

# Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth

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## SUMMARY

### Background

Many studies report a high prevalence of lactose intolerance in patients with functional, gastrointestinal disease.

### Aim

To evaluate the role of small intestinal bacterial overgrowth (SIBO) in condition of lactose intolerance and the mechanism by which SIBO may impact lactose tolerance in affected patients.

### Methods

Consecutive out-patients with chronic functional diarrhoea (CFD) and healthy controls underwent a validated 20 g lactose hydrogen breath test (HBT). Patients completed also a 10 g lactulose HBT with concurrent assessment of small bowel transit by scintigraphy.

### Results

Lactose malabsorption was present in 27/31 (87%) patients with CFD and 29/32 (91%) healthy controls ( $P = 0.708$ ). From the patient group 14/27 (52%) had lactose intolerance and 13/27 (48%) experienced no symptoms (lactose malabsorption controls). Only 5 (17%) healthy controls reported symptoms ( $P < 0.01$ ). The oro-caecal transit time was similar between patient groups with or without symptoms ( $P = 0.969$ ). SIBO was present in 11 (41%) subjects and was more prevalent in lactose intolerance than in lactose malabsorption [9/14 (64%) vs. 2/13 (15%),  $P = 0.018$ ]. Symptom severity was similar in lactose intolerance patients with and without SIBO ( $P = 0.344$ ).

### Conclusions

Small intestinal bacterial overgrowth increases the likelihood of lactose intolerance in patients with CFD as a direct result of lactose fermentation in the small intestine, independent of oro-caecal transit time and visceral sensitivity.

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## INTRODUCTION

Lactase deficiency and malabsorption (LM) is widespread throughout the world because of a genetically determined, age-dependent decline in lactase activity.<sup>1</sup> The prevalence of this condition varies considerably, ranging from 5% in north-west Europe to almost 100% in some Asian populations.<sup>2</sup> Lactose intolerance (LI) refers to gastrointestinal symptoms including pain, bloating and diarrhoea related to bacterial fermentation of undigested lactose in the gastrointestinal tract, usually in the colon.<sup>3</sup> However, the ingestion of lactose by an individual with LM does not always result in LI.<sup>4, 5</sup> It is clear that the amount of lactose ingested and the level of lactase activity are associated with the risk of symptoms<sup>6-8</sup> and other factors, including age and gender,<sup>9-12</sup> altered bowel flora,<sup>13</sup> anatomical pathology or dysmotility of the gastrointestinal tract,<sup>14</sup> abnormal small bowel transit,<sup>15, 16</sup> heightened visceral sensitivity<sup>17, 18</sup> and psychosocial stress<sup>19-21</sup> have also been implicated. Nevertheless, the factors that determine whether an individual with LM will experience LI are rarely established and treatment is usually empiric and not directed at a specific cause.

The relationship between LM, LI and functional gastrointestinal disorders, especially IBS-D, has been extensively investigated because of their similar symptoms and the possibility that these conditions share a common pathophysiology. A majority of studies found the prevalence of LM in IBS subjects to be virtually the same as in the normal population,<sup>22-24</sup> but few studies focused on the difference of LI symptoms in patients with functional gastrointestinal disorders compared with the healthy controls. In general, such studies found that patients with IBS more often reported symptoms following lactose ingestion than healthy subjects;<sup>25</sup> however, the mechanism underlying this interaction has not been studied.

Small intestinal bacterial overgrowth (SIBO) is a condition in which the small bowel is colonized by colonic bacteria, formally defined by the presence of  $>10^5$  colony forming units on jejunal aspiration. SIBO is more common in the elderly, in patients with underlying gastrointestinal pathology, and has also been implicated in functional gastrointestinal diseases that are characterized by increased visceral sensitivity and psychosocial stress.<sup>26</sup> Thus, SIBO and LI appear to occur in similar population groups. Moreover, the mechanism of disease is thought to be similar in both conditions, with bacterial fermentation of ingested

carbohydrates producing gas (e.g. hydrogen, methane) and fatty acids that lead to bloating, abdominal pain and diarrhoea. Increased LM in the presence of SIBO has been reported in IBS patients and others;<sup>13, 27, 28</sup> however, in populations with a low prevalence of LM, it is difficult to assess whether a positive breath test is due to lactase deficiency or to malabsorption caused by SIBO. This source of confounding is not present in Chinese populations, in which a vast majority of adults have genetically determined lactase deficiency.

