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ORIGINAL CONTRIBUTIONS

Lactulose Breath Testing Can Be a Positive Predictor Before Weight Gain in Participants with Obesity Submitted to Roux-en-Y Gastric Bypass

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Abstract

Background Small intestinal bacterial overgrowth (SIBO) is defined as the colonization of fermentative bacteria in the duodenum and jejunum. The alteration of digestive anatomy promoted by bariatric surgery may be a pre-disposing factor for SIBO. In this context, the prevalence of SIBO in participants undergoing bariatric surgery using Roux-en-Y gastric bypass (BGYR) was evaluated.

Methods Participants, both sexes, older than 18 years, were those who (a) had bariatric surgery by the BGYR technique at least 1 year before the data collection and (b) did not use antibiotics recently. The SIBO diagnosis was established through the hydrogen breath test (H_2BT), with intake of lactulose and serial collection of breath samples over 2 h. A test with ≥ 12-point elevation over the basal sample at 60 min after substrate intake was deemed positive.

Results A total of 18 participants (14 females (77.8%)) were enrolled with a mean age of 50.5 years (range, 23 to 79 years). The interval between surgery and data collection ranged from 5 to 20 years (mean, 11.2 years). The mean preoperative body mass index (BMI) was 44.6 kg/m^2 (range, 36.7–56.2 kg/m^2). The H_2RT with lactulose was positive for SIBO in seven (six female) participants. The participants with negative test measured trough H_2BT with lactulose had a lower mean BMI of 28.69 kg/m^2, in comparison with the positive group, which presented a mean BMI of 33.04 kg/m^2 (p value = 0.041).

Conclusion Our data point to a high prevalence of SIBO (38.8%) in patients undergoing BGYR with a value in accordance with the literature. Moreover, the differences in BMI between negative and positive groups by H_2BT with lactulose evidenced a weight gain relapse in participants with SIBO.

Keywords Bacterial overgrowth · Bariatric surgery · Breath test · Lactulose · Obesity · Small intestine

Introduction

Obesity is a public health problem in industrialized and developing countries [1]. Among the various treatments proposed, the bariatric surgery is indicated in cases of severe obesity that did not satisfactorily respond to hygienic/dietary measures, medicinal, or other conservative methods [2]. Roux-en-Y gastric bypass (RYGB) is presently the most used surgery in

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reference centers to treat the obesity [2]. The surgical procedure creates a small pouch derived from the stomach, bypassing the main portion of the stomach and most of the duodenum; the pouch is connected to the distal jejunum forming a "Y" with the bypassed stomach and proximal duodenal components of the digestive tract.

The literature demonstrated the importance of the digestive tract microbiota for the maintenance of the digestive weighted equilibrium [3–11]. Morbidly patients with obesity exhibit a greater prevalence of small intestinal bacterial overgrowth (SIBO), when compared with the general population [12, 13]; and this fact should have clinical implications (i.e., proper absorption of nutrients, genesis of digestive symptoms, and recurrence of weight gain) [14, 15]. Research on bacterial overgrowth can be performed through the expired hydrogen breath test (H_2BT) [16, 17], a low cost examination, with a simple application procedure and usable in daily clinic [18–20]. The most commonly used substrates in H_2BT are glucose and lactulose [17, 21–24]. Lactulose is a sugar that is not absorbed by the digestive tract; thus, it is exclusively fermented by microbiota bacteria [23, 25, 26]. In contrast, glucose is absorbed and undergoes other metabolic processes, which could interfere with the interpretation of the results [27]. There are contradictions about the advantages and disadvantages of the both substrates [23, 28]; however, lactulose has now been agreed upon as a consensus substrate for the diagnosis of the SIBO [24].

In this context, the aim of the study was to evaluate the prevalence of SIBO in participants subjected to bariatric surgery with the Roux-en-Y gastric bypass after at least 1 year of surgical procedure, through the expired H_2BT using lactulose.

