The Effect of *IGF2BP2* Gene Polymorphisms on Pioglitazone Response in Chinese Type 2 Diabetes Patients

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Key Words

IGF2BP2 rs1470579 · *IGF2BP2* rs4402960 · Genetic polymorphisms · Type 2 diabetes mellitus · Pioglitazone · Therapeutic efficacy

Abstract

Background: Genome-wide association studies identified that insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) genetic polymorphisms are related to type 2 diabetes mellitus (T2DM) in several populations. This study aimed to investigate whether the *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms were associated with T2DM and pioglitazone efficacy in Chinese T2DM patients. **Methods:** A total of 281 T2DM patients and 111 healthy volunteers were enrolled to identify the *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms; 86 patients were randomly selected and given a 12-week pioglitazone treatment (30 mg/day). Fasting plasma glucose, postprandial plasma glucose (PPG), glycated hemoglobin, serum triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined before and after pioglitazone treatment. **Results:** The results showed that the *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms were associated with T2DM in a Chinese

population (OR = 2.002, 95% CI 1.170–3.426, $p < 0.05$; OR = 1.879, 95% CI 1.110–3.182, $p < 0.05$). The effect of pioglitazone on PPG ($p < 0.05$), TG ($p < 0.01$) and HDL-C ($p < 0.05$) was lower in patients with the rs1470579 AC+CC genotypes than in AA genotype carriers. Its effect on PPG level was also lower in patients with the GT+TT genotypes of rs4402960 than in patients with the GG genotype ($p < 0.05$). **Conclusions:** The *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms were associated with T2DM and therapeutic efficacy of pioglitazone in this Chinese population.

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Introduction

Diabetes mellitus is a kind of metabolic disease which is characterized by high blood sugar. Around the globe, there were 366 million diabetes patients in 2011, and it is estimated that there will be 552 million patients in 2030 [1]. Type 2 diabetes mellitus (T2DM) accounts for 90–95% of new-onset diabetes annually [2]. The development of T2DM is influenced by genetic components and

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environmental factors [3–5]. Genetic studies such as high-throughput technology genome-wide association studies have identified some new loci related to T2DM in recent years [6–11]. It has been proved that the insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) gene rs1470579 and rs4402960 polymorphisms [6] are associated with susceptibility to and the development of T2DM. This association was also replicated in Asian populations [7–9].

IGF2BP2 is an mRNA-binding protein which is involved in RNA location, stability and translation [10]. *IGF2BP2* regulates insulin-like growth factor 2 (*IGF2*) translation by binding to the 5' UTR of the *IGF2* mRNA. *IGF2* also plays an important role in the growth and insulin signaling pathways [11]. *IGF2BP2* gene rs1470579- and rs4402960- mutated carriers showed a moderately increased risk of T2DM in genome-wide association study results. T2DM patients with different *IGF2BP2* genotypes showed various levels of insulin secretion. It has been demonstrated that variants in the *IGF2BP2* gene affect first-phase insulin secretion and the disposition index detected by hyperglycemic clamps [12].

Thiazolidinediones (TZD) are insulin-sensitizing agents which could decrease fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels by increasing glucose uptake in the peripheral tissue [2]. Pioglitazone is a new TZD, and the only available one which has been widely used for T2DM therapy [13, 14]. The therapeutic efficacy of pioglitazone showed individual differences. It has been proved that T2DM patients with different peroxisome proliferator-activated receptor- γ [15] or resistin [16] genotypes showed distinctive effects in multiple-dose pioglitazone therapy.

In this study, we intended to investigate the effect of the *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms on the therapeutic efficacy of pioglitazone in Chinese T2DM patients.

