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CHARACTERISTICS OF SMALL INTESTINE BIOCENOSIS AND THE IMPACT OF DISORDERS ON FUNCTIONAL DYSPEPSIA

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The purpose of the study to determine the prevalence of small intestinal bacterial overgrowth by conducting a lactulose breath test in patients with functional dyspepsia, to evaluate differences in clinical course of functional dyspepsia. To study the effectiveness of standard therapy (pantoprazole) and an approach with small intestinal bacterial overgrowth eradication (pantoprazole and rifaximin). Small intestinal bacterial overgrowth prevalence in the group with functional dyspepsia was significantly higher ($p<0.038$). Patients who had functional dyspepsia and small intestinal bacterial overgrowth overlap had higher scores on the modified symptom scale, corresponding to a more severe course compared to patients without small intestinal bacterial overgrowth. The obtained results show that intestinal dysbiosis in the form of small intestinal bacterial overgrowth worsens the course of both subtypes of functional dyspepsia and may act as one of the pathogenic links in its development.

Key words: functional dyspepsia, small intestinal bacterial overgrowth, rifaximin.

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ОСОБЛИВОСТІ СТАНУ БІОЦЕНОЗУ ТОНКОЇ КИШКИ ТА ВПЛИВ ПОРУШЕНЬ НА ПЕРЕБІГ ФУНКЦІОНАЛЬНОЇ ДИСПЕПСІЇ

Метою дослідження було визначити поширеність синдрому надмірного бактеріального росту у пацієнтів з функціональною диспепсією для оцінки відмінностей у клінічному перебігу функціональної диспепсії. Вивчити ефективність стандартної терапії (пантопразол) та підходу з ерадикацією синдрому надмірного бактеріального росту (пантопразол та рифаксимін). Поширеність синдрому надмірного бактеріального росту в групі з функціональною диспепсією була достовірно вища ($p<0,038$). Пацієнти з функціональною диспепсією та синдромом надмірного бактеріального росту мали вищі бали в опитувальнику, що відповідає важчому перебігу, в порівнянні з пацієнтами без синдрому надмірного бактеріального росту. Отримані результати показують, що дисбіотичні зміни тонкого кишечника у формі синдрому надмірного бактеріального росту, погіршують перебіг обох підтипів функціональної диспепсії і можуть виступати одним з патогенетичних механізмів її розвитку.

Ключові слова: функціональна диспепсія, синдром надмірного бактеріального росту, рифаксимін.

The study is a fragment of the research project: "Characteristics of gut microbiota in patients with functional dyspepsia and correction of its disturbances", state registration No. 0122U200965.

Functional dyspepsia (FD) is a gastrointestinal disorder that includes a set of typical symptoms (epigastric pain, postprandial fullness, epigastric burning, epigastric bloating, and others) and dominates among other functional disorders of the gastroduodenal region [13, 14]. Up to 20 % of people worldwide have symptoms of dyspepsia. As a result of routine examination, including upper endoscopy, no organic changes are found in 80 % of such cases, allowing them to be considered as functional dyspepsia [14]. In fact, the number of patients with FD is higher because not everyone seeks medical help, and some patients have another established diagnosis. According to the Rome IV Criteria, FD is classified into two types: epigastric pain syndrome (EPS), which accounts for 15 % of cases, and postprandial distress syndrome (PDS), making up 67 %. These types can occur separately or in combination, referred to as overlap syndrome, representing 18 % of cases [13, 14].

In duodenal biopsies of patients with FD, an increased presence of Rothia, Clostridium, Haemophilus, Actinobacillus, Streptococcus was noted. Furthermore, there was a positive correlation between the quantity of Streptococcus and the severity of gastrointestinal symptoms [3, 5]. Higher bacterial loads and reduced bacterial diversity negatively impacted the quality of life for these patients [5]. Another study examining the duodenal microbiota revealed a decrease in the relative abundance of the phyla Firmicutes, Bacteroidota, and Fusobacteriota. Inverse relationships were observed between the relative amounts of Streptococcus and Prevotella and the quantity of Veillonella spp. with gastric emptying time [11]. Additionally, the number of bacterial cells in the duodenal tissues of patients with FD was significantly more than three times higher compared to those in remission from irritable bowel syndrome (IBS) and the control group [10].

