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Research Article

Clinical Serum Lipidomic Profiling Reveals Potential Lipid Biomarkers for Early Diabetic Retinopathy

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ABSTRACT
Diabetic Retinopathy (DR) is a major micro vascular complication of Diabetes Mellitus and a leading cause of preventable vision loss. Recent evidence suggests that disturbances in lipid metabolism occur before visible retinal damage develops. Lipidomic analysis enables comprehensive profiling of circulating lipid molecules and may assist in identifying novel indicators for early DR detection.
Objective: To analyze serum lipid variations associated with early diabetic retinopathy and explore their potential role as biomarkers for its early diagnosis.
Methods: A cross-sectional study was carried out on 60 type 2 diabetes mellitus (T2DM) patients—30 with early non-proliferative diabetic retinopathy (NPDR) and 30 without any retinal abnormalities. Serum lipidomics was performed using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS). Statistical and multivariate analyses were applied to identify significantly altered lipid species between the two groups.
Results: Distinct lipidomic alterations were identified in patients with early DR. Levels of lysophospha- tidyl cholines (LPCs), sphingomyelins (SMs), and ceramides (Cers) were significantly higher, while phosphatidylcholines (PCs) and certain triglycerides were reduced. Lipid species such as LPC (17:0), Cer(d17:1/24:0), and SM(d17:1/15:0) showed strong correlations with HbA1c and DR severity ($p < 0.01$). Combined ROC analysis of Cer(d17:1/24:0) and LPC(17:0) produced an AUC of 0.88, indicating excellent diagnostic accuracy.
Conclusion: Serum lipidomic analysis highlights early metabolic disruptions in DR. Elevated ceramide and lysophosphatidylcholine species may serve as promising biomarkers for the early identification of retinal microvascular injury. Incorporating lipidomic markers into diabetic screening could enhance early detection and risk assessment strategies.

Keywords: Diabetic Retinopathy, Lipidomics, Ceramides, Lysophosphatidylcholines, Biomarkers, LC–MS/MS.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common and serious microvascular complications of diabetes mellitus, contributing significantly to visual impairment worldwide. Nearly one-third of individuals with diabetes develop DR, often progressing silently until advanced stages lead to irreversible damage [(1).] while chronic hyperglycemia has long been recognized as the primary trigger, increasing evidence emphasizes the involvement of lipid metabolism disturbances, oxidative stress, and inflammation in DR pathogenesis[(2,3).]

Traditional lipid parameters such as Total Cholesterol, Triglycerides (TG), Low-Density Lipoproteins (LDL), and High-Density Lipoproteins (HDL) provide limited insight into the complex lipid alterations underlying retinal microvascular dysfunction [(4).]

Advanced lipidomics, utilizing mass spectrometry, offers a detailed examination of various lipid subclasses, helping reveal subtle metabolic perturbations associated with early disease [(5,6).]

Specific lipid species like Ceramides, Sphingomyelins and Lysophosphatidylcholines have been implicated in endothelial injury,

inflammation, and apoptosis - processes central to retinal damage [7].

Despite these findings, comprehensive lipidomic data in Indian diabetic populations, especially from Central India, particulary in Chhattishgarh state remain scarce.

MATERIALS AND METHODS

Study Design:

A cross-sectional study was conducted in the Departments of Biochemistry and Ophthalmology at Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg,C.G., between June to December 2025.

Study Population:

- **Inclusion Crireria:**

Sixty adults with Type 2 diabetes mellitus (T2DM), aged 40–65 years were enrolled and divided into two groups :----------

- **Group I:** 30 diabetic patients without signs of DR
- **Group II:** 30 diabetic patients with mild to moderate non-proliferative diabetic retinopathy (NPDR)
- **Exclusion Criteria:** Individuals with other retinal disorders, systemic inflammatory diseases, hepatic or renal dysfunction, or those on lipid lowering medications within the last three months were excluded.

All participants gave written informed consent, and the study received ethical approval from the Institutional Ethics Committee.

Evaluation of Clinical and Biochemical Parameters:

Each participant underwent detailed clinical history taking, anthropometric assessment, and ophthalmic evaluation using slit-lamp biomicroscopy and indirect ophthalmoscopy.

