Int J Clin Exp Pathol 2015;8(11):15191-15197
www.ijcep.com /ISSN:1936-2625/IJCEP0016670

Original Article

Association of GSTs polymorphisms with risk of gestational diabetes mellitus

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Received September 22, 2015; Accepted October 25, 2015; Epub November 1, 2015; Published November 15, 2015

Abstract: We conducted a case-control study to investigate the association between *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphisms and development of gestational diabetes mellitus in a Chinese population. A total of 320 patients with gestational diabetes mellitus and 358 pregnancy subjects were consecutively collected between January 2013 and December 2014. Genotyping for detection of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val was conducted by using PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphisms) method. By Fisher's exact test, we found that the genotype distributions of *GSTP1* Ile105Val were in line with the Hardy-Weinberg equilibrium in control subjects (P=0.57). By Chi-square test, we found significant differences in the genotype distributions of *GSTM1* (χ^2=11.49, P=0.001) and *GSTT1* (χ^2=18.50, P<0.001). Using unconditional logistic analysis, individuals carrying the null genotypes of *GSTM1* and *GSTT1* were associated with an increased risk of gestational diabetes mellitus when compared with the present genotype, and the adjusted Ors (95% CI) were 1.71 (1.24-2.36) and 2.00 (1.44-2.79), respectively. However, the *GSTP1* Ile105Val polymorphism was not associated with an elevated risk of gestational diabetes mellitus. In conclusion, we suggest that the *GSTM1* null genotype and *GSTT1* null genotype are correlated with an increased risk of gestational diabetes mellitus in a Chinese population.

Keywords: *GSTM1*, *GSTT1*, *GSTP1* Ile105Val, polymorphism, gestational diabetes mellitus

Introduction

Gestational diabetes mellitus is one type of diseases which only occurs in pregnant women [1], which is defined as carbohydrate intolerance during pregnancy. It is estimated that the incidence of gestational diabetes mellitus is between 2.4% and 22.3% among pregnant women worldwide [2, 3]. The development of gestational diabetes mellitus is resulted from complex multifactorial environmental and lifestyle factors, such as pregnancies at older age, prepregnancy high weight and BMI, family history of diabetes mellitus, dietary habit, physical inactivity and a history of gestational diabetes [4-9]. However, not all the pregnancies would develop gestational diabetes mellitus even when they expose to the same risk factors of gestational diabetes mellitus, which suggests that the hereditary factors may contribute to the development of gestational diabetes mellitus. Currently, many studies have reported that the genetic factors play an important role in the development of gestational diabetes mellitus, such as KCNQ1, MTHFR, FVL, G22A, Calpain 10 and TCF7L2 [10-14].

Glutathione-S-transferases (GSTs) belong to the family of cytosolic enzymes, which play an important role in the cellular defense system [15]. The main function of GSTs is to detoxify environmental toxicants and reactive oxygen species mediated cell injury in body, catalyze the harmful compounds in the combined with glutathione, and finally prevent the DNA damage in body [15, 16]. Three functional genes have been found in GSTs, including *GSTM1*, *GSTT1* and *GSTP1* Ile105Val. The polymorphisms of *GSTM1* and *GSTT1* could reduce the enzyme activities and binding activity of the two genes [17]. Only one previous study has investigated the association between the genetic polymorphisms and development of gestational diabetes mellitus [18]. Therefore, we conducted a case-control study to investigate the association between *GSTM1*, *GSTT1* and *GSTP1* Ile-

105Val polymorphisms and development of gestational diabetes mellitus in a Chinese population.

Patients and methods

Patients

Between January 2013 and December 2014, a total of 320 patients with gestational diabetes mellitus were consecutively collected from our hospital. All patients with gestational diabetes mellitus were between 25 and 40 years old. The diagnosis of gestational diabetes mellitus was based on the criteria from American Diabetes Association [19], and the gestational age is between 24 and 28th weeks of gestation with a 75 g, 2 h OGTT after overnight fast. The inclusion criteria for the gestational diabetes mellitus were patients without using oral hypoglycemic agents. The exclusion criteria were patients with pre-existing diabetes and hepatic and kidney diseases as well as endocrine disorders.

A total of 358 pregnancy subjects without gestational diabetes mellitus were randomly selected from individuals who received the regular prenatal in the Department of Obstetrics and Gynecology during the same period time. Controls that had a history of hypertension, diabetes and hepatic and kidney diseases as well as endocrine disorders were excluded from our study.

