THE HEPATOBILIARY PATHOLOGY IN PATIENTS WITH OBESITY

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ABSTRACT: *The hepatobiliary system is the most vulnerable area in patients with obesity. The visceral fatty tissue releases large amount of biologically active substances determining formation and characteristics of course of such diseases as biliary dysfunctions, cholelithiasis, and non-alcoholic fatty disease of liver. The therapy of pathology of this kind is to be based on the combination of non-medicamental and medicamental methods. The impact on insulin resistance promotes both normalization of metabolic disorders and treatment of pathology of liver and bile-excreting tracts.*

Key words: *obesity, biliary dysfunction, cholelithiasis, non-alcoholic fatty disease of liver*

Obesity has been declared a non-infectious pandemic of the 21st century by the World Health Organization. In developed countries, the proportion of people with excess body weight reaches 50-60% [11]. The significant contribution of obesity to cardiovascular mortality is a proven fact. At the same time, the polymorbidity of an obese patient is also beyond doubt. An increase in body weight entails changes that become the pathogenetic basis for the development of many diseases, including those of the digestive organs [19]. In this case, the hepatobiliary region is the most vulnerable. Changes in the functional activity of visceral adipose tissue adipocytes are a key link in the pathogenesis of obesity. Increased lipolysis leads to an increase in the flow of free fatty acids (FFA) into the portal bloodstream. This is a consequence of the excessive formation of triglycerides, cholesterol and very low-density lipoproteins, their oversaturation of the bloodstream and hepatocytes [30]. It has been shown that an increase in fat

mass by 1 kg leads to an increase in cholesterol excretion into bile by 20 mg per day [8].

An integral part of the metabolic changes that occur in visceral obesity is insulin resistance. Biologically active peptides (adipokines), actively synthesized by visceral adipose tissue, participate in the formation of this phenomenon. Along with a hypercaloric diet, low physical activity and excessive bacterial growth in the intestine, which are characteristic of an organism with increased body weight, adipokines are able to block insulin signals and induce the activity of many inflammatory cytokines that affect lipid metabolism and motor activity of the biliary tract [5]. Thus, leptin causes the induction of immune-inflammatory reactions. The ability of this hormone to stimulate cell proliferation and inhibit apoptosis causes an increased risk of neoplasia in obese patients and also explains the increase in liver fibrogenesis [9].

Thus, pathophysiological changes occurring in obesity contribute to the formation of characteristic pathology of the hepatobiliary region. These are functional disorders of the biliary tract, cholelithiasis, cholesterosis of the gallbladder, non-alcoholic fatty liver disease (NAFLD). According to the decisions of the Rome Consensus (1999), at present, dysfunctions of the biliary tract are a complex of clinical symptoms that develop as a result of motor-tonic dysfunction of the gallbladder, bile ducts and sphincters [16, 39]. Excess visceral adipose tissue as one of the manifestations of insulin-resistant metabolic syndrome provokes the development of biliary dysfunctions. They are secondary in nature. The mechanisms of their development have not been fully elucidated. A certain relationship is observed between gallbladder volumes, body mass index (BMI), severity of abdominal obesity and decreased glucose tolerance. This could be explained by a disturbance in the synthesis of bile excretion stimulants. However, there are data on normal levels of circulating basal and postprandial cholecystokinin (CCK) in individuals with obesity and gallbladder hypotension. The authors explain this fact by the development of resistance of the receptors of

muscle cells of the gallbladder wall to endogenous CCK, possibly provoked by chronic hyperinsulinemia [22].

Reduced sensitivity of receptors to CCK inevitably leads to the formation of hypomotor variants of dyskinesia in obese patients, especially in women. They are accompanied by prolonged, constant dull pain in the right hypochondrium [1]. The pain is caused by overfilling of the gallbladder with bile and stretching of its wall. It has been shown that the presence and severity of hypotonic disorders directly depend on the degree of abdominal obesity, especially on the amount of visceral fat accumulation. These changes prevail among obese patients suffering from gallstone disease [28]. Diet therapy is the cornerstone of the system of therapeutic measures for dysfunctional disorders of the biliary tract [7]. For obese patients, 5-6 meals a day are relevant, stimulating bile secretion. It is necessary to introduce into the diet foods that regulate bowel function (vegetables, dried fruits, bran). Normal bowel movement helps to reduce intra-abdominal pressure and freer flow of bile into the duodenum [29]. In the treatment of biliary dysfunctions, the drugs of choice are selective myotropic antispasmodics. The positive effect of the drug mebeverine on the dynamics of clinical symptoms, motor-tonic function of the biliary system, biochemical parameters of bile and quality of life parameters in obese patients has been shown. A feature of this drug is a pronounced clinical effect regardless of the type of biliary dysfunction [35]. Correction of biliary dysfunctions in obese patients is of great importance due to the high risk of developing organic pathology of the hepatobiliary zone against this background: cholesterosis of the gallbladder, cholelithiasis and NAFLD. Cholelithiasis is a metabolic disease characterized by the formation of gallstones in the hepatic bile ducts, common bile duct or gallbladder.

