METABOLIC CHANGES / INSULIN RESISTANCE IN TUBERCULOSIS PATIENTS: CAUSE OR EFFECT (REVIEW)

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Abstract

This review article contains current scientific literature data about the impact of infectious diseases, tuberculosis particularly, on the formation of systemic insulin resistance in patients. A number of immune reactions have been reported in the host body in response to tuberculosis infection, which may lead to the development of hyperglycemia in Tuberculosis (TB) patients. Some authors believe that such disorders are transient and disappear after a course of specific treatment, others are inclined to believe that tuberculosis can cause diabetes in people who have not previously suffered from it, and long-term impairment of carbohydrate metabolism that occurs under the time of active tuberculosis process forms a vicious circle in which insufficiently controlled blood glucose levels can lead to aggravated TB and provoke complications in the form of cardiovascular disorders. Also, we found data on the transformation of latent disorders of carbohydrate metabolism in manifest diabetes mellitus during 1-4 years of follow-up of patients with tuberculosis.

Key words: *tuberculosis, carbohydrate metabolism, insulin resistance.*

Tuberculosis (TB) is one of the most dangerous infectious diseases with high mortality rates. According to the World Health Organization (WHO), global efforts to combat this formidable disease since 2000 have saved approximately 53 million lives and reduced mortality by 37%. However, in 2018, TB was recognized as the infectious disease that caused the highest number of deaths. Thus, there were 10 million cases and 1.6 million deaths from TB in the world [1]. According to the literature data, mycobacterium tuberculosis (MTB) infects a third of the world's population, of which about 10% can develop active disease throughout life [2, 3, 4].

However, the risk of active TB increases significantly among people who have such risk factors as comorbidities, pathological conditions or harmful habits that weaken the body's defenses. The five most significant risk factors for TB, according to the WHO experts, include:

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HIV infection, malnutrition, diabetes mellitus (DM) and harmful habits (smoking and alcohol abuse). Thus, HIV-infected people suffer from TB 20 times more often than the population without comorbidities, people with malnutrition have TB on average three times more often, and patients with DM are 2.3 - 4 times more likely to develop TB [5, 6, 7, 8, 9]. At the end of 2017, there were about 36 million people living with HIV in the world, while the number of people with DM was almost 13 times higher - 460 million people [1, 10]. The incidence of DM is growing every year. Thus, according to experts of the International Diabetes Association (IDA), in 2045 the number of patients with DM may reach 629 million [1, 10, 11]. Therefore, despite the fact that the individual risk of TB in patients with DM is much lower than the risk in people with HIV/AIDS, in countries with a high burden of DM, this disease plays a key role in controlling the incidence of TB.

Comorbidity of TB/DM is no less important issue for our country. According to the Center for Public Health of the Ministry of Health of Ukraine, in 2016 the incidence of combined TB/DM in Ukraine reached 2.5 per 100 thousand

population (detected 1 044 cases), which is about 3.1% of the total number of detected TB cases, and in 2015 this percentage was 2.7%. Also, the number of cases of combined pathology among patients with multidrug-resistant TB has increased: DM as a concomitant disease was detected in 4.2% of patients in 2016 as opposed to 3.7% in 2015 [10, 11].

Diabetes mellitus is a recognized risk factor and background disease that complicates the course of TB and its treatment process, reduces the effectiveness of therapy and causes early relapses of TB [5, 7, 12, 13]. There is an opinion about the two-way relationship between these two diseases [14, 15, 16], but there is no consensus on whether TB can cause DM.

From the time of infection with MTB to the development of active disease, the patient's body undergoes a number of immunological reactions aimed at destroying the foreign infectious agent. These include the synthesis of proinflammatory and anti-inflammatory cytokines, the release of nitric oxide and reactive oxygen species by macrophages [17, 18]. The pathogenesis of DM associated with obesity is also due to increased secretion of proinflammatory cytokines, formation of reactive oxygen species and nitric oxide, which cause insulin resistance and hyperglycemia [19]. Therefore, identical immune reactions that occur in the host body in response to the penetration of the MTB, may be the basis for the development of hyperglycemia in TB patients [4]. Some authors believe that such disorders are transient in nature, disappearing after a course of specific treatment [20]. Other authors are of the opinion that TB can cause DM in people who have not previously suffered from it, and longterm disruption of carbohydrate metabolism during active tuberculosis creates a vicious circle in which insufficiently controlled blood glucose levels can lead to aggravated TB and provoke complications in the form of cardiovascular disorders. There are data on the transformation of latent disorders of carbohydrate metabolism in manifest DM in 22% of cases during 1-4 years of follow-up of TB patients [21].

