INTRODUCTION

Functional dyspepsia is characterized by a set of chronic and recurrent symptoms that are usually located in the epigastric region, in the absence of structural or metabolic and biochemical abnormalities that justify the symptomatology. These symptoms must be present in the last 3 months and its start at least 6 months before diagnosis. There should be no evidence that symptoms improve or are associated with changes of intestinal rhythm or on evacuation characteristics.

The pathogenesis of functional dyspepsia symptoms is not completely clarified, having as possible etiologic mechanisms: gastroduodenal motor disorders, changes in visceral sensitivity and the involvement of emotional disturbances in the modulation of motor and sensory functions.

Small intestine bacterial overgrowth (SIBO) is characterized by the increase in number and/or type of colonic bacteria in the upper gastrointestinal tract. It is defined as the finding of more than $10^5$ Colony Forming Units (CFU/mL) in the upper small intestine region: epigastric pain, epigastric burning, postprandial fullness and early satiety, without evidence of structural changes justifying the symptoms. These symptoms must be present in the last 3 months and its start at least 6 months before diagnosis. There should be no evidence that symptoms improve or are associated with changes of intestinal rhythm or on evacuation characteristics.

The hypothesis of SIBO being associated to functional dyspepsia must be considered, since the impaired motility of the gastrointestinal tract is one of the main etiologic factors involved on both pathologies.
or $10^4$ CFU/mL if isolated bacteria are typical from large intestine\(^4, 19\).

Affected patients may be asymptomatic or have symptoms such as: fullness, abdominal discomfort, diarrhea, steatorrhea, flatulence, dyspepsia, malabsorption of nutrients, weight loss or no weight gain\(^21, 25, 26\).

The gold standard for diagnosis of SIBO is the jejunal aspirate, but it has several limitations\(^8, 25\). \(H_2\) breath test, using glucose or lactulose, is a non-invasive, low cost, simple and safe alternative with good sensibility and specificity\(^15, 19\).

After analysis on the latest studies of SIBO, it may be observed that the change in gastric acidity and gastroduodenal motility are its main causes\(^4, 5, 25\).

The hypothesis that SIBO is associated with functional dyspepsia should be considered, once the motility disorder is one of the main etiologic factors involved in both entities.

From these available data and considering the importance of functional dyspepsia in the medical context today, we built this investigation study for the presence of SIBO in functional dyspeptic patients, by using the hydrogen breath test.

**METHOD**

This is a case-control study conducted at Instituto Goiano de Gastroenterologia e Endoscopia Digestiva (IGGED), Goiânia, GO, Brazil, from July 2011 to February 2012. This study was previously submitted and approved by the Ethics Committee of Pontifícia Universidade Católica de Goiás. We evaluated 34 patients between ages 18 and 65, with normal upper endoscopy and upper abdominal ultrasonography, being 23 patients (6 men and 17 women) with one or more dyspeptic symptoms (postprandial fullness, epigastric burning, early satiety and epigastric pain) compared with 11 patients (6 men and 5 women) without dyspeptic symptoms (control group). Patients accepted to participate in the study after signing the free and informed consent term. Patients excluded this study were: individuals under the age of 18 years or over 65, pregnant women, patients with chronic obstructive pulmonary disease, smokers, patients with gastroesophageal reflux disease, irritable bowel syndrome or any other organic disease involving gastrointestinal tract, and patients that did not agree to participate on the study or did not sign the free and informed consent term.

A questionnaire on dyspeptic symptoms was applied. It was developed by the researchers, based on Rome III criteria (2006). Patients with symptoms in the last 6 months and its start at least the last 6 months and not associated with symptoms that could meet irritable bowel syndrome criteria were considered as having functional dyspepsia.

Patients were tested using \(H_2\) breath test. A basal sample of exhaled air was collected corresponding to the 8 hours fasting sample. After ingestion of 15 mL of lactulose 667 mg/mL (EMS Sigma Pharma Ltd), exhaled air samples were collected at the following times: 15, 30, 45, 60, 75, 90, 105 e 120 minutes. The result was considered positive for SIBO when the peak of \(H_2\) was greater than 20 parts per million (ppm) in relation to fasting, or two peaks greater than 10 ppm sustained until 60 minutes after ingestion of lactulose\(^1\).

