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NEUROHORMONAL CHANGES AND INTESTINAL BARRIER FUNCTION DISORDERS IN IRRITABLE BOWEL SYNDROME IN PATIENTS WITH METABOLIC-ASSOCIATED FATTY LIVER DISEASE AND THEIR CORRECTION

Yelyzaveta Sirchak

The study of neuropsychometric disorders in patients with irritable bowel syndrome (IBS) in combination with metabolic associated fatty liver disease (MAFLD) can expand the diagnostic aspects and treatment options for patients with combined pathology.

The aim of this study *was to evaluate the impact of neurohormone levels and intestinal barrier function disorders on neuropsychometric changes in patients with IBS and MAFLD, as well as their correction.*

Materials and methods. *We examined 60 patients with IBS in the setting of MAFLD. The level of melatonin (MT) and serotonin (ST) in the blood serum was determined. The levels of α1-antitrypsin (α1-AT) and zonulin in the blood serum and faeces of the examined patients were evaluated. Patients were divided into two groups. The first group of patients (n=30) received only basic therapy. The second group of patients (n=30), in addition to the basic treatment, received the symbiotic drug Lothardi-A. The subjects were assessed for central nervous system dysfunction (Spielberg and Khanin self-esteem scale; Beck Depression Scale; Zang scale; Toronto Alexithymic Scale).*

Research results. *The obtained results confirm the positive effect of Lothardi A on improving the permeability of the intestinal barrier and the level of neurohormones in the blood serum in IBS and MAFLD. Additionally, a pronounced positive dynamic in the indicators of neuropsychotrauma is observed in these patients.*

Conclusions: *Changes in the level of ST and MT in the blood serum, which correlate with the severity of intestinal barrier function disorders, were diagnosed in patients with IBS and MAFLD. In patients with IBS and MAFLD, neuropsychometric status disorders were found. The course prescription of Lotardi-A as part of complex therapy for patients with IBS and MAFLD is pathogenetically justified and leads not only to the improvement of clinical symptoms but also contributes to the improvement of dysbiotic changes, impaired intestinal barrier function, normalization of serum levels of ST, MT, which is a prerequisite for improving the mental status of these patients*

Keywords: *non-alcoholic fatty liver disease/metabolic-associated fatty liver disease, irritable bowel syndrome, neurohormones (serotonin, melatonin), intestinal barrier function, neuropsychometric tests, probiotic*

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1. Introduction

Irritable bowel syndrome (IBS) is a functional disease of the gastrointestinal tract (GIT) that is more common in women than in men (1.5-3 times), mainly in young people (under 35 years of age) [1, 2]. Experts estimate that more than 40% of people worldwide meet the criteria for functional gastrointestinal disorders, including (but not limited to) IBS [3].

Irritable bowel syndrome is a disorder of gut-brain interaction that leads to recurrent abdominal pain associated with defecation and impaired bowel movements. Patients are considered to have IBS if they meet the diagnostic criteria of the Rome IV protocol, which includes bowel movements (constipation, diarrhoea, or a combination of both) associated with frequent abdominal pain and abdominal distension or bloating for at least 6 months before diagnosis [4]. A systematic review and meta-analysis indicate that the prevalence of IBS worldwide is 9.2%, with significant regional variation [5]. The highest prevalence rates of IBS are found in South America (17–21%), the lowest in South Asia (7–9%) and 5.6% in the Middle East and Africa. The prevalence of IBS ranges from 10 to 25% in the US population [3].

Mental health disorders such as anxiety and depression are also very common worldwide and are a major cause of disability and suicide. IBSis often associated with these disorders, and evidence suggests that people with IBS are at increased risk of anxiety and depression [6, 7]. The prevalence of anxiety and depression has increased over the past few decades. The COVID-19

pandemic has accelerated this growth [6, 8]. The prevalence of IBS has also been increasing in recent years, which is due, on the one hand, to increased awareness of doctors and correct diagnosis of IBS, and, on the other hand, to westernisation, changes in eating behaviour and lifestyle of modern people [9].

Non-alcoholic fatty liver disease (NAFLD) (or metabolic-associated fatty liver disease (MAFLD)) is the leading cause of morbidity and mortality associated with liver disease [10]. Its rapid growth is driven by the pandemic of obesity and type 2 diabetes [11, 12]. In this context, the number of metabolic conditions that a person has not only increases the risk of developing NAFLD but also the risk of progression to end-stage liver disease and mortality. In addition to adverse clinical outcomes, such as increased mortality, NAFLD is also associated with significant economic costs and health-related quality of life [13, 14].

Certain species of gut microbiota, especially Firmicutes and Bacteroidetes, have been shown to affect mental health through the microbiota-gut-brain axis, and gut microbiota dysbiosis may be associated with mental disorders such as anxiety, depression and other mental disorders. On the other hand, dietary components, including probiotics (lactobacilli and bifidobacteria), prebiotics (dietary fibre and alpha-lactalbumin), symbiotics, postbiotics (short-chain fatty acids), dairy products, spices (Zanthoxylum bungeanum, curcumin and capsaicin), fruits, vegetables, medicinal plants, etc. may have a protective effect on mental disorders by enhancing the beneficial gut microbiota and suppressing the harmful one [15].

Therefore, the study of neuropsychometric disorders, as well as the factors underlying their formation in patients with IBS in combination with MAFLD, can expand the diagnostic aspects and treatment options for patients with combined pathology.

The aim of this study was to evaluate the impact of neurohormone disorders and intestinal barrier function on neuropsychometric changes in patients with IBS and MAFLD, as well as their correction.

2. Materials and methods

The study included 60 patients with IBS and NAFLD/MAFLD. The examined patients with IBS and MAFLD in 2024 were examined and treated at the clinical base of the Department of Propedeutics of Internal Diseases of the State Educational Institution ‘Uzhhorod National University'. Among the examined men, there were 12 (20.0%), the average age was 34.8±6.2 years; women were 48 (80.0%), and the average age was 32.5±5.3 years. The control group consisted of 30 practically healthy individuals (6 (20.0%) men and 24 (80.0%) women). The average age of the control group was 33.6±4.8 years for women and 34.1±5.2 years for men.

