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Hydrogen breath test as a diagnostic tool

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Abstract
Introduction and Purpose:
Hydrogen breath tests serve the crucial purpose of evaluating the absorption of nutrients in the small intestine, particularly when carbohydrates are not properly absorbed, leading to bacterial overgrowth. These tests are non-invasive, cost-effective, and widely accessible diagnostic tools used to assess various gastrointestinal disorders. The objective of this review is to evaluate the effectiveness and methodology of Hydrogen breath testing (HBT).
State of knowledge:
The disposal of hydrogen gas is essential for maintaining efficient microbial fermentation processes in the gut. Hydrogenotrophic microbes, including acetogens, methanogenic archaea, and sulfate-reducing bacteria, are responsible for this process. Hydrogen breath tests, conducted with substrates like glucose and lactulose, aid in diagnosing conditions such as small intestinal bacterial overgrowth (SIBO), lactose and fructose intolerance, and other carbohydrate absorption disorders. These tests generate a large volume of data, which can be analyzed using data mining techniques to uncover new hypotheses.
Conclusions:
Hydrogen breath tests, using various substrates, are effective in diagnosing gastrointestinal disorders such as SIBO and carbohydrate malabsorption. They offer valuable insights into microbial processes in the gut and can inform individualized treatment strategies. However, careful consideration of contraindications and proper test administration protocols is essential for accurate diagnosis and interpretation of results.

Keywords: Hydrogen breath test, Carbohydrate malabsorption, Lactose malabsorption, Fructose malabsorption, SIBO

1. Introduction and Purpose

Hydrogen is produced when dietary carbohydrates are not properly absorbed in the small intestine, leading to bacterial overgrowth. These bacteria are primarily located in the colon. The detectable amount of this hydrogen is transported through the bloodstream, then exhaled by the body, and can be identified through breath analysis [1]. Intestinal gases originate from four sources: the air we swallow and the air ingested with food, chemical reactions, microbial metabolism in the intestines, and diffusion of gases from the bloodstream [2]. The removal of gaseous H2 is crucial for maintaining efficient microbial fermentation processes.

Hydrogenotrophic microorganisms include acetogens, methanogenic archaea (MA), and sulfate-reducing bacteria (SRB).
These are present in small numbers. Hydrogen sulfide (H2S), a byproduct, is a potent genotoxin and plays a role in the pathogenesis of chronic inflammatory diseases of the colon [3].
A comprehensive breath collection apparatus was designed, allowing for formal breath tests to assess intestinal nutrient absorption. This has applications in clinical use [4]. Breath tests (BT) are conducted using a variety of substrates (e.g., glucose, lactulose, fructose, sorbitol, sucrose, and inulin) at different dosages to evaluate a range of both established and experimental indications, such as small intestinal bacterial overgrowth (SIBO), orocecal transit time, and carbohydrate malabsorption [5]. Breath tests are cost-effective, non-invasive, simple, and widely accessible diagnostic tools [6].
Due to the extensive data generated from frequent use, hydrogen breath tests are ideal for analysis with data mining techniques. One major benefit of using these techniques is the ability to generate new hypotheses that had not been previously considered [7].

2. The state of knowledge

Increased H2 production results from the fact that certain components, such as carbohydrates or proteins, are not absorbed at the mucosal level of the small intestine but instead undergo fermentation with the release of H2 or CH4. This process is carried out by bacteria colonizing the colon. Anaerobic bacteria, during metabolic processes, favor sugar molecules, which are initially metabolized into short-chain fatty acids (SCFA), CO2, and H2 during fermentation. The presence of short-chain fatty acids creates an osmotic gradient, causing increased water absorption into the intestinal lumen, consequently leading to diarrhea. Additionally, a considerable amount of CO2 becomes retained in the intestines, contributing to gas accumulation and bloating. Hydrogen is absorbed into the bloodstream through the mucosa and transported to the lungs, where its presence can be detected in exhaled air within a few minutes. Oral administration of carbohydrates (e.g., D-lactose, D-sucrose) or similar substances (e.g., xylitol) therefore results in an increase in H2 concentration in exhaled air, which can be detected [8,9].

