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SMALL INTESTINAL BACTERIAL OVERGROWTH IN THE INTESTINE AND MICROBIOME ALTERATIONS AS A RISK FACTOR FOR LIPID METABOLISM DISORDERS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Kh. B. Kvit, N.V. Kharchenko

Danylo Halytsky Lviv National Medical University, Department of Therapy No. 1, Medical Diagnostics, Hematology, and Transfusiology of FPDO, Lviv, UkraineShupyk National University of Health of Ukraine, Department of Gastroenterology, Dietetics, and Endoscopy, Kyiv, Ukraine
ORCID: 0000-0003-1394-9429, email: akskris88@gmail.com,
ORCID: 0000-0001-7443-2314, email: gastro_endo@ukr.net,

Abstract. Dysbiosis, or microbial imbalance, can lead to diseases like obesity, insulin resistance, lipid metabolism disorders, and non-alcoholic fatty liver disease (NAFLD). NAFLD, a leading chronic liver disease globally associated with metabolic syndrome, highlights the significance of gut health. Small intestinal bacterial overgrowth (SIBO) is an example of microbiota imbalance, characterized by excessive bacterial growth in the upper intestine, causing nutrient absorption disruption and bile acid imbalance.

Recent studies show a strong association between SIBO and lipid metabolic disorders in NAFLD patients, where gut-liver interactions enable bacterial toxins and products to impact liver function through a weakened gut barrier. Current studies show gut microbiota alterations significantly influence NAFLD and related metabolic disorders. Key bacterial groups like Firmicutes, Bacteroidetes, and Actinobacteria, and the Firmicutes/Bacteroidetes index are of particular interest. Patients with NAFLD show elevated Firmicutes and lower Bacteroidetes. An increased Firmicutes/Bacteroidetes index is a marker of NAFLD, correlating with obesity and hypercholesterolemia progression.

This study aims to assess gut microbiome composition and SIBO prevalence in NAFLD patients, determining their role as risk factors in disease progression.

A total of 342 patients with dyslipidemia from St. Panteleimon Hospital, Truskavetskurort LLC, and Intersono Medical Center were included, aged 21-69 (mean 45.03±0.67). The inclusion criteria were confirmed hyperlipidemia by clinical lab tests and family history. 150 control patients without dyslipidemia (mean age 45.98±0.43) were also included, matched in age, gender, and comorbidities. NAFLD diagnosis was based on ultrasound or liver steatometry, with stages (S1-S3) established by parenchymal echogenicity and hepato-renal index. Diagnostic criteria included ultrasound, steatometry, and cardiometabolic risk factors (waist circumference, blood pressure, triglyceride, HDL levels, fasting glucose, HOMA-IR, and C-reactive protein). Exclusion criteria included significant alcohol consumption, hepatitis B/C, autoimmune liver diseases, cirrhosis, and prior antibiotic use. All patients underwent biochemical tests, stool sample DNA extraction, and qPCR for Firmicutes, Actinobacteria, and Bacteroidetes. SIBO was assessed using hydrogen breath tests, with a positive result being hydrogen levels above 20 ppm.

Gut microbiome analysis showed significant differences between dyslipidemia patients and controls, with lower Bacteroidetes and higher Other bacteria. SIBO was found in 53.4 % of dyslipidemia and 52.2 % of NAFLD patients, but only 34 % of controls. The Firmicutes/Bacteroidetes ratio increased in NAFLD patients and correlated with higher triglycerides and TNF-α levels. Actinobacteria levels correlated with C-reactive protein and TNF-α, indicating that Firmicutes growth influences lipid metabolism disruption.

This study confirms gut microbiome's critical role in dyslipidemia and NAFLD, with SIBO prevalent in NAFLD, particularly in steatosis and type IIb dyslipidemia. Key findings show the increased Firmicutes/Bacteroidetes ratio and Firmicutes' role in lipid metabolism disorders, highlighting SIBO's impact on NAFLD progression. Further research is needed to determine microbiome changes as predictive markers for NAFLD and dyslipidemia and explore SIBO treatment as a potential treatment strategy.

Keywords: nonalcoholic fatty liver disease, gut microbiome, SIBO, dyslipidemia, hyperlipidemia, small intestinal bacterial overgrowth.