The incidence of cholelithiasis in the general population is 1.5-2.7%, while in obesity it is 9.8-18.4% [2]. The chemical properties of bile depend on the percentage of the main components: cholesterol (4%), bile acids (67%) and phospholipids (22%). A sufficient amount of bile acids helps to convert

cholesterol and phospholipids into stable micelles. Cholesterol is practically insoluble in water, but for transport by bile it interacts with bile acids and phospholipids, which sharply increases its solubility. The resulting excess cholesterol passes into single-lamellar vesicles, from which precursors of dense cholesterol microcrystal precipitates are formed [20].

The causes of disturbances in the physicochemical properties of bile in obese patients may be a high-calorie diet with a high content of fat, cholesterol, sucrose in food, consumption of refined foods containing little fiber, hypersecretion of bile with an increased content of cholesterol, which easily crystallizes and precipitates, a sedentary lifestyle typical of obese people, which leads to hypotension of the gallbladder and stagnation of bile, the use of low-calorie diets for weight loss, inflammatory diseases of the gallbladder.

Thus, activation of the synthesis of proinflammatory cytokines and lipid peroxidation processes in obese patients in combination with slow emptying of the gallbladder significantly increases the likelihood of stone formation, which predominantly contain cholesterol [2]. Elimination of risk factors is one of the principles of treatment of cholelithiasis. For obese patients, this is primarily normalization of body weight. The diet should exclude foods with lithogenic properties, add foods with essential fatty acids, choleretic plant fiber [31]. However, it should be remembered that with a sharp decrease in body weight, the likelihood of gallstones increases. When body weight loss increases from 1.5 to 3 kg per week, the formation of new gallstones increases from 0.5 to 3% [49]. A low-fat diet (about 4 g) also promotes stone formation (emptying of the gallbladder is weakly stimulated) [37].

The risk of stone formation during dieting becomes lower with the consumption of up to 15-30 g of fat per day, as well as with the prescription of ursodeoxycholic acid (UDCA), which reduces the lithogenic properties of bile [37, 48]. UDCA is prescribed at a dose of 10 mg / kg per day once in the evening for 6 months - 2 years. In addition to the litholytic effect, a hypolipidemic effect

has been revealed in the treatment with bile acids. It has been shown that UDCA reduces the level of total cholesterol (TC) in the blood serum in cholelithiasis by 9%, LDL-C by 19%, and increases the content of HDL-C by 40% [18]. However, cholecystectomy remains the most frequently used method of treating cholelithiasis. In terms of the number of surgical interventions, it ranks second in the world after appendectomy [33]. Cholelithiasis is one of the causes of chronic and acute pancreatitis [27]. Obesity causes increased excretion of cholesterol into bile, which causes its high viscosity and increases the occurrence of pancreatitis [24]. In addition, due to excessive fat deposition in the abdominal organs and retroperitoneal tissue, intra-abdominal pressure increases, which changes the pressure gradient in the duodenum and the main pancreatic duct, leading to duodenopancreatic reflux [21]. Obesity determines the prognosis in acute pancreatitis. J. Martinez et al., having conducted meta-analyses in 2004 and 2006, showed an increase in the number of systemic complications by 2 times, local complications by 4 times, mortality by 1.3-2.1 times in patients with a BMI of more than 30 kg/m2 [45, 46]. The course of chronic pancreatitis in obese patients is characterized by the absence of specific clinical manifestations and a tendency to decrease the exocrine function of the pancreas [3, 10, 17]. Obesity is considered an independent risk factor for the development of NAFLD [35, 41]. Steatosis and nonalcoholic steatohepatitis (NASH) develop in 94 and 36% of obese patients, respectively [8].

There are no highly specific clinical manifestations of NAFLD [13, 14]. From 20 to 80% of patients have no symptoms at all, 25-40% complain of discomfort in the right hypochondrium, 50-75% of patients are bothered by weakness. Objective examination data do not reveal any deviations from the norm in 20-30%. Hepatomegaly is detected in 25-50% of cases, signs of liver dysfunction are noted in approximately 10% of patients. Significantly more often in the presence of steatohepatitis, the level of alanine transaminase (ALT) is elevated compared to aspartic (AST). Signs of cholestasis are often absent [23, 25, 42].