This study proposes that fermentation of lactose in the small bowel due to SIBO increases the likelihood of LI symptoms occurring. This hypothesis was tested in a Chinese population with functional diarrhoea because any effect of SIBO on lactose digestion and symptoms is likely to be of particular clinical relevance in this group.<sup>29-31</sup> The results document (i) SIBO prevalence in LM patients with functional diarrhoea (ii) the impact of SIBO on the likelihood of LI symptoms occurring after lactose ingestion. In addition, the underlying mechanism of disease and cause of symptoms was assessed by comparing and contrasting the results of physiological measurements in patients with and without SIBO.

## METHODS

### Participants

Consecutive out-patients referred for chronic diarrhoea and no alarm symptoms or other evidence of relevant organic diseases were investigated prospectively. Chronic diarrhoea was defined as having one or more of the following symptoms at least 25% of the time in the past 3 months: (i) three or more bowel movements a day; (ii) loose or watery stools or (iii) faecal urgency.<sup>32</sup> All patients underwent colonoscopy, routine blood biochemistry (renal, liver and thyroid function), haematology and immunology (coeliac antibodies) plus faecal microbiology. Subjects diagnosed with neoplastic, infective, autoimmune or inflammatory bowel disease were excluded. In addition, patient records were carefully reviewed to exclude other medical conditions or medication use as a cause of symptoms, including antibiotic use in the previous 4 weeks. Intake of proton pump inhibitors (PPIs) therapy was recorded, but was not an exclusion criterion. All participants completed standard questionnaires to assess symptoms (Rome III questionnaire), and the presence of psychological disease (HAD).

Lactose hydrogen breath test (HBT) findings from 32 healthy individuals with no history of gastrointestinal symptoms are provided as healthy control data. The study was approved by the ethical committee of Sir Run Run Shaw Hospital and all participants signed consent for study procedures.

### Lactose hydrogen breath test

To minimize basal hydrogen excretion, subjects avoided foods containing incompletely absorbed carbohydrates, such as bread, pasta, corn, and potatoes on the evening before the breath test and attended after a minimum 12-h fast.<sup>33</sup> Immediately before the procedure, subjects used 30 mL of antiseptic mouthwash containing 1.5% compound borax solution (Winguidehp, Shanghai, China) to eliminate lactose fermentation by oropharyngeal bacteria. Other extra-intestinal influences on breath hydrogen concentrations, such as cigarette smoking, physical exercise and hyperventilation,<sup>34</sup> were avoided during the test. Subjects fasted for the duration of the test.

After determination of the baseline H<sub>2</sub> breath concentration, the subject underwent a validated 20 g lactose breath test (equivalent of 400 mL milk) validated for use in populations with a high rate of lactase deficiency.<sup>35–37</sup> Exhaled hydrogen was recorded every 15 min for 3 h by a portable analyzer (Micro H<sub>2</sub> Meter, Micro Medical Limited, Rochester, UK) with sensitivity of  $\pm 1$  ppm. Lactose malabsorption was present if the peak of H<sub>2</sub> breath excretion over the baseline was  $\geq 20$  ppm.<sup>35</sup> Total excretion of H<sub>2</sub> in ppm over the 3 h study was computed according to Rumesen *et al.*,<sup>38</sup> and expressed as area under the concentration–time curves (AUC, ppm, 3 h).

