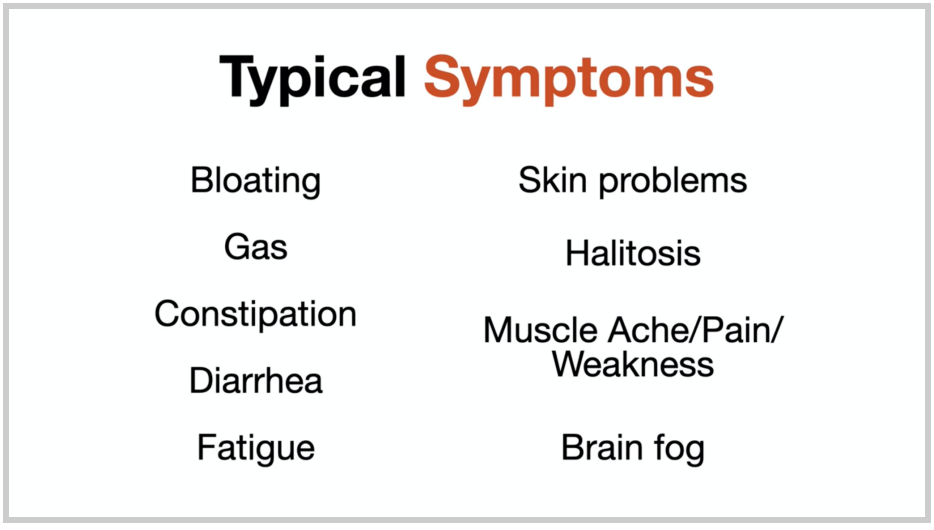
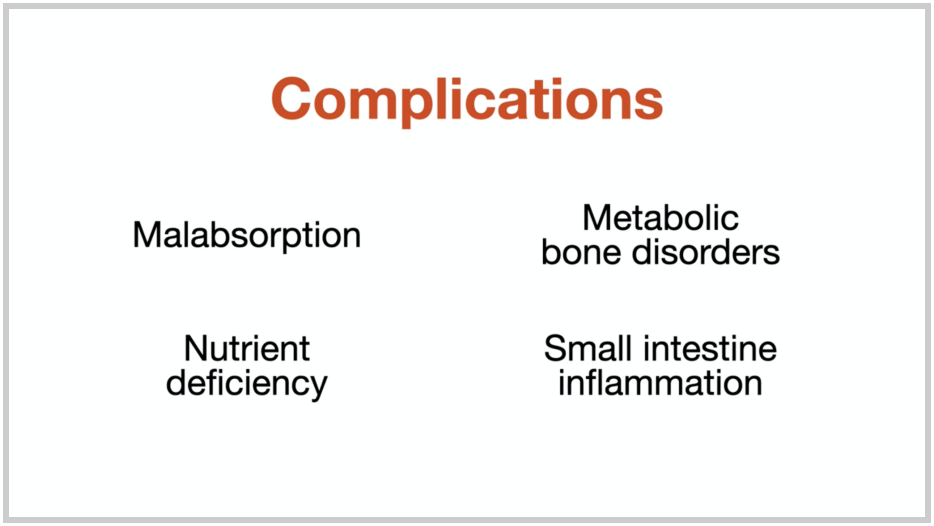
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Identifying Gut Pathologies: Small Intestinal Bacterial Overgrowth Breath Test (Part 2)

The symptoms of [small intestinal bacterial overgrowth] (SIBO) are diverse and non-specific and often not limited to the gut. So let's talk a little bit more about each of these [symptoms]. They are diverse, as I mentioned earlier; not all of your SIBO patients will present with gut symptoms, like bloating or gas or constipation and diarrhea. They may only have fatigue. They may only have things like skin problems or bad breath or maybe muscle ache or pain like fibromyalgia. In fact, in one study, up to 50 percent of SIBO patients didn't have gut symptoms at all. But 100 percent of fibromyalgia patients had SIBO, and only 50 percent of them had gut symptoms. So you had a whole bunch of people who had muscle aches and pains and weaknesses that were only a manifestation of SIBO. I've also seen patients who are completely healthy and don't have any symptoms at all that are noticeable for them. The only manifestation of their SIBO might be an increase in cholesterol levels. And when we treat the SIBO, their cholesterol levels come down. So it's really important to be aware of this connection. You can't always assume that if a patient doesn't have gut symptoms, they don't have SIBO. And it's one of the reasons why we test almost everyone who comes into our clinic for SIBO.



