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ORIGINAL CONTRIBUTIONS

Impact of Oral-Cecal Transit Time on the Interpretation of Lactulose Breath Tests After RYGB: a Personalized Approach to the Diagnosis of SIBO

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Abstract

Background Traditionally, small intestinal bacterial overgrowth (SIBO) is diagnosed when there is an early peak in breath hydrogen or methane. Given unclear intestinal transit time in Roux-en-Y gastric bypass (RYGB) patients, it is unknown if the traditional approach at diagnosing SIBO is adequate in this patient population.
Aim To assess oral-cecal transit time (OCTT) and its impact on the interpretation of breath tests in the diagnosis of SIBO in patients with RYGB.
Methods This study was a retrospective review of prospectively collected data on RYGB patients who underwent testing for SIBO using lactulose breath test (LBT) with or without small bowel follow-through (SBFT) to assess OCTT. Outcomes of SIBO test based on LBT alone versus LBT with OCTT were compared using a chi-squared test.
Results Sixty-two of the 151 RYGB patients who underwent LBT underwent an additional SBFT to assess OCTT. Median OCTT was 60 min. Of these, 59.7% had OCTT shorter than 90 min. Based on LBT alone, 36/62 patients (58.1%) were classified as positive SIBO. When LBT results were combined with OCTT, 26/36 patients (72.2%) had hydrogen or methane rise within OCTT, suggesting 27.8% false positive rate. Patients with true positive SIBO based on LBT and OCTT had a higher response rate to antibiotics compared to those with false positive SIBO (78.3% vs. 33.3%, $p = 0.03$).
Conclusion A personalized approach of combining LBT with SBFT to assess OCTT may improve the accuracy of SIBO testing and enhance clinical outcomes in patients with RYGB.

Keywords RYGB · Bariatric · SIBO · Bacterial overgrowth · Breath test · Bloating · Abdominal pain

Background

Roux-en-Y gastric bypass (RYGB) is commonly performed for the treatment of obesity and its related metabolic comorbidities. The surgery involves creation of a small gastric pouch, division of the small bowel to create a Roux limb and pancreatobiliary limb (with jejunojejunal anastomosis), and creation of a gastrojejunal anastomosis connecting the gastric pouch and Roux limb. This results in a bypass of the remnant stomach, duodenum, and proximal jejunum. Historically, studies have suggested that the risk of developing small intestinal bacterial overgrowth (SIBO) increases after RYGB. This is thought to be due to the pancreatobiliary limb acting as a relatively blind loop, which predisposes bacterial stasis and overgrowth due to abnormal motility and ineffective clearance of secretions [1–3].

Traditionally, SIBO is diagnosed by either bacterial culture of small bowel contents or breath testing. Due to its simplicity and lack of invasiveness, breath testing has become a predominant strategy for SIBO diagnosis [4]. The test relies on the quantification of an exhaled gas produced by the bacterial metabolism of an ingested carbohydrate substance (lactulose or glucose). SIBO is diagnosed when there is an early peak, usually defined as within the first 90 min after carbohydrate ingestion, of breath hydrogen or methane due to metabolism of lactulose or glucose by small bowel bacteria.

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Previous studies have shown that RYGB is associated with more rapid intestinal transit time [5–8]. Therefore, we hypothesize that using the traditional criteria to diagnose SIBO that relies on a standard time after oral carbohydrate load may be misleading. Specifically, by 90 min, the carbohydrate substrate may have already reached the colon, where anaerobic metabolism is normal. As a result, using a 90-min cutoff for positive SIBO diagnosis may lead to overdiagnosis and low treatment response rate in this patient population.

This study aims to assess oral-cecal transit time (OCTT) and its impact on the interpretation of breath tests in diagnosing SIBO in RYGB patients.

