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Lipidomics in Obesity: Unveiling Metabolic Pathways Contributing to Hyperlipidemia

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ABSTRACT

Obesity, a global public health challenge, is intricately linked to hyperlipidemia, which significantly increases the risk of metabolic syndrome, cardiovascular diseases, and type 2 diabetes. Lipidomics, the comprehensive study of lipid profiles within biological systems, has emerged as a powerful tool for unraveling the complex lipid metabolic alterations that occur in obesity. This review provides a detailed analysis of lipidomics and its application in understanding the dysregulated metabolic pathways contributing to hyperlipidemia in obesity. We examine key lipid species, including fatty acids, triglycerides, phospholipids, sphingolipids, and cholesterol, and their roles in adipose tissue dynamics, insulin resistance, and inflammation. Furthermore, the review highlights the involvement of critical lipid metabolic pathways such as de novo lipogenesis, fatty acid oxidation, glycerophospholipid metabolism, and sphingolipid signaling in obesity-induced hyperlipidemia. Emerging lipidomic technologies and their potential to uncover novel biomarkers and therapeutic targets for managing dyslipidemia in obese individuals are also discussed. By integrating lipidomics into obesity research, we can gain a more nuanced understanding of the lipid-related molecular mechanisms driving hyperlipidemia and develop more targeted, personalized therapeutic strategies.

Keywords: Lipidomics, Obesity, Hyperlipidemia, Metabolic Pathways, Fatty Acid Metabolism, De Novo Lipogenesis, Sphingolipids, Biomarkers, Cardiovascular Risk, Dyslipidemia

INTRODUCTION

Obesity is a multifactorial disease characterized by excessive accumulation of body fat, resulting in serious health consequences, including hyperlipidemia and related metabolic disorders[1–4]. The global rise in obesity rates has been paralleled by an increase in the prevalence of hyperlipidemia, a condition marked by elevated levels of lipids, including triglycerides, cholesterol, and phospholipids, in the blood[5, 6]. Hyperlipidemia is a significant risk factor for the development of atherosclerosis, cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD) [4] .Lipidomics, the large-scale study of pathways and networks of cellular lipids, has emerged as an essential tool for understanding lipid metabolism and its dysregulation in obesity[7]. By analyzing lipid species and their metabolic pathways, lipidomics provides insights into how lipid alterations contribute to obesity-related hyperlipidemia[8, 9]. This review explores the major lipid species implicated in obesity, examines the key metabolic pathways affected, and discusses how lipidomics can help identify novel biomarkers and therapeutic targets. Lipidomics focuses on identifying and characterizing lipid species, revealing their roles in metabolic conditions like obesity-induced hyperlipidemia. These lipid species include fatty acids, triglycerides, phospholipids, sphingolipids, and cholesterol, each contributing to the complex lipid dysregulation observed in obesity. Understanding these lipid classes helps elucidate the mechanisms behind obesity-associated metabolic disturbances and cardiovascular risk

Fatty Acids: Fatty acids are essential in energy metabolism and cellular function, but in obesity, their regulation becomes disrupted. Adipose tissue expansion in obesity promotes the release of free fatty acids (FFAs) into circulation.[10, 11]. Elevated FFA levels overwhelm normal metabolic processes, leading to lipid

accumulation in non-adipose tissues such as the liver and skeletal muscle, promoting ectopic fat deposition. This phenomenon, termed lipotoxicity, exacerbates insulin resistance and metabolic syndrome. Saturated fatty acids, particularly palmitic acid, intensify inflammation via toll-like receptor (TLR) activation, stimulating pro-inflammatory cytokines and impairing insulin signaling. In contrast, unsaturated fatty acids, especially omega-3 polyunsaturated fatty acids (PUFAs), exhibit anti-inflammatory properties and improve lipid profiles by promoting lipid oxidation and enhancing insulin sensitivity[12–14]. Thus, the balance between saturated and unsaturated fatty acids plays a pivotal role in lipid homeostasis and metabolic health in obesity.

Triglycerides: Triglycerides (TGs) are the primary storage form of energy in adipose tissue and a major contributor to hyperlipidemia in obesity. In obese individuals, the enhanced delivery of FFAs to the liver, along with increased de novo lipogenesis driven by hyperinsulinemia, leads to elevated triglyceride production.[15] Triglyceride-rich lipoproteins, such as chylomicrons and very low-density lipoproteins (VLDL), accumulate due to impaired lipoprotein lipase (LPL) activity, reducing triglyceride clearance from circulation[16]. This contributes to atherogenic dyslipidemia, characterized by elevated TGs and reduced high-density lipoprotein (HDL) cholesterol. Excess TGs are stored not only in adipose tissue but also in the liver, leading to non-alcoholic fatty liver disease (NAFLD), a common complication of obesity[17]. The increased hepatic triglyceride pool also fuels VLDL production, further driving hypertriglyceridemia and systemic lipid imbalances.

Phospholipids: Phospholipids, as the primary constituents of cellular membranes, play critical roles in cell signaling and lipid metabolism. In obesity, changes in phospholipid composition, such as elevated lysophosphatidylcholine (LPC) levels, have been implicated in systemic inflammation and insulin resistance. LPCs act as bioactive lipid mediators that promote pro-inflammatory pathways, exacerbating metabolic disturbances.[18] Additionally, the altered ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) affects membrane integrity and mitochondrial function, influencing lipid metabolism and contributing to conditions like NAFLD. An imbalance in the PC/PE ratio is linked to mitochondrial dysfunction, which impairs fatty acid oxidation and promotes the accumulation of lipids in the liver, contributing to obesity-related metabolic complications[19].

