Current Aspects Of The Pathogenesis Of Insulin Resistance Development

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ABSTRACT

The article is devoted to the study of the diet of schoolchildren and their health. Nutrition is one of the main factors that determine not only the quality of life, but also the conditions for a child's development. It is known that any deficiency, especially protein and vitamin deficiency, can slow down growth processes and worsen the psychophysiological state of the developing organism.

Keywords: primary school students, vitamins, proteins, carbohydrates, rational nutrition, proper nutrition.

In contemporary medicine, the issue of type 2 diabetes (T2D) is considered one of the most pressing and socially significant concerns. T2D and its associated conditions, notably abdominal obesity, rank among the leading causes of mortality in the population.

The relevance of epidemiological studies of insulin-dependent diabetes mellitus (IDDM) is primarily due to the fact that it accounts for 85-90% of all diabetes cases. A second important factor is that the actual prevalence of IDDM is 2-3 times higher than its recorded prevalence due to underreporting. These two factors not only underscore the medical and social significance of IDDM among other forms of diabetes, but also among chronic non-communicable diseases. Insulin resistance refers to a disturbance in the metabolic response to endogenous or exogenous insulin. This condition leads to an elevated insulin concentration in the blood plasma compared to physiological levels for the prevailing glucose concentration. The concept of insulin resistance applies to all physiological effects of insulin, including its influence on protein and lipid metabolism, as well as the state of vascular endothelium. Resistance can develop towards one insulin effect independently of others, as well as in combination.

Since 1988, the World Health Organization (WHO) has been collecting standardized information on the prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) among adults aged 30-64 worldwide. Preliminary data suggests that diabetes is either completely absent or very rare among certain populations in Melanesia, East Africa, South America, and among indigenous populations in

the North. In populations of European descent, the prevalence of DM ranges from 3-15%, slightly higher (15-20%) in groups of immigrants from India, China, and individuals of Spanish descent. The highest rates have been reported among the Pima Indians in Arizona (USA) and urbanized Micronesians in Nauru. In individuals aged 30-64 years, the prevalence of NCDs was found to reach 50% [5, 20]. In European populations and among the white population in the USA, the prevalence of NCDs ranges between 10-20%, while it reaches 30% among Arabs in Oman and the black population in the USA. NCDs are detected in one-third of the adult population in populations such as Chinese in Mauritius, Indian immigrants, urban Micronesians, and in two-thirds of the adult population of Pima Indians and inhabitants of Nauru. These data led a group of WHO experts on diabetes to draw the following conclusions: there is an epidemic of NCDs among the world's adult population; the increase in NCD prevalence is likely related to lifestyle characteristics and ongoing socio-economic changes; the greatest risk of NCD development is observed in populations of developing countries, as well as in ethnic minority populations and low-income groups in industrialized countries. Based on this, NCDs are becoming not only a disease of the few.

From a pathophysiological standpoint, insulin resistance (IR) is considered a condition characterized by a reduced response of peripheral tissue target cells to the biological action of the hormone insulin [Demidova, Zenina, 2019; Gutiérrez-Rodelo et al., 2017]. The main biological effects of insulin at the cellular level include facilitating membrane glucose and ion transport, regulating enzyme activity to promote anabolic processes (glycogenesis, lipogenesis, and protein synthesis), and inhibiting catabolic processes. Insulin also plays a role in maintaining optimal levels of free fatty acids (FFA) in the blood. The mechanism of insulin action at the cellular level in insulin-dependent tissues (skeletal muscle, adipose tissue, and liver tissue) is the most extensively studied. It is known that insulin increases the uptake of glucose by muscle and adipose tissues, promotes glycogen formation in the liver and muscles, while inhibiting the formation of glucose from non-carbohydrate products, thereby reducing gluconeogenesis. By suppressing the activity of enzymes that break down glycogen, insulin also inhibits glycogenolysis. Literature describes the mechanism of glucose entry into cells, which depends on the involvement of proteins known as carriers, whose activity is regulated by insulin. For instance, the primary glucose carrier in muscle and adipose tissues is GLUT-4 transporter, which, in the absence of insulin, is located in cytosolic vesicles. However, in the presence of insulin, its molecules transition to the plasma membrane, facilitating glucose transport into the cell. Conversely, when insulin levels decrease, the glucose transporter returns to the cytosol, halting glucose transport accordingly [Haddad et al., 2020]. In adipose tissue with a high density of insulin receptors, the most important biological effects include increased formation of adipose tissue under its influence - lipogenesis, and decreased breakdown of adipose tissue - lipolysis.

