REVIEW ARTICLE

CARBOHYDRATE MALABSORPTION. INTERPRETATION OF THE BREATH TEST.

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Abstract

Carbohydrate malabsorption, especially of lactose and fructose, is a common condition in clinical practice. Accurate diagnosis is essential to avoid unnecessary dietary restrictions that could compromise bone and cardiovascular health. The breath test with hydrogen (H_2) and methane (CH_4) determination is becoming the preferred technique due to its non-invasive nature and high sensitivity. In this review, we will focus on lactose and fructose malabsorption, as these are the most frequent types.

Keywords: carbohydrate malabsorption, breath test.

Lactose Malabsorption

Lactose is a disaccharide composed of galactose and glucose, linked by a β-1,4-glucosidic bond. It is the primary sugar in mammalian milk and is widely used as an additive in the food industry (cold cuts, sauces, medications, etc.)[1]. In addition to providing energy, it facilitates calcium absorption and promotes a bifidogenic microbiota[2].

The hydrolysis of lactose depends on lactase, a disaccharidase enzyme located at the brush border of the enterocyte, encoded by the LCT gene (chromosome 2). Its activity is highest in the jejunum and is absent in the colon and stomach. After hydrolysis, glucose and galactose enter the enterocyte via the SGLT1 transporter and exit into the interstitial space via GLUT2. When more glucose is needed, GLUT2 migrates to the apex of the enterocyte and assists SGLT1 in taking up glucose.

The loss of this enzyme is called "lactase non-persistence." This decline exhibits marked epidemiological variations globally. In East Asian populations, lactase non-persistence affects over 90% of individuals, with enzyme activity declining progressively from childhood onwards. Conversely, in Europe, there is a pronounced latitudinal gradient driven by natural selection: northern and north-western European populations display high rates of lactase persistence, with malabsorption prevalence ranging between only 2% and 15%, whereas in southern Europe this figure rises progressively, reaching values between 15% and 55%.

The types of lactose malabsorption include:

1. **Primary (late-onset) hypolactasia:** This is the most common form (non-persistence). It is genetically mediated and associated with the CC or CG

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polymorphisms. Persistence is associated with the TT and CT genotypes.

2. **Secondary form:** Resulting from damage to the intestinal mucosa (acute gastroenteritis, celiac disease, small intestinal bacterial overgrowth (SIBO), inflammatory bowel disease, etc.). It is usually transien (Table 1).

Intestinal diseases	Multisystem disorders	Iatrogenic causes
SIBO/IMO	Carcinoid syndrome	Aspirin
HIV enteropathy	Cystic fibrosis	NSAIDs
Regional enteritis	Diabetic gastropathy	Antibiotics
Coeliac disease	Kwashiorkor	Alcohol
Whipple's disease	Zollinger–Ellison syndrome	Radiation-induced enteritis
Severe gastroenteritis		
Crohn's disease		

Table 1. ***Secondary causes of lactose malabsorption.***

3. **Congenital:** An extremely rare autosomal recessive disorder (cases have only been reported in Finland). It presents with severe diarrhea from birth and requires a strict diet for life.

Recent evidence[3-5] suggests that consumption of dairy products, especially fermented ones, is associated with a reduced risk of cardiovascular disease and improved bone mineral density. Furthermore, the implementation of restrictive dietary regimens adversely affects other facets, including health-related quality of life, social interactions, and psychological well-being.

Fructose and Sorbitol Malabsorption

Fructose is a monosaccharide found in fruits and processed sweeteners. Unlike lactose, its absorption is limited and occurs by diffusion, facilitated by the GLUT5 transporter. Its prevalence is estimated at around 30% in Europe.

The presence of glucose stimulates the GLUT2 transporter, which migrates to the apical membrane, facilitating fructose absorption. In contrast, sorbitol competes for GLUT5, hindering its absorption. Likewise, rapid intestinal transit impedes the absorption of this sugar.

Types of fructose malabsorption include:

1. **Congenital or Fructosemia:** Hepatic aldolase B deficiency (Hereditary Fructose Intolerance). This is a serious condition with systemic toxicity[6].

2. **Primary:** GLUT5 deficiency (SLC2A5 gene), with a genetic basis that has not yet been fully elucidated.

3. **Secondary:** The most common type. Caused by excessive fructose consumption or damage to enterocytes (celiac disease, dysbiosis, SIBO, etc.).

