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THE EFFICACY OF ERADICATION OF SMALL INTESTINAL BACTERIAL OVERGROWTH IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Background. Emerging evidence suggests a strong interaction between the gut, gut microbiota and liver. Derangement of gut flora, particularly small intestinal bacterial overgrowth (SIBO), occurs in a large percentage of patients with non-alcoholic fatty liver disease (NAFLD) and plays an important role in its pathogenesis.

Aim. Study of the frequency of SIBO in various forms of non-alcoholic fatty liver disease, as well as the possibilities of its pathomorphosis as a result of eradication of SIBO as a result of the use of rifaximin or multicomponent probiotic.

Material and methods. There were investigated 125 patients with non-alcoholic fatty liver disease (70 men, 55 women aged 18 to 65 years, mean age 37±6.7 years) developed at obesity or type 2 diabetes mellitus, including 85 patients with liver steatosis (group 1) and 40 patients with non-alcoholic steatohepatitis (group 2). Patients with concomitant SIBO (70 patients) was treated with rifaximin or multicomponent probiotic. As the main endpoints of the study, the frequency of achieving eradication of SIBO was evaluated (estimated from the results of a repeated H2-lactulose hydrogen test after treatment), as well as a decrease in the severity of liver steatosis by steatometry and a decrease/normalization of transaminase levels 3 months after the start of the treatment. Secondary endpoints included the change in BMI and the HOMA-IR index 3 months after the start of the treatment.

Results. SIBO in patients with non-alcoholic fatty liver disease was significantly more frequent than in control ($p<0.005$), and in patients with non-alcoholic steatohepatitis – significantly more often than in patients with liver steatosis (80 % vs 47.1 %, $P<0.01$). Eradication of SIBO after use of rifaximin was recorded in 30 of 36 patients with non-alcoholic fatty liver disease (83.3 %), including 16 of 20 patients with steatosis (80 %) and 14 of 16 (87.5 %) patients with non-alcoholic steatohepatitis. In the group of patients taking multicomponent probiotics after treatment, eradication of SIBO was noted in 12 of 36 patients (33.3 %), including 7 patients with steatosis (35 %) and 5 patients (31.3 %) with non-alcoholic steatohepatitis

Conclusion. The investigation shows that the eradication of small intestinal bacterial overgrowth has the positive influence on the natural course of NAFLD and use of rifaximine should be discussed as a perspective therapeutic strategy at this pathology.

Keywords: non-alcoholic fatty liver disease, syndrome of bacterial owergrowth, prophylaxis and treatment, rifaximin.

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1. Introduction

Non-alcoholic fatty liver disease is probably the most common chronic diffuse liver disease in the world. Affecting from 20 to 40 % of total population and being closely connected with diabetes mellitus, obesity, insulin resistance and cardiovascular pathology, non-alcoholic fatty liver dis-

ease is considered as a hepatic manifestation of the metabolic syndrome. Non-alcoholic fatty liver disease includes the wide spectrum of pathological changes in the liver, from the simple steatosis to steatosis with an inflammation (non-alcoholic steatohepatitis), fibrosis and cirrhosis. It has been established, that non-alcoholic fatty liver disease develops on average in 95 % of obese patients, and non-alcoholic steatohepatitis develops in 20% of patients with steatosis [1].If the simple hepatic steatosis usually has a favorable prognosis, non-alcoholic steatohepatitis tends to progress to fibrosis, cirrhosis, hepatocellular carcinoma and liver failure that requires a liver transplantation [2].

In 1998 a classical "double hit" hypothesis was proposed that explains the pathogenesis of non-alcoholic fatty liver disease and its progression to non-alcoholic steatohepatitis. In this model the first "hit" is represented by the deposition of fats in the liver which is promoted by insulin resistance, whereas for the second "hit" is necessary the development of an inflammatory process supported by the cytokines system with secretion of high amounts of tumor necrosis factor-alpha (TNF-α) [3]. New experimental and clinical findings made it possible to propose a model of "multiple hits" that determine the occurrence of non-alcoholic steatohepatitis which is obviously a result of the combined effect of genetic, social, behavioral factors and environmental ones [4].

Last years the great importance in pathogenesis of non-alcoholic fatty liver disease is given to disorders of the intestinal function and changes in intestinal microbiota. As it is known, the liver and intestines are closely connected with each other, because products synthesized by the liver are absorbed in the intestine, and about 70 % of blood, passing through the portal vein and liver is provided by the venous outflow from the intestine [5]. The liver which collects the most part of blood from the intestine through the portal vein, is one of organs most susceptible to the toxic effects of the intestine microflora, including microorganisms and products of their vital activity. The disturbance of the normal intestinal barrier leads to increased influence of toxic factors on the liver, and liver dysfunction itself can cause intestinal disorders [6].