Materials and Methods

Study Design, Study Population, and Data Collection

This study was a retrospective review of prospectively collected data on patients with RYGB who underwent testing for SIBO using lactulose breath test (LBT) from January 2010 to December 2017. Patients with RYGB who underwent testing for SIBO prior to the gastric bypass were excluded. Demographics, weight profile, time from RYGB, presenting symptoms that prompted SIBO testing, and response to antibiotics were collected. Additionally, serum folate, vitamin B12, and 25-OH vitamin D levels prior to antibiotic treatment for SIBO were recorded. The study was approved by the Institutional Review Board (IRB) (IRB Protocol Number, 2013P001597).

Diagnostic Tests

Instructions were provided to all patients as per hospital protocol. LBT was performed after an overnight fast. Patients were instructed to avoid taking antibiotics or bismuth preparations, such as Pepto-Bismol, for 2 weeks prior to the test. Additionally, laxatives, stool softeners, or stool bulking agents were discontinued for 1 week prior to LBT. Patients were recommended to avoid fermentable foods such as complex carbohydrates on the day prior to the test. On the day of the test, a baseline breath sample was collected. Subsequently, patients ingested a fixed amount of lactulose solution (10 g of lactulose mixed in 120–200 cc of water). Breath samples were then collected at times 0, 5, 10, 15, 30, 60, and 90 min after ingestion with a positive LBT defined as a rise in hydrogen level by ≥ 20 parts per million (ppm) from baseline or a methane level of ≥ 10 ppm within 90 min, as traditionally defined by the North American Consensus [9].

A subgroup of patients underwent small bowel follow-through to assess OCTT. The test was performed using an oral barium-based contrast. Multiple spot radiographs were obtained of the esophagus, stomach, and duodenum. Subsequently, a standard barium small bowel series was performed with multiple overhead radiographs, while the small bowel was examined fluoroscopically from the jejunum to the terminal ileum. OCTT was measured using time elapsed between ingestion of the barium and when it first reached the cecum. OCTT was used as a surrogate of intestinal transit time. Positive SIBO based on a combination of LBT and small bowel follow-through (SBFT) (true positive) was defined as a rise in hydrogen level by ≥ 20 ppm from baseline or a methane level of $\geq$ 10 ppm at a time less than OCTT. A rise in hydrogen level by ≥ 20 ppm from baseline or a methane level of ≥ 10 ppm within 90 min but exceeding OCTT was considered a false positive result.

Statistical Analysis

All continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as proportions (%). A Student's t test was used to compare continuous variables. A chi-squared test was used to compare categorical variables and outcomes. A significant two-sided p value was set at 0.05 or less. All statistical modeling was performed using SAS version 9.2 software (Cary, NC, USA). The study was approved by the Institutional Review Board.

Results

From 2010 to 2017, a total of 151 RYGB patients underwent LBT to assess for SIBO. Of these, 89 patients (58.9%) underwent LBT only. The remaining 62 patients (41.1%) underwent SBFT to assess OCTT in addition to LBT. Baseline characteristics are shown in Table 1. Presenting symptoms included abdominal pain (60.9%), bloating (53.6%), diarrhea (47.0%), gas/flatulence (39.1%), and constipation (23.2%).

Of the 151 patients, LBT was positive within 90 min in 69 patients (45.7%). Of these, 54 (78.3%), 58 (84.1%), and 45 (65.2%) had positive hydrogen, methane, or hydrogen and methane breath tests.

A subgroup analysis of 62 RYGB patients who underwent SBFT in addition to LBT demonstrated that the median OCTT was 60 min [range 10 to 345]. Of these, 37 (59.7%), 11 (17.7%), and 14 (22.6%) had OCTT shorter than, equal to, and longer than 90 min, respectively. Based on LBT alone, 36 out of 62 patients (58.1%) were classified as positive SIBO ($p = 0.10$ compared to the entire cohort). When LBT results were combined with the patient's specific OCTT, 26 out of the 36 patients had an increase in hydrogen level by ≥ 20 ppm or a methane level of ≥ 10 ppm, within OCTT. This suggests a true positive rate of 72.2% with a false positive rate of 27.8% if LBT were to be used alone with a traditional 90-min cutoff (Fig. 1).

