Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1139 – 1144
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Common polymorphisms of the peroxisome proliferator-activated receptor−γ (Pro12Ala) and peroxisome proliferator-activated receptor−γ coactivator−1 (Gly482Ser) and the response to pioglitazone in Chinese patients with type 2 diabetes mellitus

Ming-Chia Hsieh[a], Kun-Der Lin[a], Kai-Jen Tien[b], Shih-Te Tu[c], Jeng-Yueh Hsiao[a], Shun-Jen Chang[d], Shiu-Ru Lin[e], Shih-Jang Shing[a], Hung-Chun Chen[f,*]

[a]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University/Chung-Ho Memorial Hospital, Kaohsiung 807, Taiwan*
[b]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan*
[c]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*
[d]*Faculty of Medicine, Department of Public Health, College of Medicine, Kaohsiung, Taiwan*
[e]*Department of Medical Research, Fooyin University Hospital, Taiwan*
[f]*Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*

Received 26 December 2008; accepted 16 October 2009

Abstract

We investigated the effects of the common polymorphisms in the peroxisome proliferator-activated receptor−γ (PPAR-γ; Pro12Ala) and in PPAR-γ coactivator−1(PGC-1; Gly482Ser) genes on the response to pioglitazone in Chinese with type 2 diabetes mellitus. A total of 250 patients with type 2 diabetes mellitus were treated with pioglitazone (30 mg/d) for 24 weeks without a change in previous medications. All patients were genotyped for the PPAR-γ Pro12Ala and PGC-1 Gly482Ser polymorphisms. The Ala12Ala and Pro12Ala genotypes (26.0% vs 13.5%, $P = .025$) and Ala allele (15.6% vs 7.3%, $P = .008$) were significantly more frequent in pioglitazone responders than in nonresponders. The distribution of PGC-1 genotypes and alleles was not significantly different between responders and nonresponders. The decrease in fasting glucose (50.4 ± 52.2 vs 43.3 ± 51.7 mg/dL, $P < .001$) and hemoglobin A_{1c} (0.57% ± 1.44% vs 0.35% ± 1.10%, $P = .004$) levels was significantly greater in subjects with the Ala12 carriers (Pro12Ala and Ala12Ala) than in those without the allele (Pro12Pro). Baseline fasting glucose and triglyceride levels were related to the response of pioglitazone. Only the PPAR-γ Pro12Ala polymorphism was found to be associated with the response of pioglitazone by multiple logistic regression analysis. The PPAR-γ Pro12Ala gene polymorphism is associated with the response to pioglitazone in Chinese patients with type 2 diabetes mellitus. These findings may be helpful for targeted treatment of diabetes by identifying patients who are likely to respond to pioglitazone.

1. Introduction

Thiazolidinediones (TZDs) are agonists for the peroxisome proliferator-activated receptor−γ (PPAR-γ), a protein that plays a role in insulin resistance and adipogenesis [1]. Because of their unique insulin-sensitizing mechanism of action, TZDs have been widely used to treat patients with type 2 diabetes mellitus. However, a sizable proportion of diabetic patients fail to achieve a meaningful reduction in blood glucose levels on TZD treatment [2-5]. The reasons for the different responses have not been clearly determined. A recent meta-analysis study [6] has found only a patient's baseline hemoglobin A_{1c} (HbA_{1c}) level, but not other factors including age, sex, duration of diabetes, and prior use of antidiabetic therapy, to be associated with the TZD effect. It is reasonable to suspect that genetic factors may contribute to the variability in TZD response.

Peroxisome proliferator-activated receptor−γ and PPAR-γ coactivator−1 (PGC-1) are high-priority candidate genes in

* Corresponding author. Tel.: +886 7 3121101x; fax: +886 7 3122810.
E-mail address: tkzzkimo@gmail.com (H.-C. Chen).

