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# *Research Progress on Glucose and Lipid Metabolism*

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***Abstract:*** Glucose and lipid metabolism are crucial metabolic processes for two important nutrients in the human body. Maintaining the homeostasis of glucose and lipid metabolism is of self - evident significance for the body. The glucose and lipid metabolism system is so complex and extensive that almost all tissues in the body are involved. From our lifestyle and rhythms to a single molecule in our body, everything may affect the process of glucose and lipid metabolism and the overall state of our body. Once a problem occurs in any link of glucose and lipid metabolism, the operation of certain parts of the body or even all organs may be abnormal, leading to various diseases. This article selects recent literature on glucose and lipid metabolism research to explore the newly discovered influencing factors of glucose and lipid metabolism and the relationship between glucose and lipid metabolism and related diseases.

## 1. Introduction

The processes of glucose and lipid metabolism are numerous, involving a large number of enzymes and various hormones. Glucose metabolism includes physiological processes such as glycolysis, the tricarboxylic acid cycle, the pentose phosphate pathway, glycogen synthesis and decomposition, and gluconeogenesis. Lipid metabolism includes processes such as fat mobilization, β-oxidation, and ketone body utilization, involving multiple key enzymes. If any one of these key enzymes is defective, glucose metabolism will be disrupted, leading to related diseases. The hormones that regulate these enzymes are mainly insulin, glucagon, and glucocorticoids. If there are problems with the secretion of these hormones, it is likely to cause systemic endocrine diseases. As the central organ of glucose and lipid metabolism, the liver is the first to be affected when there are problems in glucose and lipid metabolism. Conversely, if the liver has problems, glucose and lipid metabolism will also be affected. Our lifestyle can also affect energy utilization and hormone secretion, thus influencing the process of glucose and lipid metabolism.

Precisely because glucose and lipid metabolism involve many steps, not only the molecules directly related to our cognition can affect glucose and lipid metabolism, but also short-chain fatty acids, miRNAs, and some signaling molecules can indirectly regulate it. Moreover, diseases related to glucose and lipid metabolism are not limited to endocrine and liver diseases. Tumors and even some neurodegenerative diseases may also be associated with glucose and lipid metabolism.

## 2. Influencing Factors of Glucose and Lipid Metabolism

### 2.1 Lifestyle

#### 2.1.1 Exercise

We know that exercise can increase the body's utilization of nutrients by consuming ATP, thereby regulating glucose and lipid metabolism at the substrate level. A study on exercise methods for diabetic patients pointed out that among people with different glucose metabolism levels, after aerobic exercise, fasting plasma glucose (FPG), 2-hour post-meal blood glucose (2hPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) and other glucose and lipid metabolism-related indicators have improved. After resistance exercise, the 2hPG, TC, and HDL indicators in different glucose metabolism populations have also improved.[1] It can be seen that exercise can effectively improve the level of glucose and lipid metabolism, and aerobic exercise has a stronger effect. This may be related to peroxisome proliferator-activated receptor γ (PPARγ) and phosphatidylinositol 3-kinase (PI3K).[2] PPARγ is an important target for regulating glucose and lipid metabolism. It can increase the body's sensitivity to insulin and the utilization of glucose to lower blood sugar. PI3K is a key enzyme for glucose to enter cells. Aerobic exercise can activate the expression of PPARγ, promote the conduction of the PI3K/AKT pathway, enhance the decomposition of triglycerides, and improve the disorder of glucose and lipid metabolism in diabetic patients.[2]

#### 2.1.2 Rhythm

The human body's hormone secretion has its own rhythm, and hormone secretion is also affected by people's daily routines. Both glucose and lipid metabolism have a circadian rhythm. For example, the body's glucose tolerance is higher in the morning and lower at noon and in the evening. Many genes related to rhythm regulation also affect glucose and lipid metabolism because clock genes can affect almost all endocrine molecules to regulate the body's metabolism.[3] For example, both Cry1 and Cry2 genes can inhibit the expression of liver gluconeogenesis genes. Correspondingly, knocking out the Cry genes will relieve the inhibition of liver gluconeogenesis.[3] A study found that when the circadian rhythm of mice was disrupted by continuous light, compared with normal mice, their fatty acids, triglycerides, total cholesterol, and fasting blood glucose were higher, insulin sensitivity decreased, and adipose tissue was damaged to varying degrees.[4] This all shows the importance of rhythm for metabolic homeostasis.