All examinations and treatments were performed with the consent of the patients (written consent for appropriate diagnosis and treatment was obtained from all patients and control subjects), with all measures taken to ensure the anonymity of the information obtained. The study's methodology complied with the Helsinki Declaration of Human Rights of 1975 and its 1983 revision, the Council of Europe Convention on Human Rights and Biomedicine, and Ukrainian legislation. The research and treatment were approved by the Bioethics Committee of the SHEI “Uzhhorod National University”, Protocol No. 1/12, from 31.01.2025.

The inclusion criteria were as follows: patients with MAFLD and IBS.

The criteria for exclusion from the study were: liver damage of alcoholic, viral (hepatitis B, C, D viruses) etiology, autoimmune hepatitis; Wilson-Conovalov disease; haemochromatosis; chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis); lactose intolerance; celiac disease; intestinal surgery (including appendectomy for up to 6 months); colon cancer; doligosigma; colon diverticulosis; positive test for toxins A and B of Clostridium difficile bacteria in faeces; type 1 diabetes mellitus; type 2 diabetes mellitus (decompensation stage); pulmonary tuberculosis (active form); psychiatric diseases; pregnancy and lactation; systemic autoimmune diseases; HIV infection; oncological diseases.

All examined patients underwent general clinical, anthropometric, instrumental, and laboratory assessments. To verify the diagnosis, the nature of the complaints and medical history were detailed. During the anthropometric examination, height, weight, and waist circumference were determined, and body mass index (BMI) was calculated.

The diagnosis of IBS was made based on the IV Rome criteria and clinical guidelines of the Ukrainian Gastroenterological Association for the management of patients with irritable bowel syndrome.

The diagnosis of NAFLD (steatotic liver disease associated with metabolic disorders) was verified following the criteria of the unified clinical protocol (Order of the Ministry of Health of Ukraine of 06.11.2014, No. 826) and EASL-EASD-EASO clinical guidelines for the diagnosis and treatment of these patients. The degree of liver damage was assessed using online calculators, including the NAFLD Fibrosis Score (NFS), Fibrosis-4 Calculator (FIB-4), FibroTest, FibroIndex, Forns, APRI, and the commercial licensed test FibroMax, as well as liver elastometry results. All patients underwent an ultrasound examination of the abdominal cavity, conducted according to the generally accepted methodology, with an emphasis on indicators of the hepatobiliary system.

Standard general and biochemical tests were performed in the blood serum to determine the functional state of the liver, kidneys, lipid and carbohydrate metabolism. All examined patients underwent serum melatonin (MT) levels by radioimmunoassay using test kits (LDN Labor Diagnostika Nord GmbH, Germany), and serum serotonin (ST) levels were determined by high-performance liquid chromatography on an Agilent 1100 chromatograph using an Agilent Technologies test system (USA).

The level of α1-antitrypsin (α1-AT) was determined in serum and faeces by enzyme-linked immunosorbent assay (ELISA) using a test system from Immundiagnostik AG (Germany), and its clearance was calculated based on the values obtained. The level of zonulin in blood serum and faeces was also measured by ELISA using a test system from Elabscience (USA).

Changes in the quantitative and qualitative composition of the colon microflora were determined using the unified working classification of intestinal dysbiosis

by Kuvaeva-Ladodo (1991), which distinguishes four phases of dysbiotic disorders.

The examined patients with IBS and MAFLD before and after treatment, as well as those in the control group, were assessed for central nervous system (CNS) dysfunction using the following tests:

1. Self-esteem scale_- (by C.D. Spielberg (1972) and modified by Y. L. Khanin (1976) – allows us to determine the level of anxiety at present (reactive anxiety as a state) and personal anxiety (as a stable characteristic of a person). The results were assessed as follows: up to 30 – low; 31–45 – moderate; 46 and more – high anxiety.

2. Beck Depression Inventory (BDI) – allows to characterise the emotional sphere of patients. The results were evaluated as follows:

– 0–13 – variations considered normal;
– 14–19 – mild depression;
– 20–28 – moderate depression;
– 29–63 – severe depression.

3. Zung Self-Rating Depression Scale (ZS-RDS) – used to quantify the severity of depressive disorders in various somatic diseases. The results were evaluated as follows: 20–49 – normal; 50–59 – mild depression; 60–69 – moderate depression; 70 and above – severe depression.

4. The Toronto Alexithymia Scale (TAS) is designed to assess three main qualities of alexithymia: difficulty in identifying and describing one's own experiences; difficulty in distinguishing between feelings and bodily sensations; and focusing more on external events than on internal experiences. According to the authors of the methodology, an 'alexithymic' personality type receives 74 points and above, and a 'non-lexithymic' personality type receives 62 points and below.

Neuropsychometric testing was performed at intervals of 2–3 hours to restore attention and concentration in the examined patients.

Patients with IBS in combination with MACP were divided into two groups based on the treatment method. The first group of patients (group I – n= 30) received only basic therapy aimed at correcting the functional state of the intestine and liver. The second group of patients (group II – n= 30), in addition to the basic treatment, received the symbiotic drug Lothardi-A containing Saccharomyces boulardii (5.0×10^9 CFU (colony-forming units)), Lactobacillus acidophilus (1.0×10^9 CFU), Lactobacillus paracasei (1.0×10^9 CFU), Lactobacillus rhamnosus (1.0×10^9 CFU), Enterococcus faecium (1.0×10^9 CFU), Lactobacillus salivarius (1.0×10^9 CFU), Lactobacillus plantarum (1.0×10^9 CFU), Bifidobacterium bifidum (1.0×10^9 CFU), Bifidobacterium lactis (1.0×10^9 CFU), Bifidobacterium longum (1.0×10^9 CFU), as well as fructooligosaccharides (25 mg), enzymes (alpha-amylase – 25 mg), 1 capsule 2 times a day for 1 month.

