The changes of Lp-PLA2 in patients with gestational diabetes and its clinical significance

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Abstract
Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy and associated with adverse pregnancy outcomes. The aim of this study was to investigate the changes of lipoprotein-associated phospholipaseA2 (Lp-PLA2) level and its correlation with biochemical indexes in patients with GDM.

This observational cross-sectional study was performed among 52 GDM and 48 healthy pregnant women. Automatic biochemical analyzer was employed to test the biochemical indexes, including fasting plasma glucose (FPG), Hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). The lipoprotein-associated phospholipaseA2 (Lp-PLA2) level was evaluated by enzyme-linked immunosorbent assay, and homeostatic model assessment for insulin resistance (HOMA-IR) was calculated.

The levels of FPG, HbA1c, HOMA-IR, TG, TC and LDL-C were significantly increased while high-density lipoprotein cholesterol (HDL-C) level was significantly decreased in the GDM group when compared with those in the control group. Lp-PLA2 level in maternal blood in the GDM group was significantly higher than that in the control group (199.125 ± 23.494 vs 165.825 ± 15.576 ng/mL, P < .05) and logistic regression analysis further confirmed the association of Lp-PLA2 levels with GDM. Furthermore, Lp-PLA2 positively correlated with HOMA-IR, TC, and LDL-C.

Our results confirmed the association of Lp-PLA2 with GDM. This broadens our knowledge on the pathophysiology of GDM and provides insights into the development of new targets for the prevention and treatment of GDM.

Abbreviations: CI = confidence interval, FPG = fasting plasma glucose, GDM = gestational diabetes mellitus, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment for insulin resistance, IR = insulin resistance, LDL = low-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, Lp-PLA2 = lipoprotein-associated phospholipaseA2, OR = odds ratios, TC = total cholesterol, TG = triglyceride.

Keywords: gestational diabetes mellitus, insulin resistance, lipoprotein-associated phospholipaseA2, parameters of glycolipid metabolism

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1. Introduction
Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance that first discovered during pregnancy and is one of the most common metabolic diseases during pregnancy,[1] affecting about 4% to 15% of pregnant women. It is closely associated with adverse maternal and neonatal outcomes, including spontaneous abortion, hydramnios, macrosomia, gestational hypertension, postpartum hemorrhage, ketoacidosis, preterm delivery, fetal distress, hypoglycemia, neonatal asphyxia and hyperbilirubinemia. Women with a history of GDM have an increased risk of metabolic diseases, mainly type 2 diabetes. The offspring of mothers with GDM are predisposed to obesity, neuropsychiatric disorders, autism spectrum disorder, metabolic diseases and chronic diseases in the long term.[2–4]

Lipoprotein-associated phospholipase A2 (Lp-PLA2), encoded by PLA2G7 gene, is a hydrophobic protein and belongs to group VII of the phospholipase A2 superfamily, which currently includes 6 types and is divided into 16 groups.[5] Human plasma lipoprotein-associated phospholipaseA2 (Lp-PLA2) is mainly synthesized and secreted by mature macrophages and lymphocytes, and exists primarily in the form of lipoprotein particles in the human blood cycle, with most of which bind to low-density lipoprotein (LDL) and a small number to high-density lipoprotein (HDL) as well as other lipoproteins.[6] Lp-PLA2 is commonly recognized as a new biomarker of vascular inflammation. It
promotes the formation of oxidation of LDL, which is the producer of proinflammatory mediators, such as lysophosphatidylcholine and oxidized free fatty acids. These mediators are often abnormally up-regulated during various inflammation-associated diseases.[6]

Nowadays, studies on the Lp-PLA2 have mostly focused on cardiovascular disease. There is abundant evidence showing that the level of Lp-PLA2 is abnormally elevated in patients with cardiovascular disease such as coronary heart disease. Inhibiting the activity of Lp-PLA2 may have a beneficial role in the prevention and treatment of these diseases.[11-16] It is noteworthy that insulin resistance (IR) is the common pathophysiological basis of coronary heart disease and diabetes.[11] Recently, Lp-PLA2 has been found to be abnormally up-regulated in type 2 diabetes, and its inhibitors have been used to treat the complications of type 2 diabetes with remarkable effects.[12-16]

Since GDM is a special type of diabetes with similar pathophysiological characteristics as type 2 diabetes, we speculate that the inflammatory marker Lp-PLA2 may also be associated with GDM to some extent.

In this study, we investigated the changes of Lp-PLA2 and its correlation with the parameters of glycolipid metabolism in patients with GDM. Our results could provide helpful information for prevention and treatment of GDM.

