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Abnormal breath tests to lactose, fructose and sorbitol in irritable bowel syndrome may be explained by small intestinal bacterial overgrowth

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SUMMARY

Background: Small intestinal bacterial overgrowth and sugar malabsorption (lactose, fructose, sorbitol) may play a role in irritable bowel syndrome. The lactulose breath test is a reliable and non-invasive test for the diagnosis of small intestinal bacterial overgrowth. The lactose, fructose and sorbitol hydrogen breath tests are widely used to detect specific sugar malabsorption.

Aim: To assess the extent to which small intestinal bacterial overgrowth may influence the results of hydrogen sugar breath tests in irritable bowel syndrome patients.

Methods: We enrolled 98 consecutive irritable bowel syndrome patients. All subjects underwent hydrogen lactulose, lactose, fructose and sorbitol hydrogen breath tests. Small intestinal bacterial overgrowth patients were treated with 1-week course of antibiotics. All tests were repeated 1 month after the end of therapy.

Results: A positive lactulose breath test was found in 64 of 98 (65%) subjects; these small intestinal bacterial overgrowth patients showed a significantly higher prevalence of positivity to the lactose breath test ($P < 0.05$), fructose breath test ($P < 0.01$) and sorbitol breath test ($P < 0.01$) when compared with the small intestinal bacterial overgrowth-negatives. Small intestinal bacterial overgrowth eradication, as confirmed by negative lactulose breath test, caused a significant reduction in lactose, fructose and sorbitol breath tests positivity (17% vs. 100%, 3% vs. 62%, and 10% vs. 71% respectively: $P < 0.0001$).

Conclusions: In irritable bowel syndrome patients with small intestinal bacterial overgrowth, sugar breath tests may be falsely abnormal. Eradication of small intestinal bacterial overgrowth normalizes sugar breath tests in the majority of patients. Testing for small intestinal bacterial overgrowth should be performed before other sugar breath tests tests to avoid sugar malabsorption misdiagnosis.

INTRODUCTION

The irritable bowel syndrome (IBS) is a common chronic disorder of unclear origin characterized by abdominal pain, bloating and altered bowel habits.[1–3] IBS is a gastrointestinal disorder in which abnormal visceral sensation, altered motility and psychosocial factors may play a role.[1, 2] The IBS-related symptoms are difficult to quantify. Multiple symptom-based criteria have been proposed, such as Manning, Rome I and Rome II criteria.[4–6] Currently, the Rome II criteria provide a uniform framework for the selection of patients in diagnostic and therapeutic trials of IBS.[6]

Small intestinal bacterial overgrowth (SIBO) is a condition characterized by abnormally high bacterial population level in the small intestine, exceeding

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10^5 organisms/mL. Clinical significance of SIBO is defined as the presence of symptoms such as pain, meteorism, diarrhoea and/or signs of malabsorption, all of which are similar to symptoms observed in patients with IBS.[7]

Lactulose breath testing (LBT) has been proposed as a sensitive and simple tool for the diagnosis of bacterial overgrowth, because of its non-invasiveness and low cost when compared with the gold standard (culture of intestinal aspirates).[8–10] In the absence of hypochlorhydia, SIBO often occurs from proximal migration of colonic flora with a substantially higher levels of bacteria in distal small bowel.[11] There are critical advantages of LBT over direct culture is that culture-based diagnosis: first, culture is technically limited to bacterial overgrowth involving only the upper 60 cm of the small intestine, while LBT may detect fermentation elsewhere. Secondly, the subset of gut flora that can easily grow in culture is limited to approximately 40% of the estimated total.[12] The glucose BT has been proposed as an alternative method to assess SIBO; however, as glucose is completely absorbed in the proximal tract of the small intestine, the test sensitivity seems lower than for LBT.[8, 9]

Recent findings suggested that SIBO may play a role in IBS: SIBO is highly prevalent in IBS (78–84%) and its eradication significantly improved IBS symptoms in single centre trials.[11, 13]

Lactose,[14–17] fructose and sorbitol malabsorption[18, 19] have also been blamed for IBS symptoms. In general terms, sugars malabsorption could be primary (congenital enzymatic/carrier deficiency) or acquired (developing after intestinal damage: acute gastroenteritis, medications, celiac disease, Crohn's disease, other).[20] When carbohydrates are malabsorbed, their passage in the bowel causes the bacterial production of short chain fatty acids and gas, with the onset of a syndrome characterized by meteorism, abdominal pain and diarrhoea, thus mimicking IBS symptoms. H_2 lactose, fructose and sorbitol BTs are commonly used to detect specific sugar malabsorptions.