The analysis and processing of the results was carried out using the computer program Statistics for Windows v.10.0 (StatSoft Inc, USA) using parametric and nonparametric methods of evaluating the results.

3. Results of the study

The irritable bowel syndrome in patients with MAFLD is clinically more often manifested by constipation (in 46.7–43.3 % of patients), as well as constipation followed by diarrhoea (in 30.0–36.7 % of patients, respectively) (Fig. 1).

In determining quantitative and qualitative changes in the colon microflora, mainly second-degree CD was found (in half of the subjects of both groups) before treatment. Degree I of colon dysbiosis was diagnosed in 36.7% of patients in group I and 40.0% of patients in group II. Before the treatment, III degree of CD was diagnosed in 13.3–10.0 % of the subjects. The results are presented in Fig. 2.

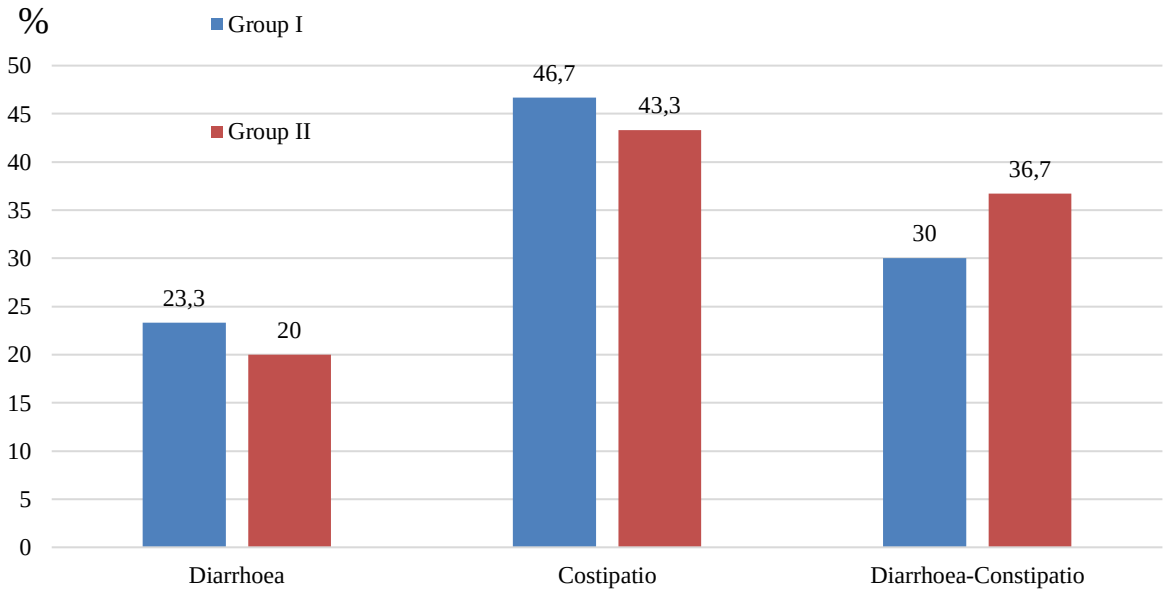

Fig. 1. Frequency of clinical manifestations of IBS in patients with MAFLD before treatment

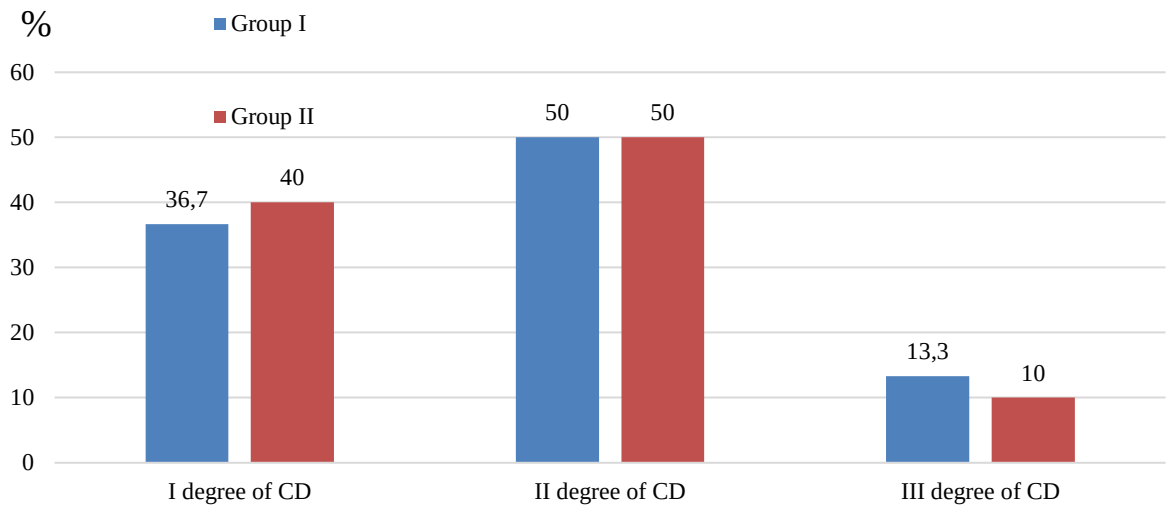

Fig. 2. Severity of colon dysbiosis in patients with IBD and MAFLD before treatment

The level of zonulin and α1-antitrypsin (α1-AT) in the blood serum and faeces in patients with MAFLD and IBS was determined (Table 1). The results obtained indicate an increase in the level of zonulin and α1-AT both in the blood serum and in the faeces of the examined patients with IBS and MAFLD and indicate a violation of the intestinal barrier function in these patients.