For collection of exhaled air, the device “AlveoSampler” (Quintron Instrument Co. Inc., Milwaukee, WI, USA) was used. It consists of an intermediate containing a small whole syringe, from where air is withdrawn to be analyzed. At the inlet end, a nozzle adapted to the intermediate was perfectly coupled to the patient’s mouth, meanwhile the other end of the intermediate contained a polyethylene bag. After this bag was filled, 20 mL of alveolar air were withdrawn by syringe and immediately analyzed in a BreathTracker \(H_2\) gas chromatograph (Quintron Instrument Co. Inc., Milwaukee, WI, USA) which quantifies the exhaled hydrogen in ppm.

Data obtained were analyzed by Epi Info, version 3.5.1, in order to study the association between the variables (SIBO and functional dyspepsia), for which we used the Yates corrected chi-square test with significance level of 5% \((P < 0.05)\).

**RESULTS**

Of the 34 patients analyzed, 22 (64.7%) were females and 12 (35.3%) were males. Age ranged from 18 to 65 years with an average of 38.8 ± 12.62. The group of patients with dyspepsia was composed by 23 patients, being 6 (26%) males and 17 (74%) females. The control group was composed by 11 patients, being 6 (54.5%) males and 5 (45.5%) females (Table 1).

<table>
<thead>
<tr>
<th>Number of patients according to gender in each group</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspeptic</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>

Of all dyspeptic patients, 13 (56.5%) tested positive for SIBO through \(H_2\) breath test (Figure 1). Of these, 10 (76.9%)
were women and 3 (23.1%) were men (Figure 2). On the control group, SIBO was not shown through H_2 breath test. The association between the dyspeptic group and the control group in relation to SIBO showed a P value of 0.0052.

Dyspeptic patients were classified according to the dyspepsia presented: 4 (18%) patients with predominance of pain, 10 (43%) with fullness and 9 (39%) mixed (Figure 3). Of 4 (18%) patients with dyspepsia type pain, 3 (75%) were tested positive for SIBO through H_2 breath test. Of 10 (43%) patients with dyspepsia type fullness 5 (50%) were tested positive for SIBO. Of 9 (39%) patients with dyspepsia type mixed, 5 (55.5%) were positive for SIBO (Figure 4)

In the group of dyspeptic patients, 12 (52.2%) were using proton pump inhibitor (PPI); of these 9 (75%) were positive for SIBO. In the same group, 11 (47.8%) patients did not use PPI and of these, 5 (45.4%) were positive for SIBO. The association between the use of PPIs in dyspeptic patients and its lack of usage in the same group with SIBO was not statistically significant (P = 0.3065) (Table 2).

<table>
<thead>
<tr>
<th>SIBO+</th>
<th>SIBO-</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia with PPI</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia without PPI</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

*chi-square test

In the control group, none of the 11 patients used PPIs and SIBO was not observed.

The association of the dyspeptic group using PPI (12 patients) that were positive for SIBO and the control group was statistically significant, with P = 0.0011 (Table 3).

<table>
<thead>
<tr>
<th>SIBO+</th>
<th>SIBO-</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia with PPI</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Control group</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

*chi-square test

The association of the dyspeptic group without any use of PPI (11) that were positive for SIBO and the control group (11) was statistically significant, with P = 0.0419 (Table 4).

<table>
<thead>
<tr>
<th>SIBO+</th>
<th>SIBO-</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia without PPI</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Control group</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>17</td>
</tr>
</tbody>
</table>

*chi-square test

**DISCUSSION**

This study evaluated the occurrence of intestinal bacterial overgrowth in patients with dyspeptic symptoms, with functional dyspepsia diagnosis, using the H_2 breath after ingestion of lactulose. In the present study, 13 (56.5%) of the 23 dyspeptic patients analyzed, showed abnormalities in the breath test, thus being considered as having intestinal bacterial overgrowth, contrasting with the control group in which there was no evidence of this occurrence. The difference in frequency of SIBO was statistically significant.