Concurrent symptoms following the test were recorded. Abdominal pain, nausea, bloating, borborygmus and diarrhoea were ranked: 0 = absence, 1 = trivial, 2 = mild, 3 = moderate, 4 = strong, 5 = severe symptoms. LI was defined by reports of more than one point rise in at least two symptoms and the total symptom score (TSS) was calculated.<sup>18</sup>

### Concurrent lactulose hydrogen breath test with <sup>99m</sup>Tc scintigraphy

Within 7 days of the lactose HBT, subjects with lactose malabsorption returned for evaluation of the presence of SIBO. Controls did not complete the lactulose HBT with scintigraphy to avoid unnecessary exposure of

healthy individuals to ionizing radiation. Preparations were identical to those detailed for the lactose breath test. A 10-g lactulose HBT/scintigraphy was performed, using a test meal of 15 mL Duphalac (Solvay pharmaceuticals B.V., Weesp, The Netherlands) and 37MBq <sup>99m</sup>Tc-diethylene triamine pentaacetic acid (DTPA; HTA Co., Ltd, Beijing, China) in 100 mL water, as validated by Riordan *et al.*<sup>39</sup> The subjects were positioned comfortably in a supine position with a gamma camera (Millennium VG, General Electric, Milwaukee, WI, USA) in position over the abdomen. Starting after ingestion of the test meal, end-expiratory breath samples were collected concurrently with scintigraphic images every 15 min for up to 3 h. For the scintigraphy, the geometric mean of the anterior and posterior values was used to correct for depth changes [geometric mean counts = square root (anterior counts  $\times$  posterior counts)] corrected for radioisotope decay.<sup>40</sup> Breath test results and scintigraphy images were reviewed independently and in a blinded manner to determine the H<sub>2</sub> rise and arrival of the tracer in the caecal region-of-interest (ROI).

Small intestinal bacterial overgrowth was diagnosed if the initial H<sub>2</sub> rise, involving at least two consecutive values  $\geq 5$  ppm above baseline, commenced at least 15 min before an increase of radioactivity  $\geq 10\%$  of administered dose in the caecal region.<sup>39</sup> A secondary analysis for a diagnosis of SIBO based on a higher cut-off value of  $\geq 10$  ppm hydrogen above baseline was also performed.<sup>41</sup> Similar to lactose HBT, the total excretion of H<sub>2</sub> in the 3 h study was computed and expressed as area under the concentration–time curves.

The oro-caecal transit time (OCTT) was defined objectively as the time at which at least 10% of administered dose of isotopes had accumulated in the caecal region which has been used by previous studies.<sup>41, 42</sup>

### Data analysis

All variables were expressed as mean  $\pm$  s.d. or median with quartiles as appropriate. ANOVA was used for comparison between multiple groups with unpaired *t*-tests for comparison between two groups. Qualitative data comparisons used the chi-square test. Mann–Whitney *U* test was used for non-parametric statistical test. Linear regression was then used to compare the time at which H<sub>2</sub> excretion peaked, the maximum H<sub>2</sub> concentration and H<sub>2</sub> excretion (AUC, ppm, 3 h) between

the lactose and lactulose HBT. Alpha <0.05 was considered significant.

## RESULTS

### Study population

A total of 31 subjects with chronic diarrhoea and no evidence of relevant organic disease were enrolled in this study. In addition, 32 controls with no history of gastrointestinal symptoms were recruited. Patients and controls were well matched for age and gender; however, patients with functional diarrhoea attending the clinic had significantly lower body mass index (albeit still within the normal range). There was no significant difference on the hospital anxiety and depression (HAD) scale in patients and controls (Table 1).

### Lactose hydrogen breath test

The lactose HBT demonstrated lactose malabsorption (LM) in 27/31 (87%) subjects. Of these, 14/27 (52%) experienced clinically relevant symptoms (TSS rise >2) typical of lactose intolerance (LI group) and 13/27 (48%) had no symptoms (LM control group). In comparison, a similar number of healthy controls had LM following ingestion of a 20 g dose of lactose [29/32 (91%)], of whom 5/29 (17%) experienced typical LI symptoms ( $P = 0.708$  and  $P < 0.01$  respectively compared with patient group). Mean  $H_2$  excretion as assessed by area under the concentration–time curves

(AUC) was higher in the patient than the control group ( $7347 \pm 3937$  vs.  $5827 \pm 3968$   $P = 0.156$ ); however, this did not reach statistical significance in the presence of high inter-individual variation.

