

Genetic Polymorphism of Lipoprotein-Associated Phospholipase A2 Influences Susceptibility to Gestational Diabetes Mellitus in Chinese Population

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Purpose: This paper aims to study the relationship between lipoprotein-associated phospholipase A2 (Lp-PLA2) and GDM (gestational diabetes mellitus) by detecting Lp-PLA2 level and its gene polymorphism.

Patients and Methods: From January to June 2022, 82 GDM patients treated in our hospital were included as an experimental group, and 89 healthy pregnant women during the same period were selected as the control group. Lp-PLA2 concentration and TG, TC, HDL-C, and LDL-C levels were tested with specialized instruments in clinical laboratories. The PLA2G7 gene polymorphisms (rs1805017, rs1805018, and rs76863441) were detected by fluorescent probe method and sequencing.

Results: Lp-PLA2 concentration was significantly higher in GDM group than control group ($P < 0.05$). Among three polymorphism loci of PLA2G7 gene (rs1805017, rs1805018, and rs76863441) the significant associations were only found in GT genotype of rs76863441 loci ($P < 0.05$).

Conclusion: Pregnant women with high levels of Lp-PLA2 concentration are more likely to develop GDM, especially those with PLA2G7 rs76863441 polymorphism. Lp-PLA2 concentration and PLA2G7 rs1805017 polymorphism may be a novel marker for GDM diagnosis and prediction.

Keywords: gestational diabetes mellitus, PLA2G7, Lp-PLA2, gene polymorphism

Introduction

Gestational diabetes mellitus (GDM) is a general term for abnormal glucose tolerance, abnormal fasting blood glucose, and diabetes detected or developed during pregnancy, excluding diabetes that already existed before pregnancy. According to the International Diabetes Federation, the global prevalence of GDM in 2021 was approximately 16.7% and has become one of the major public health problems. The prevalence of GDM is 20.9% in Asia and 14.8% in China,¹⁻⁴ making gestational diabetes mellitus the most common complication of pregnancy. Current studies have shown that age, obesity, race, poor reproductive history, and family history of diabetes are the main factors affecting gestational diabetes. In general, the prevalence of GDM increases in Hispanics, African Americans, native Americans, and Asian or Pacific Islanders.^{3,4}

Lipoprotein-related phospholipase A2 (Lp-PLA2), a member of the PLA2 superfamily, is a new inflammatory marker that has been studied intensively in recent years.⁵ Encoded by the *PLA2G7* gene located in chromosome 6p12-21.1,⁶ the protein is secreted mainly by macrophages, endothelial cells, and mast cells in the vascular intima and binds to many lipoproteins. When it binds to low-density lipoprotein cholesterol (LDL-C), the production of LysoPC and free oxidized fatty acids (oxFA) can induce the production of a variety of pro-inflammatory cytokines,

chemokines, and platelet-active substances, mediating the inflammatory cascade effect.⁷ According to inflammation theory, chronic low-grade inflammation plays an important role in the occurrence and development of T2DM and GDM, involving various pathophysiological processes of obesity and insulin resistance, and suggests that chronic low-grade inflammation may be an important initiating and expanding factor of insulin resistance. High expression of Lp-PLA2 can cause vascular wall damage, resulting in production of pro-inflammatory factors, increased expression of adhesion factors in vivo, and induced activation of inflammatory factors. Most of them bind to LDL-C and a small part binds to high-density lipoprotein cholesterol (HDL-C), which induces a chronic inflammatory response through hydrolysis of phospholipid oxide to produce LysoPC and oxFA. This process is closely related to atherosclerosis, hypercholesterolemia, and diabetes.⁸

Vascular endothelial injury and various complications are common in GDM patients. Therefore, we should pay attention to the early diagnosis of GDM. Currently, it has been documented that Lp-PLA2 levels are significantly higher than normal in GDM patients and are closely related to adverse pregnancy outcomes, but the research results are inconsistent, and there are also studies that suggest that the concentration of Lp-PLA2 was not associated with diabetes, but its enzyme activity levels were significantly elevated in diabetic patients.⁹ The pathophysiological mechanism of GDM is similar to that of T2DM, showing obvious regional and ethnic correlation. Therefore, there is a need to verify the levels of Lp-PLA2 in GDM populations of different races and regions.

