NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES: THE PROBLEM OF ASSOCIATION AND STAGES OF DEVELOPMENT

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Annotation: The wide prevalence of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (DM2), as well as their relationship, determines the need for targeted consideration of this pathology in order to optimize approaches to the diagnosis and treatment of patients with NAFLD and type 2 diabetes. Being components of the metabolic syndrome, these two diseases have largely similar mechanisms of development and progression, synergistically increasing the risk of adverse outcomes in comorbid patients. Despite the commonality of pathophysiological mechanisms, the question of the sequence of development of NAFLD and T2DM remains relevant.

Based on the results of the analysis of the literature, two main theories were identified: alimentary and metabolic. According to the alimentary theory, the primary link in the pathogenesis is obesity and the associated excessive accumulation of free fatty acids and triglycerides in the liver, which subsequently leads to insulin resistance and the development of type 2 diabetes. In contrast, the metabolic theory considers the insulin resistance associated with diabetes to be the primary blow, which, regardless of obesity, creates the prerequisites for liver damage. In addition, the review pays special attention to the consideration of a new concept - metabolically associated fatty liver disease (MAFLD), considered as a hepatic component of the metabolic syndrome. Within the framework of this concept, various clinical phenotypes of NAFLD are distinguished, which determine the path along which the diseases under consideration develop. In conclusion, the review discusses pathogenetically based therapy, which focuses on overcoming insulin resistance, correcting atherogenic dyslipidemia, and restoring the structure and function of liver cells.

Keywords: non-alcoholic fatty liver disease, type 2 diabetes mellitus, obesity, insulin resistance, metabolic syndrome, FAFLD

We live in an era when infectious diseases as the main causes of death in economically developed

countries have been replaced by chronic non-communicable diseases, among which a significant place is given to cardiometabolic pathology. Massive urbanization and the rapidly changing way of life in connection with this could not but affect the health indicators of the population. The heavy burden of metabolic disorders and their consequences is forcing doctors of all specialties to increasingly raise this topic [1].

In 1922 G.F. Lang concluded that there is a clear relationship between arterial hypertension and obesity, disorders of carbohydrate metabolism and gout, which was later confirmed by numerous studies [2][3]. Later, in 1988, G.M. Reaven introduced the concept of "metabolic syndrome X", which included insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipoproteinemia, hypertriglyceridemia, and arterial hypertension [4].

Today, the accumulated knowledge allows us to take a much broader look at the problem of metabolic syndrome (MS), to focus on certain risk factors and to choose more personalized approaches to diagnosis and treatment. This review analyzes current theories of the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (DM2), which focus on insulin resistance and obesity. The literature was searched for the keywords "non-alcoholic fatty liver disease", "type 2 diabetes mellitus", "insulin resistance" and "obesity" in the Pubmed and Elibrary.ru databases for the period from 1998 to 2021.

NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES AS COMPONENTS OF METABOLIC SYNDROME

One of the diseases associated with MS is NAFLD [5][6]. According to the latest clinical guidelines of the Scientific Society of Gastroenterologists of Russia (NOGR) and the Russian Scientific Medical Society of Therapists (RNMOT), NAFLD is a chronic liver disease of metabolic origin in individuals with no exogenous factors of toxic liver damage, due to the accumulation of lipids in the cellular elements that make up the hepatic lobule, morphologically confirmed by steatosis, steatohepatitis, fibrosis, cirrhosis or adenocarcinoma [7].

To date, the prevalence of NAFLD is 25%, and there is a steady upward trend in this indicator [8]. It is alarming that NAFLD is already leading in the etiology of chronic liver diseases worldwide. However, it often tends to progress to cirrhosis of the liver and hepatocellular carcinoma (HCC), as well as to increase the risk of both overall and liver disease-associated mortality. Moreover, NAFLD and its consequences most often lead to the need for liver transplantation [9]. So, as mentioned above, NAFLD is associated with metabolic disorders, and, according to some data, it itself is MS, being its hepatic component [10][11]. Thus, in 2020, an international expert consensus statement was published offering physicians of all specialties a new definition — MAFLD: Metabolic (dysfunction) associated fatty liver disease [12]. This definition fully reflects both the relationship of fatty hepatosis with metabolic disorders, and the very versatility of this disease, which affects other organ systems and has consequences far beyond the liver. One of the tips of the iceberg of metabolic disorders, actively discussed today in the medical community, is NAFLD, or, as we now have the right to call it, MAFLD. Another equally serious problem associated with MS is DM2. Thus, in 2019, the number of patients with diabetes aged 20 to 79 years was 463 million [13]. At the same time, according to the forecasts of the International Diabetes Federation, by 2030 every tenth adult will suffer from type 2 diabetes. [fourteen]. Associating diabetes with liver diseases, it is worth noting that the incidence of NAFLD among patients with

