ORIGINAL ARTICLE

CONTENTS

Combined treatment of intestinal dysbiosis in patients with chronic Hepatitis C on the background of obesity

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ABSTRACT

Aim: To study the effectiveness of ursodeoxycholic acid use in the combined treatment of intestinal dysbiosis in patients with chronic Hepatitis C associated with obesity.

Materials and Methods: 84 patients with CHC were examined. All patients underwent a microbiological study of stool, the levels of cytokine profile indicators were determined and the psychological status and the quality of life were assessed. Two groups were formed: 1 gr (n=40) – received LA-5 and BB-12 1 gtt. x TID and 2 gr (n=44) - LA-5 + BB-12 + UDCA 500 mg qhs for 1 month.

Results: As a result of simultaneous administration of LA-5 + BB-12 + UDCA in the above-mentioned doses, in 93.2% of patients with CHC an normalization of the act of defecation and the disappearance of symptoms of intestinal dysbiosis were found. In patients taking only LA-5 and BB-12, the above-mentioned positive changes were observed in 62.5%.

Conclusions: It was found that the additional prescription of UDCA in combination with a probiotic not only contributes to the restoration of colon microbiocenosis, but also improves the course of CHC, and increases the quality of life of patients.

KEY WORDS: dysbiosis, chronic Hepatitis C, obesity, Ursodeoxycholic acid, probiotics

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INTRODUCTION

According to WHO data, approximately 71 million people are affected from chronic hepatitis C (CHC), and 350,000–399,000 die each year due to liver damage and complications caused by the hepatitis C virus (HCV) [1]. Every year, 1.75 million new cases of viral hepatitis C are registered, of which 70–85% progress to CHC [2]. Direct-acting antiviral agents (DAAs) have made a breakthrough in the treatment of CHC, leading to sustained virological response (SVR) in more than 95% of patients [3] and reducing the degree of liver fibrosis. However, in some patients, after successful eradication of HCV with DAAs, progression of liver fibrosis and/or development of hepatocellular carcinoma (HCC) may still occur [4].

The rate of fibrosis progression is associated with various factors, including alcoholic and non-alcoholic fatty liver disease, co-infection with hepatitis B virus and HIV, as well as obesity and intestinal dysbiosis (ID). In the case of prolonged intestinal ID, the risk of developing metabolic liver diseases such as non-alcoholic fatty liver disease (NAFLD), cholestasis, and dyskinetic biliary tract disorders increases due to inflammatory and immune responses both at the local and systemic levels [5, 6]. People with obesity often show reduced diversity of gut microbiota and an altered balance of major bacterial groups: the number of Bacteroidetes decreases, while the proportion of Firmicutes increases. Any imbalance leads to a reduction in protective mechanisms, increased intestinal wall permeability, and the initiation of systemic inflammation. Studies have shown that the structure of the gut microbiome in obese individuals in Ukraine is characterized by a significantly higher content of Firmicutes and a lower content of Bacteroidetes compared to individuals with normal or reduced body weight [7].

It is well known that prebiotics, probiotic preparations, and herbal products that stimulate the growth of normal microflora are used to correct dysbiotic changes [8, 9]. One such probiotic is a capsule containing at least 1×10^9 colony-forming units (CFU) of *Lactobacillus acidophilus* (LA-5) and 1×10^9 CFU of *Bifidobacterium an-*

imalis subsp. lactis BB-12. Both bacteria are components of the normal human gut microbiota and are resistant to gastric acid and bile, which increases their survival rate as they pass through the stomach and duodenum. They have GRAS status (Generally Recognized As Safe) [10].

Although probiotics and prebiotics currently play a key role in the treatment of intestinal dysbiosis and the prevention of NAFLD [11, 12], contradictory results are often observed in individuals with obesity. Therefore, a more meticulous experimental design, improved quality of clinical studies, and confirmation of therapeutic effects are necessary [13].

Ursodeoxycholic acid (UDCA) is a therapeutic bile acid used not only as a hepatoprotective agent in CHC but is also prescribed for metabolic disorders (metabolic syndrome, obesity, NAFLD) [14, 15], given its broad spectrum of therapeutic activity [16].