Types of Hydrogen breath tests

In clinical practice, the following tests are most commonly used: Fructose tolerance test (used to diagnose fructose malabsorption and intolerance), lactose tolerance test (used to diagnose lactose malabsorption and intolerance), hydrogen breath test with lactulose (used to diagnose small intestinal bacterial overgrowth, SIBO), hydrogen breath test with glucose (used to diagnose small intestinal bacterial overgrowth, SIBO)

Procedure of breath test

Participants are instructed to avoid consuming slowly digested carbohydrates (such as bread and potatoes) and fiber the night before the test, as these can delay the excretion of hydrogen in breath. The breath test is conducted after an overnight fast. Additionally, participants should refrain from smoking and physical exercise two hours before and during the test, as

hyperventilation can alter hydrogen levels in exhaled air. Before the test, they need to brush their teeth and rinse their mouth with antiseptic mouthwash and tap water to prevent an early hydrogen peak caused by oral bacteria acting on the test sugars [10].
End-expiratory breath samples are collected in bags or syringes. At the beginning of the test, fasting breath hydrogen levels are measured 3-4 times, and the average is taken as the baseline hydrogen level. This is done to compare with the amount of hydrogen that will be produced later during the test. The participant then ingests a fixed amount of the test sugar (10 g lactulose, 100 g glucose, 50 g lactose, or 25 g fructose). Breath samples are subsequently analyzed for the presence of hydrogen and methane every 15 minutes over a period of 2 to 4 hours, and these values are recorded in a diary. Specialized software is also available to record breath test results. Any symptoms that arise after the ingestion of the test sugar are also documented [11]. The lactose tolerance test, which measures blood sugar levels in a fasting state and then 30 minutes after consuming lactose, is often conducted alongside the lactose hydrogen breath test (HBT) [12].
Although hydrogen breath tests are non-invasive, it is important to remember that there are sometimes contraindications for their use. Particular caution is needed in the case of suspected fructose intolerance in children. In cases of hereditary fructose intolerance (HFI), the administration of fructose is discouraged due to the potential risk of severe hypoglycemia. Care must be taken in differentiating, as the clinical symptoms of fructose intolerance syndrome and fructose malabsorption syndrome often overlap.
Absolute contraindications include: a family history indicating hereditary fructose intolerance, diagnosed or suspected hypoglycemia.
Relative contraindications include: a recent colonoscopy within the last 4 weeks, recent antibiotic therapy within the last 4 weeks, and the presence of an ileostomy (except in the diagnosis of small intestinal bacterial overgrowth) [8].

Carbohydrate malabsorption

Carbohydrate malabsorption can cause digestive problems such as abdominal pain, bloating, and diarrhea. The term carbohydrate malabsorption syndrome refers to conditions in which carbohydrates are not properly digested or absorbed in the small intestine and instead pass into the large intestine. This is a fairly common condition [13].

Lactose malabsorption

Lactose is the main sugar found in milk. When lactase activity is insufficient, lactose may not be broken down and absorbed, and it then passes into the large intestine. In the large intestine, gut bacteria break down lactose into short-chain fatty acids (SCFAs) and gases, mainly hydrogen (H2), carbon dioxide (CO2), and methane (CH4) [5]. Lactose malabsorption occurs when lactose is not efficiently digested due to decreased expression or impaired function of the enzyme lactase. After ingestion, lactose moves into the small intestine, where it encounters lactase at the intestinal brush border. There, it is broken down into the monosaccharides glucose and galactose, which can be easily absorbed [14]. Statistics suggest that primary lactase deficiency predominates affecting more than 50% of the world's population [15]. Lactose malabsorption rates are highest among Asian populations, Native

Americans, and African Americans (60–100%), while the lowest rates are found in individuals of northern European descent and the white population in the US (2–22%) [16]. Lactose malabsorption syndrome often goes unnoticed in clinical settings.
This is because several factors influence the occurrence of symptoms, including diet, orocecal transit time, and the distribution and fermentation capacity of the gut microbiota. These factors are unique to each individual [17]. Congenital lactase deficiency, also known as hypolactasia, is a very rare lifelong disorder characterized by severe infantile diarrhea and failure to thrive from the first exposure to breast milk. It is caused by an autosomal recessive disorder resulting from five specific mutations in the coding region of the lactase gene [18].

