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OBESITY AS A RISK FACTOR FOR HEPATOBILIARY SYSTEM DAMAGE IN CHILDREN

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SUMMARY

This review provides facts about liver changes in obesity as part of non-alcoholic fatty liver disease. The review contains the pathogenesis and morphological characteristics of the development of this condition, the features of the clinical picture, as well as methods of invasive and non-invasive diagnostics.

Keywords: obesity, children, non-alcoholic fatty liver disease, diagnosis.

INTRODUCTION

Obesity in children ranks first in terms of frequency of occurrence among metabolic diseases and is a severe, progressive disease with a poor prognosis. According to experts in the developed world, up to 25% of adolescents are overweight, and 15% are obese. In the Russian Federation, these rates fluctuate between 8% and 10%, with a clear upward trend, with the number of patients projected to double every three decades. [1]. Of particular concern is the increase in obesity in the younger age group. According to the WHO, 42 million infants and young children (0-5 years old) are overweight or obese (WHO, 2015), with a high incidence of metabolic disorders and comorbidities as early as preschool age. Obesity is associated with comorbid conditions that determine the quality of life and its duration [2].

Obesity is considered as one of the manifestations of a complex of metabolic changes in the body that make up the metabolic syndrome (MS), along with insulin resistance (IR), arterial hypertension, atherogenic dyslipidemia, hyperuricemia, and non-alcoholic fatty liver disease (NAFLD) [4].

Numerous studies, both in therapeutic and pediatric practice, have shown that one of the key organs of the gastrointestinal tract (GIT) involved in lipid and carbohydrate metabolism, the development of IR and dyslipidemia is the liver. Liver changes in obesity are considered under NAFLD. This disease is progressive in nature with the subsequent development of steatohepatitis, fibrosis and cirrhosis with possible progression to hepatocellular carcinoma, which radically changes approaches to therapy and its cost [3]. NAFLD, according to numerous studies, is associated with increased morbidity and mortality from CVD, being an independent predictor of diabetes mellitus. [5]. Another factor affecting lipid metabolism in the body, directly (due to participation in the synthesis, transformation and destruction of endo- and exogenous sterols) and indirectly (through changes in the processes of enzymatic protein hydrolysis and vitamin synthesis), is the intestinal microflora. Changes in the intestinal microbiota, causing

disturbances in energy metabolism, the physicochemical composition of bile, and the hepato-intestinal circulation of bile acids, contribute to the development of deeper pathological changes not only in the liver, biliary system, gastrointestinal tract, but also in the whole organism as a whole. [3]. Taking into account the lack of data characterizing the prevalence of NAFLD, metabolic characteristics, the state of the liver, biliary system and upper gastrointestinal tract in children with overweight compared to children with obesity, there is a theoretical and practical justification for conducting studies to assess and properly interpret these changes [7]. According to the definition of the World Health Organization (WHO), excess body weight, obesity, diseases of the cardiovascular system and their complications, as well as diabetes mellitus are today an "epidemic non-communicable disease" of the 21st century. In the developed countries of the world, that is, the metabolic syndrome of obese adolescent children in France was 18.9%, in Italy and Poland 16.4%, Belarus 17.2%. As a result of the metabolic syndrome (MS), dyslipidemia, impaired glucose tolerance, hypertension and insulin resistance develop, according to WHO data in 2030, the death rate from diabetes will take the seventh place. The percentage of DM incidence has shifted to a greater extent from the developed countries of Europe and the United States to the developing countries of Africa, the Middle East and Asia. In addition, the percentage of type 1 and type 2 diabetes has changed. If earlier patients with type 2 diabetes mellitus accounted for 80-90%, then in 2011, this figure was 95%. Type 2 diabetes is widespread among children and adolescents. The main reason for the manifestation of type 2 diabetes is due to the fact that over the past 30 years the number of overweight children has increased dramatically. [8,9,10].

At present, we should talk about the multifactorial genesis of obesity, in which environmental, biological, and genetic factors play a significant role [11]. In recent years, the role of eating behavior (EB) in the development of obesity has become increasingly important [13]. Despite the exceptionally important role of LR disorders in the etiology and pathogenesis of obesity, this phenomenon has so far remained poorly understood in children. Numerous studies of eating disorders cover older age groups to a greater extent [14]. An analysis of the literature showed the absence of domestic works studying eating behavior in children before puberty and single foreign studies on the study and comparison of eating behavior in children with different body weights in different age periods [15]. Given the almost complete lack of opportunities for therapeutic correction of obesity in children, it is necessary to search for available options for the prevention and treatment of this condition, taking into account the physiological characteristics of the formation of a child at the stages of his growth and development [12]. The study of eating behavior, its features and disorders among children and adolescents is becoming increasingly relevant. Underestimation of the role of PN leads to a decrease in patient compliance, refusal of treatment, or relapse after treatment [18].