Sleep rhythm is also related to glucose and lipid metabolism. Research on sleep-deprived people shows that the increase in FPG, 2hPG, and HbA1c increases with the degree of sleep deprivation, and these indicators improve accordingly when sleep returns to normal. Moreover, lack of sleep can increase the incidence of insulin resistance, possibly due to gut microbiota disorder caused by lack of sleep, leading to low-grade inflammation, insulin signal transduction disorders and interference with insulin secretion; disruption of the rhythm of the autonomic nervous system and abnormal activation of the sympathetic nervous system; activation of the hypothalamic-pituitary-adrenal axis and excessive secretion of glucocorticoids.[5]

### 2.2 Molecules in the Body

#### 2.2.1 Regulatory Proteins

There are two types of regulatory proteins mentioned here, leucine-rich α-2-glycoprotein 1 (LRG1) and neuregulin 4 (NRG4). LRG1 is secreted by white and brown adipocytes, which inhibits insulin signaling and promotes hepatic gluconeogenesis. Under pathological conditions, it can cause hepatic

steatosis and insulin resistance. High-dose glucose can stimulate the secretion of LRG1.[6] Therefore, in the case of hyperglycemia, the presence of LRG1 will enhance gluconeogenesis, continuing to increase the glucose content in the blood and forming a vicious cycle. When the LRG1 gene is knocked out, gluconeogenesis is inhibited, insulin sensitivity is enhanced, blood sugar is improved, serum triglyceride and cholesterol levels are reduced, and the expression of genes related to β-oxidation in hepatocytes increases while the expression of lipid-generating genes decreases.[6] Therefore, the LRG1 gene can be used as a target for drugs to treat metabolic diseases such as hypoglycemic and lipid-lowering drugs in the future.

In contrast, NRG4, secreted by brown adipose tissue, can inhibit hepatic lipid generation and hepatic steatosis, promote lipid decomposition, upregulate the expression of genes related to mitochondrial function and energy metabolism, and is negatively correlated with the expression of fat-synthesis genes. It plays a protective role in the body in many metabolic diseases and maintains the balance of lipid metabolism.[7] NRG4 can also enhance the sensitivity of adipose tissue to insulin and relieve insulin resistance. [8]Insufficient NRG4 will exacerbate the development of obesity and other metabolic diseases and is considered a risk factor for the development of many metabolic diseases.

### 2.2.2 Molecules Regulating the Expression of Genes Related to Glucose and Lipid Metabolism

Methylation and miRNAs regulate glucose and lipid metabolism at the gene-expression level. Methylation is an epigenetic modification of RNA, while miRNAs inhibit gene expression at the post-transcriptional level. The mechanism is that they combine with the Ago protein family to form an RNA-induced silencing complex (RISC) that acts on specific RNAs.

Methylation modification plays an important role in many metabolic processes. Among them, N6 -methyladenosine (m6A) modification is the most abundant and common. The level of m6A methylation is positively correlated with insulin resistance. Its main methyltransferases, METTL3 and METTL14, are consistent with the levels of m6A and insulin resistance. However, the increasing levels of m6A, METTL3, and METTL14 can cause the cell cycle of pancreatic β-cells to arrest, reduce insulin secretion, and also lead to diabetes.[9]

miRNAs also play an important role in regulating metabolism. miRNAs can regulate insulin secretion by directly acting on the transcription of the insulin gene, acting on insulin inhibitors, and participating in glycolysis and the tricarboxylic acid cycle. For example, miR-30d is an important miRNA for insulin secretion. If it is missing, insulin cannot be secreted. miRNAs are also related to the occurrence and development of diabetes. An imbalance in the number of miRNAs can lead to abnormal insulin secretion and affect the function of pancreatic β-cells. The over-expression of some miRNAs can even promote the apoptosis of pancreatic β-cells. For lipid metabolism, miRNAs regulate lipid metabolism by adjusting the amount of lipids flowing into apolipoproteins, acting on the microsomal triglyceride transfer protein (MTP), an important component of lipoprotein assembly, and even the transcription factors of genes involved in fatty acid and cholesterol synthesis. miRNAs are closely related to atherosclerosis. For example, if the function of miR-33 is enhanced, the number of foam cells will increase, increasing the risk of atherosclerosis.[10]

