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CLINICAL EFFICACY OF THE SYMBIOTIC DRUG LOTARDI-A IN THE COMPLEX THERAPY OF PATIENTS WITH IRRITABLE BOWEL SYNDROME IN METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Yelyzaveta Sirchak

Irritable bowel syndrome (IBS) and metabolite-associated fatty liver disease (MAFLD) are among the most common gastrointestinal and liver diseases encountered in primary and secondary care.
The aim of the study *was to determine the clinical efficacy of treatment with the symbiotic drug Lotardi-A in the complex therapy of patients with IBS with MAFLD.*
Materials and methods. *The study included 60 patients with IBS with MAFLD. Patients with IBS in combination with MAFLD were divided into two groups, depending on the method of treatment. 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.*
Results of the study. *Additional administration of the symbiotic Lotardi-A to the subjects contributed to positive changes in the quantitative and qualitative composition of the colon microflora. A significant increase in the number of Bifidobacterium, Lactobacillus was determined. Evaluation of the dynamics of biochemical blood parameters after treatment, indicating the functional state of the liver in patients with IBS with MAFLD confirms more pronounced positive changes in laboratory parameters of cholestatic syndrome in the second group of patients. A significant decrease in the signs of cytolytic syndrome was also found.*
Conclusions: *In patients with IBS and MAFLD, it is clinically more often manifested by constipation, namely in 43.3–46.7 %, respectively. These changes occur against the background of colon dysbiosis, mainly of the II and I stages (in 50.0 % and 36.7-40.0 % of the subjects). The treatment of patients with IBS and MAFLD should be comprehensive and include probiotic drugs. Prescription of Lothardi-A is an effective method for the correction of clinical manifestations of IBS, and is also a necessary component for the treatment of MAFLD and correction of dysbiotic changes. At the same time, in patients of group I with MAFLD and IBS with constipation, an increase in the frequency of defecation by 30.0 % ($p<0.01$) was found, while in patients of group I – only by 10.0 % ($p<0.05$). In 26.7 % of patients in group II after complex treatment, dysbiosis was not detected during repeated examination, while in group I, we did not find such patients. The additional administration of a symbiotic complex to patients with IBS in MAFLD is an effective means of complex treatment to reduce the severity of disorders of the functional state of the liver and lipid metabolism. At the same time, in patients of group II, a more pronounced significant decrease in serum ALT activity was found (decrease by 43.63±0.37 U/l – $p<0.01$). The same trend was found when assessing the level of triglycerides in the blood serum (decrease by 1.65± ±0.03 mmol/l – $p<0.01$)*
Keywords: *non-alcoholic fatty liver disease/metabolically associated fatty liver disease, irritable bowel syndrome, obesity, metabolic disorders, microbiome, diagnosis, treatment (probiotics)*

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1. Introduction

Irritable bowel syndrome (IBS) and non-alcoholic fatty liver disease (NAFLD)/metabolic fatty liver disease (MAFLD) are among the most common gastrointestinal and liver diseases seen in primary and secondary care [1].

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 Rome IV diagnostic criteria, which include bowel movements (constipation, diarrhoea, or a combination of both) associated with frequent abdominal pain and abdominal distension or bloating for at least 6 months prior to diagnosis. A meta-analysis has shown that the prevalence of IBS in the world is 9.2 % with significant regional variation [2]. However, given the degree of heterogeneity in the criteria used to diagnose IBS, the true

global prevalence of IBS remains unclear, but it is estimated to affect 1 in 10 people worldwide [3, 4].

Non-alcoholic fatty liver disease, characterised by the accumulation of more than 5.0 % of fat in the liver in the absence of a secondary cause, is one of the leading causes of liver disease worldwide, and its pathogenesis is associated with metabolic syndrome, obesity and type 2 diabetes. The population prevalence of NAFLD ranges from 25 % to 44 %, but increases to 70 % in patients with type 2 diabetes [5]. Liver disease causes 38,000 and 22,000 years of lost working life in men and women, respectively. The incidence of NAFLD is increasing in Western countries, with an expected proportional increase in the number of liver transplants in both the US and Europe [6, 7].

Irritable bowel syndrome is a multifactorial disease resulting from the interaction of several factors, including genetics, epigenetics, immune activation, gut dysbiosis, impaired gut-brain communication, visceral hypersensitivity, altered gut motility, eating behaviour, psychological stress and environmental factors [8].

There is a growing understanding that both IBS and NAFLD share a number of common risk factors and etiological factors, leading to increased interest in the possibility of a link between the two conditions. However, high-quality data on the concomitant course of IBS and NAFLD are limited. As a result, symptoms of IBS may not be included in routine screening in hepatology clinics and vice versa [1]. Data on the incidence of metabolic dysfunction associated with fatty liver disease among patients with PBC are scarce [9]. To date, studies have identified a relationship between obesity and IBS. As NAFLD is closely associated with obesity, insulin resistance, and metabolic risk factors, new evidence suggests a possible correlation between NAFLD and IBS due to the alleged common pathophysiological links [1].

