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Lipidomic markers of obesity and their dynamics after bariatric surgery

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ABSTRACT

Obesity is considered as a chronic progressive disease, heterogeneous in its etiology and clinical manifestations, and characterized by excess in body fat mass and its deposition in the body. The term "morbid obesity" refers to excessive deposition of adipose tissue with a body mass index (BMI) ≥40 kg / m^2 or with a BMI ≥ 35 kg / m^2 in the presence of serious complications associated with obesity. Along with obesity, the frequency of type 2 diabetes mellitus and cardiovascular diseases closely associated with it has increased. It results from the progression of metabolic disorders, including insulin resistance, which is inextricably linked with the accumulation of visceral fat and plays a key role in the pathogenesis of obesity-related diseases.

The study of lipidomic signatures in obesity and associated conditions is a promising branch of fundamental medicine, which makes it possible to significantly and at a new conceptual level stratify a cohort of obese patients into various phenotypes, including a metabolically healthy and metabolically unhealthy obesity phenotypes. Dynamic changes in the lipidome both in the context of diet, drug treatment, and after various bariatric surgeries are of great interest for developing personalized strategies for the treatment of this disease. Currently available studies and their results suggest that we are only at the very start of studying this promising biomedical field.

Keywords: obesity, mass spectrometry, metabolic profiling, lipidome, lipids, clinical markers, biomarkers, bariatric surgery

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Липидомные маркеры ожирения и их динамика после бариатрических операций

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РЕЗЮМЕ

Ожирение рассматривается как хроническое прогрессирующее заболевание, гетерогенное по своей этиологии и клиническим проявлениям, характеризующееся избыточным и отложением жировой массы в организме. Под термином «морбидное ожирение» понимают избыточное отложение жировой ткани с индексом массы тела (ИМТ) ≥ 40 кг/м^2 или с ИМТ ≥ 35 кг/м^2 при наличии серьезных осложнений, связанных с ожирением. Одновременно с ожирением возросла частота тесно ассоциированных с ним сахарного диабета второго типа и сердечно-сосудистых заболеваний, представляющих собой итог прогрессирования метаболических нарушений, в том числе инсулинорезистентности, которая неразрывно связана с накоплением висцерального жира и играет ключевую роль в патогенезе сопряженных с ожирением заболеваний.

Исследование липидомных сигнатур при ожирении и ассоциированных с ним состояний – перспективный раздел фундаментальной медицины, позволяющий существенно и на новом понятийном уровне стратифицировать когорту пациентов с ожирением на различные фенотипы, в том числе на метаболически здоровый и нездоровый фенотип. Динамические изменения липидома, как на фоне диетических воздействий, медикаментозного лечения, так и после различных бариатрических операций, также интересны с точки зрения разработки персонализированных стратегий лечения данного заболевания. Имеющиеся на данный момент исследования и их результаты позволяют считать, что мы находимся только в самом начале этого перспективного биомедицинского направления.

Ключевые слова: ожирение, масс-спектрометрия, метаболические профилирование, липидом, липиды, клинические маркеры, биомаркеры, бариатрия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

According to data released in 2021 by the World Health Organization, more than 1.9 billion adults over 18 years of age are overweight, of which over 650 million are obese. In Russia, as of the end of 2016, 23.5 million obese people were registered, which accounts for 16% of the population [1].

Obesity is considered as a chronic progressive disease, heterogeneous in its etiology and clinical manifestations, characterized by excessive deposition of fat in the body. The term “morbid obesity” refers to excessive deposition of adipose tissue with a body mass index (BMI) ≥ 40 kg / m^2 or with a BMI ≥ 35 kg / m^2 in the presence of serious complications associated with obesity.

Along with obesity, the incidence of closely associated type 2 diabetes mellitus and cardiovascular diseases (CVD) has increased, resulting from the progression of metabolic disorders, including insulin resistance, which is inextricably linked with the accumulation of visceral fat and plays a key role in the pathogenesis of obesity-related diseases [2, 3].

To control the obesity pandemic in the 21st century, it is necessary to develop not only effective treatment methods, but also to pay attention to comprehensive research aimed at searching for metabolic markers and predictors of the development of pathological conditions associated with obesity, such as prediabetes and type 2 diabetes mellitus, arterial hypertension, dyslipidemia, non-alcoholic fatty liver disease with progression to the stage of fibrosis and cirrhosis, infertility and cancer.

