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THE ROLE OF ENDOTHELIAL DYSFUNCTION AND INSULIN RESISTANCE IN THE DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Abstract. The article analyzes literature data on the pathogenetic role of endothelial dysfunction, insulin resistance in the development of complications of metabolic dysfunction associated steatotic liver disease (MASLD), which has been considered by many to be a liver manifestation of metabolic syndrome for many years. Currently, two hypotheses of endotheliopathy development in MASLD are actively discussed. Supporters of the first hypothesis argue that endothelial dysfunction is derivative, that is, secondary to existing insulin resistance. The other hypothesis considers endothelial dysfunction as the cause of insulin resistance and concomitant conditions (hyperglycemia, hypertension, dyslipidemia). Atherosclerotic cardiovascular disease has long been recognized as an inflammatory disease, and the therapeutic benefit of anti-inflammatory drugs in the prevention of cardiovascular diseases has recently been demonstrated. The role of insulin resistance and concomitant hyperinsulinemia consists in direct and indirect atherogenic effects on

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vascular walls. This pathophysiological process is the basis for the development of atherogenic dyslipidemia, a number of hormone secretion disorders and metabolic disorders. Over time, vascular wall remodeling occurs due to thickening of the arterial wall, which leads to an increase in total peripheral vascular resistance with normal smooth muscle tone. The cause is frequent vasoconstrictor effects, in which case the wall of the resistive vessels thickens, which limits local perfusion. The article discusses the pathogenetic mechanisms of the effect of hydrogen sulfide and nitric oxide molecules on the development of complications in MASLD, the role of physical exercise to correct some pathological conditions, and the role of the sympathoadrenal system.

Keywords: metabolic dysfunction-associated steatotic liver disease (MASLD), endothelial dysfunction, insulin resistant, cardiovascular diseases, obesity, hydrogen sulfide, diabetes, physical exercises.

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РОЛЬ ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ТА ІНСУЛІНОРЕЗИСТЕНТНОСТІ У РОЗВИТКУ СЕРЦЕВО-СУДИННИХ УСКЛАДНЕНЬ У ХВОРИХ З МЕТАБОЛІЧНО-АСОЦІЙОВАНОЮ СТЕАТОТИЧНОЮ ХВОРОБОЮ ПЕЧІНКИ (МАСХП)

Анотація. У статті наведено аналіз літературних даних щодо патогенетичної ролі ендотеліальної дисфункції, інсулінорезистентності у розвитку

ускладнень при метаболічно-асоційованій стеатотичній хворобі печінки (МАСХП), яка багатьма вважається печінковим проявом метаболічного синдрому вже багато років. В даний час активно обговорюються дві гіпотези розвитку ендотеліопатії при МАСХП. Прихильники першої гіпотези стверджують, що дисфункція ендотелію є похідною, тобто вторинною щодо наявної інсулінорезистентності. Інша гіпотеза розглядає дисфункцію ендотелію як причину розвитку інсулінорезистентності та супутніх станів (гіперглікемії, гіпертензії, дисліпідемії). Атеросклеротичне серцево-судинне захворювання давно визнано запальним захворюванням, і нещодавно була продемонстрована терапевтична користь протизапальних препаратів у профілактиці серцево-судинних захворювань. Роль інсулінорезистентності і супутньої гіперінсулінемії полягає в прямому і непрямому атерогенному впливі на стінки судин. Цей патофізіологічний процес є основою для розвитку атерогенної дисліпідемії, ряду порушень секреції гормонів і метаболічних розладів. З часом відбувається ремоделювання судинної стінки за рахунок потовщення артеріальної стінки, що призводить до підвищення загального периферичного опору судин з нормальним тонусом гладкої мускулатури. Причиною є часті вазоконстрикторні ефекти, в цьому випадку стінка резистивних судин потовщується, що обмежує місцеву перфузію. У статті розглянуті патогенетичні механізми впливу молекул гідроген сульфіду та оксиду азоту на розвиток ускладнень при МАСХП, роль фізичних вправ для корекції деяких патологічних станів, а також роль симпатоадреналової системи.

Ключові слова: стеатотична хвороба печінки, асоційована з метаболічною дисфункцією (МАСХП), ендотеліальна дисфункція, інсулінорезистентність, серцево-судинні захворювання, ожиріння, сірководень, цукровий діабет, фізичні вправи.

