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INFLUENCE OF CHANGES IN THE INTESTINAL MICROBIOME ON THE COURSE AND PROGRESSION OF METABOLICALLY ASSOCIATED FATTY LIVER DISEASE

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Abstract

The frequency of detection of metabolically associated fatty liver disease in the population of developed countries is becoming a non-infectious pandemic, the growth drivers of which are obesity and diabetes mellitus. Currently, metabolically associated fatty liver disease occupies a firm position in the list of the most common liver diseases all over the world. Chronic liver diseases are accompanied by pronounced pathological changes in the composition of the human microflora, manifested by a deficiency of obligate microorganisms and microbial contamination of the small intestine, which requires a long-term therapeutic correction aimed at normalizing the gut microflora.

Objective: to study the impact of the intestinal microbiome disorders on the course and progression of metabolically associated fatty liver disease.

Materials and methods. The study included 105 patients with metabolically associated fatty liver disease. The diagnosis of metabolically associated fatty liver disease was exhibited on the basis of proven liver steatosis in combination with one of the following criteria: overweight/obesity, type 2 diabetes/insulin resistance syndrome, signs of metabolic dysregulation. Patients underwent a comprehensive clinical and laboratory study. The stage of liver fibrosis was determined using ultrasound elastography (Fibroscan). The study of the intestinal microbiome was carried out using the method of gas chromatography-mass spectrometry.

Results and its discussion. It was found that 68.6% of the cases of metabolically associated fatty liver disease were associated with obesity, 27.6% - with overweight body mass. It was revealed that in most patients there was an increase in ALT level, a violation of lipid metabolism (increased levels of total cholesterol, LDL and triglycerides, as well as a decrease in HDL levels), the development of insulin resistance syndrome. Violation of the of the intestinal microflora was revealed in 71.4% of patients. Patients with impaired intestinal microflora have higher levels of ALT, cholesterol, LDL, triglycerides, HOMA-index and lower levels of HDL, higher stage of fibrosis compared to the group without impaired intestinal microflora.

Conclusion. Disruption of the intestinal microflora occurs in the majority of patients with metabolically associated fatty liver disease and has a negative impact on the course (leading to more pronounced lipid metabolism disorders, higher ALT and HOMA index levels), as well as the progression of metabolically associated fatty liver disease (leading to a higher stage of fibrosis).

Keywords: *metabolically associated fatty liver disease, intestinal microbiome, obesity, fibrosis*

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Introduction

According to epidemiological studies, non-alcoholic fatty liver disease or metabolically associated fatty liver disease (MAFLD) [*Eslam M. et al., 2020*] is the most common metabolic liver disease [*Estes C. et al., 2018*]. At the moment, the frequency of detection of MAFLD in the population of developed countries is becoming a non-infectious pandemic [*Le M.H. et al., 2021]*, the growth drivers of which are obesity and diabetes mellitus [*Younossi Z.M. et al., 2016; Fouad Y. et al., 2020]*]. Currently, metabolically associated fatty liver disease occupies a firm position in the list of the most common liver diseases all over the world [*Chalasani N. et al., 2018*]. According to the latest systematic review, the prevalence of MAFLD in most regions of the world is well over 20 % and tends to increase [*Lim S. et al., 2021*] This negative trend is based on a steady increase in the incidence of such nosologies as diabetes, obesity, hyperlipidemia, metabolic syndrome, which, in turn, are predictors of MAFLD [*Le M.H. et al., 2021]*. Obesity is a worldwide metabolic disorder that is becoming a global pandemic [*Lin H. et al., 2021*]. In 2015, 604 million adults and 108 million children were obese. Obesity prevalence has doubled in 73 countries since 1980 [*Roeb E., 2021*].

In the Russian Federation, the frequency of MAFLD was 27% in 2007 (according to the epidemiological study DIREG_L_01903), and in 2014 it was 37.1% (an increase of more than 10%), which puts it in first place among liver diseases - 71.6% [*Klyarytskaya I. L. et al., 2015*]. Fibrosis develops in approximately 25 % of cases of MAFLD, previously considered a benign condition, and the development of fibrosis indicates a risk of progression to cirrhosis and associated death [*Yang S. et al., 2022*]. The frequency of transformation of non-alcoholic steatohepatitis (NASH) into liver cirrhosis within 10 years reaches 7%, which increases the risk of developing hepatocellular carcinoma [*Buzzetti E. et al., 2016*]. Therefore, early diagnosis and monitoring of the progression of liver fibrosis and steatosis is extremely important. The pathogenesis of MAFLD is only partially understood and remains unclear. According to modern concepts, the etiology and pathogenesis of MAFLD are considered within the framework of the concept of “multiple parallel strokes” [*Maev I.V. et al., 2022*]. One of these «strokes» is gut microbiota dysbiosis.

