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КОМПЛЕКСНАЯ ОЦЕНКА ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ТОНКОЙ КИШКИ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Assessment of the Functional Status of the Small Intestine in Patients with Non-Alcoholic Fatty Liver Disease

Резюме

Цель работы. Комплексное исследование функционального состояния тонкой кишки и изучение сопряженности его нарушений с развитием неалкогольной жировой болезни печени. **Материалы и методы.** Обследовано 86 больных неалкогольной жировой болезнью печени на стадии стеатоза и стеатогепатита по результатам ультразвукового исследования печени на аппарате «SONIX OP» (Канада) и теста FibroMax компании BioPredictiv (Париж, Франция). Пациентам проводилось исследование глюкозы сыворотки крови на анализаторе «Huma Star 600» (Германия) и инсулина методом иммуноферментного анализа. Рассчитывался показатель инсулинорезистентности HOMA-IR. Для определения нарушений полостного пищеварения в тонкой кишке проводили нагрузочный тест с растворимым крахмалом, мембранного пищеварения — с сахарозой, всасывания — с глюкозой. Избыточный бактериальный рост определяли с использованием водородного дыхательного теста на анализаторе ЛактофаН2 компании АМА (Санкт-Петербург). Для оценки толстокишечной микрофлоры проводили посев кала на дисбиоз. **Результаты.** По клиническим данным, у пациентов с неалкогольной жировой болезнью печени поражение тонкой кишки протекает в стертой форме, однако при исследовании ее функционального состояния выявляется существенное снижение полостного и мембранного пищеварения, усиление всасывания. У обследованных больных констатировано повышение инсулина сыворотки крови по сравнению с контрольной группой (16,64±0,78 мкМЕ/мл против 10,46±0,56 мкМЕ/мл, p <0,0001). Индекс HOMA-IR также был увеличен у пациентов по сравнению с контрольной группой (2,84±0,11 против 2,05±0,07, p <0,0001). Избыточный бактериальный рост был диагностирован у 62 (72%) больных, при этом при стеатозе печени — у 33 (55%), при стеатогепатите 1 степени активности — у 11 (61,1%), при стеатогепатите 2 степени — у 6 (66,7%), при стеатогепатите 3 степени — у 2 (100%) пациентов. По результатам посева кала дисбиоз был выявлен у 56 (65,1%) пациентов. При проведении корреляционного анализа выявлены отрицательные связи между степенью избыточного бактериального роста и полостным пищеварением, между степенью избыточного бактериального роста и мембранным пищеварением, положительная связь — между степенью избыточного бактериального роста и всасыванием. **Заключение.** Неалкогольная жировая болезнь печени сопровождает-

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ся нарушениями пищеварительной и резорбтивной функций тонкой кишки, развитием дисбиоза. Эти нарушения нередко носят субклинический характер и могут быть выявлены и оценены после специальных исследований.