Subjects and Methods

Subjects

The study group included 281 unrelated T2DM patients from the First and Third Affiliated Hospitals of the Anhui Medical University and 111 unrelated normoglycemic control subjects from the First Affiliated Hospital of the Anhui Medical University. The inclusion criteria were as follows: (1) T2DM was diagnosed in accordance with World Health Organization criteria in 1999 (FPG ≥ 7.0 mmol/l or 2-hour PPG ≥ 11.1 mmol/l); (2) body mass index (BMI) between 19 and 30; (3) no prior TZD use, and (4) no change in medication in the previous 3 months. Normoglycemic control subjects were selected by an FPG < 6.1 mmol/l and a 2-hour PPG

< 7.8 mmol/l. The exclusion criteria were as follows: (1) type 1 diabetes mellitus; (2) ischemic heart disease, congestive heart failure, kidney or liver diseases; (3) insulin treatment or other drugs which affect the glucose metabolism (such as glucocorticoids), and (4) pregnancy or lactation in women.

A total of 86 T2DM patients, who received a daily dose of 30 mg oral pioglitazone (Kasiping, Hangzhou, China) for 12 consecutive weeks, were recruited from the Third Xiangya Hospital of the Central South University and the Third Affiliated Hospital of the Anhui Medical University. These patients were advised to maintain the same levels of energy intake and physical activity. The local ethics committee approved the protocol, and all subjects signed the informed consent form before the study started. We also applied for clinical admission to the Chinese Clinical Trial Register (No. ChiCTR-RNC-12001949).

Clinical Measurements

Venous blood samples of the subjects were collected in the fasting state and 2 h after a standardized breakfast at week 0 and week 12 (the end of administration). The BMI was calculated as the weight in kilograms divided by body height in meters squared. Concentrations of FPG, total cholesterol (TC) and triglyceride (TG) were determined by enzymatic colorimetric assay. The high-density lipoprotein cholesterol (HDL-C) concentration was measured by lipoprotein electrophoresis. The low-density lipoprotein cholesterol (LDL-C) concentration was calculated according to the Friedewald formula [17]. Plasma HbA_{1c} levels were measured by high-performance liquid chromatography assay.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the Promega DNA Purification Kit (Promega, USA). The *IGF2BP2* gene rs4402960 and rs1470579 polymorphisms were genotyped using the polymerase chain reaction-restriction fragment length polymorphism method. All the primers and reagents were previously described [9].

Statistical Analysis

All analyses were performed with SPSS software (version 17.0 for Windows; SPSS Inc., Chicago, Ill., USA). Measurement data are expressed as means $\pm$ SD (95% CI). The Hardy-Weinberg equilibrium and frequencies were assessed with a Pearson χ^2 test. Continuous variables were compared using Student's *t* test between the T2DM and control groups. Nonnormally distributed data were analyzed by the Mann-Whitney test. OR were calculated using a logistic regression analysis while adjusting for BMI, TG and LDL. Differences between before and after pioglitazone treatment were analyzed by paired *t* tests. Statistical power was calculated by the power calculator software PASS (www.ncss.com). A *p* value < 0.05 was considered to be statistically significant.

Results

The *IGF2BP2* Gene rs1470579 and rs4402960 Polymorphisms Were Associated with T2DM

We conducted a case-control study to detect whether the rs1470579 and rs4402960 polymorphisms of the

Table 1. Association study of two *IGF2BP2* gene polymorphisms and T2DM

	Subjects, n (%)	p ^a	Univariate analysis		Multivariate analysis		
			OR (95% CI)	p ^b	OR (95% CI)	p ^c	
<i>T2DM patient group</i>							
rs1470579 AA	143 (50.89)						
rs1470579 AC+CC	138 (49.11)						
<i>Healthy control group</i>							
rs1470579 AA	67 (60.36)		1.00 (reference)		1.00 (reference)		
rs1470579 AC+CC	44 (39.64)	0.090	1.616 (1.046–2.497)	0.031	2.002 (1.170–3.426)	0.011	
<i>T2DM patient group</i>							
rs4402960 GG	136 (48.40)						
rs4402960 GT+TT	145 (51.60)						
<i>Healthy control group</i>							
rs4402960 GG	69 (62.16)		1.00 (reference)		1.00 (reference)		
rs4402960 GT+TT	42 (37.84)	0.014	1.650 (1.046–2.602)	0.031	1.879 (1.110–3.182)	0.019	

^a p values for overall comparison between T2DM patients and healthy controls by the χ^2 test. ^b p values and their OR for genotypes were calculated by logistic regression analysis in the recessive model. ^c p values for multivariate analyses were adjusted by BMI, TG and LDL.