I think you can see that the diversity of symptoms in SIBO often reflects the various complications that are associated with it. And this includes malabsorption, nutrient deficiency, metabolic bone disorders, and small intestine inflammation. To give you an example, SIBO is known to cause [vitamin] B12 deficiency because B12 is absorbed in the small intestine. And if there's overgrowth of bacteria or inflammation in that part of the small intestine, which [often occurs] because [vitamin] B12 is absorbed in the terminal ileum, and SIBO is most likely to develop in the terminal ileum, then the result of B12 deficiency will be things like neuropathy, cognitive decline, or even dementia. So given the prevalence of SIBO in the elderly, it makes you wonder how much of [vitamin] B12 deficiency symptoms that are associated with aging might actually be related to SIBO and not just aging.

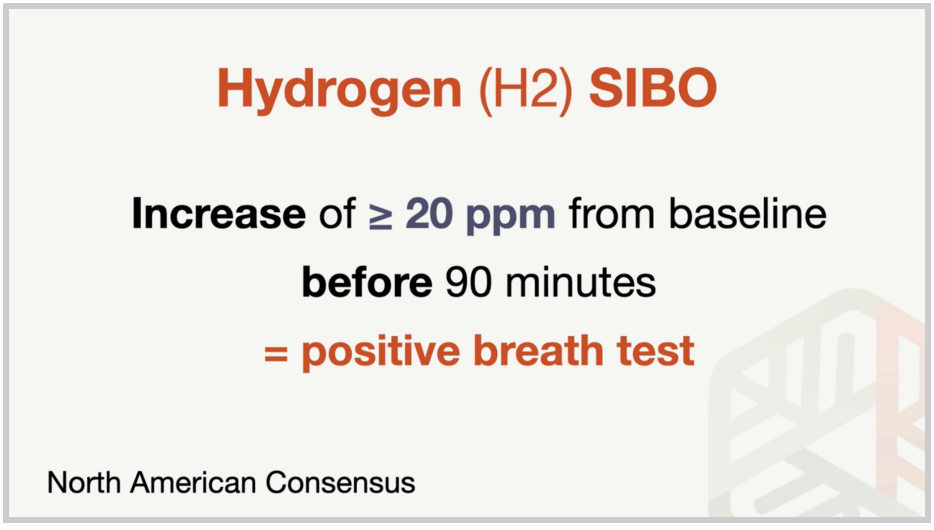


SIBO can cause fat malabsorption, which leads to a build-up of free bile salts, which also leads to mucosal inflammation, [leading] to intestinal permeability, autoimmunity, and so on. So, there's a possible connection between SIBO and autoimmunity. Also, fat malabsorption can lead to a decline in fat-soluble vitamin absorption, which leads to osteoporosis because the low vitamin D and low vitamin K2, in particular, will cause or contribute to osteoporotic changes, night blindness due to vitamin A deficiency in retinopathy, and prolonged clotting times due to vitamin K deficiency. When the brush border of the intestine is disrupted, I mentioned before that SIBO can lead to blunted small intestinal villi, [which] will affect the brush border. That can lead to decreased activity of disaccharides, which are enzymes that are required to break down carbohydrates. And that can lead to carbohydrate malabsorption. This is another vicious cycle because bacteria in the small intestine feed on carbohydrates. So if you have malabsorption of carbohydrates, then any bacteria that are present will have a field day. It'll be a feeding frenzy. And this will make the SIBO worse. You get into another vicious cycle here. Bacterial digestion of

