Lactulose Challenge Determines Visceral Sensitivity and Severity of Symptoms in Patients With Irritable Bowel Syndrome

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BACKGROUND & AIMS: **Patients with irritable bowel syndrome (IBS) can be assigned to groups with different gastrointestinal (GI) symptoms based on results from a combined nutrient and lactulose challenge. We aimed to identify factors that predict outcomes to this challenge and to determine whether this can be used in noninvasive assessment of visceral sensitivity in patients with IBS.**

METHODS: **We performed a prospective study of 100 patients with IBS diagnosed according to Rome III criteria (all subtypes) and seen at a secondary or tertiary care center. After an overnight fast, subjects were given a liquid breakfast (400 mL; Nutridrink) that contained 25 g lactulose. Before the challenge, we assessed visceral sensitivity (via rectal barostat), oro-anal transit time, and fecal microbiota composition (via 16S ribosomal RNA pyrosequencing); we determined IBS severity using questionnaires. The intensity of 8 GI symptoms, the level of digestive comfort, and the amount of exhaled H_2 and CH_4 in breath were measured before and during a 4-hour period after the liquid breakfast.**

RESULTS: **Based on the intensity of 8 GI symptoms and level of digestive comfort during the challenge, patients were assigned to groups with high-intensity GI symptoms (HGS; n = 39) or low-intensity GI symptoms (LGS; n = 61); patients with HGS had more severe IBS ($P < .0001$), higher somatization ($P < .01$), and lower quality of life ($P < .05$–$.01$) than patients with LGS. Patients with HGS also had significantly higher rectal sensitivity to random phasic distensions ($P < .05$–$.001$, compared with patients with LGS). There were no significant differences between groups in fecal microbiota composition, exhaled gas in breath, or oro-anal transit time.**

CONCLUSIONS: **We found, in a prospective study, that results from a lactulose challenge test could be used to determine visceral sensitivity and severity of IBS. The intensity of patient symptoms did not correlate with the composition of the fecal microbiota. The lactulose challenge test may help better characterize patients with IBS and evaluate the efficacy of new treatments. ClinicalTrial.gov no: NCT01252550.**

Keywords: Functional Gastrointestinal Disorder; Visceral Hypersensitivity; Research Tool; Fermentation; Carbohydrate.

Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorder. It affects 10% to 15% of the Western population and results in decreased quality of life, impaired social function, loss of work productivity, and substantial costs to health care services.[1] The etiology of IBS remains poorly understood and the search for biomarkers is ongoing. Among the pathophysiological mechanisms associated with IBS, gastrointestinal (GI) sensory motor alterations,[2,3] signs of discrete immune dysfunction,[4,5] and increased intestinal permeability[6,7] are considered as important. The majority of these putative abnormalities can be integrated in the broader concept of alterations in gut-brain interactions.[8] The possible involvement of gut microbiota in GI symptom generation also is explored in IBS.[9,10]

Lactulose is a synthetic nonabsorbable disaccharide consisting of fructose and galactose, frequently used as an osmotic laxative.[11] Bacterial metabolism of lactulose in the colon leads to production of hydrogen (H_2) and methane (CH_4), lactic acid, and short-chain fatty acids, which in turn increase motility and shorten colonic

Abbreviations used in this paper: **GI, gastrointestinal; GSRS, Gastrointestinal Symptom Rating Scale; HGS, high-intensity gastrointestinal symptom; IBS, irritable bowel syndrome; IBS-SSS, irritable bowel syndrome severity scoring system; LGS, low-intensity gastrointestinal symptom; OATT, oro-anal transit time; PCA, principal component analysis; PHQ-15, Patient Health Questionnaire 15.**

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transit time.[12] Studies using magnetic resonance imaging have shown that osmotically active carbohydrates caused a marked increase in small-bowel water content and subsequent luminal distension in healthy and IBS subjects.[13–15] In 1 study, ingestion of 10 g lactulose was shown to provoke more symptoms, higher small-bowel water content, and larger ileal distension in IBS patients as compared with healthy volunteers.[13] In theory, impaired handling of gut contents in combination with increased perception of visceral signals (visceral hypersensitivity) may result in symptoms such as bloating and abdominal distension,[16,17] but the mechanisms involved in the generation of postprandial symptoms are complex and remain to be deciphered.