IGF2BP2 gene were associated with T2DM. A total of 281 unrelated T2DM patients and 111 healthy controls were genotyped. The genotypic distributions of the two polymorphisms were in agreement with the Hardy-Weinberg equilibrium ($p > 0.05$). Considering that the frequency of the mutated homozygous genotype was limited, we thus applied a recessive model in this analysis. The recessive model showed that the rs1470579 genotype was significantly associated with T2DM and C allele carriers had a relative risk of 1.616 (95% CI 1.046–2.497). The G allelic frequency of the rs4402960 polymorphism in T2DM patients was obviously higher than that in healthy controls ($p < 0.05$). The rs4402960 genotype was also significantly associated with T2DM, and T allele carriers had a relative risk of 1.650 (95% CI 1.046–2.602). After adjustment for BMI, TG and LDL, both polymorphisms showed to be correlated with T2DM (OR = 2.002, 95% CI 1.170–3.426, for rs1470579; OR = 1.879, 95% CI 1.110–3.182, for rs4402960; table 1).

Comparisons of Baseline Blood Characteristics between T2DM Patients with Different Genotypes

The baseline clinical characteristics of all T2DM patients with different rs1470579 and rs4402960 genotypes are summarized in table 2. There were no significant differences in sex composition, age or BMI between differ-

ent genotypic groups. We found that patients with the C allele of rs1470579 had higher FPG (9.58 ± 3.49 vs. 8.84 ± 3.71 mmol/l, $p < 0.05$) and PPG (16.73 ± 6.28 vs. 15.09 ± 5.54 mmol/l, $p < 0.05$) levels than AA genotype carriers (table 2; fig. 1). With regard to the rs4402960 polymorphism, we found that patients with the T allele had higher FPG (10.21 ± 4.04 vs. 8.50 ± 2.94 mmol/l, $p < 0.01$) and PPG (17.20 ± 6.63 vs. 15.16 ± 5.11 mmol/l, $p < 0.05$) levels than GG genotype carriers (table 2; fig. 2). Therefore, patients with a mutated *IGF2BP2* gene rs1470579 or rs4402960 polymorphism showed worse blood glucose control.

Changes in Blood Characteristics of T2DM Patients after Pioglitazone Treatment

A total of 86 T2DM patients (48 male and 38 female) were treated daily with 30 mg oral pioglitazone for 12 consecutive weeks. Pioglitazone significantly decreased the concentrations of FPG (8.23 ± 1.14 vs. 7.01 ± 1.04 mmol/l, $p < 0.001$), PPG (12.62 ± 2.84 vs. 10.52 ± 2.92 mmol/l, $p < 0.001$), HbA_{1c} (7.63 ± 1.36 vs. $6.68 \pm 0.93\%$, $p < 0.001$), TG (2.27 ± 2.35 vs. 1.81 ± 1.15 mmol/l, $p < 0.001$) and TC (4.98 ± 0.95 vs. 4.70 ± 0.80 mmol/l, $p < 0.05$) in T2DM patients (table 3).

Table 2. Baseline clinical and biochemical characteristics of the different genotypes of the *IGF2BP2* gene in T2DM patients

