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ROLE OF SMALL INTESTINAL BACTERIAL OVERGROWTH IN THE DYSLIPIDEMIA AND NONALCOHOLIC FATTY LIVER DISEASE PATHOGENESIS

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Nonalcoholic fatty liver disease is one of the most prevalent chronic liver conditions, often associated with dyslipidemia and metabolic syndrome. Small intestinal bacterial overgrowth is considered a key mechanism potentially contributing to the development of non-alcoholic fatty liver disease and dyslipidemia by affecting metabolic balance, lipid metabolism, and systemic inflammation. This study examined 342 patients with dyslipidemia, assessing the prevalence of small intestinal bacterial overgrowth and its impact on lipid metabolism parameters and inflammatory markers. A significantly higher frequency of small intestinal bacterial overgrowth was found in patients with lipid metabolism disorders (53.4 %) compared to the control group (36 %, $p \leq 0.05$) and among those with non-alcoholic fatty liver disease (52 %). Correlation analysis confirmed the association of small intestinal bacterial overgrowth with elevated triglyceride levels, alkaline phosphatase, and insulin resistance index. The findings underscore the significance of small intestinal bacterial overgrowth in the pathogenesis of non-alcoholic fatty liver disease and dyslipidemia, highlighting new opportunities for the diagnosis and treatment of these conditions.

Key words: nonalcoholic fatty liver disease, small intestinal bacterial overgrowth, dyslipidemia, steatosis, steatohepatitis.

Х.Б. Квіт

ВПЛИВ СИНДРОМУ НАДМІРНОГО БАКТЕРІАЛЬНОГО РОСТУ НА РОЗВИТОК ДИСЛІПІДЕМІЙ ТА НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ

Неалкогольна жирова хвороба печінки є однією з найпоширеніших хронічних патологій печінки, часто асоціюється з дисліпідеміями та метаболічним синдромом. Синдром надмірного бактеріального росту в тонкому кишківнику розглядається як ключовий механізм, що потенційно сприяє розвитку неалкогольної жирової хвороби печінки та дисліпідемій, впливаючи на метаболічний баланс, ліпідний обмін і системне запалення. У дослідженні обстежено 342 пацієнти з дисліпідеміями, серед яких оцінено поширеність синдрому надмірного бактеріального росту в тонкому кишківнику та його вплив на показники ліпідного обміну і запальні маркери. Встановлено значно вищу частоту синдрому надмірного бактеріального росту у пацієнтів із порушеннями ліпідного обміну (53,4 %) порівняно з контрольною групою (36 %, $p \leq 0,05$), а також серед пацієнтів із неалкогольною жировою хворобою печінки (52 %). Кореляційний аналіз підтвердив зв'язок синдрому надмірного бактеріального росту із підвищенням рівня тригліцеридів, лужної фосфатази та індексу інсулінорезистентності. Результати підкреслюють значущість синдрому надмірного бактеріального росту у патогенезі неалкогольної жирової хвороби печінки та дисліпідемій, що відкриває нові перспективи для діагностики та терапії цих захворювань.

Ключові слова: неалкогольна жирова хвороба печінки, синдром надмірного бактерійного росту, дисліпідемія, стеатоз, стеатогепатит.

The study is a fragment of the research project: *"Features of pathogenesis, diagnosis, and treatment of cardiovascular, digestive, endocrine, and respiratory system diseases in clinical practice and experimental studies", state registration No. 0120U002142.*

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver pathologies worldwide, and its prevalence continues to increase due to the obesity and metabolic syndrome epidemic [14]. One of the key pathogenic mechanisms in the development of NAFLD is lipid metabolism disorder and the development of insulin resistance, which leads to dyslipidemia, particularly elevated triglycerides and total cholesterol levels. Moreover, increasing attention is being paid to the role of gut microbiota in the development of metabolic diseases, including NAFLD [3, 8].

