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ORIGINAL CONTRIBUTIONS

Study of Small Intestinal Bacterial Overgrowth in a Cohort of Patients with Abdominal Symptoms Who Underwent Bariatric Surgery

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Abstract

Introduction Small intestinal bacterial overgrowth (SIBO) is a common complication of bariatric surgery. Digestive decontamination treatments with oral antibiotic therapy vary and are not codified. This retrospective study was conducted to analyse the characteristics of bariatric surgery patients who underwent a glucose breath test (GBT) and to analyse the effectiveness of the antibiotic decontamination therapy.

Materials and Methods A total of 101 operated patients (Roux-en-Y bypass (RYB), omega bypass (ΩB) and sleeve gastrectomy (SG)) who underwent a GBT (75 g/250 mL) were included. Anthropometric data, symptoms of SIBO, type of surgery, use of proton pump inhibitors (PPIs) and antibiotic therapy were analysed. The effectiveness of the antibiotic treatment, defined by improvement of the symptoms, was evaluated during the follow-up.

Results Of the 85 women and 16 men included (48.5 ± 3.6 years old), 63 underwent RYB, 31 underwent ΩB and 7 underwent SG. The GBT was positive in 83% of the patients. A positive test was associated with age ($p < 0.001$), female sex ($p < 0.01$) and PPI use ($p < 0.01$), but there was no significant difference according to the type of surgery. Sixty-one percent of patients treated with gentamicin/metronidazole sequential antibiotic therapy and 58% of patients treated with metronidazole alone achieved treatment efficacy (with no significant difference in efficacy between these treatments).

Conclusion SIBO should be systematically considered in the context of abdominal symptoms in bariatric surgery patients, regardless the type of surgery, particularly in patients who are older or female and after PPI treatment. Digestive decontamination appears to be similar between gentamycin/metronidazole and metronidazole treatments.

Keywords Antibiotic therapy · Bariatric surgery · Glucose breath test · Obesity · Small intestinal bacterial overgrowth (SIBO)

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Introduction

Small intestinal bacterial overgrowth (SIBO) is a heterogeneous pathology defined as an excess of bacteria in the small intestine responsible for digestive symptoms such as bloating, abdominal pain, nausea or diarrhoea [1, 2]. There are a few articles in the literature about the prevalence of SIBO in the general population. In a study of 328 adults in a geriatric residence, the prevalence of SIBO was estimated to be 11% using a glucose breath test for diagnosis [3]. The diagnosis was made by quantitative bacterial cultures derived from jejunal or duodenal aspiration fluid. SIBO has historically been evaluated in studies of patients who have undergone gastrointestinal surgery with a microbial density greater than 105 CFU

(colony forming units)/mL in a culture derived from jejunal aspiration and cultured for at least 48 h [4]. However, according to the 2017 North American consensus, the glucose breath test is a useful, inexpensive, simple and non-invasive diagnostic test for the diagnosis of SIBO [5]. SIBO can occur when one or both of the main regulatory mechanisms to control the number of bacteria in the small intestine, gastric acid production and peristalsis are altered [6].

Bariatric surgery induces intestinal stasis favouring SIBO. In a recent study (2017), 40% of patients with Roux-en-Y bypass were diagnosed with a SIBO [7]. To our knowledge, there is no data in the literature comparing the prevalence of SIBO after different types of bariatric surgery.

The treatment of SIBO is based on the treatment of the causal diseases, the correction of the underlying anatomical particularities, the adaptation of the diet and the qualitative and quantitative restoration of the intestinal microbiota after antibiotic treatment. As glucose breath tests, which are commonly used for the diagnosis of SIBO, do not allow for antibiotic susceptibility testing, antibiotic treatment is therefore done empirically, and there is no consensus for reference antibiotics. The gentamicin-metronidazole combination, used to treat digestive contamination in intensive care, has never been tested in adults for the treatment of SIBO. The gentamicin-metronidazole combination may be of interest based on its efficacy, acceptable epidemiological risk and low cost [8].

The objective of this retrospective study was to analyse the characteristics of a cohort of patients who had undergone a glucose breath test for abdominal symptoms of SIBO following bariatric surgery (Roux-en-Y bypass, omega bypass and sleeve gastrectomy). In addition, this study aimed to analyse and compare the effectiveness of the most frequently used digestive decontamination antibiotics in our centre.