The main approaches of modern medicine are developing within a philosophical paradigm the main direction of which is the transition from classical clinical diagnosis to personalized regular monitoring of health status to make forecasts containing an assessment of the risks of developing both new diseases and specific complications.

Currently, there is no single approach to the treatment of obesity and metabolic syndrome that would make it possible to create a universal method of personalized monitoring that facilitates formulating a prognosis for the development of obesity based on information about genetic predisposition and risk factors for a particular patient. In routine clinical practice, obesity is diagnosed by assessing BMI, which is calculated as the ratio of body weight (kg) to height squared (m^2), which allows doctors to classify people from class 1 obesity to class 3 or high-risk obesity. For the most part, BMI only provides an indirect assessment of the risks associated with obesity. The assessment of waist circumference reflects to a slightly greater extent the biological cause of fat deposits, insulin resistance, and angiogenesis of adipose tissue, however, it does not fully characterize all its metabolic features.

The assessment of the component composition of the human body using bioelectrical impedance vector analysis and dual-energy X-ray absorptiometry is not objective for comparing the lipotoxicity of tissues of different topologies. Such a diagnosis cannot assess metabolic changes in obesity because in patients the expression of many genes associated with cellular metabolism and adipokine production changes significantly, so currently, it is impossible to reliably divide a cohort of overweight and normal BMI individuals into metabolically healthy and metabolically unhealthy phenotypes using existing tools and approaches.

OMICS

In modern medicine, the field of omics research is intensively developing. Metabolomic analysis, which is one of the most promising molecular methods in systems biology, makes it possible to evaluate the structure and quantitatively characterize molecules that can serve as products or substrates of enzymatic reactions involved in physiological and pathophysiological processes.

Metabolomics is a technological tool for monitoring the general condition of the patient and stratifying the risk of possible metabolic disorders. This is a unique way to determine the metabolic fingerprint (metabolomic signatures) of a recognizable chemical pattern specific to a particular sample.

Clinical lipidomics is a branch of metabolomics, the main analytical tool of which is gas chromatography–mass spectrometry. Due to the wide analytical coverage of lipids, together with high sensitivity and molecular specificity, it becomes possible to detect lipid imbalances in altered cell membranes and lipid droplets, including the stage of early diagnosis of clinically silent conditions [4, 5].

The main focus of this review is lipidomics, the identification of the quantitative and qualitative composition of lipids in different biological environments. In a healthy person, lipid metabolism is in balance, but various trigger factors can change homeostasis. The information presented in the review concerns lipidome studies in the context of the characteristics of obesity and its complications.

Lipid annotation is necessary to interpret the results, as well as to relate the data to other levels of biological information. The most modern and annually updated nomenclature was developed by the LIPID MAPS consortium [6], it is convenient for annotating data obtained using mass spectrometry. The lipid structure database is divided into 8 main groups:

– fatty acylites (FAc), including fatty acids (FA), eicosanoids, fatty alcohols, aldehydes, esters, acylcarnitines, acyl-CoA, wax esters and others;

– glycerolipids (GL);

– glycerophospholipids (GP), including glycerophosphocholines (PC),

– glycerophosphoethanolamines (PE), glycerophosphoserines (PS), glycerophosphoglycerophosphates (PG), glycerophosphoinositol (PI), glycerophosphates (PA);

– sphingolipids (SP), including ceramides, acylceramides, sphingomyelins, sphingosine and others;

– sterol lipids (ST). Most of the cholesterol in the plasma is esterified. Among the cholesteryl esters (CEs) of human plasma, CE (18:2) and CE (20:4) contribute to the major fraction, prenol lipids (PR). The two main prenol lipids in plasma are dolichol and ubiquinone;

– sugar lipids (SL);

– polyketides (PK).

LIPIDOMIC BLOOD MARKERS IN OBESITY

Fatty acids

The molecular mechanisms underlying lipotoxicity include endoplasmic reticulum (ER) stress, oxidative stress, mitochondrial dysfunction, impaired autophagy, and inflammation [7]. Relative hypoxia of adipose tissue is also a factor in its dysfunction. Fatty acid synthesis in adipocytes is activated by signals induced by hypoxia-inducible factor (HIF). Carnitine palmitoyltransferase I (CPTI) is inhibited by HIF, reducing the transport of fatty acids into mitochondria and channeling fatty acids into lipid droplets for storage. Increased droplet counts in cells are associated with increased lipotoxicity and altered metabolism, which contribute to further cellular dysfunction of adipose tissue.