2. Materials and methods

2.1. Study subjects

This observational cross-sectional study was performed among the pregnant women who periodically underwent prenatal examinations and delivered through caesarean section in the Affiliated Lianyungang Hospital of Xuzhou Medical University from May 2017 to May 2018. The inclusion criteria were aged 20 to 45 years, singleton pregnancy, with normal mind and with the ability to communicate with people normally. The exclusion criteria were as follows: with age less than 20 or older than 45; with pre-pregnancy diabetes or family history, with metabolic syndrome, nephritis, cardiovascular disease, hemopathy, thyroid disease or polycystic ovary syndrome; multiple pregnancy or assisted pregnancy; with a bad habit of life such as smoking or drinking; taking medications that had effects on blood glucose, lipids or blood pressure; with other complications during pregnancy; with chronic or acute infection diseases.

The oral glucose tolerance test was performed at 24 to 28 weeks of gestation. The procedure of oral glucose tolerance test was as follows: During the first 3 days of the test, the pregnant women ate and exercised normally, and the carbohydrate in the daily diet was more than 150 to 200g. Fasting plasma glucose (FPG) was measured in the morning after an overnight fast for at least 8 to 14 hours after dinner the day before the test, then 75g glucose was dissolved in 200 to 300 mL of water, and it was taken within 5 minutes. The women sat quietly and kept fasting during the test. The American Diabetes Association criteria was adopted in the current study: FPG ≥5.1 mmol/L, 1 hour plasma glucose ≥10.0 mmol/L and 2 hours plasma glucose ≥8.5 mmol/L, respectively. GDM was diagnosed when the women met one or more of the features.

Fifty two pregnant women with GDM who met all the inclusion criteria and did not meet any item of the exclusion criteria were included in the study group (GDM group) after their admittance to maternity ward in the Affiliated Lianyungang Hospital of Xuzhou Medical University. They did not receive insulin therapy during pregnancy. Forty eight healthy pregnant women without GDM who met all the inclusion criteria and did not meet any item of the exclusion criteria were randomly selected as the control. Clinical data on the participants were collected and recorded, including maternal age, height, pre-pregnancy weight and gestational age. Pre-pregnancy BMI was calculated as pre-pregnancy weight (kg) / height (m²). This study was approved by the ethics committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University and carried out in accordance with the rules of the Declaration of Helsinki. All participants gave their informed consent.

2.2. Measurements

At the time of delivery, the maternal elbow venous blood sample was obtained following a minimum of 8 to 10 hour fasting and injected into an ordinary biochemical tube. The cord blood was also collected at the time of delivery. The serum was collected after the blood sample was centrifuged and stored at −80°C until the measurement of Lp-PLA2 level. FPG (mmol/L) was detected by hexokinase method. HbA1c, % was measured by ion exchange high performance liquid chromatography method in an autoanalyzer (Bio-Rad, D-10). Insulin (μU/mL) was determined by electrochemiluminescence with Roche cobas. The homeostatic model assessment for insulin resistance (HOMA-IR) index was calculated by the formula: HOMA-IR = FPG (mmol/L) × fasting insulin (mU/L) / 22.5. The lipid metabolism parameters including total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), LDL-cholesterol (LDL-C, mmol/L) and HDL-cholesterol (HDL-C, mmol/L) were quantified by enzymatic calorimetry in a biochemical autoanalyzer (Beckman Coulter Inc, AU5800). The levels of Lp-PLA2 (ng/mL) both in maternal and cord blood were measured using enzyme-linked immunosobent assay (Guangrui biotechnology co, Shanghai, China).

2.3. Statistical analysis

SPSS19.0 statistical analysis package was used to analyze the data. Shapiro–Wilks test was used to assess data distribution normality. Measurement data were expressed as mean ± standard deviation (x ± s) and distinction between groups was evaluate by Student t test. Enumeration data was analyzed by Chi-Squared test between 2 groups. Besides, correlations between Lp-PLA2 and biochemical parameters were demonstrated by Spearman’s correlation test. Logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence interval (95% CI), P < .05 was considered statistically significant.

3. Results

3.1. Comparison of clinical and biochemical parameters between the gestational diabetes mellitus group and the control group

Firstly, we compared the clinical and biochemical parameters between the GDM group and the control group. As shown in Table 1, there were no significant differences in age, gestational week and pre-pregnancy BMI between the GDM group and the control group. Compared with the control group, the serum Lp-PLA2 level in the GDM group was significantly increased (159.125 ± 23.494 vs 165.825 ± 15.576 ng/mL, P < .05). The levels of glucose metabolism indexes, including FPG, HbA1c and...
HOMA-IR, in the GDM group were all significantly higher than those in the control group. As to the fat metabolism indexes, the levels of TC, TG and LDL-C were significantly higher, while high-density lipoprotein cholesterol (HDL-C) level was significantly lower in the GDM group than those in the control group.