Methods

A pilot study with intervention by bariatric surgery with Roux-en-Y gastric bypass in participants with obesity with a follow-up period was done and the prevalence of SIBO was measured in use of expired H_2BT using lactulose**.**

Participants and Body Mass Index

Participants of both sexes, older than 18 years, were enrolled. All participants were subjected to bariatric surgery with the Roux-en-Y gastric bypass more than a year before the data collection and had not used antibiotics for at least 6 months when submitted to the H_2BT. The body mass index (BMI) was measured through the formula: body weight (kg)/height (m^2).

From the registry of the participant, the preoperative BMI (BMI-1) and the minimal post-surgical BMI (BMI-2) were retrieved. Also, the measurement of the current BMI (BMI-3) was done.

The project was approved by the research ethics committee from the institution. Informed consent was obtained from each participant.

Hydrogen Breath Test in Use of Lactulose

The diagnosis of SIBO was carried out through the expired H_2BT using lactulose as the substrate. Participants were instructed to ingest a low-fermentation diet on the eve of the exam; followed by 12 h of fasting and 4 h abstaining from smoking or physical activity. At the start of the test, a basal sample of expired air was collected by means of an H_2BT device (EasyH_2–Dynamed®, São Paulo, Brazil). The results were expressed as parts per million (ppm).

At the first measure, the subjects presented a basal level of expired $H_2BT < 10$ ppm. After, the participants ingested 10 g of lactulose diluted in 100 mL of water. Six expired air samples were collected every 20 min, totaling 120 min. An elevation of more than 12 ppm relative to the basal sample, at any time within to the first 60 min of collection was deemed to be a positive result, indicating bacterial overgrowth.

Statistical Analyses

A descriptive analysis was performed using two approaches: (i) categorical—N (%), sample size (percentage); and (ii) numerical—mean (standard deviation) or median (interquartile range), according to parametric or nonparametric data distribution, respectively. Normal distribution of numerical data was evaluated by the following techniques: (i) analysis of descriptive measures for central tendency; (ii) graphic method (normal Q-Q plot, Q-Q plot with no trend, and boxplot; and (iii) the statistical test method (normality tests): the Kolmorov-Smirnov and Shapiro-Wilk tests.

The comparison between groups Fisher exact test and Mann-Whitney test is according to normality and sample size. Alpha level of 0.05 (p value used as cutoff significance level, type I error) was considered and no technique was used to establish missing data values. Statistical analysis was performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Results

In our casuistic, a total of eighteen Caucasian participants (14 females, representing 77.8%) were enrolled. The H_2BT proved positive for SIBO in seven (six females) participants (38.8%).

Table 1 displays the analysis of the tested quantitative variables (current age, surgery time, preoperative BMI, lower BMI obtained after surgery, and current BMI, respectively

Table 1 Age and body mass index (BMI) in participants with obesity subjected to bariatric surgery with the Roux-en-Y gastric bypass, distributed in the groups considered negative and positive for SIBO

Variable	Negative ($N = 11$)	Positive ($N = 7$)	p value
Present age (years)	49 ± 15.79; 46 ± 8.8 (23 to 79)	56.86 ± 8.67; 59 ± 6.5 (44 to 67)	0.14711
Years after surgery	11.82 ± 5.12; 12 ± 4.5 (5 to 20)	7 to 16; 7 ± 3.5 (10.29 ± 4.19)	0.68142
BMI-1 (kg/m^2)	44.75 ± 6.01; 42.7 ± 3.3 (36.7 to 56.2)	43.17 ± 3.08; 43 ± 1.8 (37.9 to 46.7)	0.96386
BMI-2 (kg/m^2)	25.81 ± 3.52; 28.7 ± 2 (20.8 to 32.4)	25.61 ± 7.1; 31.6 ± 2.4 (19.4 to 39.8)	0.44141
BMI-3 (kg/m^2)	28.69 ± 3.3; 26.3 ± 2 (23.9 to 35.1)	33.04 ± 5.18; 23.9 ± 3.2 (25.3 to 40.1)	**0.04157**

