Research Article

Small Intestinal Bacterial Overgrowth and Lactose Malabsorption in Iraqi Patients with Irritable Bowel Syndrome

Trifa A. Mahmood[1,2]*, Dana T. Gharib[2], Heero I. Faraj[2] and Taha A. Mohamad[1,2]

[1]College of Medicine, University of Sulaimani, Sulaymaniyah, Republic of Iraq; [2]Kurdistan Centre of Gastroenterology and Hepatology (KCGH), Sulaymaniyah, Republic of Iraq

Corresponding author:
Trifa A. Mahmood, College of Medicine, University of Sulaimani, Kurdistan Centre of Gastroenterology and Hepatology (KCGH), Sulaymaniyah, Republic of Iraq, Tel: 009647701470657;
E-mail: trifa.mahmood@univsul.edu.iq

Abstract

Background and objectives: This prospective study aimed to assess the benefits of glucose and lactose hydrogen breath tests (GHBT and Lactose HBT) on the diagnosis of respectively small intestinal bacterial overgrowth (SIBO) and lactose malabsorption in patients with irritable bowel syndrome (IBS), and also efficacy evolution of te Rifaximin in the treatment of SIBO. **Materials and Methods:** It was cross-sectional study with treatment and follow-up of diagnosed cases. From January 2017 to December 2018, 74 patients with IBS who visited the Gastroenterology and Hepatology Center and were diagnosed based on Rome IV criteria were studied. Patients underwent both GHBT and Lactose HBT by portable LactoFAN2. IBS symptoms severity score (IBS-SSS) was used to assess their symptoms before and after the treatment. Positive GHBT patients were given rifaximin 200 mg 3 times a day for 2 weeks followed by repeating GHBT and symptoms scoring. **Results:** Thirty-six patients (54%) had IBS-D, while the remaining 31 (46%) had IBS-A. glucose HBT was positive in 12(18%) patients, whereas lactose HBT was positive in 7(10%). All GHBT positive patients became negative one month after rifaximin, and their symptoms improved dramatically. **Conclusion:** Rifaximin is an effective therapy even at low doses for SIBO. Lactose malabsorption is prevalent mostly among diarrheal-IBS patients and those with higher calprotectin level.

Keywords: Hydrogen breathe test; Gastrointestinal symptoms; Irritable bowel syndrome; Small intestinal bacterial overgrowth; Lactose malabsorption

Introduction

Common gastrointestinal symptoms like abdominal pain, bloating, and chronic diarrhea have a diverse differential diagnosis from organic causes, like inflammatory bowel disease (IBD), colorectal cancer, celiac disease, food intolerance, to functional causes like irritable bowel syndrome (IBS). [1] Irritable bowel syndrome is the most commonly diagnosed gastrointestinal disorder that affects approximately 11% of the population worldwide. In Asia, the prevalence of IBS is around 10-20%. [2]

It is of interest to note that IBS-like symptoms may also be produced by small intestinal bacterial overgrowth (SIBO) and lactose malabsorption. Small intestinal bacterial overgrowth refers to the high growth of colonic bacteria in the small intestine exceeding 106 colony-forming units (CFU) per mL of upper gut aspirate. Therefore, the small bowel is colonized by excessive aerobic and anaerobic microbes that are normally present in the colon. [3] Small intestinal bacterial overgrowth usually impairs the normal physiological function of the upper gut and might be asymptomatic. [4,5] It might exist even in the absence of predisposing anatomical factors. [6] The true prevalence of SIBO is unknown as some patients are asymptomatic and thus do not seek medical help or might be treated without a proper diagnosis. Furthermore, the prevalence may vary according to which diagnostic method is used. [7] In patients with IBS, SIBO is five times more common than normal individuals [8] and this condition might worsen. [9] The gold standard technique for diagnosis of SIBO is the culture of the intestinal aspirate obtained through endoscopy. However, this diagnostic method has its limitations due to its invasive nature and the need for a time-consuming microbial culture. It is a fact that all hydrogen (H_2) and methane (CH_4) gases in the gut are pure of microbial rather than human cell origin [10,11] which led to the development of breath tests for the diagnosis of SIBO. Breath tests are inexpensive, practical, and non-invasive diagnostic techniques in which H_2 and CH_4 gases in the exhaled air are measured. [8]

The H_2 breath test is considered the most accessible diagnostic test for SIBO, as well as lactose and fructose intolerance. [7,12] Hydrogen breath test following ingestion of glucose is called Glucose Hydrogen Breath Test (GHBT). This test is characterized by its low false-positive results; therefore, it is the most widely used test for diagnosis of SIBO. [7,12,13] The main treatment for SIBO with antibiotics is to decrease (rather than eradicate) small intestinal bacteria. Rifaximin is a non-

