Literature Review of Breathing Test Assessment Involving GBT, LBT, and the Gold Standard

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Abstract. The gold standard for diagnosing SIBO is a small bowel aspirate and fluid culture via endoscopy. However, due to its invasiveness, breath tests are more commonly used. These tests measure hydrogen and methane levels in the breath after ingesting a substrate, either lactulose (LBT) or glucose (GBT). Increased gas levels may suggest SIBO. Recent research indicates that LBT has greater sensitivity compared to GBT, with sensitivity rates ranging from 34.3% to 85% for LBT and 6.2% to 75% for GBT. Despite higher sensitivity, LBT's accuracy is questionable as it sometimes produces positive results for both SIBO patients and controls, making it less effective in differentiating between the two groups. Conversely, GBT has higher specificity (92.3% to 100%) than LBT (70% to 100%), making it better for ruling out SIBO. Nonetheless, GBT also has a high rate of false positives, which suggests that combining it with other diagnostic methods, like scintigraphy, might improve accuracy. This article will review the literature on the performance of substrates relative to the gold standard, with the propouse of acknowledging which one is more appropriate in the diagnosis.

Keywords. SIBO, HBID, GBT, LBT, breath test.

1. Introduction

Small Intestinal Bacterial Overgrowth (SIBO) is a gastrointestinal condition characterized by the abnormal growth of bacteria in the small intestine, which are not typically found in this region (1)(2). The causes of SIBO can vary widely and include structural problems in the intestine, changes in local pH, malfunctioning of the immune system, and impaired muscular activity in the area. Additionally, SIBO may be associated with other conditions such as viral gastroenteritis, celiac disease, Crohn's disease, hypochlorhydria, gastroparesis, cirrhosis, irritable bowel syndrome, and gastric bypass surgery (3).

The main symptoms of SIBO include loss of appetite, abdominal pain, nausea, bloating, abdominal distension, gas, and diarrhea (1)(2). These manifestations are present in most gastrointestinal tract diseases, making it very difficult to identify SIBO based solely on patient history. Therefore, medical tests are crucial for diagnosing this condition (1).

Currently, the gold standard for diagnosing SIBO is the small bowel aspirate and fluid culture via endoscopy (4). However, due to its invasive nature, the more commonly used alternative is the breathing test. This test measures the amount of methane and hydrogen exhaled by the patient after ingesting a substrate, which can be lactulose (LBT) or glucose (GBT). An increase in gas levels may indicate the presence of SIBO (2).

However, the latter method is less specific and has high rates of false-positive results (5). Recent studies by S.V. RANA (14) highlights a disparity in diagnostic accuracy depending on the type of substrate used in the breathing test. In most cases, the test is unable to distinguish between the metabolism of substrates in the small intestine and the colon. Therefore, this article will review the literature regarding the performance of GBT compared to LBT and the gold standard to determine which substrate offers greater diagnostic accuracy.

Aim: This study aims to conduct a systematic review of the literature on the performance of the GBT compared to the LBT in the breath test for the diagnosis of SIBO. Additionally, it will compare these tests with the gold standard for diagnosing the condition

2. Methodology

The following keywords will be searched in the PUBMED, Google Scholar, and Web of Science databases: SIBO, HBID, GBT, LBT, breath test. Articles in Portuguese and English discussing SIBO will be included in this review.

Expected Outcome: It is expected that the breath test using the GBT substrate will have higher accuracy compared to the LBT substrate.

3. Discussion.

3.1 Hydrogen and methane measurement

The hydrogen breath test is based on the principle that bacterial metabolism (fermentation) of non-absorbable carbohydrates is the sole source of hydrogen and methane in exhaled air (6). Since humans do not utilize methane, after its absorption into the bloodstream through the intestinal mucosa, the gas must be expelled either as flatulence (80%) or through respiration (20%). Despite most people having methanogenic bacteria, only those with a critical concentration can measure methane production (7).

