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ORIGINAL ARTICLE

Impaired glucolipid metabolism in gestational diabetes mellitus with T variation of TCF7L2 rs7903146: A case–control study

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Abstract

Background Transcription factor 7-like 2 (TCF7L2) rs7903146 polymorphism has been shown to display a significant association with gestational diabetes mellitus (GDM). But the effects of TCF7L2 rs7903146 on glucose and lipid metabolism are not clear.

Objective The purpose of this study was to assess the role of TCF7L2 rs7903146 genotypes on glycolipid metabolism in GDM.

Methods In total, 484 individuals (239 in GDM group and 245 in control group) were included in the final analysis from January 2015 to February 2022. Their baseline demographics, plasma lipid concentration in the first trimester and third trimester, blood glucose values of the OGTT during gestational 24–28 weeks, glycosylated hemoglobin, fasting plasma glucose and fasting insulin in third trimester, 1 min Apgar scores, 5 min Apgar scores, glucose values of cord blood, and umbilical artery pH were collected. TCF7L2 rs7903146 genotypes were analyzed by polymerase chain reaction-Sanger sequencing.

Results The frequencies of TCF7L2 rs7903146 genotype were found to have no significant differences between the two groups; however, the plasma lipid concentrations during the first trimester were higher in GDM group than control group. In GDM group, women carried the risk allele (T) in TCF7L2 rs7903146 displayed the significantly higher glucose values at 1-h during OGTT, and the higher TG and lower fasting insulin levels than those in non-carriers.

Conclusion Our results indicate that the risk allele (T) in TCF7L2 rs7903146 plays an important role in the abnormality of glucose and lipid metabolism in GDM women. For the risk allele(T) carriers of TCF7L2 rs7903146, low-fat and low-sugar diets, exercise interventions can be carried out at an early stage, and insulin therapy should be considered when their blood glucose were inadequately controlled.

Keywords Gestational diabetes mellitus · Polymorphism · TCF7L2 rs7903146 · Glucose metabolism · Lipid metabolism

Introduction

Gestational diabetes mellitus (GDM) is defined as abnormal glucose tolerance with onset or first recognition during pregnancy. GDM has been shown to be associated with adverse perinatal outcomes: for mothers who are diagnosed with GDM, there are increased risks of preeclampsia, cesarean and type 2 diabetes (T2D); newborns are at increased risks of respiratory distress syndrome, premature birth, macrosomia, shoulder dystocia, and even death. Globally, the incidence of GDM has gradually increased [1]. Therefore, early detection, diagnosis, and treatment are the keys to improve maternal and fetal adverse outcomes. It is well-known that the islet β-cell dysfunction and insulin resistance are the main pathologic mechanisms of GDM [2]. Islet β-cell dysfunction leads hyperglycemia, which in turn exacerbates islet β-cell dysfunction. On the other hand, hyperglycemia plays a key role in maternal dyslipidemia, while abnormal lipid metabolism can cause insulin resistance, leading to a vicious cycle [3, 4]. Therefore, glucose metabolism disorders, lipid metabolism disorders, and their interactions may be closely related to the incidence of GDM.

Genetic factors, especially gene polymorphisms related to islet β-cell function are risk factors for GDM [5, 6]. Many studies had reported that higher frequency of risk transcription factor 7-like 2 (TCF7L2) rs7903146 allele (T) was found in GDM women [6–9]. Lu J and colleagues found that women harboring TCF7L2 rs7903146 TT genotypes displayed significantly higher 1-h blood glucose values than CC genotypes during OGTT; these results suggested that TCF7L2 rs7903146 SNP had significant effects on glucose homeostasis

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[10]. Other studies showed that TT genotypes in TCF7L2 rs7903146 were associated with decreased insulin secretion [11, 12]. In islet β-cells, TCF7L2 gene encodes a transcription factor with a high mobility group (HMG) domain; activated by WNT signal, β-catenin in the cytoplasm is transferred into the nucleus, interacts with TCF7L2, and forms a transcriptional complex; then, the transcriptional complex initiates transcription of target genes after raising a range of activating factors [13, 14]. However, whether TCF7L2 rs7903146 risk allele regulates 1-h blood glucose levels in Chinese population has not been investigated in detail.

