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To Analyze the Differences in Plasma Lipid Composition Among Healthy, Prediabetic and Type 2 Diabetic Populations Based on Lipidomics

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Abstract: Pre-diabetes and type 2 diabetes mellitus (T2DM) are important stages of metabolic disorders, in which abnormal lipid metabolism plays a key role. In recent years, the development of lipidomics technology has provided a new perspective to reveal the differences in plasma lipid composition between pre-diabetes and T2DM patients. This paper discusses the changes of plasma lipid profile in patients with prediabetes and T2DM based on lipidomics, and looks forward to future research directions, in order to provide new ideas for early intervention and treatment of prediabetes patients.

Keywords: Prediabetic; Type 2 Diabetic; Lipidomics.

1. Introduction

Prediabetes refers to impaired fasting glucose (IFG) (fasting blood glucose 6.1mmol/ L-7.0 mmol/L) or impaired glucose tolerance (impaired glucose tolerance) tolerance (IGT) (2-hour postprandial blood glucose 7.8mmol/L to 11.1mmol/L) and a mixed state (IFG+IGT). In 2021, the American Diabetes Association also included elevated glycosylated hemoglobin (HbA1c) (HbA1c 5.7%-6.4%) in the criteria for the diagnosis of prediabetes [1]. Prediabetes is an inevitable stage for normal glucose tolerance to progress to Type 2 Diabetes (T2DM), so it is also called a high-risk diabetic state [2]. In China, the results of two surveys showed that the prevalence of prediabetes was 15.15% [3] and 35.70% [4] respectively. With the development of economy and society, more and more people take a sedentary, stay up late, smoking and drinking lifestyle, as well as high sugar, high salt and high fat diet habits, the number of patients with prediabetes and its adverse progress has been increasing year by year. Previous studies have shown that 5%-10% of pre-diabetic patients progress to type 2 diabetes each year [5].

Moreover, some patients with prediabetes have no symptoms of chronic complications of diabetes, or no diabetic complications have been detected, but related target organs are still damaged. For example, one study showed that a small number of patients with long-term prediabetes, without diagnosed diabetic retinopathy, had degenerative changes in retinal nerve and vascular structure and function. Retinal function is impaired [6]. A recent meta-analysis confirmed that the HbA1c threshold of ≥ 6.5% is a strong inflpoint for increased risk of diabetic retinopathy, but the evidence for risk stratification of other microvascular complications (diabetic nephropathy and/or neuropathy) at this threshold is less clear [7]. Studies have confirmed that intervention of abnormal glucose metabolism in patients before diabetes can delay the progression of patients to type 2 diabetes and reduce the risk of complications, and may even help patients return to normal glucose metabolism [8]. A number of clinical indicators have been confirmed to be associated with the progression of prediabetes to type 2 diabetes, such as Body mass index (BMI), Visceral adiposity index (VAI), Lipid accumulation product, and lipid accumulation product. LAP), Triglyceride glucose index (TyG), etc., more and more studies have investigated the relationship between lipid metabolism disorders and the pathogenesis of type 2 diabetes. [9].

In recent decades, the emergence of omics has provided clinicians with another way to study the changes of disease-related metabolites with unprecedented clarity and coverage [10]. Metabolomics captures both endogenous and exogenous changes, thereby providing further insights into the complex pathophysiology of diseases such as diabetes, whose phenotypic features integrate genetic and environmental factors [11]. Lipidomics has become an independent branch of metabolomics, and more and more studies have explored the relationship between lipid metabolism disorders and the pathogenesis of type 2 diabetes.

Therefore, this review mainly summarizes the differences of existing lipid metabolites among healthy people, pre-diabetes people and type 2 diabetes patients, in order to find the unique biomarkers or biomarkers that change at each stage of the development of type 2 diabetes in healthy people, and provide new ideas for the timely intervention and treatment of pre-diabetes in the future. The details are as follows.

2. Regarding the Differences in Lipid Metabolites Between Healthy Individuals and Prediabetic Individuals

Compared with healthy controls, prediabetic patients had changes in a number of lipids, including Free fatty acids (FA), Phosphatidylcholine (PC), ceramides (Cer), Lysophosphatidylethanolamine (LPE) and Phosphatidylethanolamine (PE), Phosphatidylinositol (PI), Triacylglycerol (TG), Lysophosphatidylcholine (LPC), Acylcarnitines (AC), Phosphatidicacid (PA), Phosphatidylserine (PS), Cholinesterase (ChE), Sphingomyelin (SM) and other lipids.