In the normal individual, gut bacteria are primarily located in the colon and in the distal small intestine. When a defective sugar absorption is present, unabsorbed sugars in excess are available in the colon for bacterial fermentation. In contrast, when SIBO is present, the bacterial population migrates proximally into the small intestine to gaining access to sugars, even if digestive capacity for sugars is preserved.[21] This shift in the fermentation site might lead to falsely abnormal sugar BT, even in patients with normal levels of disaccharidase activity.

Aim of this study was to test the hypothesis that, in patients with IBS, SIBO is associated with false-positive BTs to lactose, fructose and sorbitol, and that eradication of SIBO may revert these false-positivities.

PATIENTS AND METHODS

Participants, inclusion and exclusion criteria

Ninety-eight patients (mean age 33.3 ± 12 years; 40 males, 58 females) with a diagnosis of IBS according to Roma II criteria were consecutively enrolled from our Internal Medicine and Gastroenterology Outpatient Units. Use of laxative or antibiotics within the previous 2 months, a previous LBT, a history of diabetes, thyroid disease, intestinal surgery (except cholecystectomy or appendectomy), connective tissue disease, narcotic use and known gastrointestinal disease other than IBS were exclusion criteria. Patients were also asked if they were receiving chronic therapy with antisecretory agents [proton-pump inhibitors or histamine $(H)_2$-receptor antagonists].

Breath tests

Lactulose breath test. All patients underwent to LBT to detect SIBO. To minimize basal hydrogen (H_2) excretion, subjects were asked to have a carbohydrate-restricted dinner on the day before the test and to be fasting for at least 12 h. On the testing day, patients did a mouthwash with 20 mL of chlorhexidine 0.05%; smoking and physical exercise were not allowed for 30 min before and during the test.

End-alveolar breath samples were collected immediately before lactulose ingestion. Subsequently, a dose of 10 g of lactulose was administered and samples were taken every 15 min for 4 h using a two-bag system. Such two-bag system is a device consisting of a mouthpiece, a T valve and two collapsible bags, for collection of dead space and alveolar air. From this system, the breath sample is aspirated into a 20 mL plastic syringe. Samples were evaluated for H_2 using a model DP Quintron Gas Chromatograph (Quintron Instrument Company, Milwaukee, WI, USA). The measurements were then plotted and analysed. Results were expressed as parts per million (p.p.m.).

According to the literature, LBT was categorized as abnormal in presence of at least one of the following: (i) at least two distinct peaks, consisting of two consecutive H_2 values >10 p.p.m. above the basal value after lactulose ingestion, (ii) H_2 production <90 min after lactulose ingestion.[8–10] An abnormal LBT was considered as diagnostic of SIBO.

The reproducibility of LBT in our laboratory in patient populations ($n = 20$) is good, with a κ- statistic of 0.88 and 95% agreement on tests performed 1–2 weeks apart.

Lactose, fructose and sorbitol breath tests. At least 1 week after LBT, all patients underwent H_2 lactose, fructose and sorbitol BTs, performed by administering 20 g of lactose, 25 g of fructose and 20 g of sorbitol. Breath samples were collected every 30 min for 4 h. According to the literature[13–18] the tests were considered positive for sugar malabsorption when an increase in H_2 value more than 20 p.p.m. over baseline value was registered.

Antibiotic treatment

Patients with SIBO were treated in an open-label fashion with 1-week course of antibiotics (rifaximin, metronidazole or fluoroquinolones).

The LBT was reassessed 1 month after the end of treatment in all patients with SIBO. Eradication of SIBO was confirmed when the post-treatment LBT no longer met the above criteria for positivity. Treated patients were reassessed for the secondary end-point of IBS symptoms (Rome II criteria fulfilment) after the post-treatment LBT. At least 1 week after LBT, all patients underwent repeated BTs with lactose, fructose and sorbitol.