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absorbable rifamycin derivative, although it is well tolerated and is effective in the therapy of SIBO, its high cost limits its use. [14,15]

This study aims to assess the benefits of glucose and lactose hydrogen breath tests (GHBT and Lactose HBT) for diagnosis of respectively SIBO and lactose malabsorption in a group of Iraqi patients with IBS in Sulaimaniyah. Moreover, the study aims to assess the efficacy of Rifaximin in the treatment of SIBO by symptom severity scoring and hydrogen breath test after treatment.

Materials and Methods

Patients

This prospective study was conducted in a center for Gastroenterology and Hepatology (KCGH) in Sulaymaniyah City from January 2017 to December 2018. A total of 154 patients were studied, and only 74 patients with IBS-like symptoms met the inclusion criteria. A thorough history was obtained, and detailed physical examination was performed. The patients were fully informed about the objective of the study, and written informed consent was obtained from them before enrolment. Seven patients could not follow the preparatory instructions for GHBT and thus were excluded. Approval of the College of Medicine Ethical committee, University of Sulaimani was obtained.

Inclusion and exclusion criteria

Patients with diarrhea-predominant (IBS-D) and alternating bowel habit (IBS-A), according to Rome IV criteria, were enrolled in the study.

Exclusion criteria included patients who were younger than 18 years, had red flags including unexplained rectal bleeding, fever, weight loss, anemia, nocturnal diarrhea that prevents sleep, the onset of symptoms after 50 years of age, and had the first-degree relative with IBD or early colon cancer. Also, patients on non-steroidal anti-inflammatory drugs (NSAID) or proton pump inhibitors (PPI), as well as pregnant or lactating ladies, were excluded. Moreover, patients with tumors, hepatic and/or renal insufficiency, congestive heart failure, bleeding tendency, major gastrointestinal procedures, recent respiratory or urinary tract infection, or inflammatory bowel disease (IBD), abnormal colonoscopy, and/or endoscopy findings were also excluded.

Experimental procedure

Before the onset of the study, routine blood tests, thyroid function test, and tissue transglutaminase antibody test (to exclude celiac disease) were conducted for all patients. Also, abdominal ultrasound, esophagogastroduodenoscopy, and colonoscopy were carried out. Additionally, general stool examination (to exclude parasitic infestation) and fecal calprotectin to differentiate non-constipating IBS from IBD were done. [16] Simultaneously, body mass index (BMI) of all patients were calculated by the equation BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is his/her height in meters squared. Accordingly, the patients were classified as having a healthy body weight if their value was ranged between 18.5 - 24.9.

Before conduction of the GHBT, the symptoms of IBS were scored according to IBS-symptom severity scoring (IBS-SSS) used by Francis et al. [17] in which a score of <7.5 indicated remission, 7.5 - 17.5 mild, 17.5 - 30.0 moderate, and >30 severe symptoms (Appendix A).

The participants then underwent both GHBT and Lactose HBT to exclude SIBO and lactose intolerance test using LactoFAN2, respectively. Initially, GHBT was performed, and negative cases underwent LHBT one week later. While patients with positive GHBT were given rifaximin 200 mg tablet 3 times a day for 2 weeks. [18] After 4 weeks of last treatment dosage, IBS-SSS was rechecked, and GHBT was repeated. One week later, Lactose HBT was conducted to exclude lactose malabsorption.

Patient's recommendations

A recommendation leaflet was given to and discussed with every patient before the GHBT, explaining the aim of the test and necessary preparation. GHBT was performed under standard conditions. The patients were recommended not to receive antibiotics and laxatives in the month preceding the test. Subjects were advised to have carbohydrate-restricted foods the day before the test, as well as eggs, chicken, fish, and white rice, and water were also recommended on that day. Then, the patients were commanded to fast at least 12 hours before the commencement of the test. On the day of the test, the patients had a mouth wash with water and toothbrush without paste. Smoking and physical exercises were forbidden 12 hours before and during the test day.

Test procedure

Regarding the GHBT, the patients with at least 12 hours of fasting and a baseline H_2 level of <5 ppm were asked to drink a 250 mL glucose solution which was prepared by dissolving 75 glucose in normal tap water. Then, H_2 levels were measured every 20 minutes for 6 consecutive times using portable LactoFAN2 by FAN. GHBT was regarded as positive for SIBO if the level of H_2 was 20 ppm more than the basal record, as recommended by the North American consensus. [7]

Instantly, LHBT was performed after a similar preparation and instruction to that of GHBT. The test was based on the measurement of H_2 that is exhaled in samples every 30 minutes for 6 consecutive times, after the oral administration of 250 mL lactose which was prepared by dissolving 25 g of lactose in normal tap water. The LHBT was considered positive when exhaled H_2 level was at least 20 ppm higher than that of the baseline value.