Ключевые слова: *неалкогольная жировая болезнь печени, мальабсорбция, избыточный бактериальный рост*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The aim. A comprehensive study of the functional state of the small intestine and the study of the relationship of its disorders with the development of non-alcoholic fatty liver disease. **Materials and methods.** 86 patients with non-alcoholic fatty liver disease at the stage of steatosis and steatohepatitis were examined according to the results of ultrasound examination of the liver using the SONIX OP apparatus (Canada) and the FibroMax test of BioPredictiv company (Paris, France). Patients underwent a blood glucose test using an Huma Star 600 analyzer (Germany) and insulin using an enzyme-linked immunosorbent assay. The HOMA-IR insulin resistance index was calculated. In order to determine abnormal digestive disorders in the small intestine, a stress test was performed with soluble starch, membrane digestion with sucrose, absorption with glucose. IDBs were evaluated using a hydrogen breath test on a LactofN2 apparatus from the AMA firm (St. Petersburg). To assess colonic microflora, stool was sown for dysbiosis. **Results.** According to clinical data, in patients with non-alcoholic fatty liver disease, damage to the small intestine occurs in a non-manifest form. However, in the study of the functional state of the small intestine in patients, a significant decrease in cavity and membrane digestion, increased absorption are detected. In patients with non-alcoholic fatty liver disease, an increase in blood insulin was observed compared with the control group (16,64±0,78 μIU/ml versus 10,46±0,56 μI/ml, p=0,000002). The HOMA-IR insulin resistance index was also increased in patients compared with the control group (2,84±0,11 versus 2,05±0,07, p=0,00003). Excessive bacterial growth was diagnosed in 62 (72%) of patients with non-alcoholic fatty liver disease, while with liver steatosis — in 33 (55%), with steatohepatitis 1 degree of activity — in 11 (61,1%), with steatohepatitis 2 degrees — in 6 (66,7%), with steatohepatitis 3 degrees — in 2 (100%) of patients. According to the results of stool stool, dysbiosis was detected in 56 (65,1%) of patients with non-alcoholic fatty liver disease. A correlation analysis revealed negative relationships between the severity of excessive bacterial growth and digestive digestion, between the severity of excessive bacterial growth and membrane digestion, and a positive relationship between the severity of excessive bacterial growth and absorption. **Conclusion.** Non-alcoholic fatty liver disease is accompanied by disorders of the digestive and resorptive functions of the small intestine, and the development of dysbiosis. These disorders are often subclinical in nature and can be identified and evaluated after special studies.

Key words: *non-alcoholic fatty liver disease, malabsorption, excessive bacterial growth*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, EBG — excessive bacterial growth, NAFLD — non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease [1–5]. NAFLD includes fatty degeneration, fatty degeneration with inflammation and hepatocyte damage — non-alcoholic steatohepatitis and fibrosis with possible progression to liver cirrhosis [6]. Despite the active study of various factors contributing to NAFLD, many aspects of its pathogenesis are still not fully clear.

Information on the possible significance of intestinal dysbiosis in the development of NAFLD has emerged in recent times [3, 7, 8]. At the same time, there are no comprehensive studies on intestinal microbiota, although intestinopathy may be a risk factor for metabolic liver disorders. Solving the problem from this point of view would allow studying the functional relationships of the liver and intestines with NAFLD.

The **objective of our work** is a comprehensive study of the functional status of the small intestine and the study of the relationship between its disorders and NAFLD.

Materials and methods

The analysis included 86 patients with NAFLD; 60 of them with hepatic steatosis (69.8%), and 26 with steatohepatitis (30.2%). As for disease activity, steatohepatitis of grade I was found in 18 (69.2%) patients, grade II — in 6 (23.1%) patients, and grade III — in 2 (7.7%) patients, respectively. The mean age of the patients was 46.3 ± 7.5 years. Sixty-four women (74.4%) and 22 (25.6%) men were examined. The mean age of female patients was 49.1 ± 5.6 years, and of the male patients — 41.2 ± 6.3 years.

Inclusion criteria: age 18–60 years, NAFLD at the stage of steatosis and steatohepatitis according to the results of liver ultrasound using the SONIX OP device (Canada). Ultrasonic signs of NAFLD included an enlarged liver, increased liver echogenicity compared to the echogenicity of kidneys, relatively reduced density of the liver compared with that of the spleen (liver spleen index less than 1), decreased sound conductivity, and difficult visualization of the branches of hepatic and portal veins. Steatohepatitis activity was determined by biochemical blood tests for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using the Huma Star 600 apparatus (Germany). Assessment of the extent of liver fibrosis was carried out by sonoelastography using the AIXPLORER analyzer (France) and FibroTest and FibroMax tests manufactured by BioPredictiv (Paris, France).

Exclusion criteria: liver injury of another etiology (alcoholic, drug, viral, autoimmune), inflammatory bowel diseases, pregnancy and lactation, cancer, mental disorders.

