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STEATOZNING MOLEKULYAR ASOSLARI VA KASALLIK DAVRIDA GEPATOTSITLARDAGI STRUKTURAVIY O‘ZGARISHLAR.

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ANNOTATSIYA. Ushbu maqolada jigarda yog‘ to‘planishi bilan bog‘liq bo‘lgan o‘zgarishlar, ayniqsa gepatotsitlar ichida katta yog‘ tomchilari hosil bo‘lish jarayoni atroflicha tahlil qilinadi. So‘nggi yillarda bu holat tobora ko‘proq uchrayotgani va ko‘pincha dastlab sezilmay rivojlanishi muammoning dolzarbligini oshirmoqda. Maqolada yog‘li jigar kasalligining asosiy sabablariga e’tibor qaratilib, noto‘g‘ri ovqatlanish, kamharakat turmush tarzi va metabolik buzilishlar muhim omil sifatida ko‘rib chiqiladi. Shuningdek, gepatotsitlarda yuz beradigan strukturaviy o‘zgarishlar oddiy misollar orqali tushuntiriladi, bu esa mavzuni yanada aniqroq tasavvur qilishga yordam beradi. Jarayonning bosqichma-bosqich rivojlanishi, ya’ni oddiy yog‘ to‘planishidan tortib yallig‘lanish va og‘ir asoratlarga olib kelish ehtimoli ham tahlil qilinadi. Maqolaning asosiy maqsadi – ushbu kasallikning yashirin kechishi va vaqtida e’tibor berilmasa jiddiy oqibatlarga olib kelishi mumkinligini ko‘rsatishdir. Shu bilan birga, sog‘lom turmush tarzining ahamiyati va profilaktika choralariga ham qisqacha to‘xtalib o‘tiladi.

KALIT SO’ZLAR. jigarning yog‘li degeneratsiyasi, gepatik steatoz, gepatotsitlarda lipid vakuolizatsiyasi, intrahepatik lipid akkumulyatsiyasi, metabolik sindrom, insulin rezistentligi, dislipidemiya, alkogolsiz yog‘li jigar kasalligi (NAFLD), steatohepatit, jigar fibrozisi

СТЕАТОЗНИНГ МОЛЕКУЛЯРНЫЕ ОСНОВЫ И СТРУКТУРНЫЕ ИЗМЕНЕНИЯ В ГЕПАТОЦИТАХ ВО ВРЕМЯ ЗАБОЛЕВАНИЯ.

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АННОТАЦИЯ. В данной статье рассматриваются изменения, связанные с накоплением жира в печени, в частности процесс образования крупных жировых капель внутри гепатоцитов. В последние годы данное состояние встречается всё чаще, при этом на ранних этапах оно нередко протекает бессимптомно, что повышает его актуальность. В статье особое внимание уделяется основным причинам жировой болезни печени, среди которых выделяются неправильное питание, малоподвижный образ жизни и метаболические нарушения. Кроме того, структурные изменения, происходящие в гепатоцитах, объясняются на простых примерах, что облегчает понимание материала. Также анализируется поэтапное развитие процесса — от простого накопления жира до возможного перехода в воспаление и более тяжёлые осложнения. Основной целью статьи является показать, что данное

заболевание может длительное время протекать скрыто и при отсутствии своевременного внимания приводить к серьёзным последствиям. Также кратко рассматривается значение здорового образа жизни и профилактических мер.

КЛЮЧЕВЫЕ СЛОВА. жировая дистрофия печени, гепатический стеатоз, липидная вакуолизация гепатоцитов, внутрипечёночная аккумуляция липидов, метаболический синдром, инсулинорезистентность, дислипидемия, неалкогольная жировая болезнь печени (НАЖБП), стеатогепатит, фиброз печени

MOLECULAR BASIS OF STEATOSIS AND STRUCTURAL CHANGES IN HEPATOCYTES DURING THE DISEASE.