Introduction. The gut microbiome plays a significant role in maintaining human health and regulating metabolic processes. Dysbiosis, or an imbalance in the gut microbiota, can lead to various metabolic diseases, such as obesity, insulin resistance, lipid metabolism disorders, and nonalcoholic fatty liver disease (NAFLD) [1]. NAFLD is one of the most common chronic liver diseases, closely associated with metabolic syndrome, and presents a global public health challenge [2, 3].

Small intestinal bacterial overgrowth (SIBO) is one manifestation of microbiota imbalance, characterized by excessive bacterial growth in the upper intestine. SIBO can disrupt nutrient and bile acid absorption, promoting lipid metabolism disorders and NAFLD progression [4, 5]. Studies confirm that NAFLD patients more frequently have SIBO, potentially exacerbating metabolic disorders by altering fat metabolism [6].

Gut-liver axis, through which microbiota influences liver function, plays a crucial role in NAFLD pathogenesis. Bacterial products and toxins may pass through a weakened intestinal barrier, reach the liver, and cause inflammation and lipid metabolism disruption [7,8]. Microbiota dysbiosis also affects bile acid metabolism, an important factor in NAFLD development [9].

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Thus, the gut microbiome and SIBO may play a key role in NAFLD pathogenesis and associated lipid metabolism disorders. However, whether these microbiome changes precede lipid metabolism disorders or result from prolonged metabolic imbalances accompanying NAFLD remains an open question requiring further investigation.

Base of the Study. Current research suggests that alterations in gut microbiota composition may significantly impact the development of NAFLD and metabolic disorders, particularly lipid metabolism. Special attention is given to the imbalance between major bacterial groups, such as Firmicutes, Bacteroidetes, and Actinobacteria, and the Firmicutes/Bacteroidetes index [10, 11].

Patients with NAFLD exhibit increased Firmicutes and decreased Bacteroidetes. Specifically, an increased Firmicutes/Bacteroidetes index is a characteristic marker for these patients and is associated with the progression of metabolic disorders, including obesity and hypercholesterolemia [12, 13] Actinobacteria levels are also elevated, potentially contributing to increased plasma lipid levels, including total cholesterol and triglycerides [14].

In patients with hypercholesterolemia, a significantly higher Firmicutes/Bacteroidetes index may be linked to increased fat absorption and bile acid metabolism disruption [15]. A high Firmicutes level is associated with enhanced lipid absorption, while Bacteroidetes promote lipid breakdown and excretion [16, 17]. This explains the increased cholesterol and triglyceride concentrations in NAFLD patients with associated lipid metabolism disorders [18].

Thus, the imbalance in gut microbiota composition, particularly changes in Firmicutes, Bacteroidetes, Actinobacteria, and Firmicutes/Bacteroidetes index, are key factors in NAFLD pathogenesis and cholesterol metabolism disorders, requiring further research to develop new therapeutic approaches.

Aim of the Study. The study aimed to determine the gut microbiome composition and SIBO prevalence in NAFLD patients and assess the role of these changes as potential risk factors in the progression of these diseases.

Materials and Methods. A total of 342 patients with dyslipidemia were examined, who were either hospitalized in the therapeutic department of St. Panteleimon Hospital of the First Territorial Medical Association of Lviv or visited outpatient facilities in the therapeutic department of Truskavetskurort LLC or Intersono Medical Center, consulting units No. 1 and No. 2.

Among the patients examined, there were 139 men and 203 women, aged 21 to 69 years, with an average age of 45.03 ± 0.67 years.

The inclusion criteria for patients in the study were as follows:

- Presence of hyperlipidemia, confirmed by clinical laboratory tests and family history.
- Patient consent to participate in the study.

Additionally, 150 patients without dyslipidemia were included as the control group, with an average age of 45.98 ± 0.43 years. This group consisted of 53 women and 32 men. Both groups were comparable in terms of age, gender, and comorbidities.

NAFLD was diagnosed in 152 (44.4%) patients with lipid metabolism disorders based on ultrasound examination and/or liver steatometry.

NAFLD diagnostic criteria included diffuse echogenicity increase in liver parenchyma and the brightness ratio between the liver and kidney. The stages of hepatic steatosis by ultrasound criteria were as follows: S1: Increased parenchymal echogenicity. S2: Mild hepatomegaly, increased parenchymal echogenicity, fragmentation, and smoothing of vascular patterns. S3: Hepatomegaly, increased parenchymal echogenicity, loss of vascular pattern, echo signal attenuation to the diaphragm contour, and loss of diaphragm clarity.