To date, the role of the gut microbiota in the pathogenesis of NAFLD/IBD has been proven. Several mechanisms have been proposed to explain the role of the gut microbiota in the development of NAFLD, including the impact on the amount of energy absorbed from food, changes in intestinal permeability, leading to bacterial migration and the concomitant release of toxic bacterial products, alteration of gene expression involved in de novo lipogenesis and metabolic signalling pathways, intestinal ethanol production, and interaction with innate immunity [10–12]. Various metabolites produced by the gut microbiota may modulate the susceptibility to IBD, for example, fermentation of indigestible carbohydrates (dietary fibre) by the gut microbiota leads to the production of metabolites such as short-chain fatty acids, propionate, butyrate and succinate, which may play a beneficial role in controlling body weight, inflammatory status, glucose levels and lipid homeostasis [13]. Impaired bile acid metabolism in NAFLD can lead to increased energy expenditure and chronic inflammation [10], while increased deoxycholic acid formation in patients with nonalcoholic steatohepatitis is associated with an enrichment of secondary bile acid-producing bacteria, inhibiting farnesoid receptor (FXR) signalling, interfering with lipid and glucose metabolism in the liver and intestine. Dysregulation of amino acids and choline leads to lipid accumulation and chronic inflammation [14, 15].

Thus, scientists around the world have made considerable efforts to study the role of the gut microbiome on the human body [16], especially in the case of NAFLD. Epidemiological studies have evaluated the distribution of the gut microbiota between healthy individuals and patients with NAFLD. A decrease in bacterial α- or β-diversity in patients with NAFLD has been observed in some, but not all, studies [17–19]. Regarding individual microbial taxa, a meta-analysis of 54 studies (8894 participants) found a depletion of anti-inflammatory microbes (i.e. Ruminococcaceae and Coprococcus) and an enrichment of pro-inflammatory microbes (i.e. Fusobacterium and Escherichia) in patients with NAFLD [20, 21].

The role of the microbiome is also being actively studied in functional digestive diseases, including IBS. Studies have examined such factors as changes in the gut microbiota (dysbiosis), changes in intestinal motility and mucosal inflammation, as well as the role of the central nervous system, including visceral hypersensitivity and the gut-brain axis. With the expansion of the genomic database of the microbiome, the understanding of the role of the microbiome in bidirectional signalling through the gut-brain axis has also expanded [22–24].

Thus, the gut microbiome may become a promising therapeutic target in the treatment of not only IBS, but also comorbidities, especially IBS, obesity and carbohydrate metabolism disorders.

The aim of the study was to determine the clinical efficacy of treatment with the symbiotic drug Lotardi-A in the complex therapy of patients with IBS and MAFLD.

2. Materials and methods

The study included 60 patients with IBS in the MAFLD setting. 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 Higher Educational Institution (SHEI) "Uzhhorod National University". Among the examined patients, there were 12 men (20.0 %), the average age was 34.8±6.2 years; there were 48 women (80.0 %), 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 methodology of the study complied with the Helsinki Declaration of Human Rights of 1975 and its revision of 1983, the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine. 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: PCOS in patients with IBD.

The criteria for exclusion from the study were: liver damage of alcoholic, viral (hepatitis B, C, D virus-

es) etiology, autoimmune hepatitis; Wilson-Konovalov 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 were subjected to general clinical, anthropometric, instrumental and laboratory methods. To verify the diagnosis, the nature of complaints and medical history were detailed. During the anthropometric examination, height, weight, and waist circumference were determined, and body mass index (BMI) was calculated. In accordance with WHO recommendations, patients were divided according to BMI, with BMI of 16.0 or less corresponding to severe underweight; 16.0–18.5 – to underweight; 18.0–24.9 – to normal weight; 25.0–29.9 – to overweight; 30.0–34.9 – to obesity of the first degree; 35.0–39.9 – to obesity of the second degree; 40.0 and more – to obesity of the third degree.

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

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

Standard general and biochemical studies were performed in the blood serum to determine the functional state of the liver (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB) and its fractions, alkaline phosphatase (ALP), γ-glutamyltransferase (GGT)), renal function (creatinine urea), lipid parameters (total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL)) and carbohydrate metabolism (glucose, insulin, C-peptide, glycated haemoglobin (HbA1c, %)).

The study of the species and quantitative composition of the colon microflora was carried out by sowing tenfold dilutions (10^{-1}–10^{-9}) on a standard set of selective and differential diagnostic nutrient media for the isolation of aerobic and anaerobic microorganisms.

