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HYDROGEN AND METHANE BREATH TESTING FOR ABDOMINAL BLOATING OF SMALL INTESTINAL ORIGIN

Introduction

Abdominal bloating with or without excessive gas production and with or without abdominal distention is common, very bothersome for patients, and is poorly understood. Bloating can be associated with gastrointestinal disorders, nutrient malabsorption, and systemic illnesses. The origin of abdominal bloating is often unclear, though it is usually associated with food intake and bowel motility dysfunction. Often, food allergies, food intolerance, or food poisoning are considered by the patient or physician as potential causes for bloating. A common concern in the patient's mind is that healthcare professionals will dismiss or misdiagnose their complaint. The limited understanding of the pathophysiology of bloating leads to current empirical management, and bloating is often characterized as a "functional" disorder. Bloating carries a heavy clinical, psychological, and economic burden. Proper diagnosis will provide the patient with peace of mind and lead to effective treatment. This review focuses on the mechanisms and management of abdominal bloating associated with different small intestinal disorders identified by non-invasive hydrogen and methane breath tests.

The pathophysiology of bloating

Bloating is a heterogeneous condition produced by a combination of pathophysiological mechanisms that differ among individual patients and, in most cases, are subtle and undetectable by conventional methods.[1,2] Gas transit studies have provided evidence that patients with bloating have impaired reflex control of gut handling of content leading to ineffective motility [3]. The build-up of liquid or gas in a section of the intestine may induce bloating, particularly in patients with altered gut perception.[3]

The small intestine is richly innervated by vagal sensory nerves. These nerves are associated with various types of receptors, including mechanoreceptors, chemoreceptors, thermoreceptors, and osmoreceptors. These receptors transmit information to the nucleus tractus solitarius, an important control center for autonomic regulation. The response to this sensory information is influenced by many nuclei in the central autonomic network, including the amygdala, such that various factors, including stress, can influence perception and the experience of bloating. To avoid bloating, intestinal distention needs to evoke proper motor patterns. During fasting, the migrating motor complex (MMC), which is a cyclical wave of neural excitation that generates motor activity in the stomach and proximal intestine, moves slowly across the intestine, approximately every 130 minutes, to remove waste, including bacteria. In fact, the MMC serves as a natural protection against bacterial overgrowth[4-6]; hence, a sufficient period of fasting is needed for its development.

In response to food intake while awake, stomach distention triggers vagal sensation that will evoke peristaltic activity in the stomach and in the small intestine. In addition, the intrinsic enteric nervous system is, independent of the central nervous system, capable of initiating distention-induced peristalsis.[7] These neural activities trigger excitation in the pacemaker cells of the gut, termed the interstitial cells of Cajal, which orchestrate peristaltic and segmental contractile activity.[8,9] A reduction of intestinal pacemaker cells can lead to bacterial overgrowth.[10]
When any of the factors involved in contraction generation to move gas in the anal direction are weakened, bloating may develop. In addition, medications, such as anticholinergics, can potentially influence motility, and therefore, medication intake may have to be adjusted. The activity of the sympathetic nervous system normally inhibits motility but this can become excessive due to stress, anxiety, spinal injury, and general autonomic dysfunction.[11-13] Hence, in concert with testing for bacterial overgrowth, motility disorders need to be evaluated and incorporated into the treatment strategy.

A diet rich in fermentable products can exacerbate bacterial overgrowth, thus, a discussion with the patient about diet should also be included in the treatment strategy.[14] Patients taking proton pump inhibitors (PPIs) have a 3-fold higher risk of developing bacterial overgrowth.[15] Since PPIs are massively oversubscribed,[16] speaking with the patients about their use is warranted.

Clinical features of small intestine bacteria and methanogen overgrowth

Excessive gas content in the small intestine can induce uncomfortable sensations and symptoms such as bloating, fullness, belching, flatulence, increased abdominal girth, and associated difficulty of breathing. In a healthy person, normal gas formation in the intestine is removed by motility-induced transit. Excessive gas may be caused by swallowing air associated with gulping food or liquids, anxiety, gum chewing, smoking, products of fermentation such as

