

Irritable Bowel Syndrome and the Small Intestinal Microflora. What We Do Know?

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Irritable bowel syndrome, one of the most common functional gastro intestinal disorders all over the world is considered to have a multi factorial pathogenesis. Recently more and more studies are focusing on the changes that take place in the micro biota of patients with irritable bowel syndrome, underlining the bacterial role in this pathogenesis. As a consequence, bacterial overgrowth, along with intestinal dysmotility, altered brain-gut axis and genetic factors are considered part of this pathophysiology. This report intends to summarize the actual knowledge on irritable bowel syndrome and small intestinal bacterial overgrowth syndrome, from details on the epidemiology, clinical manifestation, pathophysiology, diagnosis, treatment to details on the relationship between these two syndromes.

Key words: Irritable bowel syndrome, Small Intestinal bacterial overgrowth, Hydrogen breath tests, Rifaximin.

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional disorder with a clinical diagnosis that is characterized by abdominal pain or discomfort, associated with abnormal bowel habits, bloating, flatulence, passage of mucus, and feeling of incomplete evacuation [1].

The prevalence of IBS in North America estimated from population-based studies is approximately 10 to 15% [2-7]. A study performed in Europe found a prevalence of 11.5 % (a value almost similar to that noted in reports in the United States); but, the prevalence varied widely among countries [8]. Having no specific disease marker, IBS is diagnosed according to the standardized diagnostic criteria based on symptoms, the Rome criteria [9].

The pathophysiology of IBS used to be considered only a psychosomatic one. During the past years it has been proven to be more complex, due to several factors: visceral hypersensitivity, intestinal dysmotility, abnormal brain-gut axis, genetic factors and altered intestinal micro biota [10, 11]. Over the past years, there has been a considerable amount of studies suggesting that gut flora plays an important role in the occurrence of symptoms and in the pathogenesis of IBS [12, 13].

2. INTESTINAL BACTERIAL MICROFLORA

The human gut is first colonized at birth; this micro biota gradually increases in size and diversity and by the end of the first year of life it has come to resemble that of the adult remaining relatively stable thereafter [14]. The composition of the gut micro biota varies according to age, sex, diet, geographical origin of the individual and it can be influenced by environmental factors, such as the use of antibiotics [15].

The human intestinal micro biota contains more than 1000 different bacterial species and 10^{14} cells, essential in the development, function, and homeostasis of the intestine, and for individual health [16]. The micro biota main functions are metabolic, protective, and trophic, helping in the digestion and absorption of nutrients, production of beneficial compounds such as short-chain fatty acids (SCFA), acting as a barrier against pathogens, generating immune response, influence the differentiation and proliferation of the intestinal epithelial cells and the development of the enteric immune system [15].

On the other hand, beside the beneficial effects, bacterial fermentation may result in a large amount of gas that accumulates in the bowel,

contributing to the symptoms of bloating, flatulence, and abdominal distension, which are commonly reported by patients with IBS [16].

In the small intestine there is a large proportion of Gram-positive and aerobic bacteria, whereas the large intestine consists largely of Gram-negative and anaerobic bacteria [17, 18]. Alteration in the composition or number of the bacteria that compose the micro biota and alteration of the colonic fermentation process may play an important role in the development of IBS symptoms. The major families of bacteria in the small intestine include Bacilli, Streptococcaceae, Actinobacteria, Actinomycinaea, and Corynebacteriaceae [14]. Changes of qualitative or quantitative order in the micro biota of the small intestine may lead to the clinical manifestations of SIBO [19, 20]. SIBO is traditionally defined by a bacterial count of $\geq 10^5$ colony forming unit (cfu) per mL of bacteria in the proximal small bowel [21].

3. DIAGNOSTIC METHODS FOR SIBO

There are several methods to diagnose SIBO, demonstration of excessive bacterial concentration in the jejunal aspirate performed during endoscopy or fluoroscopy being considered by most authors as the “gold standard” [22]. Using aspirative culture, Ghoshal *et al.*, in a study performed on 80 patients with IBS diagnosed according to Rome III, demonstrated a 19% prevalence of SIBO [23].

Because small bowel culture through jejunal aspirate is time-consuming, invasive, and potential for contamination with oro-pharyngeal flora, a number of non-invasive and indirect tests for diagnosing SIBO have been developed like the hydrogen breath tests (HBT). Breath tests are inexpensive, simple and non-invasive, tests which can be used for [24] the (1) detection of excess bacteria in the small intestine; (2) evaluation of carbohydrate maldigestion; and [25] estimation of intestinal transit time (Fig. 1). In order to diagnose IBS, all the above should be ruled out.