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ABSTRACT. This article explores the changes associated with fat accumulation in the liver, particularly the formation of large fat droplets within hepatocytes. In recent years, this condition has become increasingly common, often developing silently without noticeable symptoms in its early stages, which makes it especially relevant. The article focuses on the main causes of fatty liver disease, including unhealthy diet, sedentary lifestyle, and metabolic disorders. In addition, structural changes occurring in hepatocytes are explained through simple examples, making the topic easier to understand. The step-by-step progression of the process is also analyzed, from simple fat accumulation to inflammation and potentially severe complications. The main aim of the article is to highlight that this condition can remain unnoticed for a long time and may lead to serious consequences if not addressed in time. The importance of a healthy lifestyle and basic preventive measures is also briefly discussed.

KEY WORDS. hepatic steatosis, fatty liver degeneration, hepatocellular lipid vacuolization, intrahepatic lipid accumulation, metabolic syndrome, insulin resistance, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), steatohepatitis, liver fibrosis

Introduction. One of the primary hepatic manifestations of metabolic syndrome is nonalcoholic fatty liver disease (NAFLD). From basic steatosis to nonalcoholic steatohepatitis (NASH) with or without fibrosis and, ultimately, cirrhosis and hepatocellular cancer, it encompasses a broad range of histological abnormalities. The accumulation of highly toxic free fatty acids linked to insulin resistance-induced massive free fatty acid mobilization from adipose tissue and the increased de novo hepatic fatty acid synthesis from glucose acts as the "first hit" for

the development of NAFLD, even though hepatic simple steatosis appears to be a rather benign manifestation of hepatic triglyceride accumulation. Hepatic steatosis is a condition characterized by the excessive accumulation of triglycerides within hepatocytes. It is mainly associated with two major diseases: non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (ALFD). In addition, metabolic and nutritional disorders, certain medications (chemotherapy drugs and steroids), as well as hepatitis C virus (CGV) infection, also play an important role in its development. (7) The course of hepatic steatosis depends on its cause and accompanying conditions, such as inflammation and fibrosis, which can eventually lead to liver cirrhosis and liver failure. Therefore, early detection of the disease and assessment of its severity are of great importance. (12) Liver biopsy is currently considered the "gold standard" for diagnosis. However, it has disadvantages such as the possibility of incorrect sampling, differences in the interpretation of results, high costs, and the risk of complications. (1,4) Therefore, various methods of representation are often used in practice. This article examines the causes, descriptive features, and quantitative assessment methods of hepatic steatosis based on traditional and modern diagnostic technologies. (8) Non-alcoholic fatty liver disease (NAFLD) is the most common form of hepatic steatosis. It occurs in approximately 30-40% of men and 15-20% of women in the general population. (3) This disease is often considered a liver-related manifestation of metabolic syndrome. In particular, it is closely associated with conditions such as insulin resistance, atherosclerosis, obesity, dyslipidaemia, and arterial hypertension. (9) The development of the disease is based on the excessive accumulation of fat in hepatocytes. This increases oxidative stress in cells and triggers inflammatory reactions. As a result, simple fatty deposits can gradually transition into non-alcoholic steatohepatitis (NASH). At this stage, liver cells are damaged, and the process deepens further. (2,10). If this condition is not stopped or controlled in time, the inflammatory process leads to fibrosis, meaning an increase in connective tissue in the liver tissue. (6) Over time, these changes can lead to the development of liver cirrhosis. Cirrhosis results in a sharp decline in liver function and even liver failure. (11) According to specialists, a certain proportion of patients with NAFLD reach these severe stages. Therefore, it is very important to detect the disease early and prevent its progression. (5) Today, NAFLD is viewed not only as a liver disease but also as a complex metabolic problem affecting the entire body. Therefore, during the treatment process, it is necessary to monitor not only the liver but also the overall metabolic state. Proper nutrition, increased physical activity, and weight loss play an important role in the prevention and treatment of this disease. "Parallel, multiple-hit" damage, including oxidative stress-induced mitochondrial dysfunction, endoplasmic reticulum stress, endotoxin-induced, TLR4-dependent release of inflammatory cytokines, and iron overload, among many others, appear to be involved in the pathogenesis of NAFLD. Numerous signaling cascades that result in inflammation, cell death, and fibrosis—the hallmarks of NASH—are set off by these harmful substances. In order to better understand the factors driving the onset and course of the illness, this review aims to integrate the tremendous progress made in characterizing the physiopathological mechanisms of NAFLD at a molecular level. (8,9)

The main purpose of the presented manuscript is to provide a brief analysis of the molecular basis of steatosis and structural changes in hepatocytes during the disease period based on the results of authoritative scientific works.