After the oral ingestion of certain substrates, hydrogen and methane can be measured in exhaled breath, with their concentration quantified in parts per million (ppm) (7). Based on this information, it can be concluded that an increase in hydrogen and methane gases after ingestion of specific substrates may be indicative of SIBO.

3.2 Types of substrate and how they work

Glucose (GBT)

Glucose is a monosaccharide that is normally completely absorbed in the proximal small intestine under normal conditions. However, in cases of SIBO, glucose can be fermented by bacteria before it is absorbed, leading to an increase in hydrogen production expelled in the breath. In individuals with SIBO, fermentation of glucose by bacteria in the proximal intestine can result in a significant increase in hydrogen in the breath after glucose ingestion. A notable increase in hydrogen concentration after glucose ingestion is a classic sign of SIBO (10).
According to the North American Consensus and European Guidelines, 75g of glucose diluted in 250mL of water is recommended, with samples collected every 15 minutes during the period of 120 to 240 minutes. The result is considered positive if hydrogen or methane levels are equal to or greater than 20 ppm and 10-12 ppm after 90 minutes, respectively (12)(13).

LACTULOSE (LBT)

Clinically used as an osmotic laxative, lactulose is a synthetic disaccharide, non-absorbable, composed of fructose and galactose. Lactulose passes intact through the small intestine to the cecum, where it is metabolized by colonic bacteria into short-chain fatty acids and gases, including hydrogen and/or methane, which are systemically absorbed and eventually excreted in the exhaled breath. These characteristics explain the rationale for developing the lactulose breath test (LBT) as a means to evaluate orocecal transit time (8).
The result is positive when hydrogen and methane levels are equal to those mentioned for glucose. The only difference is that only 10g of lactulose are used, diluted in 250mL of water (12)(13).

Additionally, one argument for using lactulose in the diagnosis of SIBO is that it is exposed throughout the entire small intestine, unlike glucose, which is rapidly absorbed in the more proximal part (9).

3.3 Article analysis

Article 1: Comparison of Lactulose and Glucose Breath Test for Diagnosis of Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome (14)

In the article by V. RANA (Article I), a direct comparison is made between the use of the LBT and GBT for the diagnosis of SIBO. In the study, 325 individuals were tested, including 175 patients with diarrhea-predominant irritable bowel syndrome and 150 used as controls.

As a result, LBT was positive in 60/175 (34.3%) of patients, whereas GBT was positive in 11/175 (6.2%). In the control group, LBT had a result of 45/150 (30%) and GBT 1/150 (0.66%).
In conclusion, LBT did not show a significant difference in diagnosing patients with SIBO (34.3%) compared to control cases (30%). On the other hand, GBT showed a significant difference between patients (6.2%) and controls (0.66%). Thus, LBT demonstrates a much lower specificity compared to GBT.
Additionally, despite being a much more costly method that could lead to more complications, the study would be more comprehensive if all 175 patients underwent intestinal content culture, as it is the gold standard in diagnosing SIBO. This would allow for a more precise comparison of the effectiveness of each type of substrate in the breath test.

Article 2: Comparison of the 1-gram [14C]xylose, 10-gram lactulose-H2, and 80-gram

glucose-H2 Breath Tests in Patients with Small Intestine Bacterial Overgrowth (15)

In the article by C.E. King (Article 2), the methodology differed from the first article. In this study, all patients underwent intestinal content culture, allowing for a more accurate determination of how many patients actually had SIBO. This enabled a better comparison of the effectiveness of GBT, LBT, and the gold standard.

The study was conducted with 30 individuals who complained of gastrointestinal symptoms, 20 of whom had positive bacterial cultures in the intestine. As a result, GBT was positive in 15/20 patients with SIBO and 0/10 patients without SIBO. LBT was positive in 11/20 patients with SIBO and 0/10 patients without SIBO.

Although the study included bacterial cultures to better assess the sensitivity of the substrates, its sample size is much smaller than that of the previous article, which may have affected the precision of the data, particularly regarding the specificity results for both GBT and LBT.