Xuan, Q et al. analyzed the differences in lipid metabolites between 150 patients with early diabetes and 94 healthy

subjects, and showed that two lipid metabolites FA (20:2) and PC (32:0) were up-regulated in prediabetic patients compared with healthy controls, and were correlated with the three subtypes of prediabetes, $p<0.05$ [12]. A study published by Barrangco-Altirriba, M et al., in 2024, showed that lipid metabolites of Cer, LPE, PE, PI and TG in prediabetic patients increased compared with healthy controls [13]. Yang, J et al. 's study showed that several lipid metabolites belonging to LPC, PC, Cer and TG in the pre-diabetes group were increased compared with the healthy control group, while 7 lipid metabolites belonging to SM were decreased in the pre-diabetes group [14]. Zhong, H et al. found that acylcarnitine was increased in prediabetic patients, four lysophosphatidylcholine was decreased [15]. Shao, F's study, which included 52 patients with prediabetes and 49 healthy people, showed that LPE (20:4), PA (18:2/10:4), PS (14:0/14:0), Cer (m32:0), ChE (20:5) were up-regulated in patients with prediabetes. Three ceramide metabolites showed downregulation [16].

Table 1. Differences in lipid metabolism between healthy individuals and prediabetic patients

Author and Year	Sample	Lipid metabolites upregulated or downregulated in prediabetic individuals compared to healthy controls
Xuan, Q2022	Serum	Up:FA(20:2), PC(32:0)
Barranco-Altirriba, M 2024	Serum	Up:Cer(m18:1_22:0),Cer(m18:0_22:0), Cer(m18:1_23:0),Cer(m18:0_23:0),Cer(m18:0_24:1),Cer(m18:0_24:0),LPE(20:3), PE(20:0p_18:2),PE(18:0_20:3),PI(16:0_20:4),TG(16:0_14:0_18:3),TG(12:0_18:2 _18:2),TG(16:1_16:1_18:2)
Yang, J 2023	Serum	Up:LPC(22:6), PC(16:0/20:4), PE(22:6/16:0), Cer(d18:1/24:0), Cer(d18:1/23:0), Cer(d18:1/22:0), TG(18:1/18:2/18:2), TG(16:0/16:0/20:3), TG(18:0/16:0/18:2) Down:SM (d18:2/24:1), SM (d18:1/24:1), SM (d18:2/23:0), SM (d18:1/19:1), SM (d18:1/19:0), SM (d16:0/19:0) and SM (d18:0/16:0)
Zhong, H2017	Serum	Up:AC Down: LysoPC (18:2), LysoPC (18:1), LysoPC (18:0), and LysoPC (17:0)
Shao, F2023	Serum	Up:LPE(20:4),PA(18:2/10:4),PS(14:0/14:0),Cer(m32:0),ChE(20:5) Down:Cer(m22:0/18:0),CerG3GNAc1(d34:1),CerG3GNAc1(t37:6)

Abbreviations: FA, Fatty acid; PC, Phosphatidylcholine; Cer, Ceramide; LPE, Lysophosphatidylethanolamine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; TG, Triacylglycerol; LPC, Lysophosphatidylcholine; AC, Acylcarnitines; PA, Phosphatidic acid; PS, Phosphatidylserine; ChE, Cholinesterase; SM, Sphingomyelin

3. Regarding the Differences in Lipid Metabolites Between Healthy Individuals and Patients with Type 2 Diabetes Mellitus

Our pooled lipidomic studies of patients with type 2 diabetes identified changes in 17 classes of lipids, including Acylcarnitine (AC), FA, SM, PC, PE, Cer, PI, TG, LPE, LPC, Co(Q10), PA, Phosphatidylglycerol (PG), Phospholipid (PL), ChE, dihexyl N-acetylhexyl ceramide (CerG3GNAc1), trihexyl diN-acetylhexyl ceramide (CerG3GNAc2) and other classes of lipids.

Table 2. Differences in lipid metabolism between healthy individuals and patients with type 2 diabetes mellitus

Author and Year	Sample	Upregulated and downregulated lipid metabolites in patients with type 2 diabetes compared to healthy controls
Xuan, Q2022	Serum	Up:FA(18:2),FA(20:2),SM(32:1),SM(40:7),PC(38:7) and PC(40:6)
Barranco-Altirriba, M 2024	Serum	Up:PC(18:0_22:5),PC(18:0_20:3),PE(20:0p_18:2),PE(18:0_20:3),PE(16:0_18:2),Cer(m18:1_22:0),Cer(m18:0_22:0), Cer(m18:1_23:0),Cer(m18:0_23:0),Cer(m18:0_24:1),Cer(m18:0_24:0),PI(16:0_20:4),TG(16:0_14:0_18:3),TG(12:0_18:2_18:2) Down:Co(Q10),LPE(20:3),TG(16:1_16:1_18:2)
Yang, J 2023	Serum	Up:LPC(22:6), PC(16:0/20:4), PE(22:6/16:0), Cer(d18:1/24:0), Cer(d18:1/23:0), Cer(d18:1/22:0), TG(18:1/18:2/18:2), TG(16:0/16:0/20:3), TG(18:0/16:0/18:2) Down:SM (d18:2/24:1), SM (d18:1/24:1), SM (d18:2/23:0), SM (d18:1/19:1), SM (d18:1/19:0), SM (d16:0/19:0) and SM (d18:0/16:0)
Zhong, H2017	Serum	Up:AC Down:LPC (18:2), LPC (18:1), LPC (18:0), LPC (17:0)
Shao, F2023	Serum	Up:Cer(m32:0) Down:PA(18:2/10:4),PG(30:3),Cer(m32:0),ChE(20:5),CerG3GNAc1,CerG3GNAc1(t37:6),CerG3GNAc2
Suvitaival, T2017	Serum	Up:TG(LC9-12), PLs (LC8) Down:PC(LC5),LPC(18:2)

