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ORIGINAL ARTICLE

Non-Targeted Metabolomics Analysis of Mother and Infant in Gestational Diabetes Mellitus and Neonatal Clinical Characterization

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SUMMARY

Background: **The goal was to analyze serums of GDM patients and healthy pregnant women using HPLC-MS and preliminarily screen differential metabolites by metabolomics.**
Method: **Sixty pregnant women who underwent elective cesarean section at term in Dongguan Dalang Hospital from January 2023 to April 2023 were selected and divided into the GDM group and healthy pregnancy group. Pre-pregnancy and pregnancy examination information, such as age, BMI, OGTT results, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and other clinical data were collected for statistical analysis. Non-targeted metabolomics of serum from 30 GDM patients and 30 healthy pregnant women were studied by HPLC-MS, and different ions were searched. The structures of differential metabolites were identified by HMDB database. The metabolic pathways of differential metabolites were analyzed by KEGG database.**
Results: **The OGTT result, pCO_2, pO2, HCO3, BE, Apgar score, and bilirubin levels in the GDM group were higher than those in the healthy pregnancy group ($p < 0.05$). However, there were no significant differences in age, triglyceride, total cholesterol, newborn birth weight, newborn birth blood glucose, and blood gas pH between the two groups (all $p > 0.05$). Using $p < 0.05$ as the screening standard, 55 differential metabolites were identified in serum, mainly including fatty acyl, carboxylic acids and their derivatives, steroids and their derivatives, ketoacids and their derivatives, and pyrimidine nucleosides, etc., all of which were up-regulated or down-regulated to varying degrees. The 55 metabolites were mainly involved in the metabolism of pyrimidine, pyruvate, alanine, aspartic acid, glutamic acid, and arachidonic acid, glycolysis, and biosynthesis of unsaturated fatty acids.**
Conclusions: **The discovery of these metabolites provides a theoretical basis for an in-depth understanding of GDM pathogenesis. Non-targeted metabonomics analysis of blood metabonomics research technology has shown great potential value in the early diagnosis of obstetric diseases and the study of disease mechanisms.**
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KEYWORDS

gestational diabetes mellitus, metabonomics, blood gas analysis, newborn

INTRODUCTION

Gestational diabetes mellitus (GDM) is a glucose metabolism disorder that often happens in middle or late pregnancy [1,2]. Statistics released by the International Diabetes Federation show that the number of pregnant women suffering from GDM in China exceeded 1 mil-

lion in 2013. Increased fat during pregnancy, changes of placental secretion hormone, and increased inflammatory factor secretion may be the pathogenesis of insulin resistance [3,4]. GDM often leads to a variety of short-term and long-term metabolic complications, such as pregnancy-induced hypertension, cholestasis, macrosomia, etc. [5], and increased risk of long-term type 2 diabetes and cardiovascular diseases in newborns [6]. Metabolic disorder is a significant feature of GDM. Small metabolic molecules can affect fetal metabolism through umbilical cord blood. The poor environment in utero also has an inclement effect on the fetus. Elevated blood glucose levels in pregnant women increase fetal protein and fat synthesis, leading to macrosomia. Hyperglycemia can lead to fetal hyperinsulinemia, reduce the production of fetal pulmonary surfactant, and increase the risk of neonatal respiratory distress syndrome [7]. After the newborn is removed from the maternal hyperglycemic environment, neonatal hypoglycemia, hyperbilirubinemia, and NICU occupancy rate increase. The National Institutes of Health conducted a worldwide multi-center prospective study [8] and showed that with the increase of blood glucose level, the risk of adverse pregnancy outcomes is increased such as premature delivery, neonatal hypoglycemia, and surgical delivery. Blood glucose indexes are often used to monitor and evaluate the condition of GDM patients in clinical practice. However, simple blood glucose monitoring is usually instantaneous and cannot accurately reflect the continuous condition. Therefore, it is of little significance to predict pregnancy outcomes. Moreover, sensitive and reliable markers have been reported to not predict the correlation between maternal changes and poor fetal prognosis.

