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ORIGINAL RESEARCH

Serum Lipidomic Analysis of T2DM Patients: A Potential Biomarker Study

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Purpose: Comprehensive analysis of serum lipidomics is important for the treatment and prevention of type 2 diabetes (T2DM). The purpose of this study was to provide a profile of lipid changes in the serum of T2DM patients and identify potential lipid biomarkers.
Patients and Methods: In this study, we collected clinical physiological parameters and determined the serum lipid profiles of 30 T2DM patients and 30 matched healthy volunteers using the UPLC-MS method. *T* test and multivariate statistical analyses were used to identify candidate lipid predictors using the GraphPad Prism 9.5 software and MetaboAnalyst 5.0 online platform.
Results: Based on the above test, 1162 lipid metabolites were detected, of which 267 were significantly altered in the T2DM group (FDR < 0.05), which belonged to the five main lipid classes. Eleven lipids were identified as potential lipid biomarkers with the specific screening criteria (variable importance in the projection (VIP) >1.0; P < 0.05; $\log_2$(Fold Change) > 1) in the MetaboAnalyst 5.0 online platform. The Pearson rank correlation test showed that ten differential lipids were significantly correlated with T2DM-related physiological parameters (2h-loaded blood glucose and HbAc1 (glycated haemoglobin)). ROC curve analyses revealed that the combined 11 lipids or LPI classes can be as candidate features for the development of an integrated diagnostic biosignature for T2DM.
Conclusion: The results of this study revealed important changes in lipids in T2DM patients, expanded the knowledge of lipid levels and T2DM progression, and provided important metabolic information for the therapy and diagnosis of T2DM.
Keywords: diabetes mellitus type 2 (T2DM), lipidomic, UPLC-MS

Introduction

T2DM is a chronic metabolic disease characterized by deficient insulin secretion, insulin resistance, and an inadequate compensatory insulin response,[1] and has become a major cause of death and disability. According to the IDA (International Diabetes Alliance) statistical data for 2021, there are approximately 537 million T2DM patients worldwide, and the incidence rate of T2DM in China is as high as 10.6%. The pathogenesis of diabetes is complex, and the main indication for diabetes is an increase in blood glucose levels.[2] In fact, they do not have significant symptoms in T2DM patients at the initial stage, and most are diagnosed after hyperglycemia-damaged organs. Therefore, it is an urgent task for researchers to understand the pathogenesis of T2DM and identify new biomarkers or pathways for T2DM.

Recent studies have shown that dyslipidemia is a common event in diabetes and may occur earlier than abnormal blood glucose.[3–6] Lipids can be divided into non-glycerides (such as cholesterol esters and sphingolipids) and glycerides (such as phospholipids and glycerols) based on the molecular structure of their headgroups, and the attached fatty acids increase the diversity of lipids. The main sources of blood lipids are adipose tissue, liver, and dietary lipids. Dyslipidemia is the balance of lipids that is disrupted in the body, which further leads to the occurrence of diseases.

At present, clinical blood lipid testing mostly focuses on detecting the total content of a certain type of lipid (total cholesterol, total triglycerides, LDL-cholesterol, HDL-cholesterol, etc.), and we cannot determine the changes in specific lipids in the body; however, the emergence of lipidomics has solved this problem. Lipidomics is an independent branch of metabolomics, and serum non-targeted and targeted lipidomics can provide detailed information regarding lipid composition

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in the body.[7,8] It can explain the relationship between lipid metabolism and the physiological and pathological processes of cells, organs and even the body, which enables researchers to accurately analyze the association between serum lipids and diseases, as well as the effects of dietary or drug interventions. Nowadays, lipidomics has provided an unprecedented opportunity to understand a profile of lipid change in the serum of T2DM patients. Studies have shown significant changes in phospholipids and sphingomyelin in the serum of patients with newly diagnosed Chinese prediabetic and T2DM patient and proposed that acid sphingomyelinase is the cause of acid sphingomyelinase is responsible for significant disruptions in ceramide and sphingomyelin homeostasis,[9,10] and the other study indicated that Cer (d18:1/24:0), SM (d18:1/24:0), SM (d18:1/16:1) and SM can be used to predict the risk for the development of T2DM in individuals with dyslipidemia but no clinical signs of high blood sugar,[11] which proved that lipid is a sensitive metabolic indicator of T2DM. In addition, acylcarnitines, fatty acids, phosphatidylcholine, lyso-phosphatidylcholine, phosphatidylethanolamine, and diacylglycerol have also been reported to be associated with the progression of T2DM.[12–14]

Although T2DM has attracted increasing attention due to the complexity of lipids and diseases, limited lipid metabolite detection may lead to one-sided or erroneous results (some studies can only detect dozens or hundreds of lipids) and our understanding of lipids in the body is only the tip of the iceberg. In this study, we used the UPLC-MS method developed by the SCIEX Support Center to conduct serum lipidomic analysis (up to 1162 lipids) of T2DM patients.[15] This method can reliable and convenient to simultaneously targeted monitor changes of over 1000 lipids in the body. Based on this, we identified 11 lipids as T2DM biomarkers and analyzed the relationship between these characteristic biomarkers and clinical biochemical indicators. Overall, this serum lipidomic analysis discovered the changes in serum lipids in patients with diabetes, which is helpful for the diagnosis and course detection of diabetes.