Faeces were collected in sterile, hermetically sealed containers (provided by the microbiological laboratory). Faeces were collected in a sterile manner. The sample for the study was taken from the last portion of faeces. The amount of material collected was 1–3 g. The faeces for the study were delivered to the microbiological laboratory without preservatives, no later than two hours after collection. Faeces were collected in pre-weighed vials in an amount of 0.5–1.0 g, after re-weighing, the sample weight was determined, and such an amount of isotonic NaCl solution was added to obtain a 10^{-1} solution. A solution of 10^{-3}, 10^{-5}, 10^{-7}, 10^{-8}, 10^{-9} was prepared from the main sample by successive dilutions using separate sterile pipettes.

To detect pathogenic enterobacteria, the native material of liquid consistency or a solution of dense stool 10^{-1} was looped onto Endo, Ploskirev, bismuth-sulfite medium and 1–2 ml was inoculated onto enrichment media (magnesium, selenite, poured into 5–7 ml tubes). From solution 10^{-3}, 0.1 ml was inoculated onto Sabouraud medium with the addition of antibiotics (levomycetin 0.05 mg/ml) to detect Candida fungi and 0.1 ml was inoculated onto egg-salt agar to detect staphylococci. From solution 10^{-5}, 0.1 ml was inoculated onto Endo, Simons medium and 0.05 ml onto 5 % blood agar for the isolation and quantification of enterobacteria, coccus group of microorganisms and haemolytic forms. From solutions 10^{-7}, 10^{-8}, 10^{-9}, 1 ml was inoculated into regenerated Blaurock's medium for the detection of bifidobacteria.

For the quantitative determination of lactobacilli, 1 ml of the same solutions was inoculated onto MRS-2 medium. Cultures on Endo medium, 5 % blood agar, and Simons medium were incubated for 18–24 hours at 37 °C. Cultures on yolk-salt agar medium were incubated for 48 hours at 37 °C, with a preliminary view after 24 hours of incubation. Sabouraud's medium was incubated for 48 hours at 37 °C and another 3 days at room temperature. Cultures on Blaurock's medium were incubated for 48 hours at 37 °C.

To detect dysbiosis during the bacteriological examination, the number of microorganisms growing on agar, Sabouraud, Endo and 5 % blood agar nutrient medium was quantified per 1 g of faeces, taking into account the dose of inoculated material and the degree of its dilution.

The number of microorganisms of each species in one gram of the test material was calculated by the formula:

$$K=E\backslash(k*V*v)$$

where K is the number of bacteria; E is the sum of colonies of this species in all solutions used; V is the volume of the suspension applied to the dish, and v is the degree of dilution.

In addition, the presence of haemolytic forms of both intestinal and coccal microflora, their percentage of the total number of colonies grown, and the ratio of intestinal and coccal microflora were noted on a plate with 5 % blood agar. The presence of bifidobacteria was determined by the nature of growth on Blaurock's medium and microscopy of Gram stained smears. The number of bifidobacteria and lactobacilli in one gram of faeces was determined by the limiting dilution at which their growth was observed.

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), according to which 4 phases of dysbiotic disorders are distinguished.

Comprehensive treatment of the examined patients with IBS and MAFLD was carried out in accordance with the current regulatory documents and local protocols. All patients received basic therapy for 1 month, which included taking the myotropic antispasmodic otilonium bromide 40 mg 3 times a day in combination with an amino acid complex containing arginine citrate, betaine, L-carnitine. The treatment was conducted against the background of lifestyle modification (increased physical activity, dietary recommendations).

Patients with IBS in combination with MAFLD were divided into two groups, depending on the method of treatment. 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. Statistical analysis included determining descriptive indicators, determining the nature of the data distribution, and assessing the statistical significance of the results. The normality of the data distribution was verified using the Kolmogorov-Smirnov test, histogram analysis, comparison of arithmetic means, and estimation of mode and median. For parametric indicators with a normal distribution, the following characteristics were calculated: maximum and minimum values, arithmetic mean of the sample (M), standard error of the mean (M±m), and standard deviation (s). The statistical significance of differences between groups was assessed using Student's t-test. In the case of nonparametric variables, the Mann-Whitney U test and Pearson's χ^2 test were used. To verify the null hypothesis, the statistical significance (p) was used, with differences at $p<0.05$ considered statistically significant.

3. Results of the study

The anthropometric study revealed an increase in BMI in the vast majority of patients with IBS with MAFLD – Fig. 1.

According to the results obtained, in patients with IBS with MAFLD, overweight (in 40.0–46.7 % of the subjects) and grade I obesity (in 26.7–30.0 % of the subjects, respectively) were more often detected. Normal body weight and grade II obesity were found with equal frequency in the examined patients, namely, in 13.3 % of patients in group I and in 10.0 % of patients in group II. Grade III obesity (morbid obesity) was diagnosed in only 6.7–3.3 % of patients with IBS in the setting of MAFLD.