Article 3: Comparison of Jejunal Aspirate Culture and Methane and Hydrogen Breath Test in the Diagnosis of Small Intestinal Bacterial Overgrowth (16)

The article by S. Tang has a methodology much more similar to the second article than the first. In addition to comparing the effectiveness of the substrates with each other, the article also performs jejunal aspirate culture. Thus, the substrates can be compared with the gold standard for diagnosing SIBO, providing greater precision in the results.

The study was conducted with 40 patients who complained of gastrointestinal symptoms, 14/40 (35%) of whom had positive intestinal culture results. Regarding the substrates, LBT was positive in 18/40 (45%) of the patients, while GBT was positive in 12/40 (30%).

It is concluded that GBT has greater specificity than LBT (92.3% vs. 76.9%, respectively). However, its sensitivity is lower (71.4% vs. 85.7%). The article also concludes that for individuals suspected of having SIBO, the breath test should be the primary initial examination, as it shows good agreement with the results of jejunal aspirate culture and is less invasive.

Finally, the study presents a small sample size; ideally, a larger number of participants would be better. Additionally, the study would be more comprehensive if it had separated participants by age, smoking status, previous gastrointestinal surgeries, diabetes mellitus, etc., as this would allow for comparison of the influence of these conditions on the results. The article would also benefit from providing data on the number of false negatives and false positives, as this information is also important for considering the use of each substrate.

Article 4: Diagnosing Small Intestinal Bacterial Overgrowth: A Comparison of Lactulose Breath Tests to Small Bowel Aspirates (17)

Article IV conducts a clinical trial to compare the diagnostic accuracy of LBT alone against jejunal aspirate culture (referred to in the text as duodenal aspiration - DA). Additionally, the article addresses patient conditions that may influence the results of the LBT.

The study involved 106 patients. Of these, 21/106 had evidence of contamination during culture collection, leaving 85 patients considered for DA (106-21=85). Among these 85 valid participants, 14 (16.5%) had positive results for DA. In contrast, the LBT tests, which could not be contaminated, included all 106 patients, of whom 33 (31.4%) tested positive. Additionally, it was analyzed that patients with a diagnosis of diabetes mellitus or those using PPIs during the test had a higher tendency to have a positive DA compared to others (94.4% vs. 71.4%; 62% vs. 28.6%, respectively).

It was also reported that patients with a history of small bowel resection had a higher tendency to have a positive LBT compared to those with no such history (12.1% vs. 1.4%, respectively). In conclusion, it can be inferred that LBT has high sensitivity, showing almost twice the number of positive results compared to DA (31.4% vs. 16.5%, respectively), but consequently, it has lower specificity. Additionally, it is possible to conclude that various variables can influence the results of both DA and LBT. Therefore, exclusion and inclusion questionnaires are crucial to better control fluctuations in results.

For a better comparison of results, the article should also have excluded the 21 participants whose DA results were discarded due to contamination from the LBT test, allowing for a direct comparison of SIBO patients. This would also help identify the number of false positives and false negatives in the LBT test, which was not addressed in the text.

Article 5: Scintigraphy Demonstrates High Rate of False-Positive Results From Glucose Breath Tests for Small Bowel Bacterial Overgrowth (18)

In Article V, 139 patients suspected of SIBO were analyzed using the breath test with GBT as the substrate, combined with scintigraphy. The goal was to determine whether the increase in hydrogen and methane occurred before or after the arrival of the glucose bolus to the cecum.

As a result, 46/139 (33%) tested positive in the GBT. However, 22/46 (48%) had false-positive results due to colonic fermentation of unabsorbed

glucose.
Another point highlighted in the research was that colonic fermentation caused false positives in 65% of patients who had undergone upper gastrointestinal surgery, compared to 13% of patients without prior surgery.
It is concluded that the combined use of the breath test with scintigraphy is crucial to minimize false-positive results. Its use has an even greater impact in cases of patients with a history of upper gastrointestinal surgery, who have a high incidence of false positives.