### Combined lactulose HBT with $^{99}\text{Tc}$ scintigraphy

Small intestinal bacterial overgrowth was present in 11/27 subjects with LM (41%) as defined by a consistent >5 ppm  $H_2$  rise above baseline on two occasions (i.e. >15 min) before an increase of radioactivity  $\geq 10\%$  of administered dose entered the caecal region. Of these, 9/11 subjects showed >5 ppm  $H_2$  rise at least 15 min prior to any signal in the putative caecal area. Age, gender and Body Mass Index (BMI) plus psychosocial state assessed by standardized questionnaires did not differ among the groups with and without SIBO (Table 1). The presence of SIBO was similar in patients with Irritable Bowel Syndrome with diarrhoea (IBS-D) and other chronic, functional diarrhoea as classified by the Rome III criteria.<sup>43</sup>

### Association of OCTT with LI and SIBO

The oro-cecal transit time (OCTT) assessed by scintigraphy was similar between the LI and LM groups ( $59 \pm 9$  min vs.  $58 \pm 10$  min,  $P = 0.96$ ) and there was no important difference of OCTT between patients with and without SIBO ( $63 \pm 9$  min vs.  $56 \pm 9$  min,  $P = 0.071$ ). By definition, there was a close correlation between the initial 5 ppm increase in  $H_2$  on lactulose

Table 1. Baseline demographic and clinical factors of patients and controls with LM

	Chronic, Functional diarrhoea		Healthy controls ( $n = 29$ )	$P$ -value
	SIBO ( $n = 11$ )	No SIBO ( $n = 16$ )		
Body mass index ( $\text{kg}/\text{m}^2$ ), mean $\pm$ s.d.	$20.3 \pm 3.1$	$20.5 \pm 2.2$	$22.4 \pm 3.0$	$P < 0.05^*$
Age (years), mean $\pm$ s.d.	$40.1 \pm 12.4$	$39.9 \pm 8.3$	$37.1 \pm 11.5$	N.S.
Gender: Male	8	8	10	N.S.
Female	3	8	19	
Rome III classification: IBS-D	6	8	n/a	N.S.
Other functional diarrhoea	5	8	n/a	
HAD score, mean $\pm$ s.d.	$8.2 \pm 8.0$	$13.8 \pm 9.5$	$10.8 \pm 8.1$	N.S.
Long-term PPI treatment ( $n$ )	0	2	0	

\* Between healthy controls and patients.

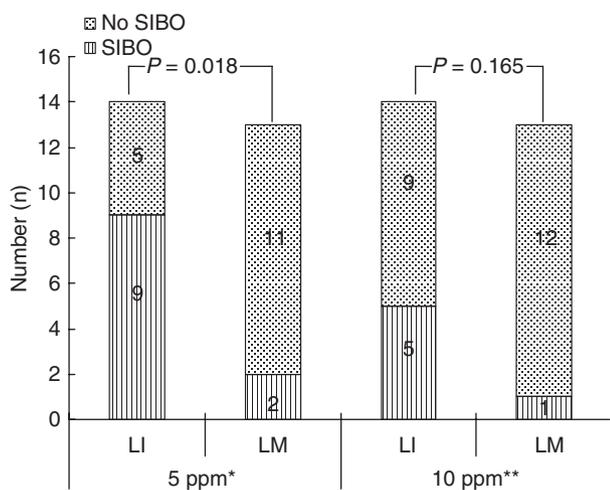
SIBO, small intestinal bacterial overgrowth; IBS-D, irritable bowel syndrome with diarrhoea; HAD, hospital anxiety and depression.

