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Small Intestinal Bacterial Overgrowth: Diagnosis, Pathophysiology and Treatment Methods

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Abstract

Small intestinal bacterial overgrowth (SIBO) is the excessive abundance of nonpatogenic microbes in the small bowel, which are characteristic to the large intestine. It is often referred to as dysbiosis. Typical symptoms include: immoderate flatulence, abdominal pain, steatorrhea or micronutrient deficiencies that may cause conditions like anemia or general fatigue associated with it. The dysfunction of the intestinal mucosal barrier and chronic inflammation, caused by SIBO, are the causes of many diseases, for example fatty liver disease and autoimmune diseases, which also act as predispositions to bacterial overgrowth. The diagnosis is based mainly on the breathing tests. The therapy is comprehensive and relies on pharmacological treatment, adequate diet (usually low-FODMAP diet is recommended) as well as preventive measures in order to avoid the relapse. The key to complete recovery is correct identification of the core cause and its removal, which is often not so clear as SIBO manifests itself with many nonspecific symptoms and therefore, may be misidentified as irritable bowel syndrome, celiac disease or other GI tract diseases.

This article reviews and summarizes the current state of knowledge about the bacterial overgrowth in the small intestine.

Key words: *Small Intestine Bacterial Overgrowth, SIBO, Irritable bowel syndrome, IBS, rifaximin, microbiome, dysbiosis, acne*

Introduction

Research, carried out as part of the Human Microbiome Project, contributed to the discovery and analysis of microbes inhabiting the human gastrointestinal tract. It indicated a great qualitative and quantitative diversity of bacteria, as well as individual variability of gut flora – that is, between people. Bacterial intestinal composition is dynamic and fine-tuned, meaning it undergoes changes depending on one's lifestyle as well as previous and ongoing diseases [1]. For this reason, changes in the level of specific strains are already being used as a diagnostic tool directed for disease detection and may also be used in the development of potential therapies based on probiotic bacterial strains [2]. However, despite many beneficial functions, an imbalanced composition of the intestinal microflora may lead to undesirable conditions. One of these digestive system disorders is SIBO – Small Intestinal Bacterial Overgrowth, which is characterized by an excessive number of bacteria in the small intestine that are specific to the large intestine. Many patients with this condition suffer from general disorders such as bloating, diarrhea or abdominal pain, and because of that, they are often misdiagnosed for IBS (Irritable Bowel Syndrome). However, some authors suggest that SIBO may also be the underlying cause of IBS [3].

Due to many common, nonspecific symptoms, it is possible that bacterial overgrowth in the small intestine is mistakenly categorized as a food allergy, inflammatory bowel disease, or a result of chronic stress, and therefore patients with mentioned conditions live with bothersome disorders for many years. However, the cause of this disease is the overgrowth of bacteria that naturally inhabit the large intestine. This lack of harmony leads to malabsorption of valuable nutrients, such as fats and vitamins. In extreme, untreated cases, this disease can lead to weight loss, major deficiencies or even osteoporosis [4, 5].

Definition

The main characteristic of SIBO is an excessive amount of bacteria in the small intestine. The disease is diagnosed when the number of bacterial populations exceeds 105–106 organisms per mL of collected sample [6]. It is worth noting that the average number of organisms in equilibrium state should not exceed 10^3 organisms per mL of sample [7, 8].

The qualitative composition of the microbes inhabiting the intestine is also taken into account during the diagnosis. For example, one of the indicators of dysbiosis is the prevalence of bacteria metabolizing bile salts to insoluble compounds. This leads to impaired fat absorption and, consequently, steatorrhea. Too abundant amount of microorganisms that are responsible for the conversion of carbohydrates to SCFAs (Short-Chain Fatty Acids) and gases can cause abdominal distension without diarrhea, fatty acids are absorbed by the intestinal epithelial cells, whereas gases are responsible for the feeling of bloating or even lower abdominal pain. Other bacterial species, such as *Klebsiella*, can produce toxins that damage the mucosa, contributing to its inflammation and impaired absorption [9, 10].