It is known that increased secretion of zonulin indicates an increase in intestinal permeability. Obesity and its complications, including high cholesterol, type 2 diabetes mellitus, coronary heart disease, high blood pressure and stroke, are associated with chronic inflammation and are often associated with changes in zonulin levels. Studies have shown a correlation between the total number of bacteria in the gut and serum zonulin levels, confirming the role of the gut microbiota, especially in obesity, in the formation of abnormal gut permeability to endotoxin [16]. Serum zonulin levels correlate with total calorie, protein, carbohydrate, sodium, and vitamin B12 intake in obese women. Ruminococcaceae and Faecalibacterium were more prevalent in the low zonulin group, suggesting that butyrate-producing gut bacteria, such as Faecalibacterium, may reduce gut permeability by lowering zonulin levels and reducing inflammation [17]. Zonulin has been shown to be associated not only with obesity but also with its metabolic complications, including insulin resistance, NAFLD, gestational diabetes, hyperlipidaemia, and type 2 diabetes [18, 19].

Increased intestinal permeability is also associated with the pathogenesis of IBS. In particular, patients with diarrhoea-associated IBS have been shown to have elevated serum zonulin levels and the involvement of protease-activated receptor 2 (PAR2) in activating the zonulin target receptor [20–22].

Table 1

Dynamics of biomarkers of intestinal barrier function disorders in the examined patients with IBS and MAFLD on the background of complex treatment

Indicator (results of the control group)	Examined patients with IBS and MAFLD			
	Group I (n=30)		Group II (n=30)	
	before treatment	after treatment	before treatment	after treatment
Zonulin:				
in blood serum, ng/ml 15.23 ± 0.31	123.15 ± 1.45***	114.21 ± 2.06	130.77 ± 2.10***	68.09 ± 0.55++##
in the faeces, ng/ml 17.56 ± 0.45	138.78 ± 2.07	130.07 ± 3.21	141.07 ± 1.88	70.60 ± 0.38++##
α1-antitrypsin (α1-AT):				
in blood serum, mg/dl 114.21 ± 1.56	190.12 ± 1.45**	179.28 ± 2.06	188.91 ± 1.30**	147.06 ± 1.09+#
in the faeces, mg/dl 12.08 ± 0.17	24.15 ± 0.29**	23.80 ± 1.15	23.57 ± 0.39**	17.60 ± 0.28+#
clearance of α1-AT, ml/day 16.77 ± 0.82	31.05 ± 0.33**	30.07 ± 1.08	30.64 ± 0.48*	20.08 ± 0.22+#

*Note: the difference between the indicators in patients of groups I and II before treatment and the data of the control group is significant: * – p<0.05; ** – p<0.01; *** – p<0.001; the difference between the indicators in patients by groups before and after treatment is significant: + – p<0.05; ++ – p<0.01; the difference between the indicators in patients of groups I and II after treatment is significant: # – p<0.05; ## – p<0.01*

Additional administration of symbiotic complex Lothardi-A to patients with IBS and MAFLD contributed to a decrease in the severity of intestinal permeability. At the same time, a significant decrease in the level of zonulin in the blood serum was found by 1.9 times and in the faeces by 2.0 times ($p<0.01$). The same trend can be observed in the assessment of the dynamics of α1-AT levels in the blood serum and faeces in these patients of group II on the background of the symbiotic complex administration.

We assessed changes in the levels of neurohormones such as melatonin and serotonin in the blood serum, as well as their dynamics during treatment (Table 2).

Experimental models have shown that autonomic nerve signals from the liver to the intestine are involved in the pathogenesis of the onset and progression of MAFLD through neural signal transduction. Serotonin has also been shown to be an effector of this gut-liver axis in MAFLD by modifying the expression of tight junction proteins, microbiota composition, and short-chain fatty acids [23].

The involvement of the autonomic nervous system is a key factor connecting different organs in the body. Activation of the autonomic nerves changes the gastrointestinal microbiota and the composition of the intestinal microbiota. It can be assumed that MAFLD is associated with a violation of the transmission of autonomic nerve signals from the liver. Serotonin is a key factor involved in this pathway. Serotonin is a monoamine neurotransmitter, 90% of which is found in the gastrointestinal tract, synthesised from tryptophan and secreted by chromaffin cells in the small intestine. Serotonin has numerous functions, such as vascular and bronchial smooth muscle contraction, acceleration of peristaltic movements, respiratory rhythm, regulation of pancreatic β-cells, liver regeneration, liver fibrosis, protection against intestinal ischaemia and food-seeking behaviour, and its reuptake inhibitors are used as an antidepressant for gastrointestinal symptoms. In addition, serotonin has been reported to be involved in fibrosis in MAFLD, the modification of lipid metabolism, and the activation of serotonin receptor signalling in hepatocytes [23–25]. Blockade of the serotonin receptor HTR3, which is expressed in the intestine, has been shown to change the strength of the tight junction and improve obesity-associated fatty liver in experimental animals. Furthermore, Choi et al. (2018) reported that selective inhibition of HTR2A, a receptor expressed in the central nervous system, prevented liver steatosis. Thus, serotonin may play a key role in animal models in the pathogenesis of NAFLD through autonomic nerve signals from the liver, and the role of serotonin in this axis is crucial [23].

Table 2

Dynamics of neurohormone levels in blood serum in the examined patients with IBS with MAFLD on the background of complex treatment

Indicator (results of the control group)	Examined patients with IBS and MAFLD			
	Group I (n=30)		Group II (n=30)	
	before treatment	after treatment	before treatment	after treatment
Serotonin, mkg/l	271.09 ± 2.15**	277.16 ± 4.28	288.17 ± 1.03**	316.90 ± 2.60+#
341.03 ± 7.12				
Melatonin, pg/ml	52.18 ± 0.30*	50.09 ± 0.44	57.25 ± 0.78**	43.16 ± 0.25+#
30.77 ± 0.77				

*Note: the difference between the indicators in patients of groups I and II before treatment and the data of the control group is significant: * – $p<0.05$; ** – $p<0.01$; the difference between the indicators in patients by groups before and after treatment is significant: + – $p<0.05$; ++ – $p<0.01$; the difference between the indicators in patients of groups I and II after treatment is significant: # – $p<0.05$; ## – $p<0.01$.*

The results of our studies indicate a decrease in serum serotonin levels in patients with IBS and MAFLD.