In the breath test, hydrogen levels in exhaled air are measured after consuming 25-50 g of lactose dissolved in 100-500 ml of water. Hydrogen concentration in end-expiratory air is then determined at 15-30 minute intervals for 4-5 hours [19,20]. An increase in hydrogen levels by 20 ppm above baseline after lactose ingestion is considered a positive result in the lactose hydrogen breath test. The absence of a rise in blood sugar by 20 mg/dl within 30 minutes of lactose ingestion is considered a positive lactose tolerance test result, indicating lactose malabsorption syndrome [11]. A positive result indicating lactose malabsorption typically peaks within 2-4 hours, while an early peak (within one hour) may suggest rapid small intestinal transit, small intestinal bacterial overgrowth (SIBO), or fermentation by oral flora. Gastrointestinal symptoms are also monitored during the test to assess subjective lactose intolerance, although it is important to note that the patient is aware of lactose consumption, which may affect the reliability of the information. Notably, there is often a significant discrepancy between abnormal lactose digestion and lactose intolerance symptoms [19,21]. Many individuals with lactose digestion disorders can tolerate small amounts of lactose, up to 240 ml of milk (12.1 g of lactose) per day, without symptoms or with minimal symptoms [19,20].

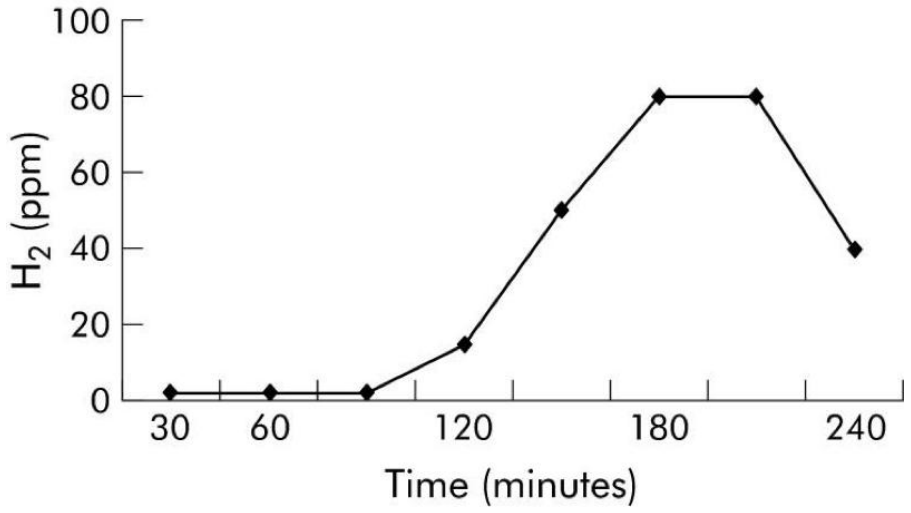

Figure 1 Schematic drawing of hydrogen breath tests (fructose with or without sorbitol and lactose) indicating carbohydrate malabsorption [22].

Fructose malabsorption

Fructose occurs as a monosaccharide, a disaccharide (sucrose) consisting of fructose and glucose, and in the forms of oligosaccharides (fructans) and polysaccharides [23]. Fructose is a ketohexose. In the form of sucrose, it is commonly used as a sweetener in various food products and confectionery, and it also occurs naturally in fruits [24].

Indications for conducting a fructose test include suspected intolerance to honey, sweets, and fruits, fructose intolerance, as well as symptoms such as bloating, excessive gas, greasy stools, and chronic or recurring diarrhea. Additionally, indications include monitoring for diseases such as celiac disease or other disorders accompanied by villous atrophy and chronic inflammatory bowel diseases [8,25].