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Small intestinal bacterial overgrowth (SIBO) is a condition characterized by an abnormal increase in the number of bacteria in the upper gastrointestinal tract (10^2–10^5). SIBO is known to be associated with digestive disorders, inflammatory processes, and metabolic disturbances [2, 13].

In particular, considering the significant role SIBO plays in disrupting the enterohepatic circulation of bile acids, this process may contribute to the development of dyslipidemia [10]. The enterohepatic circulation is a critical process of bile acid recirculation between the liver and intestine. Normally, bile acids secreted into the lumen of the small intestine to emulsify lipids are largely absorbed in the ileum and return to the liver for reuse [7, 9, 11]. However, in SIBO, this process is disrupted due to alterations in bacterial populations [4, 6].

Excessive bacterial growth in the small intestine leads to the deconjugation of bile acids under the influence of bacterial enzymes, such as β-glucuronidases. Deconjugated bile acids are less efficiently reabsorbed in the ileum, resulting in their loss through feces and a decrease in the total pool of circulating bile acids [5, 12].

The purpose of the study was to determine the prevalence of small intestinal bacterial overgrowth in patients with dyslipidemia and non-alcoholic fatty liver disease and to establish its potential association and role in the pathogenesis of these conditions.

Materials and methods. A total of 342 patients with dyslipidemia were observed, either undergoing inpatient treatment in the Therapeutic Department of St. Panteleimon Hospital of the First Territorial Medical Association of Lviv, or attending outpatient consultations at the Therapeutic Department of Truskavets Resort Agency LLC, and Consultation Departments No. 1 and No. 2 of the "Intersono" Medical Center.

Among the examined patients, both inpatient and outpatient, there were 139 men and 203 women, aged 21 to 69 years (mean age: 45.03±0.67 years).

The inclusion criteria for patients in the study were:

– Presence of hyperlipidemia confirmed by clinical laboratory tests and family history.

– Patient consent to participate in the study.

In 152 patients (44.4 %) with lipid metabolism disorders, NAFLD was diagnosed based on ultrasound examination and/or liver steatometry. In this group, there were 85 women (55.9 %) and 67 men (44.1 %). The age of the patients in the main group ranged from 24 to 69 years, with a mean age of 46.0±0.55 years.

The criteria for diagnosing NAFLD were – diffuse increased echogenicity of the liver parenchyma and the ratio of liver brightness to the right kidney, which was calculated to determine the hepatorenal index (HRI).

The stages of steatotic liver disease based on ultrasound criteria were as follows: increased echogenicity of the parenchyma (S1); mild hepatomegaly, increased echogenicity of the parenchyma, fragmentation, and smoothing of the vascular pattern (S2); hepatomegaly, increased echogenicity of the parenchyma, loss of the vascular pattern, attenuation of the echo signal toward the diaphragm contour, and loss of its clarity (S3).The criteria for diagnosis using liver steatometry were – a value of 0.65 dB/cm/MHz, indicating stage S1 liver steatosis; 0.71–0.76 dB/cm/MHz – S2; and 0.77 dB/cm/MHz or higher – S3.

Additionally, supplementary diagnostic criteria for NAFLD included the identification of one of the cardiometabolic risk factors in conjunction with ultrasound examination or liver steatometry.

– Waist circumference > 102 cm for men and > 88 cm for women.

– Blood pressure > 130/85 mmHg or the use of antihypertensive medication.

– Plasma triglyceride levels > 1.70 mmol/L or specific lipid-lowering therapy.

– Plasma high-density lipoprotein (HDL) cholesterol levels < 1.0 mmol/L for men and < 1.3 mmol/L for women, or specific lipid-lowering therapy.

– Fasting plasma glucose levels between 5.6 and 6.9 mmol/L or HbA1c levels between 5.7 and 6.4 %.

– Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) > 2.5.

– High-sensitivity C-reactive protein (hs-CRP) levels > 2 mg/L [1].

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

Methods of statistical analysis. The medico-biological data obtained during the study were processed using the Statistica 11.0 for Windows software package. In accordance with the study objectives,

factor and correlation analyses were performed. Results are presented as M±m, where M is the mean value of the studied parameter, and m is the standard error of the mean. The Student's t-test was used to assess the statistical significance of differences between independent means. Differences were considered statistically significant at $p<0.05$.