The statistical analysis was performed using STATA 6.0 (Stata Corporation, University of Texas, TX, USA). Differences among groups in proportion of test positives were evaluated by chi-square test. Values of $P < 0.05$ were considered to be significant.

RESULTS

The demographics for all participants, SIBO-positive and -negative patients' subgroups are presented in Table 1. Sixty-four of 98 (65%) IBS patients showed an abnormal LBT.

There was a significantly higher prevalence of positivity to lactose, fructose and sorbitol BTs in SIBO-positive with respect to SIBO-negative patients (83% vs. 64%, $P < 0.05$; 70% vs. 36%, $P < 0.01$; 70% vs. 36%, $P < 0.01$, respectively; Figure 1a).

Table 1. Characteristics of patients with abnormal lactulose breath test (SIBO-positives) and normal lactulose breath test (SIBO-negatives)

Characteristics	SIBO-positives ($n = 64$)	SIBO-negatives ($n = 34$)	P-value
Age	34.4 ± 10.4	32.3 ± 14	N.S.
Males	26 (40.6%)	14 (41.2%)	N.S.
PPI users	9 (14.1%)	3 (8.8%)	N.S.
H_2 antagonists users	4 (6.25%)	2 (5.9%)	N.S.

SIBO, small intestinal bacterial overgrowth; PPI, proton-pump inhibitor; H_2, histamine$_2$; N.S., not significant.

All patients assigned antibiotics completed treatment. No major adverse events were reported. A total of 40 of 64 (62%) SIBO patients showed normalization of LBT after treatment.

Antibiotic treatment caused a significant reduction in lactose (from 83 to 48%), fructose (from 70 to 25%) and sorbitol BTs positivity (from 70 to 33%; $P < 0.01$).

After treatment, the prevalence of positivity to lactose, fructose and sorbitol BTs was significantly higher in the 40 patients with normalization of LBT with respect to the 24 with persistence of a positive LBT ($P < 0.0001$, Table 2; Figure 1b).

The raw prevalence of positivity to H_2 BT using lactose, fructose and sorbitol was not significantly changed in SIBO patients in whom LBT was not normalized after treatment (Figure 1b).

For the secondary end-point of IBS criteria fulfilment, 60% (24 of 40) of treated but not eradicated patients were still Rome II-positive after confirmed eradication, compared with 25% (six of 24) in the group patients.

DISCUSSION

The present study found a significant association between positivity to LBT and positivity to H_2 lactose, fructose and sorbitol BT. The normalization of LBT 1 month after antibiotic treatment was associated with a normalization of the majority of previously positive lactose, fructose and sorbitol BT. These results suggest that, in presence of SIBO, the large amount of intestinal bacteria may unspecifically ferment sugars, causing an abnormal H_2 production and consequently a misleading diagnosis of lactose, fructose or sorbitol malabsorption. An alternative hypothesis could be that the bacterial