Recently, it has been reported that disorder of lipid metabolism was a risk factor for GDM [15]. In order to maintain the normal pregnancy needs, including providing fuels and nutrients to the fetus, the maternal blood lipid levels need to be elevated physiologically [16]. In fact, hypertriglyceridemia is a stimulating factor for insulin resistance, while insulin resistance is one of the underlying mechanisms of GDM [17]. Therefore, excessively elevated blood lipid levels during pregnancy can affect blood glucose metabolism. Recent study reported that embelin attenuated adipogenesis and lipogenesis through Wnt/β-catenin signaling pathway, involved increasing nuclear protein levels of β-catenin and TCF7L2 [18]. However, few reports have evaluated the effect of TCF7L2 rs7903146 polymorphism on lipid metabolism in GDM in Chinese population.

Therefore, the aim of the present study was to determine whether TCF7L2 gene polymorphism rs7903146 influences the glucose and lipid metabolism in Chinese GDM women.

Methodology

Study subjects

The genotype frequency of rs7903146 polymorphic form of TCF7L2 gene in 1000 genome data was used to calculate the required sample size [19]. The sample size was estimated using the GPower v3.1.9.2 for survival analysis, with a significance level of 0.05 (two-tailed) and a power of 0.9. The effect sizes were calculated with Cohen's d: an effect size of 0.2 corresponding to a small effect and an effect size of 0.8 corresponding to a large effect [20]. Combined with the actual situation, the minimum sample size of this study was 200 which calculated with an effect size of 0.325.

A total of 484 women in their 24–28 gestational weeks were enrolled between January 2015 and February 2022; GDM were diagnosed if one or more of the following criteria from the International Association of Diabetes and Pregnancy Study Groups guideline or Chinese Society of Gynecology and Obstetrics guideline: fasting plasma glucose (FPG) 5.1–6.9 mmol/L, 1-h OGTT plasma glucose ≥ 10.0 mmol/L, or 2-h OGTT plasma glucose 8.5–11.0 mmol/L [21, 22]. The GDM group was composed of patients who were diagnosed as GDM during the second trimester. The control group was constituted by euglycemic women. The exclusion criteria were pre-pregnancy diabetes, hyperlipidemia, other endocrine or metabolic diseases, severe liver or kidney diseases, and malignant tumors.

Baseline demographics and clinical characteristics were extracted, including maternal age, pre-pregnancy body mass index (BMI), gestational weeks at delivery, newborn birth weight, 1 min Apgar scores, 5 min Apgar scores, OGTT plasma glucose levels, lipid levels in the first trimester and third trimester, glycosylated hemoglobin (HbA1c), FPG, and fasting insulin before delivery.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University, China, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

DNA extraction

Peripheral blood samples from pregnant women and umbilical cord blood samples were collected. DNA extractions were performed using the Blood DNA Extraction Kit (Heasbio, Guangzhou, China). After the extraction, the DNA samples were stored at − 20 °C.

DNA amplification

The TCF7L2 rs7903146 polymorphism was detected by polymerase chain reaction (PCR) using GC-rich PCR Master Mix (Thermo Scientific, Shanghai, China). The following primers were designed using Primer 3 software: forward primers were (5′-GCCGTCAGATGGTAATGCAG-3′) and reverse primers were (5′-CCCAAGCTTCTCAGTCACAC-3′). The cycling program was as follows: initial denaturation at 95 ℃ for 5 min, 35 cycles including denaturation at 95℃ for 30 s, annealing at 58℃ for 30 s, elongation at 72℃ for 30 s, and a final elongation step at 72℃ for 10 min.

PCR products identifying by electrophoresis

Successful amplification was determined by 1.2% agarose gel electrophoresis at 100 V for 40 min. Single strip of each product was shown in UV light visualization.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 20) and R language (v3.4.1). The frequency

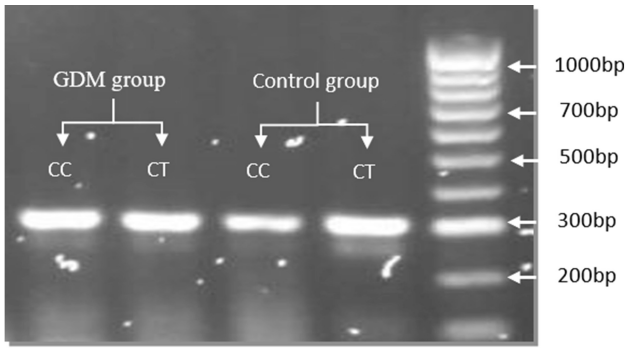

Fig. 1 Representative picture of agarose gel electrophoresis of PCR product of rs7903146

distributions were tested for Hardy–Weinberg equilibrium (HWE) by exact chi-square test. The baseline demographics and clinical characteristics were described as mean and standard deviation (SD). Independent sample *t*-test was applied in quantitative data between two groups. The qualitative data were analyzed with Pearson's chi-square test. Correction for multiple comparisons was performed using FDR-correction. A value of $p < 0.05$ (two-tailed) was considered statistically significant.