Metabonomics has become a hot topic in recent years [9]. As a holistic research model [10], metabolomics is widely used in the diagnosis, treatment, and efficacy evaluation of diseases [11]. Metabolomics has been widely applied in clinical sample analysis, such as mass spectrometry (MS), nuclear magnetic resonance, liquid chromatography, and gas chromatography to identify metabolites from biological samples (blood, urine, feces, etc.). As a metabolic disorder during pregnancy, GDM is suitable to be studied by metabonomics. At present, studies on metabolomics of GDM mainly focus on abnormalities of metabolites of small molecules related to glucose, amino acids, and lipids. Studies have identified that the concentrations of leucine, isoleucine, and valine are high in GDM pregnant women [12,13]. GDM pregnant women who delivered giant infants have strong placental leucine transport capacity [14]. Nuclear magnetic resonance technology analysis of metabolites of umbilical cord blood of newborns in full-term delivery of GDM pregnant women detects higher pyruvate, histidine, alanine, valine, methionine, arginine, and lysine [15]. Even if GDM is well controlled, the nutrient transport capacity and histopathological changes of the placenta persist [16], and multi-factor injury of GDM may lead to placental metabolic transport dysfunction and adversely affects fetuses. At present, studies on metabolomics of GDM mainly focus on metabolites in maternal blood or umbilical cord blood, but not on the metabolic pathways and overall metabolic network, as well as the correlation between differential metabolites, metabolic pathways, and neonatal prognosis. To provide a new reference in clinical practice, this study analyzed differential metabolites of GDM patients.

MATERIALS AND METHODS

Diagnostic criteria of GDM

Guidelines for Diagnosis and Treatment of Gestational Diabetes Mellitus (2014) jointly issued by the Obstetrics and Gynecology Society of the Chinese Medical Association and the Gestational Diabetes Mellitus Cooperative Group of the Perinatal Medicine Society of the Chinese Medical Association were adopted: 1) When it is first detected during pregnancy and the blood glucose level has reached the standard of diabetes, it should be diagnosed as PGDM instead of GDM; 2) During 24 - 28 weeks of gestation, OGTT test was conducted by taking 75 g glucose liquid for 2 hours (fasting for at least 8 hours before the test, normal diet for 3 days), that is, eating no less than 150 g of carbohydrates every day, sitting quietly and not smoking during this period. After oral administration of 250 mL liquid containing 75 g glucose within 5 minutes, blood samples were collected after 1 hour and 2 hours, and blood glucose level was detected by glucose oxidase method. Before taking glucose liquid and 1 hour and 2 hours after taking glucose liquid, the blood glucose level should be lower than 5.1, 10.0, and 8.5 mmol/L, respectively, and blood glucose level meeting or exceeding the above criteria was diagnosed as GDM.

Patients and samples

A total of 60 pregnant women who underwent elective cesarean section at term in Dongguan Dalang Hospital from January 2023 to April 2023 were selected and divided into the GDM group and healthy pregnancy group. Women over 40 years of age with pregnancy complications (hypertension, thyroid dysfunction, gestational cholestasis syndrome, etc.), familial hereditary diseases, infectious diseases during pregnancy, and abnormal newborn growth were excluded. Pre-pregnancy and pregnancy examination information of pregnant women, such as age, pre-pregnancy BMI, OGTT results, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and other clinical data were collected for statistical analysis. Pregnant women fasted for more than 4 hours before operation, 5 mL of maternal blood was extracted during operation, and blood was collected in a plain tube and left for 1 hour at room temperature for coagulation stratification and then centrifuged at 3,000 rpm for 5 minutes. The supernatant was then transferred to a clean centrifuge tube and centrifuged at 5,000 rpm for 5

Table 1. Comparison of the general conditions of pregnant women.

Groups	Age (years)	Pre-pregnancy BMI	OGTT results	Triglyc-eride (mmol/L)	Total choles-terol (mmol/L)	Birth weight (kg)	Birth blood glucose (mmol/L)	Blood gas PH	Blood gas pCO_2	Blood gas pO_2	Blood gas HCO 3	Blood gas BE	Apgar scores	24-hours bilirubin (μmol/L)	48-hours bilirubin (μmol/L)
Healthy group	31.4	22.466	4.47 - 6.58 - 8.15	3.61	3.46	3.46	4.16	7.31	45.95	26.83	23.33	-2.67	10	73.39	132.82
GDM group	31.3	24.271	5.03 - 8.32 - 9.74	3.21	3.47	3.47	4.179	7.29	44.88	25.96	22.11	-4.03	10	93.08	154.8
p	0.939	0.031	0.034	0.308	0.681	0.913	0.882	0.187	0.507	0.042	0.039	0.025	1	0.013	0.01
X^2	1.66	1.456	4.543	1.06	0.348	0.003	0.014	0.004	0.445	0.295	1.457	5.293	-	6.506	2.764