type 2 diabetes is twice as high as in the general population, which is 55.5% in numbers [15]. It should be noted that in routine endocrinological practice, liver pathology in patients with diabetes often remains in the shadows [16]. The lack of proper vigilance on the part of the primary care physician has its consequences. The combination of these two pathologies not only increases the risk of developing a more severe form of NAFLD and associated hospitalizations, but also makes it difficult to achieve glycemic control in people with diabetes and contributes to the development of atherogenic dyslipidemia [17].

COMMON PATHOGENETIC LINKS IN THE DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES MELLITUS

The cornerstone of the problem of the relationship between NAFLD and T2DM, as mentioned above, are obesity and insulin resistance. While obesity is certainly considered a predictor of many diseases, including cardiovascular disease, coronary heart disease, and some cancers, T2DM is most strongly associated with a high body mass index (BMI). Thus, obesity affects about 44% of people with type 2 diabetes [23]. The other side of the coin is insulin resistance. Underlying DM2, it is one of the essential components of MS [24]. Along with diabetes, NAFLD is also attributed to insulin resistance as one of the main mechanisms for the development of this disease, which is expressed both in the violation of carbohydrate and subsequently fat metabolism, which results in the accumulation of lipids in liver cells [25–27].

ALIMENTARY THEORY

According to one of the modern theories, excessive accumulation of free fatty acids (FFA) and triglycerides (TG) in NAFLD leads to damage to insulin signaling pathways and the development of insulin resistance, which, in turn, leads to a gradual impairment of insulin secretion and manifestation of T2DM [28].

This theory, seemingly simple to understand, easily explains the sequence of stages of the same process, where diabetes is seen as a natural continuation of fatty liver. The described theory can be called alimentary, since, according to it, excessive accumulation of lipids in the liver is associated with their direct intake from outside [29]. Indeed, NAFLD is detected in 100% of patients with abdominal obesity and MS [30], while 20–47% of them have non-alcoholic steatohepatitis (NASH), which is a prognostically more malignant form of NAFLD [31]. In more detail, the mechanism of influence of the alimentary factor and, as a result, obesity on the liver and carbohydrate metabolism is presented as follows.

I. Liver steatosis.

Excessive consumption of food rich in animal fats and easily digestible carbohydrates leads to the flow of large amounts of FFA from the gastrointestinal tract into the bloodstream and then into the tissues. There is an accumulation of lipids, expressed in hypertrophy and hyperplasia of adipocytes. Adipose tissue, having the function of an endocrine gland, changes its secretory activity and begins to produce a large number of inflammatory mediators (tumor necrosis factor-alpha (TNF-α), FFA, interleukin-6, etc.), causing the development of slowly progressive chronic inflammation [32] . This process is also accompanied by excessive intake of FFAs into the portal system and liver. There is an imbalance between the supply of lipids to the liver, their synthesis and utilization, which is manifested by the accumulation of triglyceride-containing fatty

vacuoles in hepatocytes, that is, the development of steatosis [33].

II. Steatohepatitis and insulin resistance.

Inflammatory mediators actively secreted by adipose tissue directly damage hepatocyte membranes, causing activation of cytochrome P450, enhancing lipid peroxidation (LPO) and inducing the development of oxidative stress, which damages liver cells. There is a death of hepatocytes by the mechanism of apoptosis and necrosis, as well as the accumulation of fibrous tissue. Chronic inflammation in the liver gradually leads to the development of NASH [34][35]. At the same time, TNF-α in adipocytes and hepatocytes activates the kappa kinase-beta (IκKβ) inhibitor, which leads to phosphorylation of the type 1 insulin receptor (ISR-1), a decrease in its affinity for insulin and, consequently, to insulin resistance. Insulin resistance is also promoted by excessive intake of FFAs in the liver, which also block the binding of insulin to the membrane of hepatocytes.

The pathogenesis of NAFLD progression and insulin resistance also involves hepatokines produced in the liver - proteins that affect the metabolic process through autocrine, paracrine and endocrine signaling. [36]. Thus, the hepatokine fetuin-A, which is actively synthesized with a pronounced accumulation of FFA in the liver, significantly increases the inflammation of the liver tissue and causes the development of insulin resistance both in the liver itself and in the muscles. This occurs due to the inhibition of the tyrosine kinase activity of the insulin receptor by hepatokine, which leads to a violation of its autophosphorylation and insulin signaling in peripheral tissues. Thus, in a large-scale prospective cohort study EPIC-Potsdam, it was found that fetuin-A is an independent predictor of the development of DM2 [37].