Results

Genotype distributions of TCF7L2 rs7903146

A single strip of each product was shown in UV light visualization (Fig. 1). After PCR amplification, products were sequenced by Sanger sequencing. Genotypes CC and CT were found in TCF7L2 rs7903146; no TT genotypes were found in this population (Fig. 2).

Baseline demographics, clinical characteristics, and genotype frequencies of the participants

The baseline demographics of participants are summarized in Table 1. There were no significant differences in maternal age, pre-pregnancy BMI, gestational weeks at delivery, and newborn birth weight between the two groups.

At the first trimester, plasma triglyceride (TG) and total cholesterol (TC) concentrations were significantly higher in GDM group than those in control group, while there were no significant differences in TG and TC values at the third trimester between the two groups. No significant differences were found in high-density lipoprotein (HDL), low-density lipoprotein (LDL), HbA1c, FPG (before delivery), fasting insulin, 1 min Apgar scores, 5 min Apgar scores, and umbilical artery pH between the two groups. Cord blood glucose levels were lower in GDM group than those in control group. No significant differences were found in the T allele frequencies between the two groups (Table 2).

Influence of TCF7L2 rs7903146 genotype on glycolipid metabolism of GDM women

The baseline characteristics of GDM patients according to TCF7L2 rs7903146 genotypes are shown in Table 3. In the first trimester, no significant differences were found in blood lipid levels between the carriers of risk allele (T) and non-carriers. In the second trimester, OGTT 1-h blood glucose levels were significantly higher in the carriers of risk allele (T). Furthermore, significantly elevated TG and decreased fasting insulin concentrations were detected in the carriers of risk allele (T) during the third trimester.

We also extracted the characteristics of control participants, and the data are shown in Table 4. There were no significant differences in OGTT 1-h blood glucose levels at the second trimester and TG and fasting insulin levels at

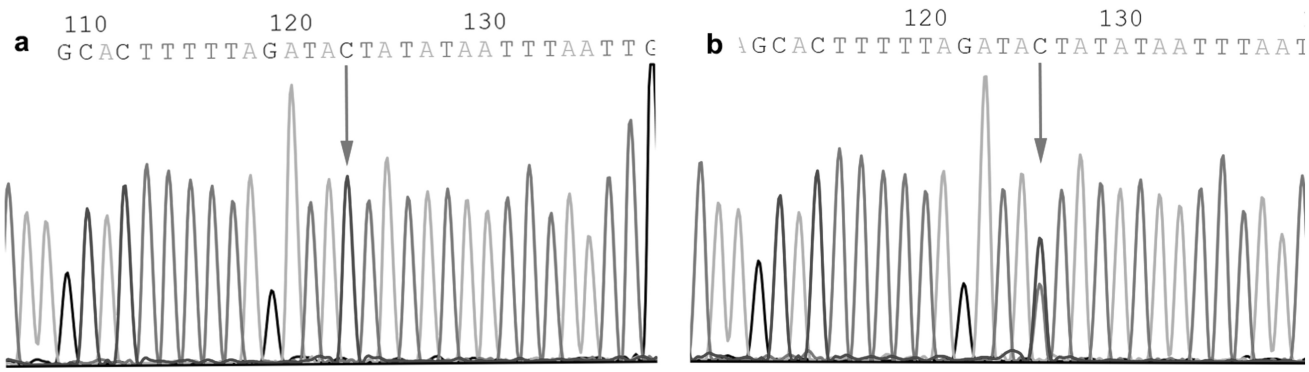

Fig. 2 Representative picture of DNA sequencing result of wild-type genotype CC (**a**) and heterozygous genotype CT (**b**)

Table 1 Baseline demographics of the participants

	GDM group	Control group	*p* value
Cases	239	245	-
Age (years)	31.50 ± 4.28	31.31 ± 4.22	0.620
BMI(kg/m^2)	21.60 ± 2.63	21.17 ± 2.43	0.062
Gestational weeks at delivery	38.98 ± 1.21	38.84 ± 2.09	0.366
Newborn birth weight (kg)	3.11 ± 0.41	3.10 ± 0.40	0.650

the third trimester between the carriers of risk allele (T) and non-carriers in control group.

