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OBESITY AND HEPATOBILIARY SYSTEM IN CHILDREN

Garifulina Lilya Maratovna

Associate Professor, Head of the Department of Pediatrics,

Faculty of Medicine

Samarkand State Medical University, Uzbekistan

Turaeva Dilafruz Kholmurodovna

Assistant, Department of Pediatrics, Faculty of Medicine, Samarkand State Medical University, Uzbekistan

Asliddinov Shakhzod Bakhriddinovich

2nd year student of Group 206, Faculty of Medicine No. 1, Samarkand State Medical University, Uzbekistan

Annotation: Obesity in children ranks first in frequency among metabolic diseases and is a severe, progressive disease with an unfavorable prognosis (Dedov I.I. et al., 2007; Kartelishev A.V., Rumyantsev A.G., 2010; Kon I Y. et al., 2011; Cattaneo A. I. et al., 2010). According to experts in developed countries, up to 25% of adolescents are overweight, and 15% are obese (De Onis M. et al., 2010). In the Russian Federation, these indicators fluctuate at the level of 8–10% with a clear upward trend and with a projected doubling of the number of patients every three decades (Kon I.Ya. et al., 2011). Of particular concern is the rise in obesity in younger age groups. According to 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 related diseases already in preschool age (E.V. Pavlovskaya et al. , 2013). Obesity is associated with comorbid conditions that determine the quality of life and its duration (M. Neef et al., 2013; E.R. Pulgaron, A.M. Delamater, 2014; L.A. Nielsen et al., 2015).

Keywords: NAFLD, Non-alcoholic, FibroMax

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

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 (Strauss R.S. et al., 2010; Tiniakos D.G. et al., 2010). Changes in the liver in obesity are considered within the framework of 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 (Brunt EM., 2010). NAFLD, according to numerous studies, is associated with increased morbidity and mortality from CVD (Alisi A. et al., 2009; Feldstein A.E. et al., 2009), being an independent predictor of diabetes mellitus (Kotronen A. et al., 2010). Another factor influencing 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 hydrolysis of proteins and synthesis of vitamins), is the intestinal microflora. Changes in the intestinal microbiota, causing disturbances in energy metabolism, the physicochemical composition of bile, and the hepatic-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 entire organism as a whole (Delzenne NM, Neyrinck AM and al., 2011; Dore J, Simren M, 2013). Given the lack of data characterizing the prevalence of NAFLD, metabolic features, liver, biliary and upper gastrointestinal tract health in overweight versus obese children, there is a theoretical and practical rationale for conducting studies to assess and properly interpret data changes.

According to the World Health Organization (WHO), excess body weight, obesity, diseases of the cardiovascular system and their complications, as well as diabetes mellitus today represent an "epidemic non-communicable disease" of the 21st century. In developed countries of the world, that is, metabolic syndrome in adolescent children with obesity, in France it was 18.9%, in Italy and Poland 16.4%, in Belarus 17.2%. As a result of metabolic syndrome (MS), dyslipidemia, impaired glucose tolerance, hypertension and insulin resistance develop; according to WHO, in 2030, the mortality rate from diabetes will take seventh place. The incidence of diabetes has shifted more from developed countries in Europe and the United States to developing countries in Africa, the Middle East and Asia. In addition, the percentage of diabetes types 1 and 2 has changed. If previously patients with type 2 diabetes 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 children who are overweight has increased sharply.

Currently, we should talk about the multifactorial genesis of obesity, in which environmental, biological and genetic factors play a significant role (M. Tanvig, 2014). In recent years, the role of eating behavior (EB) in the development of obesity has become increasingly important (E.V. Mitroshina et al., 2010; R.M. Akhmedova, L.V. Sofronova, 2013; M.B. Zhunisova et al. , 2015; V. Svensson et al., 2011). Despite the extremely important role of PP disorders in the etiology and pathogenesis of obesity, this phenomenon still remains poorly studied in children (D.A. Loh, F.M. Moy, N.L. Zaharan, 2013). Numerous studies of eating disorders cover mostly older age groups (R.M. Akhmedova, L.V. Sofronova, 2013; H.M. Snoek, T.Van Strien, J.M. Janssens, 2007, 2008; J.R. Silva et al., 2013) . An analysis of the literature showed the absence of domestic works studying eating behavior in prepubescent children and isolated foreign studies on the study and comparison of eating behavior in children with different body weights at different age periods (T. Van Strien, P. Osterveld, 2008; T. Ledoux et al., 2011; J.R. Silva, G. Capurro, M.P. Saumann, 2013). Considering the almost complete lack of possibilities 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 child's formation at the stages of its growth and development (N.N. Minyailova, 2012; R.M. Akhmedova, L. V. Sofronova, 2013; C. Braet et al., 2013; The study of eating behavior, its characteristics and disorders among children and adolescents is becoming increasingly relevant (R.M. Akhmedova, L.V. Sofronova, 2013). Underestimation of the role of PN leads to a decrease in patient compliance, refusal of treatment, or relapse after treatment (R.M. Akhmedova, L.V. Sofronova, 2013; Ya.V. Girsh et al., 2013; M.E. Telnova , 2014).