In metabolic disorders, lipid metabolic intermediates accumulate intracellularly, leading to cellular dysfunction and apoptosis of cells in various tissues, including kidneys, brain, skeletal muscles, and heart. Intermediates of lipid metabolism, such as ceramides, diacylglycerides, and acylcarnitines, disrupt intracellular signaling cascades and are largely considered as toxic lipid signaling molecules.

Saturated fatty acids are thought to be particularly harmful to all cell types by inducing a wide range of adverse cellular responses: apoptosis, inflammation, accumulation of reactive oxygen molecules, and oxidative stress [8]. Short-chain fatty acids (SCFA), including acetate, butyrate, and propionate, inhibit lipolysis and promote adipogenesis in visceral adipose tissue, because they are substrates for glucose and lipid synthesis. SCFAs act on G protein-coupled receptors, which leads to inhibition of lipolysis and a decrease in free fatty acid levels in plasma [9]. SCFAs have no more than six carbon atoms and are the main metabolites of the intestinal microbiota, and modern science confirms their role as biomarkers of central obesity [10].

A meta-analysis of randomized clinical trials on obesity [11] showed a characteristic pattern of the lipid profile in this disease: an increase in palmitic, palmitoleic, stearic, and oleic acids, as well as stearoylcarnitine [12]. Also in obesity, the pattern of disturbances in the structure of triacylglycerols (TAGs) was determined; a shorter carbon chain length and fewer double bonds were associated with a higher BMI, while a relatively long acyl chain and a larger number of double bonds were associated with a lower BMI [13].

In a cross-sectional study involving 1,443 Spanish women, it was shown that with increased BMI, the relative concentration of total saturated fatty acids increased in the phospholipid fraction of blood serum, and an increase was also observed in the concentration of palmitoleic, dihomo-γ-linolenic, arachidonic (AA), and α-linolenic acids, while the concentration of oleic, gondoic, trans-vaccenic, linoleic, and γ-linolenic acids decreased [14]. Patients with metabolic syndrome have elevated plasma levels of C16:0, C18:0, C21:0, C16:1, C18:1, C18:2, C18:3n6, C20:3n6, C20:4n6, C22:4n6, C22:5n6 [15], as well as lactic and β-hydroxybutyric acids [16].

Thus, an increase in the level of saturated fatty acids relative to unsaturated fatty acids in plasma correlates with the trend toward an increase in BMI. The results of studies on fatty acids from tissues are thought-provoking, since the ratio of saturated / unsaturated fatty acids in the TAG fraction from visceral and subcutaneous adipose tissue decreased in patients with metabolic syndrome, while it was higher in the control group [17].

Free fatty acids (C14:0, C18:1, C20:2, C20:3, C20:5 and C22:6) were significantly increased in both obesity and type 2 diabetes mellitus, and the C22:6 level was determined as an independent risk factor for type 2 diabetes mellitus [18]. Another meta-analysis of plasma lipidomic studies in obesity showed an association of higher concentrations of circulating fatty acids 20:0, 22:0, and 24:0 with a lower risk of type 2 diabetes mellitus [19].

ACYLCARNITINES

Beta-oxidation of intracellularly stored lipids leads to the production of acetyl-CoA through oxidative degradation of fatty acids. Acetyl-CoA produced by each β-oxidation cycle can subsequently be incorporated into the tricarboxylic acid cycle to generate NADH and FADH2 for the electron transport chain and ATP products [20].

Cell oversaturation with fatty acids and overload of mitochondria with them leads to incomplete

β-oxidation of fatty acids and accumulation of carnitine esters and fatty acids-acylcarnitine in the cell, which was shown in patients with obesity and type 2 diabetes mellitus [21]. Also, the accumulation of a wide range of acylcarnitines with an even number of carbon atoms (from C6 to C22) is specific for obese individuals [22].

Decreased fatty acid oxidation leads to elevated circulating lipid levels, which further increases oxidative stress. Therefore, acylcarnitine (C18:2) has got a negative association with the phenotype of metabolically healthy obesity [23] and a positive association with increasing BMI [24]. Acylcarnitine accumulation is associated with increased insulin resistance in obese patients and the development of a higher risk of CVD [25, 26].