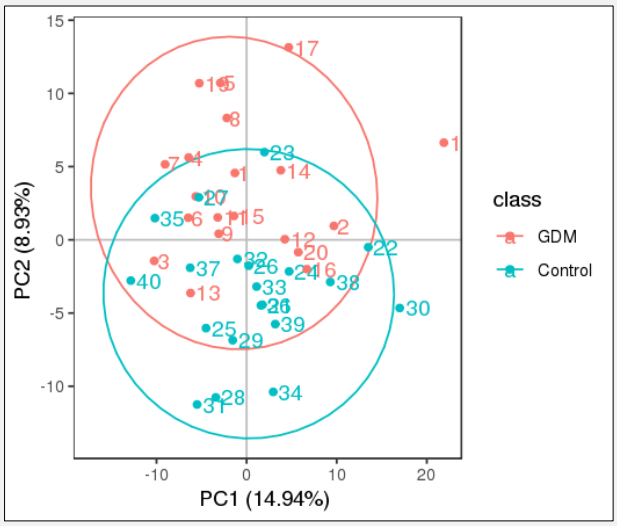

Figure 1. PCA scores of GDM and healthy pregnancy women.

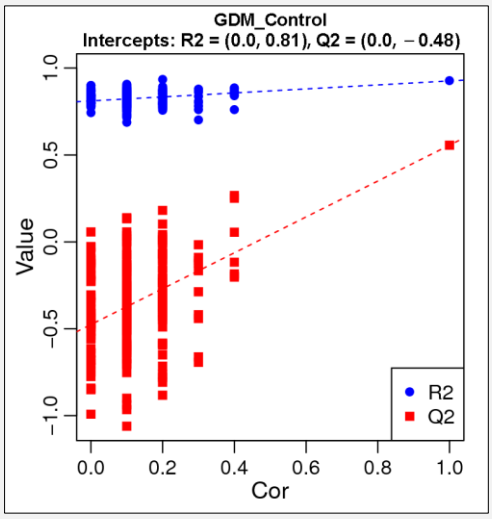

Figure 2. Score charts and replacement test charts of GDM and healthy pregnancy women.

minutes. The supernatant was then put into 2 mL centrifuge tubes, 0.2 mL each, marked, frozen at -80°C, and finally tested by non-targeted metabolomics using liquid chromatic-mass spectrometry (LC-MS). Birth weight, blood glucose at birth, blood gas analysis, Apgar score, 24-hour and 48-hour bilirubin levels were recorded.

Experimental procedures

The collected blood samples were kept at room temperature for 1 hour for coagulation and stratification and centrifuged at 3,000 rpm for 5 minutes. Then, the supernatant was centrifuged at 5,000 rpm for 5 minutes, and the final supernatant was taken and divided into 2 mL centrifuge tubes with 0.2 mL per tube. After labeling, the supernatant was frozen at -80°C.

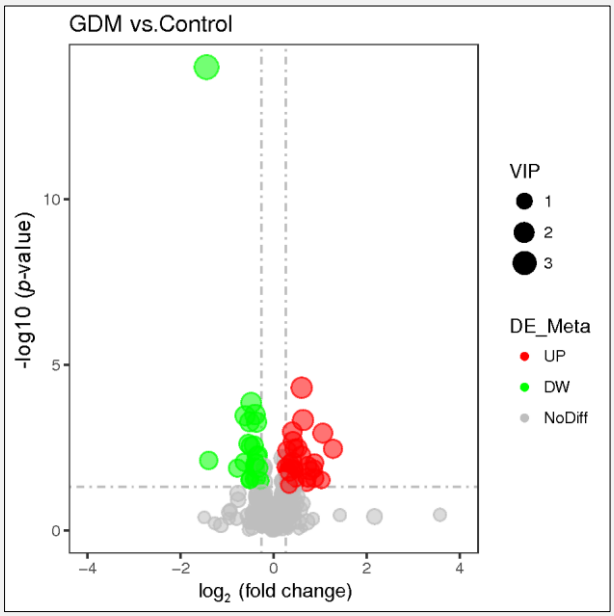

Figure 3. Heat maps of differential metabolites between GDM and healthy pregnancy women.