The demographic and clinical information of patients with gestational diabetes mellitus and control subjects were collected from a self-designed questionnaire or medical records. The demographic information included sex, age, Body Mass Index and a history of gestational diabetes mellitus. The clinical information included systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol (TC), triglyceride (TG), low density lipopolysaccharide cholesterol (LDL-c) and high density lipopolysaccharide (HDL-c). The signed written informed consents were collected from all patients with gestational diabetes mellitus and control subjects.

DNA extraction and genotyping

Five ml of fasting venous blood were drawn from all patients and control subjects after participating into this study. The blood samples were stored in tubes with ethylene diamine tetraacetic acid (EDTA), and then the blood was centrifuged to separate the plasma content. The genomic DNA was extracted from the EDTA treated whole blood using the TIANamp Blood DNA Kit (Tiangen, Beijing, China). Genotyping for detection of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val was conducted by using PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphisms) method. Genotyping for detection of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val was amplified by the following forward and reverse primers. For *GSTM1*, the primers were 5'-CTGCCCTACTTGATTGATGGG-3' (forwards) and 5'-CTGGATTGTAGCAGATCATGC-3' (reverse); For GSTT1, the primers were 5'-TTCCTTACTGGTCCTCACATCTC-3' (forwards) and 5'-TCACCGGATCATGGCCAGCA-3' (reverse); For GSTP1, the primers were the primers were 5'-GAA GAG CCA AGG ACA GGT AC-3' (forwards) and 5'-CAA CTT CAT CCA CGT TCA CC-3' (reverse). The fragment lengths for *GSTM1*, *GSTT1* and *GSTP1* Ile105Val were 215 bp, 480 bp and 176 bp. The PCR conditions were as follows: an initial denaturation at 95°C for 5 min, 35 cycles of amplification with denaturation at 95°C for 30 sec, annealing at 56°C for 30 sec, and extension at 72°C for 30 sec, followed by a final extension step of 7 min at 72°C. For quality control, 10% of the samples were randomly selected to evaluate the reproducibility of the genotyping procedure. The genotyping success rate was 100%.

Statistical methods

Continuous variables were expressed as means ± standard deviation, and categorical variables were expressed as N (%) of study participants. Differences of the characteristics between patients with gestational diabetes mellitus and control subjects were compared using the Chi-square test or student t-test. Whether confirming with the Hardy-Weinberg equilibrium was analyzed by the Fisher's exact test. The association between *GSTM1*, *GSTT1* and *GSTP1* Ile105Val and risk of gestational diabetes mellitus was analyzed using conditional logistic regression analysis. The results were evaluated by the odds ratio (OR) and 95% confidence intervals (CIs). The wide-type genotype of *GSTM1*, *GSTT1* and *GSTP1* Ile105Val was considered as reference group. Statistical analysis was conducted using the SPSS 17.0 package (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a significant difference.

Table 1. Characteristics between patients with gestational diabetes mellitus and control subjects

Variables	Patients N=320	%	Controls N=358	%	Chi-square test or student t-test	*P* value
Age, years	32.23 ±10.43		27.35± 11.53		4.50	<0.001
<30	135	42.19	224	62.57		
≥30	185	57.81	134	37.43	28.18	<0.001
Gestational age	26.16±5.11		26.35±5.35		0.47	0.32
BMI, kg/m^2	30.62±6.14		27.65±5.26		6.72	<0.001
<28	107	33.44	232	64.80		
≥28	213	66.56	126	35.20	66.49	<0.001
Fasting plasma glucosa, mg/dl	92.30±24.25		75.65±15.32		10.80	<0.001
HOMA-IR	4.57±2.75		3.44±2.01		6.15	<0.001
TG, mg/dl	261.10±115.20		265.55±112.75		0.51	0.31
TC, mg/dl	232.47±48.60		238.42±44.42		1.67	0.05
HDL-C, mg/dl	51.52±13.25		52.15±12.68		0.63	0.26
LDL-C, mg/dl	121.43±26.20		124.37±25.36		1.48	0.07

BMI: body mass index; HOMA-IR: homeostasis model assessment index for insulin resistance; TG: Triglycerides; TC: Total Cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

Table 2. Association between *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphisms and development of gestational diabetes mellitus