NAFLD's physiopathological processes. The histological spectrum of NAFLD is broad, ranging from pure triglyceride (TG) accumulation in droplets within hepatocytes linked to minimal, if any, inflammation (simple, macrovesicular steatosis) to overt inflammation (with or without fibrosis), a condition known as NASH, which affects 3–15% of the general population. Radiation-

induced liver disease (radiation hepatitis) is one of the complications that can develop after radiation therapy. This condition usually manifests within 2–8 weeks after radiotherapy and is characterized by ascites without jaundice, liver enlargement (hepatomegaly), and an increase in liver enzymes. (5) Radiation-induced liver parenchyma is detected in the form of reduced density (hypodensity) in a non-contrast examination on computed tomography. When using a contrast agent, it may appear hypodensely or hyperdensely in some cases. These changes are associated with blood circulation in liver tissue and damage at the cellular level. (8) This condition would increase the liver's susceptibility to additional harmful factors, collectively referred to as "second hit." These factors include oxidative stress (OS), genetic polymorphisms that increase susceptibility to the disease, activation of inflammatory pathways by the release of pro-inflammatory cytokines by Kupffer cells or adipokines from adipocytes, dysregulated hepatocyte apoptosis, and activation of hepatic stellate cells (HSCs). When operating independently, they make up the "second hit" that propels the progression from macrovesicular steatosis to NASH. (11,12,13)

NAFLD pathogenesis's metabolic foundation. An imbalance between increased FFA availability from hepatic FFA synthesis and uptake and decreased FFA removal by mitochondrial β-oxidation, very low density lipoprotein (VLDL) exportation, and lipophagy leads to excessive hepatic FFA accumulation in NAFLD. Adipocyte FFAs are mostly obtained from dietary fat and are then released and reesterified in the liver. The most significant and common underlying component in hepatic FFA accumulation is IR, which predisposes to both lipolysis of peripheral fat with mobilization of FFAs to the liver and increased hepatic lipogenesis. In fact, more than 80% of the entire circulating FFA pool in NAFLD patients is made up of circulating FFAs from dysregulated lipolysis in adipose tissue; this FFA pool accounts for 59% of the hepatic fat, with a smaller percentage coming from de novo lipogenesis (26%) and diet (15%). Type-2 diabetes and obesity have a strong correlation with insulin resistance (IR) and are interconnected: central nerve IR causes obesity, and anybody who is obese has IR to some degree. The compensatory increase in pancreatic β-cell insulin secretion caused by peripheral and hepatic IR eventually results in β-cell secretory failure and overt type-2 diabetes. Therefore, this condition arises in obese people who do not secrete enough insulin to overcome their degree of insulin resistance. Numerous metabolic pathways can be disrupted and IR can be induced in various tissues, including the adipose one, as a result of obesity leading to IR and the ensuing persistently increased FFAs in serum. The special physiological lipid deposit that stores extra energy from food consumption is adipose tissue. However, the massive buildup of fat in adipose tissue linked to obesity causes dysfunctional adipocytes with aberrant adipokine release, including inflammatory cytokines like resistin, monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and plasminogen activator inhibitor 1. (1-9)

In magnetic resonance imaging, the affected areas appear as a low signal (hypointens) in T1 mode and a high signal (hyperintensity) in T2 mode. This condition is mainly explained by the accumulation of fluid in the tissues, i.e., edema. (9) It is noteworthy that these changes do not correspond to clear anatomical boundaries, but are often distinguished by straight-line boundaries corresponding to the shape of the radiation area. (8) As a result of radiation damage, degenerative changes occur in liver cells, the sinusoids dilate, and microcirculation is disrupted. This can lead to a decrease in liver function over time. In some cases, the process is reversible, but in severe cases, there is a possibility of developing fibrosis or chronic liver failure. (6.7) Therefore, it is important to regularly monitor the condition of the liver in patients receiving radiotherapy. Early detection of changes using imaging methods is of great importance in preventing the progression of the disease. (6) Hepatic steatosis is manifested by various etiological factors and various descriptive signs,