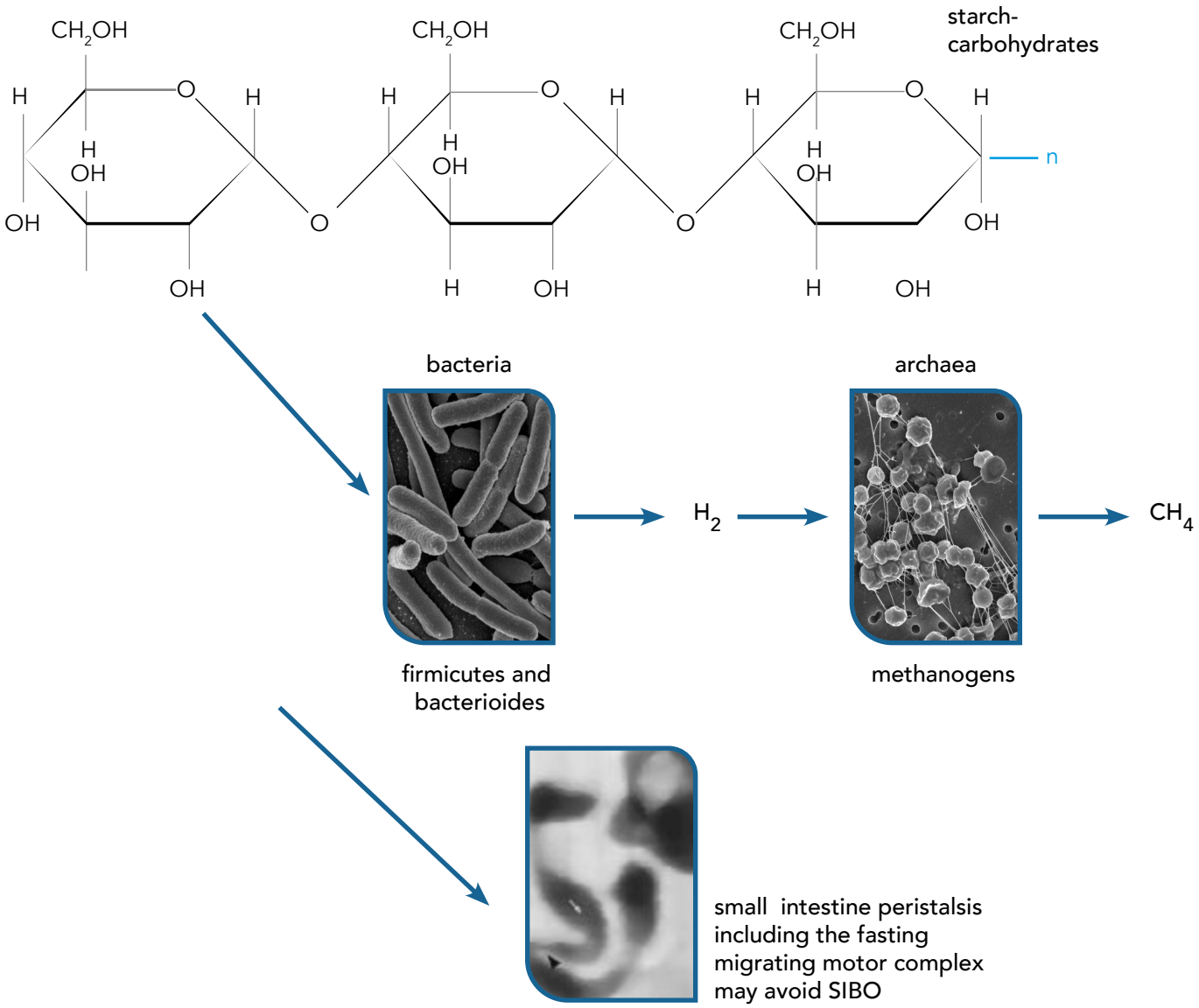

Figure 1: *Gas production in the small intestine Bacterial overgrowth can lead to excessive hydrogen (H2) production, hydrogen, which may feed methanogens to produce methane (CH4). Excessive gas production may be a result of poor small intestinal peristalsis, including a diminished fasting motility pattern, known as the migrating motor complex,[42] that may hinder bacterial removal. Adpated from Der-Silaphet T. et al, 1998*

carbon dioxide from the digestion of fat and protein, hydrogen from bacteria, or methane from archaea, such as *Methanobrevibacter smithii*.[17]

Small intestine bacterial overgrowth (SIBO) is defined by the presence of excessive bacterial growth in the small intestine, which often causes diarrhea and may cause weight loss and malnutrition. Intestinal methanogenic overgrowth (IMO) is defined as methanogen overgrowth in the small intestine and/or in the colon.[14,18,19] Elevated methane levels induce slow intestinal transit through the small intestine, leading to constipation that may be irresponsive to laxatives.[20] A patient may experience up to two weeks without bowel movements despite laxatives and prokinetics. When IMO is demonstrated by breath tests, patients are five times as likely to have constipation compared to hydrogen-dominant SIBO.[14]

In addition, the degree of breath methane production in irritable bowel syndrome (IBS) correlates with the severity of constipation.[21]