The crucial anabolic effects are realized through its influence on protein metabolism. Thanks to the influence of insulin, the absorption of amino acids by tissues is enhanced, thereby increasing protein synthesis (Dedov et al., 2017). It is important to note that the biological role of insulin is not limited to its influence on basic metabolic processes; its involvement in cell division and proliferation is known, neuroendocrine mechanisms of insulin influence on neurogenesis have been described, its neuroprotective properties have been studied, and its role in regulating cognitive processes and eating behavior has been recognized [Spinelli et al., 2019; Sposato et al., 2019]. A vivid example of the multifaceted effects of insulin is evident in the endothelium of blood vessels, where its action is directed towards reducing vascular tone and diminishing tissue ischemia. It is understood that insulin in endothelial cells stimulates the activity of several enzymes, which increase the synthesis of nitric oxide (NO). Through the involvement of NO in smooth muscle cells (SMCs) located in the vessel wall, a mechanism involving secondary messengers is activated:

guanylate cyclase enzyme is activated, stimulating the synthesis of cGMP, which subsequently triggers protein phosphorylation and contributes to the decrease in calcium levels in cells. Changes in the level of calcium in the cytoplasm of vascular smooth muscle cells lead to relaxation of the smooth muscles and inhibition of platelet aggregation. This results in the dilation of blood vessels and a decrease in peripheral blood pressure, demonstrating a vasodilatory effect. Additionally, by reducing the aggregation of blood elements within the vessel lumen, an antiplatelet effect is achieved. Consequently, impaired sensitivity to insulin in the blood vessels can increase peripheral vascular resistance due to spasm, enhance platelet aggregation in the vessel lumen, and ultimately raise blood pressure, disrupt microcirculation, lead to tissue ischemia, and increase the risk of thrombus formation. [Brozovich, 2016]. The action of insulin in cardiomyocytes can be divided into two main functions: energy production and anabolic processes. The energy function is carried out through GLUT-4, which facilitates the transport of glucose into cardiomyocytes. The anabolic function involves processes such as glycogen synthesis, lipid metabolism, protein synthesis, growth, contractility, and apoptosis [Gutiérrez-Rodelo et al., 2017]. Therefore, even a brief overview of insulin's key actions in various organs and tissues underscores the importance of maintaining good tissue sensitivity to this hormone for the normal functioning of individual cells, tissues, and organs as a whole. Insulin, a peptide hormone containing 51 amino acids in its chemical structure, plays a crucial role in regulating these physiological processes. The gene encoding the primary structure of insulin precursor is located on the short arm of chromosome 11. Insulin structure consists of an A chain with 21 amino acids and a B chain with 30 amino acids. The mechanism of insulin synthesis in the β-cells of the pancreatic islets is well understood and occurs in specific stages: first, preproinsulin is synthesized, which transforms into proinsulin; both these metabolites are inactive. Subsequently, transformation into the active hormone, capable of acting on organs and tissues, occurs. It is important to note that insulin synthesis and secretion are not directly linked processes, as insulin production depends on blood glucose levels and is specifically stimulated by glucose [Zhu et al., 2017]. The secretion of insulin depends on calcium ions (Ca^{2+}), specifically, it is stimulated by Ca2+ ions. Therefore, even with high levels of glucose, if the Ca^{2+} level is low, insulin secretion will also be low [Hyeon-Jeong et al., 2018]. Insulin receptors located in insulin-dependent tissues consist of 4 subunits connected by disulfide bonds. There are 2 alpha subunits located practically outside the membrane, while 2 beta subunits penetrate the membrane and extend into the cytoplasm. Insulin binds with high specificity and interacts with the 2 outer alpha subunits, but due to established enzymatic connections between the subunits, the inner beta subunits undergo autophosphorylation. Thus, the insulin receptor serves as a structural model of an enzyme-linked receptor with internal tyrosine kinase activity. Phosphorylation of the β-subunit of the receptor leads to local activation of tyrosine kinase and induces phosphorylation of other intracellular proteins, including a group known as substrates of the insulin receptor (SIR) 1 and 2. Activated SIR-1, with the help of the enzyme phosphatidylinositol-3-kinase, initiates a signaling pathway that stimulates the translocation of the glucose transporter GLUT-4 from the cytosol to the plasma membrane, facilitating the transmembrane transport of glucose into adipose and muscle cells. Understanding possible disruptions in insulin synthesis processes, changes in its chemical structure, receptor abnormalities, or malfunctions in the action of intracellular insulin mediators helps identify levels of insulin resistance: pre-receptor, receptor, and post-receptor [Demidova, Zenina, 2019]. The pre-receptor level involves all abnormalities prior to the action of insulin on the cell itself. These abnormalities can be caused by a mutation in the encoding gene, a disruption in the synthesis of insulin precursors by β-cells of the islets of Langerhans, as well as a disturbance in the chemical structure of the active insulin itself, which in this case cannot be recognized by the receptor. Accordingly, in the receptor