Recent studies indicate that the key role in the normal interaction between the liver and intestine, including the development non-alcoholic fatty liver disease can play various disorders of intestinal microbiota, which were first described more than 80 years ago [7]. These disorders include intestinal dysbiosis which is an imbalance of intestinal microbiota, associated with harmful effects as well as the syndrome of bacterial overgrowth in the small intestine occurring in 20–75 % of patients with chronic diffuse liver diseases [8].The syndrome of bacterial overgrowth is traditionally defined as a semination of the proximal parts of the small intestine more than 10^5colony-forming units (CFU)/ml of intestinal contents due to opportunistic microflora, coming from the upper parts of gastrointestinal tract or as a result of the retrograde translocation of opportunistic microbiota from colon. Today the syndrome of bacterial overgrowth is considered as one of the most important causes, due to which the intestinal microbiota affects the liver. Patients with chronic diffuse liver diseases often have factors predisposing to the syndrome of bacterial overgrowth, such as a small intestine motility disorder, increased intestinal permeability and slowing of intestinal transit. Motility changes of the stomach and intestine in patients with non-alcoholic fatty liver disease, especially against the background of diabetes mellitus, are associated with the autonomic nervous system dysfunction , changes in intestinal permeability and intestinal barrier, disturbance of the level of neuropeptides and/or pro-inflammatory cytokines and the effect of inflammatory mediators on the gastrointestinal neuro-muscular apparatus [9]. Together, these changes lead to disorders that connect the intestinal motility, stasis, increased intestinal permeability and translocation of bacteria and endotoxins with the development and progression of liver diseases and their complications.

Various studies established an increased intestinal permeability and a high incidence of bacterial overgrowth syndrome in patients with non-alcoholic fatty liver disease associated with severity of steatosis [10]. Although the pathogenetic connection between the syndrome of bacterial overgrowth, the development and progression of non-alcoholic steatohepatitis still be insufficiently studied, its key role needs paying attention. These data are confirmed by the fact that the use of antibacterial drugs reduces the severity of steatosis in both mice and humans [11]. In addition, in recent years the role of modulation of intestinal microbiota in the treatment of non-alcoholic fatty liver disease, particularly, the potential possibilities of prebiotics, probiotics and eubiotics are inten-

sively studied [12]. Thus, in the study [13] in the system review is demonstrated the beneficial effect of prebiotics on non-alcoholic fatty liver disease due to the modification of intestinal microbiota, weight loss of and improved regulation of glucose levels, and prebiotics therapy is presented as an attractive therapeutic strategy. Unfortunately, there are only few studies on effectiveness of antibiotic therapy in non-alcoholic fatty liver disease Nevertheless, positive effects of polymixin B and metronidazole in steatosis, arising on the background of complete parenteral nutrition and after bypassing operations on the intestine, open up wide possibilities for using antibiotics in the treatment of non-alcoholic fatty liver disease [14]. In particular, if there is a syndrome of bacterial overgrowth it is reasonable to study the potential efficacy of rifaximin which has a wide spectrum of action against gram-negative and gram-positive microorganisms, anaerobic and aerobic bacteria [15]. The drug has a comparable high placebo safety profile due to low absorption and has no systemic side effects. Rifaximin works only in the gastrointestinal tract and excreted mainly with feces. The drug is not metabolized in the liver, so the system of cytochrome P450 is not involved and no clinically relevant interactions with other drugs are detected. Its effect on the normal intestinal microflora is limited to the period of use, it doesn't cause the development of resistance. In addition, in recent years, it has been established that rifaximin has its own probiotic properties, in particular, increases the amount of useful Lactobacillus [16]. In this regard, recently rifaximin is not even considered even as a selective intestinal antibiotic, but as an intestinal eubiotic.

2. Aim of research

The study of the frequency of small intestinal bacterial overgrowth (SIBO) in various forms of non-alcoholic fatty liver disease, as well as the possibility of its pathomorphosis as a result of eradication of SIBO as a result of use of rifaximin or multicomponent probiotic.

3. Material and methods of research

To achieve the main aim there were examined 125patients with non-alcoholic fatty liver disease (70 men, 55 women, 18–65 years old, the mean age 37±6,7 years), developed at the background of obesity or diabetes mellitus type 2, including 85 patients with simple liver steatosis (1 group) and 40 patients with non-alcoholic steatohepatitis(2 group). The control group consisted of 20 practically healthy volunteers (12 men, 8 women, 18–49 years old, the mean age 27±4,6), in whom a non-alcoholic fatty liver disease was excluded at the complex examination. All patients gave an informed consent for the participation in the study.