The human gut microbiome is a unique collection of microorganisms. Our body is a habitat for a large population of microorganisms, a kind of microbial ecosystem, characterized by its genetic regulation and complex interactions, and reacting to the influence of external and internal environmental factors [*Martín-Mateos R., Albillos A., 2021*]. It is so unique that there are no two people in the world with an identical microbiome [*Vajro P. et al., 2013*]. The gut microbiome is currently regarded as the main metabolic internal organ, consisting of more than 1014 species of microorganisms and containing a second genome (metagenome) that is 100–400 times larger than that of humans [*Aron-Wisnewsky J. et al., 2020*]. The total mass of all inhabitants of the intestine reaches 2.5-3 kg. The number of bacteria in 1 g of the contents of the colon exceeds the population of our planet. The invisible presence of the microbiome mediates a range of important processes, from metabolic and immune to cognitive.

To date, the experiment has proven the relationship between inflammation and damage in the liver, fibrogenesis and bacterial endotoxinemia [*Boursier J. et al.,2016]*. When a large amount of bacterial cell endotoxins enters the liver through the portal circulation system, endotoxins activate hepatocyte Toll receptors, which is accompanied by the expression of pro-inflammatory cytokines (for example, TNF-α, IL-6) [*Albillos A. et al., 2020*].

Since the liver and intestine are connected anatomically through the hepatic portal system, the intestinal microflora and its metabolic by-products may influence hepatic pathology [*Leung C. et al., 2016*]. Currently, the intestinal microflora is considered as a new virtual metabolic organ that interacts in our body with other organs and systems. But, of course, such an axis as the intestine-liver is attracting more and more attention. This axis is a consequence of the close anatomi-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

cal and functional, bidirectional interaction between the intestine and the liver, primarily through the portal blood flow [*Parthasarathy G. et al., 2020*]. The relationship between the gut microbiota and the liver is mediated through complex metabolic, immune, and neuroendocrine cross-talk between them [*Wiest R. et al., 2017*]. Violation of the quantitative and qualitative composition of the intestinal microbiota can lead to the emergence and progression of various diseases, among which liver diseases occupy a significant place.

Chronic liver diseases are accompanied by pronounced pathological changes in the composition of the human microflora, manifested by a deficiency of obligate (bifidum-, lacto-, colibacilli) microorganisms and microbial contamination of the small intestine, which requires a long-term therapeutic correction aimed at normalizing the microflora with probiotics, prebiotics and synbiotics.

In recent years, the possible role of the microflora of the digestive tract in the development of metabolic disorders and metabolically associated liver damage, such as non-alcoholic steatohepatitis, has been actively discussed, which is confirmed by a steadily growing number of experimental studies in animal models and humans [*Shen F. et al., 2017*]. Despite the fact that in recent years there have been more and more publications on the relationship of intestinal microflora with liver diseases (including MAFLD), insulin resistance and overweight, we are still waiting for the start of large prospective studies on this issue in humans.

The role of the intestinal microbiota in the pathogenesis of atherosclerosis has been actively studied only in recent years. New facts have appeared that indicate an unambiguous relationship between intestinal biocenosis and diseases such as obesity, metabolic syndrome, dyslipidemia, atherosclerosis, etc. The results of studies have shown that maintaining the qualitative and quantitative composition of the intestinal microflora is essential in the regulation of lipid metabolism.

It is known that disruption of the intestinal microflora and dissociation of tight intercellular junctions leads to an excessive intake of pathogen-associated molecules, such as lipopolysaccharides, peptidoglycans, into the portal bloodstream and then into the liver [*Aron-Wisnewsky J. et al., 2020*]. In the liver, the processes are implemented due to the direct effect of these pathogen-associated molecules on the hepatocytes themselves and also the implementation of the immune response by the liver in response to this dysbiosis factors [*Martín-Mateos R., Albillos A., 2021*]. This is expressed in the production of pro-inflammatory cytokines in response to the activation of toll- and nodd-like receptors, the activation of stellate cells, the production of collagen, with the progression of fibrosis to cirrhosis and the subsequent development of hepatocellular carcinoma [*Boursier J. et al., 2016*]. Thus, the study of the qualitative and quantitative composition of the intestinal microbiome and its influence at the course of various diseases is currently a promising direction.