mechanism of insulin resistance formation, changes occur at the level of insulin receptors located on the insulin-dependent tissues' cells. This can be associated with either a decrease in the total number of insulin receptors on such cells or with a defect in the structure of the receptors themselves, preventing them from properly recognizing insulin of normal structure. However, the majority of disruptions in insulin action occur at the post-receptor level, which is associated with structural or functional changes in intracellular proteins that act as secondary messengers. For instance, when examining the mechanisms of tissue insensitivity to insulin separately at the level of muscle, adipose, and hepatic tissues, it has been established that muscle tissue insulin resistance is due to impairments at the intracellular glucose transporter GLUT-4 level, resulting in a deficit in glucose uptake and utilization by myocytes [Sushko et al., 2019]. At the same time, muscle insulin resistance is associated with the accumulation of excess free fatty acids (FFAs), which serve as a substrate for the excessive synthesis of triglycerides (TGs). This finding was established through in vitro muscle biopsy studies, leading to the conclusion that hypertriglyceridemia specifically contributes to impairments in function and a reduction in the quantity of intracellular glucose transporters GLUT-4. In this scenario, TGs act as non-hormonal insulin antagonists [Пашенцева и др., 2017]. In the mechanisms of liver insulin resistance (IR), several pathological moments can be distinguished. Firstly, despite compensatory hyperinsulinemia (HI), insulin does not exert a suppressive effect on hepatic gluconeogenesis due to decreased tissue sensitivity to insulin, leading to uncontrolled increase in glucose production by the liver. Secondly, excessive synthesis and influx of free fatty acids (FFAs) into the bloodstream block the processes of glucose phosphorylation, leading to activation of gluconeogenesis, exacerbating IR. As a result of these pathological processes, there is an increase in blood glucose levels, which in turn enhances insulin secretion by β-cells, forming a "vicious cycle". Furthermore, in the context of insulin resistance due to changes in the activity of enzymes such as lipoprotein lipase and hepatic triglyceride lipase, pathological alterations in the lipid profile occur as a result of increased synthesis and secretion of very low-density lipoproteins (VLDL), elevated levels of low-density lipoproteins (LDL), and decreased levels of high-density lipoproteins (HDL). It has been established that the severity of insulin resistance is associated with intracellular lipid accumulation, as intracellular lipids disrupt the signal transduction from the insulin receptor and reduce insulin-dependent glucose uptake in insulin-sensitive tissues, exacerbating insulin resistance and leading to the development of type 2 diabetes mellitus (T2DM). The deposition of triglycerides in clusters in the pancreatic islets due to elevated levels of serum triglycerides has a lipotoxic effect on β-cells, leading to impaired insulin secretion [Pashentseva et al., 2017]. The accumulation of triglycerides and glycerol in the body is a result of the loss of insulin's anti-lipolytic action due to adipose tissue insulin resistance. Literature also suggests a link between insulin resistance and inflammation of adipose tissue. Morphological changes in adipose tissue cells such as cellular infiltration, increased adipocyte hypertrophy, fibrosis, and changes in microcirculation are observed in obesity. Elevated levels of nonspecific inflammatory markers in the blood (such as C-reactive protein, fibrinogen, and leukocytes) are also significant. Furthermore, alterations in the synthetic function of adipocytes have been observed, as they gain the ability to synthesize immune complexes and cytokines (TNF-α, IL-6), triggering the inflammation process [Pashentseva et al., 2017; Herold, Kalucka, 2021]. It is also important to consider the genetic predisposition to insulin resistance (IR). This is evidenced by the findings of a study involving patients with type 2 diabetes (T2D), in whom point mutations in the encoding gene of SIR-1 were detected. The results of these studies have identified five classes of such mutations: 1) leading to a decrease in the biosynthesis rate of insulin receptors; 2) impairing intracellular transport and post-translational processing; 3) causing defects in insulin binding; 4) accompanied by a decrease in receptor tyrosine kinase activity; 5)