0026-0495/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.10.030

the investigation of TZD response. Peroxisome proliferator-activated receptor–γ is located on chromosome 3 and has numerous known variants. The Pro12Ala polymorphism, the most common variation in the PPAR-γgene, occurs in 12% to 15% of the population [7-9], whereas other variants are rare [10-12]. However, 2 studies [13,14] evaluating the possible association between the PPAR-γ Pro12Ala polymorphism and TZD response in patients with type 2 diabetes mellitus have yielded conflicting results.

The PGC-1 gene is mapped to the 4p15.1 chromosomal region. The PGC-1 Gly482Ser gene polymorphism has been associated with type 2 diabetes mellitus [15] and insulin resistance [16]. No study to our knowledge has evaluated the potential association between PGC-1 Gly482Ser gene polymorphism and response to TZD.

Some clinical characteristics of Chinese patients with type 2 diabetes mellitus are different from those of white patients. The 2 populations appear to have different frequencies of the PPAR-γ Pro12Ala [17-20] and PGC-1 Gly482Ser gene polymorphisms [21,22]. Therefore, we investigated whether these 2 common polymorphisms are associated with response to the TZD pioglitazone in Chinese patients with type 2 diabetes mellitus.

2. Research design and methods

2.1. Population

A total of 250 patients with type 2 diabetes mellitus were recruited from the diabetic clinic of the Metabolism Division at Kaohsiung Medical University Hospital in Taiwan. We excluded patients with *type 1 diabetes mellitus* (defined as a patient having diabetic ketoacidosis or acute hyperglycemia symptoms with heavy ketonuria [≥3] or requiring regular insulin treatment throughout the year after diagnosis), ischemic heart disease, or congestive heart failure (New York Heart Association class II-IV); those receiving insulin therapy; and pregnant or lactating women. The inclusion criteria were as follows: (1) HbA_{1c} values ranging from 7.0% to 11.0% and fasting plasma glucose (FPG) levels ranging from 130 to 250 mg/dL, (2) no prior TZD use, and (3) no change in medication in the previous 3 months. The Human Research Ethics Committee at our hospital approved the protocol, and informed consent was obtained from each patient. All patients were treated with pioglitazone for 24 weeks with no change in previous medications. Patients were counseled to consume a fixed-calorie diet and were instructed to maintain the same level of physical activity during the study.

An average systolic and diastolic blood pressure (SBP and DBP) was arrived at based on the mean of 3 measurements of these variables taken in sitting positions after 10 minutes of rest. Body mass index (BMI) was calculated by body weight divided by body height squared (in kilograms per square meter). A biochemistry automatic analyzer (Beckman-Coulter, Fullerton, CA) was used to measure blood samples for plasma glucose, total cholesterol (Chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and creatinine after an 8-hour overnight fast. Hemoglobin A_{1c} was measured in whole blood using ion exchange high-performance liquid chromatography (Variant II Turbo; Bio-Rad, Hercules, CA).

Patient response to pioglitazone treatment was assessed using the criteria suggested by Bluher et al [13]. Briefly, *responders* were defined as those with a greater than 15% decrease in HbA_{1c} levels or a greater than 20% decrease in FPG levels (or both) after 24 weeks of pioglitazone treatment.

2.2. Genotyping

After each participant provided peripheral blood samples, we extracted genomic DNA samples from leukocytes using either QIAamp mini kits (Qiagen, Hilden, Germany) or Generation Capture Column kits (Gentra Systems, Minneapolis, MN). The PPAR-γ Pro12Ala and PGC-1 Gly482Ser gene polymorphisms were genotyped using the polymerase chain reaction–restriction fragment length polymorphism method. The primers for PPAR-γ Pro12Ala gene polymorphism were 5′-GCCAATTCAAGCCCAGTC-3′ and 5′-GATATGTTTG-CAGACAGTGTATCAGTGAAGGAATCGCTTTCCG-3′.