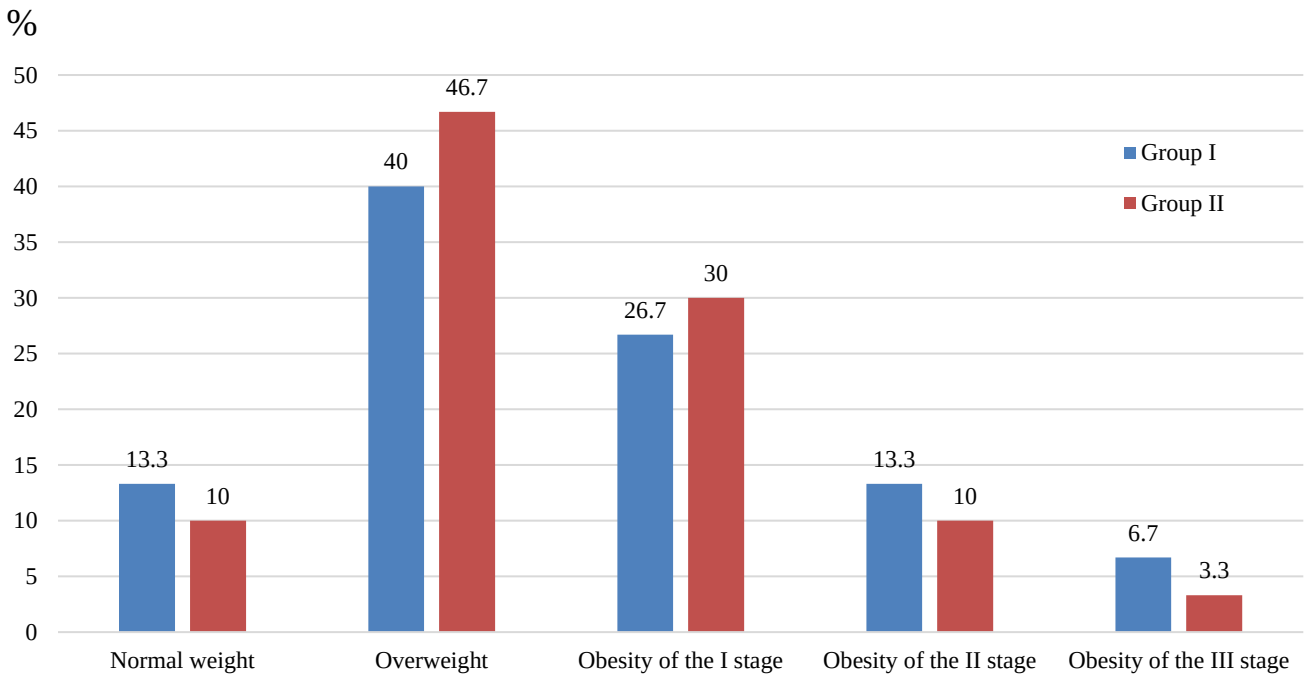

Fig. 1. Changes in BMI in patients with IBS with MAFLD

Irritable bowel syndrome in the vast majority of patients with MAFLD is clinically manifested by constipation (Fig. 2). In patients of both groups, before treatment, IBS was clinically manifested by constipation (in 46.7–43.3 % of the subjects), as well as constipation followed by diarrhoea (in 30.0–36.7 % of patients, respectively).

Thus, as indicated by the results of the data obtained, the distribution of patients by groups was homogeneous.

The dynamics of clinical manifestations of IBS in patients with MAFLD on the background of complex treatment with Lothardi-A was evaluated (Table 1).