The pathophysiology of IBS is not fully understood, but it is known that changes in the connections between the gut and the brain, impaired information processing in the central nervous system (CNS), motor disorders, and visceral hypersensitivity contribute to the formation of IBS. Other less important or less understood mechanisms involved in the development of IBS include genetic associations, changes in the gastrointestinal microbiota, and mucosal and immune dysfunction [26]. Changes in the gut-brain connection and differences in brain function are the main factors contributing to the development of IBS; however, the impact of key neurotransmitters such as norepinephrine, serotonin, glutamate, GABA and acetylcholine on IBS is still unknown. Dysfunctions of neurotransmitters may contribute to the onset of IBS. Some of the most common symptoms used to diagnose it are grouped into two main aspects: visceral hypersensitivity and motor disorders, although they can also be associated with other symptoms such as diet-related digestive disorders, psychosocial disorders, anxiety, depression, fatigue, hypertension, dyslipidaemia, etc. [27]. Thus, targeting these dysfunctions may open up new ways to treat IBS, taking into account that these symptoms may also be indirect effects mediated by other biological and psychological factors.

Our findings indicate a significant increase in serum serotonin levels during Lotardi-A administration in patients with IBS and MAFLD. This occurred against the background of a decrease in blood melatonin levels in these patients.

The correlation analysis allows us to assert the role of serum levels of the neurohormones serotonin and melatonin and the severity of colon dysbiosis (CD) in IBS in patients with MAFLD (Table 3).

Table 3

Comparison of neurohormone levels with the severity of colon dysbiosis and indicators of intestinal barrier function in the examined patients

Indicator	Examined patients with IBS and MAFLD			
	Serotonin		Melatonin	
	Group I (n=30)	Group II (n=30)	Group I (n=30)	Group II (n=30)
Colon dysbiosis:				
I degree	r= –0.74; p<0.05	r= –0.70; p<0.05	r= 0.68; p<0.05	r= 0.70; p<0.05
II degree	r= –0.80; p<0.01	r= –0.82; p<0.01	r= 0.76; p<0.01	r= 0.78; p<0.01
Zonulin:				
in blood serum, ng/ml	r= –0.88; p<0.01	r= –0.84; p<0.01	r= 0.76; p<0.01	r= 0.78; p<0.01
in the faeces, ng/ml	r= –0.92; p<0.01	r= –0.92; p<0.01	r= 0.84; p<0.01	r= 0.80; p<0.01
α1-AT:				
in blood serum, mg/dl	r= –0.76; p<0.01	r= –0.74; p<0.05	r= 0.76; p<0.01	r= 0.70; p<0.05
in the faeces, mg/dl	r= –0.80; p<0.01	r= –0.82; p<0.01	r= 0.78; p<0.01	r= 0.82; p<0.01
clearance of α1-AT, ml/day	r= –0.82; p<0.01	r= –0.88; p<0.01	r= 0.84; p<0.01	r= 0.82; p<0.01

At the same time, not only the severity of duodenal dysbiosis, but also the impairment of duodenal barrier function according to its biological markers (serum and faecal levels of zonulin and α1-AT) negatively correlates with serotonin and affects the level of melatonin in IBS in patients with MAFLD.

We also evaluated the features of neuropsychometric changes and their dynamics when using Lothardi-A in patients with IBS and MAFLD (Fig. 3–6).

We assessed the state of the emotional sphere and its severity in the examined patients using neuropsychometric testing. The analysis of the data of the self-esteem scale by C.D. Spielberg and Y.L. Khanin revealed pronounced situational anxiety in the examined patients with IBS and MAFLD (in 53.3–60.0% of the examined patients) – Fig. 3.

The index of reactive anxiety, which depends on the life situation, was also increased in all groups of patients. After the course of treatment in patients of group II, a decrease in the severity of anxiety (mainly situational anxiety – by 40.0% – p<0.01) was determined.

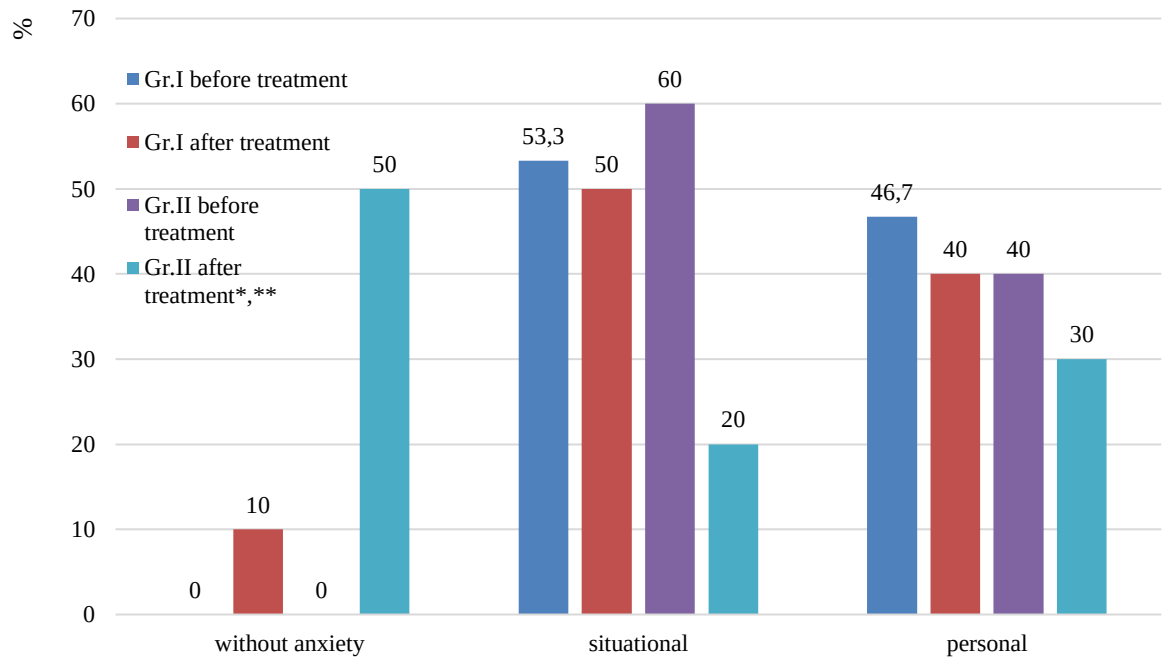

Fig. 3. Indicators of the Spielberg-Khanin self-esteem scale in the subjects and their dynamics during treatment: the difference between the indicators in patients of group II before and after treatment is statistically significant: * – p < 0.05; ** – p < 0.01