Genotypes	Patients N=320	%	Controls N=358	%	Chi-square test	*P* value	HWE	OR (95% CI)[1]	*P* value
GSTM1									
Present	171	53.44	237	66.20				1.0 (Reference)	-
Null	149	46.56	121	33.80	11.49	0.001		1.71 (1.24-2.36)	0.001
GSTT1									
Present	178	55.63	256	71.51				1.0 (Reference)	-
Null	142	44.38	102	28.49	18.50	<0.001		2.00 (1.44-2.79)	<0.001
GSTP1 Ile105Val									
Codominant									
Ile/Ile	145	45.31	178	49.72				1.0 (Reference)	-
Ile/Val	142	44.38	152	42.46				1.15 (0.82-1.59)	0.39
Val/Val	33	10.31	28	7.82	2.00	0.37	0.57	1.45 (0.81-2.61)	0.19
Dominant									
Ile/Ile+Ile/Val	287	89.69	330	92.18				1.0 (Reference)	-
Val/Val	33	10.31	28	7.82	1.28	0.26		1.36 (0.77-2.39)	0.26
Recessive									
Ile/Ile	145	45.31	178	49.72				1.0 (Reference)	-
Ile/Val+Val/Val	175	54.69	180	50.28	1.32	0.25		1.19 (0.87-1.63)	0.25

[1]Adjusted for age, BMI, fasting plasma glucosa and HOMA-IR.

Results

The characteristics of patients with gestational diabetes mellitus and control subjects were observed in **Table 1**. The mean ages of patients and controls were 32.23 ± 10.43 and 27.35 ± 11.53 years, respectively. By Chi-square test or student t-test, patients with gestational diabetes mellitus were more likely to have higher age (t=4.50, P<0.001), BMI (t=6.72, P<0.001), fasting plasma glucose (t=10.80, P<0.001) and HOMA-IR (t=6.15, P<0.001), when compared with the control subjects. However, no significant differences between patients with gesta-

Table 3. Interaction between *GSTM1* polymorphism and demographic and clinical characteristics in the risk of gestational diabetes mellitus

Variables	Patients		Controls		OR (95% CI)	*P* value
	Present	Null	Present	Null		
Age, years						
<30	79	56	149	75	1.41 (0.88-2.24)	0.13
≥30	38	147	29	105	1.07 (0.60-1.90)	0.81
BMI, kg/m^2						
<28	65	42	145	87	1.08 (0.65-1.77)	0.76
≥28	52	161	33	93	1.10 (0.64-1.87)	0.72
Fasting plasma glucosa, mg/dl						
<80	59	45	131	81	1.23 (0.74-2.04)	0.39
≥80	58	158	47	99	1.29 (0.79-2.10)	0.27
HOMA-IR						
<4.0	75	55	146	92	1.16 (0.73-1.84)	0.49
≥4.0	42	148	32	88	1.28 (0.73-2.25)	0.36

Table 4. Interaction between *GSTT1* polymorphism and demographic and clinical characteristics in the risk of gestational diabetes mellitus

Variables	Patients		Controls		OR (95% CI)	*P* value
	Present	Null	Present	Null		
Age, years						
<30	82	53	143	81	1.14 (0.72-1.81)	0.56
≥30	35	150	35	99	1.52 (0.86-2.67)	0.13
BMI, kg/m^2						
<28	69	38	150	82	1.01 (0.60-1.67)	0.98
≥28	48	165	28	98	0.98 (0.56-1.72)	0.95
Fasting plasma glucosa, mg/dl						
<80	61	43	131	81	1.14 (0.69-1.89)	0.59
≥80	56	160	47	99	1.36 (0.83-2.21)	0.19
HOMA-IR						
<4.0	83	47	155	83	1.06 (0.66-1.69)	0.81
≥4.0	34	156	23	97	1.09 (0.58-2.03)	0.78

tional diabetes mellitus and control subjects in terms of gestational age (t=0.47, P=0.32), and levels of TG (t=0.51, P=0.31), TC (t=1.67, P=0.05), HDL-C (t=0.63, P=0.26) and LDL-C (t=1.48, P=0.07).

By Fisher's exact test, we found the genotype distributions of *GSTP1* Ile105Val were in line with the Hardy-Weinberg equilibrium in control subjects (P=0.57) (**Table 2**). By chi-square test, we found significant differences between the present and null genotype distributions of *GSTM1* (χ^2=11.49, P=0.001). Moreover, significant differences were also observed between the present and null genotype distributions of *GSTT1* (χ^2=18.50, P<0.001). Using unconditional logistic analysis, individuals carrying the null genotypes of *GSTM1* and *GSTT1* were associated with an increased risk of gestational diabetes mellitus when compared with the present genotype, and the adjusted Ors (95% CI) were 1.71 (1.24-2.36) and 2.00 (1.44-2.79), respectively. However, the *GSTP1* Ile105Val polymorphism was not associated with an elevated risk of gestational diabetes mellitus.

