Original Research Article

A study on the role of small intestinal bacterial overgrowth in patients with functional dyspepsia

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Abstract

Background: Functional dyspepsia (FD) accounts for majority of dyspepsia. Before labeling them as FD, a bunch of investigations to be done to rule out organic cause. Small intestinal bacterial overgrowth (SIBO) which is one of the cause for dyspepsia is not commonly sought and always neglected among physicians. So we aimed to study the frequency of SIBO in patients with dyspeptic symptoms and whether to include investigations to diagnose SIBO in the algorithm of approach to dyspepsia.

Materials and methods: We consecutively enrolled 50 newly diagnosed functional dyspepsia patients based on Rome III criteria and 50 healthy controls in this study. They underwent glucose hydrogen breath test (GHBT) after overnight fasting.

Results: In the cases with FD, 6 (12%) subjects were found to have positive GHBT and diagnosed as SIBO, whereas in the controls 2 (4%) had positive GHBT with no statistical significant difference among groups with a P value of 0.140. In the cases with FD, the most common subtype was post prandial distress syndrome (46%), followed by epigastric pain syndrome (36%) and mixed type

(18%). Patients with SIBO were treated with rifaximin 1200 mg/day in divided doses for 10 days. GHBT was repeated after 4 weeks and found to be normalized in all cases.

Conclusion: SIBO should be considered before making a diagnosis of FD. GHBT is a simple non-invasive method to diagnose SIBO. One could avoid taking unnecessary drugs by timely diagnosis of SIBO in patients with dyspepsia.

Key words

Functional Dyspepsia, Small Intestinal Bacterial Overgrowth, Glucose Hydrogen Breath Test, Postprandial Distress Syndrome, Epigastric Pain Syndrome.

Introduction

Functional gastrointestinal disorders (FGID) are considered as the most common disorders of gastrointestinal tract. It has huge impact on health care costs [1]. By definition, FGID are disorders of gut-brain interaction [2]. Functional dyspepsia (FD) is classified under functional gastro-duodenal disorders that constitutes postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), moreover an overlap of both can occur [3]. The majority of dyspeptic patients are diagnosed as FD [4]. The estimated worldwide prevalence of dyspepsia is about 20-30% [5]. The prevalence of dyspepsia in India is accounted to about 30.4% [6]. Small intestinal bacterial overgrowth (SIBO) is defined as an abnormally high bacterial population (10^5-10^6 colony forming units (CFU)/mL) in the proximal small intestine [7]. By recent studies, SIBO renders a contributory role in the pathogenesis of FD [8]. It is also estimated that the prevalence of an abnormal microbial fermentation in the patients with FD to be 56.5% [9]. Studies presenting the relationship between SIBO and refractory dyspepsia are well established [1]. But by literature only few studies indeed suggested the existence of relation between SIBO and FGID pathogenesis [9]. A study conducted in North Indian patients demonstrated the association between SIBO and irritable bowel syndrome [10]. However, studies establishing the link between SIBO and functional dyspepsia in India are lacking. So our study aimed at incurring the relationship between newly diagnosed functional dyspepsia and SIBO using Glucose Hydrogen Breath Test (GHBT).

Materials and methods

A prospective case control study was conducted from January 2016 to December 2016 with prior institutional ethical committee approval. Informed consent was obtained from all the patients who were enrolled for the study. Patients with history of any co-morbidities, surgery, malignancy, diseases of any organ systems, autoimmune diseases, or on chronic drug therapy (proton pump inhibitor (PPI) intake/ probiotics/ steroids) were excluded from the study.