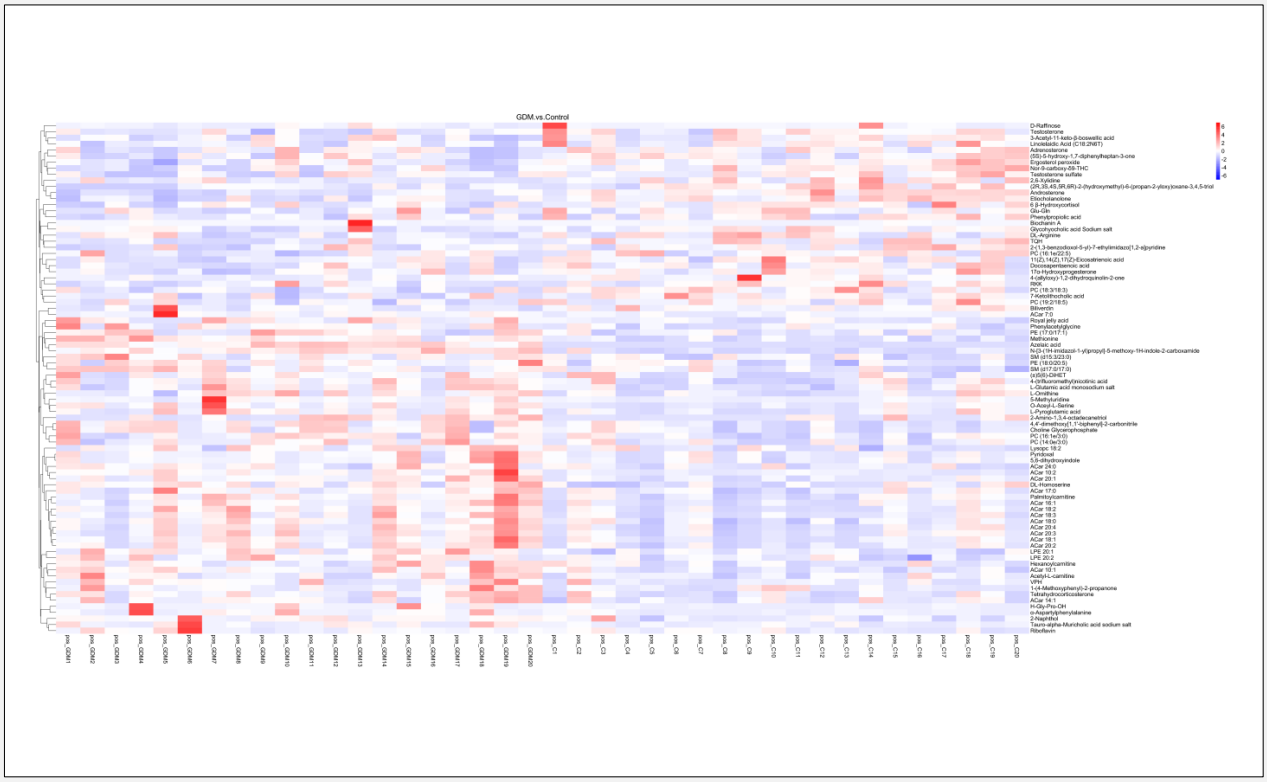

Figure 4. Heat maps of differential metabolites enriched in pathways between GDM and healthy pregnancy women.