The results of Pearson T. et al. (2019) indicate a close relationship between the gut microbiome and the composition of bile acids, which changes under the influence of UDCA in patients with colon polyps [17]. An excessive growth of *Faecalibacterium prausnitzii* was observed in the group of patients receiving UDCA, and an inverse relationship was found between *F. prausnitzii* and *Ruminococcus gnavus*. In animal models, intestinal inflammation was shown to decrease through the regulation of macrophage polarization, involvement of FXR, and suppression of NF-kB activation during UDCA treatment, which occurs due to changes in bile acid metabolism associated with dysbiosis [18]. Changes in the gut microbial profile have also been demonstrated in experimental animal models of NAFLD following intragastric administration of UDCA. UDCA treatment significantly reduced liver inflammation in mice with NASH and partially restored intestinal microbiota dysbiosis [19].

Thus, experimental studies using UDCA, considering its multifaceted properties, allow for the expansion of its therapeutic potential beyond its well-known effects and support its use as part of combined treatment of intestinal dysbiosis in patients with CHC associated with obesity.

AIM

The aim of the research was to study the effectiveness of ursodeoxycholic acid use in the combined treatment of intestinal dysbiosis in patients with chronic hepatitis C associated with obesity.

MATERIALS AND METHODS

A total of 84 patients with chronic hepatitis C (CHC) on the background of obesity and intestinal dysbiosis (ID) were under observation. Among them, 41.7% (35) were men and 58.3% (49) were women. The average age of the patients was 56.7 ± 1.3 years.

The study was conducted at the clinical base of the Department of Faculty Therapy, Medical Faculty, Uzhhorod National University, during the period 2023–2024. The scientific research was carried out within the framework of the initiative theme of the Department of Faculty Therapy of the State University "UzhNU": «Combined pathology and correction of disorders of homeostasis of residents of the Carpathian region, taking into account the effect of adverse factors», state registration number 0121U110808. The research was carried out with informed consent from the patients, and the methodology complied with the Declaration of Helsinki (1964–2016), the Council of Europe Convention on Human Rights and Biomedicine (1997), the International Code of Medical Ethics (1983), and relevant laws of Ukraine. The study was approved by the local bioethics committee (Protocol No.7/3 dated 16.03.2023) of Uzhhorod National University. All patients provided signed consent for the collection of personal data for the database, for the use of blood and stool samples for research purposes, and for participation in the study. The diagnosis of CHC was established according to the International Classification of Diseases, 10th Revision (ICD-10), and confirmed by the detection of total anti-HCV IgG antibodies using the ELISA method, as well as by detection of HCV RNA in the blood using the polymerase chain reaction (PCR). The classification of chronic hepatitis proposed at the International Congress of Gastroenterologists (Los Angeles, 1994) was also used. Markers of hepatitis B and C were determined using ELISA, followed by detection of HCV RNA, genotype, and viral load using PCR.

The degree of liver fibrosis and steatosis was determined using the non-invasive diagnostic method FibroMax (BioPredictive, Paris) and liver elastography (FibroScan-502 F01261, M 7 70129 probe, France, Regional Clinical Infectious Diseases Hospital, Uzhhorod). Abdominal ultrasound (US) was performed for all patients using a Philips HDI-1500 device with a convex probe operating at a frequency of 3.5 MHz. General clinical, biochemical, serological, and molecular-genetic tests were performed in certified laboratories of the Regional Clinical Infectious Diseases Hospital (Uzhhorod) and in commercial laboratories ("Dila" and "Synevo"). The functional state of the liver was assessed by measuring the activity levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), conjugated bilirubin, and gamma-glutamyl transpeptidase (GGT). The degree of activity of the pathological process was evaluated

based on ALT elevation levels according to the international classification of liver diseases (Los Angeles, 1994). The blood lipid profile was determined, including total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides (TG). The trophological status of the patients was assessed using standard anthropometric indicators. Obesity was determined based on the Quetelet index or body mass index (BMI).

The state of the intestinal microbiocenosis was assessed by microbiological analysis of fecal samples. To detect colonic dysbiosis, a quantitative analysis of microorganisms grown on nutrient media (agar, Sabouraud, Endo, and 5% blood agar) was performed, recalculating the results per 1 g of feces while accounting for the amount of inoculated material and its dilution. Identification of bacterial cultures was carried out using biochemical tests and the Enterotest system. All patients had their cytokine profile levels measured, and psychological status and quality of life were assessed.

Depending on the prescribed treatment, patients were divided into two subgroups: Subgroup 1a (n=40): Patients with CHC, obesity, and colonic dysbiosis who received a probiotic containing *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis* subsp. lactis (BB-12), 1 capsule three times a day. Subgroup 1b (n=44): Patients who, in addition to the probiotic (LA-5 and BB-12), received UDCA 500 mg at night for 1 month. The treatment lasted for 1 month.