When assessing the emotional sphere according to the BDI test results, moderate and mild depression was diagnosed more often (Fig. 4). The minimum deviation in scores was found in patients of group II after treatment

(13.02±0.76 points – p<0.05), and the maximum values were diagnosed before treatment in these patients (19.51±1.28 points, respectively – p<0.01).

In the analysis of the BDI test after treatment, 50.0% of patients in group II had no signs of depression, and a pronounced form of depression was not detected in these patients at all. In contrast, in group I, no changes were actually detected. At the same time, the analysis of the BDI test data revealed most of the answers to the questions characterising apathetic and somatic manifestations of depression.

As with the BDI test, the Zung scale indicates that there are no patients who had no signs of depression before treatment. However, complex therapy with the use of the probiotic complex Lothardi A in patients with IBS and MAFLD contributed to a decrease in the severity of depression by 46.7 % (p<0.01). In addition, 56.7 % of patients, after a course of symbiotic complex Lothardi-A, did not show signs of depression (Fig. 5).

The ability to verbalise the emotions experienced by the subjects or other people is indicated by the results of the Toronto Alexithymic Scale (Fig. 6).

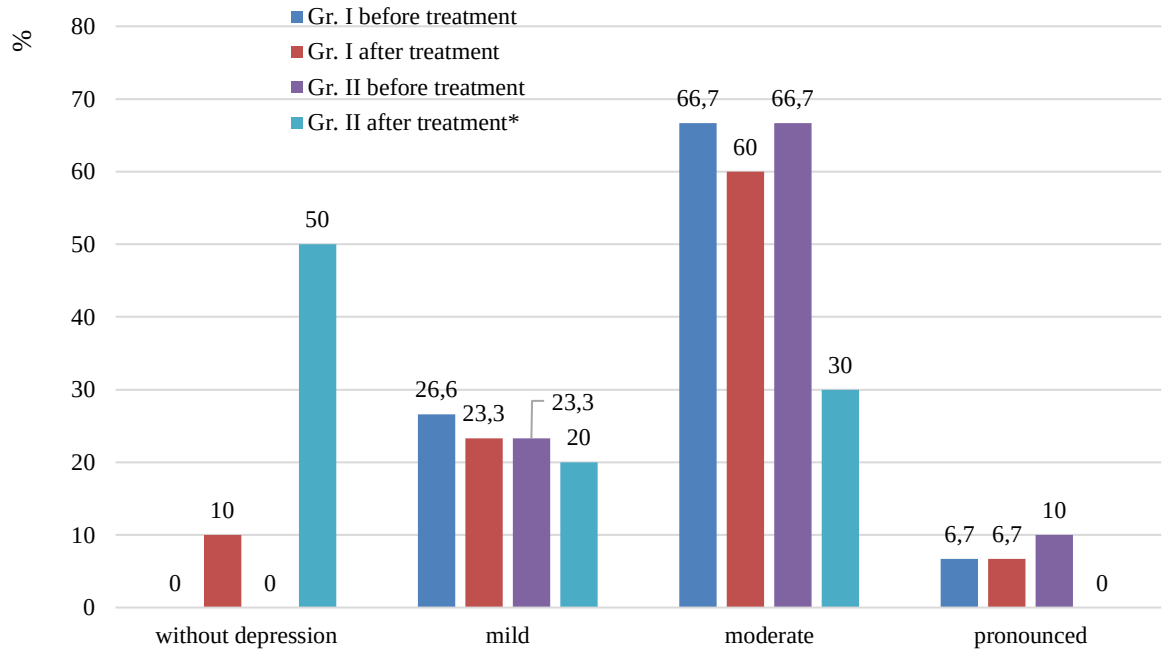

Fig. 4. Severity of depression according to the BDI scale in the subjects and their dynamics during treatment: the difference between the scores of patients in group II before and after treatment is statistically significant: * – p < 0.01