The hypothesis of an association of increasing cardiovascular risk with the accumulation of acylcarnitines is confirmed by the identification of high levels of short-chain acylcarnitines (C2, C3, C4DC), free carnitine (C0), and long-chain acylcarnitines (C16, C18OH) in individuals with metabolic syndrome [27]. A 2020 meta-analysis established a similar pattern with a high degree of evidence; elevated concentrations of acylcarnitine (14:2) were associated with increasing age and BMI of patients [28].

SPHINGOLIPIDS

Research over the past ten years has shed light on the role of changes in lipid metabolism, namely bioactive sphingolipids, in the development of obesity and complications associated with it. Obesity is characterized by a decrease in sphingomyelin [29] and an increase in ceramide synthesis due to stimulation of the so-called salvage pathway, which leads to the production of ceramides through the catabolism of hexosylceramides [30].

Long-chain saturated non-esterified fatty acids (NEFAs) are the main source of ceramide synthesis (palmitic acid is involved in the synthesis of ceramide C16:0, stearic Cer-C18:0, arachidonic Cer-C20:0, and linoceric Cer-C24:0). An increased content of the substrate, long-chain saturated fatty acids, promotes increased synthesis of ceramides and their accumulation in the cell. As is known, C16:0-ceramide has the highest pathogenic potential [31].

In the development of the disease, it is the localization of the ceramide accumulation and not the total mass of ceramides in adipose tissue that matters most (if it is a specific intracellular localization or in specific pools). For example, an increase in the content of ceramides in mitochondria, endoplasmic reticulum (ER), and nucleus inversely correlated with insulin signal transduction, while the accumulation of ceramides in the cytosolic fraction did not affect insulin signaling [32].

The largest population-based study of plasma sphingolipidome conducted by W.S. Chew in 2019 revealed a positive correlation of ceramide levels with BMI and a negative correlation with hexosylceramide levels [33]. This was confirmed by other studies, which showed that the content of sphingomyelins, on the contrary, was inversely associated with the waist-to-hip ratio and BMI [34, 35].

The study by J.M. Weir et al. found a strong specific relationship between ceramide 18:0 and BMI, as well as an increase in all types of dihydroceramides in obese patients [36]. These data are also supported by another more recent study in a large population-based cohort using a targeted lipidomic approach, which found that Cer (18:1/18:0) and Cer (18:1/20:0) levels increased proportionally with BMI [28]. At the same time, W.H. Tell-Hansen et al. found no significant differences in sphingomyelin levels in the plasma of metabolically healthy and metabolically unhealthy obese patients [30].

A 2020 meta-analysis described a positive association of person's age with the C18:1 / 21:0 ceramide content [28]. A study of the serum lipidomic profile in children with abdominal obesity showed that elevated levels of sphingomyelin (d21:1) were associated with central obesity and might mediate the relationship between abdominal obesity and dysregulation of glucose homeostasis [37].

PHOSPHOLIPIDS

Data on changes in the metabolism of the glycerophospholipid (GPL) group are debatable. Obesity is characterized by an increase in the total concentration of GPL in blood plasma. For example, a metabolomics study от serum profiles of diabetic and obese patients found increased concentrations of glycerol, which was positively associated with the established phenotype of type 2 diabetes mellitus and BMI [16].

An Australian metabolomics study in patients with diabetes and obesity found a positive association of glycerolipids with waist circumference [24]. However, phospholipids and most types of lysophospholipids were negatively associated with BMI [28]. An increase in BMI is associated with a significant decrease in the levels of circulating phosphatidylcholines and lysophosphatidylcholines [29, 35, 38].

Another study observed a significant reduction in the levels of five lysophosphatidylcholine (LPC) species (LPC18:2, LPC18:1, LPC20:2, LPC20:1 and LPC20:0) in obese adolescents [39]. PC (15:0/0:0), PE (18:0/0:0), LPC (15:0), LPE (0:0/18:0), and PI (14:0/22:2) were also reduced [40]. Lysophosphatidylcholines LPC 18:2, PC 18:1 were negatively correlated with BMI [41]. However, acyl-lysophosphatidylcholine C16:1, diacyl-phosphatidylcholine, and LPCa C16:1 had the highest correlation indices with high BMI [42]. Phosphatidylcholines, which contain polyunsaturated omega-6 fatty acids, such as 20:3, 20:4 or 22:4, were also positively associated with BMI [28].