which is of great importance in radiological diagnosis. Particularly in patients with oncological diseases, certain forms of steatosis may resemble metastases. Therefore, in cases where the results of ultrasound or computed tomography are unclear, magnetic resonance imaging is recommended for differential diagnosis. (3) Today, it is possible not only to identify hepatic steatosis but also to accurately assess its extent. For this purpose, the proton density-based fat fraction determination (PDFF) method is widely used and is considered an important biomarker in monitoring patients with non-alcoholic fatty liver disease. (4) In the future, it is expected that using more advanced technologies, special maps (fatty acid mapping) will be developed that show the precise distribution of fatty acids in liver tissue. (11.12) This allows for the assessment of not only fat content but also its composition. As a result, the possibility of more early detection of the disease, a deeper analysis of its progression, and the development of individual treatment strategies will be expanded. (3) Thus, modern imaging diagnostic methods serve as an important tool for the detection, differentiation, and control of hepatic steatosis, and more precise and effective approaches are expected to emerge in this field in the future. (5,9)

Inflammation of the liver in NASH. Inflammation is essential for the onset and progression of NASH, because NAFLD is a pro-inflammatory disorder. The long-term prognosis of NAFLD is actually significantly influenced by inflammation and its primary consequence, fibrosis, while "pure" steatosis does not negatively impact the disease's outcome. As a secondary effect of the hepatic lipotoxic attack, inflammation in NASH is linked to increased production of inflammatory factors that originate from extrahepatic sites (such as the gut and adipose tissue) as well as from Kupffer cells and hepatocytes themselves within the liver. A variety of hormones (such as leptin, resistin, and visfatin), proinflammatory cytokines (such as TNF-α, IL-1 β, IL-6, and IL-8), and chemokines (such as MCP-1) are produced and released by adipose tissue, which is an endocrine organ. Peripheral and hepatic IR are caused by dysregulation of adipokine synthesis in obese patients' enlarged adipose tissue, which results in increased production of inflammatory chemokines and cytokines and decreased production of favorable ones (5-11). The liver parenchyma contains receptors for pro-inflammatory adipokines that trigger signaling cascades involved in IR (by activating suppressors of cytokine signaling [SOCS]), proinflammatory cytokine production (by activating nuclear factor-κB [NF-κB]), and HCC development (by activating JAK/STAT signaling). For instance, leptin, a classic adipokine that increases energy expenditure and inhibits food intake, stimulates macrophages, most likely via JAK/STAT signaling. Leptin has also been shown to have fibrogenic and inflammatory effects on Kupffer cells and HSCs, respectively. In NASH, some dietary and microbial components that enter the liver after intestinal absorption also play a pro-inflammatory function. Intestinal motility is altered by diets high in fat and sugar, which causes dysbiosis, including bacterial overgrowth, and damages the intestinal barrier by increasing intestinal permeability to products derived from the gut. This change encourages the release of pro-inflammatory food components into the bloodstream, including fructose, trans-FFAs, and ligands of the aryl hydrocarbon receptor (AhR), such as indolo-(3,2-b)-carbazole and 3,3′-diindolylmethane. The powerful pro-inflammatory agent LPS (endotoxin) is found in the walls of Gram-negative bacteria found in the microbiota, such as Bacteroidetes, Cyanobacteria, and Verrucomicrobia. Bacterial endotoxin metabolism is impacted by a diet high in fat or carbohydrates, which raises LPS serum plasma levels (1-5).