Materials and Methods

Reagents

UPLC-MS-grade methanol, acetonitrile, and isopropyl alcohol were obtained from Thermo Fisher Scientific (Waltham, MA, USA). HPLC-MS-grade methyl tert-butyl ether and ammonium acetate were purchased from Merck KGaA (Darmstadt, GERMANY). Ultrapure water (18.2 MΩ) was obtained using a Milli-Q water purification system (Millipore, Billerica, MA, USA).

Study Design

Thirty T2DM patients (defined as FBG $\geq$ 6.1 mmol/L) and 30 matched healthy individuals without chronic diseases were included in our experiment, and blood was obtained from the vein at 7:00–9:00 am after an overnight fast and 2 h after a meal. All participants were from Beijing Shijitan Hospital, Capital Medical University (Beijing, China) and provided informed consent and detailed physiological information, including age, sex, and clinical parameters. This study was approved by the Ethics Committee of the Beijing Shijitan Hospital, Capital Medical University (permission No. sjtkyll-lx-2021(4)), registered in the Chinese Clinical Trial Registry (ChiCTR2200056980), and conducted in accordance with the guidelines of the Helsinki Declaration.

Sample Pre-Treated Method

After collection, the samples were centrifuged at 3000 rpm at 4 °C for 10 min to obtain serum, which was stored in a refrigerator at −80 °C before analysis. Fifty microliters of serum were mixed with 50 μL methanol, 250 μL methyl tert-butyl ether, 75 μL water, vortexed for 1 min, centrifuged at 12000 rpm for 20 min, and then take 200 μL supernatant to dry using vacuum freeze-drying equipment. One hundred microliters of isopropyl alcohol-acetonitrile-water (2:1:1) solution was re-dissolved, centrifuged at 12000 rpm for 10 min, and the supernatants were collected for UPLC-MS analysis.

Chromatographic and Mass Spectrometric Conditions

Chromatographic separation was performed using a Waters ACQUITY ultra-performance liquid chromatography (UPLC) system. The column used was an ACQUITY BEH C8 column (100 mm × 2.1 mm, 1.7 μm) (Waters, Milford, USA) with

column temperature at 40 °C. Mobile phase A was Methanol-acetonitrile-water (1:1:1) solution containing 5 mmol/L ammonium acetate and mobile phase B was an isopropanol solution containing 5 mmol/L ammonium acetate. The elution time was 17.0 min. The elution gradient started at 80% A and then decreased linearly to 60% A over 2.5 min. After kept for 1.5 min at 60% A, the elution decreased linearly to 10% A after 14 min and was held for 1 min. The gradient was then increased to 80% A for 0.1 min and held for 1.9 min. The injected volume was 4 μL for all samples at a flow rate of 0.30 mL/min.

Mass spectrometric conditions were as follows: MS system was operated using an AB SCIEX Triple TOF 5500 mass analyzer with information dependent acquisition (IDA).

The MS system was operated using an AB SCIEX Triple TOF 5500 mass analyzer with information-dependent acquisition (IDA). A total of 585 candidate ions (positive mode) and 603 candidate ions (negative mode) were selected for subsequent analyses, and the MS parameters including cone energy (CE) and declustering potential (DP) were shown in Tables S1 and S2. The MS conditions were set as follows: ion spray voltage: + 5500 V (positive) and −4500 V (negative); gas 1, 50 psi; and gas 2, 55 psi; curtain gas, 25 psi; drying temperature, 500 °C; CAD is set as medium.

Data Analysis

MetaboAnalyst 5.0 online platform was used to perform partial least square-discrimination analysis (PLS-DA), principal component analysis (PCA), a heat map for hierarchical clustering analysis, volcano plot, fold change (FC) and variable importance in the projection (VIP) among the relative levels of significant lipid metabolites. Relative quantitative analysis of the significantly changed lipid metabolites and Pearson's correlation analysis were conducted with GraphPad 9.5 version software, and the significance threshold was set at $p < 0.05$. Receiver operating characteristic curve (ROC) analysis was performed on the MetaboAnalyst 5.0 online platform with biomarker analysis function to calculate the predictive value of the lipids and T2DM.

Results

Study Population

Sixty participants were recruited, and based on their fasting serum glucose (FBG) levels, their serum samples were classified into two groups: 30 T2DM and 30 matched healthy volunteers without cardiovascular disease or other chronic diseases. Clinical physiological parameters included BMI (body mass index), 2h-post load glucose, HbA1c (glycated haemoglobin), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured. There were no statistically significant differences in age, sex and height between 2 groups, and detailed characteristics are provided in Table 1.