Additional NAFLD diagnostic criteria included the cardiometabolic risk factors, in addition to ultrasound or steatometry findings:

- Waist circumference >102 cm for men and >88 cm for women.
- Blood pressure >130/85 mm Hg or taking medication for arterial hypertension (AH).
- Plasma triglyceride level above 1.70 mmol/L or specific lipid-lowering therapy.
- High-density lipoprotein (HDL) levels in blood plasma <1.0 mmol/L for men and <1.3 mmol/L for women or specific lipid-lowering therapy.
- Fasting blood glucose from 5.6 to 6.9 mmol/L or HbA1c from 5.7 to 6.4%.
- Insulin resistance index (HOMA-IR) >2.5.
- Plasma high-sensitivity C-reactive protein level >2 mg/L.

The exclusion criteria for patients in this study were history of significant alcohol consumption (> 20 g/day), evidence of hepatitis B or C infection, autoimmune hepatitis, histological evidence of other concomitant chronic liver diseases, pregnant women, cirrhosis with and without complications (ascites, variceal bleeding, systemic infection, or hepatocellular carcinoma), history of chronic inflammatory bowel disease or bariatric surgery, or treatment with antibiotics within 1 month before inclusion

Biochemical tests. Both groups of patients underwent biochemical evaluation of serum that included blood cell count, lipid profile (total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), triglycerides (TG)), high sensitive C-reactive protein (hsCRP), alaninaminotransferase (ALT), aspartataminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), bilirubin (total, direct, indirect), urea, uric acid, albumin, total protein, tumor necrotizing factor-α (TNF-α), apolipoprotein B (apo B), apolipoprotein A1 (apo A1), HOMA index, tumor necrosis factor alpha (TNF-α). Biochemical tests were carried out using commercially available test kits.

Sample collection and DNA extraction for microbiome detection. PCR reaction was performed in real-time thermal cycler Rotor-Gene 6000 (QIAGEN, Germany).

All patients underwent a hydrogen breath test to detect small intestinal bacterial overgrowth (SIBO) using the Gastrolyzer® device (manufactured by Bedfont Scientific Ltd.). A positive result was considered if the hydrogen level in the initial breath exceeded 20 ppm, or if an increase of more than 20 ppm from the baseline level was recorded every 20 minutes over a 90-minute period.

Statistical analysis. The reliability of changes in indicators in the normal distribution in the sample was determined by the paired Student's t test, in case of difference from the normal - by the criterion of F. Wilcoxon. Differences were considered statistically significant for $p<0.05$.

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The data distribution was investigated by the graphical method and by the Shapiro-Wilk normality test. Correlational relationship was examined by calculating Pearson's product moment correlation coefficients (r) on raw data. All calculations charting were carried out in the programming language R in the development environment of RStudio.

Study Results. The gut microbiome composition was examined in patients with dyslipidemia in comparison with the control group.

According to the data in Table 1, patients in the group with dyslipidemia had significantly increased level of Bacteroidetes (p≤0.05), while levels of Other bacteria were higher compared to the control group.

Table 1

The composition of the gut microbiome in patients with dyslipidemia (n=342) and in the control group (n=150)

	Main group (n=342)	Control group (n=150)	p
Bacteroides	33.17±2.36	47.66±1.18	≤0,05
Firmicutes	35.26±2.34	29.93±1.63	≥0,05
Actinobacteria	18.37±2.39	14.4±2.5	≥0,05
Other	13.22±1.34	7.99±1.98	≤0,05
Firmicutes/Bacteroides індекс (0.9-5)	3.52±0.4	2.57±1.48	≥0,05

Table 2

The composition of the gut microbiome in patients with dyslipidemia depending on the type of dyslipidemia (n=168)

	Dyslipidemia type			p
	IIa (n=56)	IIb (n=49)	IV (n=63)	
Bacteroides	30.29±2.11	21.65±2.41	9.62±2.1	p^1p^2 ≤0.05, p^2p^3≥0,05, p^1p^3≤0.05
Firmicutes	31.3±2.46	40.17±2.41	39.7±3.8	p^1p^2 ≤0.05, p^2p^3≥0,05, p^1p^3≥0.05
Actinobacteria	15.34±2.87	18.9±2.87	12.4±2.7	p^1p^2 ≥0.05, p^2p^3≤0,05, p^1p^3≤0.05
Other	11.67±1.34	8.56±1.08	8.22±1.12	p^1p^2 ≤0.05, p^2p^3≥0,05, p^1p^3≥0.05
Firmicutes/Bacteroides index (0.9-5)	3.76±1.25	2.77±1.63	1.89±1.7	p^1p^2 ≤0.05, p^2p^3≥0,05, p^1p^3≥0.05