p values for the Mann-Whitney test; significant difference is highlighted in bold. *SIBO*, small intestinal bacterial overgrowth; *N*, number of participants. From the registry of the participant the preoperative BMI (BMI-1) and the minimal post-surgical BMI (BMI-2) were we retrieved. Also, the measurement of the current BMI (BMI-3) was done. The data is shown as mean ± standard deviation; median ± interquartile interval (range)

namely as BMI-1, BMI-2, and BMI-3) in relation to the results achieved in the H_2BT. Moreover, Table 2 displays the individual data of the age, BMI-1, BMI-2, and BMI-3 in relation to the results achieved in the H_2BT. The average age of the patients was 50.5 years (range, 23–79 years), while the time from surgery to H_2BT ranged from 5 to 20 years (average 11.2 years); positive versus negative H_2BT results showed no difference for the latter parameter. The general average of the pre-operative BMI was 44.6 kg/m^2 (range, 36.7–56.2 kg/m^2). In both negative and positive groups, the BMI decreased during the postoperative period, reaching a minimum BMI level of 25 kg/m^2 in both groups. No difference occurred in the statistical tests between the two groups for BMI-1 (p value = 0.96) and BMI-2 (p value = 0.44). However, a significant statistical difference ($p = 0.041$) for BMI-3 occurred between the negative versus positive values for H_2BT as marker of SIBO: range, 23.9–35.1 kg/m^2 and 25.3–40.1 kg/m^2; average, 28.69 ± 3.3 kg/m^2 and 33.04 ± 5.18 kg/m^2, respectively. The average weight loss versus preoperative levels was 30.6% (for negative H_2BT) and 33% (for positive H_2BT). Figure 1 presents BMI profiles for the 18 participants. In the negative H_2BT, one participant presented a BMI-3 of 35 kg/m^2 (obesity grade 1); all others were below 30 kg/m^2. In the positive H_2BT, one patient participant presented a BMI of 25 kg/m^2 (overweight), four participants between 30 and 32 kg/m^2 (obesity grade 1), and two participants between 39 and 40 kg/m^2 (obesity grade 2).

The expired H_2 curves of the negative and positive groups are shown in Fig. 2. No participant with a negative H_2BT showed side effects during the test. But, ~ 50% of the participants with a positive H_2BT presented cramps (three cases), diarrhea (two cases), and headache (two cases).

Discussion

Human microbiota is composed of a mosaic of microorganisms that varies between individuals, which can confer personalized microbiological identity [29–31]. The quantitative and qualitative imbalance between these colonies seems to be the key to the origin of various pathologies [6, 10, 14, 15, 32–42]. Under physiological conditions, the number of intestinal bacterial colonies increases according to the proximity of the ileocecal valve [43]. However, increases of colonies in proximal portions can occur in asymptomatic patients, as observed in studies that used the H_2BT in control subjects, whose clinical significance lacks specific studies [17, 18, 21, 24, 29, 44–46]. In individual health controls, the revision of

Table 2 Individual age and body mass index (BMI) in participants with obesity subjected to bariatric surgery with the Roux-en-Y gastric bypass, distributed in the groups considered negative and positive for SIBO

Sex	Age (years)	BMI-1 (kg/m^2)	BMI-2 (kg/m^2)	BMI-3 (kg/m^2)
Participants negative for SIBO				
Female	79	36.7	26.8	27.2
Female	59	56.2	30.5	31.6
Female	23	40	22.9	25.7
Male	46	42.7	26.3	29.9
Male	48	53.5	32.4	35.1
Female	41	40.8	20.7	23.9
Male	39	46.4	22.2	30
Female	56	40.7	23.7	28.1
Female	69	46.5	26.5	28.7
Female	42	48.1	27.6	30.8
Female	37	40.7	24.3	24.6
Participants positive for SIBO				
Male	62	46.7	39.8	40.1
Female	67	37.9	20.1	25.2
Female	49	43	23.4	30.8
Female	44	46.7	25.2	39.4
Female	65	41.7	29.2	31.6
Female	52	44	21.6	31.6
Female	59	41.9	19.3	32.2

SIBO, small intestinal bacterial overgrowth. From the registry of the participant, the preoperative BMI (BMI-1) and the minimal post-surgical BMI (BMI-2) were retrieved. Also, the measurement of the current BMI (BMI-3) was done

Uday et al. found average positivity of 21% for H_2BT [46]; similar data were described in other studies (Table 3).