Discussion

In present study, no TT genotypes were found in the all selected participants and no significant difference was found in genotype distribution between GDM group and control group (Table 2). There may be three possible reasons. Firstly, the frequencies of the risk allele (T) of TCF7L2 rs7903146 vary in different countries, races or regions. According to 1000 genome data, the minor allele frequency (MAF) of TCF7L2 rs7903146 was 2% in East Asian, 32% in European, and 30% in South Asian populations [19]. Some studies have shown that CC/CT/TT genotype frequency of TCF7L2 rs7903146 was related to GDM, while others found that CC/CT genotype of TCF7L2 rs7903146 was susceptibility to GDM [23–26]. Secondly, it may be attributed that 90% of the participants in our study were Cantonese, and the MAF of TCF7L2 rs7903146 was 2.93%(Table 2), which was close to the MAF in Southern Han Chinese (2.86%) [19]. Thirdly, it might be that our sample size was relatively small. Therefore, a larger sample size study was further needed.

In our study, we found that GDM group showed a significantly higher TG and TC levels in the first trimester than control group, which indicated that hyperlipidemia might induce

Table 2 Clinical characteristics and genotype frequencies

		GDM group	Control group	*p* value
Cases		239	245	-
First trimester	TC (mmol/L)	5.31 ± 1.20	5.09 ± 1.01	0.033
	TG (mmol/L)	1.74 ± 0.79	1.55 ± 0.74	0.005
	HDL (mmol/L)	1.87 ± 0.81	1.89 ± 0.32	0.663
	LDL (mmol/L)	2.86 ± 0.96	2.79 ± 0.86	0.415
Second trimester	OGTT-0H (mmol/L)	4.54 ± 0.58	4.26 ± 0.37	< 0.001
	OGTT-1H/(mmol/L)	9.82 ± 1.40	7.44 ± 1.31	< 0.001
	OGTT-2H/(mmol/L)	8.85 ± 1.31	6.48 ± 1.07	< 0.001
Third trimester	TC (mmol/L)	6.01 ± 1.21	5.88 ± 1.30	0.243
	TG (mmol/L)	2.09 ± 0.90	2.09 ± 0.87	0.998
	HDL (mmol/L)	1.83 ± 0.43	1.85 ± 0.36	0.576
	LDL (mmol/L)	3.24 ± 1.10	3.34 ± 1.04	0.304
	HbA1c (%)	5.15 ± 0.48	5.12 ± 0.34	0.514
	FBG (mmol/L)	4.97 ± 0.87	4.76 ± 0.81	0.192
	Fasting insulin (mU/L)	9.62 ± 5.49	9.69 ± 5.70	0.894
Delivery	1 min Apgar score	9.96 ± 0.19	9.96 ± 0.30	0.827
	5 min Apgar score	9.98 ± 0.14	9.99 ± 0.19	0.574
	Glucose level in cord blood	5.31 ± 1.83	5.90 ± 1.38	< 0.001
	Umbilical artery pH	7.25 ± 0.07	7.24 ± 0.08	0.112
Allele(*n*/%)	C	464 (97.07%)	477 (97.35%)	0.847
	T	14 (2.93%)	13 (2.65%)	
Genotype (*n*/%)	CT	14 (5.86%)	13 (5.31%)	0.845
	CC	225 (94.14%)	232 (94.69%)	
Hardy–Weinberg equilibrium		0.218	0.182	-

All continuous variables were represented as mean and standard deviation. Independent sample *t*-test was performed to compare the quantitative data between GDM and Control subjects. Qualitative data were analyzed with Pearson's chi-square test. $p < 0.05$ was considered significant

Allele frequencies fit the Hardy–Weinberg genetic equilibrium

TG triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HbA1c* glycated hemoglobin, *FBG* fasting blood glucose