Table 1 Clinical Characteristics of the Participants

	Health group (n=30)	**T2DM group (n=30)**
Age (years)	50.17±2.27	55.77±2.39
Sex (%Male)	50.00% (15/30)	60.00% (18/30)
Course of disease (year)	–	10.7±1.66
BMI (Kg/m^2)	21.81±0.25	25.21±0.83***
Height (cm)	167.5±1.59	167.43±1.76
Weight (kg)	61.5±1.51	70.97±2.94**
Fasting serum glucose (mmol/L)	5.23±0.07	7.90±0.52***
2h-post load glucose (mmol/L)	5.55±0.05	16.61±0.85***
HbA1c	5.03±0.06	9.14±0.40***

(*Continued*)

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Table 1 (Continued).

	Health group (n=30)	T2DM group (n=30)
Uric acid (μmol/L)	243.86±8.91	284.54±18.49
Total cholesterol (mmol/L)	3.92±0.07	5.03±0.24***
HDL-cholesterol (mmol/L)	1.54±0.05	1.06±0.04***
LDL-cholesterol (mmol/L)	2.47±0.09	2.81±0.14**
Triglyceride (mmol/L)	1.02±0.04	2.06±0.20***

Notes: All data are presented as mean ±SD, **P<0.01, ***P<0.001 compared with the healthy group.
Abbreviations: HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Analytical Method Assessment

The above methods were used to determine the relative content of lipid metabolites in the serum of T2DM patients and healthy individuals. The MRM (multiple reaction monitoring) chromatograms of the lipidomics are shown in Figure S1. To provide repeatable and high-quality data, QC samples were used to evaluate the reproducibility of lipid metabolomics analysis. QC samples were obtained by taking aliquots from each study sample and thoroughly mixing them into homogeneous pooled samples. One QC sample was inserted after every 10 serum samples, and 12 QC samples were obtained in positive or negative mode in this study. The aggregation of QC in the PCA and PLS-DA figure showed that the UPLC–MS system had relatively high reproducibility and stability during the sample analysis (Figure 1).

Lipidomics Analysis

For serum lipid analysis, 1162 lipid metabolites were detected (585 lipids in positive mode and 577 lipids in negative mode). Of the 1162 detected lipids, 267 were significantly altered in the T2DM group (FDR < 0.05, Figure S3), indicating a serious lipid metabolism disorder in T2DM. PE (phosphatidylethanolamines), TAG (triacylglycerol), PA (phosphatidic acid), PG (Phosphatidylglycerol) and PC (phosphatidylcholines) are the five main lipid classes present in the 267 significantly altered lipids, accounting for up to 70% of these lipids (76 PEs, 44 TAGs, 27 PAs, 22 PGs, 21 PCs, 21 CERs (ceramides), and 15 PSs (phosphatidylserine)). In the volcano plot analysis, 44 lipids met the criteria of $\log_2$ (fold-change) >1 (Figures 2A and S2). Importantly, the levels of CEs (Cholesterol Ester), PSs (Phosphatidylserine), and PGs increased, whereas the concentrations of unsaturated PEs and CERs decreased in T2DM. Based on the PLSDA-VIP values, we selected the most important 30 lipids to generate a heat map (Figure 2B). In the heatmap, the HCA of the feature (left of the heatmap) is displayed, and we also observed that the lipids were obviously clustered into two groups, and the largest one was significantly down-regulated. These results were in agreement with those of the PCA analysis, showing that there was a significant difference in lipid levels between the two groups.

As shown in Table 2, 11 lipids showed significant differences in T2DM groups in terms of VIP >1, FC >2, and FDR <0.05 (Figures S2–S4), while 10 lipids, including PEs (PE (P-18:0/20:5), PE (P-18:0/18:3), PE (P-16:0/20:5), PE (O-18:0/20:4), PE (O-18:0/20:3), PE (P-18:1/20:5)), PA (20:0/20:5), LPI (18:2), LPI (18:3), and CE (20:5), were significantly lower in the serum of T2DM patients; however, CE (20:0) was significantly higher in T2DM patients than in healthy individuals (Figure 3).

Correlation Analysis Between 11 Significantly Changed Lipids and Physiological Parameters

To explore the association between the 11 significantly altered lipids and physiological traits, Pearson's correlation tests were performed. In total, 10 differential lipids were significantly correlated with at least one of the physiological parameters (FBG, 2h-post load BG, HbAc1, etc.; Figure 4A). Among these correlations, we observed medium relationships between lipids and 2h-post load BG or HbAc1 (r>0.40, P<0.05) and a weak relationship with FBG (r>0.20, P<0.05). For example,

