

## CONCISE REPORT

# A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing

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**Background:** An association between irritable bowel syndrome (IBS) and small intestinal bacterial overgrowth (SIBO) has been found.

**Objective:** To compare the prevalence and test results for bacterial overgrowth between IBS and fibromyalgia.

**Methods:** Subjects with independent fibromyalgia and IBS were compared with controls in a double blind study. Participants completed a questionnaire, and a lactulose hydrogen breath test was used to determine the presence of SIBO. The prevalence of an abnormal breath test was compared between study participants. Hydrogen production on the breath test was compared between subjects with IBS and fibromyalgia. The somatic pain visual analogue score of subjects with fibromyalgia was compared with their degree of hydrogen production.

**Results:** 3/15 (20%) controls had an abnormal breath test compared with 93/111 (84%) subjects with IBS ( $p < 0.01$ ) and 42/42 (100%) with fibromyalgia ( $p < 0.0001$  v controls,  $p < 0.05$  v IBS). Subjects with fibromyalgia had higher hydrogen profiles ( $p < 0.01$ ), peak hydrogen ( $p < 0.0001$ ), and area under the curve ( $p < 0.01$ ) than subjects with IBS. This was not dependent on the higher prevalence of an abnormal breath test. The degree of somatic pain in fibromyalgia correlated significantly with the hydrogen level seen on the breath test ( $r = 0.42$ ,  $p < 0.01$ ).

**Conclusions:** An abnormal lactulose breath test is more common in fibromyalgia than IBS. In contrast with IBS, the degree of abnormality on breath test is greater in subjects with fibromyalgia and correlates with somatic pain.

Fibromyalgia is a condition resulting in excessive somatic hyperalgesia, but also bowel complaints.<sup>1</sup> These intestinal complaints are considered similar to those of irritable bowel syndrome (IBS). Up to 32% of patients with fibromyalgia are labelled as having IBS, and 81% report irregular bowel habits.<sup>1–3</sup>

Recently, we reported an association between IBS and abnormal findings on the lactulose breath test (LBT), which suggested bacterial overgrowth of the small intestine.<sup>4–5</sup> Small intestinal bacterial overgrowth (SIBO) is a condition whereby colonic aerobic and anaerobic bacteria expand to include the small intestine. This clinical relationship between IBS and an abnormal LBT seems to suggest a causal relationship because clinical improvement of IBS is dependent on normalisation of the LBT with antibiotics.<sup>4–5</sup> In addition, results of a recently published retrospective study suggest at least some relationship between the LBT status of patients with fibromyalgia and their bowel complaints.<sup>6</sup>

In this study we tested in a prospective study the hypothesis that an abnormal LBT is associated with both IBS and fibromyalgia. We further tested whether any differences are

seen in the LBT between these two conditions. Lastly, because research suggests a relationship between hydrogen levels on breath testing and degree of bacterial load,<sup>7</sup> we evaluated whether there is a correlation between the hydrogen level and somatic pain in subjects with fibromyalgia.

## PATIENTS AND METHODS

### Patient population

Recruitment of patients with fibromyalgia was carried out through a rheumatology practice group at Cedars-Sinai Medical Center as well as at local fibromyalgia support groups. The diagnosis of fibromyalgia was based on American College of Rheumatology criteria,<sup>8</sup> not on the presence of abdominal complaints. Recruitment of subjects with IBS and normal controls<sup>9</sup> was exclusively through newspaper and radio advertising as part of a double blind study.<sup>5</sup> Subjects were included if they met Rome I criteria for IBS.<sup>9</sup>

All subjects were excluded if they had used antibiotics within the previous 3 months, or had had a previous LBT, history of diabetes, thyroid disease, intestinal surgery (except cholecystectomy or appendectomy), connective tissue disease, narcotic use, or known gastrointestinal disease. Subjects with renal insufficiency, hearing impairment, probiotic use, and allergy to aminoglycosides were also excluded because they were recruited as part of a treatment study. Approval from the institutional review board and written informed consent from the participating subjects were obtained.

### Lactulose hydrogen breath test

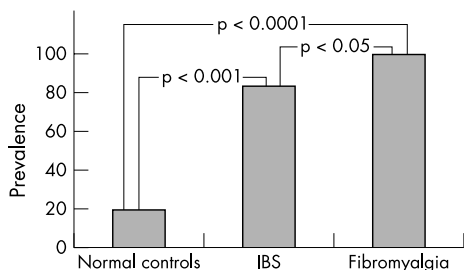
After an overnight fast, subjects ingested 10 g of lactulose syrup (Inalco Spa, Milano, Italy, packaged by Xactdose Inc, South Beloit, IL) after a baseline breath sample had been obtained. Breath sampling then continued every 15 minutes for 3 hours. All breath samples were end-expiratory and analysed immediately by a model DP Quintron gas chromatograph (Quintron Instrument Company, Milwaukee, WI). The concentration of hydrogen and methane was measured in parts per million (ppm). Measurements were determined and plotted by a technician independent of the research team.