HBT and the arrival of scintigraphic marker in the caecum in SIBO negative ( $r = 0.889$ ,  $P < 0.001$ ), but not in SIBO positive patients ( $r = 0.143$ ,  $P = 0.674$ ).

### Association of SIBO with LI symptoms

The primary outcome was that the prevalence of SIBO was significantly higher in (lactose intolerance) LI patients than in the lactose malabsorption (LM) control group [9/14(64.3%) vs. 2/13(15.4%),  $P = 0.018$ ]. If the diagnostic cut-off for SIBO was raised from 5 ppm to 10 ppm initial rise in breath hydrogen, the number of subjects with SIBO dropped from 11/27 (41%) to 6/27 (22%) of whom only one did *not* experience LI symptoms during Lactose HBT (Figure 1).

The LM control group was, by definition, symptom-free. Within the LI group, patient reports of all five individual symptoms and the total symptom score (TSS) were similar in those with and without SIBO (Table 2). The onset of symptoms during the lactose HBT occurred somewhat earlier in patients with SIBO than in those without SIBO ( $76 \pm 54$  min vs.  $114 \pm 39$  min,  $P = 0.207$ ) and  $H_2$  excretion during the lactose HBT (AUC, ppm, 3 h) was somewhat higher in



**Figure 1.** Patients with small intestinal bacterial overgrowth (SIBO) were more likely to experience symptoms following lactose ingestion than those without SIBO. LI, Lactose Intolerance; LM, Lactose Malabsorption; \* 5 ppm of initial rise in breath hydrogen as the diagnostic cut-off for SIBO; \*\* 10 ppm of initial rise in breath hydrogen as the diagnostic cut-off for SIBO; A consistent rise in hydrogen before the arrival of radioactive marker in the caecum was required for SIBO diagnosis.

**Table 2.** Severity of symptoms after lactose oral administration in LI subjects ( $n = 14$ )

Symptoms, median (quartiles)	SIBO ( $n = 9$ )	No-SIBO ( $n = 5$ )	<i>P</i> -value
Nausea	0	0	
Bloating	1 (0–1)	0 (0–1)	0.421
Borborygmus	1 (1–2)	1 (0–1)	0.158
Abdominal pain	0 (0–1)	0 (0–1)	0.653
Diarrhoea	5 (4–5)	5 (5–5)	0.310
TSS	8 (5–9)	6 (6–6)	0.344

TSS, total symptom score; SIBO, those with a small intestinal bacterial overgrowth diagnosis; No SIBO, those without a small intestinal bacterial overgrowth diagnosis.

SIBO patients than in non-SIBO patients ( $8621 \pm 4753$  vs.  $6473 \pm 3131$   $P = 0.168$ ). There was no association of overall  $H_2$  excretion (AUC, ppm, 3 h) and the severity of symptoms ( $r = 0.356$ ,  $P = 0.212$ ); however, the early appearance of symptoms during the lactose HBT was strongly associated with the severity of symptoms (TSS) in LI patients ( $r = 0.730$ ,  $P = 0.003$ ) and subgroup analysis revealed that this association was present in SIBO patients ( $r = 0.781$ ,  $P = 0.013$ ), but not in those without SIBO.

### Comparison of lactose and lactulose HBT

There was a significant association between the time at which  $H_2$  excretion peaked ( $r = 0.412$ ;  $P = 0.033$ ), maximum  $H_2$  concentration measured ( $r = 0.534$ ;  $P = 0.004$ ) and  $H_2$  excretion AUC ( $r = 0.568$ ,  $P = 0.002$ ) during the lactose and lactulose HBTs (Figure 2).

### DISCUSSION

This study provides direct evidence of SIBO effects on lactose digestion and tolerance, which may explain why patients with functional diarrhoea experience lactose intolerance more often than healthy individuals.