Parameters	rs1470579 genotypes		p	rs4402960 genotypes		p
	AA	AC+CC		GG	GT+TT	
Number (M/F)	143 (72/71)	138 (66/72)	0.716 ^a	136 (66/70)	145 (72/73)	0.850 ^a
Age, years	50.51±10.33 (48.77–52.25)	52.12±10.99 (50.14–54.09)	0.226	50.82±10.79 (49.06–52.59)	51.81±11.25 (49.76–53.86)	0.467
BMI	25.69±3.39 (25.11–26.27)	25.38±3.62 (24.72–26.04)	0.479	25.81±3.44 (25.12–26.27)	25.83±3.40 (25.20–26.45)	0.747
FPG, mmol/l	8.84±3.71 (8.24–9.44)	9.58±3.49 (9.03–10.12)	0.021 ^{a,b}	8.50±2.94 (7.99–9.02)	10.21±4.04 (9.54–10.88)	0.002 ^{a,b}
PPG, mmol/l	15.09±5.54 (14.15–16.02)	16.73±6.28 (15.72–17.75)	0.025 ^b	15.16±5.11 (14.22–16.09)	17.20±6.63 (16.07–18.33)	0.018 ^{a,b}
HbA _{1c} , %	9.33±6.13 (8.26–10.40)	8.65±2.49 (8.23–9.08)	0.235	9.18±6.38 (8.00–10.37)	8.98±2.65 (8.51–9.44)	0.623 ^b
TG, mmol/l	3.39±3.59 (2.75–4.04)	2.71±2.29 (2.27–3.15)	0.237 ^b	3.28±3.66 (2.63–3.93)	2.74±2.10 (2.34–3.15)	0.722 ^b
TC, mmol/l	4.99±1.96 (4.66–5.32)	4.95±1.53 (4.68–5.21)	0.833	5.04±2.06 (4.67–5.42)	4.92±1.48 (4.66–5.19)	0.525 ^b
HDL-C, mmol/l	1.47±1.02 (1.28–1.65)	1.32±0.56 (1.21–1.43)	0.519 ^b	1.40±1.10 (1.20–1.60)	1.30±0.57 (1.17–1.41)	0.980 ^b
LDL-C, mmol/l	2.72±0.99 (2.54–2.90)	2.78±1.23 (2.58–2.97)	0.657	2.83±1.00 (2.64–3.03)	2.68±1.15 (2.47–2.88)	0.282

Data are given as means ± SD with 95% CI in parentheses unless specified otherwise. * $p < 0.05$; ** $p < 0.01$. ^a p values represent the statistical difference between the AA and AC+CC (GG and GT+TT) genotype groups and were assessed by the two-sample t test. ^b p values were determined by the Mann-Whitney test.

Fig. 1. Comparisons of the baseline levels of FPG (a) and PPG (b) in T2DM patients with different *IGF2BP2* gene rs1470579 genotypes. Data are means ± SD. * $p < 0.05$ compared with the AA genotype ($n = 281$).

Fig. 2. Comparisons of the baseline levels of FPG (a) and PPG (b) in T2DM patients with different *IGF2BP2* gene rs4402960 genotypes. Data are means ± SD. * $p < 0.05$, ** $p < 0.01$, compared with the GG genotype ($n = 281$).

Influence of the IGF2BP2 Gene Polymorphisms on the Therapeutic Efficacy of Pioglitazone in T2DM Patients

We analyzed all the differences between post- and pre-treatment values (DV) between different *IGF2BP2* genotypes. The effect of pioglitazone was significantly lower in

patients with the *IGF2BP2* gene rs1470579 AC+CC genotype with regard to PPG (DV -1.07 ± 4.04 mmol/l), TG (DV 0.05 ± 0.72 mmol/l) and HDL-C (DV -0.02 ± 0.29 mmol/l) compared with AA genotype carriers (DV for PPG: -2.65 ± 3.85 mmol/l, $p < 0.05$; DV for TG: $-0.66 \pm$

Table 3. Clinical characteristics of all T2DM patients before and after pioglitazone treatment

Parameters	Before	After	p
FPG, mmol/l	8.23±1.14 (8.00–8.47)	7.01±1.04 (6.78–7.24)	<0.000**
PPG, mmol/l	12.62±2.84 (11.99–13.25)	10.52±2.92 (9.87–11.16)	<0.000**
HbA _{1c} , %	7.63±1.36 (7.33–7.93)	6.68±0.93 (6.47–6.88)	<0.000**
TG, mmol/l	2.27±2.35 (1.75–2.79)	1.81±1.15 (1.56–2.07)	0.003**
TC, mmol/l	4.98±0.95 (4.77–5.19)	4.70±0.80 (4.52–4.87)	0.036*
HDL-C, mmol/l	1.10±0.31 (1.03–1.17)	1.12±0.37 (1.03–1.21)	0.252
LDL-C, mmol/l	2.89±0.80 (2.71–3.06)	2.73±0.73 (2.57–2.89)	0.082

Data are given as means ± SD with 95% CI in parentheses. p values were determined by the paired Student t test. * p < 0.05; ** p < 0.01.