Statement of the problem. The endothelium is a multifaceted, multiregulated active metabolic system whose function is to regulate and maintain vascular homeostasis. This happens through the effect on vascular tone, providing a trophic function for endothelial cells, and also a protective function in case of damage. [1]. Endothelial activation leads to phenotypic changes that include the synthesis and expression of adhesion molecules by which endothelial cells interact with blood cells. Endotheliocytes play a huge role in such stages of development of acute and chronic inflammation as primary vasodilatation; increase in vascular permeability, adhesion, transmigration and activation of leukocytes; angiogenesis and fibroplasia. The mechanism of the endothelium's participation in the emergence and development of various pathological conditions is multifaceted and related not only to the regulation of vascular tone and protection of the integrity of the vascular wall, but also to participation in the processes of atherogenesis and thrombus formation. [2]. Cause a reaction of the endothelial cell: change in blood flow rate (increase in shear

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stress); platelet mediators (serotonin, thrombin, ADP); circulating and/or "intramural" neurohormones (acetylcholine, bradykinin, histamine, catecholamines, endothelin, vasopressin, etc.).

Under physiological conditions, endothelial cells increase the synthesis of a number of substances such as nitric oxide, prostacyclin, endothelium-dependent hyperpolarization factor, which promotes the relaxation of all local smooth muscle structures, in particular the cells of the vascular wall.

The structure and functions of the endothelium in different organs are not the same, and this fact has its own explanations that depend on the main function of the organ. The presence of pro-inflammatory cytokines and pathogenic bacteria forces the liver to increase the synthesis of nitric oxide to protect the body's internal environment. Toxic substances that enter the human body in different ways are also destroyed [3].

The purpose of the article is to determine the role of endothelial dysfunction and insulin resistance in the development of cardiovascular complications in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Main material. There are two hypotheses for the development of endotheliopathy in metabolic syndrome are being actively discussed [4]. The first hypothesis claim that the dysfunction of the endothelium is derivative, that is, secondary to the existing IR, that is, it is a consequence of those factors that characterize the state of IR - hyperglycemia, dyslipidemia, arterial hypertension. If hyperglycemia occurs, the enzyme protein kinase-C is activated in endothelial cells, which disrupts endothelium-dependent relaxation of blood vessels, increasing the permeability of proteins to vascular cells. It is also known that a high level of glucose in the blood activates the processes of peroxidation, the products of which suppress the vasodilator function of the endothelium [5]. With arterial hypertension, increased pressure on the vascular wall mechanically disrupts the architecture of endothelial cells, increases their permeability to albumin, increases the secretion of vasoconstrictor endothelin-1, and remodels the vessel walls. Violation of lipid metabolism contributes to the expression of adhesion molecules on the surface of endothelial cells, as a result of which atheroma begins to form [6]. Thus, all of the above conditions, increasing the permeability of the endothelium, the expression of adhesion molecules, reducing the endothelium-dependent relaxation of blood vessels, contribute to the progression of atherogenesis [7].

The second hypothesis claim that endothelial dysfunction is the cause of the development of IR and associated conditions (hyperglycemia, hypertension, dyslipidemia). After all, in order to connect with its receptors, insulin must pass through the endothelium and enter the intercellular space. Transendothelial transport of insulin is disrupted in the primary defect of endothelial cells. Therefore, the condition of IR may develop. In this case, IR will be secondary to endotheliopathy. To date, the conducted studies are not enough to make a statement about primary or secondary endothelial dysfunction in the development of IR [8]. If the endothelium

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is not damaged, it releases anticoagulants that prevent the growth of vascular smooth muscle, while the diameter of the vessels does not change. The endothelium adsorbs numerous anticoagulants from blood plasma, which promotes adequate blood flow, which is especially important for improving microcirculation [9]. When the endothelium of vessels is damaged, when the layers under the endothelium are exposed, the physiological reactions of aggregation and coagulation are triggered, which aims to prevent blood loss, causes spasm of the vessel, and stops the formation of antiplatelet agents. This mechanism works with short-term exposure to damaging agents, the endothelium prevents blood loss, which is its protective function. But the situation changes with long-term damage. In this situation, the endothelium begins to play a key role in the pathogenesis of a number of systemic pathologies [10]. Thus, in the described situation, platelets can bind to endothelial cells, in which case they can cause leukocytes to stick to the artery wall 11]. It is also known that a high level of homocysteine has a negative effect on endothelial cells [12]. It has been proven that patients with MASLD had a higher level of homocysteine in blood plasma than healthy people [13]. The level of homocysteine is inversely related to the level of vitamin B 12 in blood plasma. [14]. There are also scientific works that describe damage to hepatocytes due to a lack of vitamins, substantiating the pathophysiological mechanisms of this phenomenon. [15, 16].