Results of the study and their discussion. Fig. 1 illustrates the distribution of different types of NAFLD progression among patients with dyslipidemia. Specifically, the prevalence of steatosis, steatohepatitis, and cases without changes characteristic of NAFLD was determined based on liver ultrasound results in the main group (n=342).

The most common type of NAFLD among patients with dyslipidemia was steatosis (30.4 %), while steatohepatitis was observed in 14 % of cases. In 22 % of patients, no liver changes indicative of fatty infiltration were detected. These findings allow for an assessment of the prevalence of different forms of NAFLD among patients with lipid metabolism disorders.

Given the high percentage of steatosis and steatohepatitis among patients with dyslipidemia (44.4 %), it was essential to evaluate biochemical parameters and markers of liver inflammation. Anthropometric data associated with cardiovascular risk criteria were also taken into account.

Table 1 demonstrates the statistical significance of differences in biochemical parameters depending on the stage of steatotic liver disease compared to patients without pathological liver changes.

Table 1

Biochemical parameters in patients with different types of NAFLD and dyslipidemia (n=342)

Value	Steatosis (n=104)	Steatohepatitis (n=48)	Without NAFLD (n=78)
Age	35.2±0.76*	43.9±0.27***	33.6±0.9
BMI	28.61±0.73	26.37±0.7	24.5±0.7
Glucose	5.6±0.28	5.9±0.10	5.05±0.10
ALT	34.99±5.32*.**	42.65±6.09***	23.65±6.09
AST	27.02±3.01*	44.9±2.23***	23.9±2.23
GGT	41.82±5.65*	54.45±3.58***	31.45±3.58
Hs-CRP	2.6±0.80***	3.28±0.43***	1.01±0.29
Uric acid	369.57±16.46*	442.4±15.. ***	322.40±15.7
Alkaline phosphatase	74.59±3.75	78.40±4.28	69.40±4.28
HOMA index	3.2±0.45	3.6±1.23	2.5±1.34

Note: 1. Statistical significance of differences compared to the "Steatosis" group and the "Steatohepatitis" group (* – $p<0.05$).
2. Statistical significance of differences compared to the "Steatosis" group and the group with "Without NAFLD" (** – $p<0.05$).
3. Statistical significance of differences compared to the "Steatohepatitis" group and the group with "Without NAFLD" (*** – $p<0.05$).

The levels of ALT, AST, and GGT were significantly different in patients with steatosis and steatohepatitis. Additionally, ALT levels were higher in patients with steatohepatitis compared to those without fatty liver infiltration. The age of patients in the steatohepatitis group was the highest, whereas the age in the steatosis group and the group without liver changes did not differ significantly.

The uric acid level in patients with steatohepatitis was significantly higher compared to the steatosis group and the control group. Furthermore, high-sensitivity C-reactive protein (hs-CRP) levels were significantly elevated in both the steatosis and steatohepatitis groups.

The intestinal microbiocenosis is primarily composed of bacteria in the large intestine, where an average of 10^{12}–10^{15} diverse microbial species are present. However, a smaller bacterial population (10^{2}–10^{5}) is also found in the small intestine, and its overgrowth is often the cause of small intestinal bacterial overgrowth (SIBO).

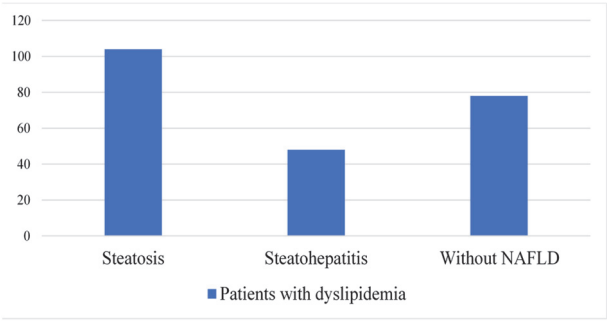

Fig. 1. Prevalence of different types of NAFLD progression in patients with dyslipidemia (n=342).