For the assessment of fructose malabsorption, 25-50 g of fructose dissolved in 150-250 ml of water is typically administered. It is important to note that the method for symptom evaluation during the test and the reliability of this evaluation are uncertain, as there are very few blinded studies, and most studies lack control. Another important consideration is that the simultaneous intake of glucose increases the absorption of fructose [26,27]. Many dietary sources of fructose also contain glucose.

For children and adolescents, the dose of fructose is calculated as 1 g per kilogram of body weight, with a maximum dose of 25 g of fructose dissolved in 10 ml of water per gram of body weight, up to a maximum volume of 250 ml. Breath hydrogen concentration is assessed at the beginning of the test (before ingestion), and then at 15, 30, 60, 90, and 120 minutes after consuming fructose. To detect fructose-dependent small intestinal bacterial overgrowth, an additional measurement at 45 minutes is recommended [8,25]. In some patients, measurements should be extended to 180 minutes due to possible delayed intestinal transit [8]. An increase in hydrogen levels by 20 ppm above baseline after consuming fructose is considered a positive result in the fructose hydrogen breath test [28]. Under normal physiological conditions, individuals without fructose malabsorption typically do not exhibit an increase in exhaled H2 levels. However, in about 5% of cases, the test may yield a negative result—indicating no H2 production—even in the presence of clinical symptoms. In such cases, it is recommended to perform a lactulose test for these patients [8].

Hydrogen breath testing (HBT) is widely regarded as the most reliable and straightforward method for diagnosing fructose malabsorption (FM). According to a recent consensus conference in North America [29], the recommended protocol for the fructose breath test involves administering a dose of 25 g of fructose, conducting the test for at least 3 hours, and considering an increase in hydrogen concentration by 20 ppm above baseline as the threshold for a positive result. The appropriate dose of fructose for this test remains a topic of discussion. A study [27] showed that after consuming 50 g of fructose, most patients had a

positive breath test result, and about 25% experienced abdominal symptoms during the test. In contrast, at a dose of 25 g, only 11% of patients exhibited fructose malabsorption, and only one patient reported symptoms.
A double-blind study [31] conducted on 20 healthy individuals found that 80% had positive test results, and 55% experienced abdominal symptoms after a 50 g dose of fructose. Recent research has indicated that hydrogen breath tests (HBT) for fructose have no positive predictive value for a fructose-free diet. Additionally, fructose breath tests showed poor repeatability and low predictive value in 21 patients with functional bowel disorders [32].

SIBO

SIBO (Small Intestinal Bacterial Overgrowth) is a condition characterized by the presence of an excessive number of aerobic and anaerobic bacteria in the small intestine, which are typically found in the large intestine [33]. This is quantitatively defined by the presence of colony-forming units (CFU/ml) exceeding 10^5 bacteria per milliliter in the proximal small intestine. Another definition is based on observing a CFU increase exceeding 10^3 bacteria in the fasting state, provided that the type of bacteria either does not occur in saliva and gastric juice or is very similar to those found in the large intestine. SIBO is increasingly recognized as a key factor contributing to various gastrointestinal symptoms, including those corresponding to irritable bowel syndrome (IBS) [6].

The primary substrates used in breath tests for diagnosing SIBO are glucose and lactulose. Patients consume 75 g of glucose or 10 g of lactulose dissolved in 250 ml of water. Subsequently, the levels of hydrogen and methane in the exhaled breath are measured. To diagnose SIBO, an increase in hydrogen concentration of ≥20 ppm above baseline within 90 minutes is necessary. For methane, a concentration of 10 ppm at any time during the test indicates the presence of methanogens (methane-producing microorganisms). Since methanogens are archaea and not bacteria associated with SIBO, ACG experts recommend using the term 'Intestinal Methanogen Overgrowth' (IMO) instead of SIBO [35,36,6].

