Original Paper

Small Intestinal Bacterial Overgrowth Syndrome Prevalence in Romanian Patients with Inflammatory Bowel Disease

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ABSTRACT: Background: small intestinal bacterial overgrowth (SIBO) is an entity commonly associated with digestive disease. Recently, its association with inflammatory bowel diseases (IBD) made the object of an increasing number of investigations. Sometimes symptoms of excessive bacterial populations may overlap or mimic flares of inflammatory disease. Method: patients with IBD (CD – Crohn disease and UC – ulcerative colitis) in remission underwent screening for the presence of SIBO using the hydrogen breath test. Results: of the 75 patients tested, the breath test was positive for SIBO in 25.3% (30.77% of patients with CD and 19.4% of patients with UC). The risk factors associated with the presence of this syndrome were identified as: pancolonic impairment in UC, perianal and ileo-colonic involvement in CD, postoperative absence of the ileocecal valve. Patients in remission with bacterial overgrowth tend to present more frequently: a higher daily average of stools, a lower BMI (body mass index) and much more frequent complaints of persistent flatulence. Conclusions: patients with Crohn's disease suffer from small intestinal bacterial overgrowth syndrome more frequently than those with ulcerative colitis. The hydrogen breath test may be used, along with other laboratory methods, to distinguish between an inflammatory bowel disease and an overlap of small intestinal bacterial overgrowth.

KEYWORDS: *small intestinal bacterial overgrowth, inflammatory bowel disease, hydrogen glucose breath test, intestinal microbiome*

Introduction

SIBO (small intestinal bacterial overgrowth) is a clinical entity associated with either bacterial overpopulation of the small intestine [1] or with alterations in the type and ratio of the microorganisms that constitute the totality of the intestinal microbiome [2]. It is defined by the presence of at least 10^5 CFU (colony forming units)/ ml of jejunal aspirate [3].

A recent review [4] concluded that there is no standard diagnostic method. Hydrogen breath tests that use glucose or lactulose as a substrate have good clinical applicability. Of these, apparently the hydrogen glucose breath test (HGBT) has a high diagnostic accuracy, even when compared with jejunal culture test [5, 6].

Clinical manifestations of SIBO may vary: from asymptomatic patients to severe consequences of malabsorption; from abdominal flatulence, persistent abdominal pain, excessive flatulence to vitamin B12 deficiency or even iron deficiency anaemia, weight loss, signs of malnutrition, fat-soluble vitamin deficiencies, hypoalbuminemia, severe weight loss [7,8,9].

Occurrence of inflammatory bowel diseases (IBD) appears to be influenced by the composition of the intestinal microbiome [10]. The causes behind SIBO overlap in patients with IBD are multiple: intestinal dysbiosis, postoperative absence of the ileocecal valve, presence of strictures and fistulas, or dilations, intestinal motility disorders. According to various reports, the frequency of SIBO occurrence is between 18-30% for Crohn's disease [5, 11, 12] and 14-17.8% for ulcerative colitis [12, 13] when the hydrogen breath test is used as a diagnostic method.

Aim

The main purpose of this study is to identify the prevalence of SIBO in patients with chronic intestinal inflammatory diseases, using the hydrogen breath test as a method of diagnosis. The secondary objective is to identify the clinical or biological conditions that predispose to the association of this syndrome with Crohn's disease or ulcerative colitis.

Material and method

Study Design

The present research is a prospective study, conducted between January 2013 - December 2015 at Elias University Emergency Hospital in Bucharest.

Inclusion Criteria

All adult patients diagnosed with IBD, Crohn's disease or ulcerative colitis, under remission maintenance treatment with different types of molecules (5-ASA derivatives, immunomodulators or biologic therapy) were included in the study. Patients were in clinical and biological remission, defined by: absence of clinical or biological activity signs (CRP and ESR negative, no coprologic syndrome to suggest flares or rectal bleeding, and CDAI score must be below 150 points for patients with CD). Both asymptomatic patients and those who accused abdominal pain or flatulence (persistent for at least 2 weeks) were accepted, along with those who had an increased frequency of daily stools compared to the considered basic value.