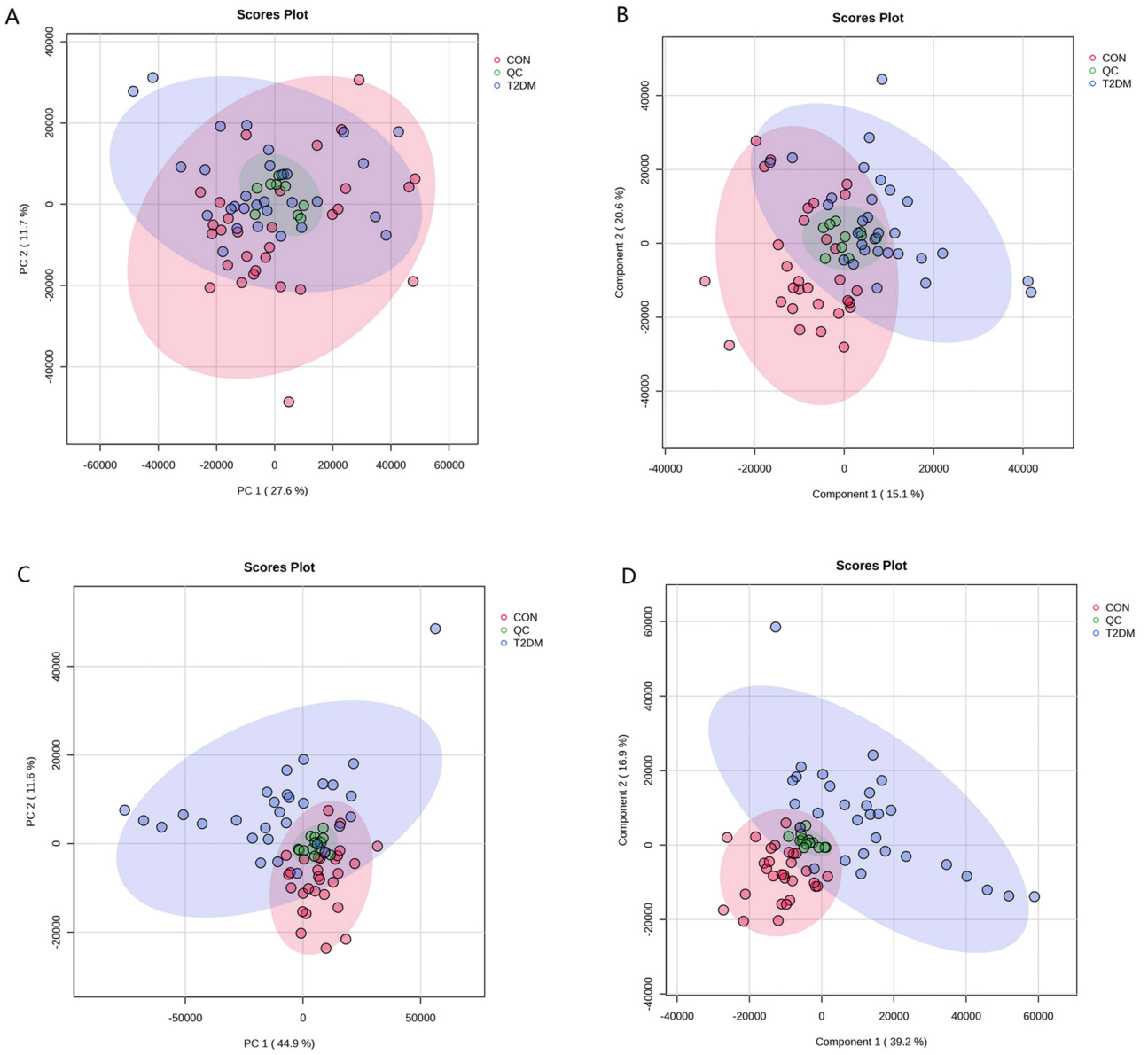

Figure 1 PCA (principal component analysis) and PLS-DA (partial least square-discrimination analysis) score plots between healthy group (CON) and T2DM group. ((**A**) PCA in positive mode, (**B**) PLS-DA in positive mode, (**C**) PCA in negative mode, (**D**) PLS-DA in negative mode).

LPI (18:3) showed higher negative correlations with 2h-post load BG (r=−0.46, P<0.001) or HbAc1 (r=−0.52, P<0.001), PE (O-18:0/20:4) also showed higher negative correlations with 2h-post load BG (r=−0.56, P<0.001) or HbAc1 (r=−0.53, P<0.001) (Figure 4B–E), while CE (20:0) was found to be significantly positively correlated with FBG (r=0.30, P<0.05), 2h-post load BG (r=0.32, P<0.05), and HbAc1 (r=0.30, P<0.05) (Figure S5A–C). CE (20:0) was positively correlated with total cholesterol and triglycerides (r>0.30, P<0.05), whereas LPI (18:3) was negatively correlated with triglycerides (r=−0.33, P<0.05) (Figure S5D–F). In addition, PE (O-18:0/20:3) and PE (O-18:0/20:4) were moderately negatively correlated with body weight and BMI (r>0.40, P < 0.01, Figure S5G–J).

Eleven Significantly Changed Lipids for Predicting T2DM

To investigate whether 11 significant changed lipids can predict T2DM, we performed binary logistic regression and ROC curve analyses for 11 lipids on the Metaboanalyst 5.0 online platform, respectively. As shown in Table S3, LPI (18:3) have higher predictive power with AUC (the area under the curve) of 0.933, and the AUC of the other 10