The two-sided Fisher's exact test was used with the program Statistica 8.0 for Windows. Differences were considered statistically significant at $p < 0.05$. Statistical analysis of the obtained results was performed using Jamovi software.

FRAMEWORK

The scientific research was carried out within the framework of the initiative theme of the Department of Faculty Therapy of the State University "UzhNU": «Combined pathology and correction of disorders of homeostasis of residents of the Carpathian region, taking into account the effect of adverse factors», state registration number 0121U110808.

RESULTS

Combined therapy on the background of standard treatment positively affected the quantitative and qualitative composition of the colonic microflora in patients with CHC, especially in patients of subgroup 1b, who received UDCA in addition to the probiotic. Follow-up microbiological analysis of fecal samples showed a significant increase in the number of bifidobacteria and lactobacilli, which was accompanied by a decrease in aggressive pathogenic flora. The most pronounced positive dynamics were observed in subgroup 1b: in 100.0% of patients, the number of *Bifidobacterium* increased to 8.07 ± 0.05 lg CFU/g, whereas in subgroup 1a patients, an increase to 7.21 ± 0.06 lg CFU/g was detected in only 87.5% ($p < 0.05$).

Similarly, in 100.0% of subgroup 1b patients, *Lactobacillus* increased to 6.11 ± 0.08 lg CFU/g, while in subgroup 1a, the increase was only up to 5.02 ± 0.06 lg CFU/g ($p < 0.05$) in 80.0% of cases. A significant increase in *E. coli* with normal enzymatic activity up to 7.05 ± 0.07 lg CFU/g was observed in 90.9% of patients, compared to only 70.0% in subgroup 1a, where levels rose to 6.33 ± 0.09 lg CFU/g ($p < 0.05$).

Elimination of intestinal microbiocenosis imbalance was accompanied by a reduction in pathogenic and opportunistic microflora. The frequency of *E. coli* with hemolytic properties decreased 2.0-fold ($p < 0.05$) to 2.23 ± 0.05 lg CFU/g ($p < 0.01$) in subgroup 1b, compared to a 1.3-fold decrease in subgroup 1a. *Enterobacter* was detected in 6.8% of subgroup 1b patients at 1.64 ± 0.06 lg CFU/g, compared to 2.67 ± 0.08 lg CFU/g in 17.5% of subgroup 1a patients ($p < 0.01$). The *Citrobacter* count decreased to 1.25 ± 0.11 lg CFU/g in subgroup 1b, while higher concentrations (1.98 ± 0.09 lg CFU/g) were found in subgroup 1a patients.

After treatment, *Klebsiella* levels were 2.37 ± 0.05 lg CFU/g in subgroup 1a and significantly lower at 1.34 ± 0.03 lg CFU/g in subgroup 1b ($p < 0.05$). Staphylococcus aureus decreased 2.2-fold in subgroup 1b, to 2.88 ± 0.04 lg CFU/g, compared to a 1.3-fold reduction to 3.73 ± 0.07 lg CFU/g in subgroup 1a ($p < 0.05$).

Clostridium was isolated in 18.2% of subgroup 1b patients at 2.05 ± 0.08 lg CFU/g during follow-up, compared to 46.5% before treatment at 5.17 ± 0.11 lg CFU/g ($p < 0.01$). *Proteus* was detected in 11.4% of subgroup 1b patients at 1.14 ± 0.05 lg CFU/g, whereas in subgroup 1a, it was found in 20.0% of patients at 2.26 ± 0.03 lg CFU/g ($p < 0.05$). After the course of treatment, Candida was detected in only one patient (2.3%) in subgroup 1b whereas in subgroup 1a, it was isolated again in six patients (15.0%) ($p < 0.01$) (Table 1**).**

Thus, combination therapy using the probiotic LA-5 and BB-12 together with UDCA is a more effective method for normalizing the quantitative and qualitative composition of colonic microflora in CHC patients with obesity.

