

Irritable Bowel Syndrome: Symptom Severity does not Depend on Whether Hydrogen Generation Occurs in the Small Intestine or Colon

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ABSTRACT

AIM: Compare symptom occurrence and severity among IBS patients with an early vs. late increase in H₂ excretion, as measured by LBT, and evaluate the association between symptom severity and global H₂ global excretion.

METHODS: Patients with an IBS diagnosis (Rome III criteria) as well as healthy subjects were enrolled consecutively. Subjects were asked to fill in a validated symptom-severity questionnaire (IBS-SSS) and to undergo a LBT. The area under the curve (AUC) was calculated for each LBT hydrogen/time curve.

RESULTS: This analysis included 160 IBS and 45 healthy control subjects. An early increase in H₂ excretion was observed in 53% of IBS subjects, and this was not significantly different from that observed in healthy subjects. There was also no significant difference in symptom pattern or severity between IBS patients with early vs. late increases in H₂ excretion. However, a significant correlation between symptom severity and AUC value was observed ($R^2: 0.4$, 95% CI: 0.1-0.6, $p=0.02$).

CONCLUSION: Symptom pattern and severity was not significantly different among IBS patients with early vs. late increases in H₂ excretion. However, the severity of IBS symptoms was significantly associated with global H₂ excretion, as measured by the AUC.

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Key words: Breath testing; Irritable bowel syndrome; Small intestine bacterial overgrowth

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INTRODUCTION

A lot of attention has focused on a possible association between irritable bowel syndrome (IBS) symptoms and gut flora, particularly in the presence of small intestinal bacterial overgrowth (SIBO)^[1]. This has been supported, in part, by the high prevalence of abnormal lactulose breath tests (LBTs) observed in these patients^[2]. The LBT is a non-invasive test that has been used to measure orocecal transit time. In addition, since an early increase in hydrogen (H₂) excretion can be attributed to the presence of bacteria in the small intestine, it has also been used as a diagnostic tool for SIBO^[3].

Evidence suggests that a relationship exists between abnormal LBTs and symptom severity in IBS patients^[4]. The SIBO hypotheses have been questioned in recent years, however^[5]. In clinical practice, LBT results follow two H₂ excretion/time curves which represent the arrival of lactulose to the colon and its consumption by gut flora: (1) an early increase in H₂ excretion (defined as an increase in H₂ excretion of 20 parts per million [ppm] before 90 minutes) or an elevated basal value (above 12 ppm) or (2) a late increase in H₂ excretion.

In this study, we determine whether there was a difference in symptom occurrence and severity between IBS patients who had an early vs. late increase in H₂ excretion with the LBT. We also evaluated the possible association between symptom severity and global H₂ excretion, which was measured by the area under the curve (AUC) of the H₂ excretion/time curve.

METHODS

Patient population

Patients with a diagnosis of IBS (according to Rome III criteria) who met our criteria were consecutively enrolled between July 2012 and May 2013. Subjects were interviewed by a trained gastroenterologist, and those presenting with non-IBS symptoms were excluded. IBS patients who had taken antibiotics, prokinetics,

narcotics, or anticholinergics within the month prior to enrollment were also excluded.

Enrolled subjects were assessed their symptom severity using a validated Spanish translation of the Irritable Bowel Syndrome Severity Symptom Scale (IBS-SSS) severity^[6,7]. They were also asked to identify a predominant bowel pattern (diarrhea, constipation, mixed, or undetermined). The IBS-SSS is a visual analog scale-based questionnaire that consists of five items: abdominal pain intensity, abdominal pain frequency (number of days with pain over the last ten days), abdominal bloating severity, global satisfaction with bowel movements, and symptom interference with daily activities. Each item is scored between 0 and 10, and the sum of these five items is considered the global score.

Healthy control subjects without an IBS diagnosis were also enrolled. These subjects also completed the questionnaire and underwent a LBT.

The study was approved by the Institutional Review Board at CEMIC hospital (IRB number C0036). All patients gave informed consent prior to receiving a LBT.

Lactulose breath test

The LBT was performed at 08:00 hours after an overnight fast of at least twelve hours. Patients were instructed to avoid slow-digesting food (beans, bran, or high-fiber foods) or a heavy meal the day before the test. Good oral hygiene was also recommended.