Table 3 Characteristics of GDM group

		CT group	CC group	*p* value[#]
Cases		14	225	
Age (years)		33.14 ± 4.13	31.40 ± 4.28	0.390
BMI (kg/m^2)		20.69 ± 2.53	21.66 ± 2.63	0.390
Gestational weeks at delivery		38.62 ± 1.87	39.01 ± 1.15	0.390
Newborn birth weight (kg)		3.04 ± 0.56	3.12 ± 0.40	0.642
First trimester	TC (mmol/L)	5.32 ± 1.67	5.31 ± 1.17	0.963
	TG (mmol/L)	1.78 ± 0.86	1.74 ± 0.78	0.933
	HDL (mmol/L)	1.64 ± 0.59	1.88 ± 0.83	0.400
	LDL (mmol/L)	2.92 ± 1.43	2.85 ± 0.93	0.933
Second trimester	OGTT-0H (mmol/L)	4.78 ± 0.80	4.53 ± 0.57	0.390
	OGTT-1H (mmol/L)	11.99 ± 1.47	9.68 ± 1.28	0.011
	OGTT-2H (mmol/L)	9.04 ± 1.31	8.84 ± 1.31	0.697
Third trimester	TC (mmol/L)	6.05 ± 1.08	6.01 ± 1.22	0.949
	TG (mmol/L)	3.90 ± 0.92	1.98 ± 0.77	0.011
	HDL (mmol/L)	1.60 ± 0.49	1.84 ± 0.43	0.225
	LDL (mmol/L)	3.60 ± 1.04	3.21 ± 1.10	0.390
	HbA1c (%)	5.30 ± 0.23	5.14 ± 0.49	0.390
	FBG (mmol/L)	5.24 ± 0.93	4.85 ± 0.87	0.390
	Fasting insulin (mU/L)	6.45 ± 3.71	9.82 ± 5.53	0.183
Delivery	1 min Apgar score	9.93 ± 0.27	9.96 ± 0.19	0.642
	5 min Apgar score	9.93 ± 0.27	9.98 ± 0.13	0.390
	Glucose level in cord blood	4.60 ± 1.49	5.35 ± 1.85	0.390
	Umbilical artery pH	7.23 ± 0.11	7.25 ± 0.07	0.390

TG triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HbA1c* glycated hemoglobin, *FBG* fasting blood glucose.

[#]Data were corrected for FDR by Benjamini–Hochberg program.

GDM by injuring the endothelium [27–29]. But no differences about TG and TC levels were found in the third trimester. And with regard to neonatal outcomes, such as 1 min Apgar scores, 5 min Apgar scores, or umbilical artery pH value, there was no significant difference between GDM group and control group, except that the mean glucose concentrations in cord blood were significantly lower in GDM group (Table 2), and neither group experienced serious hypoglycemia. The possible reason may be related to the well-controlled blood glucose levels of GDM patients in the present study is that, the GDM patients received standard treatment for lifestyle adjustment and their blood glucose were well controlled during pregnancy [30].

In this study, women carrying risk allele (T) showed significantly higher 1-h blood glucose levels in OGTT than those carrying the non-risk genotypes in GDM group (Table 3), while no difference was found in control group (Table 4). This finding was consistent with the Potasso's findings which showed that TCF7L2 rs7903146 T carriers presented significantly higher OGTT 1-h glucose levels and were more likely to require insulin therapy [31]. Compared with the 2-h blood glucose concentration, 1-h blood glucose had a stronger correlation with β-cell dysfunction [32]. The underlying mechanism included early insulin response disorder and insulin resistance [33]. Shah et al. found that a genetic T variant harbored in TCF7L2 rs7903146 impaired glucose tolerance through effects on glucagon as well as insulin secretion [34]. Therefore, it is hypothesized that, for GDM patients which already have existing insulin resistance, carrying risk allele (T) can further affect insulin production, which in turn induces early insulin response disorders and leads to glucose increase at 1 h. In the control group, despite the presence of T risk genes affecting glucose homeostasis, there was no OGTT 1-h glucose increase due to the absence of insulin resistance. So the T variation in TCF7L2 rs7903146 may be very important on regulating 1-h blood glucose levels which is the key indicators in Chinese population, because 1-h blood glucose level on OGTT was a strong predictor of future risk for T2D [35]. But how the risk allele (T) in TCF7L2 rs7903146 regulates islet function on 1-h blood glucose levels needs to be further studied.