Objective: to study the impact of the intestinal microbiome disorders on the course and progression of metabolically associated fatty liver disease.

Materials and methods.

The study included 105 patients with metabolically associated fatty liver disease aged 42 to 75 years, among them female patients predominated (63,8% of women (67 patients) and 36% of men (38 patients), respectively). Average age of patients – 51.5±4.7 years.

The diagnosis of metabolically associated fatty liver disease according to the 2020 international expert consensus statement, in which 32 experts representing 22 countries took part, was exhibited on the basis of proven liver steatosis (according to abdominal ultrasound, abdominal CT) in combination with one of the following criteria: overweight/obesity, type 2 diabetes/insulin resistance syndrome, signs of metabolic dysregulation. For diagnosis of MAFLD is no longer a prerequisite for the exclusion of the fact of abuse of hepatotoxic doses of alcohol, as well as other etiological variants of chronic liver disease.

Patients underwent a comprehensive clinical and laboratory study, including a complete blood count, a biochemical blood test with the determination of the level of alanin aminotransferase (ALT), aspartat aminotransferase (AST), alkaline phosphatase, gamma glutamil transferase (GGT), bilirubin and fractions, lipid profile, homeostatic model assessment (HOMA) index. The criterion for exclusion from the study was the presence of diabetes mellitus.

The stage of fibrosis in the liver was determined using ultrasound elastography (Fibroscan). The study of the intestinal microbiome in the small and large intestine was carried out using the method of gas chromatography-mass spectrometry.

According to the data of the clinical examination (BMI), the following were determined: among patients with MAFLD, patients with obesity of the 1st degree prevailed (40%), patients with excess body weight (in 27.6% of cases) and obesity of the 2nd degree (25.7%) were found in approximately equal proportions, and among men, it was most often registered obesity of the 1st degree (44.7%), and obesity of the 1st and 2nd degree is approximately the same among women (in 37.5% and 32.9% of cases, respectively) (Table 1).

To verify insulin resistance in patients with MAFLD, the HOMA-index was determined. The calculation of the HOMA-index was carried out according to the formula: HOMA-IR=fasting glucose in mmol/l*fasting insulin in μU/ml/22.5. The value of the HOMA index ≥ 2.5 was considered insulin resistance.

Based on the results of the ultrasound examination, a light (1 point), moderate (2 points) and severe (3 points) degree of fatty infiltration was verified. The criteria for a mild degree of diffuse fatty infiltration of the liver were a slight increase in echogenicity of the liver with loss of the borders of normal intrahepatic arteries, but normal visualization of the diaphragm. A moderate degree of diffuse fatty infiltration of the liver was defined as an increase in echogenicity of the liver with impaired visualization of the distal parts of the liver parenchyma and a moderate loss of echogenicity of the diaphragm. With sonographically expressed steatosis, an increase in the echogenicity of the liver is determined, with the absence of visualization of the diaphragm or the posterior segment of the right lobe of the liver. Moderate degree of hepatic steatosis was determined most often (60%) in the studied groups of patients.

Table 1

Distribution of patients in the study groups according to BMI

Groups of patients		Men (n=38)	Women (n=67)	Total
Norm		3 (7.9%	1 (1.5 %)	4 (3.8%)
Excess body weight		13 (34.3%	16 (23.8%)	29 (27.6%)
Degreeof obesity n (%)	1st	17 (44.7%)	25 (37.3%)	42 (40 %)
	2nd	5 (13.2%)	22 (32.9%)	27 (25.7 %)
	3rd	-	3 (4.5%)	3 (2.9%)
Total		38	67	105

Table 2

Level of biochemical indicators in patients with metabolically associated fatty liver disease