The criteria for inclusion patients in the study were: age over 18 years, consent for the participation in the study, the presence of the diagnosed non-alcoholic fatty liver disease in the patient with overweight and/or obesity. All examined persons, included in the study, did not abuse alcohol (intake of <21 alcoholic Un/week for men, <14 alcoholic UN/week for women) during the last year. The study did not include patients with viral, alcoholic and drug-induced hepatitis, storage diseases, cardiac liver fibrosis, liver cirrhosis, secondary forms of obesity.

All patients underwent the complex clinical, biochemical and ultrasound examination, anthropometric study with the calculation of the body mass index and indirect indicator of immune resistance – HOMA-IR index (Homeostatic Model Assessment) according to the formula: fasting glucose (mmol/l) x fasting insulin concentration in blood (mcUn/l)/22,5.

The diagnosis of simple steatosis was based on specific data of the ultrasound examination of the liver with steatometry and elastography (ultrasound scanner Soneus P7 Ultrasign) in the presence of an overweight and/or obesity in the patient. The degree of steatosis was determined by the ultrasound attenuation coefficient:

S1 – 2,20–2,29 dB/cm(mild steatosis with involvement of 5–33 % of hepatocytes);

S2 – 2,30–2,90 dB/cm (moderate steatosis with involvement of 33–66 % of hepatocytes);

S3 – >2,90 dB/cm (severe steatosis with involvement of more than 66 % of hepatocytes).

The diagnosis of non-alcoholic steatohepatitis was made with the additional increase in liver size and increase in the level of ALT above normal values. The diagnosis of the bacterial overgrowth syndrome was based on positive results of H_2-lactulose hydrogen test (micro-H_2-meter made by Micromedical, Great Britain). Positive test results considered a level of more than 20 ppm

in the presence of a double peak of hydrogen levels, an early increase (within 90 minutes) of more than 20 ppm or a sustained increase of more than 12 ppm compared to the initial hydrogen level.

Demographic and clinical features of examined patients are presented in **Table 1**.

Table 1
Initial characteristics of the examined patients

Parameter	1 group (steatosis), n = 85	2 group (NASH), n = 40	Control, n = 20
Age, years	56,3±3,4	53,2±3,6	50,1±3,9
Sex, m/f	50/35	20/20	11/9
BMI (kg/m^2)	30,4±2,0	33,1±2,8	24,1±1,4
HOMA-IR index	6,2±0,48	6,6±0,62	2,8±0,30
Ultrasound attenuation coefficient, dB/cm	2,45±0,22	2,58±0,28	2,02±0,18
ALT level Un/l	37,2±2,6	59,1±3,8	30,5±2,3
SIBO(%)	40 (47,1 %)	32 (80 %)	2 (10)
Rifaximin treatment, n	20	16	
Probiotic treatment, n	20	16	

All patients (72) with bacterial overgrowth syndrome identified by the H_2-lactulose hydrogen test were randomized to 4 groups using a 1:1 random number generator depending on the received treatment. Groups 1A and 2A consisted of patients with simple liver steatosis (20 patients) and non-alcoholic steatohepatitis (16 patients), who were prescribed with rifamixin (Alpha Normix, Alpha Vasserman, Italy) at a dose of 600 mg (3 tablets) 2 times a day for 14 days. Groups 2A and 2B consisted of patients with simple liver steatosis (20 patients) and non-alcoholic steatohepatitis (16 patients), who were prescribed with the multicomponent probiotic (Probis, Sun, India), containing a mixture of diffetent strains of bifido- lactobacilli and Saccharomyces boulardii twice a day for 1 month. All patients were recommended a lifestyle modification including a hypocaloric diet and increased physical activity. As the main endpoints of the study, the frequency of eradication of bacterial overgrowth (estimated by the results of the repeated H_2-lactulose hydrogen test after the treatment) as well as a decrease in the severity of the liver steatosis according to steatometry and decrease/normalization of serum transaminase levels 3 months after the start of treatment. Secondary endpoints included BMI and HOMA-IR decrease after 3 months of the treatment. The results of the study were processed using methods of variational statistics with the calculation of Student criterion.