Prevalence and follow-up studies in use of better protocols and methodology are needed to evaluate the standards of normalcy, taking into account ethnic, constitutional, and cultural traits, as well as feeding habits [46, 49–51, 59–62].

A large retrospective cohort conducted at Germany evaluated 1809 subjects with a diagnosis of SIBO through H_2BT, regardless of whether the substrate used was glucose or lactulose [59]. The objective was to determine which of the most significant factors would be related to SIBO and was concluded that the following order of importance prevails: gastric resections, immunosuppressant medications, factors that alter intestinal motility (gastroparesis, intestinal surgeries, and intestinal pseudo-obstruction syndrome), the use of levothyroxine in the supplementation of hypothyroidism and sigmoid diverticulosis.

Other H_2BT tests using different substrates (lactose, fructose, xylose) may also suggest the presence of SIBO, whenever an elevation occurs in H_2 levels in the early phase of sample collection [63]. However, glucose and lactulose are the most common substrates in use [28]; in fact, it has recently been recommended by the American Consensus that lactulose should be the first choice for research in SIBO [24].

In relation to SIBO and obesity, Table 3 presents the results in participants with obesity who have demonstrated a high prevalence (38.8%) of H_2BT positive for SIBO being in accordance with the literature when compared with their respective healthy control groups.

The mechanism by which SIBO could be involved in the pathophysiology of obesity is not well established, but it is inferred that competition for nutrients, changes in the permeability of the mucous barrier and activation or inhibition of immunological cascades maybe significant [4, 6, 7, 13, 52, 64, 65].

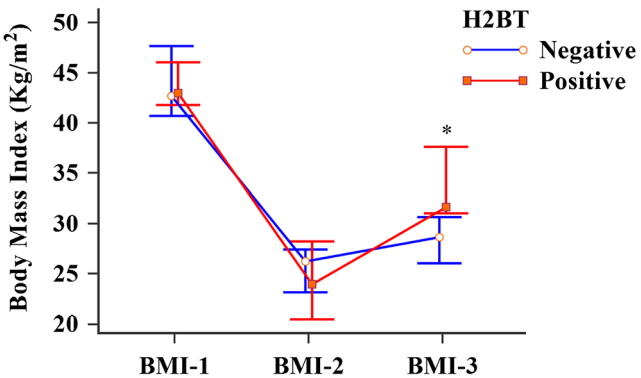

Fig. 1 Body mass index of participants with obesity subjected to the Roux-en-Y gastric bypass bariatric surgery, separated into negative and positive groups for H_2BT. From the registry of the participant the preoperative BMI (BMI-1) and the minimal post-surgical BMI (BMI-2) were retrieved. Also, the measurement of the current BMI (BMI-3) was done. *, *p* value with a significant value

Table 3 presents four studies concerning participants with obesity subjected to bariatric surgery with the Roux-en-Y gastric bypass. Three of them used glucose and one lactulose as substrate, but all provided evidence the presence of a high level of SIBO prevalence in participants that operated.

Some factors may limit the interpretation of H_2BT results in participants with obesity due to changes in intestinal motility [66]. Such digestive motility disorders have also been described in bariatric surgery [4, 8, 67]. The possibility of false positive results could be due to substrate hyperosmolarity associated with the changes of anatomy promoted by the surgery; an early contact of the substrate with the usual colon bacteria might be responsible for the early rise of the H_2 curve [3, 5, 24, 68]. However, the previous hypothesis is rebutted by some studies, which report a slow orocecal transit time in participants with obesity in relation to the healthy control group [11, 12, 29, 69]. Accelerated gastric depletion has been reported in participants that operated; however, the small intestine transit is retarded in participants subjected to the Roux-en-Y gastric bypass [66, 70]. In our group of bariatric subjects with a negative H_2BT for SIBO, there was no elevation of the H_2 levels up to the 120-min collection sample, suggesting a slow orocecal transit, which agrees with reported findings. Despite this, we decided to set the time of elevation of $H_2 \leq$ 60 min after ingestion of the substrate, to minimize the possibility of interpretation of false positive results. Another variable that can interfere with the interpretation of the results is the enzymatic and metabolic disorders observed in participants with obesity [14, 64]. In this scenario, the glucose would be a less suitable substrate than lactulose for the evaluation of this group of subjects [24, 39].