Indicator	Men (n=38)	Women (n=67)
ALT, (*U/l*)	57.32 ± 7.43	62.03 ± 8.94
AST, (*U/l*)	43.87 ± 3.47	41.54 ± 2.89
Total bilirubin, (μmol/l)	18.87 ± 0.97	17.64 ±1.05
Alkaline phosphatase, (*U/l*)	136.03 ± 10.32	144.67 ± 9.56
GGT, (*U/l*)	45.02 ± 3.91	42.76 ± 2.98
Cholesterol, (*mmol/l*)	6.75 ± 0.31	6.87 ± 0.42
LDL, (*mmol/l*)	3.65 ± 0.28	3.72 ± 0.34
HDL, (*mmol/l*)	0.87 ± 0.08	0.93 ± 0.07
Triglycerides, (*mmol/l*)	2.26 ± 0.18	2.18 ± 0.16
HOMA index	3.24 ± 0.36	3.42 ± 0.31

The work was performed in accordance with the research work of the Department of Therapy, gastroenterology, cardiology, general practice (family medicine), V.I. Vernadskiy Crimean Federal University, Institute «S.I. Georgievsky Medical Academy» «Diagnostics and treatment of comorbid pathology in the clinic of internal diseases" (state registration No.122041900051-5).

Results and Discussion.

According to the results of the biochemical blood analysis, the following changes were revealed (Table 2): statistically significant differences in the deviation of the level of biochemical indicators among men and women were not revealed: most often in both groups an increase in the level of ALT up to 2 norms, a violation of lipid metabolism (an increase in the level of total cholesterol, triglycerides, low-density lipoprotein (LDL,) and a decrease in high-density lipoprotein (HDL), as well as an increase in the level of the

Table 3

Stages of fibrosis in patients with MAFLD

Stage of fibrosis	Men (n=38)	Women (n=67)	Total (n=105)
F0	10 (26.3 %)	20 (29.8 %)	30 (28.6 %)
F1	16 (42.1 %)	29 (43.3 %)	45 (42.9 %)
F2	9 (23.6 %)	9 (13.4 %)	18 (17.1 %)
F3	2 (5.3 %)	6 (9 %)	8 (7.6 %)
F4	1 (2.7 %)	3 (4.5 %)	4 (3.8 %)

HOMA-index, which indicates the syndrome of insulin resistance, were registered.

When elastometry was performed on patients, this or that stage of fibrosis was registered in 71.4 % of patients, most often in both men and women, stage F1 according to the Metavir scale was found (in 42.9% of patients) (Table 3), however, in men, both the absence of fibrosis and the F2 stage occurred in approximately the same proportion (in 26.3% and 23.6% of patients, respectively).

When conducting a study of the intestinal microbiome in patients with IBD, the following changes were revealed: a violation of the intestinal microbiome was registered in 71.4% of patients: in 63.1% of men and 76.1% of women, respectively. The most frequently reported decrease of Bacteroides, Lactobacillus spp, Ruminococcus, Bifidobacterium spp, increase of Prevotella, Eubacterium Porphyromonas.

For further study and evaluation of the impact of intestinal microbiome disorders on the course and progression of MAFLD, patients were divided into 2 groups comparable by gender and age: group 1 (n=35) included patients with impaired intestinal microflora according to the results of gas chromatography-mass spectrometry, group 2 (n=30) - patients without disorders of the gut microbiome. A comparative study was carried out to assess the level of biochemical parameters in groups with and without intestinal microbiome disorders. The following patterns were identified: in group 1 there was a significant increase in ALT (60.54 ± 3.48 vs. 46.03 ± 7.04), total cholesterol (6.95 ± 0.41 vs. 5.87 ± 0.52), LDL (3.96 ± 0,38 vs. 3.06 ± 0.31), triglycerides (2.42 ± 0,19 vs. 2.05 ± 0.14) and HOMA index (3.54 ± 0.56) and a decrease in HDL levels (0,83 ± 0,05 vs. 1,15 ± 0,04) compared with group 2, where there were no violations of the intestinal microflora (table 4).