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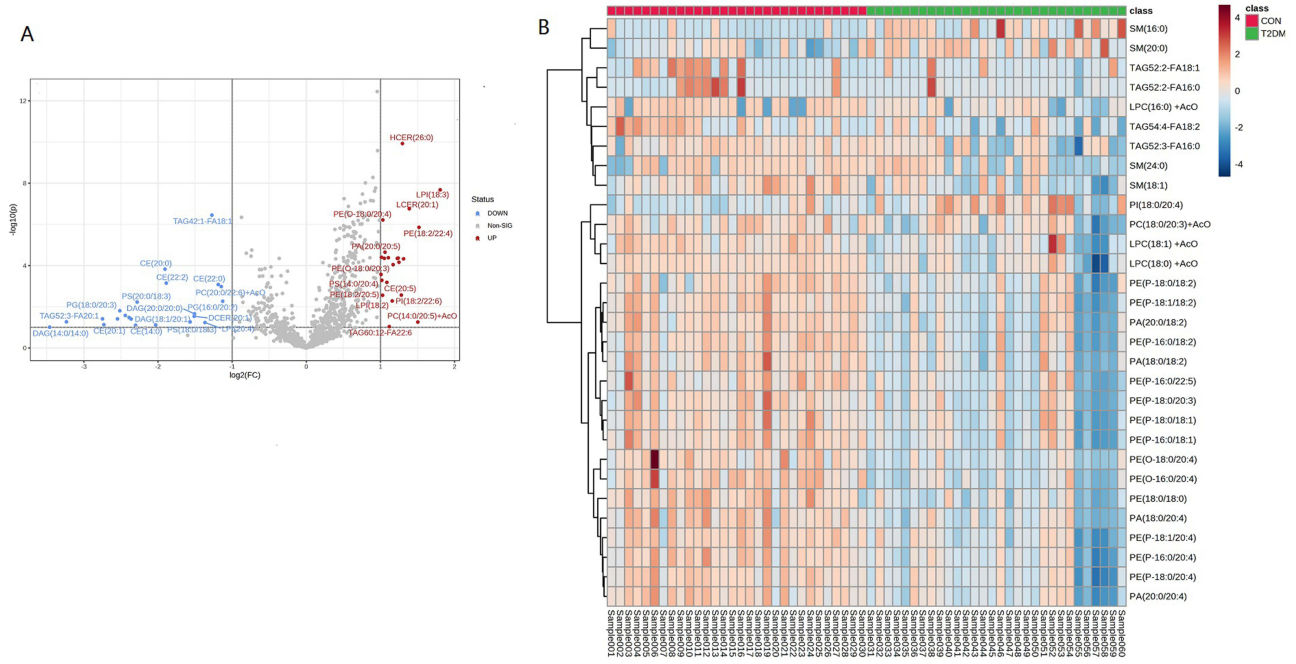

Figure 2 (**A**) Volcano plot of the significantly changed lipids in T2DM; (**B**) heatmap of lipid metabolites in serum sample. Columns represent the samples (Con, T2DM groups), and rows represent the lipid metabolites. Red represents up regulation, blue represents down regulation.

lipids was also higher than 0.7. Then, we divided 11 significant changed lipid into 3 classes: LPI, CE and PE, and carried out binary logistic regression and ROC curve analyses. The results indicated these 3 classes have the great prediction with AUC >0.90, especially the AUC of LPI class reached 0.95 (Table S3 and Figure 5A–C). In addition, we conducted 11 screened lipids for multivariate analysis, these 11 lipids as a combined form had an AUC of 0.986, which indicated that these 11 lipids had better predictive value in predicting T2DM (Figure 5D). Therefore, we suggested to select the combined 11 lipids or LPI classes as candidate features for the development of an integrated diagnostic biosignature for T2DM.

Table 2 The Significantly Changed Lipid Metabolites in T2DM Group

	Q1	Q3	DP	CE[b]	FC (CON/T2DM)	Log_2(FC)
CE[a] (20:0)	698.7	369.4	150	25	0.26677	−1.9063
LPI (18:3)	593.273	277.217	−80	−50	3.4969	1.8061
PE (P-16:0/20:5)	720.5	301.217	−80	−50	2.3435	1.2287
PE (P-18:0/18:3)	724.5	277.217	−80	−50	2.2519	1.1712
LPI (18:2)	595.289	279.233	−80	−50	2.2327	1.1588
PE (P-18:1/20:5)	746.5	301.217	−80	−50	2.1541	1.1071
CE (20:5)	688.6	369.4	150	25	2.1236	1.0865
PA (20:0/20:5)	749.513	301.217	−80	−50	2.0884	1.0624
PE (P-18:0/20:5)	748.5	301.217	−80	−50	2.0752	1.0532
PE (O-18:0/20:4)	752.56	303.233	−80	−50	2.0459	1.0328
PE (O-18:0/20:3)	754.576	305.249	−80	−50	2.0111	1.008

Abbreviations: CE[a], cholesterol ester; LPI, lyso-phosphatidylinositol; PE, phosphatidylethanolamines; PA, phosphatidic acids; DP, declustering potential; CE[b], cone energy; FC, fold change.

