SMALL INTESTINAL BACTERIAL OVERGROWTH AND LOW-GRADE SYSTEMIC INFLAMMATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Background and Aim: *To investigate the incidence of small intestinal bacterial overgrowth (SIBO) and low-grade systemic inflammation in patients with inflammatory bowel disease (IBD).*

Methods: *From August 2018 to December 2019, 71 patients with inflammatory bowel disease were recruited, and 30 healthy people who came to our hospital for physical examinations at the same time were selected as the control group. The lactulose hydrogen breath test (LBT) and methane LBT were used to detect the prevalence of SIBO. The incidence of low-grade systemic inflammation in IBD patients was determined by the fractional exhaled nitric oxide (FeNO) breath test. The chi-squared test was used for statistical analysis.*

Results: *The positive rate of SIBO in the IBD group was 33.8 %, which was significantly higher than that in the healthy control group (6.6 %) (P<0.01). The incidence of SIBO between UC and CD groups was not significantly different (P = 0.551). The SIBO positive rate was significantly increased in CD patients with no ileocecal valve, ileocecal valve malformation, or intestinal stenosis (P<0.05). The SIBO negative rate of IBD patients treated with infliximab (IFX) was significantly higher than that of IBD patients treated with 5-aminosalicylic acid (5-ASA) (P = 0.006). The FeNO positive rate in IBD patients with SIBO was higher (17/24) than that of IBD patients without SIBO (6/47), and the difference was statistically significant (P<0.01).*

Conclusion: *SIBO in IBD patients was significantly higher than in healthy people, but there was no significant difference between UC and CD groups. The combination of the absence of the ileocecal valve, ileocecal valve malformation, and intestinal lumen stenosis was associated with CD combined with SIBO. IBD patients using IFX were less likely to incorporate SIBO than IBD patients using 5ASA. SIBO was associated with a low inflammatory response in IBD patients.*

Keywords: *Inflammatory bowel disease, low-grade systemic inflammation, small intestinal bacterial overgrowth.*

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Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), are chronic and relapsing inflammatory disorders of the gastrointestinal (GI) tract[1]. The precise pathophysiology of IBD is unknown, while the interaction between the intestinal microbiome and the intestinal immune system is associated with IBD[2, 3]. Microbial dysbiosis, defined as an alteration in composition, density, and function of intestinal microbes, is likely central to developing IBD[4, 5].

Small intestinal bacterial overgrowth (SIBO) is defined by abnormally high colonic bacteria levels (≥105 organisms/mL) in the small intestine[6, 7]. Several studies have reported an increased prevalence of SIBO in patients with IBD, and the frequency of SIBO occurrence is between 18-30 % for Crohn's disease[8, 9 10] and 1417.8 % for ulcerative colitis[1o, 11] when the hydrogen breath test is used as

a diagnostic method. Exhaled nitric oxide (FeNO) can be used to assess the inflammatory activity of IBD[12]. Fair correlations were found between FeNO and several systemic inflammatory markers (13). However, no study has thus far evaluated the relationship between SIBO and FeNO in patients with IBD in Asian countries.

The purpose of this study was to use the latest expiratory hydrogen analyzer technology to detect the abundance of hydrogen, methane, and nitric oxide in the exhaled air of IBD patients, and to predict the incidence of SIBO and low-grade systemic inflammation in IBD patients, to provide a new approach for the clinical treatment of IBD patients.

Patients and methods

From August 2018 to December 2019, Patients with IBD treated for >3 months were enrolled in the study. All patients were aged >18 years. All patients underwent colonoscopy after completing the hydrogen lactulose breath test (LBT), methane LBT, and FeNO expiratory tests.

The following were the exclusion criteria:

• A history of diabetes, thyroid disease, scleroderma, false intestinal obstruction, functional gastrointestinal disease, and other diseases that cause gastrointestinal motility changes;

• Current use of PPIs, neuroactive drugs, antibiotics, narcotics, probiotics, corticosteroids, or antidiarrheal drugs which are potentially responsible for SIBO;

• The presence of gastrointestinal diseases except for IBD;

• Renal insufficiency;

• Severe cardiac and pulmonary insufficiency;

• A history of chronic obstructive pulmonary disease or pulmonary insufficiency;

• Liver diseases;

• Major psychiatric diseases;

• Hearing impairment;

• A colonoscopy within the past 4 weeks.