One clear signal of plasma lipid ratios associated with BMI was the plasma alkenylphosphatidylethanolamine/ alkylphosphatidylethanolamine ratio; for example, the ratio PE (P-16:0/22:6)/ PE (O-16:0/22:6) [29, 43, 44]. Glycerophosphoethanolamines PE P-16:0/20:3 showed a significant positive association with BMI [41]. LPE with shorter carbon length and fewer double bonds were associated with lower BMI [13].

Metabolically healthy obese patients had elevated diacyl-phosphatidylcholines C32:1 and C38:3, while acyl-lysophosphatidylcholine C18:1 and C18:2 were inversely associated with the patients' condition. In the metabolically unhealthy obesity phenotype, the content of acyl-lysophosphatidylcholine C16:1 was higher, and the level of acyl-lysophosphatidylcholines C18:1 and C18:2 was reduced [45].

Current results of lipidome studies in obesity and diabetes in animals suggest that overexpression of lipoprotein lipase (LPL) may lead to increased activity of the Krebs cycle and proteinogenic amino acid metabolic pathways in skeletal muscle, and these improvements may play an important role in the biological mechanisms underlying antidiabetic features of LPL overexpression [46]. This is confirmed by another study by P.J. Ferrar et al. which revealed that mice with skeletal muscle-specific knockout of lysophosphatidylcholine acyltransferase 3 (LPCAT3), an enzyme involved in phospholipid transacylation, demonstrated an increase in the lysophosphatidylcholine/phosphatidylcholine ratio and an increase in skeletal muscle insulin sensitivity [47].

LIPIDOMIC TISSUE MARKERS IN OBESITY

To assess adipose tissue, we can rely on the in-depth human lipidome atlas AdipoAtlas, which includes the lipidomic profile of adipose tissue from patients with obesity and normal body weight. Quantitative analysis of subcutaneous and visceral adipose tissue samples from the studied cohort allowed to divide the global lipidome into main classes. The lion's share of the total amount belongs to TAG (96.2 nmol / μg of protein), containing mainly saturated and monounsaturated fatty acyl chains, with an average of two double bonds per three chains. The second most common class is cholesterol esters. In terms of quantity, non-polar lipids were followed by phosphatidylcholines, phosphatidylethanolamines, and sphingomyelin. Phosphotidylethanolamines are characterized by a higher concentration of polyunsaturated fatty acids. Ceramids are another class of lipids of high metabolic importance, with C16:0 and C18:1 being the most abundant species. A large number of potentially lipotoxic deoxyceramides are detected in the fat depot, accounting for more than 10% of all ceramide subclasses [48].

LIVER BIOPSY SPECIMENS

In a small cohort of obese patients , the absolute amount of ceramides, SM, PC, PE, PE(e), Lyso (tot) and LPC was higher in the liver compared to adipose tissue. The amount of PC(e), LPE, LPE(e), and triacylglycerols was lower in the liver than in adipose tissue. DAG concentrations in the liver were comparable to those in adipose tissue. In subcutaneous and visceral adipose tissue, TAGs accounted for 99.2% of lipids, phospholipids – for 0.8%, while in the liver, this distribution was 75.5 and 24.5%, respectively [49].

In obese patients, the lipid composition of triglycerides, phosphatidylcholines and sphingomyelins in liver biopsy specimens correlated with sphingomyelins in LDL [50].Significant positive correlations were revealed between the proportions of ceramide C14:0, C18:0, C20:0, and C24:1 in liver and total plasma. These subspecies may be markers of the species composition of hepatic ceramides in obese patients [51].

BIOPSY SPECIMENS OF EPICARDIAL FAT

When analyzing the lipidomic profile of blood plasma, 9 species of lipids were identified that were associated with an increase in epicardial fat: triacylglycerol, hydroxylated acylcarnitine, deoxyceramide, alkyldiacylglycerol, ubiquinone, diacylglycerol, dihydroceramide, phosphatidylinositol, and phosphatidylglycerol. The strongest associations observed were with two species of deoxyceramides [52]. Cer (m18:1/18:0) and Cer (m18:1/20:0) and sphingosine are also elevated, confirming an earlier study of biopsy specimens in obesity [53].

Lipidomic analysis of subcutaneous and epicardial adipose tissue in patients with coronary artery disease and type 2 diabetes revealed multiple changes in the content of fatty acids with an odd number of carbon atoms (15:0, 15:1, 17:0, 17:1). More pronounced changes were found in epicardial adipose tissue compared to subcutaneous adipose tissue [54].