Considering the increasing incidence of liver cirrhosis and hapatocellular carcinoma, the problem of timely detection and treatment of CDLD, in the pathogenesis of which liver fibrosis and steatosis play a key role, is becoming increasingly important today [23,24]. It is believed that hepatic steatosis is characterized by the accumulation of lipids in hepatocytes in excess of 5.0% of the mass of the liver[25,26]. It is noteworthy that in the authoritative guide to hepatology E. Kuntz and H.D. Kuntz, there are the following definitions: a) liver steatosis - a condition where there are small or medium-sized fat droplets in individual liver cells and fat

makes up 3-10% of the weight of the liver; b) fatty liver (fatty liver, fatty hepatosis, liver steatosis) - the state of the liver, when the fat content is more than 10% of the body weight, and more than 50% of hepatocytes contain fat droplets of different sizes and fatty accumulations are diffusely distributed throughout the liver parenchyma [27,28].

In 1980, Ludwig first introduced the new concept of "non-alcoholic steatohepatitis", which is an independent nosological unit, which is characterized by an increase in the activity of liver enzymes in the blood and morphological changes in liver biopsies, similar to changes in alcoholic hepatitis. However, patients with NASH do not consume alcohol in quantities (at an average daily dose of 40 g or more of pure ethanol for men and 20 g or more for women) that can cause liver damage. [29]. The prevalence of NASH in the general population is unknown. Among patients who have undergone liver biopsy, NASH is approximately 7–9%, while alcoholic hepatitis is 10–15 times more common. The disease, as a rule, develops at the age of 40–60 years; women get sick more often (ratio of men and women 1:3). At autopsy, steatohepatitis is observed in approximately 6% of patients in whom alcohol abuse has been ruled out, and in 20% of liver biopsies due to chronic hepatitis of unspecified etiology. [30]. And NAFLD is based on insulin resistance (IR) and impaired energy metabolism between adipose tissue, skeletal muscles and the liver. Fatty liver occurs due to increased intake of fatty acids in the liver, which is associated either with excessive intake of fat from food or with increased lipolysis in insulin-resistant adipose tissue. An additional contribution is made by increased synthesis of fats, a decrease in the oxidation of free fatty acids and a violation of the output of triaciglycerol. Unfortunately, the pathogenesis of NASH is not well understood. It is believed that an increase in the synthesis of pro-inflammatory cytokines by fatty tissue of internal organs, Kupffer cells and hepatocytes, a decrease in the synthesis of adiponectin, a cytokine that suppresses inflammation, fibrosis and proliferation of adipocytes, plays a role in it. This leads to cell damage, inflammation, apoptosis, and fibrosis, which are typical manifestations of hepatitis in non-alcoholic fatty liver disease. [31].

Clinically, NAFLD is characterized by an asymptomatic or asymptomatic course [32]. Some patients complain of mild abdominal discomfort, heaviness or pain in the right upper quadrant of the abdomen, weakness, and malaise. Often, patients go to the doctor for other reasons, and liver dysfunction is detected by chance. Most often, during a clinical examination, there is an increase in the size of the liver without symptoms characteristic of its chronic diffuse diseases. Non-alcoholic fatty liver disease occurs in 8-70% of obese children [19]. Differences in frequency are due to the use of different diagnostic methods. The need for early diagnosis of NAFLD is due to the fact that the disease, which began in childhood, can cause liver cirrhosis in 10-20% of patients in adulthood. At the same time, with timely therapy, liver steatosis in children is reversible. Conflicting data on the frequency and structure of biliary dysfunction in obesity in children. In recent years, a highly informative method for determining NAFLD has been proposed by studying a complex of blood biomarkers - the so-called. "non-morphological liver biopsy", however, the availability of such a test is limited by high cost. Given the progressive nature of the course of NAFLD in obesity, it is justified to search for new non-invasive methods for diagnosing NAFLD in children for early intervention and prevention of the progression of liver fibrosis and cirrhosis. [41].