4. Results of research

Based on the results of positive H_2-lactulose hydrogen test, the syndrome of bacterial overgrowth was diagnosed in 40 patients of the 1st group (47,1 %), 32 patients (80 %) of the 2nd group and only 2 patients (10 %) of the control group. Thus, the syndrome of bacterial overgrowth in patients with non-alcoholic fatty liver disease was significantly more frequent than in control ($p<0,005$), and in patients with non-alcoholic steatohepatitis – significantly more frequent than in patients with simple hepatic steatosis (80 % vs 47,1 %, $p<0,01$). The eradication of bacterial overgrowth after the use of rifamixin was observed in 30 of 36 patients with non-alcoholic fatty liver disease (83,3 %), including 16 of 20 patients with simple steatosis(80 %) and 14 of 16 (87,5 %) patients with non-alcoholic steatohepatitis. In the group of patients taking the multicomponent probiotic after the treatment, the eradication of bacterial overgrowth was observed in 12 of 36 patients (33,3 %), including in 7 patients with simple steatosis (35 %) and 5 patients (31,3 %) with non-alcoholic steatohepatitis (**Fig. 1**).

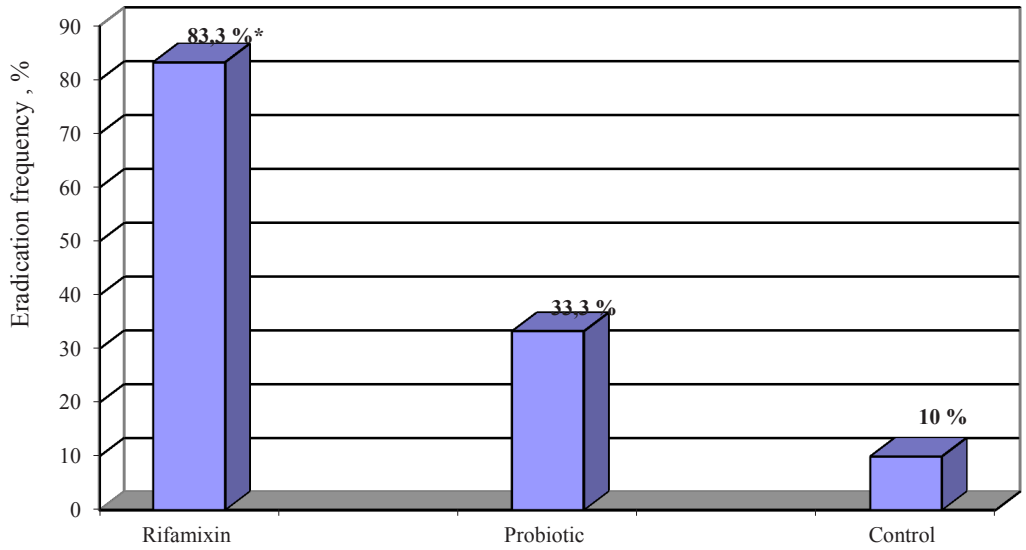

Fig. 1. Frequency of eradication of BO after the use of rifamixin and probiotic:
* – p<0,005 (rifamixin vs probiotic)

Thus, the efficacy of rimamixin in eradication of bacterial overgrowth was significantly higher than that of the multicomponent probiotic (p<0,005). In addition, the use of rifamixin accompanied by the decrease of the liver steatosis (p=0,065) and body mass index, leading to the reliable decrease of ALT level in patients with non-alcoholic steatohepatitis(p<0,05) and HOMA-IR index in all patients with non-alcoholic fatty liver disease (p<0,05) (**Table 2**). In the group of patients, who received the multicomponent probiotic, the reliable dynamics of ALT level and steatosis intensity degree was not observed, only an unreliable decrease of HOMA-IR and BMI was noted.

Table 2
Dynamics of several parameters after the treatment with rifamixin, M±m

Parameters	Examined groups			
	1 group (steatosis), n = 20		2 group (NASH), n = 16	
	Before treatment	After treatment	Before treatment	After treatment
BMI (kg/m^2)	30,4±2,0	28,5±2,1	33,1±2,8	30,6±2,6
HOMA-IR index	6,2±0,48	4,2±0,38*	6,6±0,62	4,8±0,42*
Ultrasound attenuation coefficient, dB/cm	2,45±0,22	2,20±0,18	2,58±0,23	2,32±0,24
ALT level, Un/l	37,2±2,6	32,7±0,30	59,1±3,8	43,0±0,40*

*Note: * – p<0,05*

The studies allow to draw a conclusion that changes in intestinal microbiota, especially the presence of the syndrome of bacterial overgrowth can play a significant pathogenetic role in the development and progression of non-alcoholic fatty liver disease. Eradication of bacterial overgrowth in patients with non-alcoholic fatty liver disease is attended by a decrease in the severity of steatosis and hepatic inflammation as well as a decrease in insulin resistance in most patients. Rifamixin

is an effective therapeutic agent for the treatment of the syndrome of bacterial overgrowth, so it may be considered as a promising drug for the treatment of non-alcoholic fatty liver disease.

