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## **Glucose substrate in the hydrogen breath test for gut microbiota determination: A recommended non-invasive test**

Xie QQ *et al.* Hydrogen breath test and gut microbiota

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### **Abstract**

Intestinal dysbiosis and small intestinal bacterial overgrowth (SIBO) are common in patients with liver cirrhosis. Existing studies have not explored the association between gut dysbiosis and SIBO. A study by Maslennikov *et al*<sup>[1]</sup> explored the relationship between gut dysbiosis and SIBO in patients with liver cirrhosis. We propose some suggestions for the author's experimental methods and concepts, and we hope these suggestions can be adopted. The hydrogen breath test is worthy of recommendation due to its high accuracy and convenient operation. We suggest changing the substrate of the hydrogen breath test from lactulose to glucose to improve the accuracy of each parameter. SIBO is a small subset of gut dysbiosis, and we propose clarifying the concept of both. SIBO may be caused by liver cirrhosis or one of the pathogeneses of gastrointestinal diseases. Therefore, interference from other gastrointestinal diseases should be excluded from this study.

**Key Words:** Glucose; Hydrogen breath test; Lactulose; Liver cirrhosis; SIBO

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**Core Tip:** The sensitivity of the hydrogen breath test is higher with glucose than lactulose as the substrate. We recommend using the hydrogen breath test in this experiment for measuring intestinal flora but replacing the test substrate with glucose. We recommend that the authors clarify the relation and concept of small intestinal bacterial overgrowth (SIBO) and gut dysbiosis. When exploring the relationship between gut dysbiosis and SIBO in cirrhosis, the etiology of SIBO in patients with SIBO should be considered. After estimating the sample size, we determined that the sample size included in the experiment was small and should be expanded.

### **TO THE EDITOR**

The exact cause of intestinal dysbiosis and small intestinal bacterial overgrowth (SIBO) is unknown. However, studies have reported that SIBO is more common in patients with liver cirrhosis. Most of the existing studies focus only on the association between intestinal dysbiosis and various manifestations of liver cirrhosis, with few studying intestinal dysbiosis and/or SIBO alone. Recently, an original article by Maslennikov *et al*<sup>[1]</sup> published in the *World Journal of Gastroenterology* evaluated SIBO using a lactulose hydrogen breath test to explore the connection between gut dysbiosis and SIBO in patients with liver cirrhosis. Their findings suggest that gut flora disorder and SIBO are likely to be independent diseases of the gut microbiota in cirrhosis. We strongly agree with the author's point of view. Based on the author's research, we carried out further investigations and discussions. We put forward some suggestions for the author's experimental methods and hope they will be adopted.

At present, the gold standard for detecting SIBO is still small intestinal aspiration and quantitative culture<sup>[2,3]</sup>. However, there are obvious shortcomings, such as invasiveness to the human body and high detection costs. In addition, small intestinal aspiration and quantitative culture are prone to sampling errors. It may also result in distorted reports due to improper operation, and it has high professional and technical requirements for operators. Hydrogen breath testing is commonly used due to its higher

accuracy and ease of operation, providing a simpler non-invasive and widely available diagnostic modality for suspected SIBO<sup>[3]</sup>.

In this study, the accuracy of the hydrogen breath test could be improved if the test substrate were changed from lactulose to glucose. According to the study by Yao *et al*<sup>[4]</sup>, we estimated the sample size of SIBO patients with liver cirrhosis (power and sample size calculation), and concluded that a sample value of about 400 cases is reasonable. However, the study sample of Maslennikov *et al*<sup>[1]</sup> had only 47 cases. For this reason, we consider the sample size of this study to be small. The impact on the experimental results may be more significant in studies with a small sample base if the test accuracy is not high enough. In this study, the assessment of SIBO is the premise and basis, and the accuracy of SIBO assessment would affect the number of patients with liver cirrhosis detected with SIBO. This would affect the parameters of bacterial abundance in the two sample groups, which would further affect the researchers' judgment on the experimental conclusions and analysis. Therefore, we believe that the hydrogen breath test with glucose as the substrate would benefit this study.

Microbial dysbiosis refers to changes in the composition, density, and function of gut microbes. The gut microbiome can be characterized by relative abundance and density and by the metabolites produced by microorganisms colonizing the mucosal lining of the gastrointestinal tract. SIBO is an example of intestinal disorder, traditionally defined as the presence of an excessive or abnormal microbiome in the proximal portion of the small intestine<sup>[5]</sup>. Conceptually, SIBO is a small part of gut dysbiosis<sup>[2,6]</sup>, but the interaction and link between the two remain unclear. Whether SIBO can lead to the imbalance of microorganisms in other parts of the intestinal tract, and conversely, whether the imbalance of intestinal bacteria outside the small intestine can lead to SIBO, are worthy of further consideration and research.

Symptoms of SIBO are non-specific, including bloating, diarrhea, and gas formation, and may overlap with other gastrointestinal diseases<sup>[7-9]</sup>. SIBO has been implicated in the pathologic process of various gastrointestinal diseases, for example irritable entrails syndrome<sup>[2]</sup> and inflammatory bowel ailment<sup>[5]</sup>. When exploring the relationship

between intestinal flora is in an imbalanced state and SIBO in cirrhosis, the cause of SIBO in patients with SIBO should be considered. Since SIBO may also be caused by gastrointestinal diseases, interference from other gastrointestinal diseases should be excluded from this study. If a patient with cirrhosis also has a gastrointestinal disease associated with SIBO, for instance inflammatory intestines disease, the linkage among the three can become complicated and difficult to define. We recommend that investigators exclude confounding gastrointestinal diseases before grouping patients with cirrhosis with or without SIBO, and that patients should be grouped separately to see whether gastrointestinal disease has an effect on this study.

## **CONCLUSION**

Hydrogen breath testing has higher accuracy and operability than small bowel aspiration and quantitative culture and is, therefore, more commonly used. The sensitivity of the hydrogen breath test is higher with glucose than lactulose as the substrate. For this reason, we propose using the hydrogen breath test to measure the gut microbiota in this experiment and replace the test substrate with glucose. While SIBO is a small subset of gut dysbiosis, the interaction and relationship between the two are unclear. We recommend that the authors clarify the relationship and concept between the two. SIBO may be caused by pathogenesises of liver cirrhosis or by gastrointestinal diseases. For this reason, interference from other gastrointestinal diseases should be excluded from this study.

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