A laboratory study was conducted to compare the effectiveness of LBT (Lactulose Breath Test) with GBT (Glucose Breath Test) in diagnosing SIBO in patients with IBS and control subjects [37]. SIBO was detected in 60 out of 175 (34.3%) patients using LBT and in 11 out of 175 (6.2%) patients using GBT. Among the control group, LBT identified SIBO in 45 out of 150 (30%) individuals, while GBT detected it in only 1 out of 150 (0.66%). The positive rate of LBT for SIBO did not differ significantly between patients and the control group; however, using GBT, SIBO was significantly more frequent in patients compared to the control group ($p < 0.01$). When GBT is utilized as the benchmark for SIBO, among IBS patients, the sensitivity, specificity, positive predictive value, and negative predictive value of LBT were 63.6%, 67.7%, 11.7%, and 96.6%, respectively. It was concluded that GBT is a significantly better test than LBT for differentiating SIBO in patients.
Recent studies indicate a significant association between SIBO and IBS, as demonstrated in several studies using the lactulose breath test [38,39]. However, other studies employing lactulose, glucose, and xylose breath tests, as well as jejunal cultures, have not consistently

confirmed these findings [40,41]. It has been suggested that the discrepancy between the lactulose breath test and jejunal cultures, as well as other breath tests, may stem from the fact that lactulose is not absorbed in the small intestine. Therefore, it is believed that the lactulose breath test is more effective in detecting bacterial overgrowth in the ileum [38,39].

3. Summary

Hydrogen breath tests (BTs) offer a valuable means of assessing intestinal absorption, particularly in cases of carbohydrate malabsorption and small intestinal bacterial overgrowth (SIBO). These tests detect hydrogen produced from the fermentation of undigested carbohydrates by gut bacteria, with breath analysis revealing the presence of hydrogen. Various substrates such as glucose, lactulose, fructose, sorbitol, sucrose, and inulin are used in BTs to diagnose conditions like SIBO, fructose malabsorption, and lactose malabsorption.

The procedure involves collecting end-expiratory breath samples after fasting and ingesting a specified amount of test sugar. However, certain precautions are necessary to ensure test accuracy, such as avoiding certain foods and activities before the test. Contradictions exist regarding the preferred substrate for diagnosing SIBO, with glucose breath tests (GBT) often preferred over lactulose breath tests (LBT) due to their higher sensitivity and specificity.

SIBO, characterized by excessive bacterial growth in the small intestine, is increasingly recognized as a contributor to gastrointestinal symptoms, including those resembling irritable bowel syndrome (IBS). Glucose and lactulose BTs are commonly used to diagnose SIBO, with specific criteria for interpretation.

Carbohydrate malabsorption, encompassing lactose malabsorption and fructose malabsorption, presents with symptoms like abdominal pain, bloating, and diarrhea. Lactose malabsorption occurs due to inadequate lactase enzyme activity, while fructose malabsorption involves the inability to properly digest fructose. Hydrogen breath tests are essential for diagnosing these conditions, with specific protocols and interpretation criteria.

In conclusion, hydrogen breath tests are invaluable diagnostic tools for assessing carbohydrate malabsorption and SIBO, providing clinicians with valuable insights into gastrointestinal disorders and guiding appropriate treatment strategies.

Disclosures

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References:

1. Ghoshal UC. How to interpret hydrogen breath tests. J Neurogastroenterol Motil. 2011;17(3):312-7. https://doi.org/10.5056/jnm.2011.17.3.312
2. Levitt MD, Bond JH, Jr. Volume, composition, and source of intestinal gas. Gastroenterology. 1970;59(6):921-9. https://doi.org/10.1016/S0016-5085(19)33654-6
3. Nava GM, Carbonero F, Croix JA, Greenberg E, Gaskins HR. Abundance and diversity of mucosa-associated hydrogenotrophic microbes in the healthy human colon. ISME J. 2012;6(1):57-70. https://doi.org/10.1038/ismej.2011.90
4. Schwabe AD, Cozzetto FJ, Bennett LR, Mellinkoff SM. Estimation of fat absorption by monitoring of expired radioactive carbon dioxide after feeding a radioactive fat. Gastroenterology. 1962;42:285-91. https://doi.org/10.1016/S0016-5085(62)80027-4
5. Gasbarrini A, Corazza GR, Gasbarrini G, Montalto M, Di Stefano M, Basilisco G, et al. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther. 2009;29 Suppl 1:1-49. https://doi.org/10.1111/j.1365-2036.2009.03951.x
6. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. Am J Gastroenterol. 2020;115(2):165-78. https://doi.org/10.14309/ajg.0000000000000501
7. Oquendo MA, Baca-Garcia E, Artes-Rodriguez A, Perez-Cruz F, Galfalvy HC, Blasco-Fontecilla H, et al. Machine learning and data mining: strategies for hypothesis generation. Mol Psychiatry. 2012;17(10):956-9. https://doi.org/10.1038/mp.2011.173
8. Ledochowski M. Hydrogen Breath tests. Verlag Ledochowski. Innsbruck. 2008.
9. Wetzel K. H2-breath tests for medical research and clinical diagnosis. Fischer Analysen Instrumente GmbH (FAN). Leipzig. 2015.
10. Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. Indian J Gastroenterol. 2006;25(1):6-10. PMID: 16567886.
11. Gupta D, Ghoshal UC, Misra A, Misra A, Choudhuri G, Singh K. Lactose intolerance in patients with irritable bowel syndrome from northern India: a case-control study. J Gastroenterol Hepatol. 2007;22(12):2261-5. https://doi.org/10.1111/j.1440-1746.2007.04986.x
12. Babu J, Kumar S, Babu P, Prasad JH, Ghoshal UC. Frequency of lactose malabsorption among healthy southern and northern Indian populations by genetic analysis and lactose

hydrogen breath and tolerance tests. Am J Clin Nutr. 2009;91:140-6. https://doi.org/10.3945/ajcn.2009.27946
13. Hammer HF, Hammer J. Diarrhea Caused By Carbohydrate Malabsorption. Gastroenterol Clin North Am. 2012;41:611-27. https://doi.org/10.1016/j.gtc.2012.06.003
14. Brannon PM, Carpenter TO, Fernandez JR, et al. NIH consensus development conference statement: lactose intolerance and health. NIH Consens State Sci Statements. 2010;27:1-27. PMID: 20186234.
15. Kretchmer N. On the homology between human development and pediatrics. Pediatr Res. 1968;2:283-6. https://doi.org/10.1203/00006450-196807000-00007
16. Srinivasan R, Minocha A. When to suspect lactose intolerance; symptomatic, ethnic, and laboratory clues. Postgrad Med. 1998;104:109-23. https://doi.org/10.3810/pgm.1998.09.577
17. Zhao J, Fox M, Cong Y, et al. Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2010;31:892-900. https://doi.org/10.1111/j.1365-2036.2010.04252.x
18. Kuokkanen M, Kokkonen J, Enattah NS, Ylisaukko-Oja T, Komu H, Varilo T, et al. Mutations in the Translated Region of the Lactase Gene (LCT) Underlie Congenital Lactase Deficiency. Am J Hum Genet. 2006;78:339-44. https://doi.org/10.1086/500053
19. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. N Engl J Med. 1995;333:1-4. https://doi.org/10.1056/nejm199507063330101
20. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. Am J Clin Nutr. 1996;64:197-201. https://doi.org/10.1093/ajcn/64.2.197
21. Vesa TH, Seppo LM, Marteau PR, et al. Role of irritable bowel syndrome in subjective lactose intolerance. Am J Clin Nutr. 1998;67:710-5. https://doi.org/10.1093/ajcn/67.4.710
22. Simrén M, Stotzer PO. Use and abuse of hydrogen breath tests. Gut. 2006;55:297-303. https://doi.org/10.1136/gut.2005.075127
23. Putkonen L, Yao CK, Gibson PR. Fructose malabsorption syndrome. Curr Opin Clin Nutr Metab Care. 2013;16:473-7. https://doi.org/10.1097/MCO.0b013e328361c556
24. Rumessen JJ. Fructose and related food carbohydrates. Sources, intake, absorption, and clinical implications. Scand J Gastroenterol. 1992;27:819-28. https://doi.org/10.3109/00365529209000148
25. Eisenmann A, Amann A, Said M, et al. Implementation and interpretation of hydrogen breath tests. J Breath Res. 2008;2:1752-5. https://doi.org/10.1088/1752-7155/2/4/046002
26. Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent monosaccharides. Gut. 1986;27:1161-8. https://doi.org/10.1136/gut.27.10.1161
27. Truswell AS, Seach JM, Thorburn AW. Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of glucose. Am J Clin Nutr. 1988;48:1424-30. https://doi.org/10.1093/ajcn/48.6.1424
28. Ghoshal UC, Kumar S, Mehrotra M, Lakshmi C, Misra A. Frequency of small intestinal bacterial overgrowth in patients with irritable bowel syndrome and chronic non-specific diarrhea. J Neurogastroenterol Motil. 2010;16:40-6. https://doi.org/10.5056/jnm.2010.16.1.40

29. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, Schmulson M, Valdovinos M, Zakko S, Pimentel M. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. Am J Gastroenterol. 2017;112:775-84. https://doi.org/10.1038/ajg.2017.46
30. Wilder-Smith CH, Materna A, Wermelinger C, Schuler J. Fructose and lactose intolerance and malabsorption testing: The relationship with symptoms in functional gastrointestinal disorders. Aliment Pharmacol Ther. 2013;37:1074-83. https://doi.org/10.1111/apt.12306
31. Rao SS, Attaluri A, Anderson L, Stumbo P. Ability of the normal human small intestine to absorb fructose: Evaluation by breath testing. Clin Gastroenterol Hepatol. 2007;5:959-63. https://doi.org/10.1016/j.cgh.2007.04.008
32. Yao CK, Tuck CJ, Barrett JS, Canale KE, Philpott HL, Gibson PR. Poor reproducibility of breath hydrogen testing: Implications for its application in functional bowel disorders. United Eur Gastroenterol J. 2017;5:284-92. https://doi.org/10.1177/2050640616657978
33. Rezaie A, Pimentel M, Rao SS. How to test and treat small intestinal bacterial overgrowth: an evidence-based approach. Curr Gastroenterol Rep. 2016;18:8. https://doi.org/10.1007/s11894-015-0482-9
34. Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am. 2010;24:943-59. https://doi.org/10.1016/j.idc.2010.07.007
35. Daniluk J. Management of Small Intestinal Bacterial Overgrowth Syndrome. A Discussion of the 2020 American College of Gastroenterology Guidelines. Med Prakt. 2020;9:39-47. Polish.
36. Jabłkowski M, Białkowska-Warzecha J, Jabłkowska A. Small intestine bacterial overgrowth – SIBO. How to diagnose and treat it in the practice of the family physician according to new guidelines. Lekarz POZ. 2022;8(1):24-36. Polish.
37. Rana SV, Sharma S, Kaur J, Sinha SK, Singh K. Comparison of lactulose and glucose breath test for diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Digestion. 2012;85:243-7. https://doi.org/10.1159/000336174
38. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2003;98:412-9. https://doi.org/10.1016/S0002-9270(02)05902-6
39. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000;95:3503-6. https://doi.org/10.1016/S0002-9270(00)02161-4
40. Posserud I, Stotzer PO, Björnsson ES, Abrahamsson H, Simrén M. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Gut. 2007;56:802-8. https://doi.org/10.1136/gut.2006.108712
41. Walters B, Vanner SJ. Detection of bacterial overgrowth in IBS using the lactulose H breath test: comparison with C-D-xylose and healthy controls. Am J Gastroenterol. 2005;100:1566-70.
https://doi.org/10.1111/j.1572-0241.2005.40795.x