Table 1 Baseline characteristics of RYGB patients who underwent lactulose breath test (LBT) to evaluate for small intestinal bacterial overgrowth (SIBO). Data presented as mean ± standard deviation

Baseline characteristics	Entire cohort $N = 151$	Subgroup (LBT + SBFT) $N = 62$	p value
Age (years)	54 ± 11	52 ± 11	0.23
Female (N (%))	138 (91)	57 (92)	0.90
Duration from RYGB (years)	8.0 ± 4.6	9.0 ± 5.2	0.17
Weight prior to RYGB (kg)	131.1 ± 27.1	128.7 ± 24.9	0.73
BMI prior to RYGB (kg/m^2)	48.1 ± 9.4	48.1 ± 9.5	1.00
Weight prior to LBT (kg)	89.2 ± 24.2	88.7 ± 23.0	0.89
BMI prior to LBT (kg/m^2)	32.6 ± 7.8	33.0 ± 8.0	0.74
Weight regain (% of maximal lost weight)	31.1 ± 24.2	32.3 ± 24.3	0.74

All 26 patients with a true positive result received antibiotic(s), while 7 out of 10 patients with a false positive result received empiric antibiotic(s) for SIBO treatment. Follow-up data were available in 29 out of the 33 patients (87.9%) who received the therapy (23/26 (88.5%) in the true positive cohort versus 6/7 (85.7%) in the false positive cohort, $p = 0.84$). Antibiotic treatment of those with true positive SIBO led to improvement in symptoms in 78.3% of patients. This antibiotic response rate was significantly higher than those with false positive SIBO (33.3%) ($p = 0.03$).

The pre-treatment vitamin B12 level in the true positive SIBO group was significantly lower than that of the false positive group (416 pg/ml vs. 659 pg/ml, $p = 0.04$). Additionally, the true positive SIBO group had a higher level of folate and a lower level of 25-OH vitamin D compared to those of the false positive group, although this difference was not statistically significant (folate, 23 ng/ml vs. 14 ng/ml, $p = 0.42$, and 25-OH vitamin D, 27 ng/ml vs. 30 ng/ml, $p = 0.44$, respectively).

Discussion

This study is the first to propose an individualized approach at diagnosing SIBO in patients with RYGB anatomy. Specifically, as shown in the study, intestinal transit time varies after gastric bypass with the majority of the patients having a more accelerated transit time. As a result, using the standard criteria for LBT alone would likely lead to an overdiagnosis of SIBO in this patient population.