The biological function of Lp-PLA2, an independent risk factor for atherosclerosis, is controlled by *PLA2G7* gene in the body. Mutations in the *PLA2G7* gene affect the expression and activity formation of Lp-PLA2.¹⁰ Its cDNA was cloned in 1995 and contains 12 exons encoding 441 amino acids.¹¹ El-Saed et al¹² found that some of *PLA2G7* gene loci are independent risk factors for coronary heart disease in Asian population, while there is no such correlation in European population. The polymorphism of *PLA2G7* gene may have different mechanisms of action in different regions and races, which is controversial. At present, there are limited studies on Lp-PLA2 level and its gene polymorphism in GDM population, especially among the Chinese population, so it is necessary to carry out this study.

Materials and Methods

Study Subjects

GDM patients at 24–28 weeks of pregnancy treated in our hospital from January to June 2022 were included as an experimental group. There were 82 patients with GDM. In the same period, 89 healthy pregnant women without GDM were selected as control group. We have set extremely strict inclusion criteria and following inclusion criteria were assessed. According to the guidelines of International Association of the Diabetes and Pregnancy Study Groups (IADPSG, 2014), the diagnostic criteria of “one-step method” for GDM: a 2-h 75g-OGTT should be fasted for at least 8 h, and the blood glucose values of pregnant women should be measured on fasting and 1 h and 2 h after drinking glucose. GDM can be diagnosed if the blood glucose level reaches any of the following criteria: fasting blood glucose (FBG) ≥ 5.1 mmol/L, blood glucose ≥ 10.0 mmol/L at 1 h, and blood glucose ≥ 8.5 mmol/L at 2 h. Patients were aged 20–45 and have a single pregnancy. Women with pre-pregnancy diabetes, heart disease, or liver, kidney, or other related diseases were excluded. The study was approved by Minzu Hospital of Guangxi Zhuang Autonomous Region.

Detection Methods

Serum samples and EDTA-K2 anticoagulant samples of pregnant women at 24–28 weeks were collected according to inclusion and exclusion criteria, and they were divided into pregnant women with GDM (case group) and healthy pregnant women without GDM at the same time (control group) according to OGTT blood glucose results.

A total of 4mL of maternal peripheral venous blood was collected, and 2mL of which was put into a tube without anticoagulant. After centrifugation, serum was used to detect blood glucose, Lp-PLA2 concentration, HDL-C, LDL-C, and so on. The other 2mL was stored with EDTA-K2 anticoagulant and used for genomic DNA extraction of peripheral

blood in strict accordance with the requirements of the kit. The extracted genomic DNA samples were stored at -80°C until detecting *PLA2G7* gene polymorphism.

Wego AUTOLUMIS3000 and original reagent (Weihai City, China) to detect Lp-PLA2 concentration; Hitachi 7600 automatic biochemical analyser (Japan) and related reagents (Meikang Biotechnology Co., Ltd, Ningbo, China) to detect blood glucose, HDL-C, LDL-C, triglyceride (TG), and total cholesterol (TC); Fluorescence quantitative PCR instrument (AnalytikJena qTOWERE2.2 and Biometra EasyCycler Gradient, Germany) and direct DNA sequencing were used to detect *PLA2G7* gene polymorphisms. The PCR primers and products are shown in Table 1. DNA extraction reagent was provided by Guangdong Kaipu Biotechnology Co., Ltd. The amplification reagent was provided by Takara Biotechnology (Dalian) Co., Ltd. and Jiangsu Kangwei Century Biotechnology Co., Ltd (China). The experiment was conducted according to the reagent manufacturer's protocol or the operating rules of the instrument. PCR conditions were the following for rs1805017 and rs1805018: initial steps at 95°C for 1 min, and then repeating the following 40 cycles, denaturing at 95°C for 10 s, annealing at 59°C for 10 s, and extending at 72°C for 20 s. PCR conditions were the following for rs76863441: initial steps at 95°C for 3 min, and then repeating the following 35 cycles, denaturing at 94°C for 30 s, annealing at 55°C for 30 s, and extending at 72°C for 30 s with a final extension of 5 min. PCR products were sequenced (Beijing Tsingke Biotech Co., Ltd.), shown in Figures 1–3.