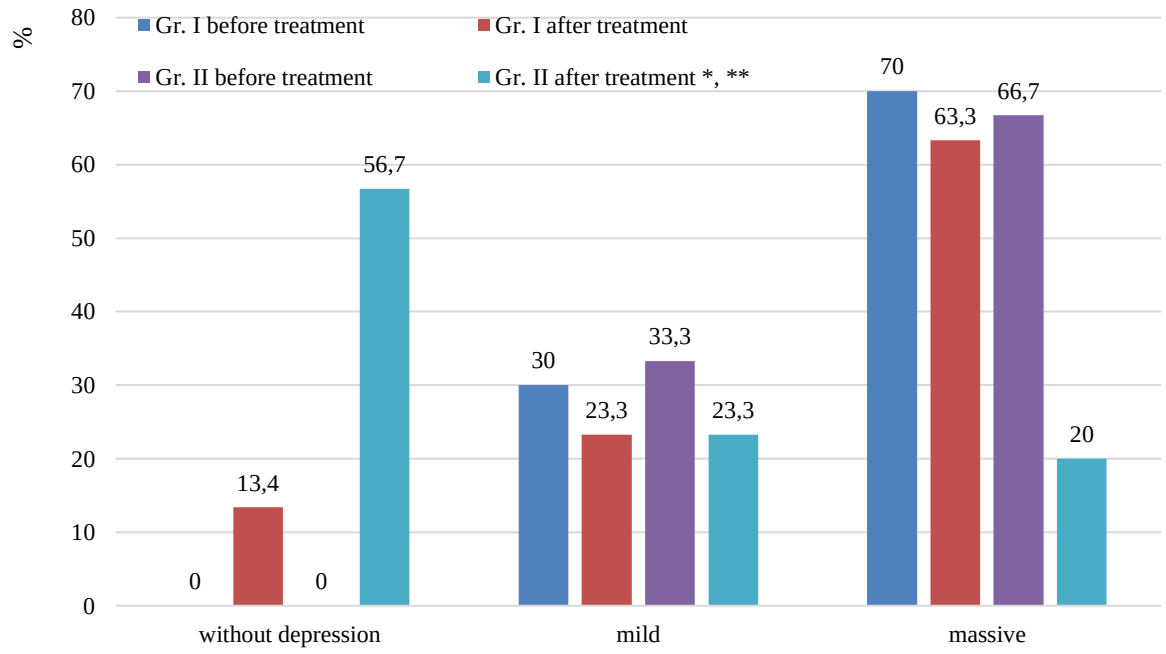

Fig. 5. Severity of depression according to the Zung scale in the subjects and their dynamics during treatment: the difference between the indicators in patients of group II before and after treatment is statistically significant: * – p < 0.05; ** – p < 0.01

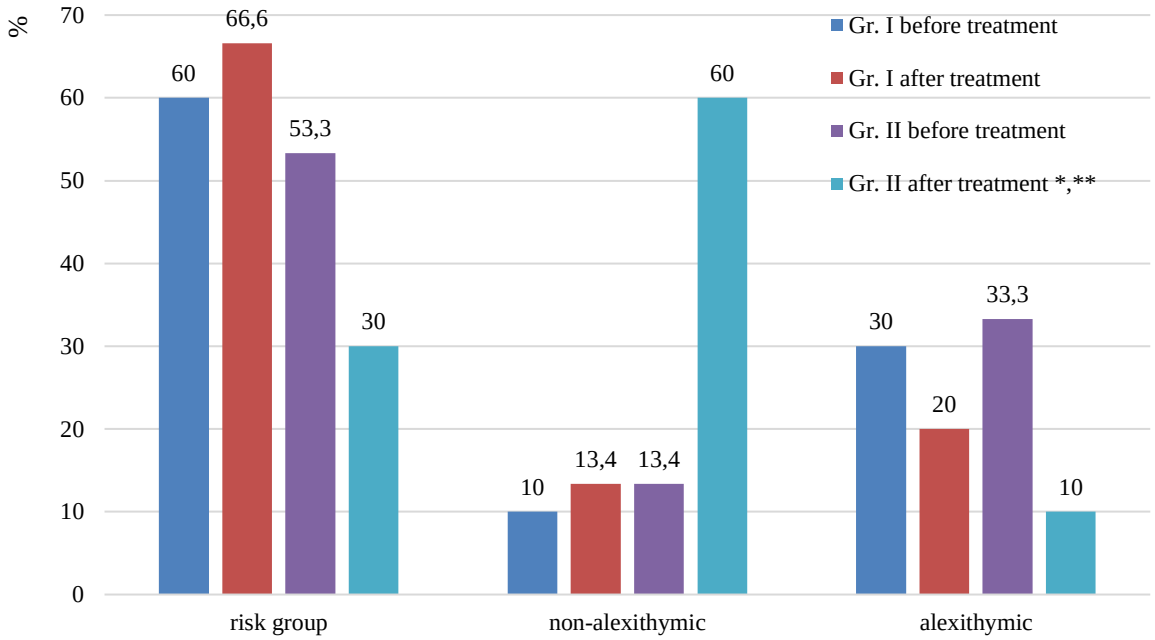

Fig. 6. Toronto Scale score in the examined patients and their dynamics during treatment: the difference between the control group and the examined patients is statistically significant: * – $p < 0.05$; ** – $p < 0.01$

According to the results of the Toronto Alexithymia Scale, 30.0–33.3% of patients with irritable bowel syndrome in the setting of non-alcoholic fatty liver disease have impaired communication function, which manifests itself in difficulties in verbal expression of emotional state. The characteristic features of these patients are a reduced ability to adequately verbalise the experience and an insufficient ability to differentiate and articulate their own emotional experiences.

The results of the neuropsychometric testing made it possible to establish that the comorbidity of somatic and functional gastrointestinal pathology in the examined patients is accompanied by pronounced manifestations of depression, anxiety, and self-doubt, which is especially important when choosing treatment tactics for these patients.

Clinical trials have shown that Lothardi-A, which contains verified strains of lactobacilli, bifidobacteria, and saccharomycetes, demonstrates therapeutic efficacy in treating the clinical manifestations of irritable bowel syndrome in patients with non-alcoholic fatty liver disease. The multistrain complex, which includes nine strains of lactobacilli and bifidobacteria, has a favourable effect on intestinal microbiocenosis, which is accompanied by an improvement in the quality of life of patients with irritable bowel syndrome. The probiotic strains contained in Lothardi-A play a key role in maintaining the homeostasis of the intestinal microbiota, demonstrate immunomodulatory activity, increase the body's immunological reactivity and exhibit antioxidant properties. The components of the product have an inhibitory effect on the proliferation of pathogenic microorganisms in the intestine. Studies have confirmed the clinical significance of the additional prescription of this symbiotic agent not only for the correction of dysbiotic disorders of the colon but also for the optimisation of metabolic processes in the body and the improvement of the functional state of the liver. Lothardi A has also been shown to have a positive effect on indicators of impaired intestinal permeability and the dynamics of serum serotonin and melatonin levels in patients with IBS and MAFLD.