NASH hepatocellular autophagy. Autophagy is a lysosomal, self-degradative cell death mechanism that helps the remaining cells survive by giving them energy during cellular stress. It also serves as an adaptive mechanism to cellular damage by enabling the engulfment and subsequent removal of damaged organelles and misfolded/aggregate-prone proteins. As a result, in

situations where autophagy is lacking, cells would be more likely to die when faced with a death stimulus. Hepatic steatosis may arise from impaired autophagy since it also controls the breakdown of lipids found in hepatocellular droplets. Furthermore, by preventing cellular damage or encouraging the elimination of tumorigenic started cells, autophagy would limit tumor initiation; hence, its impairment could be a contributing factor to the development of HCC in advanced NASH. Macroautophagy and chaperone-mediated autophagy are the two primary types of autophagy whose disruption has been linked to the pathophysiology of NAFLD. Cellular organelles like mitochondria (also known as "mitoautophagy") or lipid droplets (also known as "lipophagy") are trapped in double-membrane structures called "autophagosomes" during macroautophagy. These structures fuse to lysosomes, causing lysosomal breakdown. Soluble proteins with a certain pentapeptide moiety attach to a chaperone protein for lysosomal translocation in chaperone-mediated autophagy, releasing the catabolic products into the cytosol for either reuse or energy supply. The number of autophagosomes carrying lipid cargo rises in response to fasting, indicating the function of macroautophagy in lipid disposal; the FFAs thus released fuel mitochondrial β-oxidation for energy supply. Conversely, suppression of hepatocellular macroautophagy leads to increased TG buildup and decreased lipolytic breakdown. There are reports of reduced macroautophagy in human NAFLD based on surrogated criteria, despite the fact that there are currently no trustworthy techniques to determine macroautophagy activity in human liver tissues. There is also experimental evidence that obesity caused by nutrition and genetics reduces autophagy. Autophagy inhibition in NAFLD appears to be multifactorial and has been linked to altered fusion of autophagic vacuoles with lysosomes, downregulation of autophagy genes, and lower levels of lysosomal enzymes (1-12).

Discussion. Given the robust association of NAFLD with metabolic syndrome and the worldwide epidemic of obesity, the prevalence of NAFLD is increasing at an alarming rate, making this hepatopathy the most frequent liver disease nowadays. NAFLD comprises a heterogeneous group of hepatic disorders that share common features, including hepatic fat infiltration (from a histological point of view) and IR (from a pathogenic point of view). NAFLD pathogenesis is particularly complex, since it involves the interplay between genetics and environmental factors, many of them having been elucidated recently. It is well accepted that OS, ER stress, mitochondrial damage, and hepatocellular dysfunction result from the overwhelming of adaptive mechanisms meant to prevent hepatic FFA-induced lipotoxicity. The ensuing cellular damage eventually sets off immune-mediated hepatocellular damage and apoptotic/necrotic cell death pathways, which in turn cause HSC activation and fibrogenesis, additional cirrhosis development, and ultimately HCC (4,5,6). Numerous intriguing targets for treatments have been identified as a result of the wealth of knowledge that has been gathered in recent years regarding the molecular mechanisms behind NAFLD development. As a result, a number of clinical trials investigating new therapy options—mostly based on preclinical research—have been conducted concurrently with this. There are currently no approved treatments for this extremely common illness, despite these obvious advancements. Since liver biopsy is typically not advised, robust biomarkers to predict evolution, choose patients for treatment, and track therapeutic response are similarly missing; their discovery and validation are highly anticipated (13,14).

Conclusions. Numerous intriguing targets for treatments have been identified as a result of the wealth of knowledge that has been gathered in recent years regarding the molecular mechanisms behind NAFLD development. As a result, a number of clinical trials investigating new therapy options—mostly based on preclinical research—have been conducted concurrently with this. There are currently no approved treatments for this extremely common illness, despite these obvious

advancements. Since liver biopsy is typically not advised, robust biomarkers to predict evolution, choose patients for treatment, and track therapeutic response are similarly missing; their discovery and validation are highly anticipated.

Therefore, it is evident that more research is required to identify patients who are more likely to progress by using genetic/epigenetic typification in conjunction with omics technology. This will enable a stratified approach to the management of NAFLD patients and identify those who would benefit most from current and future therapies. We hope that this review will help raise important questions regarding the pathogenesis of NAFLD to be investigated in cellular, animal, and human models of this liver disease, in order to eventually use this new knowledge to envision new therapeutic targets and predictive indicators of this global epidemic disease.

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