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POSSIBLE MECHANISMS OF THE DEVELOPMENT OF INSULIN RESISTANCE IN OBESITY

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Abstract: *Metabolic syndrome was previously associated with an increased risk of cardiovascular disease. However, research in recent decades has shown that the components of the metabolic syndrome have an effect on other systems of substances. The article provides a review of the literature on the modern definition of metabolic syndrome, pathogenetic mechanisms of the development of some of its components.*

Key words*: metabolic syndrome, obesity, body mass index, pathogenetic features, leptin, insulin resistance.*

In recent decades, the problem of obesity has gained a global scale. According to data from the World Health Organization (WHO), from 1975 to 2021, the prevalence of this pathology among the adult population aged 18 years and older has increased almost threefold. As of 2021, 41% of men and 46% of women in this age group were overweight, and about 13% of the world's adult population (11% of men and 15% of women) were obese. It has been established that excess weight affects not only the functioning of the cardiovascular system, but also can potentially cause a number of concomitant diseases.

Metabolic syndrome (MS) is a complex of metabolic disorders and cardiovascular diseases (CVD), pathogenetically interconnected due to insulin resistance (IR) with impaired glucose tolerance (IGT), atherogenic dyslipidemia (increased triglycerides, low-density lipoproteins (LDL) , a decrease in high-density lipoproteins (HDL), arterial hypertension (AH) against the background of abdominal obesity. MS - a pandemic of the 21st century. Among the population of economically developed countries, according to various authors, the prevalence of MS ranges from 25 to 40%. Today, the "rejuvenation" of this pathology is registered. Thus, the frequency of development of MS in adolescents and young adults has increased 1.5 times over the past 60 years, and the presence of excess body weight in children in economically developed countries reaches 14%. Obesity, high blood pressure,

disorders of carbohydrate and lipid metabolism are risk factors for the development of CVD, which occupy a leading place among the causes of mortality among the population of industrialized countries. Disturbances that are characteristic of MS have an asymptomatic course for a long time, often begin to form in adolescence and young adulthood, long before the clinical manifestation of hypertension, atherosclerotic vascular lesions, type 2 diabetes mellitus, which determines the heterogeneity of clinical manifestations at different stages of the development of this pathology . Almost all components of MS are dangerous risk factors for the development of CVD. The presence of MS increases the risk of hypertension, type 2 diabetes and mortality by 3-6 times. According to modern ideas about the regulation of glucose metabolism and lipid metabolism, the basis of the pathogenesis of MS is formed by two pathophysiological defects that control the dynamics of glycemia levels: IR — a decrease in insulin sensitivity of insulin-dependent tissues; dysfunction of b-cells of the pancreas. At the first stage, hyperglycemia is caused by a decrease in glucose uptake by muscle and adipose tissue as a result of primary IR and compensatory hyperproduction of glucose by the liver. In response to hyperglycemia, insulin secretion by b-cells of the pancreas increases to maintain normal glucose metabolism. Under these conditions, primary IR against the background of inadequate insulin secretion leads to the development of IGT. At the second stage, chronic persistent hyperglycemia is accompanied by glucose toxicity, which contributes to the development of secondary IR and desensitization of b-cells of the pancreas with deterioration of their secretory activity. IR is considered as a disturbed biological response of the body's peripheral tissues to the influence of endogenous or exogenous insulin. The biological action of insulin consists in the regulation of metabolic reactions and mitogenic processes. Therefore, the modern concept of IR is not reduced to parameters that characterize only carbohydrate metabolism, but also includes changes in the metabolism of fats, proteins, endothelial cell function, gene expression, etc. When type 2 diabetes (or IGT) is combined with dyslipidemia, hyperuricemia, and hypertension, that is, with the main components of MS, the frequency of IR detection reaches 95%. This indicates that IR is really the driving mechanism of MS development. IR of peripheral tissues is important for the development of MS. Clinically, the most important is the loss of sensitivity to insulin on the part of muscle, adipose tissue, and liver. IR of muscle tissue is manifested by a decrease in the supply of glucose from the blood to myocytes and its utilization in muscle cells. IR of adipose tissue manifests itself in resistance to the antilipolytic effect of insulin, which leads to the accumulation of free fatty acids and glycerol. Free fatty acids enter the liver, where they become the main source of formation of atherogenic very low density lipoproteins. IR of liver tissue is characterized by a decrease in glycogen synthesis and activation of the processes of breakdown of glycogen into glucose (glycogenolysis) and de novo synthesis of glucose from amino acids, lactate, pyruvate, glycerol (gluconeogenesis), as a result of which glucose from the liver enters the bloodstream. These processes in the liver are activated due to the absence of their inhibition by insulin. IR of peripheral tissues long precedes the development of type 2 diabetes and can be detected in close relatives of patients with type 2 diabetes who do not have disorders of carbohydrate metabolism. Long-term existing IR is compensated by excessive production of insulin