Materials and Methods

Characteristics of the Subjects

In this retrospective cohort study, all patients with digestive symptoms suggestive of small intestinal bacterial overgrowth (abdominal pain, diarrhoea and bloating) who had undergone a glucose breath test at the University Hospital Center of Dijon between January 2018 and April 2019 were included. Of the 134 patients who underwent a glucose breath test, 101 had undergone bariatric surgery (Roux-en-Y bypass, omega bypass or sleeve gastrectomy).

Anthropometric data (weight, height and body mass index), symptoms of SIBO (diarrhoea defined by at least 3 loose or liquid stools per day, chronic abdominal pain or bloating), type of bariatric surgery (Roux-en-Y bypass, omega bypass or sleeve gastrectomy), proton pump inhibitor treatments (PPIs), antibiotic therapy (type and dosage of the prescribed molecules) and treatment duration were collected.

When the glucose breath test was positive, patients received either probabilistic antibiotic therapy with metronidazole alone or a combination with gentamicin and metronidazole. The choice of antibiotic therapy was made according to the prescriber's habit and not according to the pathology of the patient. Sequential antibiotic therapy with metronidazole was prescribed in 2 doses: 250 mg 3 times daily or 500 mg twice daily for 7 days per month for 3 months. Antibiotic therapy with gentamycin-metronidazole consisted of taking a 40-mg drinking ampoule of gentamycin twice a day, morning and night, with a metronidazole pill at a dosage of 500 mg morning and evening for 7 days a month for 3 months. Other antibiotics were used: rifaximin at a dosage of 550 mg in the morning and evening for 7 days per month for 3 months or quinolone-norfloxacin 400 mg, one tablet daily for 7 days per month for 3 months.

The effectiveness of the antibiotic treatment was defined by an improvement of the symptoms (diarrhoea, abdominal pain or bloating) observed during follow-up consultations or by phone by the referring physician, 3 months after the beginning of the treatment.

The data were made anonymous and collected from the computerised file of the University Hospital of Dijon. Computerised files were declared to the Commission Nationale Informatique et Liberté in accordance with the French law. As this study was a retrospective study, in accordance with French legislation on medical research, patient consent was not necessary.

Glucose Breath Test

The glucose breath tests were carried out at the University Hospital of Dijon in the morning with quiet subjects who had fasted since midnight the night before (with a no-fibre diet) and who had not smoked a cigarette for at least 6 h. No antibiotics were prescribed in the month prior to the test. At 8 h, the patient ingested 75 g of glucose diluted in 250 ml of water. Expired air samples were taken every 20 min for 4 h. A Breathtracker SC (Quintron, Milwaukee, WI, USA, 2016) was used to measure hydrogen (H_2), methane (CH_4) and carbon dioxide (CO_2) in expired air. Assays were centralised and performed by a trained operator. Respiratory tests were considered positive when the concentration of hydrogen increased by 20 ppm compared with the basal value (i.e. before ingestion) or the concentration of methane increased by 12 ppm compared with the basal value.

Statistical Analyses

Qualitative variables are expressed as numbers and percentages, while quantitative variables are expressed as the means

and standard deviations. Chi^2 and Fisher tests were used to study differences between groups and to compare antibiotics. Student's *T* tests were used to compare quantitative values of population characteristics and glucose breath tests. A *p* value less than 0.01 was considered statistically significant (Bonferroni correction). The XLSTAT software (XLSTAT 2019.1, Addinsoft®, Paris, France) was used for all analyses.

Results

Characteristics of the Population

One hundred and one patients with a history of bariatric surgery with abdominal symptoms of SIBO were included in this retrospective cohort. The characteristics of the subjects are shown in Table 1. Of the 101 patients included (85 women and 16 men, mean age 48.5 ± 3.6 years, mean BMI 28.1 ± 4.7 kg/m^2), 63 received a Roux-en-Y bypass, 31 received an omega bypass and 7 received a sleeve gastrectomy. Seventy-six patients had diarrhoea, abdominal pain and bloating. Forty-eight percent of patients were treated regularly with proton pump inhibitors (PPIs).

Glucose Breath Test (Fig. 1)

Glucose breath tests were positive in 83% of the patients (n = 84). The mean concentrations of hydrogen and methane are shown in Fig. 1. The test became rapidly positive with a positive hydrogen level as early as 20 min after ingestion of the glucose, whereas to obtain a positive methane level, the test became positive only after 60 min. On average, hydrogen and methane levels reached a plateau approximately 80 min after the beginning of the test. The mean hydrogen level appeared to be higher in the Roux-en-Y-type bariatric patients than in the omega bypass patients, with hydrogen peaks of 119 ± 37 ppm and 98 ± 51 ppm, respectively, at 80 min (p = 0.07). There was no difference in the expired methane concentrations between Roux-en-Y bypass, omega bypass and sleeve gastrectomy groups.