Fig. 3. Comparisons of the DV of PPG (a), TG (b) and HDL-C (c) between the AA genotype and the AC+CC genotypes of the *IGF2BP2* gene rs1470579 polymorphism in T2DM patients. Data are means ± SD. * p < 0.05, ** p < 0.01, compared with the AA genotype (n = 86).

2.18, p < 0.01 mmol/l; DV for HDL-C: 0.08 ± 0.38 mmol/l, p < 0.05; table 4; fig. 3). Meanwhile, pioglitazone showed a lower effect in patients with the GT+TT genotypes of rs4402960 with regard to the PPG level (DV -0.70 ± 3.92 mmol/l) compared with GG genotype carriers (DV -2.80 ± 3.81 mmol/l, p < 0.05; table 4; fig. 4).

Discussion

In the present study, we explored the effects of the *IGF2BP2* gene rs1470579 and rs4402960 polymorphisms on pioglitazone response in Chinese T2DM patients. These polymorphisms have been shown to be associated with T2DM in several populations [18–20]. The relation between polymorphism rs1470579 and T2DM has been found in Japanese [8, 19], Israeli [21], Lebanese [22] and Tunisian Arabs [23]. Our results showed that the frequencies of different genotypes of polymorphism

Fig. 4. Comparison of the DV of PPG between the GG genotype and the GT+TT genotypes of the *IGF2BP2* gene rs4402960 polymorphism in T2DM patients. Data are means ± SD. * p < 0.05 compared with the GG genotype (n = 86).

Table 4. Comparisons of DV in T2DM patients with different rs1470579 and rs4402960 genotypes before and after pioglitazone treatment