Cases (group-A)

Patients attending the Medical Gastroenterology outpatient department (OPD) aged above 18 years, who were newly diagnosed of functional dyspepsia (FD) by Rome III criteria [11] with no organic cause for their abdominal symptoms assessed by blood investigations (complete blood count, renal function tests, liver function tests), stool examination, endoscopy, and radiology test like ultrasonography (USG) or computed tomography (CT) of abdomen which revealed a normal study were enrolled as cases (group-A). Clinical symptoms and signs of those patients were detailed in the proforma. The patients who fulfilled the criterion of FD were further sub-classified into 3 groups; those with postprandial distress syndrome (PPDS), and those with epigastric pain syndrome (EPS) or mixed type. Once the diagnosis of functional dyspepsia was made, the cases underwent GHBT in the next two days to know the presence of SIBO.

Controls (group-B)

The healthy individuals aged above 18 years, who attended the master health checkup OPD, and were not on any medications like antibiotics, PPI and with no gastrointestinal symptoms were included. Laboratory investigations like complete blood count, renal function tests, liver function tests, USG abdomen when done and in those revealed normal, the controls underwent GHBT in the next two days.

Technique - Glucose Hydrogen Breath Test

The Gastro+ Gastrolyzer (Bed font–UK) was an instrument used in measuring the hydrogen levels in expired breath.

Precautions taken to overcome false negative and false positive results

Basal hydrogen breath test was performed after the overnight fast. The subjects were advised to avoid the slowly absorbed carbohydrate diets such as bread, potato, corn or fiber diet at least for 24 hours prior to GHBT, as the diet could cause delayed excretion of hydrogen in the breath resulting in a false negative result. Cigarette smoking and physical exercise were also restricted for about 2 hours before and during the test as that could lead on to hyperventilation and thereby change in breath hydrogen content. The subjects were also instructed to brush their teeth and rinse their mouth with an antiseptic solution. This was done to eliminate an early hydrogen peak due to action of oral cavity bacteria on test glucose. Basal breath hydrogen level was measured by averaging the three basal values done on the first visit.

Subjects were then advised on ingestion of 100 grams of glucose dissolved in 200 mL of water. Thereafter, breath hydrogen levels were measured once in every 15 minutes for about 2 hours at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. An increase in hydrogen excretion, in parts per million (ppm), following glucose administration, was calculated by subtracting the fasting value from the highest value of hydrogen excretion obtained. A rise of breath hydrogen by more than 12 ppm above basal value following glucose administration was considered positive for SIBO. In subjects with the average value of basal breath hydrogen more than 20 ppm, the test was repeated on the next day [12, 13].

Statistical analysis

Cases with positive hydrogen breath test were compared with that of the healthy controls. The results were expressed in either mean with standard deviation or median with range. Comparison of various parameters between the cases and the controls were performed using Student's t test or Pearson's chi-square test with Yates' continuity correction. P-value of <0.05 was considered as the level of significance. Statistical analysis was performed using IBM SPSS 15 statistical package.

Results

A total of 50 cases (group-A) and 50 controls (group-B) were enrolled in the study. The demographic findings and characteristics of patients are shown in the **Table - 1**. The mean age was 37.46±11.36 and 39.10±9.33 in group-A and group-B respectively. There was no statistically significant difference in the age of two groups (P value 0.433). Females were predominantly present in both the groups of about 72% and 62% respectively (P value 0.288). Both the groups were screened for the parameters such as body weight, body mass index (BMI), hemoglobin, total count, platelet count, fasting blood sugar, blood urea, serum creatinine, total bilirubin, SGOT, SGPT, serum alkaline phosphatase, total protein and albumin, and all these levels were within normal limits in both the groups. Among those parameters, though there existed a statistically significant difference in the total count, total bilirubin, and albumin among the groups, all the values were within the normal defined levels.

As shown in the **Table – 2**, the most common (>25%) symptoms that the patients experienced were postprandial fullness, epigastric burn, epigastric pain, bloating, nausea, belching, loss

of appetite and early satiation. The other symptoms included indigestion, heartburn, occasional vomiting and regurgitation. In the cases with FD, the most common subtype was PPDS (46%), followed by EPS (36%) and mixed type (18%).

Table – 1: Demographic and laboratory parameters of cases and controls (mean±SD).