Another risk factor for TB is prediabetes, which is also associated with a high risk of developing DM with an annual progression of 510% [22, 23]. Prediabetes is a disorder of carbohydrate metabolism that precedes the manifestation of diabetes and is defined as an intermediate state of hyperglycemia with a glucose level higher than normal, but lower than the diagnostic level of DM. This term was introduced by the American Diabetes Association (ADA) in 1997 and has been officially used since 2005. This condition contains several levels: fasting blood glucose disorders, impairred glucose tolerance and prediabetes itself [24]. Diagnostic criteria for prediabetes vary in different countries, thus the data on its prevalence can vary widely [25]. But despite these differences, estimates suggest that the number of people with prediabetic carbohydrate metabolism is growing rapidly in all parts of the world. According to the CDC (US Centers for Disease Control and Prevention), in 2016 there were nearly 86 million adult prediabetic adults in the United States alone, 90% of whom were unaware of the problem. Unfortunately, there are no statistics on prediabetes in Ukraine, although, according to the maximum forecasts of the International Diabetes Association (IDF 2017), its prevalence is about 10% among the adult population. In total, about 7.8 million people in Ukraine suffer from DM and prediabetes [10, 24, 26]. Scientists around the world are increasingly recognizing prediabetes as a serious metabolic condition that not only predicts a high probability of DM in the future, but also increases the risk of many diseases that often accompany diabetes: diabetic retinopathy, neuropathy, nephropathy and macrovascular complications [27, 28]. Prediabetes is included in the International Classification of Diseases, 10th revision and assigned the code R 73.09, which indicates "prediabetes" as a separate pathological condition [29]. In the vast majority of people (70%) suffering from prediabetes, the risk of DM persists for life and only in 25% of cases there is a transformation of prediabetes into type 2 DM within the next 3-5 years [30, 31]. Prediabetes is associated with coexisting insulin resistance and pancreatic β-cell dysfunction, which usually develop before the onset of dysglycemic disorders [32, 33].

Today, the problem of carbohydrate metabolism disorders in TB patients is the subject of study by many scientists around the world. According to the modern scientific literature, disorders of carbohydrate metabolism in the form of prediabetes are diagnosed in 27.0% -

37.5% of TB patients [34, 35, 36, 37]. The authors point to the important role of glycosylated hemoglobin as a prognostic marker of the clinical course of pulmonary tuberculosis and the results of its treatment [38].

Under physiological conditions, the body of a healthy person strictly controls the fluctuations in glucose levels during the day. The concentration of glucose in plasma depends on the relative rate at which glucose circulates in the blood, as well as the rate of its distribution at the level of target cells [39, 40]. The processes of regulation of glucose homeostasis on an empty stomach and in the postprandial period are under multilevel multihormonal control and have a number of significant differences. About half of the glucose that enters the systemic human bloodstream on an empty stomach is formed by glycogenolysis (breakdown of glycogen deposited in the liver), the other half is newly synthesized (during gluconeogenesis) glucose molecules. The substrate for the formation of such glucose is lactate, glycerin, alanine and other amino acids, and the only organs capable of gluconeogenesis in humans are the liver and kidneys (due to the fact that they contain significant amounts of the enzyme glucose-6-phosphatase). Studies in recent years have shown that in the post-absorption period, the human liver and kidneys synthesize almost the same amount of glucose. Thus, after nocturnal fasting, 75-80% of glucose synthesized by the liver and 20-25% of glucose synthesized by the kidneys enter the systemic bloodstream. Glycogen stores in the liver are quite limited and after 48 hours of fasting almost all the glucose circulating in the bloodstream is the result of gluconeogenesis. It is important to note that the liver and kidneys use different substrates that are precursors of gluconeogenesis and have different hormonal regulation of de novo glucose synthesis. Although lactate is the main substrate of gluconeogenesis in both organs, the kidneys use mainly glutamine and the liver uses alanine [40]. Insulin inhibits glucose synthesis by both organs, while glucagon stimulates glucose production only by the liver, due to glycogenolysis. Catecholamines directly affect the production of glucose by the kidneys, although they may indirectly affect the synthesis of glucose by both the kidneys and the liver by increasing the availability of gluconeogenic substrates and suppressing insulin secretion. Cortisol, growth hormone, and thyroid hormones have a long-lasting stimulating effect on hepatic glucose production (within a few days) [40]. Suppression of endogenous glucose synthesis prevents the development of hyperglycemia after meals. Insulin plays a leading role in suppressing glucose production in the liver, which is responsible for disposing of more than a third of the oral glucose load in healthy individuals [41]. The rest of the glucose coming from the intestines enters the general bloodstream. About 2/3 of its amount is absorbed by muscles and adipose tissue, due to increased permeability of muscle and fat cell membranes for glucose under the influence of high concentrations of insulin. Glucose in the muscles is stored in the form of glycogen, and in fat cells it is converted into fat. The rest of the glucose from the general bloodstream is absorbed by other (noninsulin-dependent) cells. Hepatic gluconeogenesis is also slowed down and glucose molecules obtained as a result of this transformation pathway usually do not enter the systemic circulation, but largely go to the synthesis of glycogen in the liver. Renal gluconeogenesis is approximately doubled after a meal and accounts for about 60% of endogenous glucose production [42].