Exclusion Criteria

From the point of view of IBD were excluded: patients undergoing remission induction corticosteroid therapy, patients with other significant organic (cirrhosis, cancer, chronic pancreatitis) or immunological digestive diseases, or those from whom no informed consent was obtained.

All patients were tested for fecal calprotectin, and there were excluded patients with a value greater than 250 µg/g; a recent study found that in patients with IBD, a cut-off value of calprotectin below 250 µg/g corresponded with remission of disease [14].

There were excluded patients with suspected or confirmed acute flare, infectious overlap including acute Clostridium difficile colitis (the patients were screened for this infection).

Protocol and HGBT

Using a standardized questionnaire, all data regarding demographic characteristics of the patient, the time of diagnosis of IBD, the present and previous treatments, number of flares / year, presence or absence of surgical interventions, present symptoms (flatulence, the presence of more than 3 stools / day) were recorded.

Patients considered eligible were screened for the presence of SIBO. The test was performed between the hours 9-12 AM, after a 12-hour period of fasting. In order to determine the hydrogen level in the expired air the Gastrolyzer ® kit was used.

In terms of respiratory testing conditions, the required ones were: absence of antibiotic treatment or colonoscopy investigations for at least 1 month prior; restricted diet for at least 24 hours beforehand (no milk and derivative products, no carbonated drinks or fruit juices, no dietary fibre consumption, no laxatives); fasting and refrainment from smoking at least 12 hours prior to the test.

The protocol used was according to the Rome consensus [15]. The first test was carried out at time 0. If the base value was over 10 ppm the test was considered possibly corrupted by failure to meet the previously mentioned conditions, so that the patient was rescheduled. Subsequently, after the patient has ingested a quantity of 250 ml of decarbonized mineral water in which 50 g glucose was dissolved, tests were performed every 15 minutes until a total of 120 minutes was reached. The test was considered positive if there was an increase of at least 12 parts-per-million compared to the base value.

Prior to the test, patients were asked to brush their teeth, use mouthwash and refrain from physical exercise and eating chewing gum during hospitalization.

Results

Initially, testing was recommended to 88 patients, but 8 patients were undergoing corticosteroid therapy and 5 refused to participate in the study, so testing was conducted in a total of 75 patients diagnosed with IBD (39 with CD and 36 with UC). The main characteristics of the patients are summarized in Table 1, and the comparative SIBO / non-SIBO data are presented in Table 2.

The test group was comprised of approximately the same number of women / men; there was no significant difference between median ages of either gender (47.8 years for men and 46.9 years for the women's group), nor in terms of the progression period of the disease, from the moment of diagnosis to performing the breath test (28 months for the men and 30.1 months for the females).

The body mass index (kg/m^2) calculated for each patient presented a median value of 24.8 ± 3.5. Its values were at the lower limit of the range in patients with CD (23.4 ± 2.6) and near the upper limit in patients who presented with ulcerative colitis (26.3 ± 3.7), particularly those with proctitis or left sided-colitis.

Type of IBD and involvement found: 39 patients (52%) with CD and 36 patients (48%) with ulcerative colitis. In patients with CD, the inflammatory pattern prevailed (46.1%), followed by patients with stenosis form (25.7%), and those with perianal involvement (only 8 patients in our group). Regarding the extension of damage: 48.7% of patients had ileo-colonic

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involvement, 30.8% exclusively colonic involvement, and the remaining 20.5% presented enteral damage. Of the 36 patients with ulcerative colitis, most showed pancolonic involvement (E3 Montreal, 38.9%) and proctosigmoiditis (33.3%), the remaining 27.8% being represented by ulcerative proctitis.

