G/A				
G	209 (65.3)	GG	65 (40.6)	0.26
A	111 (34.7)	GA	79 (49.4)	
		AA	16 (10.0)	
11482 G/A				
G	212 (66.2)	GG	72 (45.0)	0.53
A	108 (33.8)	GA	68 (42.5)	
		AA	20 (12.5)	
13041 A/G				
T	235 (73.4)	TT	86 (53.7)	0.91
C	85 (26.6)	TC	63 (39.4)	
		CC	11 (6.9)	
14995 A/T				
A	117 (36.6)	AA	22 (13.8)	0.84
T	203 (63.4)	AT	73 (45.6)	
		TT	65 (40.6)	

P value assessed by Hardy-Weinberg equilibrium χ^2 test.

Table 3—*Patient clinical characteristics before and after rosiglitazone treatment*

	Before	After	*P* value
Body weight (kg)	67.17 ± 9.22	68.13 ± 8.99	<0.001
FPG (mmol/l)	9.36 ± 2.61	7.88 ± 2.61	<0.001
2-h postprandial glucose (mmol/l)	14.08 ± 4.34	11.88 ± 4.07	<0.001
A1C (%)	8.49 ± 1.37	7.77 ± 1.33	<0.001
Total cholesterol (mmol/l)	4.99 ± 0.97	5.27 ± 1.05	<0.001
Triglyceride (mmol/l)	2.88 ± 1.85	2.85 ± 2.06	0.860
HDL cholesterol (mmol/l)	1.24 ± 0.36	1.22 ± 0.32	0.696
LDL cholesterol (mmol/l)	2.78 ± 0.79	3.07 ± 0.87	<0.001
Fasting insulin (pmol/l)	60.71 ± 37.58	53.86 ± 38.18	0.038
HOMA-IR	3.15 ± 2.05	2.37 ± 1.83	<0.001
Adiponectin (μg/ml)	4.86 ± 4.47	9.33 ± 6.90	<0.001

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

One microliter of the final reaction samples containing the extension products was added to 9 μl of Hi-Di formamide (ABI). The mixture was incubated at 95°C for 5 min followed by 5 min on ice and then analyzed by electrophoresis in an ABI Prism 3730 DNA analyzer (ABI). Results were analyzed using Gene Mapper software (ABI).

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). Comparisons of the continuous variables between the genotypes were assessed using an ANOVA test. The statistical analysis of triglyceride, HDL cholesterol, fasting insulin, and HOMA-IR levels were performed using log-transformed values because the data were not normally distributed. *P* values < 0.05 were considered significant. The allelic distribution of each SNP was verified by the Hardy-Weinberg equilibrium.

RESULTS

The allele and genotype distribution of the *PLIN* SNPs are shown in Table 2. No significant deviation from Hardy-Weinberg equilibrium was observed for any SNP. The frequencies for the major alleles of the 6209G>A, 11482G>A, 13041A>G, and 14995A>T *PLIN* polymorphisms were 0.653, 0.663, 0.734, and 0.634, respectively.

The clinical characteristics of the patients before and after rosiglitazone treatment are shown in Table 3. The FPG, 2-h postprandial glucose levels, and A1C values decreased significantly after 12 weeks of treatment. Mean body weight was significantly higher after the rosiglitazone treatment (67.17 ± 9.22 vs. 68.13 ± 8.99 kg, $P < 0.001$). The range of mean body weight change was from −4.9 to +6.4 kg. The serum adiponectin concentration was also significantly higher after the rosiglitazone treatment (4.86 ± 4.47 vs. 9.33 ± 6.90 μg/ml, $P < 0.001$). Total cholesterol and LDL cholesterol levels increased significantly with rosiglitazone treatment, whereas there was no significant change in HDL cholesterol or triglyceride levels (Table 3). Insulin resistance was improved as shown by HOMA-IR and insulin level studies (Table 3).

There were no significant differences in terms of age, duration of diabetes, lipid profiles, HOMA-IR, FPG, A1C, insulin, adiponectin, or high-sensitivity C-reactive protein levels between the SNP 11482 genotypes (Table 4). Initial mean body weight was also not different between the genotypes. However, after 12 weeks of treatment, a significant difference was seen in the amount of weight gain in response to rosiglitazone treatment, and this difference was associated with the *PLIN* 11482G>A polymorphism. There was an additive dose-response relationship between number of A allele and the degree of weight gain (GG, 1.33 ± 1.59 kg; GA, 0.85 ± 1.89 kg; and AA, 0.03 ± 1.46 kg; $P = 0.010$) (Table 4). Multiple regression tests were performed and revealed that age, sex, and baseline weight were not found to be major confounding factors of degree of weight gain (Table 5). No statistically significant interaction terms were found for the other *PLIN* polymorphisms (data not shown).

CONCLUSIONS

TZDs reduce blood glucose levels and the degree of insulin resistance but promote body weight gain (4–8) and adipogenesis (9–11). These are among the major side effects of TZD treatment. The weight gain associated with the use of TZDs is likely to be due to an increase in subcutaneous adipose tissue. Fluid retention is thought to

Table 4—*Clinical and biochemical characteristics of the subjects by* PLIN *11482 genotype*