After the treatment, all patients showed improved well-being. As a result of simultaneous administration of LA-5 and BB-12 with UDCA in the above doses in CHC patients with obesity, there was an increase in the num-

Table 1. Evaluation of the dynamics of quantitative and qualitative composition of colonic microflora in patients with CHC during treatment

Indicator	Examined patients		
	Before treatment	After treatment	
		Subgroup 1a (n=40), abs./%	Subgroup 1b (n=44), abs./%
Bifidobacterium:			
frequency(%)	52 / 61.9 %	35 / 87.5 %*	44 / 100.0 %**+
lgCFU/g	5.07±0.12	7.21±0.06*	8.07±0.05**+
Lactobacillus:			
frequency(%)	45 / 53.6 %	32 / 80.0 %*	44 / 100.0 %**+
lgCFU/g	3.71±0.08	5.02±0.06*	6.11±0.08**+
***E. coli* with normal enzymatic properties:**			
frequency(%)	40 / 47.6 %	28 / 70.0 %*	40 / 90.9 %**+
lgCFU/g	4.67±0.12	6.33±0.09*	7.05±0.07**
***E. coli* (hemolytic form) before treatment**			
frequency(%)	19 / 22.9 %;	7 / 17.5 %	5 / 11.4 %*
lgCFU/g	5.07±0.21	3.75±0.07*	2.23±0.05**+
Enterobacter:			
frequency(%)	17 / 20.2 %	7 / 17.5 %	3 / 6.8 %**++
lgCFU/g	3.46±0.17	2.67±0.08*	1.64±0.06**+
Citrobacter:			
frequency(%)	34 / 40.5 %	9 / 22.5 %*	5 / 11.4 %**+
lgCFU/g	2.94±0.12	1.98±0.09*	1.25±0.11**
Klebsiella:			
frequency(%)	24 / 28.6 %	8 / 20.0 %	4 / 9.1 %**++
lgCFU/g	(3.86±0.15)	2.37±0.05*	1.34±0.03**+
Staphylococcus:			
frequency(%)	21 / 25.0 %	6 / 15.0 %*	4 / 11.4 %**
lgCFU/g	4.96±0.08	3.73±0.07*	2.88±0.04**+
Clostridium:			
frequency(%)	39 / 46.5 %	10 / 25.0 %*	8 / 18.2 %**
lgCFU/g	5.17±0.11	3.44±0.08*	2.05±0.08**+
Proteus:			
frequency(%)	28 / 33.3 %	8 /20.0 %*	5 / 11.4 %**+
lgCFU/g	3.15±0.14	2.26±0.03*	1.14±0.05**+
Candida:			
frequency(%)	24 / 28.6 %;	6 / 15.0 %*	1 / 2.3 %**++
lgCFU/g	4.20±0.17	2.03±0.06**	1.48±0.07***+

Note: Differences between indicators before and after treatment are significant: * - $p < 0.05$; * * - $p < 0.01$; * * * - $p < 0.01$. Differences between indicators in patients of subgroups 1a and 1b after treatment are significant: + - $p < 0.05$; ++ - $p < 0.01$

Source: compiled by the authors of this study

ber of bifidobacteria, lactobacilli, and *E. coli* with normal activity, and a decrease in the number of hemolytic microorganisms, *Proteus, Staphylococcus*, and yeast-like fungi. This was accompanied by normalization of bowel movements and disappearance of intestinal dysbiosis symptoms. Elimination of dysbiosis symptoms, including constipation and flatulence, contributed to positive dynamics in the clinical course of CHC. Thus, the number of patients complaining of pain, heaviness in the right hypochondrium, flatulence, weakness, and rapid fatigue significantly decreased, with a reliable predominance in the second group.

Analysis of the obtained data indicates a 3.7-fold reduction ($p < 0.01$) in manifestations of astheno-vegetative syndrome in patients of subgroup 1b, whereas in subgroup 1a patients, signs of rapid fatigability, irri-

Table 2. Dynamics of dyspeptic syndrome symptoms in CHC patients during treatment

Clinical signs	Examined patients		
	Before treatment (n=84)	After treatment	
		1a subgroup (n=40)	1b subgroup (n=44)
Manifestations of biliary dyspepsia:	52 / 61.9 %	18 / 45.0%*	7 / 15.9 %***++
- Nausea	29 / 34.5 %	12 / 30.0 %	2 / 4.5 %**++
-Vomiting	6 / 7.1 %	2 / 5.0 %	0
- Bitter belching	23 / 27.4 %	7 / 17.5 %	1 / 2.3 %***++
- Bitterness in mouth	19 / 22.6 %	6 / 15.0 %	1 / 2.3 %**++
- Decreased appetite	23 / 27.4 %	6 / 15.0 %*	3 / 6.8 %**+
Manifestations of intestinal dyspepsia:			
Complains of impaired defecation			
Constipation	58 / 69.0 %	11 / 27.5 %**	2 / 4.5 %***++
Diarrhea	26 / 31.0 %	4 / 10.0 %**	1 / 2.3 %***+
Flatulence	32 / 38.1 %	6 / 15.0 %**	1 / 2.3 %***++
Intestinal dysfunction	55 / 65.5%	-	0