Table 1
Baseline characteristics of patients by response to pioglitazone treatment after 24 weeks

	Response to pioglitazone (yes or no)		
	Yes (n = 154)	No (n = 96)	*P* value
Sex (M/F)	78/76	41/55	.243
Age	57.4 ± 11.8	58.6 ± 10.9	.442
BMI	26.6 ± 4.0	26.4 ± 4.9	.727
Waist	90.0 ± 10.7	89.1 ± 9.5	.507
SBP	129.0 ± 15.3	130.0 ± 15.0	.638
DBP	78.2 ± 12.1	79.1 ± 9.4	.556
Fasting glucose	204.1 ± 60.5	159.4 ± 42.7	<.001
HbA_{1c}	8.56 ± 1.79	8.24 ± 1.88	.179
Chol	197.1 ± 65.3	184.3 ± 41.9	.089
TGLog	2.09 ± 0.26	2.01 ± 0.23	.032
LDL	121.7 ± 57.8	109.4 ± 34.9	.063
HDL	47.3 ± 14.1	49.7 ± 16.4	.214
Creatinine	0.9 ± 0.4	0.9 ± 0.3	.512
Oral antidiabetic drugs			
Sulfonylurea (%)	45	34	
Metformin (%)	68	69	
Others (%)	9	10	
Antihypertensive treatment			
ACEI (%)	20	17	
ARB (%)	45	55	
Diuretic (%)	27	23	
CCB (%)	21	27	
β-Blocker (%)	29	29	
Lipid-lowering drugs			
Statin (%)	73	71	
Fibrate (%)	6	2	

Data are mean ± SD. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker.

Table 2
Baseline characteristics of responders by different definition

	The definition of response			
	Only HbA_{1c} (n = 21)	Only fasting glucose (n = 85)	Both (n = 48)	*P* value
Sex (M/F)	12/9	42/43	25/22	.811
Age	57.0 ± 8.0	57.2 ± 12.2	58.0 ± 12.6	.923
BMI	28.1 ± 3.7	26.4 ± 4.4	26.1 ± 3.1	.140
Waist	91.1 ± 11.0	89.7 ± 11.0	89.9 ± 10.1	.881
SBP	132.3 ± 13.2	128.2 ± 15.9	129.0 ± 15.2	.539
DBP	129.0 ± 15.3	78.1 ± 11.6	79.6 ± 9.6	.469
AC	146.1 ± 51.4	211.0 ± 51.7	217.0 ± 64.9	<.001
HbA_{1c}	8.87 ± 1.53	8.26 ± 1.45	9.19 ± 1.79	.004
Chol	194.4 ± 66.3	193.8 ± 50.5	193.6 ± 44.6	.998
TGLog	2.12 ± 0.26	2.11 ± 0.26	2.10 ± 0.29	.979
LDL	126.5 ± 48.3	119.0 ± 43.3	124.3 ± 80.4	.812
HDL	42.9 ± 9.1	46.6 ± 14.6	50.5 ± 14.6	.095
Creatinine	1.0 ± 0.3	0.9 ± 0.3	0.9 ± 0.4	.677

Data are mean ± SD.

The amplified product was digested with *Bst*UI (Biolabs, London, United Kingdom) and size-fractionated by electrophoretic separation in 3% agarose gels. The primers for PGC-1 Gly482Ser gene polymorphism were 5′-TGCTACCTGAGAGAGACTTTG-3′ and 5′-CTTTCATCTTCGCTGTCATC-3′. The polymerase chain reaction products were digested with *Hpa*II and size-fractionated by electrophoretic separation in 3% agarose gels.

2.3. Statistical analysis

Patients' clinical and biochemical characteristics were presented as mean ± SD or percentages. Because the distributions of TG levels were highly skewed, this variable was natural log-transformed for all other analyses. All analyses and calculations were performed using the SPSS statistical package, version 10.0 (SPSS, Chicago, IL). We compared means between responders and nonresponders using the Student *t* test and percentages using the χ^2d test. The observed frequencies of the genotypes were compared with the frequencies under Hardy-Weinberg equilibrium by χ^2 tests. The paired *t* test was used to evaluate the effects of pioglitazone on metabolic parameters. Multiple logistic regression analysis was performed to evaluate the major determinants of pioglitazone response. A $P < .05$ was considered significant.