This is a pioneering study, there are no publications in
Comparing such variables so far. However, studies in this direction are being made\(^{(11)}\).

Of the dyspeptic patients that were positive for SIBO on \( \text{H}_2 \) breath test, 10 (76.9\%) were females and 3 (23.1\%) were males, confirming the literature data, when dyspepsia in relation to gender is studied\(^{(10)}\). On the control group, SIBO was not observed in the \( \text{H}_2 \) breath test.

All patients were tested using \( \text{H}_2 \) breath test with 15 mL of lactulose as substrate. This substrate is not absorbed in the small intestine, but it is metabolized by the colonic flora. Therefore, every exam shows the \( \text{H}_2 \) peak lift approximately 90 minutes after ingestion of lactulose, corresponding to its arrival at the colon and representing the orocecal transit time\(^{(24)}\). The breath test is based on the quantification of the concentration of \( \text{H}_2 \) in the expired air, which is produced from intestinal bacterial metabolism\(^{(14)}\). It is a simple, safe, non-invasive diagnosis method for SIBO, with 44\% specificity and 68\% sensibility\(^{(17)}\). Its interpretation can be compromised when there are diseases associated with delayed gastric emptying (false negative) or rapid intestinal transit (false positive)\(^{(11)}\).

The colonization of the upper gastrointestinal tract by species characteristic of the colon was usually associated to structural abnormalities of the small intestine\(^{(24)}\). However, recent studies have shown that SIBO may present as mild and unspecific symptoms in patients without structural alteration of this organ\(^{(11)}\), such as functional dyspepsia patients.

In this study of the patients with dyspepsia type pain, three (75\%) had SIBO, being this the least frequent symptomatic subgroup, as accounted for 18\% of the dyspeptic symptoms. The other types of dyspepsia present were type fullness (43\%) and type mixed (39\%). Despite being more prevalent in the population studied, they presented SIBO in a lower percentage on \( \text{H}_2 \) breath test: 50\% and 55.5\%, respectively.

Rome III Consensus suggests that the inhibitors of acid secretion (proton pump inhibitors and \( \text{H}_2 \) blockers) are the first choice for patients with functional dyspepsia and predominance of epigastric pain, and the prokinetics (metoclopramide, domperidone, bromopride) for postprandial discomfort\(^{(18, 23)}\).

In the present study we observed that 12 (52.2\%) patients in the dyspeptic group were using PPIs. Of these, 9 (75\%) were tested positive for SIBO by \( \text{H}_2 \) breath test. In the same group, 11 (47.8\%) did not use PPIs and of these, 5 (45.4\%), showed SIBO quoted in the test. The control group patients did not use PPIs.

Therefore, it was observed a higher prevalence of SIBO in dyspeptic patients that were using PPIs. These results are in agreement with the studies of Lombardo et al.\(^{(12)}\), that demonstrate the association between SIBO and the prolonged use of PPIs. However, there was no significant statistical difference when compared with dyspeptic patients without the use of PPIs.

Recent studies demonstrated that gastric acidity and intestinal motility are seen as major mechanisms for the gastrointestinal flora control\(^{(26)}\). The use of PPIs reduces the gastric acidity, favoring the appearance of SIBO. The motor disorders, such as the delayed gastric emptying, may lead to the symptoms of dyspepsia and SIBO, since motility is responsible for the scanning of microorganisms that have survived to the stomach pH, inhibiting the bacterial growing in the small intestine\(^{(15, 19)}\).

This study has some limitations. We found difficulties on finding the control group volunteers, by the fact there only a few healthy patients were willing to be submitted to the breath test. The possibility that dyspeptic patients may have accelerated intestinal transit cannot be discarded, though unlikely.

In conclusion, this study demonstrated a high prevalence of SIBO in patients with functional dyspepsia. Also observed a higher prevalence of SIBO in dyspeptic patients that were using PPIs. Additional studies evaluating the effect of the treatment of SIBO in patients with dyspepsia, may clarify the role played by the intestinal bacterial overgrowth in the genesis of dyspeptic symptoms.
REFERENCES


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