Note: Differences between indicators before and after treatment are significant: * – $p<0.05$; * * – $p<0.01$; * * * – $p<0.01$. Differences between subgroups 1a and 1b after treatment are significant: + – $p<0.05$; ++ – $p<0.01$

Source: compiled by the authors of this study

Table 3. Dynamics of biochemical blood parameters in patients with CHC and colonic dysbiosis during combined treatment

Parameter	Examined patients		
	Before treatment (n=84)	After treatment	
		1a subgroup (n=40)	1b subgroup (n=44)
Total bilirubin, μmol/L	37.8±3.4	30.4±2.1	17.6±1.8*+
ALT, U/L	118.4±10.5	82.2±4.4**	43.2±3.5*+
AST, U/L	75.3±6.2	62.4±2.6	32.5±1.5*+
ALP, U/L	126.5±18.4	96.0±11.2**	52.4±2.6*++
GGT, U/L	77.6±8.4	60.3±2.0	34.8±2.4*

Note: Differences between indicators before and after treatment are significant: * – $p < 0.01$; * * – $p < 0.05$. Differences between 1a and 1b subgroups after treatment are significant: + – $p < 0.01$

Source: compiled by the authors of this study

tability, and general weakness decreased only 1.5-fold ($p < 0.01$). As a manifestation of biliary dyspepsia, skin itching in subgroup 1b patients decreased 3.4-fold ($p < 0.01$), while in patients who did not receive UDCA, it decreased only 1.4-fold ($p < 0.05$). Pain in the right hypochondrium decreased to 6.8% in subgroup 1b patients during follow-up clinical examination, while in subgroup 1a patients after treatment, 20.0% still reported this complaint.

As indicated by the results, in patients of subgroup 1a, manifestations of biliary dyspepsia decreased by only 16.9% ($p<0.05$), whereas in subgroup 1b, biliary dyspepsia decreased by 46.0% after treatment ($p<0.001$). Accordingly, in subgroup 1b, symptoms of biliary dyspepsia such as nausea, bitter belching, and bitterness in the mouth decreased by 30.0% ($p<0.01$), 25.1% ($p<0.01$), and 20.3% ($p<0.01$), respectively. In patients of subgroup 1a, who did not additionally receive UDCA as part of the treatment, the above symptoms decreased upon re-evaluation by only 4.5%, 9.9%, and 7.6%, with no statistically significant differences detected during treatment (Table 2).

The most objective criterion for determining the clinical effectiveness of the prescribed therapeutic complex in patients with CHC and colonic dysbiosis is the assessment of changes in intestinal dyspepsia. Constipation, which dominated the clinical picture, decreased by 15.3 times in subgroup 1b ($p<0.001$) and only by 2.5 times in subgroup 1a ($p<0.01$). Diarrhea, an atypical sign of colonic dysbiosis in CHC patients, decreased by 13.5 times in subgroup 1b ($p<0.001$) and only by 3.1 times in subgroup 1a. Flatulence, which frequently troubled patients with CHC and colonic dysbiosis before treatment, decreased by 16.5 times

Table 4. Dynamics of lipid metabolism indicators in serum of patients with CHC and colonic dysbiosis during combined treatment

Parameter	Examined patients		
	Before treatment (n=84)	After treatment	
		1a subgroup (n=40)	1b subgroup (n=44)
TC, mmol/L	5.89±0.11	5.62±0.07	4.78±0.08*+
TG, mmol/L	2.34±0.09	2.21±0.04	1.81±0.06*+
LDL-C, mmol/L	3.46±0.07	3.15±0.05	2.45±0.08*+
VLDL-C, mmol/L	1.42±0.06	1.29±0.05	0.90±0.04*+
HDL-C, mmol/L	1.07±0.08	1.11±0.06	1.53±0.05*+
ApoA1, g/L	0.78±0.07	0.84±0.05	1.02±0.06*
ApoB, g/L	2.08±0.09	1.97±0.07	1.59±0.08*+

Note: Differences before and after treatment are significant: * – $p < 0.05$; differences between 1a and 1b after treatment are significant: + – $p < 0.05$
Source: compiled by the authors of this study

during repeated assessment with probiotic and UDCA administration, whereas in subgroup 1a – only by 2.5 times. The prescribed treatment complex (LA-5 and BB-12 combined with UDCA) had a positive effect on intestinal dysfunction, which was completely absent in subgroup 1b by the end of therapy.