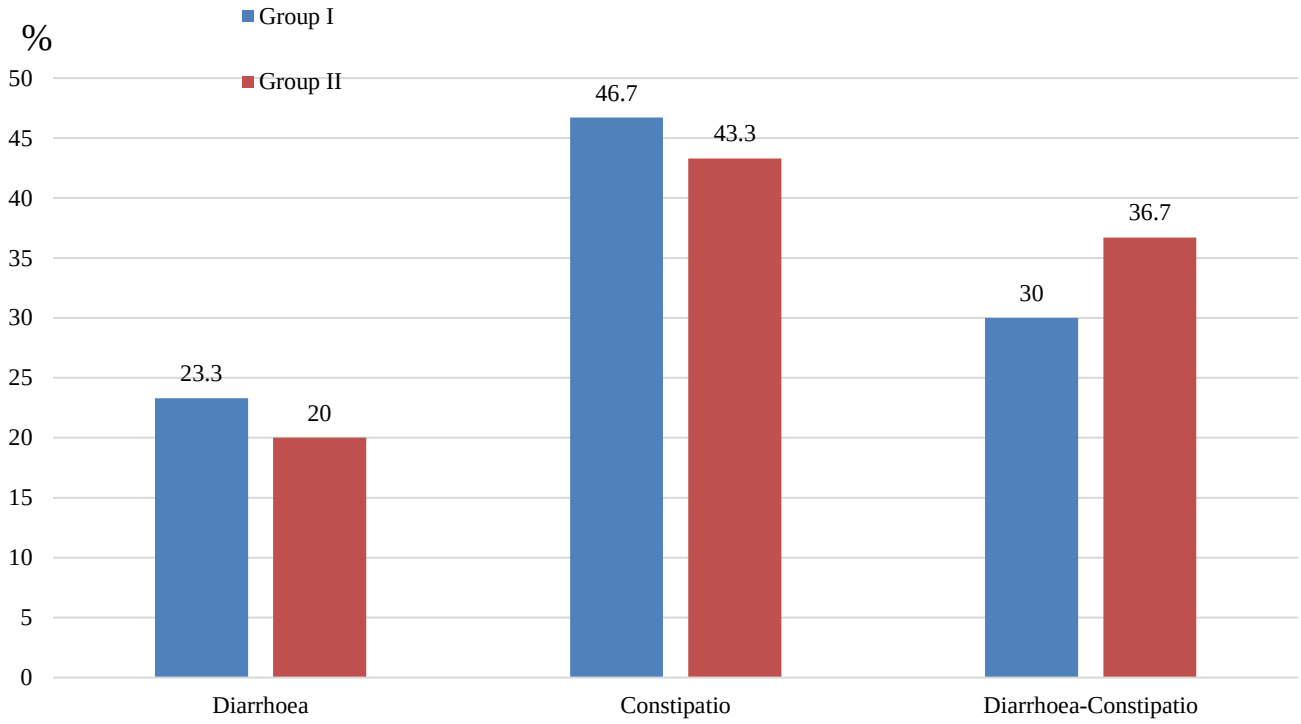

Fig. 2. Frequency of clinical manifestations of IBS in patients with MAFLD before treatment

Table 1

Dynamics of clinical symptoms of IBS in the examined patients with MAFLD on the background of complex treatment

Indicator	Examined patients			
	Group I (n=30)		Group II (n=30)	
	before treatment	after treatment	before treatment	after treatment
Constipation	46.7 %	26.7 % **	43.3 %	10.0 % ** +
Frequency of defecation (per week)				
2-3 times	28.6 %	75.0 % **	23.1 %	100.0 % *** ++
less than 2 times	71.4 %	25.0 % **	76.9 %	–
Diarrhoea	23.3 %	13.3 % *	20.0 %	3.3 % **+
Frequency of defecation (per day)				
up to 5 times	71.4 %	66.7 % *	66.7 %	100.0 % ** ++
more than 5 times	28.6 %	33.3 %	33.3 %	–
Constipation followed by diarrhoea	30.0 %	20.0 % *	36.7 %	6.7 % ** +
Flatulence	83.3 %	23.3 % **	80.0 %	–
Pain along the colon	70.0 %	13.3 % ***	70.0 %	6.7 % *** +
Feeling of incomplete bowel movement	63.3 %	26.7 % **	70.0 %	–

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

There was a significant improvement in the severity of clinical symptoms of IBS in both groups of patients, but more pronounced positive changes were found in group II of patients who additionally received Lotardi-A as part of the complex treatment. A significant improvement in the act of defecation was found – a decrease in the frequency of constipation to 10.0 % (p<0.01). At the same time, if before treatment the frequency of defecation was less than 2 times per week, then after a course of treatment with a complex probiotic

preparation, patients increased the frequency of defecation (every 2 days).

Diarrhoea, which was diagnosed in 23.3-20.0 % of patients before treatment, significantly decreased to 3.3 % in patients of group II after a month of therapy ($p<0.01$). After the treatment, in the group of patients who additionally received Lotardi-A, there was no feeling of incomplete bowel movement after the act of defecation, as well as flatulence. Pain along the colon after treatment in group II was detected in only 6.7 % of patients, compared to 13.3 % in group I patients.

The dynamics of changes in the quantitative and qualitative composition of the colon microflora in the examined patients with IBS with MAFLD on the background of treatment with Lothardi-A was evaluated (Table 2).

Table 2

Dynamics of indicators of quantitative and qualitative composition of colon microflora in the examined patients with IBS and MAFLD on the background of complex treatment