Lactulose hydrogen breath test (LBT) and methane LBT were used to detect the prevalence of SIBO. The fractional exhaled nitric oxide (FeNO) breath test determined the incidence of low-grade systemic inflammation in IBD patients.

The control group was composed of 30 healthy people who came to our hospital for physical examinations at the same time. All patients signed an informed consent form before the procedure to ensure they fully understood the purpose of this study.

LBT

The LBT (hydrogen–methane breath test) was conducted after an overnight fast of at least 12 h. Patients were instructed to have a low-carbohydrate meal for dinner the night before the test.

The patients were not allowed to smoke, exercise, or sleep 30 min before the test or while the test was being performed. During the examination, the patient should remain awake, quiet, fasting, and keep the ambient air circulating. The abundance of hydrogen and methane in the expiratory samples was detected by the Sunvou-P200 Naculum Breath Hydrogen Analyzer (independently developed and produced by Wuxi Shangwo Medical Electronics Co., LTD). Baseline expiratory hydrogen and methane abundance were measured using standard gas calibration, followed by rapid administration of lactulose oral solution 10 g (Dumek, Abbott Laboratories, USA). Exhalation was collected every 30 min for 90 min, and hydrogen and methane abundance in exhalation were detected and recorded at each time point.

The criteria for a diagnosis of SIBO with hydrogen and methane LBT were developed by referring to relevant literature and suggestions from instrument suppliers[14, 15, 16]. A GBT-positive status is defined as i) hydrogen abundance ≥20 ppm in the base expiratory state or an increase of ≥12 ppm above the baseline in the hydrogen concentration and/or ii) an increase of ≥10 ppm above baseline in the methane concentration.

FeNO

The concentration of hydrogen, methane, and nitric oxide in patients' exhaled breath can be accurately detected simultaneously by the Sunvou-P200 with a nanotube expiratory hydrogen analyzer. By adjusting the exhalation flow rate and flow rate (≥ 200 mL/s), nitric oxide diffused from the digestive tract in alveoli and small airways can be reflected. An abundance of exhaled nitric oxide (FeNO) may reflect the risk of chronic systemic inflammation in patients with IBD[13].

All subjects fasted 12 h before the examination, and breath samples were collected with a disposable sampler. Sample test after calibration with standard gas. The FBG FeNO abundance ≥10 ppb was considered positive for SIBO.

Statistical analysis

In the clinical evaluations, factors including age, sex, body mass index, clinical characteristics, positive LBT, medication history, and FeNO in the patients with IBD were considered. The profiles of the LBT-positive patients were compared with those of 30 control patients with a history of good health. LBT results were also compared between the UC and CD subgroups. The counting data were expressed by frequency and rate, and the chi-square test was used for comparison between groups. Statistical significance was assigned at $P<0.05$. Statistical analyses were performed using IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Research Ethics Board of Huadong Hospital affiliated with Fudan University (2018K116).

Results

Data were collected from 71 patients with inflammatory bowel disease (39 cases of ulcerative colitis and 32 cases of Crohn's disease) at the Outpatient Department and Gastroenterology ward of Shanghai Huadong Hospital. The patient demographics and disease phenotypes are shown in Table 1. The comparative data of SIBO/non-SIBO data are shown in Table 2.

The UC group, the CD group, and the healthy control group were composed of approximately the same number of women or men, and there was no significant difference in age, BMI, or gender. The positive rates of SIBO in the UC group, CD group, and healthy control group were 30.8 % (12/39), 37.5 % (12/32), and 6.7 % (2/30), respectively. The IBD group's SIBO positive rate was higher than that of the healthy control group, and the difference was statistically significant ($\chi^2 = 8.124$, $P = 0.004$). In contrast, no significant difference was observed in the SIBO positive rate between the UC and the CD groups ($\chi^2 = 0.356$, $P = 0.551$).

Clinical features of SIBO in patients with IBD

SIBO and its correlation in the UC subgroup

The SIBO positive rate in the UC group was 35 % (7/20) in the active stage and 26.3 % (5/19) in the remission stage; no significant statistical difference was found in the positive rate of SIBO between the active and remission groups ($\chi^2 = 0.345$, $P = 0.557$). The UC subgroup was divided into E1, E2, and E3 groups according to the lesion site, and there were no significant statistical differences in the SIBO positive rates among the three groups ($\chi^2 = 1.459$, $P = 0.556$) (Table 2).