Clinical picture

The symptoms of SIBO are very nonspecific and overlap with those assigned to IBS, lactose or fructose intolerance [11]. For this reason, the disease has been rarely diagnosed. Moreover, indicators of bacterial overgrowth in the small intestine vary in intensity between patients. The most common ones are:

- abdominal distension
- diarrhea or, on the contrary, constipation; may occur alternately,
- nausea,
- indigestion
- lower abdominal pain and discomfort

- malabsorption, which causes deficiencies of nutrients, vitamins (i.e. A, D, E, K, B vitamins), micro- and macro- elements (i.e. iron, omega-3 fatty acids)
- headaches and fatigue
- depressive and anxiety states

Typically, about 60% of patients report the presence of listed symptoms. Distended Stomach is often the most troublesome symptom. Gaseous accumulation in the initial section of the intestine can lead to reflux, as well as pain and discomfort [10]. Vitamin deficiencies (mainly from group B) contribute to the development of, among others, acne. Moreover, one study found that people with SIBO were 10 times more likely to suffer from *acne vulgaris* than healthy people [4, 12, 13].

Due to the excessive uptake of vitamin B12 by microbes, anemia can also occur. On the other hand, damage of the enterocytes in the intestine disturbs the digestion and absorption of for example disaccharides, which may be manifested by lactose and fructose intolerance [12, 13]. Additionally, the malabsorption of fats and vitamins soluble in them, is the result of improper metabolism of bile salts. However, it is worth noting that symptoms caused by hypovitaminosis of fat-soluble vitamins are rarely manifested. Therefore, night blindness, hypocalcaemia, neuropathies and retinopathies, immunodeficiencies or blood coagulation disorders occur only in extreme cases [10].

Etiology

The cause of bacterial overgrowth in the small intestine is the disturbance of microbial homeostasis. The most frequently mentioned conditions that predispose patients to this disease are associated with changes in the motility of the GI tract as well as enzymatic functions of digestive system. Hypochlorhydria increases the risk of bacteria being transferred from food and settling in the small intestine. The deficiency of hydrochloric acid, secreted by the parietal cells of the mucosal layer, allows these bacteria to survive [15]. Another major predisposition is believed to be

lying in the damage of the MMC – Migrating Myoelectric Complex, causing chyme - partially digested food, to accumulate. This promotes the growth of bacteria in the small intestine. Other factors are immune-related disorders, like congenital and secondary immunodeficiencies characterized by excess of immunoglobulin A (IgA) in the lumen of the gut, as well as anatomical abnormalities of GI tract, for example - small intestine constriction or the formation of 'blind loops' , diabetes, celiac disease, neurodegenerative diseases [10, 17, 18]. Some researchers imply that immunosuppresive therapy can also cause SIBO, although the data is quite ambiguous. The study conducted by Siniewicz-Luzeńczyk and Tkaczyk has shown that children suffering from steroid-dependent idiopathic nephritic syndrome, who underwent cyclosporine therapy (second line immunosuppressive agents), do not develop SIBO. Nevertheless, some of the children indicated having symptoms characteristic to SIBO, such as abdominal discomfort [16].

Research [7, 19, 20, 26] has shown that there are several risk factors predisposing to SIBO, including:

i. anatomical tendencies (diverticula of the small intestine, strictures, fistulas, obstructions)
ii. intestinal motility disorders (celiac disease, gastroparesis)
iii. irritable bowel syndrome
iv. metabolic disorders (diabetes, hypochlorhydia)
v. organ dysfunctions (cirrhosis, conductors, pancreatitis, immunodeficiency, Crohn's disease, malnutrition)
vi. certain medical treatments (excessive intake of antibiotics, gastric acid secretion suppressors)
vii. alcoholism
viii. age-related complications and diseases, including Parkinson's disease

Overgrowth of microbes may also contribute to the development of inflammatory state in the intestinal mucosa, further aggravating the typical symptoms of SIBO [22]. According to Miazga et al., inflammation causes changes in the patterns of expression of genes involved in the production and secretion of mucus, thus creating correlations between

such disease entities as SIBO, IBS, cystic fibrosis or chronic abdominal pain [23].