3.2. Correlation between lipoprotein-associated phospholipaseA2 and the parameters of glycolipid metabolism

As mentioned above, the levels of Lp-PLA2 and all the glycolipid metabolism parameters tested were significantly changed in the GDM group compared with those in the control group. We further investigated the correlation between Lp-PLA2 and these glycolipid metabolism parameters in the pregnant women with GDM. The results indicated that the serum Lp-PLA2 level was positively correlated with HOMA-IR, TC and LDL-C (Table 2 and Fig. 1), while not with FPG, TG and HDL-C (Table 2).

3.3. Association between lipoprotein-associated phospholipaseA2 and gestational diabetes mellitus

To study the association between Lp-PLA2 and GDM, logistic regression analysis was performed. The development of GDM was taken as the dependent variable. Lp-PLA2 as well as age, gestational age, pre-pregnancy BMI, FPG, HbA1c, HOMA-IR, TG, TC, HDL-C and LDL-C were taken as the independent variables. As shown in Table 3, higher Lp-PLA2 levels showed significant

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**Table 1**

Clinical and biochemical parameters of GDM group and the control group.

| Parameters          | GDM (n=52) | Control (n=48) | t    | P     |
|---------------------|------------|----------------|------|-------|
| Age (yr)            | 29.58±3.928| 28.52±3.995    | 1.332| .186  |
| Gestational age (weeks) | 38.77±0.9264| 38.975±0.9568 | 1.082| .282  |
| Pre-pregnancy BMI (kg/m²) | 23.175±1.360| 22.906±1.301 | 1.008| .316  |
| FPG (mmol/L)       | 4.862±0.352| 4.607±0.371    | 3.529| <.001*|
| HbA1c (%)          | 5.456±0.406| 5.185±0.276    | 3.865| <.001*|
| HOMA-IR            | 2.594±0.949| 1.783±0.534    | 5.207| <.001*|
| TC (mmol/L)        | 5.989±1.424| 4.868±1.410    | 3.953| <.001*|
| TG (mmol/L)        | 3.884±1.395| 3.003±1.064    | 3.529| <.001*|
| HDL-C (mmol/L)     | 1.741±0.392| 2.045±0.891    | 2.238| .028  |
| LDL-C (mmol/L)     | 3.649±0.817| 2.748±0.881    | 5.306| <.001*|
| Lp-PLA2 (ng/mL)    | 199.125±23.494| 165.825±15.576| 8.281| <.001*|

Data were expressed as mean±SD and compared with Student t-test. P<.05 was considered statistically significant.

BMI = body mass index, FPG = fasting plasma glucose, GDM = gestational diabetes mellitus, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment for insulin resistance, LDL-C = low density lipoprotein cholesterol, Lp-PLA2 = lipoprotein-associated phospholipaseA2, TC = total cholesterol, TG = triglyceride.

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**Table 2**

Correlation of Lp-PLA2 level with parameters of glycolipid metabolism in the GDM group.

| Variables | r   | P    |
|-----------|-----|------|
| FPG       | 0.153| .278 |
| HbA1c     | 0.268| .055 |
| HOMA-IR   | 0.393| .004*|
| TC        | 0.416| .002*|
| TG        | 0.228| .105 |
| HDL-C     | 0.115| .417 |
| LDL-C     | 0.531| <.001*|

Spearman’s correlation test was performed. P<.05 was considered statistically significant.

FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment for insulin resistance, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

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**Figure 1.** Correlation between Lp-PLA2 and parameters of glycolipid metabolism in the GDM group. (A) Correlation between Lp-PLA2 and HOMA-IR; (B) correlation between Lp-PLA2 and TC; (C) correlation between Lp-PLA2 and LDL-C. Spearman’s correlation test was performed. P<.05 was considered statistically significant. HOMA-IR = homeostatic model assessment for insulin resistance, LDL-C = low density lipoprotein cholesterol, Lp-PLA2 = lipoprotein-associated phospholipaseA2, TC = total cholesterol.
Logistic regression analysis using Lp-PLA2 and other variables.

| Variables   | OR     | 95% CI       | P value |
|-------------|--------|--------------|---------|
| Lp-PLA2     | 1.118  | 1.048–1.193  | .001    |
| HDL-C       | 0.209  | 0.059–0.737  | .015    |
| age         | 1.057  | 0.894–1.251  | .514    |
| gestational age | 0.560 | 0.248–1.263  | .162    |
| BMI         | 1.299  | 0.779–2.166  | .316    |
| HbA1c       | 7.791  | 4.53–134.028 | .157    |
| HOMA-IR     | 1.465  | 0.384–5.595  | .576    |
| TG          | 1.138  | 0.571–2.270  | .713    |
| TC          | 0.770  | 0.384–1.543  | .462    |
| LDL-C       | 2.179  | 0.712–6.669  | .172    |

Logistic regression analysis was performed. P < .05 was considered statistically significant.