Diagnosis of Lactose Malabsorption

We have several diagnostic tools at our disposal; however, table 2 shows the most commonly used ones. The breath test for sugar malabsorption is currently the test of choice because it is noninvasive, reproducible, and low-cost, with a sensitivity of 78–98% and a specificity of 98%[7].

Diagnosis of Fructose/Sorbitol Malabsorption

The diagnosis of fructose and sorbitol malabsorption presents particular challenges, since, unlike lactose, these substrates have a saturable absorption capacity even in healthy individuals.

A critical issue in the medical literature is the relationship between the administered substrate dose and the positivity rate. According to the study by Rao *et al.*[8], fructose absorption is a process with limited capacity. In healthy subjects, doses of 25 g of fructose have been observed to be absorbed properly by the majority of the population, whereas doses of 50 g cause malabsorption (detected by exhaled H_2) in up to 80% of healthy subjects.

This dose-response relationship was confirmed in subsequent reviews, which found a significant correlation ($r = 0.86$, $P < 0.001$) between fructose load and the percentage of positive test results[9]. This variability engenders controversy regarding the clinical utility of carbohydrate challenge tests, as malabsorption induced by high substrate loads may merely reflect an intrinsic physiological absorption threshold rather than an underlying pathological disorder. Due to the high rate of false positives with 50-gram doses, the Rome Consensus[2] and subsequent documents have questioned the clinical relevance

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Method	Description	Remarks
Intestinal biopsy	Measurement of enzyme activity	Gold standard, but invasive; the enzyme shows an uneven distribution throughout the intestine
Oral load	Blood glucose measurement (an increase of < 20 mg/dL indicates malabsorption)	Sensitivity 76–94%. Unsuitable for patients with diabetes mellitus and requires repeated venepuncture
Gaxilose test	Hydrolysis of a lactose analogue measured in urine/blood	Poorer concordance with breath testing; risk of false-negative results
Hydrogen/methane breath test (H_2/CH_4)	Measurement of gases produced by colonic bacterial fermentation	Investigation of choice. Non-invasive and cost-effective

Table 2. ***Diagnostic tests for lactose malabsorption.***

of fructose malabsorption as an isolated entity. It is suggested that fructose malabsorption could be considered a variant of normality when it occurs at high doses. Therefore, the European Consensus[10] recommends reducing the substrate dose to 20–25 g for the diagnostic test, with the aim of identifying those patients who truly have a pathologically reduced absorption capacity.

We recommend performing a fructose test in combination with a sorbitol test (both substrates together), since in current clinical practice this is more representative of "real-life" conditions. In foods (fruits, processed foods, etc.), both substrates typically coexist. Since sorbitol competes for the GLUT5 transporter, performing the combined test increases diagnostic sensitivity by better simulating the carbohydrate load of a standard diet.

Symptoms of Carbohydrate Malabsorption

The symptoms resulting from carbohydrate malabsorption do not depend solely on the presence of the unabsorbed substrate, but rather on the interaction between the substrate and the colonic microbiota. When carbohydrates reach the colon, they are fermented by bacteria, producing short-chain fatty acids (SCFAs), lactic acid (which acidifies the luminal pH), and gases (H_2, CH_4, CO_2).

This process triggers a clinical cascade characterized by:

- Osmotic Effect: Undigested sugar draws water into the intestinal lumen, causing explosive diarrhea and borborygmi.

- Luminal Distension: Gas production leads to bloating, flatulence, and colicky abdominal pain.

It is estimated that symptoms appear when enzymatic activity (in the case of lactose) drops below 50%. However, the severity of symptoms is strongly influenced by the patient's visceral sensitivity and the speed of intestinal transit.

Indications for the Breath Test (H_2/CH_4)

The breath test is a versatile diagnostic tool that allows for the evaluation not only of absorptive capacity but also of the state of the intestinal bacterial ecosystem.

Main Clinical Indications:

1. Evaluation of Specific Intolerances: Differential diagnosis in patients with nonspecific digestive symptoms (pain, bloating, diarrhea) following the consumption of dairy products, fruits, or processed foods containing lactose, fructose, or sorbitol.

2. Evaluation of Functional Disorders: Complementary assessment in patients with Irritable Bowel Syndrome (IBS) or functional dyspepsia to identify dietary triggers[10].

History of the Breath Test

The history of the breath test for the study of gastrointestinal disorders spans more than half a century, evolving from pioneering studies to current international consensus guidelines aimed at standardizing its use.