Recent evidence suggests that MASLD is a novel risk factor for cardiovascular disease and may be considered as part of the pathogenesis of cardiovascular disease [7]. It is interesting to note that the frequency of MASLD is constantly increasing, parallel to the epidemic of obesity and diabetes, although it is not clear whether hepatic steatosis is a cause or a consequence of impaired metabolic status [17].

Mortality of patients with MASLD from cardiovascular diseases is 48% of total mortality, and only 7% from lesions of the liver itself [18].

According to experts, cardiovascular diseases are the leading causes of death in patients with metabolic syndrome [19]. Patients with metabolic syndrome have a significantly higher prevalence of calcified and non-calcified coronary plaques than healthy subjects, regardless of the frequency of metabolic syndrome [20].

A meta-analysis by Italian scientists included 16 unique prospective and retrospective studies involving 34,043 adults (36.3% with MASLD). Approximately 2,600 CVD deaths were identified (> 70% of CVD deaths) during a mean follow-up period of 6.9 years. The risk of cardiovascular events was higher in people who had MASLD than in people without MASLD. The results of a meta-analysis indicate that MASLD is associated with an increased risk of fatal and nonfatal cardiovascular events. However, the observational design of the included studies does not allow drawing causal conclusions [21]. A meta-analysis by Chinese scientists showed that for patients with MASLD. and obesity (according to ethnic-specific BMI measures for obesity) may predict a worse long-term prognosis. And, according to them, obesity cannot be an independent factor in the development of MASH or advanced

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fibrosis in patients with MASLD., and MASH should be considered as a potential target for pharmacological treatment independent of obesity [22,23].

Patients with MASLD have an epicardial accumulation of adipose tissue [24], which acts as a source of pro-inflammatory cytokines and increases the risk of cardiovascular diseases [25]. In addition, the presence of MASLD is strongly associated with an increased risk of aortic valve sclerosis, which is an independent indicator of atherosclerosis [26].

When studying the relationship between the marker of endothelial dysfunction ET-1 and the concentration of high-sensitivity C-reactive protein, the presence of a direct correlation dependence of the average strength was established ($r = 0.58$, $p = 0.0000$) [27]. Literature data show [28] that the intensity of CRP secretion is closely related to the features of lipid metabolism and insulin resistance, which contribute to the development of atherosclerosis and atherothrombosis (due to the development of endothelial dysfunction), but the pathogenetic mechanisms of the development of these processes remain insufficiently studied.

According to modern ideas, vWF is considered a marker of the acute phase of the inflammatory reaction and thrombosis, it interacts primarily with collagen and microfibrils of the subendothelium. An increase in the level of ET-1 and the activity of vWF in blood plasma indicates a violation of the vasoconstrictor and thrombogenic function of the endothelium in patients with MASLD [29].

Nitric oxide is of great interest. It is common knowledge that nitric oxide is produced in the endothelium of blood vessels. But other cells can also synthesize NO, including neutrophils, macrophages, Kupffer cells, and even platelets. The relationship between the severity of endothelial dysfunction and the development of liver fibrosis in MASLD was revealed [30]. It has its own pathogenesis. First, it is a violation of hepatic and systemic blood flow, naturally it is accompanied by parallel stimulation of the sympathoadrenal system. At the same time, there is a further change in the ratio of humoral-metabolic factors, as well as activation of the renin-angiotensin-aldosterone system, the role of which in the process of fibrogenesis has been proven. During the development of liver fibrosis, a morphological rearrangement occurs with the deposition of extracellular matrix components mainly in the subendothelial space of Disse and the perivenular zone of the acini, which leads to the formation of the lower subendothelial basement membrane, which forms a barrier between hepatocytes and hepatic sinusoids. With metabolic syndrome, the destruction of the components of the extracellular matrix decreases and vice versa, their synthesis increases, which is the cause of the development of fibrosis and cirrhosis of the liver [31]. MASLD occurs in 80-90% of obese individuals, 30-50% of diabetic patients, and 90% of hyperlipidemic patients. There are many hypotheses for the pathogenesis of both the metabolic syndrome and MASLD, but there are common underlying pathogenetic components that are present in all theories. These are oxidative stress and IR [32], chronic inflammation [33], changes in adipocytokine secretion [34], endothelial dysfunction [7]. Accumulated data [35]

show that gamma-glutamate transferase (GGT) and alanine aminotransferase (ALT) can also be markers of endothelial dysfunction and atherosclerosis.