by b-cells of the pancreas (a state of hyperinsulinemia), which supports normal carbohydrate metabolism. Hyperinsulinemia is equated with markers of IR and is considered a harbinger of the development of type 2 DM. Subsequently, with an increase in the degree of IR, b-cells cannot cope with the increased glucose load, which leads to the gradual exhaustion of the insulin secretory capacity of b-cells and the clinical manifestation of DM. First of all, the function of rapid insulin secretion in response to a food load is negatively affected, while the second phase remains excessive. The development of hyperglycemia further increases the IR of peripheral tissues and suppresses the insulin-secretory function of b-cells - this is the so-called "glucose toxicity". IR is considered as a decrease in the response of insulin-sensitive tissues to insulin at its sufficient concentration. The following are important in the development of insulin sensitivity disorders: mutations in the genes of the insulin receptor substrate (SIP-1), glycogen synthetase, hormone-sensitive lipase, b3-adrenoceptors, tumor necrosis factor a (TNF-a), uncoupling protein (UCP-1), and as well as molecular defects in the proteins that transmit insulin signals (increased expression of the Rad protein and uncoupling protein (UPC-1) — an inhibitor of insulin receptor tyrosine kinase in muscle tissue, a decrease in the membrane concentration and activity of intracellular glucose transporters — GLUT-4 in muscle tissue). An important role in the development and progression of IR and related metabolic disorders is played by adipose tissue in the abdominal region, neurohormonal disorders associated with abdominal obesity, and increased activity of the sympathetic nervous system. The relationship between visceral adipose tissue, IR and metabolic disorders has been confirmed. Visceral adipose tissue, unlike adipose tissue of other localization, has greater innervation, a wider network of capillaries and is directly connected to the portal system. Visceral adipocytes have a high density of b-adrenoceptors (especially b3-type), corticosteroid and androgen receptors and a relatively low density of a2-adrenoceptors and insulin receptors. These features determine the high sensitivity of visceral adipose tissue to the lipolytic action of catecholamines and the low sensitivity to the antilipolytic action of insulin, ensuring proper susceptibility to hormonal changes that often accompany abdominal obesity. Hormonal disorders associated with visceral-abdominal obesity: increase in cortisol, testosterone and androstenedione in women, decrease in progesterone and testosterone in men, decrease in somatotropin hormone, increase in insulin and norepinephrine. They primarily contribute to the deposition of fat mainly in the visceral area, as well as directly to the development of IR and metabolic disorders. Intensive lipolysis in visceral adipocytes leads to the release of a large amount of free fatty acids, mostly into the portal circulation. In the liver, they prevent the binding of insulin by hepatocytes, leading to the development of IR at the level of the liver, a decrease in the extraction of insulin by the liver, and the development of systemic hyperinsulinemia. In turn, hyperinsulinemia due to impaired autoregulation of insulin receptors increases peripheral IR. Free fatty acids also inhibit the inhibitory effect of insulin on gluconeogenesis, contributing to an increase in glucose production by the liver. In muscle tissue, according to Randle's hypothesis, free fatty acids compete with the substrate in the glucose-fatty acid cycle, reduce glucose utilization by myocytes, which also contributes to the development of hyperglycemia and compensatory hyperinsulinemia. Adipose tissue performs auto-,

para- and endocrine functions and secretes a large number of substances that have various biological effects, which can lead to the development of obesity-related complications, including IR. Leptin, secreted mainly by adipocytes, exerts its influence at the level of the hypothalamus, regulating eating behavior and activity of the sympathetic nervous system, as well as a number of neuroendocrine functions. In the liver, leptin can inhibit the effect of insulin on gluconeogenesis by affecting the activity of phosphoenolpyruvate carboxykinase, an enzyme that limits the rate of gluconeogenesis. Leptin has an inhibitory effect on the tyrosine phosphorylation of CIP-1 in muscle tissue. Also, leptin is able to increase glucose uptake by fat cells. Of the external factors that negatively affect the sensitivity of tissues to insulin, hypodynamia and excessive consumption of fats are the most important. Hypodynamia is accompanied by a decrease in translocation of glucose transporters (GLUT-4) in muscle cells. Excessive consumption of animal fats containing saturated fatty acids leads to structural changes in the phospholipids of cell membranes and disruption of the expression of genes that control the delivery of the insulin signal inside the cell, that is, to the development of IR. Hypertriglyceridemia, especially postprandial, is often observed in patients with abdominal obesity and is accompanied by excessive deposition of lipids in muscles. This disrupts the activity of enzymes involved in glucose metabolism, that is, leads to IR. This is far from a complete list of possible mechanisms of IR development in abdominal-visceral obesity, which necessitates further research in this field.

Conclusions. In overweight people, biologically active substances of adipocytes stimulate the development of insulin resistance, which contributes to the development of metabolic syndrome and cardiovascular diseases. The property of insulin to decrease hepatic glucose production, inhibit the lipolytic rate of adipose tissue, stimulate skeletal muscle glucose uptake, inhibit breakdown, and increase protein synthesis is critical for maintaining metabolic function. Understanding these regulatory mechanisms and the changes that contribute to dysfunction lay the foundation for better metabolic and immune support for patients.

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