Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-024-08306-y

INVITED COMMENTARY

"It's Not a Gas": The Future of Testing for Lactose Intolerance

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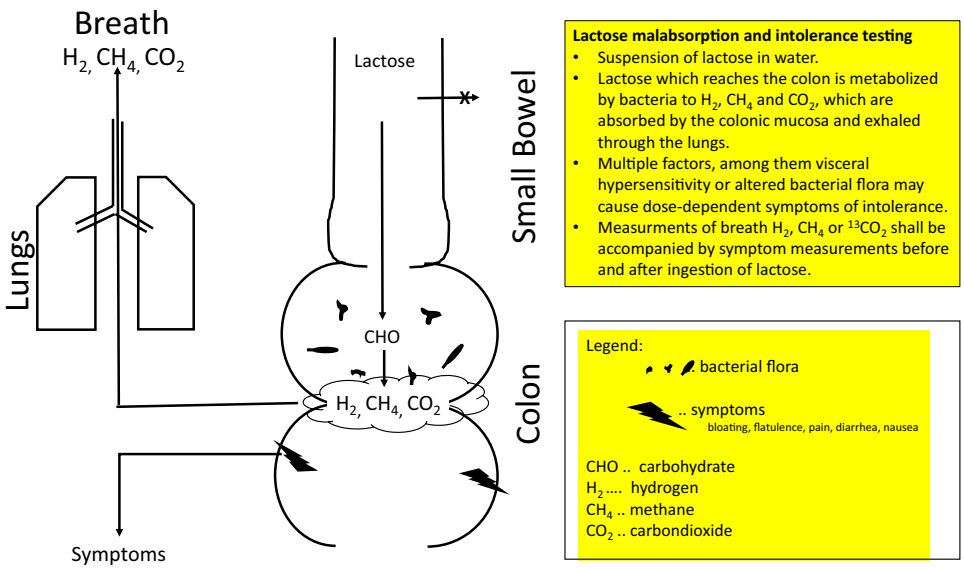
Received: 11 December 2023 / Accepted: 18 January 2024

Graphical Abstract



Bloating, flatulence, and abdominal pain in response to a carbohydrate meal may signify carbohydrate malabsorption due to deficient digestive enzymes, a condition with an estimated prevalence of 30% in Western nations[1]. Carbohydrates incompletely absorbed in the small intestine are fermented by the colonic microbiome to short-chain fatty acids and gases (CO_2, H_2, and in some cases, CH_4) [2, 3]. In addition to the osmotic effects of short-chain carbohydrates, the short-chain fatty acids influence motility and the secretion of water and sodium, leading to diarrhea [2]. Symptoms attributable to carbohydrate malabsorption may depend on many factors, including the total dose of malabsorbed carbohydrates ingested, the metabolic activity of the colonic microbiome, the structure and function of the gastrointestinal tract, and patient factors that influence intestinal perception of chemical and mechanical stimuli [4].

Breath testing is a non-invasive and safe diagnostic tool [4]. H_2 breath test results have been considered helpful in assessing common non-specific symptoms, such as bloating, flatulence, nausea, abdominal pain, and diarrhea, which may be due to carbohydrate malabsorption. The rationale for using breath H_2 excretion to detect carbohydrate malabsorption is based on three observations: first, H_2 is generated almost entirely through microbial fermentation of carbohydrates in the colon; second, this production increases rapidly when carbohydrates are metabolized by intestinal bacteria, which usually occurs in the colon; and third, increased H_2 production is easily detectable by an increase in breath H_2 concentrations. Nevertheless, methanogenic flora, dietary sulfate, or acidic colonic pH may lower colonic H_2 accumulation, with consequent false-negative tests due to a

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Published online: 18 March 2024

phenomenon termed 'H_2 non-excretion' in up to 20% of hydrogen breath tests [4]. Therefore, the measurement of CH_4 concentration should improve test accuracy, although simultaneous CH_4 measurements in children and adolescents did not significantly affect the detection rate of carbohydrate malabsorption. Therefore, a theoretical increase in test accuracy conferred by these additional measurements must be weighed against the increased costs and more complicated collection of breath samples [5].