Sphingolipids: Sphingolipids, especially ceramides, have emerged as key players in obesity-associated metabolic dysfunction. Ceramides are bioactive lipids that accumulate in tissues during obesity and are strongly associated with insulin resistance and lipid dysregulation. Elevated ceramide levels interfere with insulin signaling by inhibiting the insulin receptor substrate-1 (IRS-1) and protein kinase B (Akt), leading to impaired glucose uptake and increased lipotoxicity[20]. The ceramide-sphingosine-1-phosphate (S1P) axis plays a crucial role in adipose tissue inflammation, lipid storage, and systemic metabolic dysfunction. S1P, in contrast to ceramide, has protective effects, promoting cell survival and anti-inflammatory responses[21]. However, in obesity, ceramide accumulation overwhelms these protective mechanisms, contributing to chronic inflammation, adipose tissue dysfunction, and cardiovascular complications.

Cholesterol: Cholesterol metabolism is profoundly altered in obesity, contributing to atherosclerosis and cardiovascular disease. In obese individuals, increased low-density lipoprotein (LDL) cholesterol levels, often termed "bad cholesterol," accelerate the deposition of cholesterol in arterial walls, leading to plaque formation and the development of atherosclerosis. In contrast, high-density lipoprotein (HDL) cholesterol, known for its protective effects by transporting excess cholesterol from peripheral tissues back to the liver for excretion, is often reduced in obesity[22]. This imbalance between LDL and HDL levels exacerbates cardiovascular risk. Additionally, obesity-driven inflammation promotes the oxidation of LDL particles, which further accelerates their uptake by macrophages in arterial walls, forming foam cells and advancing the atherogenic process[23]. Dysregulation of cholesterol transport and clearance thus plays a key role in the development of obesity-related cardiovascular disease.

Key Metabolic Pathways Contributing to Hyperlipidemia in Obesity

The lipidomic alterations observed in obesity are closely linked to the dysregulation of several metabolic pathways, which promote hyperlipidemia. The following sections discuss the most critical pathways involved.

De Novo Lipogenesis: De novo lipogenesis (DNL) is the process by which carbohydrates are converted into fatty acids, which are then esterified to form triglycerides. In obesity, DNL is upregulated, particularly in the liver, contributing to elevated triglyceride levels and increased VLDL secretion. Key enzymes involved in DNL, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), are upregulated in obesity, linking excess carbohydrate intake to lipid accumulation[24].

Fatty Acid Oxidation: Fatty acid oxidation, primarily occurring in the mitochondria, is responsible for the breakdown of fatty acids to generate energy. In obesity, mitochondrial dysfunction and impaired fatty acid oxidation lead to the accumulation of lipid intermediates such as acylcarnitines, which contribute to insulin

resistance and hyperlipidemia. This dysregulation in fatty acid oxidation is also linked to ectopic fat deposition in non-adipose tissues[25].

Glycerophospholipid Metabolism: Glycerophospholipids, including phosphatidylcholine and phosphatidylethanolamine, are critical components of cell membranes and play a role in lipid signaling. In obesity, altered glycerophospholipid metabolism contributes to insulin resistance and inflammation. Changes in the PC/PE ratio, which affect membrane fluidity and function, are associated with metabolic disturbances and hyperlipidemia [26].

Sphingolipid Signaling: Sphingolipid metabolism is a critical regulator of cell signaling pathways involved in inflammation and apoptosis. Ceramides, a central component of sphingolipid metabolism, are elevated in obesity and promote insulin resistance and lipotoxicity. Inhibition of ceramide synthesis has been shown to improve metabolic outcomes, making it a promising target for therapeutic interventions [27-33].

Lipidomics as a Tool for Biomarker Discovery and Therapeutic Targeting

Lipidomics provides a comprehensive platform for identifying novel lipid biomarkers associated with obesity and hyperlipidemia. By profiling lipid species across different tissues and biofluids, lipidomics can uncover lipid alterations that serve as early indicators of metabolic dysfunction [33-36]. Potential biomarkers include specific fatty acids, ceramides, and phospholipids that are elevated in obese individuals and correlate with disease progression . In addition to biomarker discovery, lipidomics facilitates the identification of therapeutic targets for managing hyperlipidemia. Targeting enzymes involved in lipid metabolism, such as ACC, FAS, and ceramide synthase, offers promising avenues for therapeutic interventions aimed at normalizing lipid profiles and reducing cardiovascular risk in obese individuals[33-36] .

Emerging Lipidomic Technologies and Future Directions

Advances in mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy have significantly enhanced the sensitivity and resolution of lipidomic analyses. High-throughput lipidomics platforms now allow for the simultaneous quantification of thousands of lipid species, providing unprecedented insights into lipid metabolism in obesity. The integration of lipidomics with other omics technologies, such as genomics and proteomics, is poised to further elucidate the complex interplay between lipids and metabolic pathways. Future research should focus on longitudinal lipidomic studies to track lipid alterations over time in obese individuals and their responses to interventions. Furthermore, personalized lipidomics, tailored to an individual's lipid profile, may lead to more effective and targeted therapeutic strategies for managing hyperlipidemia in obesity [33-36].

CONCLUSION

Lipidomics has revolutionized our understanding of lipid metabolism in obesity, offering new insights into the metabolic pathways contributing to hyperlipidemia. By elucidating the roles of fatty acids, triglycerides, phospholipids, sphingolipids, and cholesterol in obesity-induced lipid dysregulation, lipidomics provides a foundation for identifying novel biomarkers and therapeutic targets. As lipidomic technologies continue to advance, they hold the potential to transform the diagnosis and treatment of hyperlipidemia in obese individuals, paving the way for personalized medicine approaches to metabolic disease management

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