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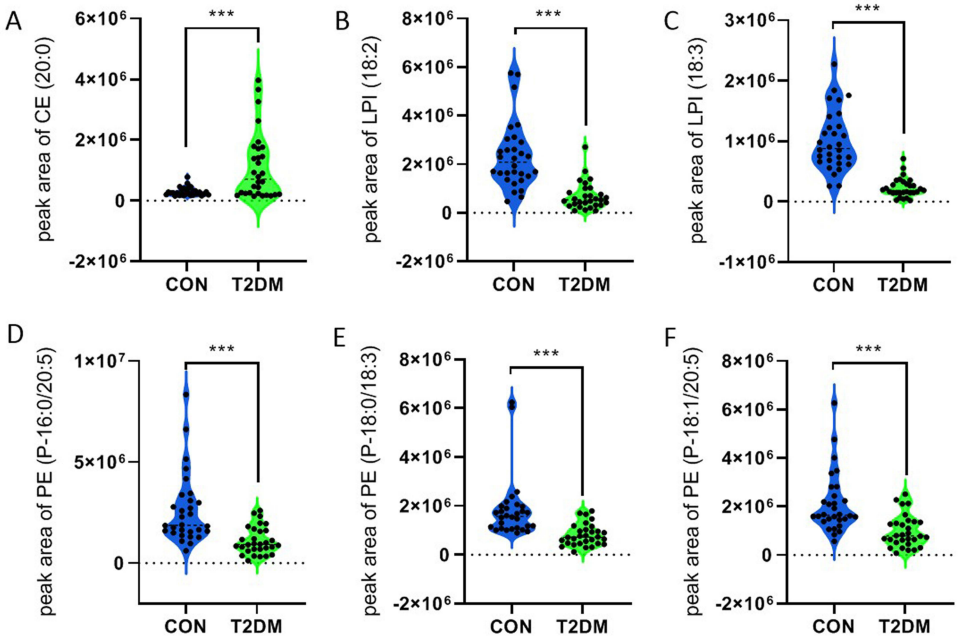

Figure 3 Relative quantitative analysis of the significantly changed lipid metabolites. A two-tailed Mann–Whitney *U*-test was applied to test for statistical significance; The asterisk denotes a significance, ***P < 0.001. The peak area of CE (20:0) (**A**), LPI (18:2) (**B**), LPI (18:3) (**C**), PE (P-16:0/20:5) (**D**), PE (P-18:0/18:3) (**E**), PE (P-18:1/20:5) (**F**) in the serum of healthy volunteers and T2DM patients.

Discussions

In our previous serum non-target metabolomics analysis of T2DM patients, we found 16 differential metabolites and establish an integrated biomarker profile for T2DM patients, meanwhile we found that amino acid and the lipid metabolism disorders have the greatest correlation with the risk of diabetes.[16] Further targeted amino acid analysis revealed that serum arginine and leucine were significantly increased in T2DM patients, while taurine, glutamic acid, glutamine, ethanolamine, alanine and α-aminobutyric acid are decreased in the serum of T2DM patients, which can help us to find functional amino acids and develop functional food.[17] In this study, we detected the serum lipids in patients with type 2 diabetes and healthy individuals using the UPLC-MS lipidomics method developed by the SCIEX Support Center. Under the positive (ESI+) and negative (ESI-) ion modes, we detected a relative abundance of more than 1000 lipids belonging to six major lipid classes. This study mainly focused on the serum lipidomic and comprehensively understood the relationship between lipid metabolism and T2DM.

After normalization of the original data, we found that 267 lipids had significant changes with FDR <0.05. Among them, the levels of CE, PS and PG in T2DM patients increased, while the concentrations of unsaturated PE and CER decreased. Finally, we took VIP >1, FC >2 and FDR <0.05 as screening criteria and found that there were 11 lipids in T2DM group that were significantly different from the healthy volunteer group (Figures 2A, S2–S4 and Table 2). Among the 11 significantly changed lipids, nine lipids (including PE, PA, and LPI) belong to the class of phospholipids, which were negatively correlated with T2DM, while the other two significantly changed lipids were CE (20:0) and CE (20:5), belonging to cholesteryl esters (Figure 3). Previous studies have reported that PE and PC are negatively correlated with T2DM,[18,19] which is consistent with our results, and phospholipids have been speculated to affect blood glucose levels by regulating insulin receptor activity and promoting insulin secretion.

We also performed a Pearson correlation test to explore the correlation between the 11 significant changes in blood lipid levels and clinical physiological and biochemical indicators. First, we found that 10 selected lipid biomarkers were associated with 2h-loaded blood glucose and HbAc1, particularly LPI (18:3) and PE (O-18:0/20:4), which showed the most significant negative correlation with 2h loaded blood glucose and HbAc1 (r>0.5). A study on the relationship between HbAc1 and blood lipids in adolescents with type 1 diabetes showed that HbAc1 levels were related to increased LDL-C levels and that there are complex genetic regulations and metabolic interactions between lipid metabolism and