According to Table 2, the Bacteroidetes level was higher among patients with type IIa dyslipidemia (30.29±2.11, p≤0.05). The level of Firmicutes was lowest in the group with type IIa dyslipidemia (p≤0.05). In the IIa group, the Other bacteria exceeded the upper limit of normal (11.67±1.34, p≤0.05). In all three patient groups, the Firmicutes/Bacteroides ratio did not exceed the value of 5, which is considered normal.

The gut microbiome composition was examined by comparing the group of patients with dyslipidemia and NAFLD to those without pathological liver changes.

Table 3

Gut Microbiome in Patients with Dyslipidemia and NAFLD and in the Control Group

Bacteria phyla	NAFLD (152)	Control group (47)	p
Bacteroides	31.29±1.11	25.65±1.48	≥0,05
Firmicutes	50.3±2.46	25.17±1.51	≤0,05
Actinobacteria	15.34±2.87	10.9±1.867	≤0,05
Other	12.88±0.84	9.68±0.25	≥0,05
Firmicutes/Bacteroides index (0,9-5)	5,02±2,61	2,1±1,74	≤0,05

He results shown in Table 3 demonstrate a significantly higher proportion of Firmicutes among patients with NAFLD compared to the control group (p≤0.05). The percentage of Actinobacteria was also significantly higher in the NAFLD group. A significant difference was fixed in the Firmicutes/Bacteroides index in the NAFLD patients, it was 5.02±2.61, which was significantly higher than the upper limit of normal and the index in the group of patients without NAFLD (p≤0.05).

Based on the obtained data, the gut microbiome composition was studied in the group of patients with NAFLD, taking into account different types of the disease — steatosis and steatohepatitis, and was compared with the control group.

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Table 4

Gut Microbiome in Patients with Dyslipidemia and NAFLD

Bacteria phyla	Steatosis (n=65)	Steatohepatitis (n=46)	Without pathological changes in liver (n=47)
Bacteroides	28,61±0.73	32,37±0,7*	25,65±1,48
Firmicutes	47,6±0,28	51,9±0,10*	25,17±1,51
Actinobacteria	12,99±5,62	16,98±4,12*	10,9±1,867
Firmicutes/Bacteroides index (0,9-5)	5,84±1,61	5,12±0,83	1,68±0,25*

*- p≤0,05, p-value, statistical significance

According to Table 4, a significant difference was observed in the Bacteroides level, which was highest in the group of patients with steatohepatitis due to the control group (p≤0.05). Firmicutes and Actinobacteria levels were highest in the steatohepatitis group (p≤0.05). The Firmicutes/Bacteroides index index differed significantly in patients without hepatic steatotic changes (1.68±0.25) compared to the groups with steatosis and steatohepatitis, where this index exceeded the upper normal limit (p≤0.05).

In the steatohepatitis group, Actinobacteria levels were the highest among the groups, at 16.98±4.12 (p≤0.05).

The prevalence of small intestinal bacterial overgrowth (SIBO) was determined using a hydrogen breath test in the group of patients with dyslipidemia and NAFLD, compared to the group without lipid metabolism disorders.

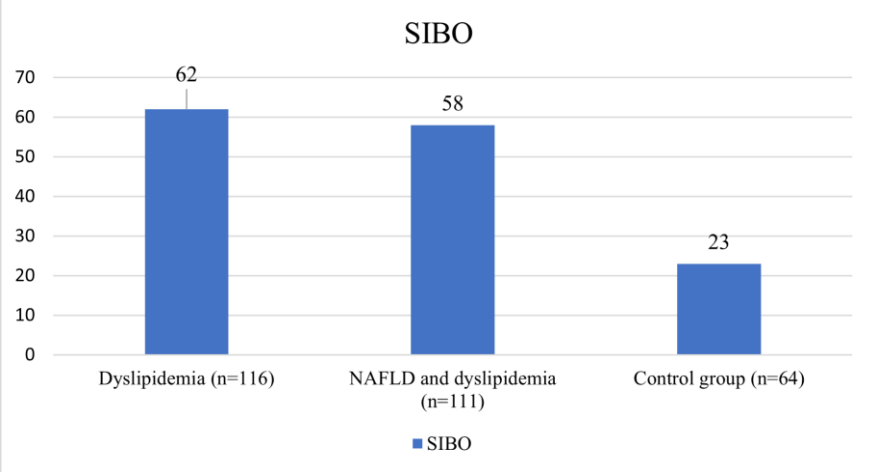

Fig. 1. Prevalence of SIBO in Patients with Dyslipidemia, NAFLD, and without Lipid Metabolism Disorders.