Parameters	rs1470579 genotype		P	rs4402960 genotype		P
	AA	AC+CC		GG	GT+TT	
Number (M/F)	57 (33/24)	29 (15/14)	0.541 ^a	61 (35/26)	25 (13/12)	0.648 ^a
<i>FPG, mmol/l</i>						
Baseline	8.18±1.03 (7.90–8.45)	8.28±1.07 (7.87–8.69)	0.653	8.28±1.12 (8.00–8.57)	8.05±0.84 (7.71–8.40)	0.359
After treatment	6.86±0.92 (6.61–7.09)	7.30±1.22 (6.83–7.76)	0.060	6.89±0.97 (6.65–7.14)	7.21±1.19 (6.72–7.70)	0.199
DV FPG	–1.32±1.04 (–1.59 to –1.05)	–0.98±1.34 (–1.49 to –0.48)	0.332 ^b	–1.39±1.11 (–1.67 to –1.10)	–0.84±1.13 (–1.31 to –0.37)	0.084 ^b
<i>PPG, mmol/l</i>						
Baseline	12.91±2.86 (12.16–13.66)	12.20±3.23 (10.97–13.43)	0.300	13.11±3.21 (12.29–13.93)	11.72±2.11 (10.85–12.59)	0.049*
After treatment	10.26±2.98 (9.47–11.04)	11.13±2.87 (10.04–12.23)	0.194	10.31±2.67 (9.63–11.00)	11.03±3.59 (9.55–12.51)	0.315
DV PPG	–2.65±3.85 (–3.66 to –1.64)	–1.07±4.04 (–2.60 to 0.47)	0.031 ^b	–2.80±3.81 (–3.78 to –1.82)	–0.70±3.92 (–2.31 to 0.92)	0.018 ^{a, b}
<i>HbA_{1c}, %</i>						
Baseline	7.63±1.44 (7.26–8.01)	7.72±1.39 (7.25–8.30)	0.671	7.56±1.47 (7.19–7.94)	7.85±1.18 (7.37–8.34)	0.383
After treatment	6.60±0.91 (6.36–6.84)	6.79±0.94 (6.43–7.15)	0.441	6.55±0.71 (6.37–6.73)	6.86±1.25 (6.35–7.38)	0.247
DV HbA _{1c}	–1.04±1.44 (–1.42 to –0.66)	–0.99±1.29 (–1.48 to –0.49)	0.570 ^b	–1.01±1.34 (–1.36 to –0.67)	–0.99±1.51 (–1.61 to –0.36)	0.571 ^b
<i>TG, mmol/l</i>						
Baseline	2.40±2.64 (1.70–3.09)	1.81±1.25 (1.34–2.29)	0.989 ^b	2.30±2.60 (1.64–2.97)	2.00±1.31 (1.46–2.54)	0.812 ^b
After treatment	1.74±1.10 (1.45–2.02)	1.86±1.23 (1.40–2.33)	0.957 ^b	1.77±1.03 (1.51–2.04)	1.82±1.40 (1.24–2.39)	0.873
DV TG	–0.66±2.18 (–1.24 to –0.09)	0.05±0.72 (–0.22 to 0.33)	0.007 ^b	–0.53±2.13 (–1.08 to 0.02)	–0.18±0.92 (–0.56 to 0.20)	0.672 ^b
<i>TC, mmol/l</i>						
Baseline	5.00±0.88 (4.76–5.23)	4.93±1.02 (4.54–5.32)	0.346	4.96±0.92 (4.72–5.19)	5.04±0.97 (4.64–5.44)	0.707
After treatment	4.80±0.78 (4.59–5.00)	4.55±0.79 (4.24–4.84)	0.154	4.73±0.83 (4.52–4.95)	4.67±0.69 (4.39–4.96)	0.759
DV TC	–0.20±0.67 (–0.38 to –0.02)	–0.39±1.01 (–0.77 to 0.00)	0.531 ^b	–0.22±0.69 (–0.40 to –0.05)	–0.37±1.04 (–0.80 to 0.06)	0.754 ^b
<i>HDL-C, mmol/l</i>						
Baseline	1.06±0.35 (0.96–1.15)	1.14±0.33 (1.02–1.27)	0.684	1.09±0.32 (1.01–1.17)	1.07±0.40 (0.91–1.23)	0.791
After treatment	1.13±0.36 (1.04–1.23)	1.12±0.42 (0.96–1.28)	0.881	1.11±0.36 (1.02–1.21)	1.18±0.44 (0.99–1.36)	0.495
DV HDL-C	0.08±0.38 (–0.02 to 0.18)	–0.02±0.29 (–0.13 to 0.08)	0.048 ^b	0.02±0.35 (–0.07 to 0.11)	0.11±0.37 (–0.05 to 0.26)	0.438 ^b
<i>LDL-C, mmol/l</i>						
Baseline	22.91±0.82 (2.69–3.13)	2.90±0.76 (2.62–3.19)	0.482	2.89±0.83 (2.68–3.10)	2.96±0.76 (2.64–3.27)	0.744
After treatment	2.84±0.68 (2.67–3.02)	2.57±0.80 (2.27–2.88)	0.101	2.75±0.72 (2.56–2.93)	2.76±0.78 (2.44–3.09)	0.922
DV LDL-C	–0.07±0.73 (–0.26 to 0.13)	–0.33±0.96 (–0.70 to 0.03)	0.161 ^b	–0.15±0.66 (–0.31 to 0.02)	–0.19±1.15 (–0.67 to 0.28)	0.549 ^b

Data are given as means ± SD with 95% CI in parentheses. * $p < 0.05$. ^a p values represent the statistical difference between the AA and AC+CC (GG and GT+TT) genotype groups and were assessed by the two-sample t test. ^b p values were determined by the Mann-Whitney test.