Diagnostic studies using visualization methods reveal typical signs: a "white" liver in ultrasound, a decrease in its density compared to the spleen in CT [15, 36]. Treatment of patients with NAFLD and obesity should begin with a reduction in the overall energy value of the diet [32]. The daily caloric intake is selected individually, depending on body weight, age, gender, and level of physical activity [26]. It has been shown that a reduction of more than 5% of weight leads to an improvement in histological manifestations in the liver [43]. However, sudden weight loss can worsen the histological picture: central necrosis, portal inflammation, and pericellular fibrosis are detected. A safe weight loss is no more than 1.6 kg per week [33]. Another principle of non-drug therapy for NAFLD is adequate physical activity. Exercises are recommended at least 3-4 times a week for 30-40 minutes, since the degree of reduction in insulin resistance usually correlates with the intensity of physical exercise and its regularity [7]. Statins are used to normalize lipid metabolism, although it is known that this group of drugs can cause liver damage and increase the level of transaminases due to impaired ubiquinone synthesis and disturbances in the mitochondrial respiratory chain [34]. At the same time, a reliable decrease in the ALT content was shown in the group receiving statins (atorvastatin) and an increase in the group not receiving this drug [38].

The basic drugs for the treatment of insulin resistance syndrome in patients with NAFLD are insulin sensitizers - biguanides (metformin) and thiazolidinediones (pioglitazone) - drugs that increase the sensitivity of cellular receptors to insulin [44]. It has been established that taking metformin at a dose of 1 g per day for 12 months leads to a decrease in insulin resistance, glucose content, an increase in the level of adiponectin, and when using the drug at a dose of 2 g per day for 12 months, a decrease in the severity of steatosis, necroinflammatory reaction and fibrosis in the liver is recorded [4, 6, 24]. The use of pioglitazone at a dose of 30 mg per day for 2 years in patients with NASH leads to a decrease in the activity of ALT, AST, a decrease in steatosis, lobular inflammation. Hepatoprotectors of different groups are used to treat NAFLD. The

effect of UDCA has been established, which at a dose of 30 mg / kg per day for 12 months reduces the values of ALT, AST, gamma-glutamyl transpeptidase, as well as the severity of steatosis [47]. Alpha-lipoic acid has a pleiotropic effect on the entire body due to its positive effect on energy, lipid and carbohydrate metabolism.

The effectiveness of essential phospholipids (EPL) in NAFLD has been demonstrated by many researchers. O.M. Drapkina et al. noted the effect of EPL on lipid metabolism: when using the drugs for 2 months, the content of HDL-C increased and the amount of total C in the blood serum decreased [12]. EPL demonstrate an antifibrogenic effect, which is realized due to the ability of these substances to stimulate collagenase activity. Thus, obesity and pathology of the hepatobiliary zone are mutually aggravating processes. Biliary dysfunctions in patients with excess body weight should be considered as risk factors for organic pathology. In the treatment of patients with obesity, the most important thing is the correction of risk factors, including the normalization of body weight and metabolic disorders.

LITERATURE

1. Анисимова Е.В., Козлова И.В., Волков С.В. В кн.: Тезисы докла дов 13-го Международного Славяно-Балтийского научного фо рума. СПб.; 2011: 3—4.

2. Барановский А.Ю., Ворохобина Н.В. Ожирение (клинические очерки). СПб.: Диалект; 2007.

3. Беляева Н.В. В кн.: Тезисы докладов 13-го международного Сла вяно-Балтийского научного форума. СПб.; 2011: 8.

4. Богомолов П.О., Павлова Т.В., Цодиков Г.В. и др. Клинические перспективы гастроэнтерологии, гепатологии. 2004; 6: 11—4.

5. Буеверов А.О. Consilium medicum. 2009; 9: 74—8.

6. Буеверов А.О., Богомолов П.О. Клинические перспективы га строэнтерологии, гепатологии. 2009; 1: 3—9. 7. Вишневская В.В., Лоранская И.Д., Малахова Е.В. Русский меди цинский журнал. 2009; 17 (4): 246—50.

8. Вовк Е.И. Consilium medicum. Гастроэнтерология. 2010; 2: 37—44.

9. Гончаров Н.П. Вестник РАМН. 2009; 9: 43—8.

10. Губергриц Н.Б., Бондаренко О.А. В кн.: Тезисы докладов 13-го Международного Славяно-Балтийского научного форума. СПб.; 2011: 22.

11. Дедов И.И., Мельниченко Г.А., ред. Ожирение: этиология, пато генез, клинические аспекты. М.: МИА; 2004.

12. Драпкина О.М., Гацолаева Д.С., Калинин А.В. Клинические пер спективы гастроэнтерологии, гепатологии. 2005; 6: 25—9.

13. Драпкина О.М., Ивашкин В.Т. Врач. 2010; 3: 30—3.

14. Звенигородская Л.А., Егорова Е.Г. Экспериментальная и клини ческая гастроэнтерология. 2007; 1: 14—9.