Parameters	Cases (n=50)	Controls (n=50)	P value
Age (years)	37.46±11.36	39.10±9.33	0.433
Male: Female	14:36	19:31	0.288
Weight (kg)	52.70±9.62	55.80±10.00	0.127
Body mass index (kg/m^2)	22.8±4.4	24.13±4.33	0.137
Haemoglobin (gm/dL)	10.79±2.17	10.89±1.77	0.798
TLC (cells/uL)	6645±1349	5900±1298	0.006
Platelet count (cells/uL)	247860±70755	244692±67078	0.819
ESR-1hour (mm/hr)	31.42±12.89	31.30±12.52	0.962
FBS (mg/dL)	81.78±11.79	80.60±10.66	0.797
Urea mg/dL)	25.78±8.2	28.54±6.23	0.063
Creatinine (mg/dL)	0.70±0.24	0.60±0.58	0.62
Total bilirubin (mg/dL)	0.59±0.17	0.67±0.17	0.022
AST (IU/L)	24.62±8.36	26.68±8.30	0.217
ALT (IU/L)	26.12±9.2	26.14±6.30	0.99
ALP (IU/L)	58.78±16.33	52.26±13.77	0.035
Total protein (mg/dL)	6.47±0.46	6.35±0.50	0.209
Albumin (mg/dL)	3.72±0.32	3.56±0.23	0.009

TLC= Total leukocyte count; ESR= Erythrocyte sedimentation rate; FBS= Fasting blood sugar; AST= Aspartate aminotransferase; ALT= Alanine aminotransferase; aminotransferase

Table – 2: Clinical characteristics of cases.

Parameters	Cases (n=50)
Symptoms	
Epigastric pain	20 (40%)
Heartburn	7 (14%)
Indigestion	7 (14%)
Belching	14 (28%)
Regurgitation	5 (10%)
Epigastric burning	21 (42%)
Nausea	18 (36%)
Occasional vomitting	7 (14%)
Early satiation	13 (26%)
Postprandial fullness	25 (50%)
Bloating	18 (36%)
Loss of appetite	14 (28%)
Diagnosis	
EPS (Epigastric pain syndrome)	18 (36%)
PPDS (Post prandial distress syndrome)	23 (46%)
EPS+PPDS	9 (18%)

GHBT

The average basal value of HBT was 7.5±5.71, 6.13±4.4 in the cases and controls respectively with no statistically significant difference between groups (P value 0.179). On the other hand, the average GHBT value (from 15 minutes to 120 minutes) was 5.06±4.98, 5.35±3.85 in the cases and controls respectively also revealed no statistical significant difference among groups with P value of 0.749 (**Table - 3**).

In the cases with FD, 6 (12%) subjects were found to have positive GHBT and diagnosed with SIBO, whereas in the controls 2 (4%) had positive GHBT with no statistical significant difference among groups with P value of 0.140 (**Table - 3**).

Among the cases there was no significant difference in demographic features, and duration of symptoms found between those patients with positive and negative GHBT. Concerning to the symptoms, there was no statistically significant difference observed between the cases with positive and negative GHBT (**Table - 4**).

Table – 3: Basal and every 15 minutes value of glucose hydrogen breath test.

HBT basal	**Cases (n=50)**	**Control (n=50)**	**P value**
1st (ppm)	7.10±5.30	6.24±4.39	0.38
2nd (ppm)	8.00±6.39	6.42±4.5	0.155
3rd (ppm)	7.44±5.7	5.76±4.73	0.112
Average (ppm)	7.5±5.71	6.13±4.4	0.179
GHBT every 15 minutes			
15 Minutes (ppm)	5.12±4.98	5.10±3.37	0.981
30 Minutes (ppm)	5.41±4.98	5.54±3.44	0.891
45 Minutes (ppm)	5.41±5.1	5.8±3.44	0.588
60 Minutes (ppm)	5.43±5.57	6.7±4.79	0.234
75 Minutes (ppm)	5.97±6.84	6.35±5.64	0.770
90 Minutes (ppm)	5.81±5.62	5.93±5.00	0.909
105 Minutes (ppm)	4.95±4.97	4.45±3.83	0.234
120 Minutes (ppm)	4.08±4.06	3.60±2.95	0.511
Average (ppm)	5.06±4.98	5.35±3.85	0.749
GHBT test result			
Positive	6 (12%)	2 (4%)	0.140
Negative	44 (88%)	48 (96%)	