According to Figure 1, the frequency of SIBO diagnosis did not differ significantly between patients with dyslipidemia and those with combined lipid metabolism changes and NAFLD (53.4 % and 52.2 %, respectively). Meanwhile, in the control group without lipid metabolism disorders or pathological liver changes, SIBO was present in only 34% of cases.

It was of interest to investigate the prevalence of SIBO in different types of NAFLD and various types of dyslipidemia.

According to Figure 2, SIBO was most frequently observed in NAFLD patients with liver steatosis (50.7 %). Among patients with dyslipidemia, SIBO was most common in those with type IIb dyslipidemia (76 %).

Based on the data on the interdependence of lipid metabolism, the presence of steatotic changes in the liver, and alterations in the gut microbiota, a correlation study was conducted among all these indicators, as well as biochemical markers reflecting changes in NAFLD and dyslipidemia.

Figure 3 shows a significant positive correlation of moderate strength between components of the gut microbiota, specifically Firmicutes, and Apolipoprotein B (r=0.78, p≤0.05).

A correlation analysis was conducted between microbiome indicators and biochemical and lipid metabolism markers in patients with NAFLD.

A strong positive correlation was noted between Actinobacteria and high-sensitivity C-reactive protein (r=0.66, p≤0.05) as well as TNF-α (r=0.81, p≤0.05). Other bacteria positively correlated with total cholesterol (TC) (r=0.45, p≤0.05). Additionally, a strong positive correlation was observed between the Firmicutes/Bacteroides index and TNF-α (r=0.77, p≤0.05) and triglycerides (r=0.78, p≤0.05) (Fig. 4).

A strong positive correlation was also noted between Actinobacteria levels and high-sensitivity C-reactive protein (CRP) (r=0.66, p≤0.05) as well as TNF-α (r=0.81, p≤0.05). This suggests a high likelihood of increased CRP and TNF-α levels as Firmicutes levels rise in patients with dyslipidemia (Fig. 5).

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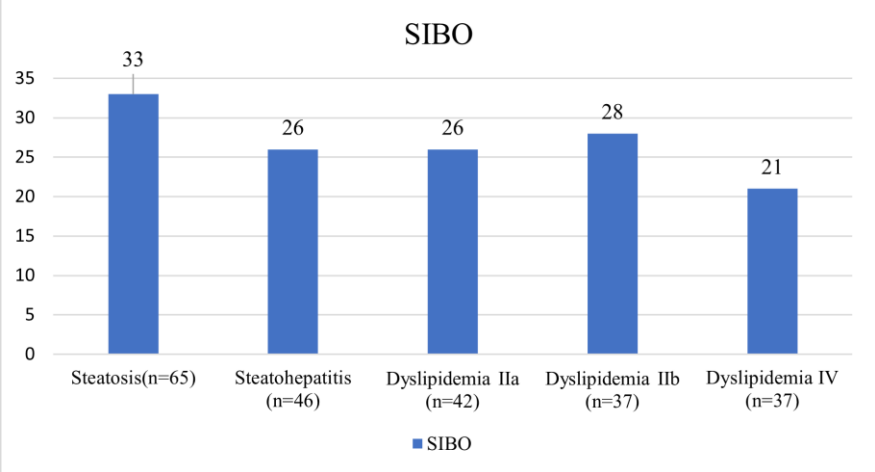

Fig. 2. Prevalence of SIBO in Patients with Dyslipidemia, NAFLD, and without Lipid Metabolism Disorders.