Abbreviations: FA, Fatty acid; PC, Phosphatidylcholine; Cer, Ceramide; LPE, Lysophosphatidylethanolamine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; TG, Triacylglycerol; LPC, Lysophosphatidylcholine; AC, Acylcarnitines; PA, Phosphatidic acid; PS, Phosphatidylserine; ChE, Cholinesterase; SM, Sphingomyelin; AC, Acylcarnitine; PG, Phosphatidylglycerol; PL, Phospholipid;

In the study carried out by Xuan, Q et al., FA, SM and PC lipid metabolites were increased in patients with type 2 diabetes compared with the control group, including 2 SM products, 2 FA products and 2 PC products [12]. In addition to the above changes in the production of lipid metabolites, the study by Barranco-Altirriba, M et al. (2024) identified many lipids that are increased in patients with type 2 diabetes, including a variety of PE and Cer lipid metabolites, while Co (Q10), LPE (20:3), TG (16:1_16: 1_18:2) compared with the healthy control group [13]. A study published in 2023 showed

that LPC, PC, PE, Cer, TG were found to be up-regulated in type 2 diabetes group compared with healthy control group, but 7 SM were down-regulated in type 2 diabetes group [14]. In the study by Zhong, H et al., AC was up-regulated and four LPC lipid metabolites were down-regulated in the T2DM group compared with the healthy control group [15]. In the study of Shao, F et al., the content of Cer (m32:0) in the type 2 diabetes group was up-regulated compared with the healthy control group, while PA, PG, and a variety of ceramide lipid metabolites were down-regulated [16]. A study published in 2017 showed that TG and PLs products were up-regulated in patients with type 2 diabetes compared with healthy controls, while one PC product and one LPC product were down-regulated compared with healthy controls [17].

4. Regarding the Differences in Lipid Metabolites Between Prediabetic Individuals and Type 2 Diabetic Patients

There are limited lipidomic comparative studies with prediabetic individuals as control group. The two available studies showed that nine Cer products, two PC products, and four PE products were significantly up-regulated in type 2 diabetic patients compared with prediabetic patients. However, Co (Q10), three TG products, LPE (20:3) and PI (16:0_20:4) were down-regulated in the type 2 diabetes group [13-14].

Table 3. Differences in lipid metabolism between prediabetes individuals and patients with type 2 diabetes mellitus

Author and Year	Sample	Lipid metabolites that were upregulated or downregulated in patients with type 2 diabetes compared to patients with prediabetes
Yang, J 2023	Serum	Up:Cer(d18:1/24:0), Cer(d18:1/23:0), Cer(d18:1/22:0)
Barranco-Altirriba, M 2024	Serum	Up:PC(18:0_22:5),PC(18:0_20:3),PE(20:0p_18:2),PE(18:0_20:3),PE(16:0_18:2),Cer(m18:1_22:0),Cer(m18:0_22:0), Cer(m18:1_23:0),Cer(m18:0_23:0),Cer(m18:0_24:1),Cer(m18:0_24:0),PE(20:0p_18:2) Down: Co(Q10), LPE(20:3),PI(16:0_20:4),TG(16:0_14:0_18:3),TG(12:0_18:2_18:2),TG(16:1_16:1_18:2)

Abbreviations: PC, Phosphatidylcholine; Cer, Ceramide; LPE, Lysophosphatidylethanolamine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; TG, Triacylglycerol

Prediabetes is a stage that almost all patients with type 2 diabetes must experience before they are diagnosed. With the increasing awareness of physical examination and unhealthy lifestyle, the incidence of prediabetes is increasing. The harm of type 2 diabetes to human health should not be underestimated. Therefore, there is an urgent need for a deeper understanding of the metabolic disorders in the process of prediabetes and its progression to type 2 diabetes, so as to propose targeted prevention and treatment measures. In recent years, lipidomics has been emerging and developing continuously. The progress of mass spectrometry technology has deepened the understanding of lipids to sub-class characteristics such as carbon atom number, unsaturation and hydroxylation, and has made continuous breakthroughs in the detection and analysis of lipid structure isomers. Lipidomics is increasingly becoming a powerful means of personalized molecular diagnosis and treatment, providing new ideas for solving this problem. This review mainly summarizes the studies on the changes of lipid metabolites in healthy people, pre-diabetes and type 2 diabetes, and finds the changes of lipid metabolites in healthy people, pre-diabetes and the development of type 2 diabetes, for the reference of researchers.

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