3. Results

A total of 250 diabetic patients (120 men and 130 women) were treated with 30 mg pioglitazone daily for 6 months. Fifteen patients were found to have pitting edema of lower legs. However, no patient was found to have heart failure symptoms or such signs as orthopnea, paroxysmal nocturnal dyspnea, and exertional dyspnea. No patient withdrew from this study. Of the 250 patients, 154 (61.6%) were responders. The baseline clinical characteristics of all 250 patients by response are summarized in Table 1. The responders had significantly higher baseline FPG and TG levels than the nonresponders. The responders and nonresponders did not differ significantly in age, sex, BMI, waist circumference (WC), blood pressure, HbA_{1c}, blood cholesterol, LDL-C, HDL-C, or serum creatinine levels.

Twenty-one patients were categorized as responders based on decreases in HbA_{1c} (Table 2). Eighty-five were categorized as responders based on decreases of FPG level; and 48, based on decreases of both HbA_{1c} and FPG level. The different types of responders did not differ significantly in age, sex distribution, BMI, WC, blood pressure, blood cholesterol, TG, LDL-C, HDL-C, or serum creatinine levels. The responders defined only by HbA_{1c} had significantly higher HbA_{1c} levels and lower FPG levels than responders defined only by fasting glucose levels. Patients who

Table 3
Distribution PPAR-γ and PGC-1 genotypes in responders or nonresponders of pioglitazone

	Nonresponders (n = 96)	Responders (n = 154)	Unadjusted		Adjusted[a]	
			P value	OR (95% CI)	*P* value	OR (95% CI)
Genotype						
PPAR-γ						
Pro12Pro	83	114	.025	2.240 (1.27-4.45)	.022	2.386 (1.132-5.031)
12Ala	13	40				
PGC-1						
Gly482Gly	21	30	.747	1.157 (0.618-2.165)	.658	1.171 (0.582-2.359)
482Ser	75	124				
Allele						
PPAR-γ						
Pro	178	260	.008	2.347 (1.256-4.386)	.016	2.295 (1.17-4.51)
Ala	14	48				
PGC-1						
Gly	122	80	.708	1.089 (0.755-1.572)	.665	1.095 (0.725-1.654)
Ser	186	112				

[a] *P* value adjusted for age, sex, BMI, HbA_{1c}, and fasting glucose.

Table 4
Logistic regression analysis for the response of pioglitazone

	OR	*P* value	95% CI	
Fasting glucose	1.001	.849	0.995	1.05
TG	2.039	.259	0.592	7.029
PPAR-γ (Ala12)	2.316	.027	1.100	4.874

responded to pioglitazone by both decreases in HbA_{1c} and decreases in FPG levels had sufficiently higher HbA_{1c} and FPG levels than responders defined only by one of the criteria.

For the PPAR-γ gene, the Ala12Ala and Pro12Ala genotypes (26.0% vs 13.5%, $P = .025$) and Ala allele (15.6% vs 7.3%, $P = .008$) were found significantly more frequently in the pioglitazone responders than in the nonresponders (Table 3). The 2 groups did not have significant difference in the distribution of PGC-1 genotypes and alleles.

The baseline fasting glucose levels, TG, and the frequency of Ala12Ala and Pro12Ala genotypes were significantly higher in pioglitazone responders than in nonresponders (Tables 1 and 3). The results of our multiple logistic regression analysis revealed that only the PPAR-γ Pro12Ala polymorphism was significantly associated with pioglitazone response rate (Table 4). Patients with the Ala12Ala and Pro12Ala genotypes were significantly more likely to respond to pioglitazone (odds ratio [OR] = 2.32; 95% confidence interval [CI], 1.10-4.87; $P = .027$).