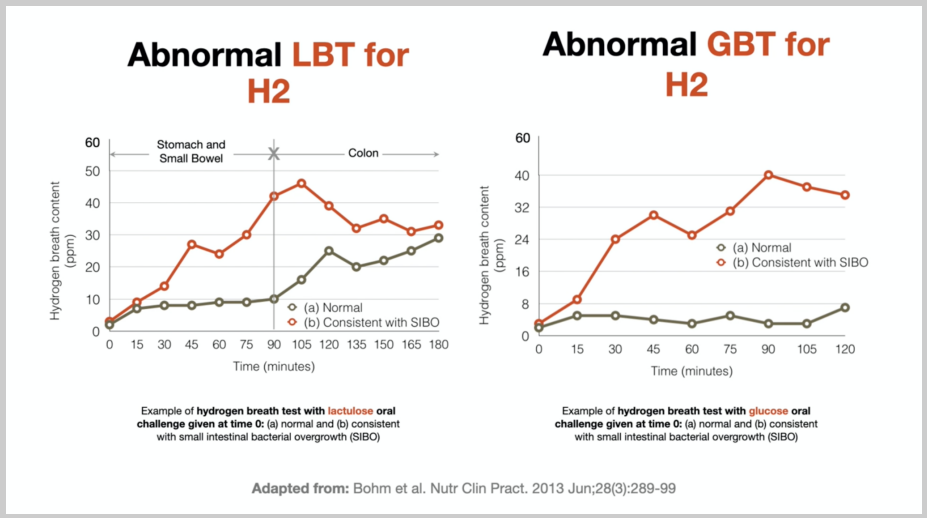
protein can lead to malabsorption of protein. So when you have too much bacteria in the upper part of the small intestine where protein is absorbed, then that will interfere with your absorption of protein. So [vitamin] B12 deficiency is very common with SIBO. Folate levels can sometimes even be high in SIBO because of increased synthesis of folate by small intestinal bacteria. This is just a small sampling of the many different complications and issues that you can see with SIBO due to its various pathological mechanisms.

Let's talk about the different types of SIBO. Currently, we have ways to diagnose hydrogen-dominant SIBO, methane SIBO (technically referred to as intestinal methanogen overgrowth), and hydrogen sulfide excess. Until recently, we didn't have a way to diagnose hydrogen sulfide excess SIBO and were diagnosing based on symptoms and particular levels and patterns that we've seen on the hydrogen and methane tests. So we have an opportunity to talk a little bit more about hydrogen sulfide SIBO and the diagnosis of it.

As we mentioned before, human cells don't have the capacity to digest fermentable sugars. So when the substrate enters the small intestine after you've ingested it as part of the SIBO breath test, the substrate is subject to digestion by organisms in the gut. The by-product[s] of that digestion are gases that are then exhaled out into the tubing and tested. The value of the gas and pattern are representative of bacterial or organism growth. For hydrogen, the North American Consensus has an increase of greater than or equal to 20 parts per million from baseline before 90 minutes as a positive breath test. Previously, the criteria were a little more flexible, and the 120-minute mark was used. And as a reminder, there are still some labs using these old criteria, like NUNM, which we are going to talk about more as we go throughout the presentation.



Symptoms seen in hydrogen-dominant SIBO include some of the typical symptoms that we listed previously, like gas, bloating, and fatigue. There tends to be some propensity for diarrhea over constipation when it comes to hydrogen-dominant SIBO. So I would say that this could be a symptom that helps differentiate between the two. But as you'll come to see, diarrhea can also be seen in hydrogen sulfide SIBO and from a variety of other causes. So I don't find it as a reliable diagnostic tool, but it can be helpful in getting a sense of what you might expect to see on that SIBO breath test result.



On this slide, I've put some examples comparing a normal and abnormal lactulose breath test and glucose breath test. You can see the differences in patterns for hydrogen production. These are just the hydrogen patterns so that you can easily see the differences between abnormal and normal results. On the lactulose breath test on the left, you can see the bottom line with gray circles is normal because it's pretty much flatlined until the lactulose hits the colon at the 105-minute mark where it then starts to rise as we expect when the substrate enters the colon. The top line in red is abnormal. This might be described as what used to be called the double peak presentation with an initial rise in hydrogen around the 45-minute mark, then dips, and then starts to rise again once the substrate enters the colon. This double peak has generally been universally agreed upon as a positive SIBO result. But per the new consensus statement, a second peak is not required for a positive test. But the first peak must occur within 90 minutes of substrate administration for the test to be considered positive.