15. Ивашкин В.Т., Драпкина О.М., Шульпекова Ю.О. Российские ме дицинские вести. 2009; 3: 70—81.

16. Ивашкин В.Т., Лапина Т.Л., ред. Гастроэнтерология: Националь ное руководство. М.: ГЭОТАР-Медиа; 2008.

17. Ивашкин В.Т., Маевская М.В. Российский журнал гастроэнтеро логии, гепатологии, колопроктологии. 2010; 1: 4—12.

18. Ильченко А.А., Дрожжина Ю.В. Экспериментальная и клиниче ская гастроэнтерология. 2007; 5: 29—34.

19. Лазебник Л.Б., Звенигородская Л.А. Метаболический синдром и органы пищеварения. М.: Анахарсис; 2009.

20. Лейшнер У. Практическое руководство по заболеваниям желч ных путей. М.: ГЭОТАР-Медиа; 2001.

21. Маев И.В., Кучерявый Ю.А. Клинические перспективы гастро энтерологии, гепатологии. 2008; 3: 3—14.

22. Махов В.М., Ромасенко Л.В., Турко Т.В. Русский медицинский журнал. 2007; 9 (2): 37—42.

23. Мехтиев С.Н., Гриневич В.Б., Кравчук Ю.А. и др. Лечащий врач. 2008; 2: 29—34.

24. Осина В.А., Кузьмина Т.Н. Клиническая геронтология. 2006; 1: 16—22.

25. Осипенко М.Ф., Бикбулатова Е.А., Холин С.И. Атмосфера. 2007; (2): 6—10.

26. Остроухова Е., Красильникова Е. Врач. 2009; 11: 33—6.

27. Петухов В.А. Желчнокаменная болезнь и синдром нарушенного пищеварения. М.: ВЕДИ; 2003.

28. Поляруш Н.А., Дворяшина И.В. Международный эндокриноло гический журнал. 2007; 3 (9): 14—8.

29. Пчелинцев М. Врач. 2012; 3: 1—5.

30. Ройтберг Г.Е., ред. Метаболический синдром. М.: МЕДпресс информ; 2007.

31. Северов М.В. Клиническая фармакология и терапия. 2008; 17 (1): 11—5.

32. Трухан Д.И. Клинические перспективы гастроэнтерологии, гепа тологии. 2012; 1: 3—9.

33. Трухан Д.И., Викторова И.А., Лялюкова Е.А. Болезни желчного пузыря и желчевыводящих путей. СПб.: СпецЛит; 2011.

34. Успенский Ю.П., Балукова Е.В. Consilium medicum. Гастроэнте рология. 2009; 1: 41—5.

Ilm fan taraqqiyotida raqamli iqtisodiyot va zamonaviy ta'limning o'rni hamda rivojlanish omillari

35. Хакамова Г.А., Хисматуллина Г.Я., Волевач Л.В. и др. Лечащий врач. 2011; 7: 83—6.

36. Almeida A.M. World J. Gastroenterol. 2008; 14: 1415—8.

37. Astrup A., Buemann B., Western P. et al. Am. J. Clin. Nutr. 1994; 59: 350—5.

38. Athyros V.G., Tziomalos K., Gossios T.D. et al. Lancet. 2010; 376 (9756): 1916—22.

39. Corazziarei E., Shaffer E., Hogan W. et al. Gut. 1999; 45 (2): 1148—54.

40. Das S.K, Balakrishnan V. Indian J. Clin. Biochem. 2011; 26 (2): 202—9.

41. Franco-Bourland R., Méndez-Sánchez N. Ann. Hepatol. 2011; 10 (2): 216—7.

42. Giboney P.T. Am. Fam. Physician. 2005; 71 (6): 1105—11.

43. Huang M.A., Greenson J.K., Cbao C. et al. Am. J. Gastroenterol. 2005; 100: 1072—81.

44. Hojo M., Watanabe S. Hepatol. Res. 2011; 41 (3): 209—16.

45. Martinez J., Sanchez-Paya J., Palazon J.M. et al. Pancreatology. 2004; 4 (1): 42—8.

46. Martinez J., Johnson C.D., Sanchez-Paya J. et al. Pancreatology. 2006; 17 (3): 206—9.

47. Ratzui D.S., Zelber-Sagi S. Clin. Liver Dis. 2009; 13 (4): 667—8.

48. Shiffman M.L., Kaplan G.D., Brinkman-Kaplan V. et al. Ann. Intern. Med. 1995; 122: 899.

49. Weinsier R.L., Wilson L.J., Lee J. Am. J. Med. 1995; 98: 115.

Ilm fan taraqqiyotida raqamli iqtisodiyot va zamonaviy ta'limning o'rni hamda rivojlanish omillari