Methanogens primarily metabolize hydrogen and carbon dioxide to produce methane. Therefore, the overgrowth of hydrogen-producing bacteria will coexist with IMO **(Figure 1)**. Abdominal pain is often present in SIBO and IMO.[22] Hence, SIBO and IMO often meet the diagnostic criteria for IBS. Therefore, patients with SIBO or IMO might be incorrectly treated for IBS for many years. Conversely, IBS may not be associated with bacterial overgrowth and should not be treated with antibiotics without carrying out the appropriate testing. Poor response to treatment and dietary confusion have a significant impact on a patient's daily life. Delayed diagnosis and treatment of severe SIBO can lead to

abnormal bacterial colonization and micronutrient deficiency of vitamin B12, fat-soluble vitamins, iron, thiamine and niacin.[23]

Etiology and risk factors

Intestinal motility disorders, together with chronic pancreatitis, account for about 90% of cases of SIBO.[24] Pancreatic insufficiency predisposes SIBO by diminishing the quantity and composition of digestive enzymes and reducing the synthesis of antimicrobial enzymes.[24] SIBO may also contribute to pancreatic insufficiency: excess bacteria in the small intestine deconjugate bile acids, which impairs micelle formation and thereby reduces the efficacy of pancreatic lipases.[25] Immune disorders affect immunoglobulins in intestinal secretions, which are important in maintaining microbial homeostasis.[26] Our own experience suggests that previous food poisoning and occupational exposure to wild animals or toxins can be risk factors. D-lactic acidosis is a rare neurologic syndrome in patients with SIBO that is associated with short bowel syndrome or a prior jejunoileal bypass.[27]

Given that both diet and bacterial metabolites influence immune responses, the influence of gut microbiota on the increasing incidence of allergies and asthma has been considered.[28] In a study that included 70 children with chronic abdominal pain, 35 tested positive for SIBO, and 71% of those with SIBO were found to have an allergic disease, in contrast to 29% of children without SIBO.[29] The association between SIBO and allergic diseases included allergic rhinitis, cow's milk protein allergy, and asthma. SIBO is also common in mast cell activation syndrome.[30]

Hydrogen and methane breath test

Hydrogen and methane breath tests are non-invasive diagnostic procedures used to identify specific conditions related to the digestion of carbohydrates (starchy foods, sugars) in the small intestine. Notably, these tests can detect SIBO and IMO. Patients with frequent abdominal bloating, cramping, increased gas production, irregular bowel function, and those whose symptoms appear to be related to prior infection[31,32] or triggered by food containing lactose or fructose may benefit from these tests. Hydrogen and methane are exclusively produced by microbial fermentation in the gut, which is the principle behind clinical breath testing. Gut microbes readily digest carbohydrates, producing these gases as byproducts, which diffuse into the abdominal venous circulation and are transported to the lungs, where they can be detected in the exhaled breath.[33] In healthy individuals, carbohydrates are hydrolyzed into glucose, fructose and galactose which

are quickly absorbed in the small intestine so that little hydrogen production will be measured in the breath. Of note, hydrogen is produced by bacteria, but archaea produce methane. Archaea are similar to bacteria in that they are single-cell microbes without nuclei; however, their membrane composition is different from that of bacteria, and they do not react to most antibiotics. When methane is detected by a breath test, the hydrogen levels in a breath test become unreliable. This is because most of the methanogenic archaea in the human gut utilize hydrogen in the generation of methane, which then impacts hydrogen measurements in the breath test. The methanogens in the gut consume 4 molecules of hydrogen and 1 molecule of carbon dioxide to produce each molecule of methane. Hence, in a situation of excess methane producers, the detection rate of an early rise in hydrogen production can significantly decrease.

Hydrogen breath test using glucose for the diagnosis of small intestinal bacterial overgrowth

Under normal conditions, glucose is absorbed in the proximal and mid small intestine and does not reach the colon. During the short time glucose is in the small intestine, there is little bacterial fermentation and little hydrogen production. However, if bacterial overgrowth occurs in the small intestine, a 75 g dose of oral glucose will be metabolized,[14] and hydrogen can be measured in the breath.

Methane breath test to assess the presence of excessive methane-producing microbes

The methane breath test will assess the presence of microbes that produce methane, termed methanogens, in response to a dose of 75 g of oral glucose.[14] These microbes are primarily archaea, such as *Methanobrevibacter smithii*. In addition, when executing a hydrogen breath test, it is critical to measure methane levels as well to rule out a compromised hydrogen breath test that may be caused by the consumption of hydrogen by methanogens.