Thus, the treatment of IBS, especially in comorbidity with morbid obesity, attracts great attention since therapy with a single drug rarely relieves symptoms in such patients. In clinical practice, there is still a lack of effective treatment for IBS, and the prescribed drugs usually relieve only one symptom of this disease. Our studies in patients with IBS and MAFLD indicate neurotransmitter dysfunction, which occurs against the background of impaired intestinal microbiocenosis and barrier function. These changes are associated not only with clinical symptoms, such as abdominal pain, bloating, and changes in stool frequency in IBS, but also correlate with neuropsychometric changes in these patients. Personalised analysis of neurohormones, as well as anxiety and CNS status in patients with IBS with MAFLD, is a necessary tool to develop more effective strategies to achieve a better understanding of the role of the gut-brain axis and its correction.

Our results confirm the effectiveness of Lothardi A not only on the dynamics of clinical symptoms and severity of colon dysbiosis (as shown in our previous studies), but also indicate a positive effect on improving intestinal barrier permeability and neurohormone levels in the blood serum in IBS and MAFLD. At the same time, pronounced positive dynamics in the neuropsymotility indicators are observed in these patients with combined functional pathology of the gastrointestinal tract and liver.

4. Discussion

Depression and anxiety impact people's everyday lives, health, and economic position. According to research, depression may overtake heart failure as the most prevalent disease in the world by 2030. Anxiety and stress are often present in conjunction with depressive disorders [28, 29]. Anxiety disorders are thought to be 47–58% more likely to develop during a depressive episode, and 56% of people with anxiety disorders experience depression. Patients' unexpectedly unpleasant life situations occur around 50% of the time before depressive episodes. Unfortunately, everyone experiences stress at some point in their life [30, 31].

Pharmacotherapy is the keystone of current therapies for depression. Selective serotonin reuptake inhibitors (SSRIs) are the most popular first-line medication, although monoamine oxidase and serotonin-norepinephrine reuptake inhibitors are also used. However, the effectiveness of currently available antidepressant medications used in clinics for symptom relief and prevention seems inconsistent. In addition, it has been shown that tolerance develops during follow-up care; using the same medication on the same patient repeatedly leads to decreased efficacy. Up to 35% of people are estimated to experience treatment-resistant depression. Therefore, there is a need to explore novel therapies for preserving the quality of life for all people suffering from depression [28].

According to studies, there is a correlation between diet, nutrition and anxiety and depression. Preliminary studies suggested that dietary changes may be an alternate treatment or preventative measure for anxiety and depression. The correlation between an unhealthy diet and the propensity to develop mental illnesses has received more attention in recent years. "Western" dietary patterns with low consumption of fruits and vegetables and high consumption of refined grains, fried and processed meals, red meat, and high-fat dairy products are linked to anxiety and depression. Stress and depression may also affect dietary preferences, how sweet and fatty foods are perceived, and taste thresholds [28, 32–34].

More than 3.8×10^{13} bacteria exist in the human gut microbiota [35]. Microflora dysbiosis is associated with increased intestinal permeability and systemic inflammation. The human gut has the second-highest concentration of neurons after the brain [35, 36]. Therefore, studies have been conducted to find the association between gut microbiota and depression.

It is especially important to find effective methods for the correction of psychological status disorders in patients with functional disorders of the digestive system in metabolic-associated conditions, such as MAFLD.

Clinical trials have shown that Lothardi-A, which contains verified strains of lactobacilli, bifidobacteria, and saccharomycetes, demonstrates therapeutic efficacy in treating the clinical manifestations of irritable bowel syndrome in patients with non-alcoholic fatty liver disease. The multistrain complex, which includes nine strains of lactobacilli and bifidobacteria, has a favourable effect on the intestinal microbiocenosis, which is accompanied by an improvement in the quality of life of patients with irritable bowel syndrome. The probiotic strains contained in Lothardi-A play a key role in maintaining the homeostasis of the intestinal microbiota, demonstrate immunomodulatory activity, increase the body's immunological reactivity and exhibit antioxidant properties. The components of the product have an inhibitory effect on the proliferation of pathogenic microorganisms in the intestine. Studies have confirmed the clinical significance of the additional prescription of this symbiotic agent not only for the correction of dysbiotic disorders of the colon, but also for the optimisation of metabolic processes in the body and improvement of the functional state of the liver. Lothardi A has also been shown to have a positive effect on indicators of impaired intestinal permeability and the dynamics of serum serotonin and melatonin levels in patients with IBS and MAFLD.

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Our results confirm the effectiveness of Lothardi A not only on the dynamics of clinical symptoms and severity of colon dysbiosis (as shown in our previous studies) but also indicate a positive effect on improving intestinal barrier permeability and neurohormone levels in the blood serum in IBS and MAFLD. At the same time, pronounced positive dynamics in the neuropsymotility indicators are observed in these patients with combined functional pathology of the gastrointestinal tract and liver.

Limitations of the study. To obtain more reliable conclusions, further studies should be aimed at involving a larger number of case patients. It is also planned to divide the patients in future studies depending on the clinical form of IBS.

Prospects for further research. Further research is needed to clearly define the tactics of introductions in patients with IBS in MAFLD, as well as to improve methods of their correction.

5. Conclusions

1. Changes in the level of serum neurohormones serotonin and melatonin in patients with IBS with MAFLD were diagnosed and correlated with the severity of intestinal barrier function disorders in these patients.

2. In patients with IBS with MAFLD, neuropsychometric status disorders were found. The course prescription of symbiotic agent Lothardi-A as part of complex therapy in patients with IBS and MAFLD is pathogenetically justified. It leads not only to improvement of

clinical symptoms but also contributes to the improvement of dysbiotic changes, impaired intestinal barrier function, normalisation of serotonin and melatonin levels in the blood serum, which is a prerequisite for improving the mental status in these patients.

Conflicts of interest

The authors declare that they have no conflicts of interest concerning this study, including financial, personal, authorship, or other, that could affect the study and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in the creation of the presented work.

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