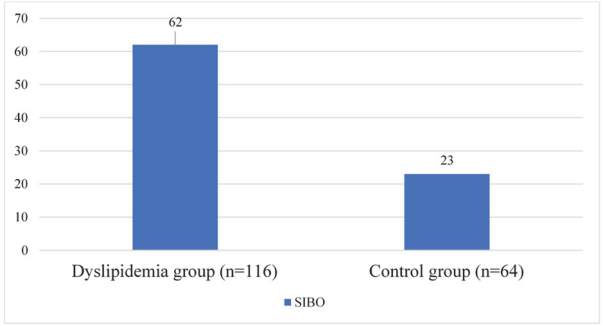

Fig. 2. Prevalence of small intestinal bacterial overgrowth (SIBO) in patients with dyslipidemia and the control group.

SIBO is a type of dysbiotic disorder in the intestine that can negatively impact the entire body, as a significant portion of metabolic processes, including bile acid and cholesterol metabolism, occur in this section of the gut.

Given the above data, SIBO diagnostics were conducted in both the main and control groups to determine the prevalence of this condition.

According to the obtained data shown in Fig. 2, the prevalence of SIBO among patients with lipid metabolism disorders was significantly higher (53.4 %) compared to the control group (36 %, $p \leq 0.05$).

Given the higher prevalence of SIBO in the main group, the frequency of bacterial overgrowth was further analyzed depending on the type of lipid metabolism disorder according to the Fredrickson classification. According to Table 2, SIBO occurred with similar frequency across different types of dyslipidemia diagnosed in the main group of patients ($p \geq 0.05$).

Table 2

Prevalence of SIBO in patients with dyslipidemia depending on the type of dyslipidemia

	Type of dyslipidemia (n=116)			p
	IIa (n=42)	IIb (n=37)	IV (n=37)	
SIBO	26 (22 %)	28 (24 %)	21 (18 %)	$p^1p^2 \geq 0.05$, $p^2p^3 \geq 0.05$, $p^1p^3 \geq 0.05$

Note: p – statistical significance of differences.

Given the significantly higher prevalence of SIBO among patients with dyslipidemia, it was essential to determine the presence of this disorder in patients with NAFLD.

Among the group of patients with NAFLD, SIBO was detected in 58 out of 111 patients. In contrast, in the control group, SIBO was diagnosed in 28 out of 69 patients. According to the obtained results, SIBO occurred significantly more frequently in patients with NAFLD and dyslipidemia (52 %) compared to the control group, where SIBO was observed in 40.5 % of cases ($p \leq 0.05$).

The prevalence of SIBO was determined among patients with different types of NAFLD. According to the results shown in Fig. 3, the prevalence of SIBO was 51 % among patients with steatosis and 56 % among patients with steatohepatitis.

Correlations were analyzed between the presence of SIBO and biochemical parameters and lipid metabolism markers in patients with NAFLD and dyslipidemia.

Fig. 4 demonstrates a moderate positive correlation between the presence of SIBO and triglyceride levels ($r=0.65$, $p<0.05$) in patients with NAFLD and dyslipidemia. Additionally, a moderate positive correlation was observed between SIBO and alkaline phosphatase ($r=0.68$, $p<0.05$), as well as between SIBO and the HOMA index ($r=0.71$, $p<0.05$).

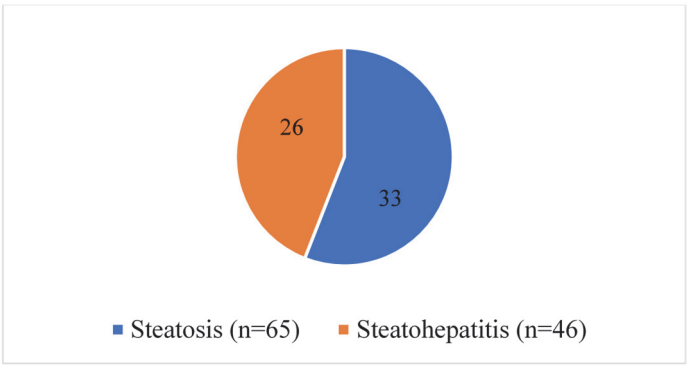

Fig. 3. Prevalence of small intestinal bacterial overgrowth (SIBO) in patients with different types of NAFLD.