The possibility of an etiological link between HGT and cardiovascular mortality is supported by the positive association observed in epidemiological studies between serum HGT levels and CVD risk factors such as diabetes, hypertension, dyslipidemia, and metabolic syndrome [36, 37]. Physiological features of GGT also predict its pathogenetic role in the atherosclerotic process. GGT levels may be indirectly associated with atherosclerosis through concomitant oxidative stress, a well-known mediator of vascular damage. Elevated serum GGT levels may be accompanied by cellular overexpression of GGT to compensate for depleted glutathione as a defense against elevated levels of reactive oxygen species.

There are studies that have shown that the level of GGT is an independent predictor of the development of metabolic syndrome and its components separately [38]. Thus, in a study by Cheung et al., in which 943 people participated, statistical analysis showed that it was the level of GGT, and no other liver enzymes, that was an independent predictor of first-onset hypertension [39].

GGT and ALT were found to be predictors of endothelial dysfunction in patients with NASH. γ-glutamyltransferase is an important enzyme involved in the metabolism of extracellular glutathione, which is a powerful antioxidant involved in several protective mechanisms of the body [40]. Also, recently, many studies have been conducted to study the hydrogen sulfide molecule. Signaling pathways using hydrogen sulfide are used by cardiomyocytes, vascular endothelial cells, smooth muscle cells, and impaired bioavailability of hydrogen sulfide are used as a new marker of endothelial inflammation and endothelial dysfunction. [41]. It is interesting that the expression of markers of endothelial damage and endothelial dysfunction determines the degree of liver damage, which was shown in many studies [42, 43]. During histological examination of liver tissues in MASLD, pathologists describe a change in sinusoidal fenestration and collagenization of Disse's space. This is accompanied by an increase in intrahepatic vascular resistance, which necessarily leads to a violation of hepatic blood circulation, and possibly necrosis of the liver tissue due to developing ischemia. Liver tissue necrosis naturally leads to fibrotic processes. Metabolic dysfunction-associated steatotic liver disease is associated with an increased risk of future cardiovascular events [44]. Hypoadiponectinemia can serve as an early marker of the formation of not only hepatic steatosis, but also the risk of cardiovascular events, the formation of not only hepatic steatosis, but also the risk of cardiovascular events [45]. Patients with metabolic dysfunction-associated steatohepatitis (MASH) have a higher risk of cardiovascular disease than patients with steatosis, which emphasizes the role of chronic inflammation in the pathogenesis of atherosclerosis in these patients [46]. In experimental models, many researchers found that nitric oxide synthase is involved in the protection of liver cells from destructive effects. This conclusion was reached by studying the role of induced and endothelial nitric oxide synthase in liver damage

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during ischemia. Increasing the synthesis of nitric oxide can be of great importance for the protection of liver cells from the destructive effects of toxic substances [47]. To ensure adequate blood flow in the microcirculatory channel, vasodilator and anticoagulant molecules are needed [48]. But the excess of substances synthesized by the endothelium has the opposite effect. Thus, with an excess of nitric oxide, the function of the endothelium deteriorates, and the contractile function of the myocardium is suppressed due to a decrease in the secretion of endothelial NO [49]. The link between inflammation and endothelial dysfunction lies through the nitric oxide molecule, which is a powerful vasodilator and has anti-inflammatory properties. The main role of oxide in the regulation of vascular tone is known. It is the endothelial cells that produce nitric oxide, so endothelial dysfunction is a decrease in the ability to produce nitric oxide and a decrease in sensitivity to nitric oxide [50]. Considering the function of the endothelium, dysfunction leads to a violation of all components of functioning, namely an increase in susceptibility to inflammation, thrombosis, and rigidity of the vascular wall. Due to the multicomponent effect of nitric oxide, endothelial dysfunction is part of the pathogenesis of many pathophysiological processes.

Hydrogen sulfide has been considered for many centuries a poisonous gas that suppresses mitochondrial respiration. Advances in science now recognize H 2 S as a third gas carrier in humans and other mammals, which plays an important role in many physiological processes such as inflammation, regulation of vascular tone. And as a consequence, the use of its properties in shock conditions, in ischemia. A new direction in the study of its properties is the study of its role in liver disease, e.g. MASLD [51].

So, it was invented that hydrogen sulfide regulates various physiological processes, such as vascular relaxation, neuromodulation and inflammatory responses [52].