The study would be even more comprehensive if jejunal aspirate culture were performed on all patients, allowing for a comparison of the accuracy of the combined GBT and scintigraphy test against the gold standard. In this study, it is necessary to assume that scintigraphy has 100% accuracy in results to conclude that there are false positives in the breath test. Considering that the culture is the gold standard with nearly 100% diagnostic accuracy, it would provide a clearer comparison with the substrates.

3.4 Article comparison table

Tab. 1 - Comparison table

Article	Year	Authors	sample	Results
I	2012	V. Rana	175 sample	LBT- s: 34,3%; e: 70%; pv+: 57,1%; pv-: 47,7%
			150 control	GBT- s: 6,3%; e:99,3%; pv+: 91,6%; pv-: 47,6%
II	1986	C.E. King	30	LBT- s: 55%; e: 100%; pv+: 100%; pv-: 52,6%
				GBT- s: 75%; e: 100%; pv+: 100%; pv-: 66,7%
III	2023	S. Tang	40	LBT- s: 85,7%; e:76,9%; pv+:66,6%; pv-: 90,9
				GBT- s: 71,4%; e: 92,3%; pv+: 83,3%; pv-: 85,7%
IV	2020	D.J. Cangemi	106	DA+: 14/85; LBT+: 33/106
				DM & PPI vs rest (DA+): 94,4% vs 71,4%; 62% vs 28,6%
				Cirurgy vs no cirurgy (LBT): 12,1% vs 1,4%
V	2015	E.C. LIN	139	GBT- s: 52%; e: 76,3%; pv+: 52%; pv-: 73,3%
				GBT+: 46/139; FALSE +: 22/46

*s: sensitivity;

*e: specificity

*pv+: positive predictive value

*pv-: negative predictive value

3.5 Equations

*s: a/a+c
*e: d/d+b
*pv+: a/a+b
*pv-: d/d+c

-a: real positive
-b: false positive
-c: false negative
-d: real negative

4. Conclusion

Based on the reviewed articles, it can be inferred that the LBT test exhibits greater sensitivity compared to the GBT (34.3-85% vs. 6.2-75%, respectively). However, having high sensitivity does not necessarily prove to be a beneficial attribute, as demonstrated in Article I (14), where LBT yielded positive results for SIBO patients similar to those for controls (34.3% vs. 30%, respectively). This indicates that LBT may not be an effective test for distinguishing whether a patient has the disease.

GBT demonstrated considerably higher specificity than LBT (92.3-100% vs. 70-100%, respectively). Therefore, GBT should be the primary substrate used in breath tests, especially as a screening tool for excluding the diagnosis of SIBO. However, it is important to note that GBT showed a high incidence of false positives, suggesting that the test might need to be combined with scintigraphy, which, according to Article V (18), improved the test's accuracy.

Additionally, patients with a history of gastrointestinal surgery, diabetes mellitus, use of PPIs, among other conditions, exhibited significant alterations in breath test results. Therefore, conducting a thorough patient history to identify any influencing variables is crucial to minimize the likelihood of false positives and negatives.

Finally, bacterial aspirate culture remains the gold standard for diagnosing SIBO. However, due to its invasive nature, high cost, and risk of contamination, it is not feasible for widespread use. Consequently, the breath test has proven to be the most appropriate initial examination for testing patients with suspected SIBO.

4.1 Final comments

The topic is still new and very specific, and there are few articles and studies being conducted at the moment. It is of great interest that more studies be carried out, as the tests have shown to be promising

5. References

[1]- Achufusi TG, Sharma A, Zamora EA et al. Small Intestinal Bacterial

Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus Journal of Medical Science. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7386065/. Acesso em 31 de janeiro de 2023.

[2]- Mayo Clinic. Small Intestinal Bacterial Overgrowth (SIBO).Disponível em: https://www.mayoclinic.org/diseases-conditions/small-intestinal-bacterial-overgrowth/symptoms-causes/syc 20370168. Acesso em 31 de janeiro de 2023.