The first scientific studies were published approximately 50 years ago. In 1970, Levitt and Donaldson laid the initial groundwork in their publication[11]. In 1975, Newcomer *et al*[12] published a prospective comparison of indirect methods for detecting lactase deficiency, solidifying clinical interest in the technique; in 1983[13], the test's application was expanded to the study of fructose malabsorption. Despite its promising beginnings, the breath test's subsequent development was uneven. For decades, the technique was hampered by inconsistent methodology, characterized by a lack of consensus regarding the doses of substrate administered, the duration of

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the tests, and the criteria for defining a result as positive or negative. Over the past fifteen years, the scientific community has made significant efforts to ensure the test's rigor and reproducibility. In 2009, the Rome Consensus[2] rrepresented the first major standardization effort in Europe, establishing basic protocols for the diagnosis of malabsorption and SIBO. In 2017, the North American Consensus[14], updated the diagnostic criteria, standardized substrate doses, and formally introduced the inclusion of methane in the measurement, in addition to establishing the 90-minute criterion for the diagnosis of SIBO. And the most recent guideline, published in 2022—the European Guideline (UEG/ESNM/ESPGHAN)[10]—, refined the methodology and emphasized the distinction between malabsorption and intolerance. Its key contribution was the recommendation to use validated symptom questionnaires (such as the aCPQ: Carbohydrate Perception Questionnaire for adults) in conjunction with gas measurements to ensure accurate clinical interpretation.

Breath Test Protocol

Proper preparation is essential to minimize false-positive and false-negative results in the diagnosis of carbohydrate malabsorption [2,10,14]. The most important guidelines to follow are detailed below:

-Fasting: A strict 12-hour fast is required before the test.

-Pre-test Diet: For the 24 hours prior to the test, the patient must follow a residue-free diet (avoiding fiber and slow-absorbing carbohydrates).

-Avoid: One month prior: The patient must not have taken antibiotics or undergone a colonoscopy. One week prior: The patient must discontinue the use of probiotics, laxatives, prokinetics, and opioids.

-Oral hygiene: The patient must rinse their teeth (with 1% chlorhexidine) prior to the baseline sample collection.

-During the procedure: Smoking, chewing gum, and physical exercise are not permitted before or during the procedure, as these factors can alter exhaled gas levels.

Performing the Test[2,10,14]

Regarding the dose of the administered substrate, the amount of sugar varies depending on the type of test and the patient:

·Lactose: 25 g.

·Fructose: 25 g.

·Fructose/Sorbitol: 25 g and 5 g, respectively.

·Pediatric population: Adjusted to 1 g per kg of body weight, with a maximum limit of 25 g.

To ensure that the analyzed air is of alveolar origin, the patient must follow three strict steps:

1. Take a deep breath.
2. Hold your breath for 15 seconds.
3. Blow into the collection device.

The recommended total duration is 3 hours, with samples collected every 30 minutes.

Breath samples were analysed using either a Quintron analyser (BreathTracker)—based on gas chromatography with solid-state detection, which quantifies H_2, CH_4, and CO_2 whilst correcting values for alveolar dilution—or a portable Gastrolyzer monitor (Bedfont), equipped with a dedicated electrochemical sensor for H_2. In parallel with the gas measurements, it is essential to record the patient's subjective experience using the aCPQ questionnaire[15], which employs a visual analog scale (0–10). The symptoms to be recorded are: abdominal pain, nausea, abdominal distension (if early-onset, dyspepsia or SIBO should be ruled out), flatulence, and diarrhea. Symptoms are assessed before the test, every 30 minutes during the test, and again 3 to 6 hours after the test ends. A positive result is considered when there is an increase of more than 2 points above the baseline value on the visual scale.

Interpretation of Results

For a correct interpretation, it is essential to simultaneously measure H_2, CH_4, CO_2, with H_2S, also gaining increasing importance, whilst accurately evaluating the time point at which any gas rise occurs, given that increments in exhaled hydrogen recorded from the 90-minute mark onwards predominantly reflect colonic bacterial fermentation, alongside assessing the presence of symptoms throughout the test (Figure 1). The interpretation must always distinguish between malabsorption and intolerance.