Hydrogen breath testing for the diagnosis of fructose or lactose maldigestion/intolerance

If fructose or lactose are not absorbed in the small intestine, bloating can occur. Fructose is absorbed by intestinal epithelial cells via the membrane transporter GLUT 5. If this transporter is not present, fructose cannot be absorbed. Lactose, exclusively found in dairy products, cannot be absorbed by intestinal epithelial cells; the enzyme lactase, present along the brush border membrane of the intestinal epithelial cells, is responsible for breaking lactose down into glucose and galactose, which can be absorbed. Normally, fructose and the metabolic products of lactose are absorbed in the small intestine, and are therefore not significantly metabolized by bacteria, resulting in a negative hydrogen breath test. If, during the test, fructose or lactose are not absorbed in the small intestine because of maldigestion or intolerance, they will enter the colon where they are fermented by bacteria that produce hydrogen. Thus, hydrogen will appear in the breath test. These breath tests should be conducted for up to 180 minutes, with the timing of the peak hydrogen level depending on small intestine transit time. Importantly, before testing for lactose or fructose intolerance, intestinal bacterial overgrowth needs to be excluded.

Hydrogen breath test using lactulose for orocecal transit time

Lactulose is metabolized in the colon by colonic bacteria, and it does not normally undergo fermentation in the small intestine. Hence, the time it takes for hydrogen to be detected in the breath after lactulose intake is considered the time that lactulose has entered the colon. Rapid transit would show a peak in the hydrogen level from ~ 30–90 minutes, and normal transit from ~ 90–180 minutes.[33] Considering that SIBO may cause an early peak in the hydrogen level, the presence of SIBO should be excluded prior to the test to interpret the transit time correctly. This test is helpful in some patients for a correct breath test interpretation, although it should not be used as a routine transit test.[14,33]

Treatment strategies for small intestine bacterial overgrowth, intestinal methanogenic overgrowth and fructose intolerance

The treatment strategy for SIBO is to control bacterial overgrowth, and for IMO, it is to control both hydrogen and methane producers in the small intestine. Approximately 40% of patients with SIBO have persistent symptoms after initial antibiotic treatment.[34] IMO is more refractory than SIBO, because methanogens are not sensitive to antibiotics.[35] SIBO recurrence is more likely to occur in older adults, those who have undergone an appendectomy, and those with long-term PPI use.[19] For patients in these circumstances, further courses of treatment need to be considered. In our clinic, one or two courses of oral amoxicillin-clavulanate 875 mg twice daily for 10 days have achieved successful control of both gastrointestinal symptoms and hydrogen/methane levels. Other antibiotic options include metronidazole and ciprofloxacin. Rifaximin, a non-absorbable rifamycin derivative, is effective in the treatment of SIBO.[36] For the treatment of IMO, neither rifaximin or neomycin are able to specifically target archaea or methanogens. Rifaximin alone and a combination of rifaximin and neomycin have shown some effectiveness in reducing methane production in the gut.[37] Owing to the high cost of rifaximin and the adverse effects of neomycin, such as neurotoxicity, this combination treatment is rarely used in clinical practice.

Recently, statins have been considered as a treatment for methane production in humans.[37,38] Lipid-soluble statins are fungal metabolites that enter *Methanobervibacter smithii* inhibiting their growth and activity.[39] Clinical trials have not yet been successful, likely because of the difficulty of maintaining levostatin in the small intestine for a sufficient amount of time.[M. Pimentel, personal communication, October 2023]

Fructose is a carbohydrate that is naturally found in fruits, fruit juices, some vegetables, and honey.[40] Patients with fructose intolerance should limit high-fructose foods, such as juices, apples, grapes, watermelon, asparagus, peas, zucchini, and large servings of tomato. Patients can experiment to determine if they can tolerate lower fructose foods, which include bananas, blueberries, strawberries, carrots, avocados, green beans, and lettuce. Patients should be aware that sweeteners in many processed foods and beverages are high in fructose, such as table sugar, corn syrup, honey, and molasses.[41]

Conclusion

Hydrogen and methane breath tests help to identify a variety of diseases of the small intestine that have bloating as the dominant symptom. These tests can be a useful addition to a diagnostic strategy to reveal anatomic (small intestine and colon), metabolic (lactose/fructose digestion), motility (transit), and infectious origins of the symptoms. Breath testing guides the optimization of clinical management. Eradicating overgrowth of bacteria and methanogens may not be sufficient to combat symptoms of bloating. Abnormal small intestinal motility plays an important role in the pathogenesis of SIBO and IMO and this issue should be addressed in concert with dietary advice and a thorough evaluation of medication use.

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