Small intestinal bacterial overgrowth (SIBO) is a condition characterized by an excessive number of microorganisms, specifically 10^5 or more, in the small intestine [1]. The primary symptoms of SIBO

include abdominal pain, bloating, diarrhea, and irregular bowel movements. Additionally, nearly two-thirds of patients with SIBO report experiencing dyspeptic symptoms [9].

Alterations in the composition of the small intestine microbiome, particularly in the duodenal region, can increase mucosal permeability. This allows for a greater entry of antigens into the internal environment, triggering both local and systemic immune responses. These changes can affect neuronal signaling and contribute to the onset of dyspeptic symptoms [15]. Additionally, even minimal alterations in pH and motility within the gastroduodenal area create favorable conditions for the development of SIBO.

The role of microbiota in gastrointestinal inflammation and symptoms of FD is particularly evident in cases of post-infectious FD, which account for approximately 10 % of cases. Research indicates that within six months following an episode of acute gastroenteritis, the likelihood of developing FD increases by 2.5 times [6].

The purpose of the study was to determine the prevalence of small intestinal bacterial overgrowth in patients with functional dyspepsia, to evaluate the clinical course in relation to its presence, and to assess the effectiveness of standard pantoprazole therapy compared with combined treatment including rifaximin eradication and dietary therapy.

Materials and methods. This research was conducted on the clinical basis of the department of gastroenterology, dietology and endoscopy of the Shupyk National Healthcare University of Ukraine and the "Oltim Clinic" medical center from March 2023 to January 2025.

The study included 45 participants, comprising 31 patients with functional dyspepsia aged between 19 and 50 years (average age: 30.0±2.6), 58 % (18) women and 42 % (13) men. Additionally, the control group consisted of 14 clinically healthy individuals (average age of 30.3±2.7), 57 % (8) women and 43 % (6) men. The groups were comparable, and the difference between them was statistically insignificant (Table 1).

Table 1

Baseline characteristics of patients with functional dyspepsia and the control group

Indicator	FD group (n=31)	Control group (n=14)
Age	30.0+/- 2.6	30.3+/-2.7
Men	42 %	43 %
Women	58 %	57 %
Alcohol consumption	32 %	36 %
Smoking	29 %	28.6 %

The patients in the study group met the Rome IV criteria for functional dyspepsia and had not received any treatment in the past 3 months. The control group consisted of clinically healthy individuals.

Within the FD group, 14 patients were diagnosed with EPS and 17 with PDS. All participants underwent a fecal Helicobacter pylori antigen test, and only those with negative results were included in the study. Upper endoscopy with biopsy, ultrasound examination revealed no significant abnormalities. Provided complete blood test, liver function tests, quantitative C-reactive protein, and glucose levels were all within normal ranges.

To determine the presence of SIBO, all participants were subjected to a hydrogen breath test using the Gastro+ device (Gastrolyzer, UK). Prior to the breath test, patients had not taken antibiotics for at least 4 weeks, nor laxatives or bowel-cleansing medications for 2 weeks. The day before the test, they followed a low-fiber diet and had their last meal 12 hours before the test.

Baseline hydrogen levels in exhaled air were measured while the patients were fasting. Then they drank 10g of lactulose dissolved in 250ml of water. Hydrogen levels were recorded every 20 minutes for three hours. The diagnostic criterion for SIBO was an increase in hydrogen levels of at least 20ppm from baseline within the first 90 minutes of the test.

A modified questionnaire known as the SAGIS (Structured Assessment of Gastrointestinal Symptoms) was utilized to evaluate the severity of upper gastrointestinal symptoms (Table 2) [7]. Patients assessed their condition over the past 4 weeks twice: at the beginning of the study and 4 weeks after treatment.

All participants in the study group received dietary therapy recommendations. They were advised to establish a regimen of 3 to 4 meals per day, avoid alcohol, limit fatty foods, reduce the intake of simple carbohydrates, and steer clear of individual trigger foods.

Participants with a negative breath test result for SIBO, regardless of the subtype of FD, received standard therapy with a proton pump inhibitor (pantoprazole 40 mg daily), for 14 days. Those with a

positive breath test result were prescribed rifaximin 1200 mg/day (400 mg 3 times daily) for 10 days, along with pantoprazole 40 mg once daily for 14 days.