Statistical Analysis

SPSS 24.0 analysis software was used for statistical research. Independent sample *t*-test was used for comparison between measurement data groups, and the mean \pm standard deviation was calculated. The distribution differences between the genotype and allele of *PLA2G7* locus were analyzed and compared between the case group and the healthy control group. Fisher's exact test and χ^2 test were used to compare the genotype and allele frequencies between the two groups. Odds ratios and 95% confidence intervals were calculated to evaluate the risk of SNPs and GDM susceptibility. The *p*-value cutoff for significance was 0.05 ($P < 0.05$ was considered to be statistically significant).

Results

General Information of Study Subjects

The information of study population is shown in Table 2, which consisted of age, TG, TC, HDL-C, and LDL-C. There is no statistically significant difference between the GDM group and control group ($P > 0.05$).

Lp-PLA2 Level and Gene Polymorphism

Lp-PLA2 concentration was significantly higher in GDM group than control group ($P < 0.05$) (Figure 4). Among three polymorphism loci of *PLA2G7* gene (rs1805017, rs1805018, and rs76863441), the significant associations were only found in GT genotype of rs76863441 loci ($P < 0.05$). The detailed information is shown in Table 3.

Table 1 PCR Primers and Products for *PLA2G7* Gene

PCR Primers	Sequences	PCR Products (bp)
rs1805017	F: 5'- ACCTTCTTGCGTTTATATTATCCATCC -3' R: 5'- CCCATAAGCCAGTGTGTTCC -3'	119
rs1805018	F: 5'-AGGGAAGGAGCATGCATAAA-3' R: 5'- CCTCCTCTTGTTTCAGGGTTC-3'	144
rs76863441	F: 5'-TCTTCTAACACCACGAAATAGC-3' R: 5'- GTCTTGTCCTCACTCTTACCC-3'	589