All test results were coded and randomised. These were then interpreted by a “blinded” reader (MP). The LBT was considered normal if there was no rise in hydrogen (H<sub>2</sub>) or methane (CH<sub>4</sub>) concentration before 90 minutes of lactulose, with a definitive rise never more than 20 ppm during 180 minutes of measurement.<sup>10–11</sup> All other tests were considered abnormal.

### Outcome measures

The prevalence of an abnormal breath test was compared between subjects with IBS and those with fibromyalgia and

**Abbreviations:** IBS, irritable bowel syndrome; LBT, lactulose breath test; SIBO, small intestinal bacterial overgrowth



**Figure 1** Comparison of the prevalence of abnormal LBT in controls and subjects with IBS and fibromyalgia.

controls. Subsequently, the degree of hydrogen production was compared between IBS and fibromyalgia. A somatic pain visual analogue score (100 mm) was completed by subjects with fibromyalgia. Subjects were asked to draw a vertical line through a horizontal line indicating the current intensity of their musculoskeletal pain. This degree of pain was then compared with the degree of hydrogen production on the lactulose breath test.

**Data analysis**

Qualitative data were compared using a  $\chi^2$  test. Any differences in breath hydrogen concentration between groups were compared using a *t* test. Finally, the degree of hydrogen production and its relationship to pain was assessed by linear correlation. Significance was established at a  $p < 0.05$  and data were expressed as mean (SE).

**RESULTS**

Forty two subjects with fibromyalgia and 111 subjects with IBS were included for analysis. The mean (SE) age of the subjects with fibromyalgia was 46.6 (0.3) and of the subjects with IBS 43.2 (0.1) ( $p = NS$ ). Of the 42 subjects with fibromyalgia, 36 (86%) were female compared with 62/111 (56%) subjects with IBS ( $\chi^2 = 10.5, p < 0.05$ ).

The prevalence of an abnormal breath test between normal controls, patients with IBS, and patients with fibromyalgia was different (fig 1). All 42 subjects with fibromyalgia had an abnormal LBT compared with 93/111 (84%) subjects with IBS ( $\chi^2 = 6.2, p < 0.05$ ) and 3/15 (20%) normal controls ( $\chi^2 = 37.9, p < 0.0001$ ).

Furthermore, significantly greater hydrogen production was seen in subjects with fibromyalgia (fig 2). The mean (SE) area under the curve for subjects with fibromyalgia was 1090 (100) compared with 767 (61) for subjects with IBS ( $p < 0.01$ ), and mean (SE) peak hydrogen production in fibromyalgia was 83.1 (1.2) compared with 47.0 (0.3) for IBS

( $p < 0.00001$ ). Even when normal breath tests were excluded from the IBS group, the difference was still significant.

Of the 42 subjects with fibromyalgia, 41 had enough information for their IBS status to be determined. Of 41 subjects, 22 (54%) met Rome I criteria for IBS. There was no difference in the hydrogen peak or the area under the curve between fibromyalgia subjects with and without IBS.

Of the 42 subjects with fibromyalgia, 41 completed the visual analogue score for pain. Among these 41 subjects there was a significant correlation between the degree of pain perceived by the subject and the peak hydrogen level seen on breath testing ( $r = 0.42, p < 0.01$ ) (fig 3). Similarly, there was a correlation between the area under the curve and pain score ( $r = 0.37, p < 0.05$ ) ( $n = 38$ ).