COMPARISON OF SUBCUTANEOUS AND VISCERAL FAT

The extent of lipidome changes depending on fat topology was analyzed by N. Al-Sari et al. [55]. Lipidomic analysis was performed on adipose tissue collected from the abdomen, chest, thigh, and lower back. Levels of triacylglycerols (TAGs) with long-chain polyunsaturated fatty acids were higher in thigh tissue. The difference between thigh and lower back adipose tissue was generally similar to the difference between the thigh and abdomen. Minor changes in the lipid spectrum were observed in the tissue of the lower back and chest, while more significant ones were observed in the adipose tissue of the thigh and abdomen [55]. It should be noted that the lipidome of muscle tissue, unlike adipose tissue, does not have such pronounced differences between patients [56].

In obese patients without diabetes, the subcutaneous fat lipidome contains high concentrations of long-chain FAs and ceramides, in particular ceramide C18:1/24:1 [57]. And in patients with obesity and type 2 diabetes mellitus-*, there is an increase in the level of ceramide C16:0 in subcutaneous fat tissue rather than in visceral deposits [58]. These changes are also confirmed by a more recent study [59].

In the visceral tissue of patients with diabetes and prediabetes, the content of Cer (d18:1/16:0), Cer (d18:1/18:0), Cer (d18:1/18:1), Cer (d18:1/20:0), Cer (d18:1/24:1) is increased in contrast to healthy individuals [60]. A similar result was obtained by Choromańska et al. in patients with metabolic syndrome, and it was also observed that saturated palmitic and stearic acids were the most abundant fatty acids of the ceramide fraction in both adipose tissues [17].

An increase in visceral tissue ceramides in obese patients with diabetes was confirmed by a previous study. The length of the acyl chain of ceramides in adipose tissue (C16–20) is shorter than in plasma (C16–24). Lower sphingomyelin concentrations were observed in obese patients [56].

Excessive accumulation of lipids in adipose tissue is observed mainly in the form of TAG. Physiological stimuli lead to hydrolysis of TAG in adipocytes, which is accompanied by an increase in plasma long-chain fatty acids and subsequent accumulation of lipids in ectopic tissues. In the group of patients with metabolic syndrome, the ratio of saturated to unsaturated fatty acids composing the TAG fraction decreased significantly in visceral and subcutaneous adipose tissues, and the pool of free fatty acids in plasma increased mainly due to palmitic, stearic, arachidonic, and nervonic acids [17].

Patients receiving fish oil supplements for 12 months were included in the research cohort of a multicenter study in which adipose tissue biopsy specimens and blood plasma were collected. Fatty acids with a carbon chain length of more than 22 carbon atoms prevail in subcutaneous adipose tissue, while polyunsaturated fatty acids prevail in visceral fat deposits [61].

Adipose tissue stores significant amounts of cholesterol in the human body, and obesity is associated with decreased serum cholesterol concentrations. In patients with metabolic syndrome, a direct relationship was found between the content of oxidized cholesterol metabolites in adipose tissue – oxysterols – and blood insulin levels, as well as resistance to the hormone. Tissue cholesterol correlates more with 27-hydroxycholesterol in subcutaneous adipose tissue and with 24S-hydroxycholesterol in visceral adipose tissue [62].

A 2022 study in which 26 obese patients without type 2 diabetes underwent bariatric surgery is of particular interest [63]. Biopsy specimens were obtained from subcutaneous adipose tissue of the thigh, subcutaneous abdominal adipose tissue, deep subcutaneous abdominal adipose tissue, intra-abdominal adipose tissue, two areas of muscle tissue (vastus lateralis muscle; rectus abdominis muscle), and liver (wedge of the right lobe). The study revealed that plasma lipidomic profiles more closely reflect the liver profile than other tissues examined. All four fat depot localizations showed similarities in their metabolic relationships with plasma; it is impossible to distinguish between different depots in terms of their metabolic relationships with plasma, but the plasma pool better reflects the TAG deposition in deep adipose tissue rather than subcutaneous adipose tissue.

Those sphingomyelin and ceramide fractions that correlate between plasma and liver also show chain length specificity, i.e. these are sphingomyelins and ceramides that contain long-chain fatty acids with an acyl chain of 22 or more carbon atoms, such as

C22:0, C24:0 and C24:1. The liver is the main source of ceramides, but given that their content in the liver correlates well with plasma fractions, it proves that plasma sphingolipids may reflect their abnormal metabolism in the liver. Sphingomyelins, which contained a smaller even total number of carbon ($C \leq 34$) and monounsaturated chain fatty acids, and their concentration correlated with indicators of intra-abdominal adipose tissue, liver, and muscles [63].