Indicator	Examined patients with IBS and MAFLD			
	Group I (n=30)		Group II (n=30)	
Bifidobacterium: Control group 100.0 % (8.66±0.11)				
frequency, %	70.0 %**	73.3 %	66.7 %**	93.3 %++##
lg CFU/gr	5.92±0.08**	5.89±0.05	5.87±0.07**	7.92±0.11++##
Lactobacillus: Control group 100.0 % (6.80±0.11)				
frequency, %	66.7 %**	70.0 %	63.3 %**	93.3 %++##
lg CFU/gr	5.12±0.06**	5.18±0.04	5.08±0.07**	6.67±0.09++#
E. coli (with normal enzymatic properties): Control group 93.3 % (7.90±0.11)				
frequency, %	73.3 %*	76.6 %	66.7 %**	90.0 %++#
lg CFU/gr	5.12±0.09	5.28±0.06	5.10±0.05	7.42±0.09++##
E. coli (haemolytic form): Control group 3.3 % (1.08±0.08)				
frequency, %	20.0 %**	16.7 %	16.7 %**	3.3 %+##
lg CFU/gr	4.89±0.11***	4.07±0.12	5.02±0.09***	2.36±0.10+++#
Enterococcus: Control group 90.0 % (7.65±0.09)				
frequency, %	46.7 %***	50.0 %	50.0 %**	86.7 %++##
lg CFU/gr	6.32±0.06**	6.54±0.08	6.18±0.05**	7.24±0.04++#
Enterobacter: Control group 23.3 % (1.14±0.08)				
frequency, %	40.0 %*	36.7 %	40.0 %*	26.7 %+#
lg CFU/gr	4.86±0.07***	4.12±0.12	4.92±0.07***	2.08±0.10++##
Citrobacter: Control group 26.7 % (1.41±0.08)				
frequency, %	56.7 %**	50.0 %	53.3 %**	26.7 %++#
lg CFU/gr	2.89±0.07**	2.72±0.07	3.02±0.10**	1.76±0.06++#
Staphylococcus: Control group 26.7 % (3.44±0.17)				
frequency, %	60.0 %**	60.0 %	60.0 %**	30.0 %++##
lg CFU/gr	5.12±0.10**	5.09±0.06	5.07±0.09**	3.67±0.08++#
Klebsiella: Control group 16.7 % (1.24±0.07).				
frequency, %	43.3 %**	40.0 %	46.6 %**	20.0 %++##
lg CFU/gr	3.11±0.15**	3.25±0.10	3.54±0.11**	1.92±0.07++#
Clostridium: Control group 13.3 % (4.38±0.14)				
frequency, %	30.0 %**	26.7 %	33.3 %**	20.0 %+
lg CFU/gr	5.87±0.13*	5.56±0.07	5.74±0.05	4.60±0.12+#
Proteus: Control group 6.7 % (0.57±0.08)				
frequency, %	23.3 %**	23.3 %	26.7 %**	6.7 %++##
lg CFU/gr	2.25±0.10**	2.30±0.08	2.44±0.09**	0.84±0.05++##
Candida: Control group 3.3 % (2.98±0.16)				
frequency, %	13.3 %*	13.3 %	16.7 %*	6.7 %+#
lg CFU/gr	4.76±0.08**	4.65±0.05	4.95±0.10**	3.32±006+#

*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: + – $p<0.05$; ++ – $p<0.01$; +++ – $p<0.001$; the difference between the indicators in patients of groups I and II after treatment is significant: # – $p<0.05$; ## – $p<0.01$*

In patients with IBS with MAFLD before treatment, a change in the quantitative and qualitative composition of the colon microflora was diagnosed in the microbiological examination of faeces, which was manifested mainly by a decrease in the number of normoflora (bifidobacteria and lactobacilli, E. coli with normal enzymatic properties), as well as an increase in the number of haemolytic form of E. coli, Enterobacter, Citrobacter,

Staphylococcus, Klebsiella, Clostridium, Proteus and fungi of the genus Candida.

The additional administration of the symbiotic Lotardi-A to patients with obesity with IBS resulted in positive changes in the quantitative and qualitative composition of the colon microflora. A significant significant increase in the number of *Bifidobacterium, Lactobacillus, E. coli* (with normal enzymatic properties) was found mainly in patients of group II, while in patients with IBS with morbid obesity of group I, no changes in the quantitative and qualitative composition of the colon microflora were determined.

The dynamics of the degree of colon dysbiosis (CD) in the examined patients against the background of the treatment was assessed (Table 3).

Table 3

Dynamics of severity of colon dysbiosis in the examined patients with IBS and MAFLD on the background of complex treatment

The degree of CD	Examined patients with IBS and MAFLD			
	Group I (n=30)		Group II (n=30)	
	before treatment	after treatment	before treatment	after treatment
Not available	–	–	–	26.7 %
I degree of CD	36.7 %	40.0 %	40.0 %	53.3 %*+
II degree of CD	50.0 %	50.0 %	50.0 %	20.0 %**++
III degree of CD	13.3 %	10.0 %	10.0 %	–

*Note: 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*

Before the complex treatment, half of the patients in both groups were diagnosed with II degree of CD, and I degree of CD was found in 26.7–40.0 % of patients with IBS in MAFLD. Only 13.3-10.0 % of the subjects were diagnosed with II degree of CD. Thus, in patients with IBS in MAFLD, deep dysbiotic changes are determined, which should be taken into account when treating these patients.