Statistical analysis

The statistical analysis was performed by SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). The data were presented in tabular forms showing the frequency and relative frequency distribution of different variables among both groups of patients (positive and negative groups). Chi-square

tests were used to compare the categorical data between these two groups of patients concerning different variables. Different types of bar and pie charts were used to describe some of the variables of the study diagrammatically.

For comparing the means of certain variables such as age and BMI between the two groups (positive and negative groups), the statistical significance of the difference in the means between two groups was assessed using independent sample t-test. P-values of 0.05 were used as a cut off point for the significance of statistical tests.

Results

Studied population characteristics

Sixty-seven patients were finally enrolled in this study including 30 males and 37 females, with a mean age of 36.9 ± 9.7 years and an age range of 18-59 years. Thirty-six patients (54%) had IBS-D, while the remaining 31 (46%) had IBS-A. Table 1 shows the socio-demographic characteristics of the studied population.

Glucose hydrogen breath test

It was demonstrated that GHBT was positive in 12 patients (18%), whereas lactose HBT was positive in 7 patients (10%) only. None of the GHBT positive cases were positive for lactose HBT [Figure 1]. However, there were no significant differences between the positive and negative cases regarding age, gender, and BMI [Table 2].

Symptoms versus results of GHBT

All cases had diarrhea but negativity to GHBT was significantly associated with bloating and heartburn (p=0.004, 0.009) [Figure 2].

Correlation between results of breath tests and type of IBS

Prevalence of positivity to GHBT in the included cases was 18% (12/67), while higher prevalence was found in the IBS-D group (25%), concerning what was observed in IBS-A (9%); however, the difference was not statistically significant (p-value >0.05) [Table 3].

Response to rifaximin treatment

Rifaximin at a dose rate of 200 mg/3 times a day led to a significant improvement in terms of GHBT normalization and patient complaints. All patients became negative for GHBT (less than 20 ppm increase H_2) after one month of therapy. Besides, IBS-SS scores improved dramatically in all of them except for one patient who needed to double the dose for an extra two weeks [Figure 3].

Lactose HBT

The prevalence of lactose malabsorption in the IBS population was 10% (7/67 cases). All of the lactose positive cases were in diarrhea-predominant IBS cases (p = 0.03). Lactose malabsorption was more common among the female patients than the males (p < 0.05). The lactose intolerant cases were younger than the negative cases (mean age of 29.3 ± 7.0 and 38.0 ± 8.1, respectively). Calprotectin level in SIBO and lactose malabsorption cases: Although there was no significant relation between calprotectin level and SIBO, the level was significantly (p < 0.001) higher among lactose HBT positive cases with a mean of 57.1 ±17.7 µg/g, while the mean in the negative cases was 23.2 ±20.1 [Figure 4].

Table 1: Demographic characteristics of the studied population.

Variables	Items	No.	%
Gender	Male	30	44.8
	Female	37	55.2
Residency	Inside the city	60	89.6
	Outside the city	7	10.4
Employment	Employed	35	52.2
	unemployed	32	47.8
Level of Education	Primary (informal)	14	20.9
	Secondary	17	25.4
	University graduates	36	53.7
Marital Status	Single	12	17.9
	Married	35	79.1
	Divorced/ widowed	2	3.0
BMI	Normal	35	52.2
	Overweight	10	14.9
	Obese	22	32.8

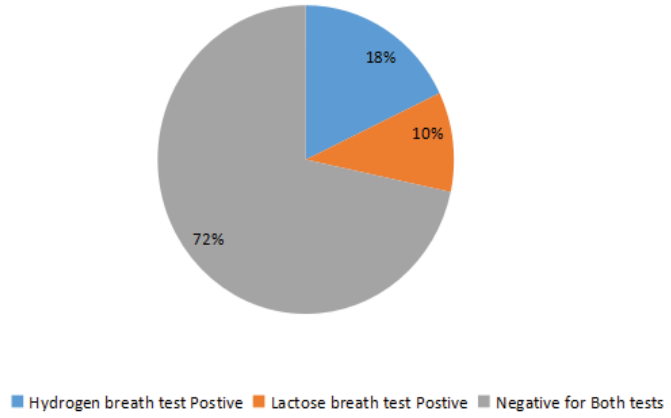

Figure 1: Percentage of SIBO and lactose malabsorption in the studied population.