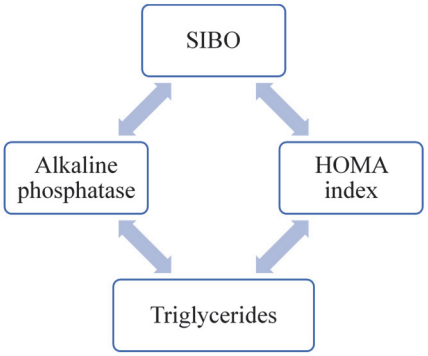

Fig. 4. Correlation relationships between biochemical parameters, lipid metabolism markers, and SIBO in patients with NAFLD and dyslipidemia.

The results of our study indicate a close relationship between the presence of small intestinal bacterial overgrowth (SIBO), lipid metabolism disorders, and the development of non-alcoholic fatty liver disease (NAFLD).

The prevalence of SIBO among patients with dyslipidemia was 53.4 %, significantly exceeding the control group (36 %, $p \leq 0.05$). These findings are consistent with the results of Gkolfakis et al., who also observed a high frequency of SIBO in patients with NAFLD [4]. Similarly, Gudan et al., in their meta-analysis, confirmed that SIBO is a common phenomenon among NAFLD patients and may serve as a key pathogenic factor in the development of this disease [5].

The presence of SIBO in NAFLD patients is associated with significant disturbances in the enterohepatic circulation of bile acids. The loss of bile acids due to deconjugation by bacterial enzymes, such as beta-glucuronidase, leads to their depletion, which impacts lipid metabolism regulation through FXR receptor activation. This may exacerbate dyslipidemia and contribute to the accumulation of triglycerides and LDL cholesterol. Our findings align with the conclusions of Chen and Vitetta, who noted that SIBO disrupts metabolic signaling pathways by influencing bile acids [3].

Among patients with NAFLD, SIBO was observed in 52 % of cases, confirming its close association with the disease. Specifically, SIBO was detected in 51 % of patients with steatosis, whereas in those with steatohepatitis, this figure reached 56 %. Similar results were demonstrated in the study by Gudan et al., who also reported that SIBO is more prevalent in patients with progressive forms of NAFLD, particularly steatohepatitis [6].

The analysis of correlation relationships confirmed that SIBO may serve as a predictor of lipid metabolism changes that contribute to the development of NAFLD. Specifically, we identified a positive correlation between SIBO and triglyceride levels ($r=0.65$, $p<0.05$), the HOMA index ($r=0.71$, $p<0.05$), and alkaline phosphatase levels ($r=0.68$, $p<0.05$). These findings are consistent with the conclusions of Lau and Wong, who emphasized that SIBO can exacerbate dyslipidemia through alterations in the gut microbiota composition and its metabolic activity [8].

The conclusion that SIBO can elevate AST, ALT, and GGT levels in patients with NAFLD is also supported by the findings of Shi et al., who indicated that intestinal dysfunction can exacerbate inflammatory processes in the liver through bacteria-derived metabolites [12]. The increase in these enzymes correlates with the risk of steatohepatitis, as noted in our study.

Thus, the results confirm that SIBO is an important factor influencing the pathogenesis of NAFLD and dyslipidemia. Further research is needed to explore the mechanisms underlying this relationship and to evaluate the effectiveness of SIBO treatment as a potential therapeutic approach for managing metabolic disorders.