[3]- Healthline Everything You Need To Know About Small Intestinal Bacterial Overgrowth (SIBO)

[4]- P.O. Stotzer, A. Brandberg, A.F. Kilander Diagnosis of small intestinal bacterial overgrowth in clinical praxis: a comparison of the culture of small bowel aspirate, duodenal biopsies and gastric aspirate

[5]- U.C. Ghoshal How to interpret hydrogen breath tests

[6]- Levitt M.D. Volume and composition of human intestinal gas determined by means of an intestinal washout technic.

[7]- N Engl J Med. 1971; 284: 1394-1398 Methane and the gastrointestinal tract. Dig Dis Sci. 2010; 55: 2135-2143

[8]- Bond Jr., J.H. - Levitt M.D. Use of pulmonary hydrogen (H2) measurements to quantitate carbohydrate absorption. Study of partially gastrectomized patients. J Clin Invest. 1972; 51: 1219-1225

[9]- Yu D.-Cheeseman F. - Vanner S. Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS.Gut. 2011; 60: 334-340

[10] -Metz G. - Gassull M.A. - Drasar B.S. et al. Breath-hydrogen test for small-intestinal bacterial colonisation. Lancet. 1976; 1: 668-669

[11] -Gasbarrini A. - Corazza G.R. - Gasbarrini G. et al. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther. 2009; 29: 1-49 https://www.sciencedirect.com/science/article/pii/S1542356513014687

[12]- 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 May;112(5):775-784. doi: 10.1038/ajg.2017.46. Epub 2017 Mar 21. PMID: 28323273; PMCID: PMC5418558.

[13]- Hammer HF, Fox MR, Keller J, Salvatore S, Basilisco G, Hammer J, Lopetuso L, Benninga M, Borrelli O, Dumitrascu D, Hauser B, Herszenyi L, Nakov R, Pohl D, Thapar N, Sonyi M; European H2-CH4-breath test group. European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and pediatric patients: European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Neurogastroenterology and Motility, and European Society for Paediatric Gastroenterology Hepatology and Nutrition consensus. United European Gastroenterol J. 2022 Feb;10(1):15-40. doi: 10.1002/ueg2.12133. Epub 2021 Aug 25. PMID: 34431620; PMCID: PMC8830282.

[14]- 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(3):243-7. doi: 10.1159/000336174. Epub 2012 Mar 30. PMID: 22472730.

[15]- King CE, Toskes PP. Comparison of the 1-gram [14C]xylose, 10-gram lactulose-H2, and 80-gram glucose-H2 breath tests in patients with small intestine bacterial overgrowth. Gastroenterology. 1986 Dec;91(6):1447-51. doi: 10.1016/0016-5085(86)90199-x. PMID: 3770368.

[16]- Tang S, Li J, Ma J, Li Y, Li Y, Wan J, Zhang R. Comparison of jejunal aspirate culture and methane and hydrogen breath test in the diagnosis of small intestinal bacterial overgrowth. Ir J Med Sci. 2024 Apr;193(2):699-703. doi: 10.1007/s11845-023-03527-y. Epub 2023 Sep 19. PMID: 37725319.

[17]- Cangemi DJ, Lacy BE, Wise J. Diagnosing Small Intestinal Bacterial Overgrowth: A Comparison of Lactulose Breath Tests to Small Bowel Aspirates. Dig

Dis Sci. 2021 Jun;66(6):2042-2050. doi: 10.1007/s10620-020-06484-z. Epub 2020 Jul 17. PMID: 32681227.

[18]- Lin EC, Massey BT. Scintigraphy Demonstrates High Rate of False-positive Results From Glucose Breath Tests for Small Bowel Bacterial Overgrowth. Clin Gastroenterol Hepatol. 2016 Feb;14(2):203-8. doi: 10.1016/j.cgh.2015.07.032. Epub 2015 Aug 1. PMID: 26241509.