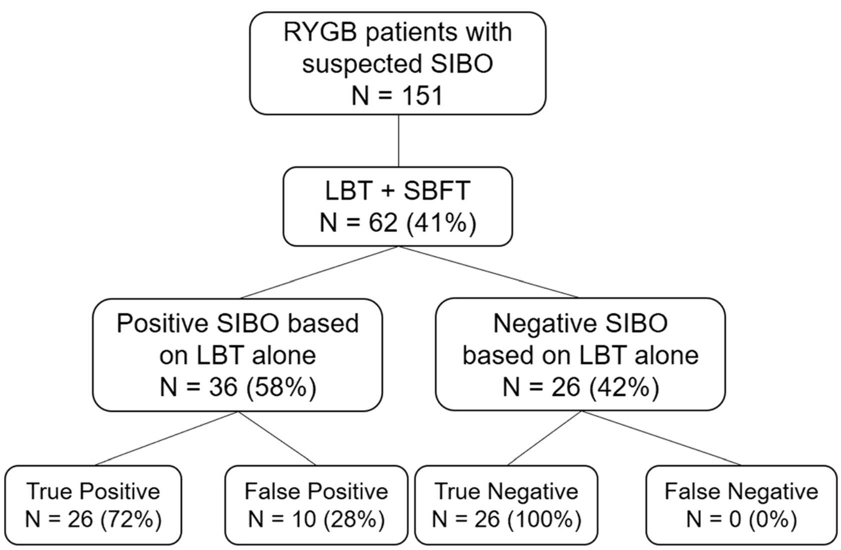

Fig. 1 Subgroup analysis of RYGB patients with suspected small intestinal bacterial overgrowth (SIBO) who underwent lactulose breath test (LBT) and small bowel follow-through (SBFT) to assess oral-cecal transit time (OCTT). True positive, an increase in hydrogen level by ≥ 20 ppm compared to baseline or a methane level of ≥ 10 ppm within OCTT. False positive, an increase in hydrogen level by ≥ 20 ppm compared to baseline or a methane level of ≥ 10 ppm within 90 min and exceeding OCTT determined by SBFT. True negative, an increase in hydrogen level by ≥ 20 ppm compared to baseline or a methane level of ≥ 10 ppm at a time greater than 90 min and OCTT. False negative, an increase in hydrogen level by ≥ 20 ppm compared to baseline or a methane level of ≥ 10 ppm at a time greater than 90 min but within OCTT

History of previous abdominal surgery has been shown to be associated with an increased risk of SIBO [2, 10]. In particular, surgeries that involve resection of the ileocecal valve or creation of a blind loop tend to predispose translocation of the bacteria into the small bowel with bacterial stasis and overgrowth. Sebate et al. recently performed a prospective study to evaluate the prevalence of SIBO using a glucose hydrogen breath test in patients with obesity prior to and after adjustable gastric banding (AGB) and RYGB. Prior to bariatric surgery, the prevalence of SIBO was 15%. This rate increased to 40% after RYGB, while it remained relatively the same in those who underwent AGB (10%) [1]. This study concluded that these results were due to the impact of a blind loop, i.e., the biliopancreatic limb which is present in RYGB and not AGB, on the increased risk of SIBO. Nevertheless, given that the breath test with a standard cutoff was used (peak hydrogen level within the first 120 min after glucose ingestion for this study), it is possible that the true prevalence of SIBO in the RYGB population may be considerably lower than the reported number.

In our study, the median OCTT was 60 min. Additionally, in approximately 60% of our RYGB cohort, their measured OCTT was shorter than 90 min, the traditional time cutoff used to define a positive breath test for SIBO. Our finding is consistent with those from previous studies that suggested a more rapid gastrointestinal transit time after RYGB. In Morínigo et al., OCTT, which was estimated by means of a LBT, was 115 min prior to RYGB, however, decreased to 75 min at 6 weeks post-RYGB [6]. While the mechanisms of how RYGB leads to an accelerated gastrointestinal transit time are unclear, it has been proposed that changes in gastrointestinal hormones, such as glucagon-like peptide-1, peptide YY, and enteroglucagon, may have played a role [6, 11].

Given the varied intestinal transit time in patients with RYGB, a personalized approach which integrates each individual's OCTT to assist with interpretation of breath test results is recommended. As demonstrated in our study, OCTT in RYGB patients ranges from 10 to 345 min. Additionally, while the majority of RYGB patients have rapid OCTT (< 90 min), 23% have slowed intestinal transit time with OCTT being longer than 90 min. As a result, it is likely not feasible to define a universal time cutoff for positive SIBO breath test in this patient population. While bacterial culture from small bowel aspirates remains a gold standard for SIBO diagnosis, this method has several technical hurdles especially in this patient population [12, 13]. First, the location where the aspirate should be performed remains unclear. One may argue that sampling fluids from the jejunojejunal anastomosis or from the biliopancreatic limb would likely lead to a higher yield. This technique would require an enteroscopy, which is associated with a low but measurable risk and an increased cost. Second, the technique of fluid aspiration remains to be standardized in order to minimize contamination. Third, many bacteria do not grow in routine culture media and quantitative culture may underestimate the bacterial population. Therefore, until these challenges are resolved, combining a non-invasive breath test with a readily available SBFT may help improve the accuracy of SIBO diagnosis while minimizing cost and risk in the RYGB patient population.