Ppm = Parts per million; GHBT= Glucose hydrogen breath test

When compared the groups with positive and negative test with respect to the three subtypes of FD revealed no significant difference with P value of 0.978 (**Table - 5**).

Similarly, as shown in Table 6 all the laboratory parameters had not shown an existence of significant difference except 1-hour high erythrocyte sedimentation rate (ESR). The ESR values were 43.67±17.67, 29.75±11.38 mm/hour in cases with positive and negative tests respectively, with a statistically significant difference with P value of 0.012 (**Table - 6**).

The average basal value of GHBT was 14.5±6.46, 6.5±5.06 in the cases with positive and negative tests respectively with a statistically significant difference between groups (P value 0.001). The average GHBT value (from 15 minutes to 120 minutes) was 13.54±10.59,

3.91±1.96 in the GHBT positive and GHBT negative cases respectively also revealed a statistical significant difference among groups P value of 0.000 (**Table - 7**).

On the other hand, the average basal value of GHBT was 12.55±11.16, 5.75±3.56 in the controls with positive and negative tests respectively with a statistically significant difference between groups (P value 0.009). The average GHBT value (from 15 minutes to 120 minutes) was 14.79±12.81, 4.75±1.48 in the GHBT positive and GHBT negative controls respectively also revealed a statistical significant difference among groups P value of 0.000 (**Table - 8**).

Table – 4: Clinical characteristics Vs GHBT among cases.

Among cases (n=50)	**GHBT Positive (n=6)**	**GHBT Negative (n=44)**	**P value**	**Odds ratio**
Age (Years)	34.33±8.6	37.89±11.76	0.478	
Sex (Male: Female)	02:04	12:32	0.756	1.333
Duration of symptoms (months)	11.00±6.57	14.43±11.99	0.498	
Epigastric pain - Present: Absent	2:4	18:26	0.722	0.722
Heartburn - Present: Absent	1:5	6:38	0.841	1.267
Indigestion - Present: Absent	0:6	7:37	0.292	1.162
Belching - Present: Absent	2:4	12:32	0.756	1.333
Regurgitation - Present: Absent	1:5	4:40	0.562	2.000
Epigastric burning - Present: Absent	3:3	18:26	0.672	1.444
Nausea - Present: Absent	3:3	15:29	0.446	1.933
Occasional vomitting - Present: Absent	0:6	7:37	0.292	1.162
Early satiation - Present: Absent	1:5	12:32	0.578	0.533
Post prandial fullness - Present: Absent	3:3	22:22	1.000	1.000
Bloating - Present: Absent	2:4	16:28	0.885	0.875
Loss of appetite- Present: Absent	1:5	13:31	0.510	0.477

Table – 5: Subtype of functional dyspepsia compared with GHBT.

Diagnosis	**GHBT Positive (n=6)**	**GHBT Negative (n=44)**	**P value**
EPS	2 (33.3%)	16 (36.4%)	0.978
PPDS	3 (50.0%)	20 (45.4%)	
Mixed	1 (16.7%)	8 (18.2%)	

GHBT= Glucose hydrogen breath test; EPS=Epigastric pain syndrome; PPDS=Post prandial distress syndrome

The sensitivity and specificity of GHBT were 75% (95% CI= 34.91% to 96.81%) and 52.17% (95% CI= 41.50% to 62.70%) respectively. The positive predictive value and negative predictive value of GHBT were 12% (95% CI=7.97% to 17.67%) and 96% (95% CI=87.67% to 98.78%) (**Table - 9**).