Table 2

The modified SAGIS
(Structured Assessment of Gastrointestinal Symptoms) questionnaire

Symptoms	No problem – 0	Mild problem – 1	Moderate problem – 2	Severe problem – 3	Very severe problem – 4
Epigastric pain					
Epigastric burning					
Postprandial fullness					
Epigastric bloating					
Sickness					
Loss of appetite					

0 – no problem
1 – mild problem, can be ignored when you do not think about it
2 – moderate problem, cannot be ignored, but does not influence daily activities
3 – severe problem, influencing your concentration on daily activities
4 – very severe problem, markedly influences your daily activities or requires rest

For data analysis, statistical processing was conducted, including the calculation of the arithmetic mean, standard error of the mean, and assessment of variability. To evaluate the statistical significance of the differences between the compared groups, Fisher's exact test, Friedman's rank variance analysis, and Kendall's coefficient of concordance were utilized. All statistical analyses were performed using the Statistica 7.0 software package.

Results of the study and their discussion. In the control group consisting of 14 clinically healthy volunteers, only 1 patient showed a positive result on the breath test, with an increase in hydrogen (H_2) levels by 22 ppm from the initial measurement. This increase is slightly above the diagnostic threshold accepted in the study, which is 20 ppm. Notably, the patient did not report any symptoms before or during the test.

In the study group, which included 31 patients with FD, a positive SIBO result was found in 12 individuals, representing 38.7 % of the group. This rate is significantly higher than in the control group, with a statistically significant difference ($p<0.038$). Among the 17 patients diagnosed with PDS, SIBO was detected in 9 patients, while only 3 out of 14 patients with EPS tested positive (fig.1). However, the difference in the occurrence of SIBO between these subtypes of dyspepsia was not statistically significant ($p>0.05$).

In FD group 6 patients reported that symptoms developed within a year after experiencing acute gastroenteritis. Of these, 4 patients had PDS, 3 of whom were diagnosed with SIBO. The remaining 2 patients were from the EPS subgroup, with 1 exhibiting a positive breath test result. When surveyed, 45 % (14/31) of the participants noted that their symptoms worsened after a forced change in residence, dietary changes. Additionally, 6 % (2/31) of patients linked the onset of FD symptoms to taking antibacterial medications, while 29 % (9/31) reported having undergone Helicobacter pylori eradication therapy, which provided temporary relief but did not lead to long term improvement, as symptoms returned after a few months. This effect could be related to how antibacterial drugs impact the intestinal microbiome.

More than half (7/12) of the patients with a positive breath test result reported abdominal bloating, a typical sign of SIBO. Four of these patients also reported having loose stools 1-2 times a week, a condition commonly seen with excessive bacterial growth and increased gas production in the small intestine. During ultrasound examination of the abdomen 51.6 % (16/31) of the FD patients exhibited intestinal hyper pneumatization, including 8 individuals with both PDS and SIBO, as well as 3 with EPS and SIBO. The remaining 5 patients had PDS but tested negative for SIBO.

Patients with FD and SIBO overlap showed higher scores during the initial questionnaire (EPS – 8.7±1.7; PDS – 10.0±1.6) compared to participants who tested negative for SIBO across both subtypes of FD (PDS – 7.8±1.3; EPS – 6.5±1.2). Higher scores on the SAGIS scale correlate clearly with the number and severity of symptoms, as well as their impact on the patient's daily activities.

During treatment, one patient taking rifaximin (1200 mg) and pantoprazole (40 mg) simultaneously reported slight nausea, which did not hinder the continuation of the medication and completely resolved after the treatment concluded. The other participants tolerated the medications well and did not report any

other symptoms during the treatment. After treatment, positive changes were observed in both FD subtypes (Fig. 2).

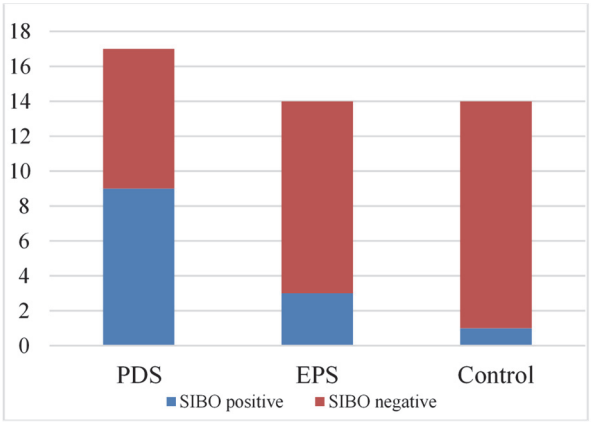

Fig. 1. Prevalence of small bacterial overgrowth (SIBO) in patients with functional dyspepsia (FD) subtypes. EPS – epigastric pain syndrome, PDS – postprandial distress syndrome.