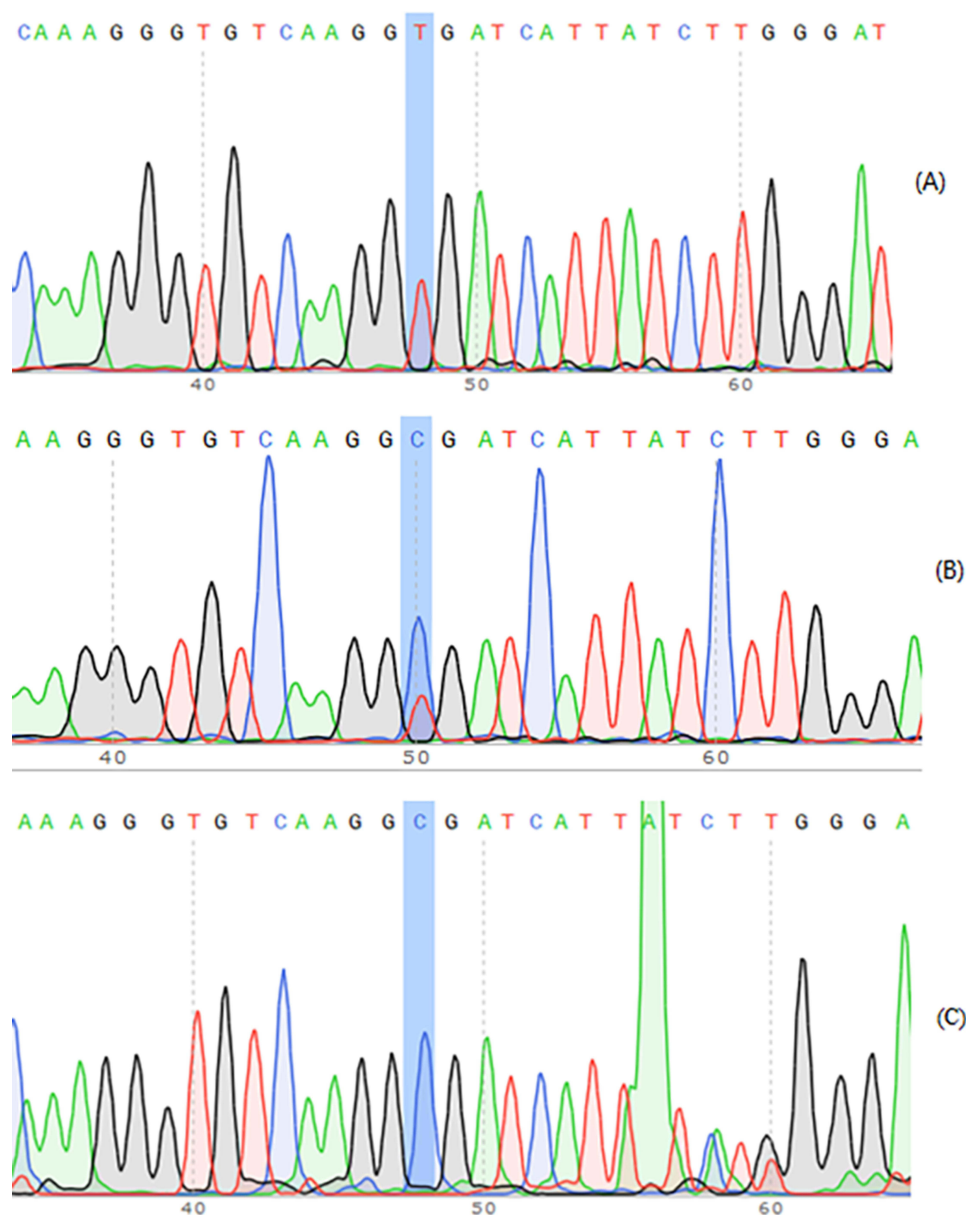


Figure 1 PCR products were sequenced for rs1805017 loci of PLA2G7 gene polymorphism (reverse sequencing). (A) rs1805017-A/A; (B) rs1805017-A/G; (C) rs1805017-G/G.

Discussion

In recent decades, with the improvement of economic conditions, the change of lifestyle and the postponement of childbearing age, the prevalence of GDM is also increasing, and the incidence of GDM is on the rise in China and the world.² If not treated in time, this disease is likely to lead to serious maternal and fetal short-term and long-term complications, including pyelonephritis and mastitis in pregnant women. It can even induce ketoacidosis. The main effects on the fetus are abortion or premature delivery, fetal growth and development restriction, macrosomia or large infant, deformed fetus, and even stillbirth. The main effects on neonates are increase in neonatal respiratory distress syndrome, hypoglycemia, erythrocytosis, and hyperbilirubinemia.

Most women were not screened for diabetes before pregnancy, and the clinical diagnosis of GDM was determined by an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. However, since glucose tolerance test was performed in late pregnancy, the health of mother and child had been affected to varying degrees before