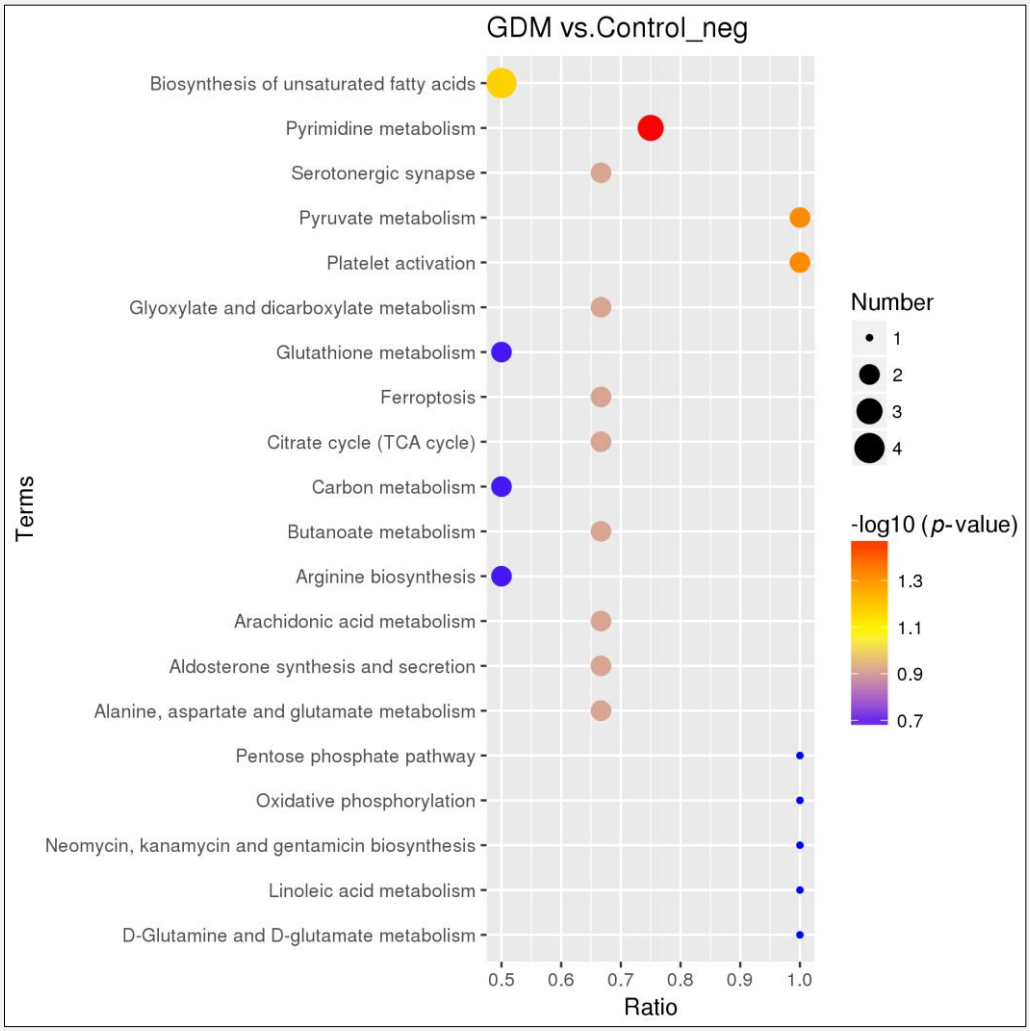

Figure 5. KEGG enrichment of different metabolites in GDM and healthy pregnancy women.

Non-targeted metabolomics was studied based on LC-MS technology. The experimental procedures mainly included metabolite extraction, LC-MS detection, and data analysis.

LC-MS analysis conditions

Chromatographic conditions were as follows: a YMC-PackODS-A column (250 mm × 4.6 mm, 5 μm) was used, and the mobile phase consisted of 0.1% formic acid (A)-acetonitrile (B). Gradient elution procedure: 0 minutes, 5% B; 0 - 45 minutes, 5% B → 30% B; 45 - 55 minutes, 30% B → 45% B; 55 - 85 minutes, 45% B → 60% B; 85 - 105 minutes, 60% B → 90% B; 105 - 110 minutes, 90% B. The detection wavelength was 254 nm, the column temperature was 35°C, the flow rate was 1 mL/minute, and the sample volume was 10 μL.

MS conditions were as follows: electrospray ionization, ion source temperature 28°C, capillary voltage 4.5 kV, detector voltage 1.5 kV, dry gas flow rate 5 L/minute, atomized gas flow rate 1.5 L/minute. In positive and negative ion modes, the total ion flow pattern was obtained, and the full scanning MS range was 100 - 1000 m/z.

Data preprocessing and metabolite identification

Data file (.raw) was imported into CD3.1 library search software, and parameters such as retention time and mass/charge ratio were simply analyzed. Then, the retention time deviation of 0.2 minutes and the mass deviation of 5 ppm were set for peak alignment of different samples, so as to make the identification more accurate. Then, mass deviation of 5 ppm, signal strength de-

viation of 30%, signal-to-noise ratio of 3, minimum signal strength, and adduct ion were set for peak extraction, at the same time, the peak area was quantified, and target ions were integrated. Then the molecular formula was predicted by molecular ion peak and fragment ions and compared with mzCloud (https://www.mzcloud.org/), mzVault and Masslist databases. The background ions were removed with blank samples and the original quantitative results were normalized. Finally, the identification and relative quantitative results of metabolites were obtained. Data analysis was based on the Linux operating system (CentOS 6.6), software R, and Python.