After 24 weeks of pioglitazone treatment, the decrease in HbA_{1c} level was significantly greater in those with the Ala12 allele (Pro12Ala and Ala12Ala) than in those without it (0.57% ± 1.44% vs 0.35% ± 1.10%, $P = .004$) (Table 5). The decrease in FPG level was also significantly greater in Ala12 carriers (Pro12Ala and Ala12Ala) than in those without it (50.4 ± 52.2 vs 43.3 ± 51.7 mg/dL, $P < .001$). There were no

Table 5
Metabolic parameters and blood pressure of patients at baseline and 24 weeks after initiation of pioglitazone treatment for different PPAR-γ genotypes

	PPAR-γ Genotype				
	Total group (N = 250)	Pro12Pro group (n = 197)	12Ala group (n = 53)	*P* value	Adjusted *P* value[a]
HbA_{1c}					
Baseline	8.47 ± 1.64	8.51 ± 1.66	8.32 ± 1.55	.456	.257
6 mo	8.08 ± 1.55*	8.16 ± 1.61*	7.78 ± 1.25*	.066	.085
ΔHbA_{1c}	0.39 ± 1.18	0.35 ± 1.10	0.57 ± 1.44	<.001	.004
Fasting glucose					
Baseline	187.2 ± 58.3	185.8 ± 58.2	192.2 ± 58.8	.484	.818
6 mo	142.4 ± 41.5*	142.6 ± 42.5*	141.8 ± 37.8*	.902	.883
ΔFasting glucose	44.8 ± 51.7	43.3 ± 51.7	50.4 ± 52.2	<.001	<.001
SBP					
Baseline	129.3 ± 15.3	130.1 ± 15.2	126.7 ± 14.9	.153	.140
6 mo	128.8 ± 16.0	129.1 ± 16.2	128.0 ± 15.5	.668	.637
ΔSBP	0.5 ± 17.8	1.3 ± 17.8	-2.2 ± 17.5	.755	.581
DBP					
Baseline	78.5 ± 11.3	79.0 ± 11.7	76.9 ± 8.3	.223	.151
6 mo	77.7 ± 9.8	77.3 ± 10.0	79.6 ± 8.7	.142	.178
ΔDBP	0.8 ± 14.2	1.8 ± 14.7	-2.8 ± 11.3	.765	.657
Chol					
Baseline	190.6 ± 48.1	192.7 ± 47.2	181.2 ± 49.1	.120	.061
6 mo	172.9 ± 39.1*	172.1 ± 36.8*	176.0 ± 46.6	.524	.130
ΔChol	17.7 ± 53.8	21.1 ± 52.3	5.6 ± 57.9	.163	.207
TGLog					
Baseline	2.08 ± 0.26	2.07 ± 0.24	2.09 ± 0.34	.702	.307
6 mo	2.03 ± 0.25*	2.02 ± 0.23*	2.06 ± 0.34	.333	.115
ΔTG	0.05 ± 0.23	0.05 ± 0.22	0.02 ± 0.25	.673	.674
HDL					
Baseline	47.8 ± 14.5	49.2 ± 15.8	44.4 ± 10.9	.037	.229
6 mo	43.7 ± 13.0*	44.2 ± 13.0*	41.8 ± 13.0	.244	.646
ΔHDL	4.1 ± 15.9	4.4 ± 17.0	2.8 ± 11.0	.309	.291
LDL					
Baseline	116.5 ± 51.5	118.1 ± 53.1	110.7 ± 42.5	.350	.380
6 mo	97.6 ± 43.2*	97.3 ± 44.3*	97.9 ± 38.7	.931	.670
ΔLDL	18.9 ± 61.0	20.6 ± 63.2	13.1 ± 52.4	.651	.352
BMI					
Baseline	26.6 ± 4.1	26.6 ± 4.2	26.6 ± 3.6	.983	.993
6 mo	26.7 ± 5.0	26.6 ± 4.2	26.9 ± 7.4	.746	.625
ΔBMI	-0.1 ± 8.0	-0.1 ± 7.3	-0.3 ± 10.1	.725	.529

Data are mean ± SD.
[a] *P* value adjusted for age, sex, and BMI.
* $P < .05$ compared with baseline.