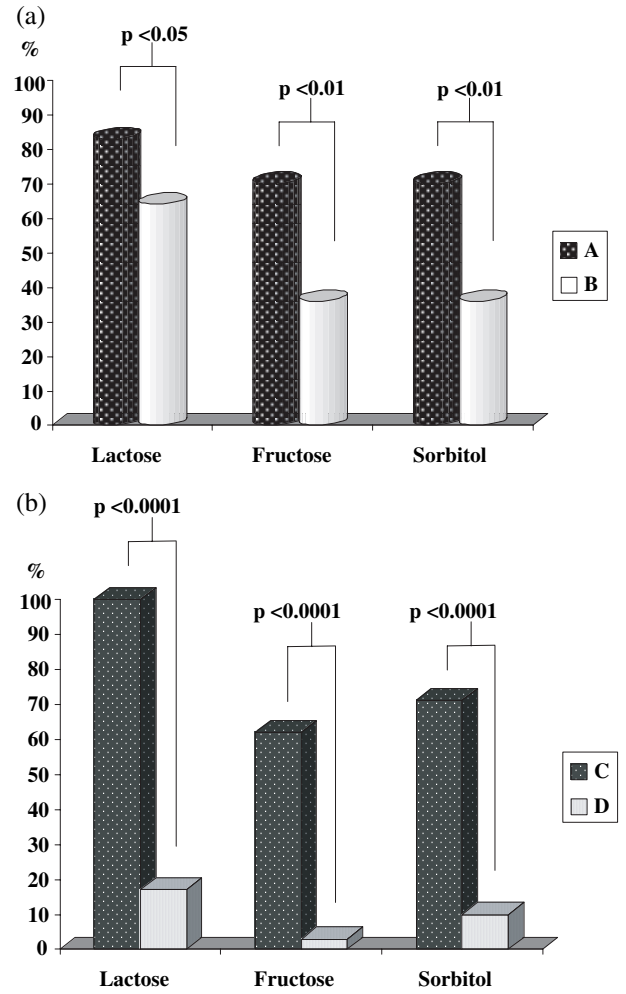

Figure 1. (a) Prevalence of positivity to lactose, fructose and sorbitol breath tests between: A, patients with abnormal lactulose breath test (LBT); B, patients with normal LBT. (b) Prevalence of positivity to lactose, fructose and sorbitol breath tests between: C, patients with persistence of abnormal LBT after antibiotic treatment; D, patients with normalization of LBT after antibiotic treatment.

Table 2. Prevalence (%) of positivity to breath test for lactose, fructose and sorbitol in patients with normalization of lactulose breath testing (LBT) and in patients with persistence of abnormal LBT after antibiotic treatment

Sugar BT positivity	Normalized LBT ($n = 40$, %)	Not normalized LBT ($n = 24$, %)	*P*-value
Lactose	17	100	0.0001
Fructose	3	62	0.0001
Sorbitol	10	71	0.0001

overgrowth leads to a damage of the small bowel mucosa, thus inducing a transient enzymatic or carrier protein deficiency and then multiple sugars malabsorptions; after SIBO eradication the intestinal mucosa comes back to play its normal functions and the sugars malabsorption disappear.

The effect of courses of antibiotics in IBS patients with concomitant bacterial overgrowth has previously been reported. Nayak *et al.* observed that metronidazole treatment resulted in a significant and prolonged improvement of IBS symptoms over placebo.[22] More recently, Pimentel *et al.* performed a double-blind trial of neomycin on 111 IBS patients. At enrolment, all subjects underwent a LBT. Normalization of LBT after neomycin treatment was associated with a significant reduction in IBS symptoms.[13] We found a high prevalence (65%) of SIBO in a population of IBS patients. Our results agree with those by Pimentel *et al.*, who reported higher prevalence (78 and 84%) of SIBO in two large series of IBS patients (202 and 111 respectively).[11, 13] The reduction in the proportion of patients fulfilling IBS criteria after eradication is of limited clinical significance, as this was neither a primary end-point nor an *a priori* hypothesis, and this observation is also limited to a short follow-up.

Differences in the population characteristics (i.e. age, geographical origin) and methodology for LBT (model of chromatograph, gases analysed, criteria to assess positivity to the test) may explain the slight discrepancy in the prevalence of SIBO across these studies. Moreover, symptom response to antibiotic treatment in IBS was not an end-point of the present study.

Literature data show a possible association between lactose, fructose, sorbitol malabsorption and IBS, suggesting a specific exclusion diet may improve symptoms in IBS patients with positive sugar BT.[14–19] However, it is well-known that IBS subjects experience abdominal symptoms after ingestion of many different food products, and correspondence between intolerances reported by patients and found at testing is often limited.[23] This non-specific intolerance could be due to a premature exposure of nutrients, in particular carbohydrates, to luminal bacteria in patients with SIBO. A recent study showed that the prevalence of true lactose malabsorption was lower than the prevalence of abnormal lactose BT in SIBO to suggest that the expansion of gut bacterial flora proximally results in abnormal interaction of substrate and gut bacteria leading to a positive lactose BT.[21] Our data are the first available to estimate the prevalence of fructose and sorbitol malabsorption, aside from bacterial overgrowth, in patients with IBS symptoms.

An abnormal BT to lactose, fructose and sorbitol was still detected in a small subset of IBS patients (ranging from 3 to 17%) after eradication of SIBO. This subset likely represents the group with true limitation of digestive capacity for these three sugars.