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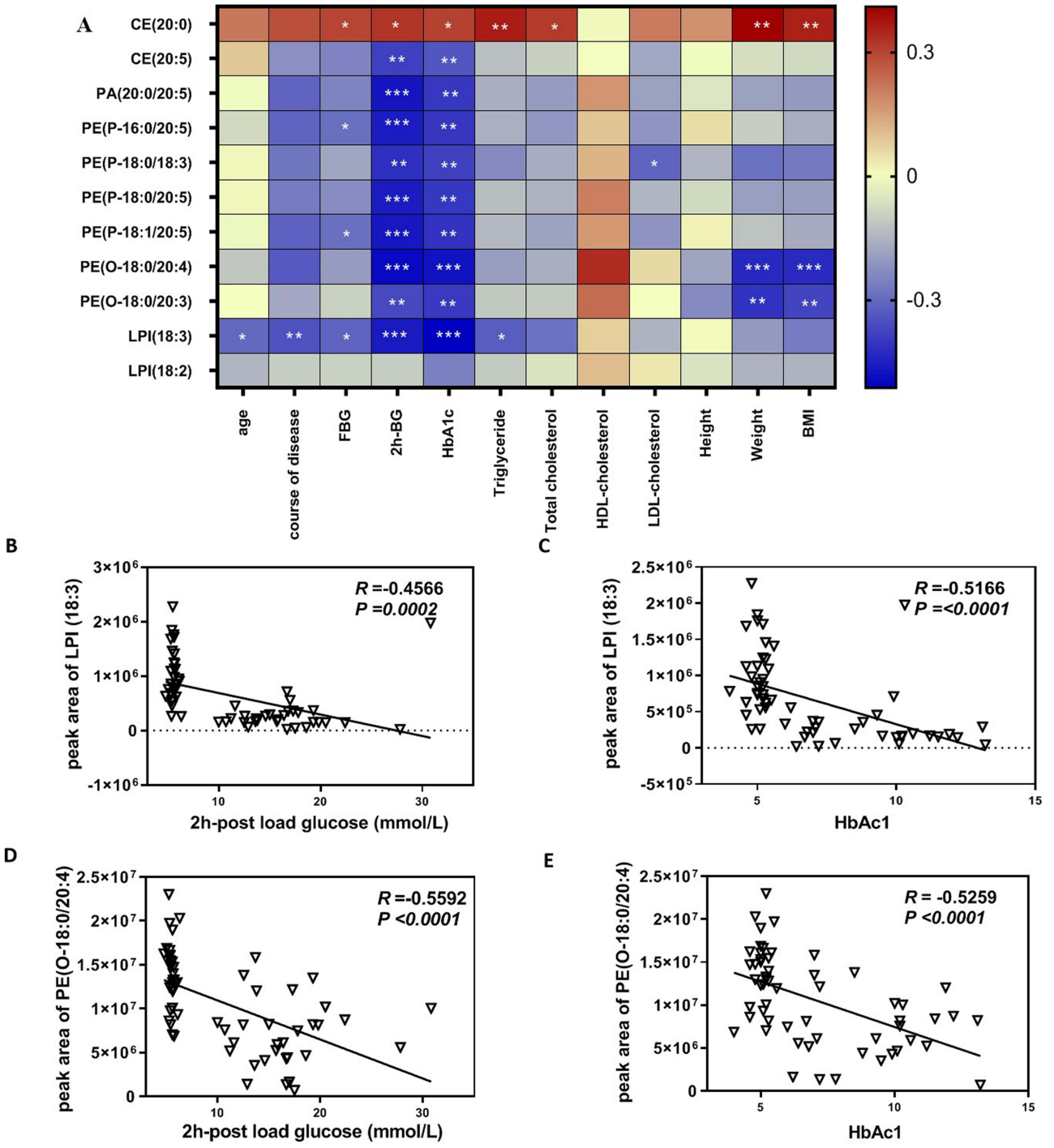

Figure 4 The heatmap of association between physiological traits and 11 significantly changed lipid metabolites (**A**). Red indicates positive correlations, and blue indicates negative correlations. The asterisk denotes a significance, *P < 0.05, **P < 0.01, and ***P < 0.001. (**B**–**E**) Linear regression of LPI (18:3) and PE (O-18:0/20:4) with 2h-post loading blood glucose or HbAc1.

glucose metabolism.[20,21] We also found that PE (O-18:3/20:3) and PE (O-16:3/20:4) were significantly negatively correlated with body weight and BMI, indicating that these two lipids play important roles in the risk of obesity-related T2D. Hornburg's study revealed that PE-P and PE-O are associated with higher levels of HDL and lower levels of fasting insulin;[22] however, our results did not observe this association, which may be related to race and region. Therefore, it needs to be validated with a larger and broader sample size in the future. Interestingly, CE (20:0) was