Disease	Reactive	Quantity
Malabsorption	D-Xylose	10 g
Lactase deficiency	Lactose	50 g
Fructose deficiency	Fructose	50 g
SIBO	Glucose	80 g
Celiac disease	Sorbitol	5 g
Oro-caecal transit	Lactulose	10 g
Sucrase deficiency	Sucrose	50 g

Figure 1. Use of respiratory breath tests.

The currently used breath tests (BT) are based on the ability of the bacteria to produce hydrogen (H_2), methane (CH_4) or radiolabeled carbon dioxide, after metabolizing a substrate such as glucose, lactulose, sucrose or d-xylose. Because the only source of gut H_2 and CH_4 results from the bacterial process of fermentation of the substrate, fasting breath H_2 and CH_4 gases have been used as markers of colonic fermentation [26]. Part of the H_2 produced by the bacteria, in the small intestine or in the colon, passes into the blood vessels from the wall of the small intestine and colon. The blood containing-hydrogen travels to the lungs where hydrogen and CH_4 is exhaled in the breath, making them available for measurement.

Pimentel and colleagues in a study performed in 2000 found 78% of 202 IBS subjects to be positive for LHBT which is suggestive of SIBO [27]. Starting with this study, SIBO has been proposed as an etiologic factor in IBS. The most common used breath tests are those with glucose or

lactulose HBT. In these tests, hydrogen exhaled in the breath is estimated using a gas chromatograph. Bacteria, especially anaerobic, colonizing the small bowel in diseased conditions, produces H_2 or CH_4 after fermentation of unabsorbed carbohydrates [28]. Under normal conditions, glucose is immediately absorbed in the small intestine but in the presence of bacterial overgrowth, bacterial fermentation of glucose resulting in gas production takes place before the absorption of glucose. These results in an increase in H_2/CH_4 concentration in the breath that can be measured [29]. The glucose BT is considered positive if there is a clear H_2 peak, exceeding 20 ppm before the 120 minutes have passed (Fig. 2).

Lactulose, a simple disaccharide is usually transported intact throughout the small intestine into the colon where it is metabolized by colonic bacteria, resulting into H_2 and CH_4 that are measured in the breath. Samples of expired air are collected every 10 minutes for 2 hours. The time interval between ingestion of lactulose and rise in

H_2/CH_4 concentration ≥ 10 ppm in two consecutive readings is considered a positive test (Fig. 3).

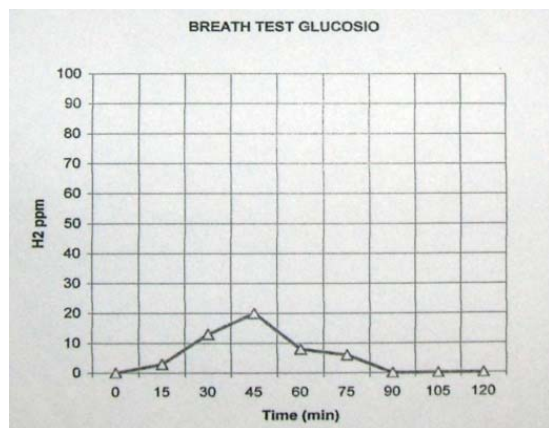


Figure 2. Glucose breath test (Recorded in the laboratory of Prof. P. Portincasa).

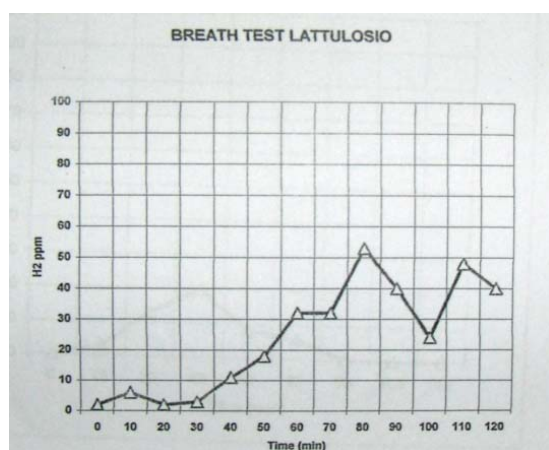


Figure 3. Lactulose breath test (Recorded in the laboratory of Prof. P. Portincasa).