Ishida et al. [5] also used H_2BT with lactulose and described results similar to ours. However, they set an 80-min limit for a positive SIBO diagnosis, with average evaluation time of 7 years, after bariatric surgery. By the way, our study is the highest average time of post-operative evaluation (11.2 years).

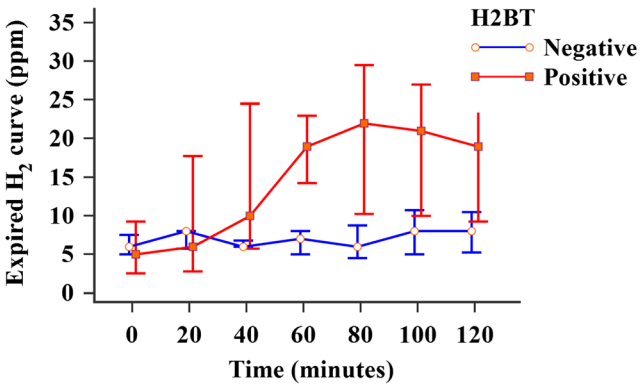

Fig. 2 Distribution curve of expired H_2 values before and after lactulose ingestion, for negative (blue) and positive (red) for SIBO

Table 3 Prevalence of SIBO among health controls subjected to H_2BT and in participants with obesity subjected to H_2BT

Author	Country	Substrate	Subjects	% SIBO
Prevalence of SIBO in health controls subjected to H_2BT.				
Pimentel [26]	USA	Lactulose	111	15
Walters [47]	Canada	Lactulose	39	20
Posserud [48]	Sweden	Lactulose	46	20
Bratten [49]	USA	Lactulose	138	22
Scarpellini [50]	Italy	Lactulose	56	7
Park [25]	Korea	Lactulose	40	40
Shanab [40]	Ireland	Lactulose	16	31
Rana [23]	India	Lactulose	150	30
Zhao [51]	China	Lactulose	13	8
Prevalence of SIBO in participants with obesity subjected to H_2BT.				
Sabaté [13]	France	Glucose	140	17
Madrid [52]	Chile	Glucose	39	41
Sabaté [53]	France	Glucose	378	15
Fialho [54]	USA	Glucose	152	44
Jung [55]	Korea	Lactulose	485	32
Roland [12]	USA	Lactulose	30	56
Prevalence of SIBO in participants subjected to bariatric surgery with the Roux-en-Y gastric bypass				
Ishida [56]	Brazil (7 years)	Lactulose	37	40
Lahkani [57]	USA (5 years)	Glucose	15	100
Andalib [58]	USA (5 years)	Glucose	63	73
Sabaté [53]	France (< 1 year)	Glucose	65	40