Acute infectious diseases lead to deep metabolic disorders of the macroorganism. All types of metabolism are involved in the pathological process: carbohydrate, lipid, protein and amino acid metabolism. One of the manifestations of the impact of an infectious agent on the human body is stress hyperglycemia.

Against the background of severe hyperglycemia, the process of glycosylation of proteins is activated, including transport proteins and insulin receptor proteins, which leads to their dysfunction. In addition, there is also a decrease in the absolute number of receptors on the cell membranes of insulin-sensitive tissues. Thus, despite the presence of hyperglycemia, insulin-dependent tissues lack energy substrates. The predominance of anaerobic breakdown of glucose over aerobic leads to depletion of glycogen stores in the liver, hyperlactataemia and increased oxidative stress, which, in turn, helps maintain hyperglycemia [43]. It has been experimentally proven that airway inflammation, which occurs during a number of lung diseases, even in patients

without overweight and manifestations of systemic hypoxemia, can lead to systemic insulin resistance (IR) [43]. The definition of insulin resistance was first proposed in 1998. According to experts of the association, IR is a violation of the biological response (metabolic and molecular genetic) to insulin (exogenous and endogenous); disorders of metabolism of carbohydrates, fats, proteins; changes in DNA synthesis, regulation of gene transcription, processes of differentiation and growth of cells and tissues of the body [43].

Hyperinsulinemia of any origin leads to the formation of insulin resistance. In conditions of excess insulin, all tissues that have insulin receptors, including β-cells of the pancreas, are involved in the pathological process. Defective transmission of insulin signal in β-cells disrupts glucose-stimulated insulin release. Hyperinsulinemia generates and maintains insulin resistance regardless of the underlying pathology. Hyperinsulinemia, insulin resistance, and impaired glucose-stimulated insulin release are biologically related. In this case, one process (hyperinsulinemia) can generate all three others simultaneously [44, 45]. It has been proven that hyperinsulinemia and IR have a detrimental effect on the body, even in people without impaired glucose tolerance. Thus, a number of researchers reported that fasting plasma insulin levels above 39 μg IU/ml or more were associated with an increased risk (31%) of cardiovascular events in people without diabetes. IR is the initial link in the process of transition from normal glycemia to impaired glucose tolerance and diabetes [45]. As long as the β-cells of the pancreas are able to produce enough -

insulin and maintain a state of hyperinsulinemia, hyperglycemia will be absent. However, depletion of β-cell reserves causes a state of relative insulin deficiency, which is manifested by an increase in blood glucose levels. As a result, the main metabolic processes in the body - carbohydrate, lipid and protein metabolism, growth, differentiation, DNA synthesis, regulation of gene transcription, and so on - are disrupted. Glycemic parameters have a steady upward trend. First, the level of glycemia increases after a meal (postprandial hyperglycemia), then - the level of fasting blood glucose. Impaired glucose tolerance (latent diabetes) can progress and lead to the development of overt DM [46].

Conclusion.

Thus, the data of scientific literature showed that tuberculosis violates carbonhydrate methabolism, causing insulin resistance and in some cases may even provoke the development of diabetes mellitus in patients.

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The author has no ethical conflicts to disclosure.
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The author gives her consent to publication.
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