Recently, special attention has been paid to methods for verifying hepatic steatosis [33,34], which can be divided into invasive, minimally invasive, and non-invasive. Invasive methods have not lost their relevance, including trephine liver biopsy, the gold standard [35]. In 2005 D.E. Kleiner et al. a histological scoring of the activity and severity of steatosis in non-alcoholic fatty liver disease (NAFLD) was proposed [25,26], however, it is rather difficult to take into account the area of the lobules involved in fatty degeneration as a percentage. The main histological characteristics of liver steatosis are well studied and primarily include the nature and extent of fatty degeneration, which in most cases is assessed qualitatively or semi-quantitatively by visual analysis of the biopsy. However, according to recent studies, an accurate quantitative analysis of the area of fat droplets and the ratio of steatosis of different nature, which can often affect the same cells, is the most effective tool in assessing the course and progression of fatty liver disease. [36]. At the Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, in the laboratory of pathomorphology, a protocol for the morphological study of the liver has been developed, in which, using morphometry, a characteristic of hepatosis, fatty degeneration (small droplet, medium droplet, large droplet), the prevalence of fatty degeneration: local (< 30% of the lobule), common (from 30 to 75% of the lobules) and pronounced (> 75% of the lobules), as well as hepatocyte dystrophy: hydropic (local, widespread and pronounced), ballooning dystrophy and / or acidophilic bodies, as well as Mallory bodies.

Minimally invasive methods for verifying liver steatosis are based on a biochemical study of venous blood. In the development and course of liver damage, in particular hepatic steatosis, an important role belongs to lipid metabolism disorders. It is known that the liver plays an important role in the synthesis and metabolism of lipids. Hepatocytes take up lipids from the bloodstream and subject them to metabolic changes. In the liver, triglycerides are synthesized and oxidized, phospholipids, cholesterol, cholesterol esters, fatty acids, lipoproteins are synthesized, about 30–50% of low-density lipoproteins and 10% of high-density lipoproteins are catabolized. [37]. With liver steatosis, the function of hepatocytes is impaired. Minimally invasive methods can be conditionally divided into routine ones — triglycerides, total cholesterol, high-density lipoproteins, etc. [25] — and calculated coefficients: steatotest, the result of which is calculated based on several indicators — 7 analyzes (alpha-2-macroglobulin, apolipoprotein 1A, bilirubin , haptoglobin, gamma-glutamine transpeptidase, total cholesterol and triglycerides). The steatotest was developed at the Pitié-Salpêtrière Hospital in Paris and allows you to determine the stage of steatosis [33]. There are a number of similar tests [38,39]. However, it should be noted that in the initial stages of hepatic steatosis, routine biochemical parameters are not changed [40] and the calculated coefficients are not always accurate.

Non-invasive verification methods include: ultrasound, CT, MRI, elastometry with SARTM function (Fibroscan, model 502). There are several ultrasound signs of liver steatosis: distal attenuation of the echo signal; diffuse hyperechogenicity of the liver ("bright liver") due to diffuse fatty infiltration; increased echogenicity of the liver compared to the kidneys; depletion of the vascular pattern (25,41–43). According to ultrasound data, it is impossible to differentiate steatosis and steatohepatitis, as well as alcoholic and non-alcoholic steatohepatitis [40]. In the absence of clinical symptoms in the patient and the detection of abnormal liver function tests, as well as when it is impossible to conduct a histological examination of liver tissue, ultrasound

may be the only method necessary to recognize liver steatosis, especially if the patient has one or more risk factors [41–43]. According to ultrasound data, it is possible with a high probability to determine the presence of severe hepatic steatosis and, by calculating the attenuation index of the echo signal, determine its degree. But at the same time, it is not possible to determine the severity and severity of destructive changes in the liver by ultrasound on the basis of the above signs. [44]. An ultrasound study performed on modern equipment, including Dopplerography of the liver vessels using color Doppler mapping, pulsed wave Doppler, tissue harmonics, Dynamic MRTM, in most cases (up to 70%) allows us to assess the severity and dynamics of liver steatosis without resorting to histological verification [34], but the authors do not write about the remaining 30% of cases of ultrasound failure to verify steatosis. Changes similar to the results of ultrasound are detected with computed and magnetic resonance imaging [40]. Proton MR spectroscopy was used to calculate the percentage concentration of lipids in the liver parenchyma. If the value exceeded 6.5%, then the presence of fatty infiltration of the liver was considered confirmed [45], but the use of this method is very limited. In our opinion, the use of ultrasound with the option of measuring arterial stiffness parameters in the WTrack mode is promising for the verification of liver steatosis. The use of the technique is based on the thesis that in liver steatosis there are disorders of lipid metabolism, dyslipidemia [46-48], which lead to changes in the vessel wall and, accordingly, change the stiffness of the artery wall. The most indicative are the arterial stiffness index SI, Peterson's modulus of elasticity EM, and the growth index AI.