accelerating insulin receptor degradation [Gutiérrez-Rodelo et al., 2017]. Recent literature has highlighted the link between vitamin D deficiency and the risk of reduced insulin sensitivity, which can predict the development of metabolic syndrome (MS), impaired glucose tolerance (IGT), and the onset of type 2 diabetes (T2D) [Egshatyan, 2018]. From the above, it can be inferred that the pathogenesis of insulin resistance (IR) is multifactorial and complex, drawing the attention of clinicians due to the numerous associated diseases and pathological conditions, primarily abdominal obesity (AO), MS, and T2D [Demidova et al., 2020]. The presence of insulin resistance (IR) in such patients may increase the risk of cardiovascular diseases (CVD) [Munwar., Ilango, 2020], as IR is pathogenetically linked to hyperglycemia, hyperinsulinemia, dyslipidemia, hypertension, endothelial dysfunction, chronic inflammation, heightened platelet reactivity, and hypercoagulability. Impaired insulin action is considered the primary pathophysiological defect in patients with type 2 diabetes (T2D) [Artyomuk, Tachkova, 2021]. The attention of practicing specialists to the issue of insulin resistance (IR) is driven by the necessity of early recognition to prevent the development of numerous pathological conditions associated with disruptions in the physiological mechanisms of insulin's impact on the body's key metabolic processes. The problem of IR calls for a comprehensive approach and collaboration among representatives of various medical specialties. In gynecological practice, IR is viewed as a key factor in the pathogenesis of polycystic ovary syndrome (PCOS), often observed concurrently with elevated levels of fasting blood sugar and abdominal obesity [Zhou et al., 2017; Drevale, 2018]. Insulin resistance (IR) can be both a consequence and a pathogenetic component of a variety of endocrine disorders, such as erectile dysfunction in men, thyrotoxicosis, hypothyroidism, Cushing's syndrome, acromegaly, pheochromocytoma, among others. Timely diagnosis of IR and its appropriate treatment in these conditions can help prevent unwanted consequences. Among the non-endocrine disorders associated with IR, ischemic heart disease (IHD), hypertension (HTN) with disturbances in lipid, carbohydrate, and purine metabolism, chronic kidney disease (CKD), liver cirrhosis, rheumatoid arthritis, gout, chronic heart failure (CHF), sepsis, and Alzheimer's disease are also considered [Ormazabal et al., 2018]. Early detection of insulin resistance in patients is of great importance due to the potential for timely therapeutic intervention and primary prevention of carbohydrate metabolism disorders, prevention of atherosclerosis development and progression, as well as the formation of cardiovascular pathology and other mentioned diseases and pathological conditions.

Conclusion: In conclusion, insulin resistance (IR) is a physiological process that acts as a compensatory reaction, often aimed at protecting the body from various stress factors. However, in the presence of genetic predisposition and the influence of risk factors, IR takes on a pathological direction, contributing to the development of type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, and other serious illnesses. The challenge lies in navigating the fine line between physiological and pathological processes and, most importantly, in effectively managing IR. The answers to these questions are still to be found in modern science. Insulin resistance is accompanied by disruptions in carbohydrate, protein, and lipid metabolism, leading to dysfunction of various organs and tissues and resulting in multimorbidity. Various methods for assessing insulin resistance have been proposed, and research is underway to discover new, effective treatment methods. However, despite the abundance of literature on this issue, optimal approaches to overcoming the pathological direction of insulin resistance have not yet been defined. It is evident that a comprehensive pathogenetic approach is necessary for correcting insulin resistance. Currently, in the arsenal of IBD treatment, there are medications with proven efficacy. However, none of them can independently target all mechanisms of pathological events. Achieving the goal requires a combination therapy in

conjunction with a balanced diet and dosed physical activity.

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