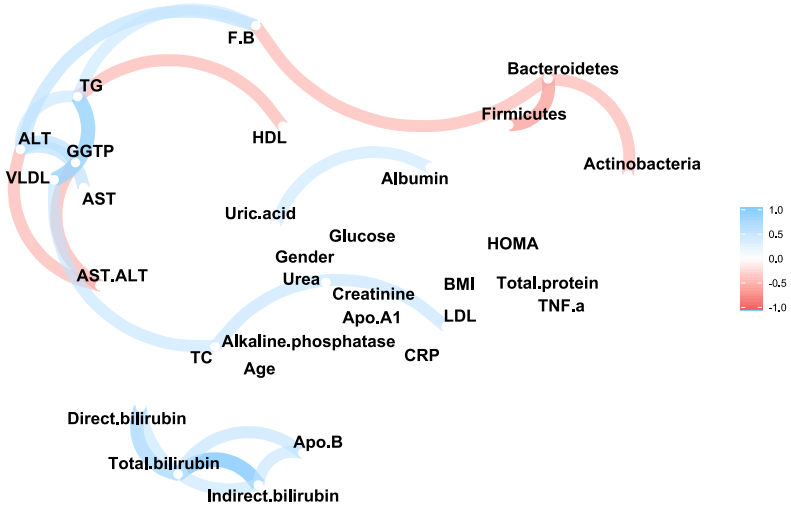

Fig. 3. Correlation relationships between biochemical markers and gut microbiota composition in patients with dyslipidemia.

Fig. 4. Positive correlations between Firmicutes/Bacteroidetes index, triglycerides, and TNF-α in patients with NAFLD and dyslipidemia.

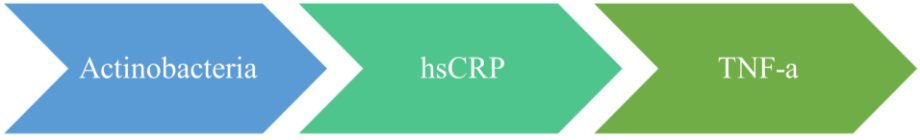

Fig. 5. Positive correlations between Actinobacteria, hsCRP, and TNF-α in patients with NAFLD and dyslipidemia.

Discussion. The study identified significant changes in the gut microbiota composition in patients with dyslipidemia and NAFLD. The primary finding is that the gut microbiota composition in patients with NAFLD and dyslipidemia differs from that of patients without lipid metabolism disorders, particularly through an increased Firmicutes/Bacteroides index. Additionally, a positive correlation was found between the Firmicutes/Bacteroidetes index and biochemical markers such as triglycerides and TNF-α, suggesting a potential

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role of the gut microbiota in the initiation of inflammatory processes in the liver and the development of steatosis and steatohepatitis. These markers are closely linked to oxidative stress, which leads to inflammatory changes in hepatocytes in NAFLD.

These results align with other studies that also observed increased Firmicutes levels and decreased Bacteroides in patients with NAFLD and dyslipidemia. For instance, a study by X et al. (2020) reported similar microbiota changes, accompanied by elevated TNF-α. Our data support these findings, adding new insights into the connection between microbial imbalance and inflammatory markers.

An intriguing finding in our study was the elevated Actinobacteria levels in patients with dyslipidemia and NAFLD, correlating with high levels of high-sensitivity C-reactive protein and TNF-α. These bacteria have not traditionally been considered key players in NAFLD pathogenesis; however, our data suggest their potential contribution to the development of inflammatory changes that exacerbate lipid metabolism disorders and liver inflammation in NAFLD.

For future research directions, a more detailed study of the roles of the Firmicutes/Bacteroidetes index and Actinobacteria as early indicators of NAFLD and dyslipidemia is recommended, along with exploring their potential as clinical markers for monitoring these conditions. Additionally, it would be valuable to investigate the impact of gut microbiota alterations during and after treatment of these diseases, particularly further correlations between gut microbiome composition and lipid profiles and inflammatory markers. An interesting and promising area for exploration could be the treatment of NAFLD and dyslipidemia through managing SIBO, which was found in more than 50% of the patients we examined.

Conclusions.

The results of this study confirm the important role of the gut microbiome in patients with dyslipidemia and non-alcoholic fatty liver disease (NAFLD).