Six patients who found to have SIBO were treated with rifaximin 1200mg/day in divided doses for 10 days. All the patients symptomatically improved. After 4 weeks GHBT was repeated and found to be normalized in all patients.

Table – 6: Comparison of various parameters with GHBT (mean±SD).

Parameters	GHBT Positive (n=6)	GHBT Negative (n=44)	P value
Weight (kg)	49.66±9.22	53.20±9.70	0.404
Body mass index (kg/m^2)	22.29±3.71	22.88±4.55	0.763
Haemoglobin (gm/dL)	9.00±2.34	11.03±2.05	0.030
TLC (cells/uL)	6416±1316	6676±1365	0.663
Platelet count (cells/uL)	272833±95574	244454±6740	0.382
ESR-1hour (mm/hr)	43.67±17.67	29.75±11.38	0.012
FBS (mg/dL)	83.83±11.46	80.82±11.92	0.562
Urea mg/dL)	20.33±2.65	20.52±8.55	0.086
Creatinine (mg/dL)	0.86±0.19	0.60±0.24	0.077
Total bilirubin (mg/dL)	0.51±0.19	0.60±0.16	0.247
AST (IU/L)	24.67±10.98	24.66±8.10	0.989
ALT (IU/L)	25.17±6.79	26.25±9.63	0.792
ALP (IU/L)	58.00±1296	58.89±17.19	0.904
Total protein (mg/dL)	6.81±0.44	6.42±0.45	0.056
Albumin (mg/dL)	3.95±0.16	3.69±0.33	0.072

GHBT= Glucose hydrogen breath test; TLC= Total leukocyte count; ESR= Erythrocyte sedimentation rate; FBS= Fasting blood sugar; AST= Aspartate aminotransferase; ALT= Alanine aminotransferase; aminotransferase

Table – 7: Comparison of GHBT result among cases with and without SIBO.

Parameters (among cases)	Patients with SIBO (n=6)	Patients without SIBO (n=44)	P value
HBT basal			
1st (ppm)	13.67±5.85	6.25±4.6	0.001
2nd (ppm)	15.5±8.33	6.97±5.4	0.001
3rd (ppm)	14.33±5.21	6.5±5.06	0.001
Average (ppm)	14.5±6.46	6.5±5.06	0.001
GHBT every 15 minutes			
15 Minutes (ppm)	18.5±5.47	3.9±2.56	0.000
30 Minutes (ppm)	21.5±2.51	3.95±1.98	0.000
45 Minutes (ppm)	19.25±6.8	4.15±2.48	0.000
60 Minutes (ppm)	21.5±4.12	3.97±2.56	0.000
75 Minutes (ppm)	27.25±2.21	4.04±2.21	0.000
90 Minutes (ppm)	22.00±1.65	4.34±2.78	0.000
105 Minutes (ppm)	18.5±4.79	3.72±2.60	0.000
120 Minutes (ppm)	14.00±3.65	3.1±2.67	0.000
Average (ppm)	13.54±10.59	3.91±1.96	0.000

Ppm = Parts per million; GHBT= Glucose hydrogen breath test

Discussion

Rome III has defined functional dyspepsia as the presence of one or more of the four chronic dyspeptic symptoms (bothersome postprandial fullness, early satiation, epigastric pain, and

epigastric burning), specific for the gastroduodenal region present for the past 3 months with onset at least 6 months before diagnosis in absence of structural abnormality on upper GI endoscopy and metabolic or systemic causes explaining the symptoms. SIBO is defined as a bacterial population in the small intestine exceeding 10^5–10^6 organisms/mL. Though the culture of jejunal aspirate is deemed as the gold standard test to diagnose SIBO, it has few disadvantages of being invasive, time-consuming and expensive necessitating sterile technique. However hydrogen breath tests, in spite of their low sensitivity, are popular for their non-invasiveness. Hydrogen breath tests use various sugars like glucose and lactulose. Among them, glucose hydrogen breath test is esteemed as the most acceptable one in comparison to lactulose hydrogen breath test, owing to insensitivity of lactulose hydrogen breath test in double-peak criterion used for diagnosis. Glucose hydrogen breath test is preferred in our study because of it being non-invasive, low cost, and safety.