Another approach to overcome the consequences of H_2 non-excretion is to measure breath $^{13}CO_2$ excretion after the ingestion of ^{13}C lactose. In this issue of the *Digestive Diseases and Sciences*, Balsiger et al. [6] report that in patients with primary lactase non-persistence, the combined measurement of breath $^{13}CO_2$ and H_2 excretion has a high sensitivity for the detection of lactose malabsorption. The measurement of $^{13}CO_2$ thus fills the diagnostic gap created by H_2 non-excretion. In the group of lactase non-persistent patients with a negative H_2 breath test, $^{13}CO_2$ measurement outperforms CH_4 measurements for the detection of malabsorption.

Given these encouraging results, doubt nevertheless persists regarding the clinical utility of the laboratory detection of lactose malabsorption [4, 7], notwithstanding the well-defined need to introduce diagnostic tools into routine clinical practice that determine whether gastrointestinal symptoms are due to the ingestion of lactose. We (the authors) are skeptical that the improvement in the detection of lactose malabsorption by breath testing, so nicely demonstrated by Balsiger et al., will be of much clinical benefit in improving the identification of patients who might benefit from treatment. In fact, the primary limitations to the clinical utility of breath testing include the weak correlation between malabsorption and the development of symptoms [8] and the lack of a consistent effect of diet or supplements on abdominal symptoms in patients with lactose malabsorption [7]. Furthermore, the high cost of ^{13}C-labeled test substance and equipment for $^{13}CO_2$ breath tests may limit its widespread adoption into general practice.

The recently published European guideline suggests that the identification of patients who may benefit from treatment should focus on the identification of lactose intolerance rather than on lactose malabsorption [4]. Unambiguous demonstration of the relation between carbohydrate intake and symptom onset is important to correctly attribute symptoms to the ingested carbohydrate and should be the primary indication for treatment aimed at improving non-specific abdominal symptoms. In both adult and pediatric patients, a history of clinical symptoms related to carbohydrate ingestion is associated with intolerance following carbohydrate challenge, whereas malabsorption is not a good predictor of intolerance [9]. To avoid the negative consequences of unnecessary dietary restrictions, recommendations for burdensome elimination diets, or the use of enzyme supplements, should be limited to situations in which an association between lactose intake and symptom development has been documented [4].

Historically, studies of treatments for patients with abdominal symptoms that were thought to be due to lactose malabsorption have primarily included patients with positive breath tests rather than patients with documented intolerance. Nonetheless, in most of these studies, symptoms were used as primary outcomes [7]. The discrepancy between inclusion criteria and outcome measures in these studies most likely results from the lack of distinction between "lactose malabsorption" and "lactose intolerance" and the misuse of the term "lactose intolerance" for patients with lactose malabsorption who did not have a documented close temporal relationship to symptoms. This confusion of terms may have been responsible for the lack of scientific evidence supporting the effect of several treatment options for lactose intolerance [7]. Since then, test-specific symptom questionnaires for carbohydrate intolerance have been developed [8, 10]; the European guideline recommends that symptom testing with validated questionnaires should be included alongside breath testing [4]. Validity of symptom measurement is not only important for the diagnosis of intolerance and initiation of treatment but also for assessing the response to treatment. Standardized questionnaires are important to minimize diagnostic bias, to harmonize symptom measurement, and to achieve generalizability among tests. Validated translated versions of the adult Carbohydrate Perception Questionnaire (aCPQ) and the pediatric Carbohydrate Perception Questionnaire (pCPQ) are available in several European languages [11].

Adherence to the strict definitions of the terms "lactose malabsorption" and "lactose intolerance" [4], and the use of validated symptom assessment tools to identify carbohydrate intolerance [8, 10], should facilitate more meaningful future research, which should be aimed at the identification and the treatment of specific intolerances in disorders, such as the irritable bowel syndrome (IBS), in which many of the reported trigger foods contain large amounts of simple or complex carbohydrates. Future research should address the question whether, for diseases such as IBS, identifying and treating specific carbohydrate intolerances ('precision knife approach') can improve quality of life, cost of living, long-term safety, and health outcomes compared with a broad dietary approach, such as reducing the FODMAP content of diets ('shotgun approach') [4]. Further studies are needed to demonstrate in more detail whether validated symptom assessment tools can be useful as a supplement or even a replacement for H_2, CH_4, or $^{13}CO_2$ breath testing in the diagnosis and clinical follow-up of carbohydrate intolerance [1].

Declarations

Conflict of interest The authors do not have to declare any conflicts of interest.

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