In addition, toll-like receptors (TLRs) may be a possible pathophysiological link in the development of insulin resistance in inflammation. They are like a link between innate, adaptive immunity and cellular damage. A number of in vitro studies show a relationship between TLR4 activity and the development of insulin resistance [38]. FFAs, which are elevated in obesity, are ligands for TLR4. This receptor is expressed by monocytes, which, by infiltrating adipose tissue, become tissue macrophages and secrete chemokines, potentiating inflammation and inhibiting insulin signaling due to IκKβ activation [39]. The state of insulin resistance causes the development of relative systemic hyperinsulinemia, which, on the one hand, is compensatory, providing a kind of overcoming of insulin resistance, and on the other hand, this state enhances metabolic disorders in the body, ultimately leading to the development of DM2 [40].

METABOLIC THEORY

On the other hand, the available evidence that hepatic steatosis is associated with insulin resistance, regardless of BMI, general and abdominal obesity, casts doubt on the alimentary theory, where the primary link in pathogenesis is precisely the imbalance between incoming / synthesized lipids and their utilization, that is, the alimentary factor [41]. According to this theory, peripheral insulin resistance in itself initiates excessive synthesis and accumulation of FFAs in liver cells, creating prerequisites for their further damage and the development of NASH against this background according to the above scheme. A decrease in insulin sensitivity can occur in various ways depending on the tissue: if the density of insulin receptors mainly decreases in adipocytes, then a decrease in tyrosine kinase activity is observed in muscles, which leads to impaired glucose uptake [32].

What is the effect of the effects of insulin on adipose tissue in normal? In insulin-sensitive patients, a postprandial increase in insulin concentration leads to a decrease in lipase activity in adipose tissue, that is, suppression of lipolysis. This is expressed in a decrease in the concentration of FFA in the blood plasma and, as a result, a decrease in the supply of these substrates to the liver. The state of insulin resistance fundamentally changes the situation: insulin-dependent inhibition of lipolysis does not occur, which means that excess FFA "attacks" hepatocytes [42]. In turn, increased intake of long-chain fatty acids in the liver predisposes to the development of hepatic insulin resistance, which is compensated by stimulation of hepatic gluconeogenesis and increased glucose release by the liver [43]. Thus, in parallel with an increase in insulin levels, plasma glucose levels also increase. Simultaneously with the activation of gluconeogenesis in the liver, there is a decrease in glycogen synthesis, as well as β-oxidation of FFA, resulting in the accumulation of triglycerides in hepatocytes. The synthesis of lipids in the liver is stimulated by an excess of long-chain fatty acids entering the hepatocytes. During this synthesis, intermediate lipids are actively formed, providing, along with other mechanisms described above, inflammation and damage to liver cells [44].

In a study by Petersen et al. administration of glucose to insulin-resistant patients induced de novo hepatic lipogenesis, which was not observed in the control group of patients with preserved insulin sensitivity. Also, in patients of the first group, an increase in the level of TG and a decrease in the level of high-density lipoproteins (HDL) in the blood plasma were detected, while inflammatory mediators and the content of intra-abdominal fat did not differ in both groups.

So, according to the metabolic theory, insulin resistance and DM2 alone can cause or exacerbate the course of NAFLD, regardless of the presence of inflammation and abdominal obesity [45].

COMMON SOLUTIONS IN THE THERAPY OF NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES MELLITUS

Application points in the treatment of NAFLD and T2DM are insulin resistance and obesity, including fat in the liver itself [52]. Due to the multicomponent and complexity of the pathology under consideration, the treatment of this cohort of patients is an interdisciplinary approach, the main principles of which should be considered to be overcoming insulin resistance, correcting atherogenic dyslipidemia, reducing fat and restoring liver function.

The importance of non-drug therapy cannot be overestimated. Despite a fairly wide choice of pharmacological drugs on the market, the action of which is aimed at conditions associated with liver pathology, there are no standard, unified approaches to the treatment of NAFLD itself [33]. In addition, none of the drugs under consideration has been evaluated in phase III clinical trials, and therefore one or another pharmacotherapy should be unequivocally recommended with caution, since any prescribed drug will be used off-label in this case [52]. In this regard, lifestyle modification seems to be an obvious and proven effective way to treat NAFLD and T2DM, as well as their combination [53].