Statistical analysis of data

KEGG database (https://www.genome.jp/kegg/pathway.html), HMDB database (https://hmdb.ca/metabolites), and LIPIDMaps database (http://www.lipidmap s.org/) annotated the identified metabolites. In multivariate statistical analysis, metaX software was used to convert the data and then principal component analysis (PCA) and Orthogonal Partial least squares discriminant analysis (OPLS-DA) were performed to obtain the variable importance projection (VIP) value of each metabolite. In univariate analysis, the statistical significance (*p* value) was calculated based on the *t*-test, and the fold change (FC) was calculated. The default criteria for differential metabolite screening were VIP > 1, $p < 0.05$, $FC \geq 2$, or $FC \leq 0.5$. The volcano map was drawn with R package ggplot2, and the VIP value, log2 (FC value), and -log10 (p-value) could be integrated to screen the metabolites of interest. The cluster heatmap was drawn using R-package Pheatmap, and the metabolite data were normalized using z-score. The correlation analysis between differential metabolites (Pearson's correlation coefficient) was conducted using R language co (r), and the statistical significance was achieved by cor.mtest in R language. $p < 0.05$ was considered statistically significant, and correlation plots were plotted using corrplot software package in R language. The bubble map was drawn with R package ggplot2, and KEGG database was used to study the function and metabolic pathway of metabolites. When x/n > y/n, the metabolic pathway was considered to be enriched. When the p-value of the metabolic pathway was < 0.05, it was considered that the metabolic pathway was significantly enriched.

RESULTS

Basic information of pregnant women

Among 30 normal pregnant women and 30 pregnant women with GDM, there were no significant differences in maternal age, triglyceride, total cholesterol, newborn birth weight, newborn birth blood glucose, and blood gas pH ($p > 0.05$). The OGTT results, blood gas analysis pCO_2, pO_2, HCO3, and BE, Apgar score, 24-hour and 48-hour bilirubin after birth, and pre-pregnancy BMI of GDM women were higher than those of healthy pregnant women ($p < 0.05$) (Table 1).

Metabolic discriminant analysis of maternal and infant metabolites

PCA: In the PCA score chart, each point represents a sample, and the closer the metabolites contained in the samples are, the more compact the sample points in the figure. Figure 1 shows the PCA diagram of quality control samples in positive ion mode. It can be seen from the diagram that the quality control samples were closely clustered and obviously separated from the experimental samples, again verifying the stable and repeatable analysis system. The metabolic spectrum differences obtained can reflect the biological differences between the samples and screen different metabolites.

OPLS-DA

OPLS-DA can filter out information irrelevant to classification and accurately analyze differences between groups. OPLS-DA analyzed the obtained MS data, and it was found that maternal and neonatal blood samples of GDM were distributed in the left and right side of the confidence interval, with differentiation effect, indicating a significant difference between the two groups (Figure 2). The model quality parameters were five principal components, the cumulative prediction rate $Q2 = 0.998$, $R^2X = 0.817$, $Q2 < 0$ in the figure, and all Q2 points from left to right were always lower than the original blue Q2 point, indicating that the evaluation model is reliable and effective.

Screening and identification of differential metabolites

Based on the precise mass number of precursor ions, isotopic composition of precursor ions, and information of fragment ions, matching scores of precursor ions, and fragment ions were performed on the identified compounds in PMDB and other databases to identify differential metabolites. According to ($VIP \geq 1$, $p < 0.05$) and the maximum variance multiple (Figure 3), 55 metabolites with significant differences were screened, including 11 fatty acyl groups, 6 carboxylic acids and their derivatives, 4 steroids and their derivatives, 3 ketoacids and their derivatives, 2 pyrimidine nucleosides, 1 ketoic acid and its derivatives, 1 fruit acid and its derivatives, 1 phenylpropionic acid, 2 organic oxygen compounds, 1 glycerol phosphatide, 1 dihydrofuran, and 24 other groups (Table 2). Among them, 31 substances were up-regulated, accounting for 56.4%, and 24 were down-regulated, accounting for 43.6%.