Notably, neither in GDM group nor control group, there were no significant differences of TG and TC levels in the first trimester between the risk allele (T) carriers and the non-carriers. But in GDM group, there were significantly higher TG levels in the risk allele (T) carriers than the non-carriers in the third trimester, while in the control group, there were no significant differences. As we all know, lifestyle adjustment is the first line of treatment for women in GDM management [36]. However, the risk allele

Table 4 Characteristics of control group

		CT group	CC group	*p* value[#]
Cases		13	232	
Age (years)		32.31 ± 4.97	31.25 ± 4.18	0.980
BMI (kg/m^2)		20.00 ± 2.47	21.24 ± 2.42	0.980
Gestation week (weeks)		38.86 ± 1.74	38.84 ± 2.12	0.982
Newborn birth weight (kg)		3.02 ± 0.54	3.10 ± 0.40	0.980
First trimester	TC (mmol/L)	5.19 ± 0.60	5.09 ± 1.03	0.980
	TG (mmol/L)	1.75 ± 0.71	1.54 ± 0.74	0.980
	HDL (mmol/L)	1.87 ± 0.19	1.89 ± 0.32	0.980
	LDL (mmol/L)	2.95 ± 0.90	2.78 ± 0.86	0.980
Second trimester	OGTT-0H (mmol/L)	4.21 ± 0.37	4.26 ± 0.37	0.980
	OGTT-1H (mmol/L)	7.91 ± 1.12	7.41 ± 1.31	0.980
	OGTT-2H (mmol/L)	6.79 ± 0.91	6.46 ± 1.07	0.980
Third trimester	TC (mmol/L)	5.96 ± 0.75	5.87 ± 1.33	0.980
	TG (mmol/L)	2.27 ± 0.67	2.08 ± 0.88	0.980
	HDL (mmol/L)	1.74 ± 0.32	1.86 ± 0.36	0.980
	LDL (mmol/L)	3.46 ± 0.91	3.33 ± 1.05	0.980
	HbA1c (%)	5.13 ± 0.33	5.13 ± 0.34	0.982
	FBG (mmol/L)	4.81 ± 0.43	4.77 ± 0.82	0.980
	Fasting insulin (mU/L)	9.89 ± 5.72	9.68 ± 5.71	0.982
Delivery	1 min Apgar score	10.00 ± 0.00	9.97 ± 0.307	0.980
	5 min Apgar score	10.00 ± 0.00	9.99 ± 0.20	0.980
	Glucose level in cord blood	5.36 ± 1.27	5.93 ± 1.38	0.980
	Umbilical artery pH	7.22 ± 0.10	7.24 ± 0.08	0.980

TG triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HbA1c* glycated hemoglobin, *FBG* fasting blood glucose.

[#]Data were corrected for FDR by Benjamini–Hochberg program.

(T) of TCF7L2 rs7903146 could influence changes in BMI and total body fat during lifestyle intervention [37, 38], which might partially explain such differences in our study. Similarly, in GDM group, we also found that the risk allele (T) carriers had lower fasting insulin level in the third trimester than the non-carriers, and the FBG levels also appeared as an elevated trend, despite no statistical significance (Table 3). Therefore, these results suggested that appropriate new strategies including insulin therapy, were needed to be introduced for controlling blood glucose in GDM patients who carry risk allele (T) of TCF7L2 rs7903146, as early as possible [31].

Conclusion

In summary, our studies have shown that TCF7L2 rs7903146 polymorphism effected glucose and lipid metabolism in GDM women. Further investigations are needed to unravel the mechanism by which TCF7L2 rs7903146 affects glycolipid metabolism. For the risk allele (T) carriers of TCF7L2 rs7903146, low-fat and low-sugar diets, exercise interventions can be carried out at an early stage, including before pregnancy or early pregnancy, and insulin treatment should be used as soon as possible when the blood glucose cannot be controlled well.

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Author contribution Changping Fang is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Shuzhen Wu and Zijing Zhang Wu were involved in data collection and data management; Jun Zhang and Qi Tian conceived and designed the study; Lingling Wu was involved in conceptualization, methodology, supervision, writing, reviewing, and editing. All authors read and approved the final version of the manuscript for publication.

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Data availability All data and material for this article is available upon reasonable request.

Declarations

Ethics approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen.

Competing interests The authors declare no competing interests.

Consent to participate Informed consent had been obtained from all the participants prior to the inclusion into the study.

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