Patients took a serum glucose test using the Huma Star 600 blood analyzer (Germany). Insulin level in blood serum was determined by enzyme immunoassay using monoclonal antibodies from DRG Insulin ELISA standard set of reagents. In order to determine the compensable degree of increased insulin level, the HOMA-IR insulin resistance index was calculated using the following formula: [fasting insulin (IU/ml) × fasting glucose (mmol/l)]/22.5.

In addition to clinical data, results of the study of the stages of the digestive process and the state of intestinal microflora were used to assess the functional status of the small intestine. In order to determine abnormalities of cavitary digestion, membrane digestion and absorption in the small intestine, stress tests were performed with polysaccharide (soluble starch), disaccharide (sucrose) and monosaccharide (glucose), respectively. All stress tests were performed the same way: first, fasting glucose level in capillary blood was determined, then patients took per os 50 g of soluble starch, sucrose or glucose dissolved in 200 ml of water, then the glycemia level was re-evaluated after 30, 60 and 120 minutes using the EKSAN-G device with MG-1 glucose oxidase membrane.

Excessive bacterial growth (EBG) was defined using a hydrogen breath test performed on the Lactofan2 device manufactured by AMA (St. Petersburg). First, the fasting concentration of hydrogen in expired air was measured. Then, patients took per os 20 g of lactulose dissolved in 200 ml of water. Hydrogen concentration was measured every 20 minutes for 2 hours. The test result was considered positive with an increase in hydrogen gradient of more than 10 ppm during the 1st hour of the study [9]. The severity of EBG was evaluated depending on hydrogen concentration: grade 1 — increase from 10 to 50 ppm, grade 2 — from 50 to 100 ppm, grade 3 — more than 100 ppm [10].

The state of colonic microflora was evaluated by the concentration of E. coli, Streptococci, Enterococci, Bifidobacteria, Lactobacilli, Staphylococcus aureus, yeast-like fungi, Proteus, Klebsiella, Clostridia, Pseudomonas aeruginosa and other opportunistic microorganisms in 1 g of feces [11]. The severity of dysbiosis was evaluated according to the classification developed by I. B. Kuvaeva and K. S. Ladodo (1991) [12].

Data obtained during this study were compared with the parameters of the control group that included 30 healthy individuals aged 18 to 60 years.

Patients were enrolled in the study after signing a Patient Informed Consent form per the order No. 390n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012 (registered by the Ministry of Justice of the Russian Federation on May 5, 2012, under No. 24082), in compliance with ethical principles.

Data analysis was performed using StatSoft Statistica 10.0.1011. Normality of distribution was checked with Kolmogorov — Smirnov and Shapiro — Wilk tests; equality of variances was checked with Levene's test. Most samples were close to normal distribution. Therefore, statistical methods for parametric distributions were used. A correlation analysis method with the calculation of Pearson's linear correlation coefficient *(r)* was used to perform dependency analysis. Statistical significance of differences (p) in quantitative values between independent groups was carried out using Student's t-test for independent samples. T-test for dependent samples was used for dependent groups. The data are presented as M ± SD, where M is the mean value, and SD is the standard deviation. Differences between the groups were considered statistically significant with a probability of the valid null hypothesis of no differences between the groups (p) < 0.05.

Results

Patients complained of discomfort and pain in the right hypochondrium — 22 (25.6%), in the paraumbilical area — 24 (27.9%), and in the large intestine area — 14 (16.3%). The following dyspeptic symptoms were mentioned: bitter taste in the mouth — in 11 (12.8%) patients, nausea — in 14 (16.3%) patients, epigastric burning — in 10 (11.6%) patients, flatulence — in 32 (37.2%) patients, constipation — in 20 (23.3%) patients, diarrhea — in 15 (17.4%) patients, a combination of constipation and diarrhea — in 7 (8.1%) patients. According to physical examination, a coated tongue was found in 67 (77.9%) patients, tender abdomen in the right hypochondrium — in 18 (20.9%) patients, in the paraumbilical area — in 28 (32.6%) patients, and in the large intestine area — in 12 (14.0%) patients. An enlarged liver was observed in 26 (30.2%) patients. Thus, NAFLD is accompanied by clinical signs of liver and intestinal damage.