	PLIN 11482 genotype			
	GG	GA	AA	*P* value
n (men/women)	72 (41/31)	68 (31/37)	20 (12/8)	0.313*
Age (years)	57.1 ± 9.3	55.5 ± 10.6	55.9 ± 9.8	0.641
Duration of diabetes (years)	6.7 ± 4.8	8.2 ± 6.8	5.5 ± 3.8	0.288
Weight (kg)				
Before treatment	67.0 ± 9.7	66.1 ± 8.9	71.2 ± 7.9	0.095
After treatment	68.4 ± 9.4	67.0 ± 8.8	71.2 ± 7.7	0.172
ΔWeight	1.33 ± 1.59	0.85 ± 1.89	0.03 ± 1.46	0.010
FPG (mmol/l)	9.34 ± 2.59	9.62 ± 2.51	8.91 ± 3.13	0.541
2-h postprandial glucose (mmol/l)	13.23 ± 4.29	14.28 ± 4.51	12.15 ± 4.64	0.156
A1C (%)	8.41 ± 1.39	8.64 ± 1.35	8.38 ± 1.28	0.549
Total cholesterol (mmol/l)	4.95 ± 0.84	5.05 ± 1.09	4.87 ± 1.03	0.745
Triglyceride (mmol/l)	3.03 ± 1.93	2.97 ± 2.05	2.51 ± 0.95	0.621
HDL cholesterol (mmol/l)	1.24 ± 0.32	1.20 ± 0.25	1.35 ± 0.70	0.367
LDL cholesterol (mmol/l)	2.73 ± 0.78	2.79 ± 0.73	2.73 ± 1.13	0.923
Insulin (pmol/l)	56.23 ± 30.21	37.32 ± 42.92	57.37 ± 42.20	0.247
Adiponectin (μg/ml)	4.75 ± 3.32	4.98 ± 5.74	4.86 ± 3.03	0.955
hsCRP (mg/l)	1.75 ± 2.69	1.65 ± 2.71	1.16 ± 1.18	0.588
HOMA-IR	2.91 ± 1.79	3.49 ± 2.36	3.17 ± 1.88	0.306

Data are means ± SD. *P* values reflect differences between the three groups and were assessed by ANOVA. **P* value assessed by χ^2 test. hsCRP, high-sensitivity C-reactive protein.

Table 5—*Multivariate regression analysis for influence of clinical and genetic factors on the amount of weight gain with rosiglitazone treatment*

Variable	Odds ratio	*P* value	95% CI
Sex (0 = men, 1 = women)	0.045	0.622	−0.473 to 0.789
Age	0.008	0.917	−0.026 to 0.028
Baseline body weight	−0.174	0.061	−0.068 to 0.001
11482 genotype (0 = GG, 1 = GA, 2 = AA)	−0.220	0.005	−0.947 to −0.171

be another potential cause of increased body weight.

In previous studies (35,36), we have shown that genetic variations in the adiponectin and PPARγ2 genes can affect the response to rosiglitazone treatment in patients with type 2 diabetes. In this study, we examined the relationship between weight gain, a major side effect of rosiglitazone treatment, and genetic polymorphisms in the perilipin gene in 160 patients with type 2 diabetic. In this study, mean body weight increased about 1 kg and HOMA-IR decreased after 3 months of treatment with rosiglitazone. However, the value of HOMA-IR in measuring insulin resistance in patients with a lower BMI, insulin secretory defect, and high fasting plasma glucose levels is limited (32).

Recent studies have revealed that perilipin null mice have markedly reduced adipose tissue mass and high levels of lipolysis (19,20). When fed a high fat diet, perilipin null mice are resistant to diet-induced obesity. PPARγ agonists are reported to stimulate perilipin gene expression in adipocytes (39). Reporter assays reveal that the 5′-flanking region of the gene contains a functional PPARγ-responsive element (40). These findings suggest that there could be a difference in the amount of weight gained during treatment with PPARγ agonists, depending on perilipin gene polymorphisms. Therefore, we have conducted a prospective pharmacogenetic study on rosiglitazone and one of its side effects, weight gain. Our results show that patients who are homozygous for the 11482A allele are more resistant to weight gain in response to rosiglitazone treatment than those who are 11482G homozygotes. This effect may be due to differences in the level of perilipin in the adipocyte tissue. This hypothesis is supported by the study of Mottagui-Tabar et al. (23) who reported that subjects with the *PLIN* 11482AA genotype had an 80% reduction in adipocyte perilipin content compared with 11482G homozygotes. Adipocyte tissue in AA individuals may have relatively decreased perilipin protein levels in response to PPARγ stimulation. Thus, triglycerides would be more easily hydrolyzed by HSL, and the half-life of stored triglyceride would be shortened. These factors could contribute to the lower increase in body weight seen in AA homozygotes in response to PPARγ agonists. Because *PLIN* SNP 11482 is located in intron 6, there is a possibility that this SNP might be simply tagging another SNP that is potentially functional, or mRNA splicing/stability could play a role in the protein amount variation. Further investigations will be needed to elucidate the functional mechanism of these polymorphisms.

Recently, Corella et al. (37) reported that *PLIN* 11482A carriers were resistant to weight loss from low-energy diets. Conversely, this study suggests that patients who are AA homozygotes at the *PLIN 11482* locus are more likely to be protected from weight gain due to PPARγ agonist treatment. Qi et al. (38) reported that the 11482A variant was associated with a lower risk of obesity (0.56 [95% CI 0.36–0.89]) in Caucasian women. However, we did not find any difference in mean body weight according to this genotype. Also, we did not observe sex-specific associations. In addition to the differences in ethnicity existing between the two studies, only 4.3% of subjects in their study group had diabetes, whereas all of our study subjects had diabetes. These factors could contribute to the different study outcomes.

In summary, our results suggest that genetic variations in the perilipin gene can affect the weight gain associated with rosiglitazone treatment in type 2 diabetic patients. These findings are potentially clinically relevant for predicting which patients will be likely to gain more weight when treated with rosiglitazone. The exact molecular mechanism for this interaction remains to be elucidated and will be the subject of further studies.

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