Thus, the combination of LA-5 and BB-12 with UDCA is a more effective method for correcting both microbiological and clinical manifestations of colonic dysbiosis in CHC patients.

An evaluation of blood biochemical parameters (indicators of cytolytic and cholestatic syndromes present in CHC patients with colonic dysbiosis before treatment) was conducted during differentiated combination therapy – Table 3.

According to the obtained data, baseline therapy combined with a probiotic preparation containing LA-5 and BB-12 did not significantly affect laboratory indicators of cytolytic and cholestatic syndromes, whereas the additional administration of UDCA led to positive changes in repeated biochemical blood testing. In patients of subgroup 1b, total bilirubin decreased by 30.2 ± 1.6 μmol/L ($p < 0.01$), whereas in subgroup 1a only by 7.4 ± 1.3 U/L ($p > 0.05$); ALP decreased by 74.1 ± 15.8 U/L ($p < 0.01$), while in subgroup 1a by only 30.5 ± 7.2 U/L ($p < 0.05$); and GGT decreased by 42.8 ± 6.0 U/L ($p < 0.01$), compared to 17.3 ± 6.4 U/L in subgroup 1a ($p > 0.05$). A pronounced reduction in cytolytic enzyme activity in serum was observed predominantly in patients with CHC and dysbiosis who received LA-5 and BB-12 combined with UDCA. In subgroup 1b, ALT activity decreased by 75.2 ± 7.0 U/L ($p < 0.01$), whereas in subgroup 1a only by 36.2 ± 6.1 U/L ($p < 0.05$). AST activity also significantly decreased only in subgroup 1b by 42.8 ± 4.7 U/L ($p < 0.01$), compared to 12.9 ± 3.6 U/L in subgroup 1a ($p > 0.05$).

Thus, the combination of the probiotic LA-5 and BB-12 with UDCA is an effective method not only for correcting dysbiotic changes in the colon but also for reducing and normalizing manifestations of cytolytic and cholestatic syndromes in patients with CHC and colonic dysbiosis.

The administration of LA-5 and BB-12 with UDCA resulted in a significant decrease in total cholesterol (TC) in subgroup 1b by 0.84 ± 0.01 mmol/L ($p < 0.05$), whereas in subgroup 1a only by 0.84 ± 0.01 mmol/L ($p > 0.05$). Triglycerides (TG) in serum also significantly decreased in subgroup 1b by 0.53 ± 0.02 mmol/L ($p < 0.05$), compared to 0.13 ± 0.05 mmol/L in subgroup 1a ($p > 0.05$). LDL-C and VLDL-C in subgroup 1b significantly decreased by 1.01 ± 0.01 mmol/L and 0.52 ± 0.02 mmol/L ($p < 0.05$), while in subgroup 1a by only 0.31 ± 0.02 mmol/L and 0.13 ± 0.01 mmol/L, respectively ($p > 0.05$). The reduction in LDL-C and VLDL-C was accompanied by an increase in HDL-C in patients with CHC and colonic dysbiosis. A significant improvement in HDL-C was observed in subgroup 1b, with an increase of 0.46 ± 0.03 mmol/L ($p < 0.05$), compared to only 0.04 ± 0.02 mmol/L in subgroup 1a ($p > 0.05$) (Table 4).

The SteatoTest index significantly decreased after treatment by 1.4 times ($p < 0.05$) in subgroup 1b, whereas no positive dynamics were observed in subgroup 1a. The AshTest result, indicating probable NAFLD development, remained unchanged in subgroup 1a, while a slight decrease (1.3 times, $p < 0.05$) was observed in subgroup 1b.

At the same time, although liver fibrosis (FibroTest and elastography) showed a trend toward improvement, no significant dynamics were established in either group. Thus, treatment of liver function and colonic dysbiosis in CHC patients is a stage aimed at improving clinical symptoms, dysbiosis severity, and biochemical indicators to prevent the addition of a "new" factor in CHC with obesity – NAFLD. However, the main stage of treatment is antiviral therapy aimed at complete elimination of hepatitis C virus.