Factors Associated with SIBO

Positive glucose breath tests were significantly associated with PPI ($p < 0.01$), age ($p < 0.001$) and female sex ($p < 0.01$). There was no significant difference according to the type of surgery previously performed (Table 2). There was no difference in weight, BMI or the weight lost after the bariatric surgery in terms of breath test results (i.e. whether or not SIBO was diagnosed).

Effectiveness of Antibiotic Therapy

Sixty-one percent of the patients treated with gentamicin/metronidazole sequential antibiotic therapy (20 out 33 patients) and 58% of patients treated with metronidazole alone (23 out 40 patients) described treatment efficacy. Twenty-seven percent of the remaining patients (i.e. 3 out of 11), who composed an inhomogeneous group receiving other antibiotic treatment (quinolone or rifaximin) or no treatment, also described a clinical improvement. Regardless of the antibiotic treatment prescribed (sequential gentamicin/metronidazole or metronidazole alone) and the type of

Table 1 Characteristics of studied patients at time of glucose breath test (n = 101)

Age (years); mean, SD		48.5 ± 3.6
Sex *n* (%)	Women	85 (84%)
	Men	16 (16%)
Weight (kg)	Before surgery	109.1 ± 4.2
	After surgery (during the breath test)	75.1 ± 11.7
BMI (kg m^{-2}) mean, SD		28.1 ± 4.7
Time between bariatric surgery and breath test (months), mean, SD		40 ± 34
Type of bariatric surgery *n* (%)	Roux-en-Y bypass	63 (62%)
	Omega bypass	31 (31%)
	Sleeve gastrectomy	7 (7%)
Symptoms *n* (%)	Abdominal pain	52 (51%)
	Chronic diarrhoea	76 (75%)
	Bloating	20 (20%)
PPI treatment *n* (%)		53 (52%)

The subjects' characteristic in the cohort are expressed as the mean ± SD (standard deviation). *n* (%) represents the number and percentage of subjects involved in the study