In conclusion, LBT can be useful in the management of patients presenting with IBS symptoms, in order to detect and treat SIBO. The presence of SIBO should be always assessed first, before starting search for sugar malabsorption and specific sugars elimination diets in IBS patients. Lactose, fructose and sorbitol BT could become a useful diagnostic approach in SIBO-negative or eradicated patients with refractory symptoms.

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REFERENCES

1 Sandler RS. Epidemiology of irritable bowel syndrome in the United States. Gastroenterology 1990; 99: 409–15.
2 Talley NJ, Gabriel SE, Harmsen WS, *et al.* Medical costs in community subjects with irritable bowel syndrome. Gastroenterology 1995; 109: 1736–41.
3 Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. JAMA 2004; 292: 852–8.
4 Manning AP, Thompson WG, Heaton KW, *et al.* Towards a positive diagnosis of the irritable bowel syndrome. Br Med J 1978; 2: 653–4.
5 Olden KW. Diagnosis of irritable bowel syndrome. Gastroenterology 2002; 122: 1701–14.
6 Thompson WG, Longstreth GF, Drossman DA, *et al.* Functional bowel disorders and functional abdominal pain. Gut 1999; 45 (Suppl. II): II43–7.
7 Singh VV, Toskes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. Curr Treat Options Gastroenterol 2004; 7: 19–28.
8 Corazza GR, Menozzi MG, Strocchi A, *et al.* The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. Gastroenterology 1990; 98: 302–9.
9 Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. Gastroenterology 1988; 95: 982–8.
10 Rhodes JM, Middleton P, Jewell DP. The lactulose hydrogen breath test as a diagnostic test for small-bowel bacterial overgrowth. Scand J Gastroenterol 1979; 14: 333–6.
11 Pimentel M, Chow EJ, Lin HC, *et al.* Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000; 95: 3503–6.
12 Tannock GW, Munro K, Harmsen HJM, *et al.* Analysis of the fecal microflora of human subjects consuming a probiotic product containing *Lactobacillus rhamnosus* DR20. Appl Environ Microbiol 2000; 66: 2578–88.
13 Pimentel M, Chow EJ, Lin HC, *et al.* Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003; 98: 412–9.
14 Bohmer CJ, Tuynman HA. The clinical relevance of lactose malabsorption in irritable bowel syndrome. Eur J Gastroenterol Hepatol 1996; 8: 1013–6.
15 Sciarretta G, Giacobazzi G, Verri A, *et al.* Hydrogen breath test quantification and clinical correlation of lactose malabsorption in adult irritable bowel syndrome and ulcerative colitis. Dig Dis Sci 1984; 29: 1098–104.
16 Vernia P, Di Camillo M, Marinaro V. Lactose malabsorption, irritable bowel syndrome and self-reported milk intolerance. Dig Liver Dis 2001; 33: 234–9.
17 Vernia P, Ricciardi MR, Frandina C, *et al.* Lactose malabsorption and irritable bowel syndrome. Effect of a long-term lactose-free diet. Ital J Gastroenterol 1995; 27: 117–21.
18 Ledochowski M, Widner B, Bair H, *et al.* Fructose- and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. Scand J Gastroenterol 2000; 35: 1048–52.
19 Goldstein R, Braverman D, Stankiewicz H. Carbohydrate malabsorption and the effect of dietary restriction on symptoms of irritable bowel syndrome and functional bowel complaints. Isr Med Assoc J 2000; 2: 583–7.
20 Swagerty DL Jr, Walling AD, Klein RM. Lactose intolerance. Am Fam Physician 2002; 65: 1845–50.
21 Pimentel M, Kong Y, Park S, *et al.* Breath testing to evaluate lactose intolerance in irritable bowel syndrome correlates with lactulose testing and may not reflect true lactose malabsorption. Am J Gastroenterol 2003; 98: 2700–4.
22 Nayak AK, Karnad DR, Abraham P, *et al.* Metronidazole relieves symptoms in irritable bowel syndrome: the confusion with so-called 'chronic amebiasis'. Indian J Gastroenterol 1997; 16: 137–9.
23 Dainese R, Galliani EA, De Lazzari F, *et al.* Discrepancies between reported food intolerance and sensitization test findings in irritable bowel syndrome patients. Am J Gastroenterol 1999; 94: 1892–7.