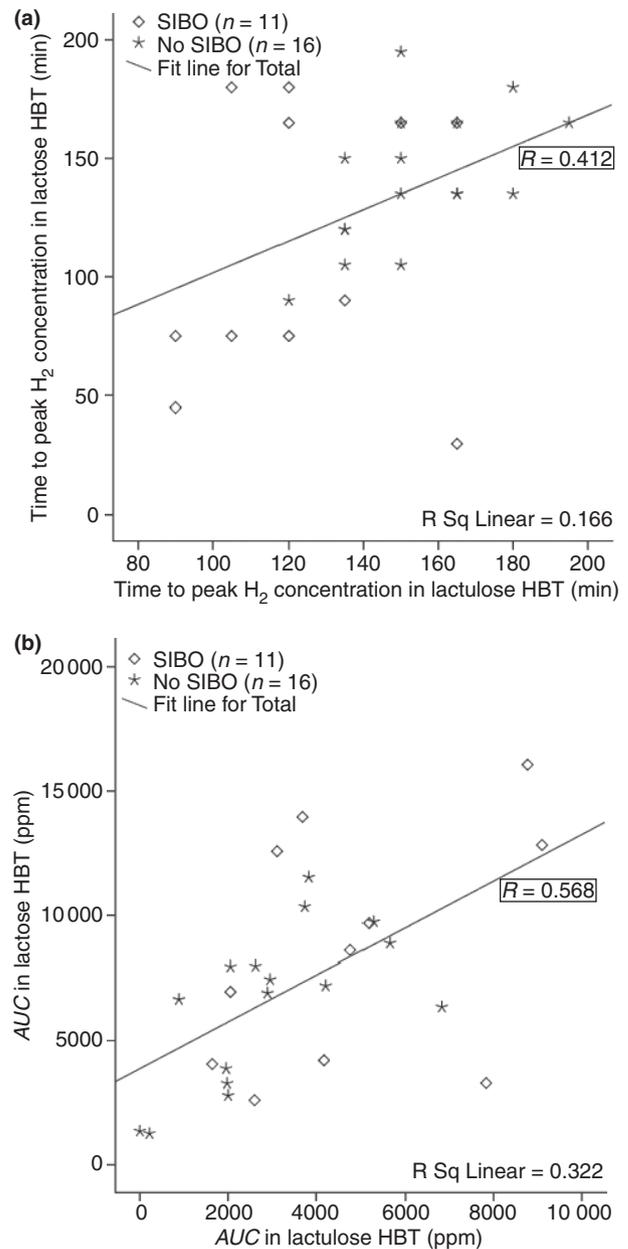
Patients attending gastroenterology clinic for investigation and treatment of chronic, functional diarrhoea and well-matched, healthy controls had a high prevalence (~90%) of lactase deficiency and lactose malabsorption (LM); however, typical symptoms of lactose intolerance (LI) were much more common in patients than in controls after ingestion of 20 g lactose

(52% vs. 17%,  $P < 0.010$ ). This result is consistent with previous studies, including preliminary reports from a large cohort study based in the same clinic<sup>25, 36</sup> and demonstrates that patients and controls respond differently to the 'physiological challenge' of dietary lactose.

The 20 g lactose HBT has similar sensitivity for LM as the 40 g lactose HBT<sup>35</sup> and is more specific for patients with functional GI disease in the Chinese population.<sup>36</sup> Moreover, the supra-physiological 40–50 g lactose dose applied in many previous studies causes severe symptoms in almost all Chinese individuals. Thus, for this study, the 20 g lactose HBT had the required sensitivity and specificity to assess the impact of SIBO (or other potential factors) on the presentation and severity of functional diarrhoea.

Patients with functional gastrointestinal disease may experience more or more severe symptoms following a defined 'dietary challenge' because of (i) location or intensity of the stimulus (e.g. gas production and distension), (ii) abnormal gastrointestinal motility and transit, or (iii) heightened visceral sensitivity at the peripheral (e.g. inflammation) or central levels (e.g. stress). Further investigation by lactulose breath test and small bowel scintigraphy for the diagnosis of SIBO and assessment of oro-caecal transit time provided insights into the causes of symptoms and the mechanism of disease. Questionnaires provided an assessment of psychosocial state.