BMI = body mass index, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment for insulin resistance, LDL-C = low density lipoprotein cholesterol, Lp-PLA2 = lipoprotein-associated phospholipaseA2, TC = total cholesterol, TG = triglyceride.

* P < .05

Table 3

4. Discussion

In this study, we examined the changes of Lp-PLA2 in patients with gestational diabetes. The Lp-PLA2 level in the maternal blood of the GDM group was significantly increased and higher Lp-PLA2 levels were associated with increased risk of developing GDM. It was positively correlated with HOMA-IR, TC and LDL-C, while not with FPG, TG and HDL-C. Furthermore, there was no significant difference in the Lp-PLA2 level in cord blood between the GDM group and the control group.

Nowadays, the research on the relationship between Lp-PLA2 and GDM in clinical trials is rare. Our results showed that the serum Lp-PLA2 in women with GDM was significantly increased compared with that in the control group. Mai et al. reported that Lp-PLA2 levels were significantly elevated in patients with a history of gestational diabetes. However, they did not detect Lp-PLA2 levels in GDM patients during their pregnancy. In 2016, Gao et al. first reported increased Lp-PLA2 activity in women with GDM, which was consistent with what we have found in this study. And we further expanded this finding by using regression analysis on the development of GDM and confirmed the association of Lp-PLA2 level with GDM. The reason for the increased expression of Lp-PLA2 in GDM may be that insulin resistance occurs in GDM patients, and aggrivated with the increase of gestational age, which puts pregnant women in a state of stress and activates Lp-PLA2 activity in the body. Lp-PLA2 has been reported to be associated with adverse outcomes, suggesting that it may be involved in the development of angiopathy. In addition, our results showed that Lp-PLA2 was positively correlated with HOMA-IR. It has been well accepted that IR and inflammation play important roles in the development of GDM. Lp-PLA2 is a novel inflammatory marker, which can lead to IR in insulin-sensitive cells. While IR can also lead to increased level of Lp-PLA2 through oxidative stress and inflammation. Our results confirmed the close relationship of Lp-PLA2 with IR in GDM.

In this study, lipid indexes were also analyzed, and the results showed that the levels of TC, TG and LDL-C were significantly higher, while HDL-C level was significantly lower in the GDM group than those in the control group. These findings were consistent with Wei et al. It suggested that patients with GDM had obvious dyslipidemia. Xiao et al. reported that patients with GDM had reduced insulin secretion, leading to increased blood glucose and decreased lipoprotein lipase activity, which ultimately resulted in decreased TG degradation and increased TG level in blood, and also increased the level of LDL-C, which is the main form of transporting TG. However, adipose β oxidation was enhanced in patients with GDM, and a large amount of acetyl-CoA synthesized TC, leading to a significant increase in plasma TC. Correlation analysis showed that Lp-PLA2 was positively correlated with LDL-C, while not with HDL-C. This may be because human Lp-PLA2 is highly glycosylated, which makes it difficult for Lp-PLA2 to bind to HDL-C. And under physiological conditions, Lp-PLA2 is mainly attached to LDL in the circulation. Akkurashi et al. also reported that in patients with cerebral stroke, Lp-PLA2 mass levels were positively correlated with very low-density lipoprotein. In our previous study, we found that the level of Lp-PLA2 in gestational diabetic rats induced by streptozocin was significantly up-regulated. Furthermore, its selective inhibitor, darpadlib, can improve lipid
metabolism and enhance insulin sensitivity by regulating the expression of inflammatory cytokines.\[29\] It seems that Lp-PLA2 may be a novel target for prevention and treatment of GDM, which deserves further investigation.

Here, we found that although Lp-PLA2 level in maternal blood of the GDM group was significantly higher than that of the control group, there was no significant difference in Lp-PLA2 level in cord blood between the GDM group and the control group. This may result from the different activities of Lp-PLA2 in fetus and adults. Schlieferstein et al reported that in the fetus, Lp-PLA2 primarily bound to HDL, which was in contrast to its activity in adults. Furthermore, fetal HDL-associated Lp-PLA2 acted as an anti-inflammatory enzyme which was also different from the role of Lp-PLA2 in adults.\[30\]

There are some limitations of this study. Firstly, it was a cross-sectional study with blood samples collected only at one time point in gestation (term pregnancy), which could not unveil the changes throughout the pregnancy. Secondly, the sample size was relatively small. Well-designed prospective studies with larger sample size are needed in our future work.

In conclusion, we found that Lp-PLA2 levels in women with GDM were signification increased and had close correlations with glucolipid metabolism indexes. These findings will broaden our knowledge on the pathophysiology of GDM and provide insights into the development of new targets for the prevention and treatment of GDM.

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