The impact of gut microbiome disturbances on

Table 4

Comparison of levels of biochemical indicators in patients with and without violations of the intestinal microflora

Indicator	Group 1 (n=35)	Group 2 (n=30)
ALT, (*U/l*)	60.54 ± 3.48	46.03 ± 7.04
AST, (*U/l*)	42.68 ± 2.17	40.37 ± 2.09
Total bilirubin, (μmol/l)	18.09 ± 0.87	18.64 ±0.95
Alkaline phosphatase, (*U/l*)	142.53 ± 8.42	143.71 ± 7.62
GGT, (*U/l*)	43.44 ± 2.65	42.54 ± 2.08
Cholesterol, (*mmol/l*)	6.95 ± 0.41	5.87 ± 0.52
LDL, (*mmol/l*)	3.96 ± 0.38	3.06 ± 0.31
HDL, (*mmol/l*)	0.83 ± 0.05	1.15 ± 0.04
Triglycerides, (*mmol/l*)	2.42 ± 0.19	2.05 ± 0.14
HOMA index	3.54 ± 0.56	3.17 ± 0.37

the progression of MAFLD was also studied by comparing the stages of fibrosis in groups with and without gut microflora disturbance. The following patterns were identified (Table 5): in group 1 (with impaired intestinal microbiota), most patients (in 97.1% of cases) had one or another stage of fibrosis, most often F2 (in 71.4% of cases), in group 2 (without violations of the intestinal microflora), fibrosis was registered in 40% of cases, most often at stage F1 (33.3%); at the same time, in group 2, fibrosis was not detected at all in 60% of cases.

Thus, according to the results of the study, it was found that among the patients with MAFLD, 68.6% of the cases were associated with obesity, and 27.6% - with overweight body mass. In women, obesity occurred in 74.7% of cases, in men - in 57.9% of cases.

According to the results of a biochemical study, it was revealed that in most patients there is an in-

Table 5

Comparison of stages of fibrosis in patients with and without violations of the intestinal microflora

Stage of fibrosis	Group 1 (n=35)	Group 2 (n=30)
F0	1 (2.9 %)	18 (60 %)
F1	3 (5.7 %)	10 (33.3 %)
F2	25 (71.4 %)	2 (6.7 %)
F3	5 (14.3 %)	0
F4	2 (5.7 %)	0

crease in ALT levels up to 2 norms, a violation of lipid metabolism (increased levels of total cholesterol, LDL and triglycerides, as well as a decrease in HDL levels), the development of insulin resistance syndrome (an increase in the level of HOMA index over 2.5).

Thus, the results of studies indicate that the majority of patients with MAFLD have a violation of the main metabolic functions of the liver. Naturally, obesity of hepatocytes leads not only to the progression of MAFLD, but also subsequently to the formation of hyper- and dyslipidemia. According to the data of domestic and foreign literature, MAFLD is often combined with disorders of carbohydrate metabolism, which is consistent with the results of our studies. Increased glucose absorption in patients with metabolically associated fatty liver disease may be associated with an increase in the permeability of the intestinal epithelium, which may be due to the effect of pathogenic and opportunistic microorganisms of the small intestine on the barrier function of the intestine.

In the study of the intestinal microbiome in patients with metabolically associated fatty liver disease, it was found that a violation of the qualitative and quantitative composition of the intestinal microflora is observed in the majority of the studied patients (in 71.4% of cases). A further comparative study of groups with and without impaired intestinal microflora revealed the following patterns: patients with impaired intestinal microflora have higher levels of ALT, cholesterol, LDL, triglycerides, HOMA-index and lower levels of HDL compared to the group without impaired intestinal microflora. It was also revealed the influence of disorders of the intestinal microflora on the progression of metabolically associated fatty liver disease in the form of a higher stage of fibrosis in patients with a violation of the intestinal microbiome. Our data are consistent with previous studies, which also studied the disturbances of the intestinal microflora in patients with metabolically associated fatty liver disease.

The obtained data emphasize the importance of studying the intestinal microflora in patients with metabolically associated fatty liver disease and the inclusion of drugs to improve the intestinal microflora (probiotics, prebiotics and synbiotics) in the treatment of metabolically associated fatty liver disease in order to stop the progression of metabolically associated fatty liver disease.

Conclusion.

According to the results of study, it was revealed that in most patients there is an increase in ALT levels, a violation of lipid metabolism, the development of insulin resistance syndrome, obesity or overweight body mass. Violation of the qualitative and quantitative composition of the intestinal microflora was revealed in 71.4% of patients. Violation of the intestinal microflora in patients with MAFLD led to higher levels of ALT, cholesterol, LDL, triglycerides, HOMA-index and lower levels of HDL and progression of stage of fibrosis.

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