Differential metabolite pathway analysis

The pathway enrichment analysis of different metabolites was further conducted by KEGG database. Different metabolites were distributed mainly in 20 metabolic pathways, including 4 metabolic pathways with $p < 0.05$, including biosynthesis of unsaturated fatty acids, pyrimidine metabolism, pyruvate metabolism, and platelet activation (Figure 4, 5). First, the metabolic pathway of the biosynthesis of unsaturated fatty acids was the most significant, with a p-value of 0.02. There

were mainly 4 differential metabolites enriched in this metabolic pathway, namely, adrenoic acid, arachidonic acid, nervonic acid, and arachidic acid. Second, pyrimidine metabolic pathway was significant, and the p-value was 0.032. There are mainly 3 detected differential metabolites enriched in this metabolic pathway, namely uridine, methylmalonic acid, and deoxycytidine. Finally, pyruvate metabolic pathway had a p-value of 0.046. There are mainly 2 detected differential metabolites enriched in this metabolic pathway, namely, fumaric acid, and L-malate dehydrogenase.

DISCUSSION

GDM is extremely harmful to mothers and infants and can increase the incidence of maternal and infant complications during pregnancy. GDM also increases the risk of developing diabetes in pregnant women and newborns. Therefore, the early diagnosis and pathogenesis of GDM have attracted more and more attention from scholars at home and abroad.

GDM is a common complication of pregnancy. Abnormal circulatory metabolism and inflammatory factors in the mother of GDM form a hypoxic environment, which affects the development of placental blood vessels. Typical histological manifestations of the placenta include immature villus development, villus fibrinoid necrosis, chorionic vascular disease, angiogenesis, etc., causing long-term, chronic, and severe gas and nutrient exchange disorders. The basic pathological changes of fetal respiratory distress syndrome are hypoxemia and acidosis. Compared with Apgar score, blood gas analysis can more objectively and directly reflect the degree of fetal ischemia and hypoxia and the status of tissue metabolism, which can exclude about 80% of the diagnosis of neonatal asphyxia [17]. Blood gas analysis has been widely used in clinical practice to judge fetal distress and evaluate the oxygen-acid-base balance state and prognosis of newborns at birth. However, there are few studies on blood gas analysis of umbilical cord blood in newborns in GDM. The study revealed that triglyceride, total cholesterol, newborn birth weight, newborn birth blood glucose, and blood gas analysis pH value of GDM women had no statistical significance compared with healthy women. The blood gas analysis pCO_2, pO_2, HCO3, and BE, Apgar score, bilirubin, and pre-pregnancy BMI of GDM women were statistically significant compared with healthy pregnant women. This is consistent with the research reports [18,19]. Domestic scholars also have similar research evidence that pregnant women with GDM have statistically significant differences in fat-free mass, lean body mass, and body fat mass [20]. This study also observed a similar phenomenon: body weight and BMI in GDM pregnant women were significantly higher than those in healthy pregnant women, and body composition parameters were increased, while BMI, body fat percentage and fat-free mass were not significantly different. Therefore, to conduct timely nutrition intervention and body quality management to prevent GDM, it may be instructive to test body composition in the second or third trimester. Pregnant mothers should exercise and eat a balanced diet to avoid rapid weight gain. In addition to the prenatal examination done during pregnancy, blood sugar monitoring and urine sugar inspection should also be done. It is recommended to screen for gestational diabetes at 24 to 28 weeks of pregnancy. Only timely detection of problems can effectively prevent gestational diabetes.

GDM pathogenesis is similar to that of T2DM, both of which are related to insulin endocrine defects and insulin resistance [21]. Although the specific pathogenesis of GDM has not yet been reported, relevant studies have found that inflammatory factors and fat factors, genetic genes, diet, and insulin resistance are associated with GDM pathogenesis [22]. Cetin et al. screened GDM patients by measuring blood glucose before and after taking glucose in pregnant women, and could not screen and diagnose GDM earlier [23]. Therefore, it is necessary to find some new biomarkers for early diagnosis. Non-targeted metabolomics based on HPLC-MS technology can analyze the metabolic information and GDM pathogenesis from a global and holistic perspective.