Fasting glucose, HbA1c, and Conventional lipid profiles were determined using enzymatic fully autoanalyzer assays.

Lipidomic Analysis:

Serum Sample:

Serum samples were collected after overnight fasting and stored at –80°C until analysis.

Lipids were extracted using a modified Bligh and Dyer method and analyzed using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS; Q-ExactiveOrbitrap, Thermo Fisher Scientific). Lipid identification and quantification were conducted using Lipid Search software, followed by normalization and quality control.

Therefore, this study is aimed to assess serum lipidomic profiles in diabetic individuals with and without early DR to identify potential lipid-based biomarkers useful for early detection of retinal complication.

Statistical Analysis:

Group comparisons were performed using Student's *t*-test with false discovery rate (FDR) correction. Multivariate models, including principal component analysis (PCA) and partial least squares-discriminant analysis (PLS-DA), were used to assess clustering patterns. Receiver operating characteristic (ROC) curves determined the diagnostic ability of significant lipids.

Analyses were performed using SPSS v29.0 and MetaboAnalyst 5.0, with $p < 0.05$ considered statistically significant.

Results:

Clinical Findings

Both groups were comparable in terms of age, BMI, and diabetes duration. However, HbA1c and fasting plasma glucose levels were significantly higher among patients with early DR ($p< 0.01$). Traditional lipid parameters revealed mild dyslipidemia but were not sufficient to distinguish early DR.

Lipidomic Alterations

More than 400 distinct lipid species were identified. PLS-DA analysis revealed clear separation between the two groups, indicating substantial metabolic variation.

Significantly altered lipid species in early DR included:

- **Increased:**
  - Lysophosphatidylcholines (LPC 17:0, LPC 19:0, LPC 18:1)
  - Sphingomyelins (SM d17:1/15:0, SM d17:1/24:1)
  - Ceramide (Cer d17:1/24:0, Cer d17:1/15:0)
- **Decreased:**
  - Phosphatidylcholines (PC 35:1, PC 37:4)
  - Triglycerides (TG 54:2, TG 56:3)

Correlation and Diagnostic Analysis

Cer(d17:1/24:0) and LPC(17:0) were positively correlated with HbA1c ($r = 0.44$ and 0.41, respectively; $p < 0.01$) and DR severity ($r = 0.52$; $p < 0.01$).

ROC analysis indicated high diagnostic accuracy for Cer(d17:1/24:0) (AUC = 0.84) and LPC(17:0) (AUC = 0.81), which improved further when combined (AUC = 0.88).

DISCUSSION

The study demonstrates that patients with early DR exhibit unique serum lipidomic changes, notably elevated Ceramides, Sphingomyelins and Lysophosphatidylcholines, independent of routine lipid levels. These alterations indicate deep-seated disruptions in lipid metabolism linked to inflammation and endothelial dysfunction.

Ceramides are key mediators of apoptosis and vascular injury, contributing to microvascular leakage and retinal degeneration [8,9]. Their accumulation has been associated with oxidative stress and mitochondrial dysfunction in diabetes (10). Similarly, LPCs produced by phospholipase A_2 activity are known to impair endothelial function and initiate inflammatory cascades [11].

The reduction in phosphatidylcholines and triglycerides could signify increased lipid turnover or altered membrane remodeling in response to metabolic stress. Collectively, these findings underline the involvement of lipid imbalance in the early molecular events of DR [12].

CONCLUSION

Serum lipidomic profiling uncovers characteristic metabolic disruptions in early diabetic retinopathy. Elevated ceramide and lysophosphatidylcholine species, particularly Cer(d17:1/24:0) and LPC(17:0), demonstrate strong associations with disease severity and may serve as reliable non-invasive biomarkers for early DR detection.

Lipidomics can thus complement conventional diagnostic methods and enhance personalized diabetes management.

Recommendations

1. Longitudinal studies should validate the predictive value of these lipid markers for DR progression.
2. Lipidomic testing can be integrated into diabetic screening for high-risk individuals.
3. The effect of lipid-modifying therapies on these biomarkers warrants further investigation.

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