SIBO and its correlation in the CD subgroup

There were no significant statistical differences in SIBO positive rates between the CD group and the remission group ($\chi^2 = 0.142$, $P = 0.706$). The CD subgroup was divided into L1, L2, and L3 groups according to the lesion site; there were no significant statistical differences in the positive rate of SIBO in the three groups ($\chi^2 = 0.349$, $P = 1.000$). SIBO was more complicated in CD patients with ileocecal valve malformation, absence of the ileocecal valve, and intestinal strictures ($P<0.05$) (Table 2).

Previous medication history

The results showed that the SIBO positive rate of patients treated with IFX was significantly lower than that of patients treated with 5ASA, and the difference was statistically significant ($P = 0.006$).

Association between SIBO and FeNO

Among the 71 IBD patients enrolled, 70.8 % (17/24) were SIBO positive and FeNO positive, which was higher than in patients without SIBO (12.8 %, 6/47), and the difference was statistically significant ($\chi^2=24.460$, $P<0.001$). SIBO is associated with systemic inflammatory response activation in IBD patients (Table 2).

Variable	CD (n=32)	UC (n=39)	control (n=30)
Age (years)	46.72±13.94	52.49±15.87	48.56±14.21
Gender (male: female)	18:14	20:19	16:14
BMI (kg/m^2)	21.9±3.24	21.90±3.20	22.0±2.45
Phenotypes of disease			
E1: E2: E3	NA	17:5:17	NA
L1: L2: L3	16:4:12	NA	NA
Intestinal strictures	18.75% (6/32)	NA	NA
Absence of the ileocecal valve	15.63 (5/32)	NA	NA
Ileocecal valve malformed	37.5% (12/32)	NA	NA
Infliximab (IFX)	11	1	NA
5-aminosalicylic acid (5-ASA)	21	38	NA

Table 1: Patient demographics and disease phenotypes.

		SIBO		χ^2	P
		Negative	Positive		
UC subgroup	Remission	14	5	0.345	0.557
	Active	13	7		
	E1	13	4	1.459	0.556
	E2	4	1		
	E3	10	7		
CD subgroup	Remission	8	4	0.142	0.706
	Active	12	8		
	L1	10	6	0.349	1.000
	L2	2	2		
	L3	8	4		
Absence of the ileocecal valve	No	19	4	11.223	0.001
	Yes	1	8		
Ileocecal valve malformed	No	17	3	9.102	0.003
	Yes	3	9		
Intestinal strictures	No	20	6	9.244	0.002
	Yes	0	6		
Medication history	S-ASA	35	24	7.374	0.006
	IFX	12	0		
FeNO	negative	41	7	24.460	< 0.001
	positive	6	17		

Table 2: Correlations between the presence of SIBO and various clinical characteristics and FeNO.

Discussion

Recently, interest in the investigation of the prevalence of SIBO in IBD has increased. IBD is a chronic idiopathic disease and is prone to recurrence. The intestinal microbiome's involvement plays a very important role in inflammatory bowel disease etiopathogenesis.

There are multiple causes of SIBO development in patients with IBD: the postoperative absence of the ileocecal valve, presence of entero-colonic fistulas, motility disorders, intestinal strictures, and alterations in the intestinal microbiome. Intestinal bacterial overgrowth is associated with gastrointestinal symptoms, including bloating, flatulence, abdominal discomfort, diarrhea, and weight loss. It may even cause structural disease changes such as small intestinal villi atrophy that alter intestinal absorption[17]. The potential pathogenic role of SIBO in gastrointestinal diseases is still controversial.

In this study, the incidence of SIBO in the IBD population was significantly higher than that in the healthy control group, and the difference was statistically significant. Moreover, the incidence of SIBO combined with CD was 37.5 %, which was higher than that of SIBO combined with UC (30.8 %). The higher incidence of SIBO in CD patients may be associated with i) the involvement of small intestinal mucosa in CD and ii) some CD patients have ileocecal valve malformation, intestinal stenosis, absence of the ileocecal valve, and other complications. Furthermore, in the subgroup of CD, it was found that all 6 patients with CD who also had intestinal stenosis were more likely to be complicated with SIBO (n = 6, P = 0.002), ileocecal valve malformation (n = 9/12, 75 %, P = 0.003), and absence of the ileocecal valve (n = 8/9, 88.8 %, P = 0.001). Although UC is primarily a disease of the colon, we speculate that changes in immune function, motor function, and/or disorders in the intestinal flora may account for the presence of SIBO in patients without significant intestinal lesions. The incidence of SIBO in the domestic population of IBD was higher than that in other countries, which may be that we included CH4 data at the same time. We also measured hydrogen and methane because 14–35 % of colon bacteria are methane-producing bacteria[18].