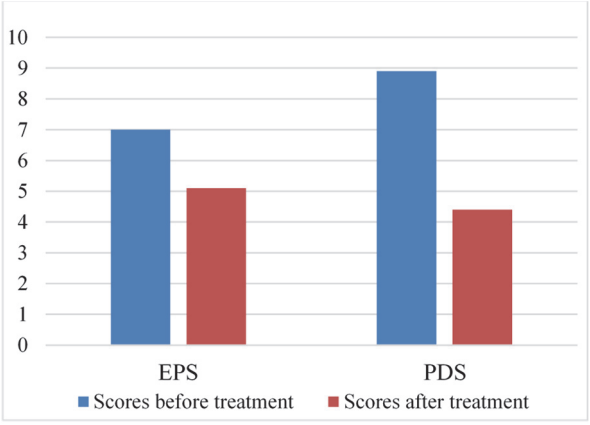

Fig. 2. Questionnaire scores of the patients with different functional dyspepsia (FD) subtypes before treatment and 4 weeks after. EPS – epigastric pain syndrome, PDS – postprandial distress syndrome.

The evaluation of symptom dynamics revealed a statistically more pronounced improvement in patients with FD and concomitant SIBO. In the PDS subgroup with SIBO the mean score decreased markedly from 10.0±1.6 to 3.7±0.8, compared to a reduction from 7.8±1.3 to 5.0±0.6 in patients without bacterial overgrowth. A similar trend was observed in the EPS subgroup, where scores declined from 8.7±1.7 to 6.0±1.1 in patients with SIBO, versus 6.5±1.2 to 4.9±0.7 in those without. These findings highlight that eradication therapy combined with standard treatment provides a greater therapeutic benefit than standard treatment alone.

The PDS+SIBO group demonstrated the most significant improvement, with scores on the SAGIS questionnaire decreasing by more than half, from 10.0±1.6 before treatment to 3.7±0.8 in 4 weeks post-treatment. The difference between the initial assessment and the post-treatment assessment in the PDS group without SIBO, based on the lactulose breath test results, was 2.8 points. Similarly, the EPS+SIBO group also exhibited positive clinical changes, with the initial SAGIS questionnaire scores dropping by nearly 3 units. In contrast, the improvement in well-being for the EPS group with a negative SIBO test was minimal, less than 2 points in 4 weeks after treatment.

The symptoms of SIBO and dyspepsia, particularly the PDS subtype, can overlap and mask each other. For instance, bloating in the upper abdomen may be present in either condition, both separately and in combination. One major challenge is in the similarity of symptoms, making it difficult to clearly differentiate between the two conditions without additional examinations.

In routine medical practice, assessing the microbiome of the gastroduodenal region and small intestine. Culture of intestinal aspirate for SIBO diagnostic can be impractical due to its invasiveness and high cost. Breath tests serve as a alternative; they are painless and simple to perform for both medical personnel and patients. However, it is important to consider their limitations; in the control group of 14 clinically healthy volunteers, 1 patient tested positive for SIBO without experiencing any obvious symptoms. Patients with FD and SIBO overlap showed higher scores during the initial questionnaire (EPS – 8.7±1.7; PDS – 10.0±1.6) compared to participants who tested negative for SIBO across both subtypes of FD (PDS – 7.8±1.3; EPS – 6.5±1.2). Higher scores on the SAGIS scale correlate clearly with the number and severity of symptoms, as well as their impact on the patient's daily activities.

Small intestine is particularly vulnerable to oxidative stress-induced injury due to its high metabolic activity and intense exposure to damaging agents. In an animal model a significant increase in free radical levels, depletion of antioxidant defenses, and subsequent damage to enterocytes in the small intestinal mucosa. These lesions were accompanied by elevated concentrations of N-acetylneuraminic acid (NANA), a marker of mucosal barrier compromise. [12] Structural and functional impairment of the mucosa may predispose to microbial imbalance, affect colonization resistance, and thereby contribute to dysbiosis-associated gastrointestinal disorders. These findings provide mechanistic support for the hypothesis that mucosal integrity and oxidative balance are key factors in shaping the small intestinal microbiota, and their disruption may play a role in the pathogenesis of conditions such as functional dyspepsia.