SIBO, small intestinal bacterial overgrowth; *H_2BT*, hydrogen breath test

Lahkani et al. [57] and Andalib et al. [58] observed SIBO positivity in all evaluated subjects, although participants presented some digestive, unspecific complaints of operated individuals, which could justify a high prevalence of positive tests. Our sample was randomly selected from participants accompanied regularly for postoperative health control of bariatric surgery, regardless of signs and clinical symptoms. Because it is an observational transversal study, one of the limitations of our results was the absence of information regarding the prevalence of SIBO in patients prior to surgery, in order to correlate them with the postoperative data. Another point that could refine the interpretation of the results was the lack of a protocol to collect an alimentary diary of the subjects; this would have allowed us to establish possible correlations between H_2BT positivity, and the eating habits of each group and eventual relapses of weight gain. Moreover, the registration of the use of medications, such as proton pump inhibitors, could also have influenced the occurrence of SIBO. Although not described in our methods session, all participants with obesity were subsequently contacted and questioned about the use of these drugs. Of the 18 subjects, four negative and two positive H_2BT participants were in continuous or frequent use of this class of medications. In contrast to our findings and according to the recent meta-analysis, the use of proton pump inhibitors would only result in a moderate increase in the possibility of SIBO [71]. Thus, the use of the proton pump inhibitors does not seem to be relevant to the prevalence of SIBO in our data.

Sabaté et al. [53] answered some of the questions that remained open until now. They prospectively evaluated 378 participants with obesity in the pre-operative bariatric surgery and found a 15% pre-operative positivity in H_2BT with glucose. Of these, 65 performed bariatric surgery with the Roux-en-Y gastric bypass. The H_2BT was repeated with less than 1 year of surgery and found positivity in the test of 40%. However, all the participants who tested positive for H_2BT in the pre-operatively, did in fact test negative in the postoperatively period. In the study of Sabaté et al. [53] was carried out the calculation of the daily caloric intake of the subjects and compared among the groups. Interestingly, the group of participants with negative examination, and who lost more weight, ingested a daily caloric rate higher than the group with the positive H_2BT for SIBO.

The previous finding suggests that at first, the diet did not have a significant role in the recurrence of the weight gain in these participants with short postoperative follow-up. In addition, in our study, we observed that the two groups of participants with obesity reached significant weight loss in the course of postoperative evolution, reaching the two groups the average of BMI of 25 kg/m^2. The group with a negative H_2BT after 11.2 years of surgery, managed mostly to keep in the BMI range considered as overweight, while the participants of the positive group presented a weighty relapse that rated them as carriers of obesity grades 1 and 2. The clinical consequences of this finding should be evaluated in clinical protocols to answer the question if the surgery was effective in preventing complications related to the obesity in the medium and long term.

Nevertheless, metagenomics sequencing before and after 3 months Roux-en-Y gastric bypass surgery showed a reduction of *Firmicutes* and *Bacteroidetes* and an increase of *Proteobacteria* and *Verrucomicrobia* [72]. Also, bariatric surgery in any of its varieties increased gut microbial diversity [73].

Limitations

(i) The inclusion of a small sample should be considered to improve the possibilities of a type II error;
(ii) No measurement of preoperative SIBO were not done in the participants with obesity in the study;
(iii) The time between the BMI measures was not standardized;
(iv) The prevalence of the *Helicobacter pylori* was not evaluated in our participants with obesity;
(v) The study lacks a control arm to corroborate with our findings;
(vi) As an exploratory statistical analysis, we are not able to solve the problem of multiple tests comparison by the use of the Bonferroni test or false rate discovery test.

Conclusion

The H_2BT with lactulose demonstrated the prevalence of bacterial overgrowth in the small intestine after the Roux "Y" gastric bypass surgery at an average 11.2 years post-surgery and with a recurrence of gain weight of 40% of participants. The relationship between cause and effect of these findings should be the subject of other studies. Nevertheless, we infer that it may not be an exam to predict weight gain independently of the ingested diet; however, it shows that the change of the intestinal flora can occur prior to weight gain. Moreover, our data point suggests to a high prevalence of SIBO (38.8%) in patients undergoing BGYR with a value in accordance with the literature.

Author Contribution All authors have approved the manuscript and agreed with its submission. Moreover, LKC, NSC, TNR, and PJCC idealized the project; collected patients' data; worked on supervision, realization, and validation based on repeatability of the exams; contribute with the safety analysis; conducted the writing and critical review of the study; FALM conducted the writing and critical review of the study, also, performed the statistical analysis of the data. All authors have contributed to manuscript writing.

Compliance with Ethical Standards

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

Ethical Statement The project was approved by the research ethics committee from the institution.

Consent Statement Informed consent was obtained from each participant.

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