Subjects ingested a 10 g lactulose solution, and breath samples were collected at baseline and every 20 minutes for three hours. Samples were then analyzed using a Quintron™ 121 Plus chromatograph (Quintron™ Instruments Company, Milwaukee, WI, USA). Test results were used to generate a H₂ concentration/time curve which was then interpreted by a blinded and experienced gastroenterologist.

Because of the confounding effects of methanogenic flora on breath H₂ levels^[8], breath H₂ profiles of methane-producing subjects were excluded from analysis as previously described^[8,9].

Categorization

LBT results from IBS patients were categorized into two groups: (1) Group A, an increase in H₂ concentration >20 ppm before 90 minutes, a basal value >12 ppm, or a double peak in H₂ excretion; and (2) Group B, low basal levels of H₂ excretion followed by an increase >20 ppm after 90 minutes. Control subjects constituted group C.

Data analysis

Categorical variables were expressed as percentages and continuous variables as the mean ± the standard deviation or median with the interquartile range when appropriate. Stata™ (v11.2, Statacorp, College Station, Texas, USA) was used for the statistical analyses. Chi square or Fisher's exact tests were used to analyze categorical variables, and Student's t or Mann-Whitney tests were used to analyze continuous variables. The AUC was calculated from the H₂ excretion/time curve. Kruskal-Wallis tests were used to compare more than two non-parametric variables, and Spearman correlations were used to analyze correlations with symptom severity (IBS-SSS score). A *p* value <0.05 was considered statistically significant.

RESULTS

During the study period, 225 patients were evaluated, and 160 of these patients were enrolled. Forty-five were excluded because of treatment with either prokinetics, anticholinergics, or recent antibiotic treatments; 20 subjects with at least one clinical feature com-

patible with organic disease and were studied further; 45 age and sex-matched healthy control subjects were also included. Group A was comprised of 75 (47%) of the IBS patients. Table 1 shows comparisons of demographic data and symptom patterns between IBS patients from Groups A and B. We then compared symptom severity using the IBS-SSS (Table 2). In Group C, which was comprised of the control subjects, 31.2% had early increases in H₂ excretion. This

Table 1 Demographics and symptom patterns of IBS subjects.

	Early H ₂ excretion (Group A) (n=75)	Late H ₂ excretion (Group B) (n=85)	<i>p</i> value
Age (yrs)	54±18	49±14	0.3
Sex (% male)	22	19.5	0.8
Basal H ₂ (ppm)	15 (9-26)	3 (0-6)	0.001
Predominant symptom (%)			
Diarrhea	30	29.6	0.79
Constipation	25.9	24.4	0.9
Mixed	34.8	38.8	0.6
Unclassified	9.3	7.2	0.5

H₂: Hydrogen.

Table 2 Symptom severity in IBS subjects.

IBS-SSS Scores	Early H ₂ excretion (Group A) (n=75)	Late H ₂ excretion (Group B) (n=85)	<i>p</i> value
Total	25.5 (12-35)	29 (8-34)	0.65
Abdominal pain severity (0-10)	4 (0-7)	4.4 (0-7)	0.7
Abdominal pain frequency (units)	6 (0-8)	5 (0-8.5)	0.9
Abdominal bloating severity (0-10)	6.4 (0-8)	7 (0-8)	0.47
Interference with daily activities	6 (0-7)	6 (0-7)	0.7
Satisfaction of bowel habits (0-10)	6 (0-7)	6 (0-7)	0.7

H₂: Hydrogen; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Score.

was not significantly different from that of the IBS subjects (*p*=0.063).

We also compared IBS-SSS scores with the AUC of H₂ excretion/time as a measure of global H₂ excretion. AUC values for Groups A (4042, range: 1834-5800) and B (4400, range: 1958-6834) were not significantly different (*p*=0.8). AUC values between IBS (4248, range: 1954-6030) and control (2484, range: 1831-3630) subjects were significantly different, however. In addition, IBS-SSS scores were significantly higher among IBS patients with higher AUC values in either group (Table 3). This correlation between IBS-SSS score and AUC value was significant (*R*²: 0.4, 95% CI: 0.1-0.6, *p*=0.02).