In cases of FD following gastroenteritis, the infectious process in the gastroduodenal region and accompanying low-intensity inflammation led to increased visceral sensitivity and the subsequent development of functional disorders [15]. Within the study group, 22 % (7/31) of patients developed functional dyspepsia following gastroenteritis. The significantly higher prevalence of SIBO among patients with FD is linked to the underlying mechanisms involved in developing FD. An increase in the number of bacteria in the intestinal lumen also impacts the composition of the mucosa-associated microbiota.

That is posited to have a more direct role in the pathogenesis of gastrointestinal diseases due to its proximity to the epithelium. The mucosal layer acts as a barrier against pathogenic microbes, preventing translocation into host tissue. Impaired mucosa-associated microbiota let the pathogenic antigens closer to the mucosa that led to the immune activation and low-grade inflammation [2].

In this context, eradicating SIBO can have a notably positive effect on FD symptoms, as demonstrated by the study's findings, particularly in patients with PDS.

Recent studies have indicated that peripheral cells, including those in the gastrointestinal tract, can stimulate brain cells. Neuroimmune activation is considered one of the primary mechanisms that lead to central sensitization of chronic pain [4].

The gut microbiota can regulate neuroinflammation by influencing the activity of various cells, including astrocytes, endothelial cells, microglia, macrophages, monocytes, pericytes, and T-cells. When these cells are activated, they begin to produce several pro-inflammatory mediators, such as C-C motif chemokine ligand 2 (CCL2, also known as MCP-1), CXCL-1, interleukin-1β (IL-1β), interferon-γ (IFN-γ), matrix metalloproteinases 2 and 9 (MMP-2/9), and tumor necrosis factor alpha (TNF-α) [2, 4].

Cytokines and chemokines released by microglia or astrocytes affect synaptic neurotransmission, increasing glutamate and reducing gamma-aminobutyric acid levels, leading to hypersensitivity to pain [4].

Our study reveals a higher prevalence of SIBO among patients with FD ($p<0.038$). This finding may suggest that one condition has significant impact on the development of another. One significant factor is changes in motility, particularly the slowing of gastric emptying, which can worsen FD symptoms and lead to excessive bacterial growth in the upper small intestine [11].

While FD is not life-threatening and does not increase mortality rates, the symptoms can severely impact daily activities, diminish quality of life, and impose additional strain on the healthcare system. Approximately 30 % of individuals with dyspepsia reported needing to take time off from work or school due to their symptoms [15].

Effective pain assessment and management are crucial for enhancing the quality of life for many patients. Although various pain management methods are available, there is still a significant need for research into the factors contributing to pain development and the exploration of new treatment options.

The findings indicate that intestinal dysbiosis, in form of SIBO, exacerbates the symptoms of both subtypes of functional dyspepsia and may serve as one of the underlying mechanisms for its development. In clinical practice, it is important to consider this connection after ruling out other potential causes and conditions that may influence the symptoms.

Conclusions

1. In patients with FD, the prevalence of SIBO reached 38.7 %, significantly exceeding that in healthy volunteers (7.1 %), ($p<0.038$). This suggests a potential association between small intestinal dysbiosis and the clinical manifestations of FD. The obtained results highlight the need for microbiota assessment in patients with unexplained or persistent dyspeptic symptoms.

2. Targeted antimicrobial therapy aimed at SIBO eradication resulted in a statistically significant reduction in both symptom number and severity in patients with both FD subtypes – PDS and EPS. The most pronounced clinical benefit was observed in the PDS group.

3. Given the frequent inefficacy of standard first-line therapy in FD, the use of lactulose breath test for SIBO detection appears justified. It allows for a more individualized therapeutic approach and may enhance treatment outcomes.

4. The findings support the inclusion of SIBO diagnostics into the clinical algorithm for managing FD with poor treatment response. Further studies are warranted to explore long-term outcomes of microbiota-targeted therapy and to clarify the role of SIBO in FD pathophysiology.

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