Table 2: Correlation between glucose hydrogen breath tests and demographic variables.

Variables		Glucose Hydrogen Breath Test		*P* value
		Negative	Positive	
Mean age ± SD		38.0 ± 8.1	36.8 ± 14.5	0.08
Gender	Male	22	4	0.38
	Female	26	8	
BMI	Normal	28	7	0.64
	Overweight and Obese	27	5	
	Mean ± SD	25.0 ± 5.0	26.3 ± 8.0	0.50

Discussion

Irritable bowel syndrome patients might have an underlying SIBO even in those without the risk factors and can be easily diagnosed with GHBT and effectively treated by rifaximin. [19] The prevalence of SIBO in the current study was 18%, which was much close to that predicted by Ghoshal et al. [20] in a group of IBS patients based on culture. It was also in agreement with

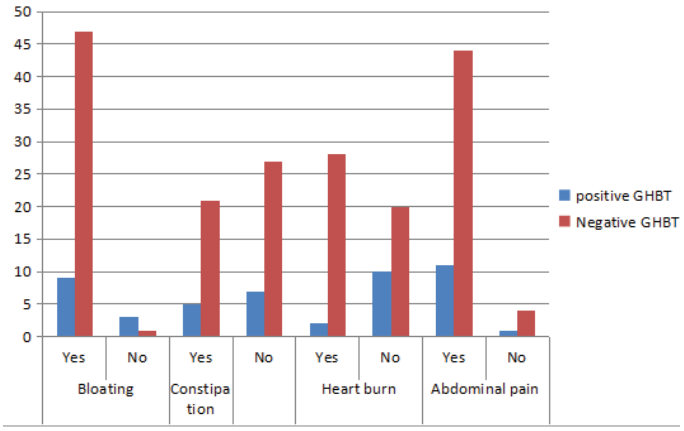

Figure 2: Comparison of abdominal symptoms in cases with and without SIBO.

Table 3: Results of glucose hydrogen breath test and IBS types.

IBS type	Results of GHBT		Total %
	Positive No. (%)	Negative No. (%)	
IBS-D	9 (13)	27 (40)	53
IBS-A	3 (5)	28 (42)	47
Total	12 (18)	55 (82)	100

No. = Number, % = Percentage

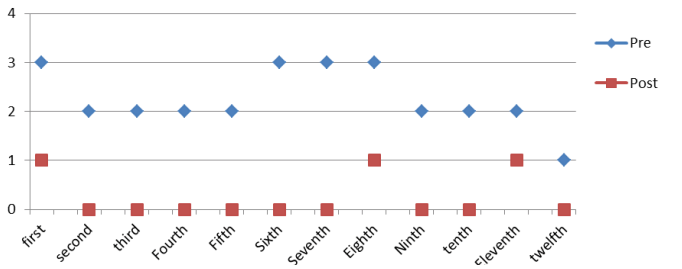

Figure 3: IBS-SSS before (pre) and after (post) rifaximin therapy in the twelve GHBT positive cases that received rifaximin.

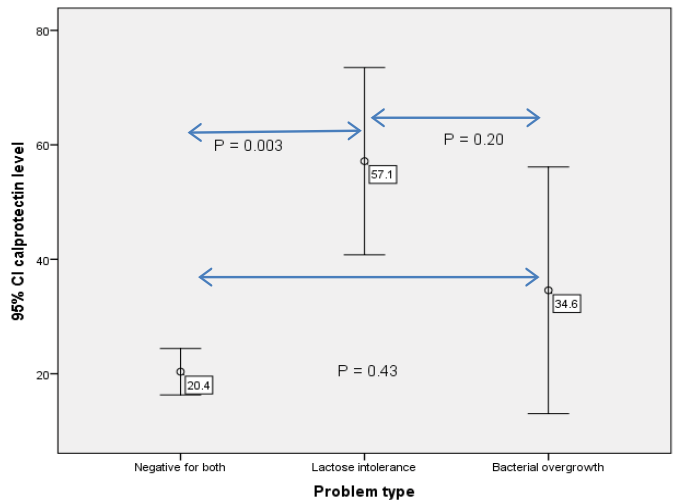

Figure 4: Mean faecal calprotectin levels in SIBO, lactose intolerant, and negative cases for both tests.