We also performed a gene-environmental association of *GSTM1* and *GSTT1* polymorphisms with age, BMI, fasting plasma glucosa and HOMA-IR for the risk of gestational diabetes

mellitus (**Tables 3** and **4**). We found null and present genotypes of *GSTM1* and *GSTT1* were not significant associated with increased risk of gestational diabetes mellitus regardless of age, BMI, fasting plasma glucosa and HOMA-IR.

Discussion

It is well known that individuals would not develop the same type of disease although they are exposing to the same environmental and lifestyle factors. Therefore, inherit factors may contribute to the development of diseases. Single nucleotide polymorphisms refer to the gene sequence of a single nucleotide bases inserting, missing or replacing to cause the polymorphism of the nucleic acid sequence [20]. Among millions of SNPs, the incidence of gene polymorphism is more than 1%, including transition, transversion, and insertion and deletion of single nucleotide. Gene polymorphisms could alter the gene expression, structure and quantity of the products, and thus influence the function of the gene [21, 22]. In the present study, we conducted a case-control study to investigate whether *GSTM1*, *GSTT1* and *GSTP1* Ile105Val polymorphisms could influence the susceptibility to gestational diabetes mellitus. We found that the *GSTM1* null genotype and *GSTT1* null genotype were associated with an increased risk of gestational diabetes mellitus.

The *GSTM1* locus is located on chromosome 1p13.3, and the *GSTT1* locus existed on chromosome 22q11.2 [23]. The *GSTM1* and *GSTT1* contribute to catalyzing the conjugation of glutathione to a variety of hydrophobic and electrophilic substrates and carcinogens such as benzpyrene and reactive oxygen species. The polymorphisms in GSTs could reduce or eliminate the detoxification activities of enzyme, and thus increase the susceptibility to disease, such as gestational diabetes mellitus. Previous studies have reported that polymorphisms in GSTs play an important role in the development of many diseases, such as type 2 diabetes, hypertension and nephropathy [24-26]. Abbas et al. conducted a study with 138 essential hypertension patients and 116 control subjects in India, and they reported that *GSTM1* null or positive genotype and *GSTT1* null or positive genotype were associated with the development of essential hypertension [24]. Pinheiro et al. conducted a study with 120 patients and 147 healthy individuals in Brazil, and they found that *GSTM1* null and *GSTT1* null genotypes may contribute to the susceptibility of T2DM patients [25]. Petrovič et al. conducted a study in 1015 Slovenian subjects with type 2 diabetes with or without essential arterial hypertension, and they reported that *GSTM1*-null and *GSTT1*-null genotypes contributed to the development of the essential arterial hypertension in patients with type 2 diabetes [26]. However, some studies reported inconsistent results [27]. Moasser et al. investigated the association between *GSTM1* and *GSTT1* gene polymorphisms and risk of diabetic retinopathy in Iranian population, and they suggested that *GSTM1* and *GSTT1* gene polymorphisms were associated with the pathogenesis of type 2 diabetes mellitus retinopathy [27].

Currently, only one previous study reported the association between polymorphisms of GSTs and risk of gestational diabetes mellitus [18]. This study conducted in a population with 50 gestational diabetes mellitus and 50 control subjects, and they found that *GSTM1* and *GSTT11* gene polymorphisms are not associated with the risk of gestational diabetes mellitus [18]. In our study, we found that the *GSTM1* null genotype and *GSTT1* null genotype were correlated with the development of gestational diabetes mellitus, which is inconsistent with the results of Orhan's. The discrepancies of the reported results might be caused by differences in ethnicities, selection of patients and controls, study design, or sample size. Further studies with large sample sizes are greatly needed to confirm our results.

We identified three limitations in our study. First, patients were selected from a single hospital, which might not be representative of the general population. Second, other genetic polymorphisms might have influenced the risk of gestational diabetes mellitus in addition to GSTs gene polymorphisms. Third, the sample size of this study was relatively small, which could limit the statistical power to identify the differences between groups. Further studies with large sample sizes are greatly needed to clarify the association of GSTs gene polymorphisms with the risk of gestational diabetes mellitus.

In conclusion, we suggest that the *GSTM1* null genotype and *GSTT1* null genotype are corre-

lated with an increased risk of gestational diabetes mellitus in a Chinese population. This finding could be helpful for identifying the genetic characteristics of gestational diabetes mellitus and developing more efficient strategies for prevention and treatment.

Disclosure of conflict of interest

None.

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