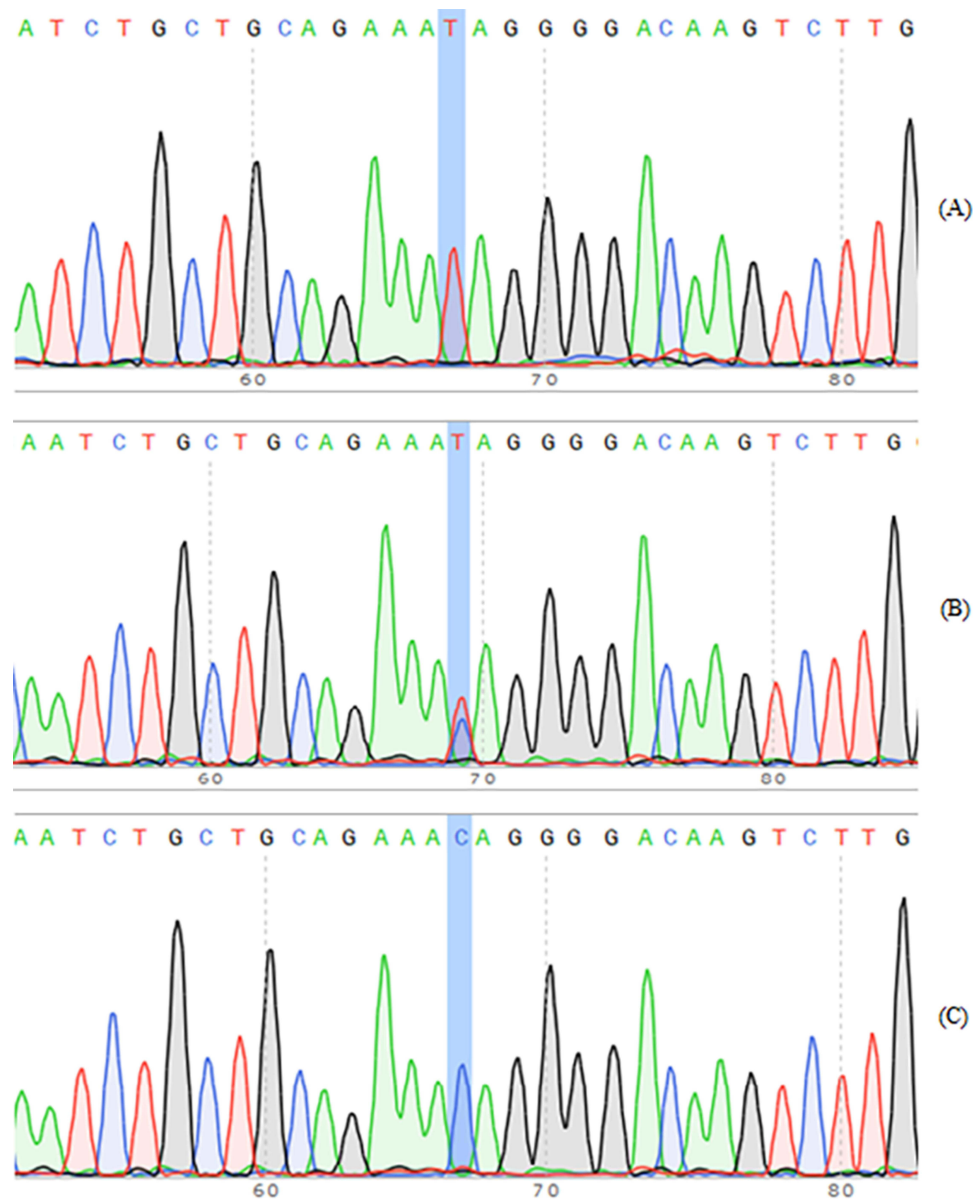


Figure 2 PCR products were sequenced for rs1805018 loci of *PLA2G7* gene polymorphism. (A) rs1805018-T/T; (B) rs1805017-C/T; (C) rs1805017-C/C.

intervention, despite positive prediction later. Early gestation is a critical period of fetal growth and development, so early screening of GDM and effective identification of risk groups are very important. Currently, the OGTT test method is a little complicated, requiring fasting and multiple blood draws, which may lead to gastrointestinal discomfort and decreased compliance in pregnant women. At present, there is still a lack of specific biomarkers for the screening of early and mid-term GDM, and the sensitivity and specificity of traditional predictors are low. For example, FPG (fasting plasma glucose) test is prone to false positives due to dietary factors,¹³ causing psychological stress in patients. Hemoglobin A1c levels are associated with GDM and adverse pregnancy outcomes,¹⁴ but HbA1c is susceptible to interference by maternal iron and hemoglobin levels, and a specific reference range for HbA1c in pregnancy has not been established, and no guidelines currently recommend its use in the diagnosis of GDM. Therefore, the search for GDM biomarkers with simple detection, easy to repeat, high sensitivity, and high specificity has a long way to go.