Non-drug treatment consists mainly in weight loss, which can be achieved in two ways: by revising the quantitative and qualitative composition of the diet and by increasing the level of physical activity. It should be noted that with a decrease in body weight by 10–15% from the initial level, an increase in the sensitivity of

muscle tissue to insulin, a regression of systemic hyperinsulinemia, and a decrease in the amount of visceral fat already occur [30][54]. Moreover, a number of studies have shown a positive effect of physical activity on fat metabolism and hepatic steatosis even in the absence of significant weight loss and dietary changes [55]. It is important to note that both aerobic and strength training have an advantage over their absence, which allows patients with the considered pathology to choose the most preferred occupation for them and, accordingly, maintain the results achieved in lifestyle modification for a long time [7][52][56]. Thus, physical activity should be considered one of the key moments in the non-drug therapy of insulin resistance and obesity as the main links in the pathogenesis of NAFLD and T2DM. Raising the issue of nutrition, it is worth noting that the ideal and at the same time universal formula does not exist. However, hypocaloric nutrition in overweight patients, as well as correction of the qualitative composition of the diet in people with normal BMI, are necessary conditions that contribute to the normalization of carbohydrate and lipid metabolism [7].

Of course, drug therapy for insulin resistance cannot be imagined without the appointment of insulin sensitizers. These include the drug from the group of biguanides metformin. The main mechanism of their action is to increase the sensitivity of insulin-dependent tissues to insulin due to the activation of cAMP kinase in them, which results in the suppression of gluconeogenesis and an increase in the utilization of glucose by muscle tissue. In addition to affecting carbohydrate metabolism, the biguanide drug metformin has the potential to lead to a decrease in TG accumulation in the liver and a decrease in chronic inflammation associated with obesity in adipose tissue [57]. However, to date, there is not enough evidence in favor of its use in the complex therapy of NAFLD and insulin resistance. More promising is the use of thiazolidinediones and their representative pioglitazone. A number of studies show that against the background of its administration, not only the histological picture of the liver improves, but also the level of alanine aminotransferase normalizes and insulin resistance is corrected. Nevertheless, long-term therapy with pioglitazone raises concerns due to a wide range of possible side effects [52]. It should be noted that drugs of this group (biguanides, thiazolidinediones) are not recommended to be prescribed in the absence of diagnosed prediabetes and diabetes, which limits their use in the group of patients with NAFLD without diabetes [32]. From the point of view of the prevention of cardiovascular diseases in patients with NAFLD and type 2 diabetes, the appointment of lipid-lowering drugs is considered to be pathogenetically justified. The most widely used among them are inhibitors of GMC-CoA reductase (statins). However, it should be noted that, despite the high prevalence of atherogenic dyslipidemia among patients with T2DM and NAFLD, statins should be used with caution due to their increased risk of hepatotoxicity [7][52].

Given the mechanisms of development of fatty hepatosis and diabetes, for which the main target organ is the liver, a promising direction should be considered the correction of hepatocyte function. One of the ways to solve this problem can be the appointment of essential phospholipids (EPL). Their membrane-stabilizing and hepatoprotective action is provided primarily by direct incorporation of EPL molecules into the phospholipid structure of damaged liver cells, resulting in the replacement of defects and restoration of the barrier function of the lipid layer of hepatocyte membranes. Due to a decrease in the viscosity of cell membranes, there is a change in the functional activity of receptor proteins built into the membrane, including insulin receptors [33]. Seven randomized clinical trials have confirmed the long-term beneficial effect of these drugs in the treatment of hepatic steatosis according to liver biopsy, ultrasound and CT [7].

Conclusion. Thus, despite the conjugation of NAFLD and T2DM, the question of the sequence of their development remains open. Based on the metabolic and alimentary theories considered in the review, it can be concluded that the paths and stages of development of DM2 and NAFLD may be different, prevailing depending on the clinical phenotype of the patient. Considering the high frequency of the combination of these diseases as the main manifestations of disorders of fat and carbohydrate metabolism, as well as the possibility of mutual influence of one process on another, one should pay closer attention to both groups of patients and remember that DM2 is not only a violation of carbohydrate metabolism, exactly the same as NAFLD is not limited to disorders of fat metabolism in hepatocytes. Overcoming insulin resistance, correcting atherogenic dyslipidemia, and repairing liver cells would then be the combination that can be used in the majority of affected NAFLD AND T2DM patients.

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