Vitamin deficiencies are not uncommon in patients with established SIBO. Specifically, SIBO has been shown to be associated with low vitamin B12 and fat-soluble vitamins (A, D, E, and K) and excessive folate levels [2]. In patients with SIBO, there is a competitive uptake of vitamin B12 by bacteria, especially aerobes, which leads to vitamin B12 deficiency, a common laboratory finding in patients with SIBO [14]. With excessive bacteria in the small bowel, bacterial deconjugation of bile salts may occur. Deconjugated bile salts are reabsorbed in the jejunum rather than in the ileum, leading to fat malabsorption and occasionally deficiencies in fat-soluble vitamins [15, 16]. While folate level can be normal, it is frequently elevated due to increased synthesis of folate by small bowel bacteria [17, 18]. In our study, patients with true positive SIBO had a significantly lower pre-treatment level of vitamin B12 when compared to those of the false positive SIBO group. This further supports an improved accuracy of combining SBFT to LBT for SIBO diagnosis in the RYGB patient population. While the true positive SIBO group appeared to have a lower vitamin D and a higher folate level than those of the false positive group, these differences were not statistically significant and may be due to the study being underpowered.

The antibiotic response rate was significantly higher in those who were diagnosed of SIBO based on a combined SBFT and LBT approach. Specifically, the treatment response rate was 78% versus 33% in those who were diagnosed with SIBO using a combined SBFT + LBT approach versus a LBT approach alone, respectively. Compared to the antibiotic response rate in the general population with SIBO diagnosis, which has been reported to be approximately 50%, the response rate in the true positive group appears to be higher [19]. This may likely be due to a more personalized method at diagnosing SIBO, which takes each individual's gastrointestinal transit time into account during the interpretation of the breath test. Interestingly, a 33% response rate in the false positive group appears to lie well within the reported placebo response rate of approximately 40% in patients with functional bowel disorders [20, 21], further supporting these findings.

The study has a few limitations. First, the study was performed at a single bariatric center of excellence. While this may affect the generalizability of our findings, the protocols for both LBT and SBFT were relatively universal, making the results likely applicable to other bariatric centers. Another limitation includes the sample size of the study. However, the study was powered enough to detect statistical and clinical difference in antibiotic response rates between the true positive and false positive SIBO groups. In addition, the follow-up rate in this study was considered high (88%) and was similar between the true positive and false positive groups (88.5% and 87.5%, respectively), which likely minimized the loss-to-follow-up bias. Currently, there is no standardized method to diagnose SIBO in patients with RYGB anatomy. While this study has attempted to define an improved method by proposing individualizing breath test interpretation based on each patient's OCTT, future prospective studies to correlate this finding with jejunal culture and standardized symptom-based questionnaire should be considered. Nevertheless, the location and the number of colony forming units per milliliter would need to be defined for patients with RYGB given the changes in their anatomy, luminal pH, and gut microbiome.

In conclusion, these findings suggest that a personalized approach to SIBO diagnosis utilizing OCTT as a more precise cutoff appears to provide more accurate diagnosis and may improve clinical outcomes. Future prospective studies to correlate this finding with other methods of SIBO diagnosis should be considered in this patient population. Additionally, it may be worth investigating simultaneous breath test with SBFT timing procedure termination with entry of contrast into the cecum. Furthermore, it may be worth exploring the impact of OCTT on SIBO diagnosis in the general population.

Author Contributions Pichamol Jirapinyo: Study design, data collection and analysis, drafting and revision of the manuscript

Tracy T. Makuvire: Data collection

William Y. Dong: Data collection

Walter W. Chan: Study design, study analysis

Christopher C. Thompson: Study design, critical revision of the manuscript

Compliance with Ethical Standards

The study was approved by the Institutional Review Board (IRB) (IRB Protocol Number, 2013P001597).

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approvement Statement For this type of study, formal consent is not required.

Informed Consent Statement Does not apply.

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