Table 6
The different definition of pioglitazone response for diabetic patients with different PPAR-γ genotypes

	PPAR-γ genotypes				
	Total group (N = 250)	12Pro group (n = 197)	12Ala group (n = 53)	*P* value	Adjusted *P* value[a]
Response definition					
HbA_{1c}	69	46	23	.005	.007
Fasting glucose	133	96	37	.008	.011
Both	48	28	20	<.001	<.001

[a] *P* value adjusted for age, sex and BMI.

significant differences in lipid profiles and blood pressure changes between the subjects with different genotypes.

Table 6 presents the dichotomous analyses of pioglitazone response and PPAR-γ genotypes. Subjects with the Ala12Ala and Pro12Ala genotypes had significantly higher response rates. The results (Tables 5 and 6) confirmed a significant association between the PPAR-γ Pro12Ala polymorphism and response to pioglitazone.

4. Discussion

Our study demonstrated that Chinese diabetic patients with the Pro12Ala and Ala12Ala genotypes of the PPAR-γ gene were more likely to have a positive response to pioglitazone than our patients with the Pro12Pro genotype (OR = 2.316; 95% CI, 1.100-4.874; *P* = .027) (Table 3). The PGC-1 Gly482Ser gene polymorphism was not associated with pioglitazone response in these patients.

Thiazolidinediones are commonly used to manage patients with type 2 diabetes mellitus. However, they are expensive agents and have been associated with troubling adverse effects. Genetic characteristics that predict individual patient's response to TZDs can, therefore, be important for clinical decisions. A meta-analysis study [6] has found that only the baseline HbA_{1c} level could be significantly associated with the effect size of TZD therapy measured by HbA_{1c}. The present study found that baseline FPG and TG levels were associated with the response to pioglitazone; but other factors including age, sex, and BMI were not. However, the relationship between baseline FPG and TG levels and the response to pioglitazone treatment disappeared after multiple logistic regression analysis.

We chose to study the PPAR-γ Pro12Ala variant because it is the most common polymorphism in the PPAR-γ gene. Previous in vitro functional studies have found the Ala12 allele capable of reducing the binding ability to PPAR-γ response elements in DNA and transcriptional activity in the presence of TZDs [23]. Therefore, PPAR-γ Pro12Ala gene polymorphism may be at least partially responsible for individual differences in TZD therapy efficacy. Bluher et al [13] found that PPAR-γ Pro12Ala gene polymorphism did not affect the efficacy of pioglitazone in white patients with type 2 diabetes mellitus. Kang et al [14] reported that Korean diabetic patients with the Pro12Ala genotype in the PPAR-γ gene had a better therapeutic response to rosiglitazone than patients with the Pro12Pro genotype. Our results showed an association between PPAR-γ Pro12Ala polymorphism and therapeutic response to pioglitazone in Chinese patients with type 2 diabetes mellitus. The different results in all of these studies [13,14] may be explained by the racial difference in study populations. Our study and the Kang et al study [14] were both conducted in Asian populations and reached similar conclusions. Bluher et al [13] concluded differently in a study of white subjects. Snitker et al [24] also reported that this gene polymorphism was not a predictor of therapeutic response to troglitazone in Mexican American women with a history of gestational diabetes. A meta-analysis [25] reported that carriers of the Ala12 allele had a 19% lower risk for type 2 diabetes mellitus than those with Pro12 homozygotes. That study pointed out that the Ala12 allele has a greater protective effect against type 2 diabetes mellitus in subjects in Asia than in individuals in Europe or North America. The ethnic factor may be important in the relationship between PPAR-γ Pro12Ala gene polymorphism and the therapeutic response to TZDs in diabetic patients.