The prescription of the complex probiotic Lothardi-A is reasonable and appropriate for these patients. At the same time, after a one-month course of treatment with Lotardi-A, a decrease in the number of patients with II degree of CD by 30.0 % was determined, which was accompanied by a significant increase in the number of patients with MAFLD in IBS with I degree of CD (by 13.3 % – p<0.05). Dysbiotic changes were not detected in 26.7 % of patients in group II after complex treatment, which was accordingly established against the background of the absence of patients in the reassessment of the severity of patients with III degree of CD.

Table 4

Dynamics of indicators of liver function in blood serum in patients undergoing complex treatment

Indicator	Examined			
	Control group (n=30)	treatment	Examined patients with IBS and MAFLD	
			Group I (n=30)	Group II (n=30)
ALT, U/l	20.85±0.48	before	92.96±0.51**	90.88±0.39**
		after	63.08±0.44+	47.25±0.76++#
AST, U/l	16.24±0.32	before	80.11±0.78***	84.15±0.51***
		after	59.25±0.56+	41.13±0.64++#
TB, mmol/l	14.62±0.12	before	32.78±0.18*	34.50±0.23*
		after	24.13±0.22+	18.79±0.30+
GGT, U/l	23.41±0.77	before	79.96±0.74**	81.15±0.50**
		after	50.77±0.66++	38.77±0.45++#
ALP, mmol/l	56.12±1.42	before	123.06±0.38**	132.01±0.67*
		after	95.42±0.72+	73.16±0.82++#

*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; +++ – p<0.001; the difference between the indicators in patients of groups I and II after treatment is significant: # – p<0.05*

Evaluation of the dynamics of biochemical blood parameters after treatment, indicating the functional state of the liver in patients with IBS with MAFLD, confirms more pronounced positive changes in laboratory parameters of cholestatic syndrome (levels of ALP, GGT, and TB) in group II of the examined patients. A significant decrease in the signs of cytolytic syndrome, namely, a decrease in the activity of AST, ALT in the blood serum, was also found mainly in group II of patients who received a symbiotic drug in addition to the amino acid complex (Table 4).

We analysed the indicators of blood lipid metabolism against the background of treatment in patients with IBS with MAFLD – Table 5.

Table 5

Dynamics of indicators of blood lipid metabolism in the examined patients on the background of complex treatment

Indicator	Examined			
	Control group (n=30)	treatment	Examined patients with IBS and MAFLD	
			Group I (n=30)	Group II (n=30)
TC, mmol/l	1.12±0.05	before	3.22±0.09**	3.54±0.07**
		after	2.07±0.07++	1.89±0.10++
TG, mmol/l	4.52±0.09	before	7.82±0.11**	7.96±0.09**
		after	6.48±0.06+	6.05±0.09++#
LDL, mmol/l	1.70±0.10	before	3.78±0.08**	3.67±0.06**
		after	2.56±0.04+	2.17±0.07++#
VLDL, mmol/l	0.58±0.08	before	1.95±0.06**	1.90±0.08**
		after	1.01±0.05+	0.84±0.06++
HDL, mmol/l	1.92±0.07	before	0.98±0.08**	1.03±0.05*#
		after	1.45±0.04+	1.67±0.09+

*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*

In patients with functional impairment of the colon in case of IBS, dyslipidaemia was diagnosed before treatment, which tended to normalise after the course of treatment. It should be noted that the efficacy was more pronounced in the group of patients who additionally received the complex probiotic drug Lothardi-A.

5. Discussion

To date, studies have found an interesting relationship between obesity and IBS. IBS is significantly associated with a higher prevalence of the metabolic syndrome, and a multitude of studies have determined a link and common pathogenic mechanisms between these two conditions. Obesity and metabolic syndrome are found more frequently in IBS patients compared with controls. A cross-sectional study from Japan showed a positive association between IBS and increased prevalence of metabolic syndrome and triglyceride levels. The odds ratio (OR) (95 % CI) in IBS subjects was 2.01 (1.13–3.55) and 1.50 (1.03–2.18), respectively, as compared with non-IBS subjects. There is a higher occurrence of pre-diabetes and higher low-density lipoprotein levels in patients with IBS. In IBS subjects, an elevated body mass index (BMI) is associated with significantly faster colonic and rectosigmoid transit and higher bowel frequency.

Various studies have been conducted worldwide to determine the relationship between IBS and MAFLD. Allam AS et al. (2023) studied the prevalence of IBS in patients with MAFLD. Their data indicate that IBS had a higher incidence of MAFLD. In addition, there is a significant association between IBS and MAFLD severity.

According to the results of our research, in patients with MAFLD, changes in anthropometric parameters, as well as the influence of dysbiosis, which occurs in these patients, have a significant impact on the formation of IBS. At the same time, disorders in the microbiocenosis in these patients are associated not only with clinical manifestations of IBS, but also have a significant impact on metabolic changes in patients with MAFLD. An integrated approach to the treatment of these patients is appropriate and reasonable, since the administration of a probiotic agent reduces not only the clinical manifestations of IBS, but also has a positive effect on the functional state of the liver and lipid metabolism.