BMI body mass index, *PPI* proton pump inhibitor

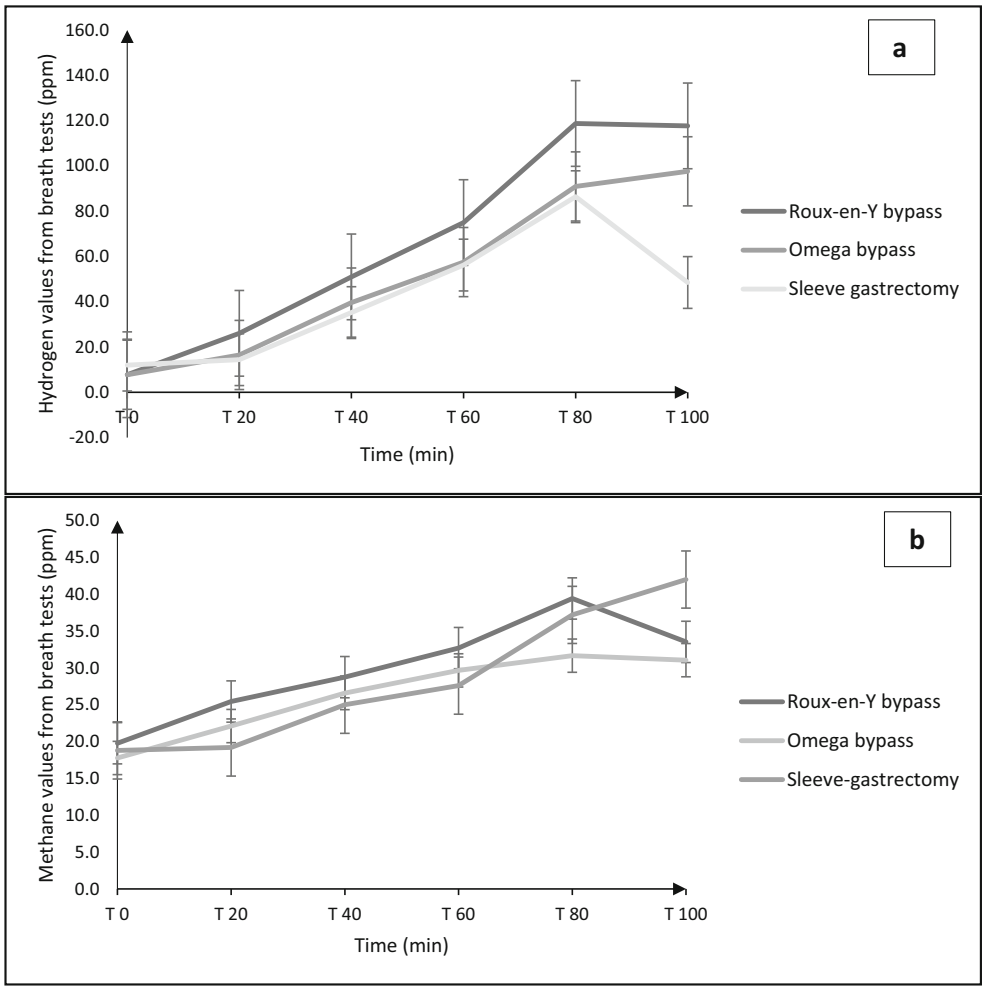

Fig. 1 Values of hydrogen (**a**) and methane (**b**) in expired air during breath tests after ingestion of 75 grams of glucose depending on the type of bariatric surgery previously performed. There was no difference in the expired hydrogen and methane concentrations between Roux-en-Y bypass, omega bypass and sleeve gastrectomy groups. Student's *T* tests were used to compare quantitative values of population characteristics and glucose breath tests

bariatric surgery, no significant therapeutic efficacy differences ($p = 0.87$) were observed (Fig. 2).

Table 2 Characteristics of the patients with small intestinal bacterial overgrowth (diagnosed by a positive glucose breath test) and the patients without bacterial colonisation (negative breath test)

		Positive breath test	Negative breath test	*p*
Age, years; mean, SD		49.9 ± 12.0	41.4 ± 3.8	$p < 0.01$
Sex *n* (%)	Women	74 (73)	11 (11)	$p < 0.01$
	Men	10 (10)	6 (6)	
BMI (kg m^{-2}) mean, SD		28.1 ± 4.5	27.0 ± 0.7	ns
Type of bariatric surgery *n* (%)	Roux-en-Y bypass	50 (50)	13 (13)	ns
	Omega bypass	29 (29)	2 (2)	
	Sleeve gastrectomy	5 (5)	2 (2)	
Symptoms *n* (%)	Abdominal pain	42 (42)	10 (10)	ns
	Chronic diarrhoea	64 (63)	12 (12)	
	Bloating	18 (17)	2 (2)	
PPI treatment *n* (%)		55 (54)	6 (6)	$p < 0.01$

Values of the parameters measured in the cohort are mean ± SD (standard deviation). *n* (%) represents the number and the percentage of the subjects involved in the cohort

Chi^2 test and Fisher test for qualitative data and Student's *T* test with Bonferroni correction for multiple analyses were used for statistical analyses