Non-alcoholic fatty liver disease (NAFLD) occurs in 8-70% of obese children [Roitberg G.E., 2007; Babayan M.L., Khavkin A.I., 2013; Bokova T.A., 2014; Ng M, Fleming T. et al., 2013; Nobili V, Alisi A, Newton KP, Schwimmer JB., 2016]. Differences in frequency are due to the use of different diagnostic methods. Ultrasound examination (ultrasound) of the abdominal organs and elastography have certain diagnostic information for the qualitative assessment of liver steatosis, but do not allow determining the stage of the process, identifying non-alcoholic steatohepatitis (NASH) and assessing the degree of its activity [Kamshilova K.A., Troshina E.A. , 2015; Strauss S., Gavish E., 2007; Yoneda M. Suzuki K., 2010; Babu BI et al., 2015]. The "gold standard" for diagnosing NAFLD is liver puncture biopsy, but this study has limitations and does not allow its widespread use [Lazebnik L.B. et al., 2015; Yu SJ. et al., 2015; McPherson S. et al., 2015]. An alternative to liver puncture biopsy can be considered the certified set of biochemical tests FibroMax [Poynard T. et al., 2005; Massard J., Charlotte F., 2006; Alvarez D. et al., 2012], which has high sensitivity and specificity in detecting steatosis, steatohepatitis and liver fibrosis. There is limited information on the use of FibroMax in pediatrics. In recent years, interest in studying hepatic hemodynamics in liver diseases using polyhepatography has increased [Ermolov S.Yu., Shabrov A.V., Dobkes A.L., 2006], however, the diagnostic significance of this method for NAFLD in children is unclear. The need for early diagnosis of NAFLD is due to the fact that the disease, which begins in childhood, can cause liver cirrhosis in 10%-20% of patients in adulthood [Peterkova V.A., Remizov O.V., 2004; Pavlov Ch.S. et al., 2010; Lazebnik L.B. et al., 2015; Koshurnikova A. S., Lukina E. V., 2017; Vernon G et al., 2011]. At the same time, with timely treatment, liver steatosis in children is reversible. Data on the frequency and structure of biliary dysfunctions in obesity in children are contradictory [Romasenko L.V., Turko T.V., 2007, Aleshina E.I. et al., 2014; Gurova M.M. et al., 2014].

The transformation of functional disorders of the biliary tract into organic pathology, such as chronic cholecystitis and cholelithiasis (GSD), increases the importance of early diagnosis of identified changes [Polunina T.E., 2015]. The initial phase of cholelithiasis is detected in 11.8% of obese children (Gubonina I.V., 2001, Bokova T.A., Ursova N.I., Potapova E.A., 2012; Mandrov S.I., Zhdanova L. A., Vinogradova I.S., 2014]; in 2% of all obese children, already formed stones are detected [Aleshina E.I. et al., 2014; Kaechele V, 2006]. not sufficiently developed.

In recent years, a highly informative method for determining NAFLD has been proposed by studying a set of blood biomarkers - the so-called. "non-morphological liver biopsy", but the availability of such a test is limited by its high cost. Considering the progressive nature of NAFLD in obesity, the search for new non-invasive methods for diagnosing NAFLD in children for early intervention and prevention of the progression of liver fibrosis and cirrhosis is justified.

Differentiating different forms of NAFLD is extremely important for prognosis, but it is still possible to reliably establish the nature of liver damage only through histological examination of liver tissue. To confirm the diagnosis of NAFLD, at least 5–10% of the liver's weight must be fat. In practice, morphologists often rely on light microscopy data. A mild form is considered when fatty deposits are present in less than 1/3 of the hepatocytes, a moderate form is when fatty deposits are present in more than 1/3 of the hepatocytes, but less than ⅔ of the liver cells, and a severe form is diagnosed when fatty deposits are visible in more than 2/3 of hepatocytes.

No therapy has been developed for the treatment of NAFLD in either children or adults. The strategy in the treatment of NASH to date is based on the modern understanding of the pathogenesis of this disease - the "two-hit" theory. The effects of weight loss/visceral fat reduction, increased insulin sensitivity, and

antioxidant therapy on the course of NAFLD are being studied. Several clinical, uncontrolled studies have shown the weight loss benefits of a low-calorie diet and exercise. This has been demonstrated by decreased or normalized transaminase levels and improvement on ultrasound, but there are no published diet and exercise studies that have demonstrated improvement in liver histology with weight loss in children. Although there is limited evidence on optimizing a healthy diet combined with exercise, it should be prescribed in all children diagnosed with NAFLD. A specific diet that will be beneficial in the treatment of NAFLD remains to be developed. Attempts have been made to treat NASH with drugs that increase insulin sensitivity. In one open-label pilot study, metformin was evaluated in 10 children with biopsy-proven NASH and elevated ALT levels. 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 liver according to MRS. However, in Russia the drug is approved after 15 years. Another drug, thiazoladinedione, which seems more promising, is not yet on the Russian market. Antioxidant therapy has also been studied in children with NASH. An open-label trial in children of oral vitamin E supplementation for 2 to 4 months resulted in normalization of alanine aminotransferase levels in all 11 obese children. Ursodeoxycholic acid (UDCA), which has a proven cytoprotective effect, has also been studied as a potential therapy for NAFLD in adults and children. A study from Italy assessed the effectiveness of UDCA in 31 obese children aged 4 to 14 years with elevated aminotransferase levels. With therapy at a dose of 10–12.5 mg/kg per day for 6 months, no significant positive results were obtained. However, among the children referred for this treatment, there were also those who did not follow a diet or exercise program, which undoubtedly influenced the statistical results of biliary tract in obese 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 deposition 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 the 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, and has antioxidant properties, which allows its successful use in liver lesions of various origins, including NAFLD. The optimal UDCA drug for use in childhood is Ursofalk, which has been produced in Germany since 1979 and is the reference drug for UDCA in the European Union. Other drugs containing UDCA and being its analogues may differ in both effectiveness and adverse reactions [4].

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