To further confirm the correlation between SIBO and IBD activity, some researchers have found that there was no significant correlation between IBD activity and SIBO by studying the correlation between fecal calprozoin and the CDAI index in CD patients, and the modified Truelove and Witts disease severity typing criteria in UC patients[10, 19]. In this study, we performed direct colonoscopy after hydrogen exhalation in all enrolled IBD patients, considering that SIBO itself may result in increased stools and abdominal pain, which could interfere with Mayo and CDAI scores. The disease activity and the correlation between the lesion site and SIBO positive results were evaluated according to the endoscopic mucosal manifestations. No correlation was found, which is consistent with the results of previous studies.

The effect of biologic agents on SIBO in IBD patients has been controversial. In a recent study, immunoregulatory agents or biologic drug use in inactive CD was independent of the occurrence of SIBO[8]. A recent Romanian study found that IBD patients treated with biologic agents or immunosuppressants had an increased incidence of

SIBO compared to those treated with conventional drugs[20]. In our study, we found that those patients who had been previously treated with IFX were less likely to develop SIBO than those treated with traditional 5ASA therapy (P = 0.006). All 12 patients who had been previously treated with IFX were negative for SIBO, which may be related to clinical and endoscopic remission in all 12 patients.

FeNO is produced by airway cells, and its concentration is highly correlated with the number of inflammatory cells as a biomarker of airway inflammation. Because the intestinal and respiratory epithelia share a common embryonic origin and similar anatomical structure, enteroepithelial inflammation can also trigger the activation of alveolar epithelial inflammation.

Inflammatory mediators may migrate directly from the gut through other parts of the systemic circulation. Gut et al.[12] proposed for the first time that FeNO could be used as an indicator to evaluate the inflammatory activity of IBD. Aggarwal et al.[13] proposed a non-invasive method that utilized handheld FeNO devices to evaluate the inflammatory activity of CD patients. The FeNO positive rate of SIBO-positive patients in our study was 70.8%, significantly higher than the 29.2% of IBD patients without SIBO. These results suggest that in the SIBO-positive IBD patients, a low-grade inflammatory response had been activated. Studies by Gut et al.[12] and Malekmohammad et al.[21] showed that the level of FeNO increased with an increase in disease activity in IBD patients. Aggarwal[13] proposed that the FeNO value between 17 and 18 minutes is the clinical threshold to distinguish CD activity. Combined with our results, it can be concluded that although the FeNO abundance of some IBD patients with SIBO did not reach the clinical threshold for disease activity under endoscopy, they still had low inflammatory activation in vivo. The FeNO, SIBO, and colonoscopic manifestations of these patients require additional follow-up.

Conclusion

SIBO was significantly higher in patients with inflammatory bowel disease than in the normal healthy control group. CD with an absence of the ileocecal valve, ileocecal valve malformation, and intestinal luminal stenosis was more likely to be associated with SIBO. Patients treated with IFX were less likely to develop SIBO than those treated with traditional 5ASA. Although the current conclusions suggest that SIBO is not correlated with disease activity, some IBD patients without significant endoscopic activity may still be SIBO positive. FeNO was significantly elevated In IBD patients who were SIBO positive, suggesting a combination of low-grade inflammatory responses. Determination of whether the intestinal microbiome disorder caused by SIBO is related to the recurrence of IBD requires additional follow-up.