5. Discussion of research results

Today there are no specific drugs for the treatment of non-alcoholic fatty liver disease. Randomized controlled trials on non-alcoholic fatty liver disease are realized with regard to the use of thiazolidinediones, ursodeoxycholic and obeticholic acid, lipid-lowering drugs, metformin, vitamins E and C, but most of them do not take into account histological nuances and have a small sample and a short observation time [17]. For these reasons, the study of the effect of modulation of intestinal microbiota in the pathogenesis and progression of non-alcoholic fatty liver disease can open new therapeutic prospects.

In particular, the modulation of the intestinal microbiota composition can be achieved by the use of pre- and probiotics. Thus, in studies on animals the additives of prebiotic fibers had a lipid-lowering effect, probably by reducing lipogenesis due to a decrease in the activity of enzymes responsible for free fatty acids esterification with the formation of new triglycerides. There were realized few studies on the use of prebiotics (inulin) in non-alcoholic fatty liver disease in humans, but the lipid-lowering effect of their use was lower comparing with the experimental data [18]. At the same time it was proved that Bifidobacterium longum and fruit-oligosaccharide supplements together with the lifestyle modification decrease the cytonectrotic activity, plasma lipid levels, insulin resistance index (HOMA-index) and non-alcoholic steatohepatitis activity index in a small sample of patients, whose disease was proved by biopsy [19].

There is also enough experimental and clinical data about the effectiveness of probiotics in non-alcoholic fatty liver disease. For example, in the study [20] was demonstrated that for obesity due to overeating, probiotic VSL#3 can prevent the development of steatosis due to the mechanism associated with T-cells natural killers (NKT)-Based on data of the studies [21], it was concluded that in non-alcoholic fatty liver disease Bifidobacterium longum is more effective than Lactobacillus acidophilus, and this effect is associated with a change in the intestinal microbiota. Unfortunately, experimental data don't always coincide with clinical ones. Thus, several studies have shown that the probiotic drug VSL#3 weakening fibrosis, does not have an effect on steatosis or steatohepatitis in non-alcoholic steatohepatitis, induced by a diet with a dificiency of methionine and choline [22]. In this study was investigated the efficacy of a multicomponent probiotic in the eradication of bacterial overgrowth syndrome and the modification of the course of non-alcoholic fatty liver disease. The data obtained in a limited number of patients showed only an unreliable decrease in the body mass index and the HOMA-IR in patients receiving the multicomponent probiotic, whereas the reliable dynamics from elevated level of ALT and the degree of steatosis after the treatment was not observed. The lack of convincing results of confirming the effectiveness of probiotics in non-alcoholic fatty liver disease in the study may be associated with a limited number of patients, insufficient term of the treatment and observation, a fixed combination of probiotic strains.

Unfortunately, today there are not enough studies devoted to the effectiveness of antibiotics, especially the selective intestinal antibiotic rifaximin in non-alcoholic fatty liver disease. This study filled this gap to some extent and demonstrated that the use of rifaxamin in the majority of patients with non-alcoholic fatty liver disease was accompanied by effective eradication of bacterial overgrowth, a decrease in the body mass index and the severity of liver steatosis and also led to the reliable decrease in the level of ALT in patients with non-alcoholic steatohepatitis and HOMA-IR index in all patients with non-alcoholic fatty liver disease. Nevertheless, since the number of studies devoted to the use of probiotics, prebiotics and antibiotics in patients with non-alcoholic fatty liver disease is limited, further large and well-planned randomized clinical trials are needed in this direction.

6. Conclusions

1. The totality of proofs existent for today allows to suggest the important role of intestinal mucrobiota disorders, in particular, small intestine bacterial overgrowth, in the development of

non-alcoholic fatty liver disease, although further studies of larger cohorts are needed to clearly understand the pathogenetic mechanisms.

2. Pharmacological modulating of the ntestinal microbiora may represent a promising therapeutic strategy for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and associated conditions in the future.

3. The results obtained, as well as the existing uncertainty in quality control, choice of strains and the optimal dose do not yet allow to recommend the wide clinical use of probiotics for non-alcoholic fatty liver disease in general, or any of their strains, in particular.

4. The obtained data allow to draw a conclusion that the eradication of bacterial overgrowth in patients with non-alcoholic fatty liver disease is accompanied by a decrease in the severity of the steatosis and hepatic inflammation as well as a decrease in insulin resistance in a significant number of patients.

5. The use of rifaxamin in the presence of bacterial overgrowth may be considered as a promising therapeutic strategy in patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

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