The study of the functional status of the small intestine revealed no significant differences depending on the stage of NAFLD. However, changes were found at all 3 stages of the digestive process (Table 1).

The test with soluble starch showed a significantly reduced increase in glycemia level in patients with NAFLD compared to the control group, indicating the inhibition of cavitary hydrolysis in the small intestine. The test with sucrose also revealed a reduced increase in glycemia level in patients with NAFLD compared to the control group, indicating the insufficiency of membrane hydrolysis in the small intestine. The increase in glycemia level during the test with glucose in patients with NAFLD was significantly higher compared to the control group, indicating increased absorption in the small intestine. Glycemia in patients with NAFLD did not decrease to baseline after 120 minutes from the beginning of the study.

The test for serum insulin level in patients with NAFLD showed basal insulin of 16.64 ± 0.78 μIU/ml vs 10.46 ± 0.56 μIU/ml in the control group (p < 0.0001). To analyze the obtained data, the HOMA-IR insulin resistance index was calculated, and its increase was observed in patients with NAFLD compared to the control group (2.84 ± 0.11 vs 2.05 ± 0.07, p < 0.0001).

A coprology test showed steatorrhea in 50 (58.1%) patients with NAFLD, creatorrhea in 22 (25.6%) patients, amylorrhea in 34 (39.5%) patients.

EBG was diagnosed in 62 (72%) patients with NAFLD (there was an increase in hydrogen content in expired air of more than 10 ppm compared with the baseline before the 60th minute of the study). Considering cases of liver steatosis, EBG was found in 33 (55%) patients, in cases of steatohepatitis of activity grade 1 — in 11 (61.1%) patients, in cases of steatohepatitis of activity grade 2 — in 6 (66.7%) patients, in cases of steatohepatitis of activity grade 3 — in 2 (100%) patients.

Overall, the increase in hydrogen concentration in expired air in patients with NAFLD by the 60th minute of the study was 64.3 ± 7.8 ppm vs 24.4 ± 6.5 ppm in the control group (p < 0.0001). EBG analysis in terms of severity demonstrated grade 1 in 40 (64.5%) patients, grade 2 in 19 (30.7%) patients, and grade 3 in 3 (4.8%) patients. At the same time, there was no reliable relationship between the stage of NAFLD and the severity of EBG.

During the EBG test, two peaks of hydrogen concentration — small intestinal and large intestinal — were observed in 24 (38.7%) patients with NAFLD, i.e., there was EBG along with retained ileocecal valve function (Fig. 1). Thirty-eight (61.3%) patients demonstrated a continuous increase in hydrogen concentration, i.e., EBG with ileocecal insufficiency (Fig. 2).

Correlation analysis with Pearson's linear correlation coefficients revealed negative associations

Table 1. *The state of the hydrolysis-resorption process in the small intestine in patients with non-alcoholic fatty liver disease (mmol/l)*