References

1) Burisch J, Vardi H, Schwartz D, Friger M, Kiudelis G, et al. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. Lancet Gastroenterol Hepatol 2020; 5: 454-464.
2) Graham DB, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. Nature 2020; 578: 527-539.
3) Aden K, Rehman A, Waschina S, Pan WH, Walker A, et al. Metabolic Functions of Gut Microbes Associate with Efficacy of Tumor Necrosis Factor Antagonists in Patients with Inflammatory Bowel Diseases. Gastroenterology 2019; 157: 1279-1292.
4) Brown EM, Kenny DJ, Xavier RJ. Gut Microbiota Regulation of T Cells During Inflammation and Autoimmunity. Annu Rev Immunol 2019; 37: 599-624.
5) Ocansey DKW, Wang L, Wang J, Yan Y, Qian H, et al. Mesenchymal stem cell-gut microbiota interaction in the repair of inflammatory bowel disease: an enhanced therapeutic effect. Clin Transl Med 2019; 8: 31.
6) He Z, Ding R, Wu F, Wu Z, Liang C. Excess Alcohol Consumption: A Potential Mechanism Behind the Association Between Small Intestinal Bacterial Overgrowth and Coronary Artery Disease. Dig Dis Sci 2018; 63: 3516-3517.
7) Jung SE, Joo NS, Han KS, Kim KN. Obesity Is Inversely Related to Hydrogen-Producing Small Intestinal Bacterial Overgrowth in Non-Constipation Irritable Bowel Syndrome. J Korean Med Sci 2017; 32: 948-953.
8) Sánchez-Montes C, Ortiz V, Bastida G, Rodríguez E, Yago M, et al. Small intestinal bacterial overgrowth in inactive Crohn's disease: Influence of thiopurine and biological treatment. World J Gastroenterol 2014; 20: 13999-14003.
9) Shah A, Morrison M, Burger D, Martin N, Rich J, et al. Systematic review with meta-analysis: the prevalence of small intestinal bacterial overgrowth in inflammatory bowel disease. Aliment Pharmacol Ther 2019; 49: 624-635.
10) Lee JM, Lee KM, Chung YY, Lee YW, Kim DB, et al. Clinical significance of the glucose breath test in patients with inflammatory bowel disease. J Gastroenterol Hepatol 2015; 30: 990-994.

11) Rana SV, Sharma S, Malik A, Kaur J, Prasad KK, et al. Small intestinal bacterial overgrowth and orocecal transit time in patients of inflammatory bowel disease. Dig Dis Sci 2013; 58: 2594-2598.
12) Gut G, Ben-Tov A, Lahad A, Soferman R, Cohen S, et al. Pulmonary functions in children with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2016; 28: 708-713.
13) Aggarwal V, Day AS, Connor S, Leach ST, Brown G, et al. Role of capsule endoscopy and fecal biomarkers in small-bowel Crohn's disease to assess remission and predict relapse. Gastrointest Endosc 2017; 86: 1070-1078.
14) Ghoshal UC, Srivastava D, Ghoshal U, Misra A. Breath tests in the diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome in comparison with quantitative upper gut aspirate culture. Eur J Gastroenterol Hepatol 2014; 26: 753-760.
15) Zhao J, Zheng X, Chu H, Zhao J, Cong Y, et al. A study of the methodological and clinical validity of the combined lactulose hydrogen breath test with scintigraphicorocecal transit test for diagnosing small intestinal bacterial overgrowth in IBS patients. Neurogastroenterol Motil 2014; 26: 794-802.
16) Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, et al. Hydrogen and methane based breath testing in gastrointestinal disorders: the North American consensus. Am J Gastroenterol 2017; 112: 775-784.
17) Bull-Henry K. Continuing Medical Education Questions: February 2020: ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. Am J Gastroenterol 2020; 115: 164.
18) Salem AI, El-Taweel HA, Madkour MA, Abd El-Latif NF, Abd-Elrazeq ES. Irritable bowel syndrome in Egyptian patients: plausible risk factors and association with intestinal protozoa. Trop Doct 2019; 49: 184-188.
19) Shah A, Morrison M, Burger D, Martin N, Rich J, et al. Systematic review with meta-analysis: the prevalence of small intestinal bacterial overgrowth in inflammatory bowel disease. Aliment Pharmacol Ther 2019; 49: 624-635.
20) Yang C, Guo X, Wang J, Fan H, Huo X, et al. Relationship between Small Intestinal Bacterial Overgrowth and Peripheral Blood ET, TLR2 and TLR4 in Ulcerative Colitis. J Coll Physicians Surg Pak 2020; 30: 245-249.
21) Malekmohammad M, Folkerts G, Kashani BS, Naghan PA, Dastenae ZH, et al. Exhaled nitric oxide is not a biomarker for idiopathic pulmonary arterial hypertension or for treatment efficacy. BMC Pulm Med 2019; 19: 188.

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