Some investigators have reported increased H_2/CH_4 production following administration of fermentable substrates in patients with IBS compared with healthy controls [30]. They explained these results by the fact that certain individuals meeting the diagnostic criteria for IBS may actually have SIBO [31].

Before performing a HBT there are a few rules that must be applied: the subjects are asked to avoid eating slowly absorbed carbohydrates and fibres, cigarette smoking and exercise are avoided 2 hours before and during the test. Antibiotics, drugs that affect the intestinal motility or those that can cause SIBO, including proton pump inhibitors, should be stopped before performing breath tests [28]. Vitamins and laxatives are forbidden at least in the 24 hrs before the HBT. Just before the test, subjects are asked to brush their teeth and disinfect their mouth.

4. IRRITABLE BOWEL SYNDROME AND SMALL INTESTINAL BACTERIAL OVERGROWTH

All over the world there have been several studies performed using HBT, with a prevalence of SIBO between 11-84% in IBS patients. Using LHBT, Pimentel *et al.* [32] found abnormal breath test results in 93/111 (84%) patients with IBS. In a study performed by Scarpellini on fifty IBS children the prevalence of SIBO diagnosed by an abnormal LBT was 66% (33/50) [33]. In a study from Pakistan, the lactose H_2 breath test was used to diagnose SIBO in IBS patients, SIBO being observed in 14% (32/234) cases [34].

A recent study by Meyrat *et al.* also observed a high percentage of positive lactulose breath tests among IBS patients (71%). IBS-associated symptoms improved following 2 wk of treatment with an antibiotic, rifaximin [35]. A study performed on 65 IBS patients and 102 controls found a positive glucose breath test in 31% and 4% respectively [36].

Almost the same results (35% positive GHBT) were obtained in the study of Reddymasu [37]. Approximately the same results were found in a multicenter study performed in Romania that evaluated the presence of SIBO in 331 patients diagnosed with IBS according to Rome III criteria and 105 HV. In this study, 31.7% of the IBS patients have been diagnosed with SIBO and 6.6% out of the HV group. In our study we have found a large proportion of patients with SIBO from the IBS-D group (48 patients out of 105, 45.7%), data that coincide with the literature [38].

Clinical studies using direct sampling of jejunal aspirates detected SIBO in 4% to 12% of patients with IBS, a smaller prevalence compared with results of breath testing [39]. Differences in the geographical origin of individuals included in the study, criteria used for the diagnosis of IBS, methods for diagnosis of SIBO, definition applied for a positive HBT and methods for performing breath tests, might explain the variation in prevalence of SIBO in different studies.

5. CONCLUSIONS

There are currently no recommendations guiding clinicians on whether they should routinely test for SIBO in their IBS patients. However, there is a lot of evidence suggesting that, especially in the case of IBS patients with diarrhea, the role of

SIBO in the pathogenesis and symptoms remains important [40].

Even if there are strong arguments supporting the concept of intestinal microbiota perturbation in patients with IBS, we are still lacking information on the pathophysiologic mechanisms through which microbiota interacts and generate symptoms. The SIBO hypothesis in IBS remains a matter of debate because the breath tests and the small bowel culture techniques have not been validated [41].

Though jejunal aspirate culture is considered as gold standard for diagnosis of SIBO, this has limitations, is invasive and difficult to be accepted by the patients. On the other hand, HBT is simpler, more acceptable by the patients than jejune aspiration and gives quicker information to the clinician than microbiologic culture of the jejune aspirate. There is an urgent need for new studies on the role of SIBO in IBS and to standardize the diagnosis of SIBO.

Sindromul de intestine iritabil, una dintre cele mai frecvente afecțiuni funcționale gastrointestinale, are o patofiziologie complexă. În ultimii ani tot mai multe studii cercetează modificările microbiomului pacienților cu sindrom de intetstin iritabil, subliniind rolul pe care bacteriile îl au în patogeneza acestuia. Ca urmare, suprapopularea bacteriană intestinală, asociată tulburărilor de motilitate intestinală, afectarea axului creier-intestin și factorii genetici sunt considerați ca având roluri importante în patofiziologia acestei afecțiuni. Prezenta lucrare încearcă să facă un rezumat al cunoștințelor actuale privind relația sindrom de intestin iritabil – suprapopulare bacteriană intestinală, pornid de la epidemiologie, manifestări clinice, patofiziologie, diagnostic și tratament.

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