It was invented that the endogenous synthesis of hydrogen sulfide was impaired in cirrhosis of the liver [53] and that hydrogen sulfide protects against liver ischemia/reperfusion and carbon tetrachloride-induced liver injury in the development of this pathological condition in rats [54,55,56].

The effect of hydrogen sulfide on the regulation of hepatic lipid metabolism and MASLD has also been extensively studied. A recent study showed that hydrogen sulfide in the liver is significantly lower in mice fed a high-fat diet than in controls [57]. Another recent study reported similar results that liver hydrogen sulfide biosynthesis was impaired in a rat model of MASLD induced by a diet deficient in methionine and choline [58]. Subsequent experiments in mice showed that treatment with sodium hydrosulfide, a hydrogen sulfide donor, prevented non-alcoholic steatohepatitis by reducing oxidative stress and suppressing inflammation [59].

These studies highlight the significant role of hydrogen sulfide in MASLD. H 2 S modulates the activity of endothelial nitric oxide synthase (eNOS), which plays a key role in the regulation of vascular tone and oxygen delivery to tissues [60,61].

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H2S also plays a key role in the regulation of vascular tone. These newer discoveries open up new target molecules for therapeutic regulation of the process. [62]. It was found that H 2 S affects the contraction of stellate cells of the liver, through K-ATP channels causes vasorelaxation of the hepatic artery and can also be the cause of microcirculatory dysfunction [62,63,64,65,66].

H2S acts through ATP-sensitive potassium channels, which are abundant in the smooth muscle of the vascular wall. The mediator that mediates this process is vascular endothelial growth factor. It will also induce angiogenesis. Together with the H2S molecule, vascular endothelial growth factor has a pro-angiogenic effect. [67]. H 2 S deficiency is associated with several cardiovascular diseases [68].

Therefore, H2S is an important molecule that controls the homeostasis of endothelial function, and a violation of its endogenous production is associated with the pathogenesis of ED [69]. Many studies have shown that H2S acts as a vasculoprotective transmitter, modulating various cellular pathways and affecting various vascular diseases. The known facts are the following: H2S inhibits atherogenic modification of low-density lipoproteins [70], prevents monocyte adhesion due to EC activation [71], indirectly provides vasodilator reactions [72], reduces intimal hyperplasia by inhibiting the migration and proliferation of vascular smooth muscle cells [73], limits vascular calcification [74], thrombogenesis and aggregation of platelets [75], inhibits the formation of macrophage foam cells and degranulation. [76], limits inflammatory reactions and reduces the level of homocysteine in plasma.

The beneficial effects of exercise have been demonstrated, not only in reducing the risk of adipose tissue accumulation and insulin resistance, but also in providing direct endogenous protection of the metabolic state [77, 78]. However, the precise mechanisms underlying exercise-induced energy mobilization and liver protection against insulin resistance remain poorly understood. Current studies suggest that these effects may be related to the regulation of cellular metabolism, functional modulation, and the influence of muscle factors that have both metabolic and anti-inflammatory effects [79, 80].

Conclusion. The above data indicate that endothelial dysfunction and insulin resistance is one of the pathogenetic mechanisms of the development of many pathological conditions, including metabolic syndrome. Currently, this process is considered one of the early stages of the development of atherosclerosis, the presence of signs of endothelial dysfunction is associated with the level of cardiovascular risk. The contribution of insulin resistance and endothelial dysfunction to the progression of metabolic dysfunction-associated steatotic liver disease is generally recognized.

Currently, the concept of endothelial dysfunction is formulated as a key link in insulin resistance, atherogenesis and arterial hypertension in metabolic dysfunction-associated steatotic liver disease. There are more and more new methods of early diagnosis of endothelial dysfunction. A review of recent studies

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has shown that the presence of systemic inflammation, endothelial dysfunction, and their severity are important predictors of cardiovascular events in humans. It is likely that endothelial dysfunction may also be involved in the pathogenesis of T2DM. Since all pathogenetic components of metabolic dysfunction-associated steatotic liver disease are able to have an adverse effect on the endothelium, endothelial dysfunction can often accompany patients with metabolic dysfunction-associated steatotic liver disease, being a predictor of increased risk of CVD and T2DM.

Thus, there is an obvious need for further study of clinical-pathogenetic aspects of metabolic dysfunction-associated steatotic liver disease, in particular, endothelial dysfunction as the most important link in the pathogenesis of this pathological condition, with the aim of improving the complex of therapeutic, diagnostic and preventive measures and reducing the risk of developing cardiovascular disorders in this category of patients.

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