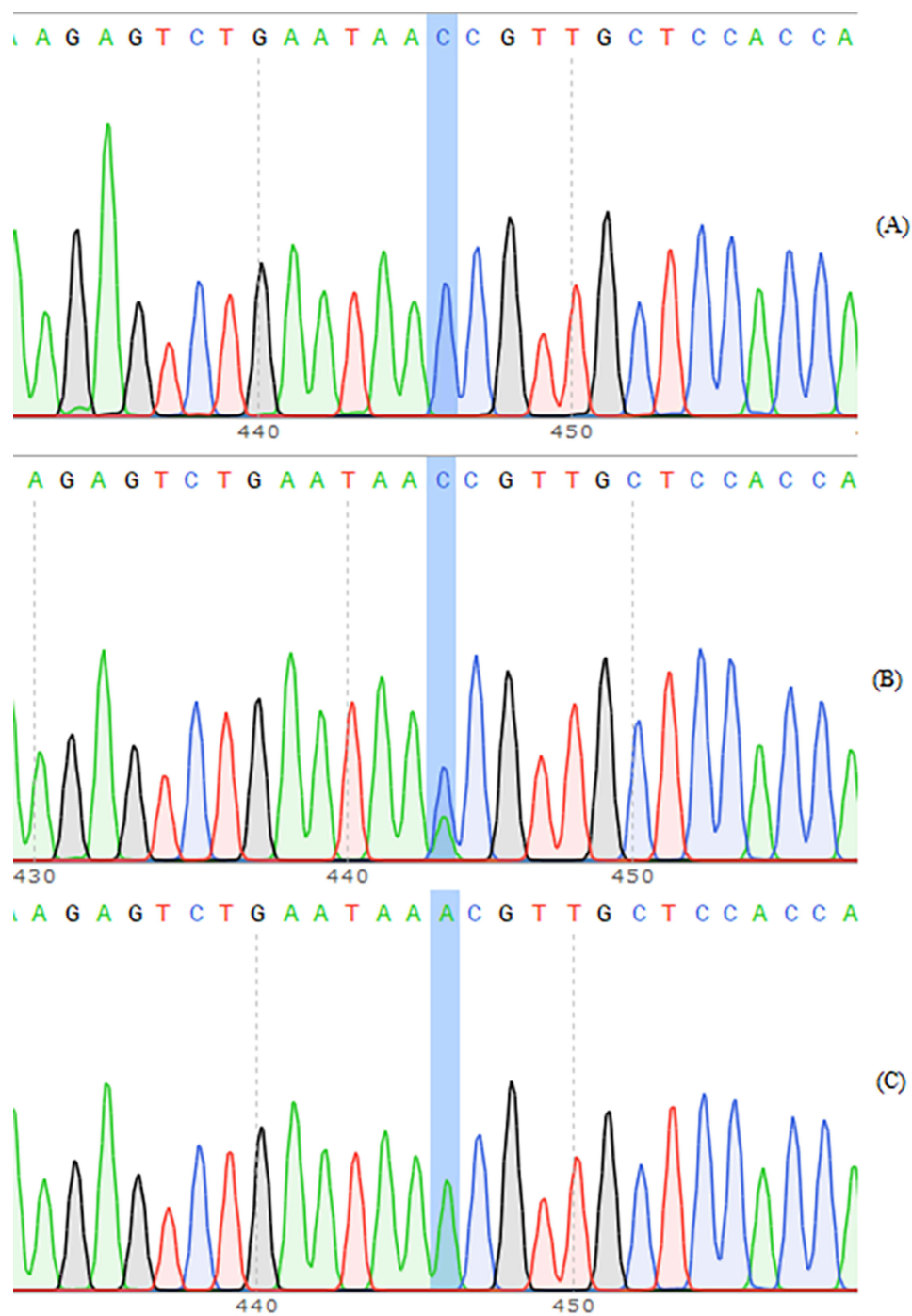


Figure 3 PCR products were sequenced for rs76863441 loci of *PLA2G7* gene polymorphism (reverse sequencing). (A) rs76863441-G/G; (B) rs76863441-G/T; (C) rs76863441-T/T.

Currently, many national and international guidelines recommend diagnostic and management strategies that focus on short-term risks during pregnancy and childbirth.¹⁵ This has led to increased direct and indirect costs of health care. Therefore, it is important to develop clear screening criteria for pregnant women and identify those at risk from an early and middle stage, which may lead to better management of gestational diabetes. In addition, we need to shift perceptions of gestational diabetes from a short-term condition that can increase the risk for babies to a long-term condition that can exacerbate obesity and cardiometabolic abnormalities in women and children in future generations. Therefore, the early

Table 2 The Participates Characteristics of Both GDM Group and Control Group (Mean \pm SD)

Basic Information	Control (N=89)	GDM Group (N=82)	P
Age(years)	30.17 \pm 3.80	31.41 \pm 4.50	0.053
TG (mmol/L)	2.10 \pm 0.64	2.25 \pm 0.80	0.156
TC (mmol/L)	6.04 \pm 1.00	5.75 \pm 1.10	0.073
LDL-C (mmol/L)	3.39 \pm 0.78	3.24 \pm 0.86	0.225
HDL-C (mmol/L)	2.00 \pm 0.33	1.90 \pm 0.34	0.053

Abbreviations: GDM, gestational diabetes mellitus; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

diagnosis, prevention, and treatment of GDM and effective control of blood sugar are of great significance to the puerpera and neonates.