Table 3 Symptom severity (AUC) in IBS subjects.

	AUC <3000	AUC 3000-6000	AUC >6000	<i>p</i> value
Group A - Early H ₂ excretion (n=75)				
Global IBS-SSS score	23 (12-25)	27 (12-34)	32 (18-35)	0.04
Group B - Late H ₂ excretion (n=85)				
Global IBS-SSS score	22 (12-34)	28 (17-38)	31.9 (19-35)	0.05

H₂: Hydrogen; AUC: Area under the curve; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Score

DISCUSSION

In this study, we did not see an association between IBS symptom severity and an early vs. late increase in H₂ excretion. In contrast, symptom severity was significantly correlated with global H₂ excretion, as measured by the AUC of H₂ excretion/time.

IBS is a common disorder that is a significant burden to health care systems around the world^[10]. Its physiopathology remains unknown. However, several mechanisms appear to contribute to its

development: visceral hypersensitivity^[11], altered brain-gut axis^[12], low-grade chronic inflammation^[13], and gut flora^[14-15].

Gut flora has received much attention since studies have shown a high prevalence of abnormal LBT results in IBS patients compared to healthy controls. This suggested that, in many IBS subjects, SIBO was an underlying trigger for their symptoms. This theory was later enforced by studies that showed a beneficial effect of antibiotics in these patients^[2]. LBT results were significantly different between IBS and healthy subjects (84 vs 20%, respectively; $p < 0.001$), and neomycin treatment significantly improved symptoms in IBS patients (35.3 vs. 13.5% in the treated vs. placebo arm; $p < 0.001$). A significant symptomatic response was also observed in IBS subjects receiving a non-absorbable antibiotic (rifaximin) in the multi-center TARGET 1 and 2 studies^[16]. However, the theory of a relationship between IBS and SIBO has been increasingly questioned in recent years due to its dubious biological plausibility^[5].

The LBT is a non-invasive test that has been used to infer the presence of SIBO^[3]. However, the utility of this test for detecting SIBO is controversial despite an increasing number of studies that confirm the association between LBT results and IBS^[17]. LBT has many pitfalls such as being highly influenced by oro-cecal transit. A comparison of LBT results in IBS subjects with simultaneous schintigraphy showed that the increase in H₂ excretion coincided with the arrival of a radionuclide marker to the cecum^[18]. Furthermore, one study showed that LBT results between 224 IBS patients and 40 healthy controls were not significantly different^[9]. In addition, the majority of both groups showed abnormal LBT results according to previously-established criteria (the same criteria used here).

LBT results have also been associated with IBS symptom severity, however. Youn *et al*^[4] compared LBT results from healthy controls, IBS patients, and patients with other functional gastrointestinal disorders. An abnormal LBT result was defined as an increase in H₂ excretion of >20 ppm from baseline before 90 minutes, a baseline value of 20 ppm or higher, or a rise in methane excretion of >10 ppm from baseline. There was a non-significant difference in the rate of abnormal LBTs between groups. However, when symptom severity and frequency were compared, flatulence severity and bloating frequency were significantly different between the three groups. These results differ from ours, since we did not observe any differences in symptom severity or pattern between subjects with abnormal vs. normal LBT results.

Our findings provide additional evidence against the SIBO theory. In subjects with IBS, symptom severity did not appear to depend on the presence of anomalous bacteria throughout the small intestine. In addition, we saw an association between symptom severity and global H₂ excretion. This suggests that gut flora play a role in IBS but not the way that was previously predicted. Differences in colonic, rather than small intestinal, bacteria could actually facilitate the development of certain symptoms. However, further studies are needed to determine whether this is the case.

According to these results, we hypothesize that LBT interpretation could imply a different view, since symptom severity seems to be related to the global amount of H₂ exhaled. This parameter may have a clinical impact on the utility of LBT in this cluster of patients.

Our study did have some limitations that should be noted. We did not take methane measurements into consideration, which would have been an interesting comparison between groups.

In conclusion, we suggest that symptom pattern and severity in IBS patients do not depend on whether H₂ excretion occurs in the small intestine or large bowel. Nonetheless, global H₂ excretion throughout the intestine could be related to IBS symptom development.

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