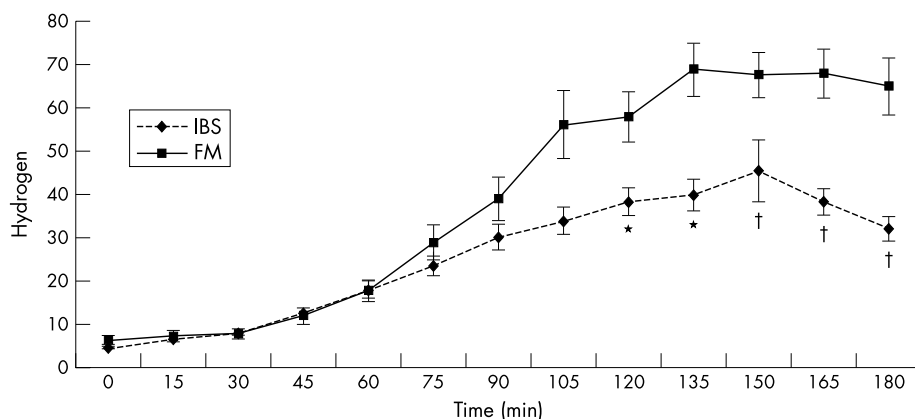
**DISCUSSION**

In this study we show that a common finding in both fibromyalgia and IBS is an abnormal LBT, suggesting the presence of bacterial overgrowth. An abnormal LBT was found in all patients with fibromyalgia in comparison with the IBS group.

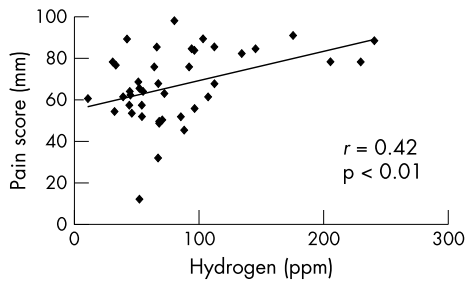
Recently, some effort has been made to understand the relationship between the hyperalgesia of fibromyalgia and that of IBS. In a paper by Chang *et al*, differences were seen in response to somatic pain such that subjects with IBS tend to have somatic hypoalgesia and higher pain thresholds than subjects with fibromyalgia.<sup>12</sup> For visceral sensation, hyperalgesia appears more prominent in IBS than in controls, with subjects with fibromyalgia somewhere in between.<sup>13</sup>

What remains to be determined is the relationship between bacteria in the gut and hyperalgesia. Studies looking at the effects of endotoxin on pain perception provide some clues. Intraventricular administration of *E coli* endotoxin to a rat produces global hyperalgesia.<sup>14</sup> By extension, endotoxin related cytokines are seen to produce rectal hyperalgesia in animal models similar to that seen in IBS.<sup>15</sup> Studies further demonstrate that in the case of SIBO, translocation of these enteric organisms does occur.<sup>16-19</sup> This translocation is not innocuous. Hepatic inflammation can be seen from this translocation, which is in part due to a tumour necrosis factor  $\alpha$  response to endotoxin from the bacterial overgrowth.<sup>20 21</sup> Therefore, translocation and/or endotoxaemia from bacterial overgrowth does occur and has the potential for systemic effects. The additional finding in our study that the degree of pain in fibromyalgia seems to correlate with the degree of hydrogen suggests a possible link between the LBT findings and hyperalgesia.

Although it is likely that endotoxin produces hyperalgesia, the common presence of bacterial overgrowth in fibromyalgia and IBS fails to explain the difference in clinical symptoms between these diseases. One possibility is a different host response. Unfortunately, this is difficult to determine and will require more research. Another possibility is that the



**Figure 2** Comparison of the mean LBT readings between subjects with fibromyalgia and those with IBS. \* $p < 0.01$ ; † $p < 0.001$ .



**Figure 3** Correlation between the hydrogen peak production on LBT and pain on visual analogue score.

types or numbers of bacteria in the small intestine resulting in the abnormal breath test in these two groups are different. To try to elucidate this possibility, we compared the hydrogen production during the breath test in subjects with fibromyalgia and in those with IBS and found a much higher level in subjects with fibromyalgia (figs 2 and 3). Therefore, one conclusion may be that the higher hydrogen level in subjects with fibromyalgia represents a larger quantity of small intestinal bacteria.

There are two concerns about the study. Firstly, the lower hydrogen production in subjects with IBS might reflect the fact that fewer subjects with IBS had an abnormal breath test, bringing the mean for IBS artificially down. However, even after excluding the normal breath tests in the IBS group, the difference was significant. Secondly, recruitment of the groups was different. For patients with IBS, it was purely through advertising. This was possible because the criteria for IBS are historical. In the case of fibromyalgia much of the recruitment was through a rheumatologist because the diagnosis required an expert examination.

In conclusion, this study suggests that an abnormal LBT may be a common link between subjects with fibromyalgia and IBS. Moreover, there appears to be a more pronounced production of hydrogen in an LBT in subjects with fibromyalgia, which appears to correlate with somatic pain perception. Further study is needed to determine if treatment and normalisation of the breath test with antibiotic treatment can produce an improvement in fibromyalgia in addition to bowel complaints.

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