### 2.2.3 Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are a class of fatty acid molecules with less than 6 carbon atoms, including acetic acid, propionic acid, butyric acid, etc. SCFAs are mainly produced in the intestine by the decomposition of cellulose by intestinal bacteria. They can participate in glucose and lipid metabolism either by directly synthesizing sugars and lipids or as regulatory molecules. When SCFAs act as substrates, they can provide 10% of the human body's calories and generate acetyl-CoA as a

substrate for lipid synthesis. When participating in glucose metabolism as regulatory molecules, they can activate fatty acid receptor 3 (FFAR3) to enhance the absorption of glucose in muscles and brown adipose tissue. By activating FFAR2, they can stimulate the secretion of glucagon-like peptide-1 (GLP-1), increase insulin secretion, reduce glucagon secretion, and promote glycogen synthesis and blood-glucose uptake by skeletal muscle. When participating in lipid metabolism, they can activate brown adipose tissue, regulate the function of liver mitochondria, and also activate hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), promote fat decomposition, increase the fat oxidation of brown adipose tissue, improve obesity and insulin resistance, and make fat cells smaller.[11] In summary, short-chain fatty acids can promote the utilization of glucose and fat.

### 2.2.4 Reactive Oxygen Species

We know that the production of reactive oxygen species (ROS) will exacerbate tissue oxidation and damage and is one of the main causes of biological aging. With the aging of organisms, more and more ROS are produced. In an experiment on glucose and lipid metabolism in aging and young mice, it was found that the expression of cholesterol-synthesis-related genes in liver cells in an ROS environment was significantly higher than that in mice without ROS in the environment, and it increased over time. Cholesterol itself and triglycerides also showed the same trend. The impact on glucose metabolism is more complex: under the induction of ROS, hepatocytes take up more sugar, GLUT2 translocates to the plasma membrane more, the expression of genes related to glycolysis increases, the expression of key enzymes for gluconeogenesis decreases, the expression of glycogen synthase 2 decreases, and the level of acetyl-CoA increases significantly. The increased acetyl- CoA will then participate in cholesterol synthesis, increasing liver cholesterol synthesis and leading to cholesterol deposition in the liver.[12]

### 2.2.5 Vitamin A and Its Derivatives

Vitamin A is a fat-soluble vitamin that is metabolized in the liver. Therefore, it and its derivatives have the opportunity to be involved in glucose and lipid metabolism. Scientists have found that lipophilic extracts in the liver can induce the expression of Pck1 and can also act synergistically with insulin to induce the expression of Gck. The substances in these extracts are vitamin A, its metabolites, and derivatives.[13] Pck1 can inhibit the action of insulin, leading to insulin resistance. Gck is the gene for glucokinase, which can regulate glucose homeostasis and promote insulin secretion. Therefore, vitamin A has a dual effect on glucose metabolism.

## 3. Relationship with Diseases Related to Glucose and Lipid Metabolism

### 3.1 Liver Diseases

As mentioned before, the liver is the central organ of glucose and lipid metabolism. If there are problems with the liver, many enzymes and related steps in glucose and lipid metabolism will be affected, and vice versa. A typical example is non-alcoholic fatty liver disease (NAFLD). First, if NAFLD occurs, insulin signaling in the liver will be abnormal, prone to causing insulin resistance and disrupting glucose metabolism. This is manifested as an increase in the values of glycosylated hemoglobin and the glucose tolerance test compared to normal conditions.[14] The TG content in the blood will also increase because insulin-mediated inhibition of the VLDL-TG complex decreases, and at the same time, VLDL clearance decreases, resulting in more VLDL-TG complexes.[15] Moreover, hyperinsulinemia caused by insulin resistance will make de novo fat synthesis more active,[14] further leading to fat accumulation in the liver and forming a vicious cycle. Similarly, the severity of glucose and lipid metabolism disorders will affect the development of NAFLD. A study shows that the severity

of liver steatosis in NAFLD is positively correlated with fasting insulin, glycosylated hemoglobin, and fasting C-peptide.[16] Therefore, NAFLD and glucose and lipid metabolism disorders form a positive-feedback relationship. If measures are not taken to prevent the disorder of glucose and lipid metabolism and it is allowed to develop, NAFLD will continue to progress and may even evolve into liver cirrhosis.