Researchers have found that an interaction between PPAR-γ Pro12Ala gene polymorphism and BMI may affect the risk of type 2 diabetes mellitus. Specifically, the Ala12 allele has been found to confer greater protection in leaner individuals [25,26] than in individuals with higher BMIs. The mean ± SD BMI was 26.43 ± 4.6 kg/m^2 in our study and 25.9 ± 2.8 kg/m^2 in the Korean study [14]. Both studies reached similar conclusions about the effect of PPAR-γ Pro12Ala polymorphism on TZD efficacy. In our study, the response rate was insignificantly higher in subject carrying the Ala12 allele with BMI less than 24 kg/m^2 than those with BMI greater than or equal to 24 kg/m^2 (83% vs 72%, *P* = .706). The study by Bluher et al [13] found no correlation between the PPAR-γ Pro12Ala polymorphism and the efficacy of TZD; the mean BMI of those subjects was 31.0 ± 3.3 kg/m^2. Thus, interaction with BMI may be a factor in the different findings.

The PGC-1 protein was first identified as a transcriptional coactivator for PPAR-γ [27]. Peroxisome proliferator-activated receptor–γ coactivator–1 Gly482Ser genetic polymorphism has been associated with type 2 diabetes mellitus in whites in a meta-analysis study [28]. Chen et al [29] have shown, however, that PGC-1 Gly482Ser polymorphism is not associated with type 2 diabetes mellitus in the Chinese population. Our results similarly suggest that PGC-1 Gly482Ser polymorphism is not associated with the therapeutic response of pioglitazone in Chinese diabetic patients.

Previous studies have shown that pioglitazone treatment improves the serum lipid profile of patients with type 2 diabetes mellitus [30]. Bluher et al [13] reported that TG levels decreased and HDL-C increased with pioglitazone treatment. In our study, patients' Chol, LDL-C, HDL-C, and TG levels all decreased with pioglitazone treatment.

One limitation of our study was that we tried to collect the duration of diabetes from all subjects. However, nearly one

fourth of our patients could not remember how long they had had diabetes. In fact, many patients might have diabetes for a period before receiving a diagnosis of it. We used limited data and found that the durations of diabetes would not influence the response of pioglitazone in diabetic patients. Another limitation of our study was that we could not isolate the effect of individual differences in dietary regimen, which may be a confounding factor because evidence has suggested possible interaction between the PPAR-γ gene and nutrient intake [31]. Nevertheless, the association between the PPAR-γ Pro12Ala polymorphism and patient response to TZD remained significant after we controlled for age, sex, glycemic control, and BMI. This study is the first to analyze possible relationships of polymorphisms in 2 genes (PPAR-γ Pro12Ala gene polymorphism and PGC-1 Gly482Ser polymorphism) and patient response to TZD.

In conclusion, PPAR-γ Pro12Ala gene polymorphism, but not PGC-1 Gly482Ser polymorphism, is associated with the response to pioglitazone in Chinese patients with type 2 diabetes mellitus. These findings may be helpful for targeted treatment of diabetes by identifying patients who are likely to respond to pioglitazone.

References

[1] Lehmann JM, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem 1995;270:12953-6.

[2] Aronoff S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000;23:1605-11.

[3] Lawrence JM, Reckless JP. Pioglitazone. Int J Clin Pract 2000;54: 614-8.

[4] Scherbaum WA, Goke B. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. Horm Metab Res 2002;34:589-95.

[5] Herz M, et al. A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. Clin Ther 2003;25:1074-95.

[6] Phatak HM, Yin DD. Factors associated with the effect-size of thiazolidinedione (TZD) therapy on HbA(1c): a meta-analysis of published randomized clinical trials. Curr Med Res Opin 2006;22: 2267-78.

[7] Yen CJ, et al. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. Biochem Biophys Res Commun 1997;241:270-4.

[8] Deeb SS, et al. A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 1998;20:284-7.

[9] Hamann A, et al. Missense variants in the human peroxisome proliferator-activated receptor–gamma2 gene in lean and obese subjects. Eur J Endocrinol 1999;141:90-2.

[10] Ristow M, et al. Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. N Engl J Med 1998;339:953-9.

[11] Barroso I, et al. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999;402:880-3.

[12] Shuldiner AR, et al. Pro115Gln peroxisome proliferator-activated receptor–gamma and obesity. Diabetes Care 2000;23:126-7.