rs1470579 were not significantly different between the T2DM patients and the control group. However, the OR was 2.002 (95% CI 1.170–3.426, $p < 0.05$) after adjustment for BMI, TG and LDL. We found that T2DM patients with the C allele of rs1470579 had higher FPG ($p < 0.05$) and PPG ($p < 0.05$) levels than those with the AA genotype. An association of polymorphism rs4402960 with T2DM has been reported in Caucasians such as Swedes [24], Danes [25] and French [21] as well as in Asians such as Japanese [26] and Chinese [27]. In our research, the frequency of T2DM occurrence was higher in mutated rs4402960 GT+TT carriers than in the GG genotype group ($p < 0.05$), and the OR was 1.879 (95% CI 1.110–

3.182, $p < 0.05$) after adjustment for BMI, TG and LDL. We found that T2DM patients with the T allele had higher FPG ($p < 0.01$) and PPG ($p < 0.05$) levels than those with the GG genotype. Ruchat et al. [28] reported a strong association between the *IGF2BP2* gene rs4402960 polymorphism and glucose tolerance, such as FPG, glucose area under the curve and PPG. These two polymorphisms in the *IGF2BP2* gene were also associated with pancreatic β -cell function [20]. All the evidence indicated that mutated *IGF2BP2* gene carriers showed worse conditions in T2DM development.

IGF2BP2 belongs to the IGF2 mRNA-binding protein family and regulates its translation. IGF2 is a member of

the insulin family of polypeptide growth factors, which plays an important role in the development, growth and stimulation of insulin action [29]. IGFBP homologs make a potential contribution to pancreatic development [30, 31]. *IGF2BP2* gene variations are also associated with pancreatic β -cell function [20] and hyperglycemia [28]. The *IGF2BP2* gene is located on chromosome 3q27.2. Polymorphisms rs1470579 and rs4402960 are in intron 2 of this gene. How the polymorphisms in this intron affect gene function should be further investigated. Possible mechanisms could be alternative splicing, microRNA or antisense mRNA transcription, etc. Other genes such as the insulin-sensitizing adipokine adiponectin (*ADIPOQ*) and protein phosphatase 1, regulatory subunit 2 (*PPP1R2*), which are located in proximity to *IGF2BP2*, could also contribute to the regulation of insulin function [32].

T2D improved insulin sensitivity by inhibiting mitochondrial fuel oxidation and increasing glucose transport in skeletal muscle cells [33]. Because the *IGF2BP2* gene showed an effect on T2DM development and insulin function and variations in this gene were associated with insulin sensitivity and glucose tolerance [28], we hypothesized that *IGF2BP2* gene mutations could change the therapeutic efficacy of pioglitazone. In this case-control study, we found that T2DM patients with the *IGF2BP2* gene rs1470579 AC+CC genotypes showed lower pioglitazone effects on PPG ($p < 0.05$), TG ($p < 0.01$) and HDL-C ($p < 0.05$) concentrations than rs1470579 AA genotype carriers. The effect of pioglitazone on the PPG level was also lower in patients with the GT+TT genotypes of rs4402960 than in individuals with the GG genotype ($p < 0.05$).

The relatively small sample size is one of the limitations of this study. Therefore, we calculated the power values for each analysis, which ranged from 75 to 95%. We will need larger sample sizes for analysis in our future study. Another limitation is the lack of pioglitazone plasma concentration values. We selected CYP2C8*1*1 genotype individuals for pioglitazone testing to exclude the pharmacokinetic influences of pioglitazone [34, 35].

In summary, the genetic polymorphisms rs1470579 and rs4402960 of the *IGF2BP2* gene were associated with the therapeutic efficacy of pioglitazone in Chinese T2DM patients. Patients with rs1470579 polymorphism AC+CC genotypes or with rs4402960 polymorphism GT+TT genotypes appeared to experience a lower therapeutic efficacy of pioglitazone. However, the exact molecular mechanism needs to be elucidated in the future.

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Disclosure Statement

The authors have no potential conflicts of interest to disclose.

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Erratum

In the article by Zhang LF, Pei Q, Yang GP, Zhao YC, Mu YF, Huang Q and Zhu YL, entitled ‘The effect of *IGF2BP2* gene polymorphisms on pioglitazone response in Chinese type 2 diabetes patients’ [Pharmacology 2014;94:115–122, DOI: 10.1159/000363414], the following additional information needs to be added:

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