Table 1. The main characteristics of the group of patients tested

Age - years	47.3 ±14.1
Sex (F/ M)	50.7% / 49.3%
Period of disease progression - months	29.1 ± 18.7
BMI (kg/m^2)	24.8 ±3.5
Disease type CD • Perianal/ fistulising involvement • Inflammatory pattern • Stenosis pattern • Involvement o Ileal/ small intestine exclusively o Ileo-colonic o Colonic exclusively UC • Proctitis (Montreal E1) • Left-sided colitis (Montreal E2) • Extended colitis (Montreal E3)	 n = 8 (20.5%) n = 21 (53.8%) n = 10 (25.7%) n = 8 (20.5%) n = 19 (48.7%) n = 12 (30.8%) n = 10 (27.8%) n = 12 (33.3%) n = 14 (38.9%)
Absence of the ileocecal valve	n = 3 (4%)
Ileo-colonic segment resections	n = 3 (4 %)
Extraintestinal manifestations • Arthritis/ arthralgia • Ocular manifestations	 n = 2 (2.6%) n = 1
Treatment undergone* • 5ASA (topic or systemic) • Immunomodulators • Biologics *15 % underwent combined therapy	 n = 30 (40%) n = 40 (53.3%) n = 5 (6.7%)

Table 2. Correlations between presence of SIBO and various clinical/ paraclinical characteristics

Characteristic	**SIBO**	**NON-SIBO**	**p**
Fistulising / perianal pattern (CD)	n = 7/8 (87.5%)	n = 1/8 (12.5%)	p = 0.0001
Extended colitis (UC)	n = 4/14 (28.5%)	n = 10/14 (71.4%)	0.49
BMI	24.7 ± 1.7	25.6 ± 2.1	NS
Absence of the ileocecal valve	3 (100%)	0	p = 0.014
Number of stools/day	3,52 ±0.41	2,65 ±0.65	NS
Presence of flatulence	8 (42.1%)	56 (83.6%)	<0.01
Extraintestinal manifestations	n = 1	n = 2	NS
Period of disease progression (months)	32.5 ±9.5	28.1 ±18.2	NS

Prevalence of SIBO in patients with Crohn's Disease - overall, of the entire group of patients screened, SIBO was present in 30.77% of patients with CD (n = 12/39). Their distribution according to the pattern of disease is as follows: stenosis pattern n = 4/10, inflammatory pattern n = 6/21, and with severe perianal involvement n = 7/8 (note that there were patients with perianal as well as inflammatory / stenosis pattern concurrently).

In terms of disease site, the highest frequency of SIBO was seen in patients with ileo-colonic involvement (3/8 = 37.5%), and in those with impaired small bowel (n = 3/8, 37.5%). SIBO was present much more rarely in patients with exclusive colonic involvement (10.5%)

Prevalence of SIBO in patients with ulcerative colitis was 7/36 (19.4%). Distribution according to the Montreal classification: 4/14 patients (28.5%) with extended colitis, 3/12 patients (25%) with left-sided colitis, and no patient with ulcerative proctitis.

Discussions

There is recently an increased interest in the investigation of the prevalence of small intestinal bacterial overgrowth syndrome in different populations. It is known that inflammatory bowel diseases are a heterogeneous group of disorders, with high degrees of geographic variability in terms of symptoms, progression pattern, clinical manifestations or overlap with other types of pathologies. Pairing/ overlapping of the two entities is more and more frequently mentioned in recent year researches, knowing that the involvement of the intestinal microbiome plays a very important role in inflammatory bowel disease etiopathogenesis.

Until now, in Romania there was no report on the frequency of overlap of the two entities.

We started from the following premise: knowing the statistics of association between the two entities (SIBO and IBD), and the predictors of the two associations, we can identify the subgroups of patients with symptoms that may suggest a flare within this population group (in this case, hydrogen breath test may determine the involvement of SIBO); along with other biological and laboratory methods, we can stratify patients and perform endoscopic investigations only in required cases.

Literature data indicates a frequency of overlap of SIBO in patients with inflammatory bowel disease of 18-30% for CD (4.7, 10) and 14-17.8% for UC (8.9). The data obtained in this work are consistent with the results reported previously in the literature.