The primary outcome of this study (Figure 1) is the striking increase in prevalence of SIBO in lactase deficient patients with compared with those without symptoms of lactose intolerance [9/14 (64%) vs. 2/13 (15%),  $P = 0.018$ ]. Several previous studies reported a rapid, early increase in  $H_2$  excretion to high levels in patients who experienced severe symptoms during lactose HBT.<sup>16, 44, 45</sup> The current study is consistent with this work; moreover, there was a highly significant association between the time to peak  $H_2$  excretion and also overall  $H_2$  excretion during the lactose and lactulose HBTs (Figure 2). Together, these findings strongly suggest that the symptoms caused by the products of bacterial fermentation following lactose or lactulose ingestion are caused by the same population of bacteria in the GI tract. These results indicate that the likelihood of symptoms was higher if bacterial fermentation began in the small bowel in the presence of SIBO than the same process in the large bowel. This is consistent with reports of impaired tolerance of small intestinal gas in irritable bowel syndrome patients compared with



**Figure 2.** There is a significant association of (a) time to peak  $H_2$  concentration and (b) overall  $H_2$  excretion (AUC) assessed during lactose and lactulose HBT. AUC, area under the concentration–time curves; HBT, hydrogen breath test; SIBO, those with a small intestinal bacterial overgrowth diagnosis; No SIBO, those without a small intestinal bacterial overgrowth diagnosis.

healthy subjects.<sup>46</sup> Additionally, overall  $H_2$  excretion was approximately 25% higher in patients with SIBO compared with those without SIBO ( $8621 \pm 4753$  vs.  $6473 \pm 3131$ ,  $P = 0.168$ ). This finding did not reach statistical significance; however, this may be a type II

error. Inter-individual variation in H<sub>2</sub> measurements is high because gas production is not limited to the small bowel ('fermentation capacity' of the large bowel is greater) and HBT fails to detect gas production that is predominantly methane rather than hydrogen.<sup>47, 48</sup> Thus, bacterial fermentation in the small bowel and, perhaps, increased 'fermentation capacity' in patients with SIBO play an important role in the generation of symptoms following lactose ingestion in patients with lactase deficiency. Moreover, as this process is not specific for lactose, it is very likely that this mechanism is responsible also for symptoms following ingestion of other poorly digested carbohydrates (e.g. lactulose, fructose, cellulose).<sup>49</sup>

There was no evidence that altered oro-caecal transit time (OCTT) mediated the effects of SIBO on lactose tolerance in patients with chronic, functional diarrhoea. This contrasts with other publications in which OCTT was more rapid in LI patients than in LM patients;<sup>16, 50</sup> however, these studies based this measurement on lactose or lactulose HBT without concurrent scintigraphy. Pimentel *et al.* have shown that this method underestimates OCTT if bacterial fermentation has already occurred in the small intestine before the substrate reaches the cecum.<sup>28</sup> Although OCTT was not relevant in this population, abnormal transit and clearance is an important cause of symptomatic SIBO in patients with anatomic disease or severe gastrointestinal dysmotility (e.g. post-surgery, scleroderma).<sup>14, 51, 52</sup> Similarly, there was little evidence that sensory function was altered in SIBO. Although the occurrence of symptoms was more common in the presence of SIBO, the individual and total symptom scores during the lactose HBT were similar in LI patients with and without this condition. Moreover, the burden of psychological pathology was similar in all patient groups. This study did not assess visceral sensitivity directly by jejunal gas infusion or rectal barostat.<sup>18, 46</sup> Such measurements would have been of interest; however, the gastrointestinal response to a 'real-life' physiological challenge (e.g. lactose) may provide more clinically relevant information than these invasive methods.