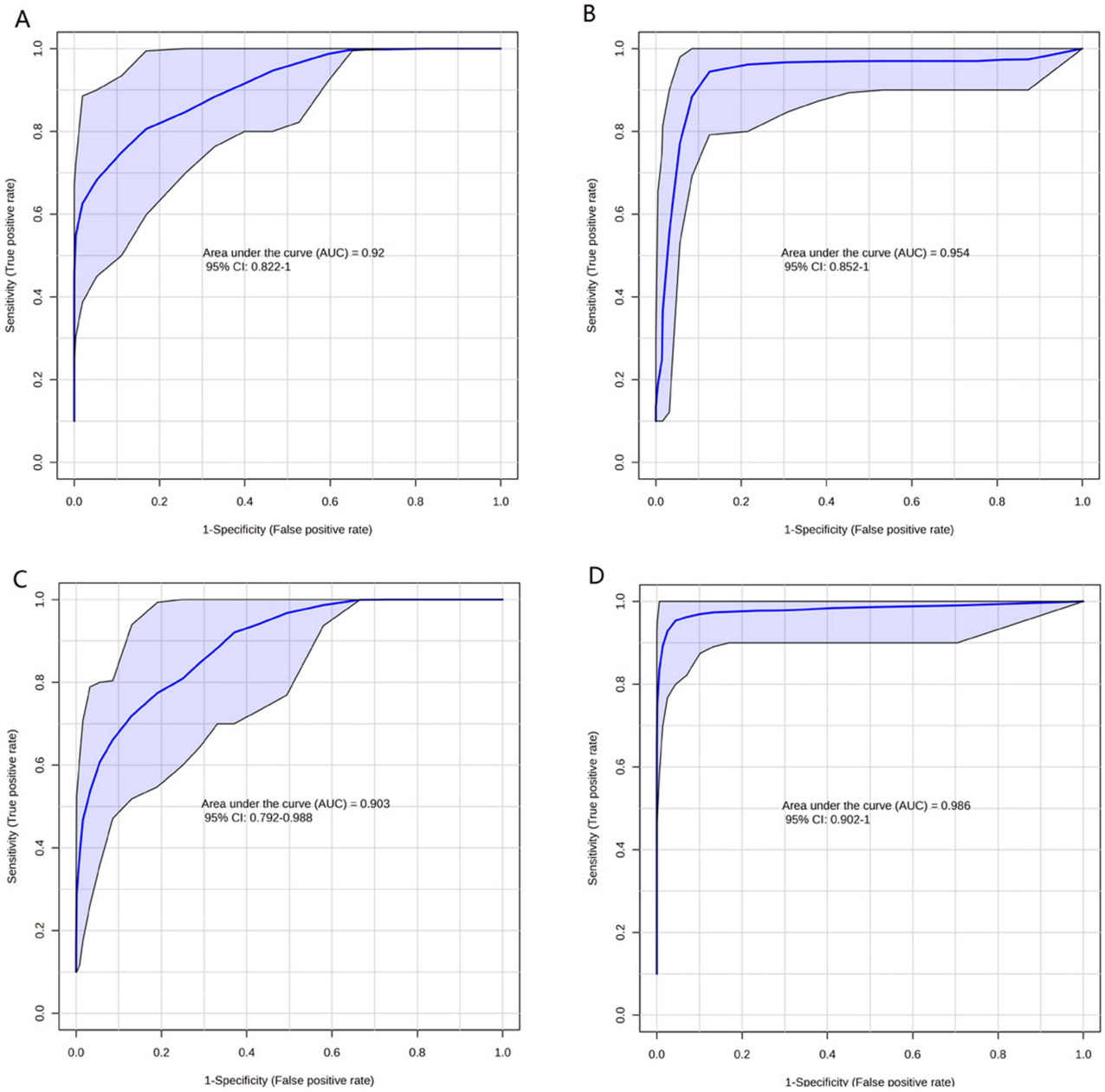

Figure 5 ROC curves of the candidate biomarker. (**A**) CE classes, (**B**) LPI classes, (**C**) PE classes, (**D**) the combined 11 significant changed lipids.

positively correlated with clinical indicators related to glucose (FBG, 2h-loaded BG, and HbAC1) and lipid metabolism (total cholesterol and triglycerides), whereas CE (20:5) was negatively correlated with 2h-loaded blood glucose (r=−0.39) and HbAC1 (r=−0.34) (Figure 4A). CE (20:0) is a saturated fatty acid, and saturated fatty acids are commonly considered pro-inflammatory molecules. Excessive consumption of saturated fatty acids is likely to cause an increase in cholesterol content, high cholesterol, hyperlipidemia, diabetes, and its complications. However, unsaturated fatty acids are also recognized as anti-inflammatory molecules that reduce the inflammatory process.[23] Many studies have confirmed that the intake of unsaturated fatty acids can improve the occurrence and development of T2DM,[23,24] and Feng et al also showed a significant negative correlation between unsaturated fatty acids and T2DM.[25]

The strength of our work is that we used the UPLC-MS method to simultaneously detect the relative abundance of more than 1100 types of serum lipids and obtained 11 types of significantly changed lipids as serum biomarkers for T2DM. However, there were also several limitations to this study, as we did not have sufficient patient cohorts to validate

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this result and the conclusions of the literature. In future studies, to demonstrate the clinical significance of lipidomic methods for detecting T2DM, we need to include a larger patient cohort to verify lipid markers and establish a more accurate diagnosis and personalized treatment system for T2DM.

Conclusions

In conclusion, serum samples from T2DM patients and healthy volunteers were successfully distinguished using lipidomic approaches, and we obtained 11 differential lipids as candidate biomarkers of T2DM. These data revealed lipid changes associated with T2DM and provided important metabolic information for the therapy and diagnosis of T2DM.

Data Sharing Statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Acknowledgments

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Disclosure

The authors declare no conflicts of interest in this work.

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