Diagnostics

SIBO diagnosis is mainly based on breathing tests and the roman criteria IV [24]. It measures the amount of hydrogen separately, or both methane and hydrogen in the exhaled air. The unit is ppm - parts per million [25]. This method is proceeded under two conditions – first measure is done after fasting and another after ingestion of a fermentable product (usually 10 grams of lactulose or 75 grams of glucose, in the form of 200 mL of solution), as these gases are produced during bacterial fermentation reactions. These measurements are taken at intervals of 15–20 minutes. Thus, the amount of gases is proportional to the size of microbial proliferation, while the time when the increase in hydrogen/methane concentration is detected, indicates the section of the intestine occupied by the questioned pathology [26].

Interpretation of the test for determination of SIBO is based on an increase of ≥ 20 ppm above the baseline in exhaled hydrogen, up to 120 minutes from the start of the measurement [19, 26]. It is worth adding that this technique is nearly noninvasive and easy to carry out. However, before testing, patients should prepare themselves by eating a low-fermenting diet for 1–2 days prior the testing, and fasting for 12 hours before coming in for the test [28].

Another method is to take a liquid aspirate from the small intestine and culture it. Although this test is considered to be the gold standard [29], it is rarely performed due to the higher invasiveness, possible complications in sampling and contamination of the sample. In addition, some species of microbes that colonize the intestines cannot be cultured *ex vivo*, which makes it impossible to accurately determine the number of bacteria. This issue is made even more difficult by the dispersed distribution of bacteria in the intestine. Thus, the sample taken may not be representative [17].

Drug treatment and diet

The first step in getting rid of SIBO is antibiotic treatment. The most commonly recommended is a course of rifaximin – typically 1200 milligrams per day for 10–14 days. Its action is particularly helpful in this disease, because as an eubiotic it has a protective effect on the beneficial microflora as well as its anti-inflammatory activity has been confirmed. Antibiotic therapy with the use of two antibiotics is also possible. This possibility is advised in the presence of severe, chronic constipation. The additional antibiotics used are metronidazole or neomycin. An important aspect is also the stimulation of intestinal motility by prokinetics and eating a properly balanced diet [30, 31].

Patients affected by SIBO should follow the diet recommended during antibiotic therapy, which facilitates the treatment process and eliminates troubling symptoms by reducing inflammation. The first step is to remove simple sugars that are rapidly broken down by bacteria, which increases their proliferation rates and enhances inflammation. Products rich in fiber cause adherence of undigested carbohydrates to the intestinal wall causing bloating or diarrhea. Therefore, the most frequently proposed diet is a low FODMAP diet, meaning low in Fermentable Oligo-, Di-, and Monosaccharides and Polyols. This diet was developed by researchers at Monash University in Australia. Therefore, food categories abundant in fructose, glucose (i.e. honey, agave syrup, many fruits), as well as lactose, galactans (found in legumes) should be eliminated [19, 23]. Recommended low-FODMAP products are listed in Table 1.

In some cases, intake of histamine-rich foods (i.e. tomatoes, peppers, red wine) should also be temporarily reduced. Intolerance to the these foods can cause allergy-like symptoms due to the lack of access to the enzyme - diamine oxidase, in the brush border of apical surface of some intestinal epithelial cells. This enzyme's activity is to break down excess of histamine [14].