While interpreting the results, it is important to understand the strengths and limitations of the investigations applied. The diagnosis of SIBO by concurrent lactulose HBT and 99Tc scintigraphy was conservative as the initial H<sub>2</sub> rise, a consistent rise above baseline, was required in at least two consecutive values. Direct comparisons of this technique with jejunal aspiration

and culture of small bowel content, the reference standard, show excellent specificity, but low sensitivity.<sup>24, 39</sup> Conversely, the clinical relevance of SIBO diagnosed on jejunal aspiration that is not related to carbohydrate malabsorption and symptoms on lactulose HBT can be questioned. Comparing the sensitivity and specificity for SIBO diagnosis for >5 ppm and 10 ppm H<sub>2</sub> rise revealed that the relative proportion of positive and negative results was similar; however, the 5 ppm cut-off was more sensitive and appeared to have a better discriminative power (Figure 1). Concerning the measurement of OCTT, it is known that concurrent application of lactulose with the 99Tc radioactive marker accelerates transit above 'normal' levels;<sup>39, 41</sup> however, this was a standardized procedure in all patients and it is unlikely that significant differences in transit time were missed.

The prevalence and pathogenic role of SIBO in functional gastrointestinal disease are controversial.<sup>26</sup> Many studies report a high prevalence of SIBO, up to 80%, in irritable bowel syndrome with diarrhoea and related conditions;<sup>53</sup> however, an early H<sub>2</sub> rise or double peak of H<sub>2</sub> on breath testing alone for diagnosis cannot be regarded as reliable.<sup>54</sup> In the current study, the prevalence of SIBO was 41% in patients with chronic diarrhoea assessed by concurrent lactulose HBT and scintigraphy. Within this group, SIBO increased the likelihood of abdominal symptoms occurring after ingestion of a 20 g dose of lactose (equivalent to 400 mL milk) fourfold, from 15% to 64%. Analysis of the physiological measurements strongly suggests that this is as a result of fermentation of lactose within the small bowel (i.e. altered peripheral stimulus), without major effects on gastrointestinal function (OCTT) or visceral sensitivity. This is consistent with studies that demonstrated impaired transit and tolerance of gas in the jejunum, but not in colon in patients with chronic abdominal symptoms.<sup>46</sup> Moreover, the presence of other fermentation products, such as free fatty acids, in the small bowel will stimulate fluid and electrolyte excretion leading to diarrhoea. Based on the evidence presented, this is the mechanism by which SIBO increases the risk of abdominal symptoms after ingestion of lactose in vulnerable patients (i.e. those with functional gastrointestinal disease).

Despite these findings, lactose ingestion alone cannot explain patient symptoms in this population as most drank milk or ate products containing lactose powder only occasionally.<sup>55</sup> The findings could,

however, be relevant to a wider population of functional diarrhoea and IBS patients if other poorly digested, fermentable carbohydrates in the diet [fructose, fructans, oligo-, di-, monosaccharides and polyols ('FODMAPs')]<sup>49</sup> are also a substrate for SIBO causing bloating and diarrhoea.<sup>56</sup>

The cause of SIBO was not studied. None of the patients had disease detected on endoscopy, a history of gastrointestinal surgery or co-morbidity that is associated with major dysmotility and delayed transit (e.g. scleroderma, diabetes). Long-term PPI usage may increase the risk of SIBO,<sup>57</sup> but only two subjects were taking these medications and neither was SIBO positive. The increased prevalence of SIBO in functional GI disease may be as a consequence of abnormal motility and clearance, mucosal immunity, dietary factors or bowel flora, etc. but, at present, the cause remains unknown.

Although healthy controls were studied, the presence of SIBO was not determined as this would have involved exposure to ionizing radiation. It is possible that healthy controls with LI also have SIBO, but this does not change interpretation of the findings.

In conclusion, this study shows that SIBO greatly increases the likelihood of symptoms occurring after lactose ingestion in patients with functional diarrhoea because fermentation and gas production in the small bowel are more likely to cause symptoms than the same process in the colon. The presence of SIBO should be considered in patients with chronic functional diarrhoea and future research will determine whether antibiotic treatment should be directed at patients with proven disease or provided on an empirical basis.

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