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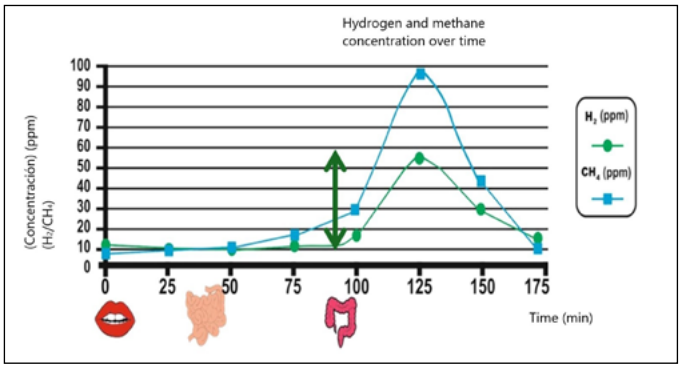


Figure 1. ***Increments in gas concentrations subsequent to the 90-minute time point (vertical arrow) are attributed to colonic bacterial fermentation. A rise of > 20 ppm for H_2 or > 10 ppm for CH_4 above baseline is considered positive, H_2: hydrogen; CH_4: methane; ppm, parts per million.***

Once we have the curve, we must first measure the baseline value. The optimal value is considered adequate when it is ≤10 ppm. An elevated baseline > 10–20 ppm may indicate poor adherence to the pre-test diet, fermentation by oropharyngeal flora, or nocturnal hypoventilation; nocturnal hypoventilation can cause slightly elevated fasting H_2 levels, produced by persistent fermentable substrates in the colon. A recent Spanish study found that light walking for one hour before the test can help reduce high levels of H_2 and CH_4 [16] allowing the test to be performed without having to repeat it. However, according to the European consensus[10], if the baseline is >10 ppm, a doubling of the initial value in three consecutive samples could be considered positive.

Subsequently, the excretion curve is analysed on the premise that any increase in hydrogen following the 90-minute time point predominantly reflects colonic bacterial fermentation; therefore, a positive test is defined as an increase of more than 20 ppm above baseline for H_2 or more than 10 ppm above baseline for CH_4 from minute 90 onwards.

Based on these results, there are four possible clinical scenarios[10]:

- Positive test result associated with symptoms: Diagnosis of intolerance.
- Positive test result with no symptoms: Carbohydrate malabsorption.
- Negative test result associated with symptoms: No malabsorption, but symptoms are the primary clinical indicator.
- Negative test result with no symptoms: Normal result.

Regarding early peaks—a rise before the 90-minute mark—this could suggest SIBO or rapid intestinal transit[17]. In a 2021 article by Piero Vierna[18], the authors analyzed whether early peaks are associated with SIBO, concluding that in most cases they are due to rapid intestinal transit. In another article published by the Laserna group[19] in 2024, they evaluated carbohydrate malabsorption curves that suggested SIBO (when an increase of ≥20 ppm in H_2 was observed relative to baseline at 90 minutes or when IMO (Intestinal Methanogen Overgrowth) (when CH4 values were ≥10 ppm at any point on the curve), and they concluded that the lactose test had high specificity for detecting SIBO and IMO, whereas the fructose test did not (false positives for SIBO: 27%, false negatives for IMO: 27%). Regarding suspected IMO in a breath test for sugar malabsorption, according to the published literature[20], CH_4 is not detected in breath until there are $>10^8$ methanogens per gram of dry stool (>1 ppm), and in Western countries, it is estimated that around 20% of the Central European population may even be classified as high-methane producers (> 5 ppm); therefore, we recommend ruling out IMO in these tests when CH_4 > 10 ppm at any point on the graph. However, according to the American consensus, SIBO should be ruled out before performing malabsorption tests to avoid false positives, and the presence of two peaks in the breath test is not diagnostic of SIBO.

Conclusions

Carbohydrate malabsorption is a common clinical condition whose significance lies in its impact on quality of life and long-term nutritional health. The H_2 and CH_4 breath test has established itself as the diagnostic tool of choice due to its safety, low cost, and ability to distinguish between malabsorption and intolerance. It is essential that the interpretation of results not be limited exclusively to exhaled gas levels but be integrated with a thorough medical history and the use of validated symptom scales. An accurate diagnosis helps avoid unnecessary dietary restrictions, ensuring that treatment is focused on those patients who will truly benefit from a reduction in substrate intake—always with a view toward maintaining nutritional balance and preventing associated risks, such as impaired bone health in the case of dairy exclusion.

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