There is promising evidence that probiotic supplementation can reduce liver enzyme levels and regulate glycometabolism in patients with MAFLD. Grasping the complex interaction between the intestine and liver, referred to as the gut-liver axis, is crucial to decipher the pathogenesis of MAFLD and identify potential therapeutic targets.

Probiotics are living microorganisms that are nonpathogenic. They are known to produce several beneficial effects, such as altering the host's immune response in the gastrointestinal tract and lowering the growth of pathogenic organisms by enhancing the microbial balance. These can be consumed in the form of food and even dietary supplements. Several strains are found to be used as probiotics and these include Lactobacillus, Bifidobacterium, and even Saccharomyces. However, the exact count of various species to be used to bring about specific therapeutic gain is not known yet.

Probiotics, which are live microorganisms offering health benefits, have garnered attention for their potential in treating MAFLD. The mechanisms of action of probiotics are explored, including their ability to modulate gut microbiota composition, enhance epithelial barrier function, and influence the immune response. Various randomized controlled trials have shown that probiotics are effective in enhancing several aspects of MAFLD, such as liver enzymes, lipid profiles, body mass index, insulin sensitivity, or even histological efficacy.

Probiotics are safe and effective in IBS patients, especially those used for a shorter duration, such as for less than eight weeks; a higher dosage of a single probiotic strain seems to show greater benefits. The adverse events associated with probiotics are found to be safer in comparison to many other treatment options available today. Probiotics have been shown to improve overall stool frequency, gut transit time, and stool consistency. *Bacillus coagulans* strain LBSC (DSM17654) has been shown to be efficacious in alleviating IBS symptoms such as bloating, abdominal pain, constipation, diarrhoea, nausea, vomiting, and stomach rumbling. It was found to

be safe for human consumption, and it helped improve the quality of life in IBS patients. Thus, probiotics have an overall positive impact on IBS patients by improving their quality of life.

Lothardi-A, which contains clinically studied strains of lacto- and bifidobacteria, saccharomycetes, is an effective remedy for the treatment of clinical signs of IBS in patients with MAFLD. Probiotic microorganisms included in Lothardi-A have a positive effect on both diarrhoea and constipation in patients with IBS. The complex of 9 strains of lactobacilli and bifidobacteria contained in Lothardi-A has a positive effect on the intestinal ecosystem, improving the quality of life in irritable bowel syndrome by reducing symptoms such as abdominal pain, bloating, distension, feeling of incomplete bowel movements, and also leads to normalisation of the frequency of defecation.

The probiotic bacteria contained in Lothardi-A play an important role in maintaining and normalising the intestinal microflora, have an immunomodulatory effect, boost immunity and exhibit antioxidant properties. Lothardi-A components inhibit the growth of pathogenic intestinal microflora. Our research confirms the importance of supplemental use of this symbiotic agent to improve metabolic disorders in the body and the functional state of the liver, as well as correct colon dysbiosis.

Limitations of the study. Lack of previous studies on the effect of this symbiotic drug on patients with IBS and MAFLD.

Prospects for further research. Further study of the clinical efficacy of the symbiotic drug Lotardi-A in the complex therapy of patients with IBS and MAFLD.

5. Conclusions

1. In patients with IBS and MAFLD is clinically more often manifested by constipation, namely in 43.3–46.7 %, respectively. These changes occur against the background of colon dysbiosis, mainly of the II and I stages (in 50.0 % and 36.7–40.0 % of the subjects).

2. The treatment of patients with IBS and MAFLD should be comprehensive and include probiotic drugs. Prescription of Lothardi-A is an effective method for the correction of clinical manifestations of IBS, and is also a necessary component for the treatment of MAFLD and correction of dysbiotic changes. At the same time, in patients of group I with MAFLD and IBS with constipation, an increase in the frequency of defecation by 30.0 % ($p<0.01$) was found, while in patients of group I – only by 10.0 % ($p<0.05$). In 26.7 % of patients in group II after complex treatment, dysbiosis was not detected during repeated examination, while in group I, we did not find such patients.

3. The additional administration of a symbiotic complex to patients with IBS in MAFLD is an effective means of complex treatment to reduce the severity of disorders of the functional state of the liver and lipid metabolism. At the same time, in patients of group II, a more pronounced significant decrease in serum ALT activity was found (decrease by 43.63±0.37 U/l – $p<0.01$). The same trend was found when assessing the level of triglycerides in the blood serum (decrease by 1.65±0.03 mmol/l – $p<0.01$).

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this study, including financial, personal, authorship, or other interests 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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Yelyzaveta Sirchak, Doctor of Medical Sciences, Professor**,** Department of Propedeutics of Internal Disease, State University «Uzhhorod National University», Narodna sq., 3, Uzhhorod, Ukraine, 88000
E-mail: sirchakliza777@gmail.com