Of the non-invasive methods for verifying liver steatosis, in a certain sense, a revolution was made by liver elastometry using the FibroScan-502-touch device with the CAPTM function. The use of this device is based on Hooke's law (the reaction of a material to compression). Mechanically, the FibroScan-strike of the transducer pin is applied through the intercostal space along the right lobe of the liver, after which, using M- and A-mode ultrasound, the shear wave propagation speed through a standard 4-cm section of liver tissue is estimated. Based on 10 reliable measurements, liver elasticity in kPa is calculated in absolute numerical values, which makes it possible to determine the stage of fibrosis (F0–4), and at the same time, measurement is carried out by the CARTM function, which is used to determine the degree (or S0–3 score) of liver steatosis. CAPTM (Controlled Attenuation Parameter) allows you to quantify the decrease in the amplitude of ultrasound signals in the liver. The decrease in the amplitude of the ultrasound signal depends on the number (total volume) of lipid vesicles in the studied part of the liver and is expressed in dB/M in absolute units. The capabilities of this technique make it possible to verify liver steatosis in the early stages of development (S0–1, i.e. < 30% of the liver volume), when diagnosis using ultrasound is difficult. The opening opportunities for early verification of liver steatosis make it possible to timely prescribe a set of therapeutic and preventive measures and create prerequisites for stopping the progression, and possibly regressing, of liver steatosis.

Currently, there is no standard method for the treatment of NAFLD and NASH, which would be based on evidence, so the main goal of therapy is to improve the biochemical parameters characterizing inflammation and cytolysis, slowing down and blocking fibrogenesis [16,17]. In any case, therapy should begin with lifestyle changes, which include both a change in diet and an increase in physical activity. There is no perfect diet. Obviously, patients with NAFLD

(especially NASH) eat more than healthy individuals, so they first need to reduce the calorie content of the daily diet. One recommendation might be to limit or replace foods high in saturated fatty acids with monounsaturated (palmitic and oleic) and polyunsaturated (docosahexaenoic and eicosapentaenoic) fatty acids. Group 1 includes milk, peanut and olive oil, and group 2 includes fish oil, linseed oil, and walnuts. Physical exercise increases insulin sensitivity, reduces organ fat, increases adiponectin levels, and reduces liver steatosis. To achieve these goals, 3-4 aerobic exercises per week are considered sufficient (at a cost of 400 kcal per 1 session). It has been proven that a decrease in body weight by 8–10% compared with the initial one is accompanied by an improvement in the histological picture of NASH. The most controversial issue is the drug therapy of NAFLD. Over the past 10 years, a large number of studies have been devoted to the search for approaches to the treatment of this category of patients. The need to correct metabolic disorders (IR, oxidative stress, hyperlipidemia) is generally recognized[21].

Attempts have been made to treat NASH with drugs that increase insulin sensitivity. In one open pilot study, metformin was evaluated in 10 children with biopsy-proven NASH and elevated ALT [21]. After 6 months of therapy, there was a significant decrease in the level of ALT in the blood and a decrease in the manifestations of fatty degeneration of the liver according to MRS. However, in Russia the drug is allowed after 15 years. Another drug - thiazoladinedione, which seems to be more promising, is not yet available. Antioxidant therapy has also been studied in children with NASH. An open trial in children of oral vitamin E from 2 to 4 months resulted in normalization of alanine aminotransferase levels in all 11 obese children [22]. Ursodeoxycholic acid (UDCA), which has a proven cytoprotective effect, has also been studied as a potential therapy for NAFLD in adults and children. One of the drugs recommended for the treatment of this category of patients is ursodeoxycholic acid (UDCA), which has a proven range of positive effects. By stabilizing the physicochemical properties of bile, preventing the precipitation of crystals in the gallbladder, compensating for the loss of bile acids and providing a weak cholekinetic effect, UDCA helps restore the motor function of the biliary tract, reduces the risk of formation of biliary sludge and stones in the gallbladder. In addition, UDCA significantly reduces cholestasis, has a hepatoprotective, moderate immunomodulatory effect, blocks the proliferative phase of fibrogenesis, has antioxidant properties, which allows it to be successfully used in liver damage of various origins, including NAFLD. [18].

Thus, in children with overweight, involvement in the pathological process of the liver and biliary system is one of the early clinical signs of metabolic disorders, in 100% of cases combined with pancreatic steatosis, with a subsequent increase in the number of cases of NAFLD in obese patients [3]. obese children are significantly more likely than children with normal BMI to have NAFLD, hypotonic gallbladder dysfunction, and the initial (prestone) stage of cholelithiasis, with insignificant differences in cholelithiasis in the calculus stage [19]. A non-invasive ultrasound method of acoustic quantitative assessment of the structure (Acoustic Structure Quantification) can be used to determine the presence and stage of fibrosis in patients with non-alcoholic fatty liver disease, which is especially important in cases where it is impossible to conduct a morphological study, which has been and remains the “gold standard” of diagnosis. liver diseases.Timely correction of metabolic and inflammatory changes in the liver and biliary

tract using UDCA preparations in children with obesity will contribute to the normalization of carbohydrate and lipid metabolism and will significantly reduce the risk of developing metabolic syndrome in adulthood.

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