CONDITIONS ASSOCIATED WITH OBESITY

The multiplicity of organ damage in obesity includes frequent pathology of the hepatobiliary system. According to autopsy data, non-alcoholic fatty liver disease is diagnosed in 70–93% of obese patients with type 2 diabetes [64]. A recent study found that plasma levels of certain lipid fractions (saturated and monounsaturated TAG) indicate early stages of fat accumulation in the liver [65].

TAG species containing low total carbon and fewer unsaturated bonds were significantly associated with steatohepatosis, vascular disease, and an increased risk of diabetes, while species containing a high amount of carbon and a higher number of unsaturated bonds were associated with a reduced risk of diabetes [66–68].

Long-term persistent obesity contributes to the development of focal segmental glomerulosclerosis, chronic kidney disease, and diabetic nephropathy. In patients with progressive diabetic nephropathy and obesity, a relative abundance of TAGs with longer chain polyunsaturated acyls and a lower content of C16–C20 acylcarnitines was identified. The increase in their levels had a compensatory adaptive mechanism for converting more toxic lipids (saturated non-esterified fatty acids) into less toxic lipids (polyunsaturated long-chain TAG). Unsaturated free FAs and TAGs with short-chain acyls and low double bond content predicted the progression of diabetic kidney disease [69].

This is confirmed by another more recent study which revealed that obese patients with chronic kidney disease (CKD) tended to have a decrease in the number of carbons in the acyl chain of predominantly unsaturated TAGs. The content of lysophosphatidylcholines is also increased in these patients, but the balance of saturation and unsaturation is preserved. LysoPC (18:0), LysoPC (20:3), and PC (35:3) had the greatest predictive ability to distinguish between obese patients and obese patients with nephropathy [64].

Other negative consequences of uncorrected systemic inflammation in obesity include damage to nerve cells and fibers. According to the results of global metabolomics and targeted lipidomics, plasma FFA levels are increased in patients with obesity and polyneuropathy, mostly due to long-chain fatty acids (more than 19 atoms). In this clinical cohort, metabolomic profiles between obese and lean individuals were most strongly correlated with gamma-glutamino acid and branched-chain amino acid metabolism. Moreover, the plasma level of gamma-glutamino acid is positively correlated with TAG, BMI, and blood pressure and is associated with oxidative stress in obesity and metabolic syndrome [70].

In another study, patients with diabetes and polyneuropathy had increased concentrations of medium- and long-chain saturated fatty acids from 8 to 18 carbons [71]. Patients with significantly reduced total medium-chain (C6–C14) acylcarnitines had a correlation with the development of peripheral neuropathy over 10 years. These patients were characterized by a decrease in plasma levels of medium-chain acylcarnitines (C2–26) and phosphatidylcholines and an increase in lysophosphatidylcholines [72]. Low plasma sphingomyelin (SM) levels may correlate with poorer neurological outcomes [71].

CHANGES IN THE LIPIDOME AFTER BARIATRIC SURGERY

Bariatric surgery is the most effective way to treat obesity. According to 2018 Russian guidelines, bariatric surgery is indicated for patients with a BMI of more than 40 kg / m^2 and a BMI of 35–40 kg / m^2 in the presence of diseases associated with obesity, in which improvement should be expected as body weight is reduced (type 2 diabetes, CVD, obstructive sleep apnea, joint damage). American clinical guidelines refer to prospective and retrospective studies confirming improved quality of life and life expectancy of patients with a BMI of 30–34.9 kg / m^2 after bariatric surgery.

Bariatric surgery includes four main procedures: biliopancreatic diversion (BPD), Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, sleeve gastrectomy, in which the main effects are achieved through malabsorption and restriction.

A meta-analysis of metabolomic profiling of blood plasma in patients after surgical procedures (Roux-en-Y and gastric banding) describes the change in insulin resistance after surgical treatment of obesity.

Thus, 92 metabolites are associated with varying degrees of reduction in HOMA-IR up to –40% of the baseline [73]. A recent study found greater accelerated weight loss in metabolically unhealthy obese patients than in metabolically healthy obesity [74].