[13] Bluher M, Lubben G, Paschke R. Analysis of the relationship between the Pro12Ala variant in the PPAR-gamma2 gene and the response rate to therapy with pioglitazone in patients with type 2 diabetes. Diabetes Care 2003;26:825-31.

[14] Kang ES, et al. Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor gamma2 gene on rosiglitazone response in type 2 diabetes. Clin Pharmacol Ther 2005;78:202-8.

[15] Ek J, et al. Mutation analysis of peroxisome proliferator-activated receptor–gamma coactivator–1 (PGC-1) and relationships of identified amino acid polymorphisms to type II diabetes mellitus. Diabetologia 2001;44:2220-6.

[16] Hara K, et al. A genetic variation in the PGC-1 gene could confer insulin resistance and susceptibility to type II diabetes. Diabetologia 2002;45:740-3.

[17] Nicklas BJ, et al. Genetic variation in the peroxisome proliferator-activated receptor–gamma2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain. Diabetes 2001;50:2172-6.

[18] Vigouroux C, et al. Human peroxisome proliferator-activated receptor–gamma2: genetic mapping, identification of a variant in the coding sequence, and exclusion as the gene responsible for lipoatrophic diabetes. Diabetes 1998;47:490-2.

[19] Iwata E, et al. Mutations of the peroxisome proliferator-activated receptor gamma (PPAR gamma) gene in a Japanese population: the Pro12Ala mutation in PPAR gamma 2 is associated with lower concentrations of serum total and non-HDL cholesterol. Diabetologia 2001;44:1354-5.

[20] Oh EY, et al. Significance of Pro12Ala mutation in peroxisome proliferator-activated receptor–gamma2 in Korean diabetic and obese subjects. J Clin Endocrinol Metab 2000;85:1801-4.

[21] Lacquemant C, et al. No association between the G482S polymorphism of the proliferator-activated receptor–gamma coactivator–1 (PGC-1) gene and type II diabetes in French Caucasians. Diabetologia 2002;45:602-3 [author reply 604].

[22] Oberkofler H, et al. Peroxisome proliferator-activated receptor–gamma coactivator–1 gene locus: associations with hypertension in middle-aged men. Hypertension 2003;41:368-72.

[23] Masugi J, et al. Inhibitory effect of a proline-to-alanine substitution at codon 12 of peroxisome proliferator-activated receptor–gamma 2 on thiazolidinedione-induced adipogenesis. Biochem Biophys Res Commun 2000;268:178-82.

[24] Snitker S, et al. Changes in insulin sensitivity in response to troglitazone do not differ between subjects with and without the common, functional Pro12Ala peroxisome proliferator-activated receptor–gamma2 gene variant: results from the Troglitazone in Prevention of Diabetes (TRIPOD) study. Diabetes Care 2004;27:1365-8.

[25] Ludovico O, et al. Heterogeneous effect of peroxisome proliferator-activated receptor gamma2 Ala12 variant on type 2 diabetes risk. Obesity (Silver Spring) 2007;15:1076-81.

[26] Florez JC, et al. Effects of the type 2 diabetes-associated PPARG P12A polymorphism on progression to diabetes and response to troglitazone. J Clin Endocrinol Metab 2007;92:1502-9.

[27] Puigserver P, et al. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 1998;92:829-39.

[28] Kunej T, et al. A Gly482Ser polymorphism of the peroxisome proliferator-activated receptor–gamma coactivator–1 (PGC-1) gene is associated with type 2 diabetes in Caucasians. Folia Biol (Praha) 2004; 50:157-8.

[29] Chen S, et al. Peroxisome proliferator-activated receptor–gamma coactivator–1alpha polymorphism is not associated with essential hypertension and type 2 diabetes mellitus in Chinese population. Hypertens Res 2004;27:813-20.

[30] Rosenblatt S, et al. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis 2001;12:413-23.

[31] Luan J, et al. Evidence for gene-nutrient interaction at the PPARgamma locus. Diabetes 2001;50:686-9.