Table – 8: Comparison of positive and negative GHBT result among controls.

Parameters (among controls)	GHBT Positive (n=2)	GHBT Negative (n=48)	P value
HBT basal			
1st (ppm)	12.33±10.01	5.89±3.72	0.013
2nd (ppm)	12.00±10.58	6.08±3.85	0.027
3rd (ppm)	13.33±13.31	5.28±3.52	0.004
Average (ppm)	12.55±11.16	5.75±3.56	0.009
GHBT every 15 minutes			
15 Minutes (ppm)	17.00±1.41	4.58±2.29	0.000
30 Minutes (ppm)	19.00±1.41	4.92±1.98	0.000
45 Minutes (ppm)	22..00±0.00	5.21±1.71	0.000
60 Minutes (ppm)	27.00±1.41	5.89±2.20	0.000
75 Minutes (ppm)	31.00±1.41	5.34±2.29	0.000
90 Minutes (ppm)	27.00±1.41	5.06±2.32	0.000
105 Minutes (ppm)	21.00±1.41	3.76±1.60	0.000
120 Minutes (ppm)	13.5±4.94	3.19±1.99	0.000
Average (ppm)	14.79±12.81	4.75±1.48	0.000

ppm=Parts per million; GHBT= Glucose hydrogen breath test

Table – 9: Sensitivity, specificity, positive predictive value and negative predictive value of GHBT.

Variables	Percentage	95% CI
Sensitivity	75%	34.91 to 96.81%
Specificity	52.17%	41.50 to 62.70%
Positive predictive value	12%	7.97 to 17.67%
Negative predictive value	96%	87.67 to 98.78%

Few studies found the co-existence of delayed gastric emptying in about 25% to 50% of patients diagnosed of functional dyspepsia [14]. Recent studies have also evinced that both gastric acidity and intestinal motility are the two major factors that render a contributory role in the control of gastrointestinal flora [9]. Thus, the delayed gastric emptying in FD could be a plausible pathogenesis of bacterial overgrowth in small intestine in our patients.

In a study conducted in Brazil, it is estimated that about 56.5% of patients with functional dyspepsia are positive for SIBO by lactulose hydrogen breath test [9]. In our study, the prevalence of SIBO in cases is estimated as about 12%. Also in few studies the prevalence of SIBO in healthy individuals was estimated to about 2.5% to 22% [15]. Whereas in our study, the estimated prevalence of SIBO in controls is 4%. SIBO, as well as sepsis, bacteremia and intestinal endotoxemia secondary to SIBO, are considered as life threatening conditions, thereby adversely affect the quality of life. When there exists a bacterial overgrowth, they interfere with the absorption of dietary vitamin B12, aminoacids and metabolism of bile salts leading onto low B12 level, hypoalbuminemia and diarrhea [16]. On the other hand bacterial synthesis of folic acid will result in high folic acid level. SIBO in turn induce inflammatory response, and it is evident by increase in values of biological markers like ESR, CRP etc. In our study, there is a statistically significant difference (P value-0.012) in one hour ESR value between cases positive and negative for SIBO.

15% of people will produce methane instead of hydrogen due to methanogenic flora in the intestine [17]. In our study methane measurement was not performed because we used Bedfont instrument in which hydrogen measurement only could be measured. Another limitation in this study was long term follow up was not done. Hence recurrence of SIBO was not known.

Conclusion

GHBT being a non-invasive technique with low cost, and it can be added as a mandatory test to be included in the evaluation of patients with dyspepsia. So it helps in early diagnosis of SIBO and preventing its complications, thereby improving the quality of life. SIBO should be ruled out before labeling a patient with FD.

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