In this context, a combined nutrient and lactulose challenge test might serve as a tool to study the postprandial worsening of symptoms that occur in some IBS patients[18] and thereby noninvasively assess visceral sensitivity. We recently showed that such a challenge discriminates patients with IBS from healthy subjects and allows symptom-based clustering of IBS patients unrelated to exhaled gas in breath and Rome III subtype.[19]

The aims of the present study were as follows: (1) to confirm and further characterize the 2 IBS clusters previously identified by us when using a combined nutrient and lactulose challenge test, (2) to identify potential predictors of the challenge outcome such as microbiota composition or transit time, and (3) to evaluate the usefulness of a lactulose challenge test in the noninvasive assessment of visceral sensitivity in IBS as compared with a rectal barostat procedure.

Methods

All authors had access to the study data and reviewed and approved the final manuscript.

Study Subjects

Adult patients fulfilling the Rome III criteria for IBS were included prospectively at a secondary/tertiary care outpatient clinic (Sahlgrenska Hospital, University of Gothenburg, Gothenburg, Sweden). The diagnosis was based on a typical clinical presentation and additional investigations if considered necessary. Classification into IBS subtypes according to Rome III criteria was performed based on the Bristol Stool Form scale characteristics. Postinfectious onset of IBS symptoms was determined at the time of inclusion. All participants, aged 18 to 65 years at the inclusion visit, provided their written informed consent and were allowed to withdraw from the study at any time. Exclusion criteria included the use of probiotics or antibiotics during the study or within 1 month before the inclusion, severe psychiatric disease, other severe disease, and history of drug or alcohol abuse. All medications with known effects on the GI tract (proton pump inhibitors, laxatives, antidiarrheals, opioid analgesics, prokinetics, spasmolytics, antidepressants) were discontinued at least 48 hours before the tests (lactulose challenge test, rectal barostat, oroanal transit time measurement). The study protocol was approved by the Regional Ethical Review Board at the University of Gothenburg.

Lactulose Challenge Test

This challenge was described in detail in our previous pilot study.[19] Briefly, all participants arrived to the laboratory at 7:30 AM after an overnight fast. The combined nutrient and lactulose challenge test (400 mL Nutridrink, 1.5 kcal/mL, 16% protein, 49% carbohydrate, 35% fat, gluten free, lactose < 0.025 g/100 mL, 25 g lactulose) was served at 8:00 AM. The severity of 8 GI symptoms, the overall digestive comfort, and the amount of exhaled H_2 and CH_4 were assessed every 15 minutes starting 30 minutes before the test meal and during 4 hours after meal intake. The amount of H_2 and CH_4 was measured in parts per million in end-expiratory breath samples.

Rectal Barostat Test

Each participant came to the laboratory at 7:30 AM after an overnight fast, received a tap water enema (750 mL) for rectal emptying, and then was positioned in a left lateral decubitus position in a bed. The barostat consisted of a polyethylene balloon attached to a double-lumen polyvinyl tube (Salem Sump Tube, 18F; Sherwood Medical, Tullamore, Ireland). The distance between the balloon attachment sites was 8 cm, resulting in a spherical balloon shape at a maximal volume of 650 mL. The catheter was positioned by leaving the distal attachment site 5 cm from the anal verge. After this, the balloon catheter was connected to a computer-driven electronic barostat (Dual Drive Barostat, Distender Series II; G&J Electronics, Inc, Toronto, Ontario, Canada). Two distensions at 25 mm Hg were performed to unfold the balloon. The operating pressure was set to 2 mm Hg above the minimal distending pressure necessary to record respiratory variations in the balloon volume. An initial habituation distension sequence was performed until the discomfort threshold was reached to have reproducible results from repeated measurements and avoid novelty effects.[20,21] Rectal sensory thresholds were assessed by ramp inflation (Supplementary Material). A 10-minute rest at minimal distending pressure occurred before proceeding with 1-minute phasic distensions at 12, 24, 36, and 48 mm Hg delivered in random order and omitting distensions above the pain threshold. The participants marked 4 separate 100-mm visual analog scales ranging from unnoticeable to unbearable 30 seconds after the onset of the distension for the sensations of gas, urgency, discomfort, and pain.[21]