### 3.2 Alzheimer's Disease

According to a study, compared with people with normal blood sugar, people with diabetes have a decline in cognitive function, manifested as significant decreases in immediate memory, language function, delayed memory, and attention. The degree of cognitive decline is positively correlated with the severity of diabetes. This may be because high levels of glycated proteins, after oxidation, will increase the level of advanced glycation end-products (AGEs), which are neurotoxic.[17] Glucose metabolism disorder is one of the bases for the occurrence of Alzheimer's disease (AD). One of the manifestations of AD is memory decline. There is a glucose metabolism disorder in the brains of AD patients, manifested as a decrease in the expression of glucose transporter genes, obstruction of the glycolysis pathway, and a decrease in the activity of tricarboxylic acid cycle enzymes. In the brain neurons of AD patients, mitochondrial function is impaired, and glycolysis occurs even under aerobic conditions, reducing the brain's energy-utilization efficiency and increasing the demand for sugar. High blood sugar levels can further damage mitochondria and aggravate AD.[18]

### 3.3 Tumors

Tumor cells mainly obtain energy through anaerobic glycolysis of glucose, which leads to greater nutrient consumption and more lactate production. Therefore, the glucose and lipid metabolism rate of tumor patients is disordered. A study shows that compared with people with normal tumor marker levels, people with high tumor marker levels have lower FPG, 2hPG, TC, and TG, but higher HDL.[19] Abnormal glucose and lipid metabolism may, in turn, increase the risk of tumor occurrence. In the same study, it was found that the levels of tumor markers such as carcinoembryonic antigen in patients with abnormal glucose and lipid metabolism but without detected tumors are higher than those in the normal population.[19] Unfortunately, this study did not explain the reason why abnormal glucose and lipid metabolism increases the carcinoembryonic antigen level, and an increase in carcinoembryonic antigen does not necessarily mean the occurrence of a tumor. Therefore, the relationship between glucose and lipid metabolism disorders and tumors needs further study.

### 3.4 Primary Aldosteronism

Abnormal glucose and lipid metabolism is not only closely related to well - known hormones such as insulin, glucagon, and glucocorticoids but also to aldosterone. Aldosterone belongs to mineralocorticoids and is secreted by the zona glomerulosa of the adrenal cortex. It is usually considered a hormone for regulating water-salt balance. However, aldosterone can induce the mineralocorticoid receptor (MR). MR can inhibit heat production and glucose uptake in adipose tissue, reduce insulin signaling, and ultimately reduce the transfer of glucose transporter 4 to the cell membrane, decreasing the uptake and utilization of glucose by skeletal muscle and other tissues. It can promote obesity, reduce insulin sensitivity, and promote inflammation, resulting in reduced insulin secretion by pancreatic β-cells and further disrupting glucose and lipid metabolism. This is the reason why the incidence of glucose and lipid metabolism disorders in patients with primary aldosteronism is higher than that in patients with primary hypertension.[20]

## 4. Summary and Prospect

Glucose and lipid metabolism play a crucial role in the human body, involving many organs, tissues, and molecules. Therefore, molecules or diseases that may not seem related to glucose and lipid metabolism are actually intricately linked to it. We can start from these newly discovered molecules to improve the disorder of glucose and lipid metabolism in patients. For many diseases, if the patient's metabolic level can be improved, the disease may not continue to progress and can be controlled to a certain extent. We can also start from lifestyle, enabling people to develop good living habits and regular routines, which can reduce the incidence of metabolic diseases. Of course, the relationships between glucose and lipid metabolism and tumors, as well as primary aldosteronism, need to be further clarified. This may provide new treatment options for tumors and glucose and lipid metabolism disorders.

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