BMI body mass index, *PPI* proton pump inhibitor

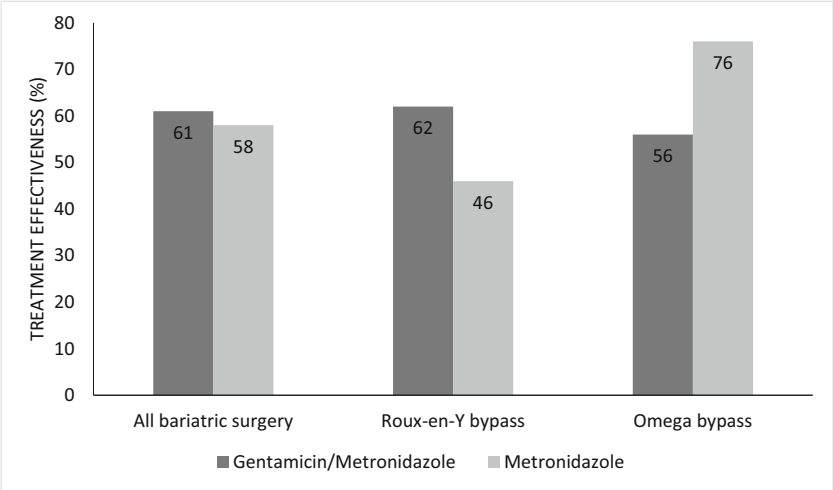

Fig. 2 Comparison of the efficacy of gentamycin/metronidazole with that of metronidazole alone in subjects with small bowel bacterial overgrowth who underwent bariatric surgery (Roux-en-Y bypass, omega bypass or sleeve gastrectomy). Sixty-one percent of the patients treated with gentamicin/metronidazole sequential antibiotic therapy and 58% of patients treated with metronidazole alone described treatment efficacy. Regardless of the antibiotic treatment prescribed and the type of bariatric surgery, no significant therapeutic efficacy differences ($p = 0.87$) were observed. Chi^2 test with Bonferroni correction for multiple analyses was used for statistical analyses

Discussion

In the present study, 84 out the 101 patients undergoing bariatric surgery with abdominal symptoms of small intestinal bacterial overgrowth had a positive glucose breath test. This high frequency (83%) of positive tests is consistent with the data in the literature. In a study published in 2015 on 63 patients with digestive disorders (bloating, nonspecific abdominal pain, diarrhoea) after undergoing a Roux-en-Y bypass, a SIBO frequency of 90% was identified using a glucose breath test [9]. Our study population, as well as that of Andalib et al., had high frequencies of SIBO because of the selection criteria: only subjects with a history of bariatric surgery with suggestive abdominal symptoms were included. Furthermore, both studies have similarities, with a clear female predominance (approximately 90%) and a very close average age (49 versus 48 years in our study). Only mean BMI was greater in the study of Andalib et al. compare with that in our study (35 ± 10 versus 28.1 ± 4.7 kg m^{-2}, respectively). The overall prevalence of small intestinal bacterial overgrowth in patients who had undergone bariatric surgery both with and without abdominal symptoms is not known precisely. To our knowledge, only Sabate et al., in 2017, reported a bacterial colonisation frequency of 40% after Roux-en-Y bypass surgery in symptomatic and non-symptomatic patients [7].

All published studies are concerned SIBO in subjects after Roux-en-Y bypass. Our study retrospectively evaluated patients who had undergone the three main types of bariatric surgery: Roux-en-Y bypass, omega bypass and sleeve gastrectomy. The frequency of SIBO in individuals with abdominal symptoms was not different among the 3 types of surgery. This lack of difference between the surgical techniques was all the more surprising, as the omega bypass is more at risk of malabsorption [10]. In fact, the alteration of intestinal peristalsis, with an omega-shaped loop, could be a risk factor for SIBO [11]. In addition, the characteristics of the glucose breath tests were not different between the three types of bariatric surgery groups. It should nevertheless be noted that the mean hydrogen content seemed to be higher in the group of patients who received Roux-en-Y bariatric surgery than in the group of patients who received an omega bypass, with a peak of hydrogen at 119 ± 37 ppm and 98 ± 51 ppm, respectively, at 80 min ($p = 0.07$). This specificity at 80 min was also observed in Andalib et al.'s study in patients with suggestive abdominal symptoms after Roux-en-Y bypass [9]. The difference in concentration of expired hydrogen and methane between different studies after breath tests can be explained by different protocols, notably the amount of ingested glucose. In our study, breath tests were performed after ingestion of 75 g of glucose. In the literature, the glucose doses used in breath tests for the diagnosis of SIBO ranged from 25 to 100 g. No study comparing the characteristics of breath tests with different doses of ingested glucose was found. In this context, the North American consensus of 2017 suggests that a dose of 75 g of glucose appears to be the most practical and inexpensive dose for diagnosis, as this dose is already used for the diagnosis of gestational diabetes mellitus [5].

Our study also demonstrated an association between a positive breath test and the use of proton pump inhibitors. Many patients are treated with PPI for gastroesophageal reflux symptomatology. Thus, Théreaux et al. found that one out of

four patients who underwent bariatric surgery remained treated with PPIs until 4 years after the surgery [12]. Although the results of the literature are contradictory, several studies have observed a significant correlation between the use of PPIs and the occurrence of SIBO [13]. For example, in a study of 450 patients, Lombardo et al. identified SIBO in 50% of patients with gastroesophageal reflux disease treated with PPIs, in 24.5% of patients with irritable bowel syndrome (IBS) and in 6% of healthy control subjects [14]. The risk of SIBO occurrence is particularly high after PPI treatment for more than 12 months [15]. In a meta-analysis of 11 studies, the risk of developing SIBO under PPI treatment increased significantly with an odds ratio of 2.3 (95% CI 1.2–4.2) [15]. The result, however, was significant only for the diagnosis of SIBO by duodenal aspiration culture and not by glucose breath test. So far, our study is the only one to study the impact of PPI use on the occurrence of SIBO in bariatric surgery patients. In bariatric surgery patients, PPIs are also suspected of aggravating malnutrition [16] but are necessary in the context of severe gastroesophageal reflux and in individuals at risk of oesophageal lesions [17].