Conclusions

1. The prevalence of small intestinal bacterial overgrowth in patients with dyslipidemia is significantly higher (53.4 %) compared to patients without lipid metabolism disorders (36 %). Small intestinal bacterial overgrowth occurs with similar frequency across different types of dyslipidemia (IIa, IIb, and IV).

2. The prevalence of small intestinal bacterial overgrowth among patients with nonalcoholic fatty liver disease combined with dyslipidemia is 52 %. Small intestinal bacterial overgrowth was more frequently detected in patients with steatohepatitis compared to those with steatosis (56 % and 51 %, respectively).

3. The presence of small intestinal bacterial overgrowth positively correlates with, and may contribute to, increased levels of triglycerides, alkaline phosphatase, and the HOMA index in patients with dyslipidemia and nonalcoholic fatty liver disease. This confirms the role of the gut microbiome as a significant factor in the pathogenesis of these conditions.

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APPLICATION OF LINEAR REGRESSION MODELS TO DETERMINE THE EFFECT OF AGE ON MEASURED ANATOMICAL DISTANCES IN THE TREATMENT OF MANDIBULAR FRACTURES IN CHILDREN

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The study was devoted to the application of linear regression models to determine the effect of age on measured anatomical distances in the treatment of mandibular fractures in children. The study involved 100 cone-beam computed tomography scans of the skull of children aged 6 to 17 years, which were performed due to traumatic injuries, inflammatory diseases, or jaw tumors. Measurements were taken to identify zones on the mandible for screw fixation during open reduction and internal fixation using mini-plates, aiming to prevent trauma to developing tooth buds, roots of permanent teeth, and the mandibular canal. The results indicated that age influences anatomical distances critical for surgical intervention, necessitating age-specific approaches to minimize the risk of complications during the treatment of mandibular fractures in children.

Key words: children, data analysis, cone-beam computed tomography, mandible, trauma.

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ВИКОРИСТАННЯ РЕГРЕСІЙНИХ ЛІНІЙНИХ МОДЕЛЕЙ ДЛЯ ВИЗНАЧЕННЯ ВПЛИВУ ВІКУ НА ВИМІРЮВАНІ АНАТОМІЧНІ ВІДСТАНІ ПРИ ЛІКУВАННІ ПЕРЕЛОМІВ НИЖНЬОЇ ЩЕЛЕПИ У ДІТЕЙ

Дослідження було присвячене застосуванню лінійних регресійних моделей для визначення впливу віку на вимірювані анатомічні відстані при лікуванні переломів нижньої щелепи у дітей. У дослідженні використано 100 конусно-променевих комп'ютерних томограм черепа дітей віком від 6 до 17 років, які були виконані внаслідок травматичних ушкоджень, запальних захворювань або новоутворень щелепи. Вимірювання проводили для визначення зон на нижній щелепі для гвинтової фіксації під час відкритої редукції та внутрішньої фіксації за допомогою міні-пластин, щоб запобігти травмуванню зубних зачатків, що розвиваються, коренів постійних зубів і нижньощелепного каналу. Результати вказували на те, що вік впливає на анатомічні відстані, критичні для хірургічного втручання, що зумовлює необхідність вікових підходів для мінімізації ризику ускладнень при лікуванні переломів нижньої щелепи у дітей.

Ключові слова: діти, аналіз даних, конусно-променева комп'ютерна томографія, нижня щелепа, травма.

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Starting from the age of six, children become particularly susceptible to traumatic injuries of the facial skeleton. This increased vulnerability is primarily due to their growing involvement in physically active sports and outdoor play, which heightens the risk of such injuries during this developmental stage [6, 7]. Among these injuries, mandibular fractures are the most frequently encountered, with traditional treatment involving bicuspid splinting to stabilize the fracture [2]. However, the management of these fractures becomes more complicated during periods of malocclusion, which may occur due to physiological dental changes such as the transition from primary to permanent teeth, as well as tooth loss resulting from trauma or carious complications. In these cases, bicuspid splinting can prove difficult or even impossible, thus necessitating an alternative approach, such as open reduction and internal fixation using mini-plates [3].

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