the findings of Sachdeva et al.,[21] David et al.,[22] and Mattsson et al.[23] On the other hand, Lupascu et al.,[4] Abbasi et al.[24] and Ford et al.[25] reported higher percentages using either glucose or Lactulose HBT (LHBT). We used GHBT that has higher specificity for SIBO in comparison to LHBT.[8,10,23] Furthermore, the difference might be attributed to our long list of exclusion criteria for any factors that might be a risk for SIBO development, or be due to variation in the population characteristics or methods used in the diagnosis.[25] On the contrary, we relied on the H_2 level only for the diagnosis, so we might have missed methane producers. On the other hand, some studies varied in their definition of positive breath tests. For instance, we regarded an increase of >20 ppm from basal H_2 level as an indication of positive breath test[25] while Cuoco and Salvagnini[26] considered >10 ppm and reported positive breath tests in nearly half of the IBS cases.

The age and sex did not show a statistically significant association, similar to David et al.[22] and Mattsson et al.,[23] while recent reviews conducted by Chen et al.[8] and Reddymasu et al.[5] assumed female predominance, which might be because of the situation explained by the small number included in their study. There is no significant association between SIBO and IBS-D, which was almost similar to was reported by Reddymasu et al.[5]; however, other studies showed that SIBO was associated with diarrhea-dominant IBS.[19,20,21,27]

Heartburn and bloating are more frequent among GHBT negative patients (those without SIBO). Bloating is regarded as a functional symptom described differently by patients. Also, the diagnosis of SIBO in this study was based on H_2 level, and constipation type of IBS was excluded, but bloating is mainly associated with constipation and methane producers.[28] On the contrary, a positive association between SIBO and bloating was observed by Sachdeva et al.[21]

There is no relation between calprotectin level and SIBO, probably due to the absence of subclinical intestinal inflammation in SIBO cases, as described by Montalto et al.[29] however; others reported subclinical inflammation in comparison to healthy controls.[21]

The high eradication rate with the used low rifaximin dosage is very impressive, which is comparable to the Kansas city study[30] that used 800 mg/day. However, others suggest that higher doses are needed for maximum eradication, but numerous recent studies conducted by as Cuoco et al.,[26] and Gatta et al.[15] have indicated rifaximin as the most effective and safest in the treatment of SIBO. The treatment decreased the patients' complaints and improved their symptoms severity scoring, which is comparable to what has been documented by several other studies.[12,18,19,27,31] All of the cases had normal breath tests after the treatment except one case who needed a double dose for an extra two weeks. This higher recovery rate than the previous studies might be due to the exclusion of all the risk factors that precipitate SIBO in our cases. The prevalence of lactose malabsorption in our IBS population was 10% which is much lower than what was reported among Saudis and Yamani healthy people (51% and 47%, respectively).[32] The presence of dairy products in our population's dietary regimes might explain this low prevalence. Likewise, the prevalence of lactose malabsorption was also low in Bedouins Saudi population whose diet is rich in dairy products. Lactose malabsorption

association with IBS diarrhea was documented by other studies [33,34] which might be due to the fact that diarrhea causes patients to seek for medical help more than constipation.

Higher fecal calprotectin level indicates the presence of inflammation in lactose intolerant cases, similar to Carroccio et al. [35] and Pal et al., [36] which may lead us to do further studies on the issue to exclude lactose malabsorption in cases with IBS like symptoms with slightly higher calprotectin level before further sophisticated and invasive investigations being performed.

Conclusion

IBS clinical presentation can be mimicked by many other diseases. Symptoms are commonly non-specific and can be produced by SIBO as well as lactose malabsorption. Given the high rate of SIBO among IBS patients and the availability of safe and effective therapy, it is imperative to exclude SIBO and initiate treatment courses for positive cases even lower than the recommended doses by literature. Lactose malabsorption is better to be excluded in IBS patients (particularly IBS-D). Although our study is prospective and the first in this field in the country, we had some limitations such as the small number of participants, lack of control group for comparison, and absence of methane measurement.

Author Contributions

Conceptualization, Trifa Mahmood and Taha Mohammad; Data collection, Trifa Mahmood; Investigation, Trifa Mahmood, Dana Gharib and Taha Mohammad; Methodology, Trifa Mahmood, Dana Gharib and Heero Faraj; Project administration, Trifa Mahmood; Resources, Dana Gharib, Heero Faraj and Taha Mohammad; Software, Trifa Mahmood; Supervision, Taha Mohammad; Visualization, Dana Gharib and Heero Faraj; Writing – original draft, Trifa Mahmood; Writing – review & editing, Dana Gharib, Heero Faraj and Taha Mohammad.

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Competing Interests

The authors declare that they have no competing interests.

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