A 2010 study found that incorporating probiotic-rich foods into the diet reduces the symptoms of SIBO. In addition, under certain circum-

stances, it is also important to include supplementation during therapy, because patients suffering from dysbiosis and subsequent malabsorption are prone to deficiencies of micronutrients, including omega-3 acids and vitamins, especially A, D, E, K. Impaired absorption of vitamins from food, in severe cases may cause several disorders linked to disturbed haematopoiesis , digestive functions, or the metabolism of bone tissue and skin. Thus, not treating SIBO could lead to additional complications such as anemia, acne, osteoporosis, night blindness or chronic fatigue syndrome [10, 34].

Table 1. Example products classified into the low-FODMAP group – with a low content of fermentable oligosaccharides, disaccharides, monosaccharides and polyols [32, 33]

Food category	low-FODMAP product
Vegetables	carrot, cucumber, lettuce, tomato, ginger, kale, okra, olives, pumpkin, algae, chicory, potatoes, spinach, eggplant, beetroot
Fruits	banana, orange, mandarins, grapes, clementines, pineapple, strawberries, rhubarb, papaya, blueberries, melon, kiwi
Milk products	lactose-free milk and yoghurt, hard cheeses
Protein sources	white and red meat, fish and seafood, tofu
Grains	gluten-free sourdough bread, spelled, rice, oats, gluten-free pasta, quinoa
Nuts and seeds	almonds, macadamia nuts, peanuts, Brazilian nuts, pumpkin seeds, poppy seeds, sesame seeds, sunflower seeds
Other	herbs (basil, coriander, mint, oregano, parsley, thyme, rosemary), natural spices, tea (black, green)

In addition to modifying the diet, probiotics are also tested as means in the treatment of SIBO. However, current studies are inconclusive [20]. A meta-analysis made by Zhong et al. [35] suggests that probiotics may suppress the proliferation of gut bacteria that are the source of SIBO, giving better breath test results and reducing abdominal pain. It is worth noting, however, that the studied sample was not very representative and heterogeneous, meaning that further research is required [35]. Whereas research conducted by Chedid [37] has shown that herbal therapies

apparently maybe be as effective as treatment with rifaximin for resolution of SIBO and because of that, can be used as a replacement for antibiotics. In the experiment, herbal therapies increased the response rate for normalizing breath hydrogen testing by over 10%, compared to SIBO patients treated with rifaximin. These commercial, herbal preparations, among others, consisted of: *Thymus vulgaris*, *Salvia officinalis*, *Glycyrrhiza uralensis*, *Origanum vulgare*, *Melissa officinalis*. Although substances derived from such plants are known to have antibacterial and anti-inflammatory activities, more research in this field is needed as cited study needs more validation, as it was not a prospective, randomized controlled trial. However, it broadens current knowledge and possible therapies that do not necessarily base on antibiotics [37].

Nevertheless, it is worth emphasizing that an adequate, elimination diet is only able to reduce some symptoms, and not remove the core cause of SIBO. Its implementation should be preceded by a recommendation from a specialist, and after the symptoms of SIBO have subsided, gradually switch to a standard, diverse diet [7]. Additionally, treatment of SIBO also requires the right amount and quality of sleep, stress reduction and physical activity, which all also stimulate metabolism.

Summary

Research indicates that up to 15% of the population might suffer from Small Intestine Bacterial Overgrowth. Middle-aged and elderly people are more prone to it, as well as those diagnosed with irritable bowel syndrome (IBS) [10]. Prevalence of SIBO is more frequent in the lower socioeconomic strata of developing countries and children from families with smaller income, thus contributing to poor carbohydrate absorption, malnutrition and worse oral vaccine results [38, 39]. These facts contribute to the improvement of current diagnostic tools and therapies, as well as raising awareness concerning the problem. It is crucial to identify the cause of SIBO, remove its cause or at least mitigate the symptoms. A significant part of the current knowledge about the pathogenesis of discussed

disease, comes from studies conducted in developed countries, where the research sample consisted of patients with co-occurring pathologies of the gastrointestinal tract. Thus, it would be important to understand what is the etiology and pathophysiology of SIBO and whether it differs between children in developing countries, who have not been diagnosed with multimorbidities, and patients from highly industrialized countries.

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