1. Patients with dyslipidemia and NAFLD had an altered gut microbiota compared to the control group, with a significant higher level of Bacteroidetes (47.66±1.18 % compared to 33.17±2.36 %). The microbiome composition varied depending on the type of dyslipidemia, with Bacteroidetes levels being higher in patients with type IIa dyslipidemia (30.29±2.11, $p \leq 0.05$), while Firmicutes levels were lowest in this group ($p \leq 0.05$).
2. The composition of gut microbiota in patients with NAFLD differed from that of individuals without liver pathology, showing an increased abundance of Firmicutes (50.3±2.46, $p \leq 0.05$), Actinobacteria (15.34±2.87, $p \leq 0.05$), and an increased Firmicutes/Bacteroides index (5.02±2.61, $p \leq 0.05$).
3. In patients with steatosis and steatohepatitis, the Firmicutes/Bacteroides ratio was significantly elevated compared to the control group ($p \leq 0.05$), exceeding the upper normal limit (5.84±1.61 and 5.12±0.83, respectively).
4. Patients with dyslipidemia and NAFLD had a significantly higher prevalence of SIBO (53.4 % and 52.2 %, respectively) compared to the control group (34 %). SIBO was most frequently observed in liver steatosis and type IIb dyslipidemia group.
5. A strong positive correlation was observed between Firmicutes levels and Apolipoprotein B (r=0.78) in patients with dyslipidemia, suggesting that the increase in these bacteria may impact the development of lipid metabolism disorders.
6. An increase in the Firmicutes/Bacteroidetes index may lead to triglyceride and TNF-α levels increasing in NAFLD patients. Additionally, higher Actinobacteria levels were associated with increased high-sensitivity C-reactive protein and TNF-α levels in patients with NAFLD.

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НАДМІРНИЙ БАКТЕРІЙНИЙ РІСТ У ТОНКОМУ КИШКІВНИКУ ТА МІКРОБІОМНІ ЗМІНИ ЯК ФАКТОР РИЗИКУ ПОРУШЕНЬ ЛІПІДНОГО ОБМІНУ У ХВОРИХ НА НЕАЛКОГОЛЬНУ ЖИРОВУ ХВОРОБУ ПЕЧІНКИ

Х.Б. Квіт, Н.В. Харченко

Львівський національний медичний університет імені Данила Галицького, кафедра терапії №1, медичної діагностики, гематології та трансфузіології ФПДО, Львів, Україна
Національний університет охорони здоров'я України імені Шупика, кафедра гастроентерології, дієтології та ендоскопії, Київ, Україна
ORCID: 0000-0003-1394-9429,
email: akskris88@gmail.com,
ORCID: 0000-0001-7443-2314,
email: gastro_endo@ukr.net,

Анотація. Мікробіом кишківника має важливе значення для підтримки здоров'я та регуляції метаболічних процесів в організмі людини. Порушення балансу мікробіоти або дисбіоз може призводити до розвитку метаболічних захворювань, таких як ожиріння, інсулінорезистентність, порушення ліпідного обміну та неалкогольна жирова хвороба печінки (НАЖХП).

НАЖХП є одним із найпоширеніших хронічних захворювань печінки, що тісно пов'язане з метаболічним синдромом і становить значну проблему для системи охорони здоров'я. Одним із проявів дисбіозу є синдром надмірного бактеріального росту (СНБР), який характеризується надмірним розмноженням бактерій у верхніх відділах кишківника. СНБР може порушувати всмоктування поживних речовин і жовчних кислот, сприяючи порушенням ліпідного обміну та прогресуванню НАЖХП.

У даному дослідженні було поставлено за мету визначити склад мікробіому кишківника та поширеність СНБР у пацієнтів з НАЖХП, а також оцінити роль цих змін як факторів ризику в прогресуванні захворювання. Було обстежено 342 пацієнти з дисліпідемією та 150 пацієнтів контрольної групи без дисліпідемії. Поширеність СНБР визначалася за допомогою водневого дихального тесту, а склад мікробіому оцінювався методом ПЛР у реальному часі.

Результати показали, що пацієнти з НАЖХП мали підвищений індекс Firmicutes/Bacteroides і високий рівень Actinobacteria, що корелювало з показниками запалення та порушеннями ліпідного обміну. Виявлено зв'язок між наявністю СНБР та типом дисліпідемії, зокрема СНБР частіше зустрічався у пацієнтів з типом дисліпідемії IIb. Отримані дані підтверджують, що дисбаланс у складі мікробіому кишківника може бути важливим фактором у патогенезі НАЖХП і порушень ліпідного обміну, що потребує подальшого вивчення з метою розробки нових терапевтичних підходів.

Ключові слова: неалкогольна жирова хвороба печінки, мікробіом кишечника, SIBO, дисліпідемія, гіперліпідемія, надмірний ріст бактерій у тонкій кишці.

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