As far as we know, this is the first article that investigates Lp-PLA2 concentration and *PLA2G7* rs76863441 polymorphism in pregnant women. Our study provides a good indicator for the development of GDM in healthy pregnant women. Several literature studies have reported the association between *PLA2G7* gene polymorphism and disease risk, including coronary heart disease, ischemic stroke, hypertension, clinical atherosclerosis, Alzheimer's disease, and acute pancreatitis.^{16–22} *PLA2G7* rs76863441 polymorphism contributes to an increased risk of coronary heart disease, hypertension, and acute pancreatitis. *PLA2G7* rs1805017 increases the risk of acute pancreatitis but decreases the risk of clinical atherosclerosis. *PLA2G7* rs1805018 contributes no risk to Alzheimer's disease.

However, the present article still has some limitations. Firstly, the number of enrolled pregnant women is not very large, and some confounding factors may cause bias to the final results. Secondly, bioinformatics and meta-analysis are very hot topics in genetic-association studies in recent years.^{23–40} Therefore, we should conduct more relevant studies about *PLA2G7* gene in bioinformatics and meta-analysis, which may contribute to GDM diagnosis, prevention, and treatment.

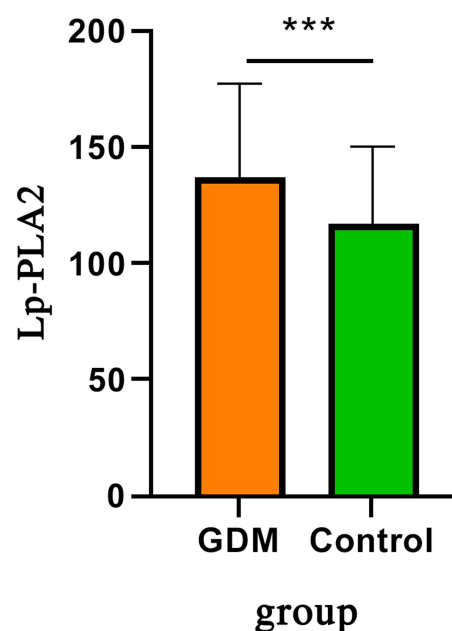


Figure 4 Lp-PLA2 concentration was significantly higher in GDM group than control group. ***P<0.05.

Table 3 Comparison of *PLA2G7* Genotype and Allele Frequency Between GDM Group and Control Group

<i>PLA2G7</i> Polymorphism	Control Group (N=89)		GDM Group (N=82)		OR (95% CI) ^a	P ^a
	n	Percentage (%)	n	Percentage (%)		
rs1805017						
GG	48	54.0	51	62.2	1.00 ^{REF}	
GA	40	44.9	29	35.4	1.47(0.79–2.72)	0.226
AA	1	1.1	2	2.4	0.53(0.05–6.05)	0.605
G	136	76.4	131	79.9	1.00 ^{REF}	
A	42	23.6	33	20.1	1.23(0.73–2.05)	0.438
rs1805018						
TT	74	83.1	70	85.4	1.00 ^{REF}	
TC	14	15.7	11	13.4	1.20(0.51–2.83)	0.670
CC	1	1.2	1	1.2	0.95(0.06–15.42)	0.969
T	162	91.0	151	92.1	1.00 ^{REF}	
C	16	9.0	13	7.9	1.15(0.53–2.47)	0.725
rs76863441						
GG	86	96.6	73	89.0	1.00 ^{REF}	
GT	2	2.2	8	9.8	0.21(0.04–1.03)	0.049
TT	1	1.1	1	1.2	0.85(0.05–13.81)	0.908
G	174	97.8	154	93.9	1.00 ^{REF}	
T	4	2.2	10	6.1	0.35(0.11–1.15)	0.073

Note: ^aAdjusted for sex and age by logistic regression model.

Abbreviations: GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidential index.

Conclusion

Pregnant women with high levels of Lp-PLA2 concentration are more likely to develop GDM, especially those with *PLA2G7* rs76863441 polymorphism. Lp-PLA2 concentration and *PLA2G7* rs76863441 polymorphism may be a novel marker for GDM diagnosis and prediction.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval Statement

This study was conducted with approval from the Ethics Committee of Minzu Hospital of Guangxi Zhuang Autonomous Region, Affiliated Minzu Hospital of Guangxi Medical University. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no competing interests in this work.

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