At present, metabolomics has been more and more applied in the study of finding biomarkers with diagnostic significance for diseases. Metabolomics, on the other hand, analyzes hundreds of metabolites at the same time and finally excavates the changes of metabolic pathways [24]. In this study, methylmalonic acid, L-glutamine, etc., were increased in GDM pregnant women, while arachidonic acid, nervonic acid, etc. were reduced, which were mainly involved in metabolism of pyrimidine, pyruvate, alanine, aspartic acid, glutamic acid, and arachidonic acid, glycolysis, and biosynthesis of unsaturated fatty acids. However, changes in these metabolic pathways and metabolic disorders of related metabolites are strongly correlated with GDM. In fact, studies have reported a high correlation between branched chain amino acids and diabetes. The amounts of some amino acids, such as valine, methionine, and phenylalanine, in GDM patients are significantly higher [25]. Tryptophan metabolism is mainly affected in GDM, while tyrosine metabolism and steroid hormone biosynthesis are mainly affected in normal pregnancy. Urinary differential metabolites in early pregnancy have reference significance for early GDM prediction, and in order to improve the accuracy of GDM prediction, multiple metabolites can be combined for detection [26]. Our metabolomics findings are consistent with these findings [27,28]. GDM caused changes in a series of metabolic pathways, mainly including glycolysis and tricarboxylic acid cycle, which also provide a basis for finding out the metabolic characteristics of GDM patients. Numerous related differential metabolic pathways will also become a breakthrough to explain GDM pathogenesis.

This study applied non-targeted metabolomics to analyze metabolic profile changes. Quality control experiments verified the instrument analysis system with good stability and reliable test data. The biological differences among the samples in the experiment can be reflected by the differential metabolic profile. KEGG metabolic pathway analysis showed that 20 potential biomarkers in both GDM pregnant women and healthy pregnant women were involved in multiple metabolic pathways, including metabolism of pyrimidine, pyruvate, alanine, aspartate, glutamate, arachidonic acid, glyoxalate, and dicarboxylate, aldosterone synthesis and secretion, arginine biosynthesis, and glutathione metabolism. This indicates that GDM not only affects the metabolism of lipids, amino acids and glucose, but also leads to the disorder of other metabolic systems, which is consistent with a previous study [29].

Using isotope-labeled tandem MS, researchers have measured several steroid hormones in blood during pregnancy and find that levels of 11-deoxycortisol, 17A-hydroxyprogesterone, and progesterone gradually increase throughout pregnancy, while cortisol and androstenedione levels remain stable after rising in the first trimester. On the other hand, dehydroepiandrosterone sulfate decreases in late pregnancy [27]. In this study, 11-deoxycortisol in GDM pregnant women was also higher than that in healthy pregnant women. However, dehydroepandrosterone sulfate was also higher in GDM pregnant women, which may be related to different population characteristics, sample collection time, sample types, and application methods. Tian et al. have conducted a metabonomics analysis of differential metabolites in serum of GDM patients and noticed 17 different metabolites including oleic acid and linoleic acid, which are mainly involved in amino acid and fatty acid metabolism [30]. Li JX et al. have detected dynamic metabolism in the serum of GDM patients and finally screened out 35 metabolites and their prenatal and postpartum metabolites. These metabolites are derived from the metabolism of steroid hormones, pyruvate, glycerol phospholipids, fatty acids, etc., and are mainly involved in metabolism of glycolipid, nucleotide or amino acid. However, serum metabolites analyzed in this study may have some differences with previous studies due to pregnancy, but from the overall analysis, GDM has a great impact on metabolism of phospholipid, glucose, amino acids, and fatty acids.

At the same time, there are still some shortcomings in this study: (1) Due to the limitation of research time and funds, the sample size was small, and the comparison of different gestational weeks was not made, which may lead to incomplete analysis of statistical results. (2) No other body fluid metabolites were used for comparison. This study did not use pooled urine metabolomics analysis for clinical prediction or evaluation, otherwise the effect might be better; (3) Postpartum data without samples. Hormone levels in various aspects of the body change greatly before and after delivery, which significantly affects body metabolism. Therefore, combined with long-term follow-up data, in-depth analysis of postpartum sample data will be of great significance for the internal relationship between GDM and the prediction of long-term diabetes. Therefore, in this study, non-targeted metabolomics analysis of maternal and infant gestational diabetes mellitus was carried out with liquid-mass combined technology. The prognosis of offspring was studied to improve the accuracy of clinical detection.

CONCLUSION

In this study, 55 different metabolites were found in serum metabolomics, and some metabolites were up-regulated in GDM, which were involved in metabolism of pyrimidine, pyruvate, alanine, aspartic acid, glutamic acid, and arachidonic acid, glycolysis, and biosynthesis of unsaturated fatty acids. Blood metabolomics based on LC-MS can well distinguish GDM patients from ordinary pregnant women and find specific differences. This study has a reference value for the early diagnosis and prognostic risk assessment of patients with sub-GDM and provides a basis for exploring the pathogenesis of GDM. However, this study lacks external validation. Therefore, further prospective, multicenter studies are needed to confirm the accuracy of these results.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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