The analysis of blood plasma proved that the content of short-chain fatty acids, mainly metabolites of the intestinal microbiota, decreases after bariatric surgery, while the level of branched fatty acids increases. Changes in short-chain fatty acid content are associated with weight loss. Elevated plasma BCFA levels have been shown to be associated with increased insulin sensitivity [75, 76]. A decrease in the concentration of free fatty acids in blood plasma after gastric bypass surgery is associated with a decrease in the distance of food passage in the intestine and, accordingly, with a decrease in fat absorption compared with laparoscopic sleeve gastrectomy, where the absorption surface is larger [77].

It was found that in plasma the cluster of phosphatidylcholines, especially phosphatidylcholines with the sum of diacyl residues C42:Ys, as well as SM (OH) C16:1, SM C26:1, lysoPC a C16:0, glutamine, glycine, citrulline, and histidine, were enriched only in patients who underwent Roux-en-Y, but not in patients who changed their lifestyle and diet [78]. Since some groups of fatty acids are considered beneficial, such as n-3 polyunsaturated FAs (PUFAs), while others are detrimental to human health, such as saturated FAs (SFAs), each change in their levels can have an important impact on the metabolic outcome of bariatric surgery.

Blood was collected from patients before and after gastric bypass surgery with a single anastomosis. A decrease in the total amount of fatty acids with an odd number of carbon atoms, branched chain and polyunsaturated fatty acids was observed in patients with morbid obesity before surgery compared to the control group. Monounsaturated fatty acid content was increased, which was mainly caused by a higher level of oleic acid (18:1). The content of monounsaturated fatty acids in triglycerides increased in patients after surgery, mainly due to a higher level of oleic acid. There was no noticeable increase in the level of polyunsaturated fatty acids. Due to the anti-inflammatory, cardioprotective, and anticancer properties of PUFAs, a decrease in their content in the long-term postoperative period makes it necessary to prescribe dietary supplements. At the same time, the content of α-linolenic acid and eicosapentaenoic acids in the blood serum did not differ significantly before and after surgery [79].

Gas chromatography was used to study the blood of patients before and after laparoscopic sleeve gastrectomy. The surgery lead to a long-term decrease in serum α-linolenic acid and eicosapentaenoic acid levels in the first year [80].

Two weeks after gastric bypass with one anastomosis, a decrease in the content of branched-chain fatty acids and an increase in the level of monounsaturated fatty acids (MUFA) were detected in the blood plasma. Obese patients also showed decreased plasma levels of some PUFAs, including linolenic acid (18:3 n-3) and eicosatetraenoic acid (EPA; 20:5 n-3 and 20:4 n-3) [81].

Blood analysis before and after Roux-en-Y revealed significant changes in the content of six metabolites (3-indoleacetic acid, 2-hydroxybutyric acid, valine, glutamic acid, 4-hydroxybenzeneacetic acid, and alpha-tocopherol), while changes in the content of the identified metabolites were associated with the changes in lipid, insulin, and glucose levels [82].

The first study using capillary electrophoresis – mass spectrometry in obese patients after laparoscopic sleeve gastrectomy found that the relative content of tricarboxylic acid cycle metabolites, including citric acid, succinate, and malic acid, was significantly increased in blood plasma after surgery [83].

Patients with CKD and severe obesity after Roux-en-Y gastric and sleeve gastrectomy showed a dramatic weight loss with a significant decrease in proteinuria, albuminuria, uric acid levels, a decrease in the degree of glomerular hyperfiltration, and an increase in HDL levels. The lipid profile and metabolome of the blood serum in patients changed significantly after surgery: the level of diacylglycerols, triacylglycerols, and branched-chain amino acids decreased. A significant decrease in their levels was positively correlated with uric acid levels, while the levels of PC (39:0) and PC (44:5) increased, and only PC (36:3) decreased [84]. Interestingly, bariatric surgery did not restore all types of lipids; some of them were decreased, and, therefore, they were considered as potential targets for early diagnosis or therapeutic intervention.

CONCLUSION

The study of lipidomic signatures in obesity and associated conditions is a promising branch of fundamental medicine, which makes it possible to significantly and at a new conceptual level stratify a cohort of obese patients into various phenotypes, including metabolically healthy and metabolically

unhealthy phenotypes. Dynamic changes in the lipidome, both after dietary changes, drug treatment, and various bariatric surgeries, are also interesting from the point of view of developing personalized strategies for treating this disease. The current studies and their results suggest that we have just begun research in this promising field in biomedicine.

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