Loading tests	Test period	Patients with steatosis (n=60) M±SD	Patients with steatohepatitis (n=26) M±SD	Group of control (n=30) M±SD
With starch	On an empty stomach	5,67±0,1** p^2 <0,0001	5,54±0,12** p^2 <0,0001	4,6±0,49
	In 30 minutes after load	5,98±0,2* ** p^1=0,002 p^2 <0,0001	5,74±0,21* ** p^1=0,003 p^2 <0,0001	6,95±0,18* p^1 <0,0001
	In 60 minutes after load	5,77±0,2* p^1=0,04	4,79±0,35* p^1 <0,0001	5,87±0,38* p^1 <0,0001
	In 120 minutes after load	4,93±0,25* p^1 <0,0001	4,79±0,38* p^1=0,0015	4,34±0,36* p^1=0,0008
With sucrose	On an empty stomach	5,93±0,11** p^2 < 0,0001	5,68±0,12** p^2 <0,0001	4,69±0,44
	In 30 minutes after load	7,02±0,88* p^1=0,005	6,93±0,67* p^1=0,002	6,89±0,18* p^1 <0,0001
	In 60 minutes after load	6,72±0,25* ** p^1 <0,0001 p^2 <0,0001	6,2±0,78	5,07±0,41
	In 120 minutes after load	4,97±0,16* ** p^1 <0,0001 p^2=0,0004	5,27±0,47** p^2=0,002	4,33±0,37
With glucose	On an empty stomach	5,41±0,1** p^2 <0,0001	5,67±0,1** p^2 <0,0001	4,71±0,2
	In 30 minutes after load	8,8±0,2* ** p^1 <0,0001 p^2 <0,0001	8,94±0,15* ** p^1 <0,0001 p^2 <0,0001	7,0±0,17* p^1 <0,0001
	In 60 minutes after load	7,9±0,33* ** p^1 <0,0001 p^2 <0,0001	6,56±0,47* p^1=0,002	5,91±0,17* p^1 <0,0001
	In 120 minutes after load	6,18±0,19* ** p^1 <0,0001 p^2 <0,0001	6,34±0,22* ** p^1=0,0004 p^2 <0,0001	4,5±0,32

Note: * — reliable changes compared to baseline (p^1 <0,05); ** — reliable changes compared to group of control (p^2 <0,05); n — number of observations

between the severity of EBG and cavitary digestion in the small intestine (r = –0.68, p < 0.05) and between the severity of EBG and membrane digestion (r = –0.53, p < 0.05). A positive association was found between the severity of EBG and absorption (r = 0.44, p > 0.05).

Results of stool culture revealed dysbiosis in 56 (65.1%) patients with NAFLD. At the same time, a decrease in the amount of obligate microflora was observed — bifidobacteria less than 10^9 CFU/g in 22 (39.3%) patients and lactobacilli less than 10^7 CFU/g in 20 (35.7%) patients. Lactose-negative and hemolytic Escherichia coli were obtained in diagnostically significant titer — in 15 (26.8%) and 12 (21.4%) with a decreased proportion of viable E. coli — in 18 (32.1%) patients, respectively. These or other pathogenic bacteria — staphylococci, yeast, clostridia and veillonella — were found in many patients.

Dysbiosis of grade 1 was diagnosed in 20 (35.7%) patients, grade 2 — in 25 (44.6%) patients, grade 3 — in 11 (19.6%) patients with NAFLD. At the same time, there was a positive association between the severity of dysbiosis and the stage of NAFLD (r = 0.54, p > 0.05). When conducting a correlation analysis between the severity of dysbiosis and the HOMA-IR index, a positive association was found (r = 0.72, p < 0.05), i.e., there is a direct relationship between the degree of intestinal microflora disturbance and the severity of insulin resistance.

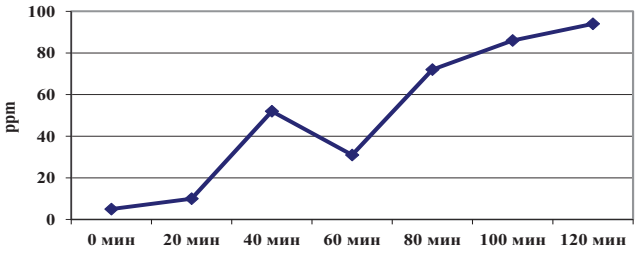

Figure 1. *Excessive bacterial growth with preserved function of the ileocecal valve*

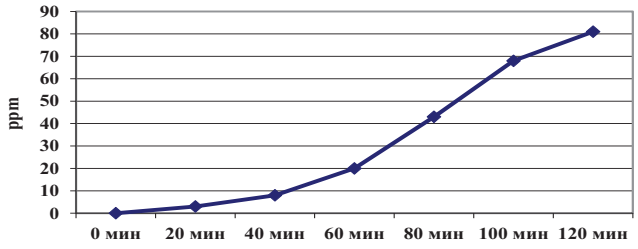

Figure 2. *Excessive bacterial growth with impaired function of the ileocecal valve*