As expected, SIBO frequency is higher among patients with CD compared to those with UC (30.77% vs. 19.4%, p = 0.04). The explanation could be represented by: involvement of the small intestine mainly in CD, extremely limited extension in ulcerative proctitis, absence of postoperative ileocecal valve found in stenosis forms of CD (all patients with this anatomical particularity had SIBO, n = 3, p = 0.014).

Among patients with CD, higher frequency of SIBO was found in the following situations: stenosis pattern (n = 4/11 36.6%, OR = 1.84, p = 0.28) and topographical perianal (n = 7/8, 87.5%, p = 0.0001) and ileo-colonic involvement (n = 7/19, 36.8%, p = 0.15).

In the group of patients with UC, as expected, none of the 10 patients with ulcerative proctitis had SIBO. SIBO frequency was greater in patients with extended colitis (n = 4/14, 28.5%, OR 1.22, p = 0.49) compared to those with left-sided colitis (n = 3/12, 25%, OR 0.97, p = 0.63).

In terms of undergone treatment, the data obtained by us are slightly different from recent reports in the literature. In a recent investigation [5] it was demonstrated that in inactive CD the administration of immunomodulatory or biological drugs is not associated with the development of SIBO. In our patients, we observed a higher frequency of SIBO in those under biologic therapy (n = 4/5, 80%, OR = 14.6, p = 0.013) and in those undergoing immunomodulatory treatment (n = 14 / 42, 33.3%, OR = 2.76, P = 0.06). The explanation probably lies in the severe form of activity that led to the initiation of biological / immunomodulatory therapy.

From a clinical point of view, patients with SIBO had a BMI value of 24.7 ± 1.7, compared to those without SIBO (median 25.6 ± 2.1, p = NS).

Published studies from previous years investigating the prevalence of SIBO in patients with IBD that report an increase in the number of daily stools or occurrence of persistent flatulence (over 2 weeks) have showed a clear overlap of these symptoms over the inflammatory bowel disease, sometimes mimicking a flare episode. In 2009, Klaus et al [11] reported a 25.3% frequency of SIBO in patients with CD who accused a worsening of the coprologic syndrome or the occurrence of flatulence; patients with CD and SIBO overlap

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had an average number of stools of 5.9 compared to those without SIBO (3.7 stools / day). In our study group: all 8 patients who reported persistent flatulence had SIBO (p = below 0.001); in terms of number of stools, we observed a daily average of 3.52 ± 0.41 in patients with SIBO, and 2.65 ± 0.65 in patients without SIBO.

Existence of extraintestinal events was not associated with the presence of SIBO (only one of the three patients presented SIBO, while the clinical form of IBD in this patient was extensive, including postoperative absence of the ileocecal valve). There was no correlation with abdominal pain or CDAI score value calculated in patients with CD.

Conclusions

This is the first study regarding the prevalence of SIBO in Romanian patients with IBD. The obtained data are similar with those reported previously in the literature.

Within the group of patients studied the prevalence of SIBO was higher in patients with CD (30.77%) compared to those with UC (19.4%). The risk factors that we identified as associated to the presence of this syndrome are: extended ulcerative colitis, perianal and ileo-colonic involvement in CD, postoperative absence of the ileocecal valve. Patients in remission, with SIBO, tend to present more frequently: a higher average of daily stools number, a lower BMI, and much more frequent complaints of persistent flatulence. We can state that SIBO represents a clinical-biological entity quite common in patients with inflammatory bowel disease, which can sometimes mimic a flare episode.

By excluding biological signs of inflammation, and by hydrogen breath test, we can establish the overlap of a small intestinal bacterial overgrowth syndrome as the cause of the exacerbation of symptoms.

Starting from the relatively high prevalence of SIBO in patients with IBD, it might be possible to use non-absorbable antibiotics as adjuvant therapy for flares; there are necessary further investigations and randomised clinical trials.

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