In the present study, there was also an association between the age of the subjects and the positivity of the glucose breath tests: advanced age increased the risk of SIBO. This observation is consistent with the data in the literature. Indeed, in a study of 328 adults in a geriatric residence, the prevalence of SIBO, diagnosed by glucose breath test, was estimated at 15.6% in patients over 60 years old compared with 5.9% in control subjects aged 24–59 years [3]. In addition, an association between female sex and a positive glucose test was found in our study. This association was demonstrated in a study with a lactulose breath test among 791 subjects: the odds ratio of a positive test increased in elderly women while it decreased in older men [18]. However, in a study comparing duodenal aspiration with respiratory glucose testing, there was no increase in sex-specific prevalence, while there was an increase with age [19].

In our study, 43 of 73 patients treated (59%) experienced symptom improvement after 3 months of sequential antibiotic therapy. In many studies, the efficacy of antibiotic therapy was assessed by symptom improvement [4]. In a meta-analysis published in 2013, the authors compared the efficacy of antibiotic treatment with that of placebo [20]. Antibiotics were more effective than placebo, with a combined standard airway clearance rate of 51.1% (95% CI 46.7–55.5) for antibiotics, compared with 9.8% (CI 95% from 4.6 to 17.8) for the placebo. Standardisation of respiratory tests correlated with clinical improvement in patients [20]. However, in a study published in 2019, Perez-Aisa et al. showed an efficacy rate of 32.4% for antibiotic treatment [21]. One study showed a recurrence rate of SIBO symptoms in 44% of patients 9 months after effective antibiotic therapy [22].

Breath tests do not allow the performance of an antibiogram, so antibiotic treatment is done empirically. Thus, given the variety of the intestinal microbiota, broad spectrum antibiotic therapy should be favoured [23]. Several different antibiotic therapies have been tested with varying degrees of success [23], since there is no consensus on the choice, dosage and duration of antibiotic treatment. In our study, there was no significant difference in clinical efficacy between oral bi-antibiotic therapy consisting of gentamicin in combination with metronidazole and sequential mono-antibiotic therapy with oral metronidazole. Metronidazole is an antibiotic used very frequently for the treatment of SIBO [24, 25]. In one study, Melchior et al. showed that 67% of patients treated with metronidazole for SIBO described a significant improvement in symptoms, compared with 25% of patients treated with Carbosylane for 10 days [25]. Gentamicin-metronidazole was never evaluated in adults in the context of SIBO. This combination has been used successfully in the reduction of intestinal necrosis and in the prevention of bacterial translocation in acute mesenteric ischaemia [8]. This association was therefore used for its broad-spectrum effect, its low rate of side effects and its low cost.

A first limitation of our study relates to the small number of patients who had undergone different surgical procedures and a scheme not designed for a therapeutic trial. A prospective study with a glucose breath test before and after antibiotic therapy comparing metronidazole alone and the metronidazole-gentamicin combination should be able to provide some answers. Another limitation is linked to the selection of bariatric surgery patients for whom glucose breath tests were proposed. However, the data collected in our study have many similarities with the data reported in the literature.

Conclusion

Given the large number of glucose-positive breath tests, small intestinal bacterial overgrowth should be routinely investigated in the context of abdominal symptoms (bloating, diarrhoea and abdominal pain) in patients with a history of bariatric surgery. The results of a retrospective observational study of 101 patients highlight that this diagnosis must be considered regardless of the type and timing of the surgery, particularly in older patients, female patients and in the event of prolonged use of proton pump inhibitors. The effectiveness of bacterial digestive eradication seems to be similar between the two oral sequential decontamination antibiotics most frequently prescribed in our cohort (gentamycin/metronidazole and metronidazole alone). Thus, simple antibiotic therapy with metronidazole appears to be sufficient for first-line treatment of SIBO. A prospective cohort study is needed to confirm this result.

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