Discussion

Patients with NAFLD are characterized by increased glucose resorption in the intestine in connection with decreased abdominal and parietal digestion. An increase in glucose absorption can be explained by increased blood insulin level and existing insulin resistance. Increased permeability of the intestinal epithelium in NAFLD may also occur due to a decreased level of ZO-1, one of the tight junction proteins of the intestinal epithelium [7]. Our data are confirmed by literature sources; according to the latter, contamination of the small intestine by pathogenic and opportunistic microorganisms leads to decreased digestive and membrane digestion, impaired enterohepatic circulation with the formation of toxic metabolites, which causes increased permeability of intestinal wall for toxins, and decreased barrier functions of liver and intestine [3].

During our study, EBG was found in most patients, and its severity correlated with the increasing severity of NAFLD. Similar data were obtained by other researchers, who found that EBG is more common in patients with steatohepatitis than in the average population and varies from 50% to 77.8% [7, 10, 13]. The reasons behind EBG in NAFLD are unknown. There is an ongoing discussion over evidence of decreased gastrointestinal motility in patients with NAFLD. The rate of orocecal transit in patients with NAFLD was slow in 22% of cases. That may be one of the conditions causing the development and progression of EBG in the small intestine [14]. Dysfunction of the ileocecal valve is critical for the development and progression of EBG since, in this situation, fecal microflora retrogradely colonizes the small intestine [2].

According to our studies, pathogenic microflora prevails in the structure of microbiota in cases of EBG. Earlier, A. A. Kozhevnikov et al. (2017) found that 16S rRNA sequencing in children with hepatic steatosis revealed an increased level of Escherichia coli compared to the control group [15]. According to E. Yu. Plotnikova (2017), patients with steatohepatitis and obesity showed an increase in the Bacteroidetes level and a decrease in the Firmicutes level at the level of phyla compared to healthy individuals. The Firmicutes level is reduced in patients with steatohepatitis and obesity mainly due to two families: Lachnospiraceae and Ruminococcaceae, with the largest decrease in Blautia and Faecalibacterium genera. An increased level of Proteobacteria is associated with an increase in the Enterobacteriaceae level (especially Escherichia) [8]. Qualitative and quantitative disorders in the composition of microbiota are considered an inducer of TNFα-stimulated inflammatory response in the liver [3, 7, 8]. Several mechanisms through which EBG contributes to the progression of NAFLD are proposed: excessive amount of bacterial endotoxins in the blood (lipopolysaccharide, peptidoglycans, lipoteichoic acid, bacterial flagellin, non-methyl fragments of bacterial DNA), increased permeability of the intestinal wall, and increased production of endogenous ethanol [13]. The close functional relationship between the state of the liver and intestinal microflora is also evidenced by the research conducted by A. A. Kozhevnikov et al. (2017), when probiotics containing Lactobacillus were used in children with NAFLD, resulting in a decreased ALT level in 80% of cases [15].

Conclusion

NAFLD is often and expectedly accompanied by the dysfunction of the small intestine, in particular, abnormal digestion and absorption, as well as dysbiosis. These disorders are often subclinical and can be found and assessed only after specific tests. The study of enteric functions broadens our understanding of the pathogenesis of NAFLD and suggests the need for not only NAFLD management but also the correction of enteric functions and restoration of microbiocenosis.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Ya.M. Vakhrushev (ORCID ID: https://orcid.org/0000-0001-9424-6316): development of the concept and design of the study; checking critical intellectual content; final approval of the manuscript for publication

A.P. Lukashevich (ORCID ID: https://orcid.org/0000-0003-4634-2658): collection, analysis and interpretation of data; justification and writing of the manuscript

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