Therefore, in treating CHC patients with colonic dysbiosis, correction should target not only the microbial profile but also liver function, using drug combinations with multifactorial effects, including reduction of hepatic steatosis to prevent and/or halt NAFLD progression in CHC.

When assessing quality of life (QoL) after treatment, improvement trends were observed in both groups, but significantly more pronounced in subgroup 1b. Pain intensity, general health, vitality, and social functioning scores increased 1.5-fold ($p < 0.01$) in subgroup 1b, while in subgroup 1a, general health and vitality improved 1.2-fold ($p < 0.05$), and pain intensity and social functioning only 1.1-fold. Significant 1.4-fold ($p < 0.01$) increases were also observed in role functioning and physical functioning in subgroup 1b, whereas in subgroup 1a, these QoL indicators improved only 1.2-fold ($p < 0.05$). Role functioning and mental health also significantly improved on the proposed treatment in subgroup 1b.

Integrated indicators of both physical functioning and mental health improved more substantially in subgroup 1b, i.e., with combined use of LA-5 and BB-12 and UDCA, by 1.4 and 1.5 times, respectively ($p < 0.01$).

Here is the professional English translation, with no added words or interpretation:

An assessment was conducted of the dynamics of the Spielberger–Khanin self-assessment anxiety scale indicators in patients with chronic hepatitis C (CHC) and colonic dysbiosis during combined therapy.

The number of patients who showed no signs of anxiety according to the Spielberger–Khanin self-assessment scale in subgroup 1b after treatment increased by 8.1 times ($p < 0.01$), whereas in subgroup 1a – only by 2.1 times ($p < 0.05$). Accordingly, this was accompanied by a decrease in the number of individuals with situational anxiety by 7.2 times ($p < 0.01$) in subgroup 1b patients compared to 1.2 times in subgroup 1a patients.

Thus, the prescribed treatment aimed at reducing the severity of colonic dysbiosis and improving liver function in patients with CHC using LA-5 and BB-12 and UDCA is an effective method not only for normalizing the quantitative and qualitative composition of the colonic microflora and liver function, but also for correcting quality of life indicators in these patients, which arises due to the reduction of clinical symptom severity.

DISCUSSION

The effectiveness of combined therapy using the probiotic LA-5 and BB-12 in combination with UDCA is due to the fact that LA-5 and BB-12 inhibit the growth of pathogenic bacteria, leading to a decrease in pH in the intestinal tract (due to the ability of LA-5 to produce lactic acid, and BB-12 to produce, in addition to lactic acid, acetic and succinic acids). The combination of LA-5 and BB-12 promotes the production of metabolites that are toxic to pathogenic bacteria (production of hydrogen peroxide). Additionally, LA-5 secretes acidocin, a broad-spectrum bacteriocin that inhibits the growth of bacteria and fungi [20]. *Lactobacillus acidophilus* and *Bifidobacterium animalis subsp*. lactis compete with pathogenic bacteria for nutrients and occupy adhesive receptors, thereby inhibiting the colonization of other potentially pathogenic microorganisms. The results obtained by us are consistent with the data obtained by Egyptian researchers led by Allam NG, who demonstrated the antibacterial activity of lactobacilli and bifidobacteria against pathogenic bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *enterobacteria, Klebsiella*. [21]. The positive impact of lactobacilli and bifidobacteria in the treatment and prevention of disorders associated with obesity has also been proven by Kyiv scientists [22].

On the other hand, it is known that UDCA, in addition to its positive effect on liver function and the biliary system, also exerts systemic effects, including on the gut microbiome. Such studies were conducted in patients with primary biliary cirrhosis (Tang R. et al., 2018), demonstrating normalization of the intestinal microbiome after UDCA administration in these patients [23].

Thus, the complementary effects of LA-5 and BB-12 and UDCA effectively reduce the severity of colonic dysbiosis in patients with CHC and obesity, which, in turn, leads to a reduction or complete disappearance of clinical manifestations of dysbiosis.

CONCLUSIONS

Combined therapy using LA-5 and BB-12 and UDCA is pathogenetically justified and leads not only to the correction of intestinal microbiocenosis disorders, but also to a reduction in the activity of cytolytic and cholestatic syndromes, a trend toward normalization of the blood lipid profile, and improvement of quality of life and emotional status in these patients.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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