For the glucose breath test on the right, you'll typically see an earlier rise in hydrogen since glucose is absorbed much farther up in the digestive tract than lactulose. For example, in this test

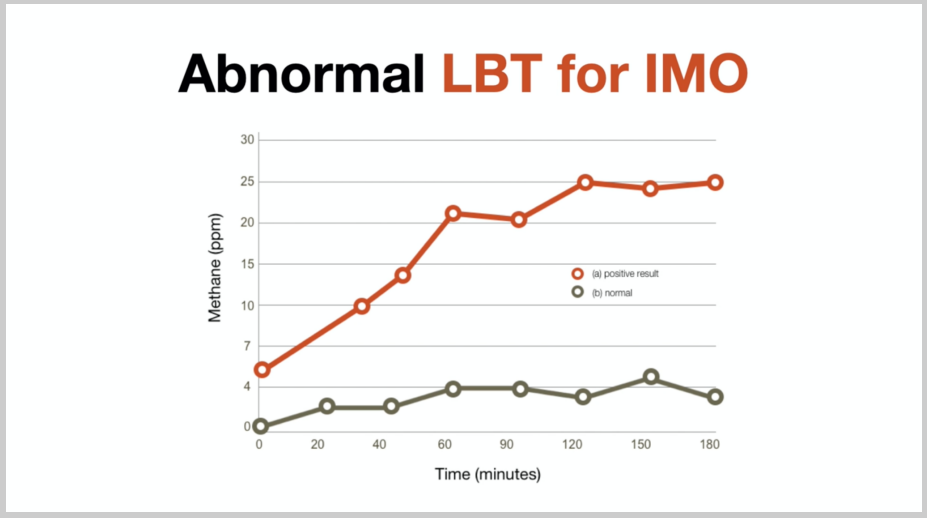
result, you're seeing that glucose is already rising compared to the normal control value at 15 minutes. At 30 minutes, there's a really substantial difference. The control value is something like four parts per million. And the elevated value is 24 parts per million, so six times that of the control. In healthy controls, it's important to note that with a lactulose breath test, you'll still see a rise in hydrogen when lactulose reaches the colon because there should be bacteria in the colon to ferment that lactulose. But you wouldn't expect to necessarily see that with the glucose because glucose is never supposed to reach the colon anyway. It's supposed to be absorbed much [farther] up in the digestive tract.

If you look at the control values here for lactulose, you'll see that gas production stays low until around 90 minutes. Then it starts to increase as lactulose enters the colon. And that's still a normal result. Whereas with the positive result, you can see that the increase in breath gases, hydrogen in this case, happens much sooner before the lactulose enters the colon. And that's indicative of SIBO. Whereas with glucose, a normal result for glucose is just to stay low the entire time throughout the test. And a positive result would typically be an increase very early on, starting around that 15- or 30-minute mark in this case.

Methane-producing organisms called archaea are responsible for intestinal methanogen overgrowth. These organisms feed off of hydrogen gas and make methane as a by-product. This helps reduce hydrogen in the body. And this is why we can often see low levels of hydrogen gas on the breath test with a high level of methane. It's possible, though, to have both hydrogen and methane gases elevated on a breath test. For methane, a concentration of greater than or equal to 10 parts per million at any point during the test is indicative of methanogen colonization. However, methanogens are not bacteria, which represent the B in SIBO, but do belong to the

domain archaea, as I mentioned, and may also overgrow in the colon and not just the small intestine. As such, a new term has been proposed and accepted, which is intestinal methanogen overgrowth, or IMO, for methanogens rather than the old SIBO. Older criteria had a range from anything greater than or equal to 3 at any point on the test to greater than or equal to 12 for positive results.

Symptoms seen in IMO include some of the typical symptoms we listed, like gas, bloating, and fatigue. But there does tend to be some propensity for constipation, straining, and incomplete evacuations with methanogen overgrowth. I tend to see this pattern of constipation with methanogen overgrowth more distinctly than diarrhea that is considered more characteristic of hydrogen overgrowth. So again, it's not a diagnostic criterion, but I see that trend more often with IMO.



On this slide, I've put some examples comparing a normal and abnormal lactulose breath test for methanogen overgrowth. So you can see the difference here in patterns. Here the bottom line is normal because it stays below 10 parts per million throughout the entire test. And the top line in red is abnormal, starting with 4 at baseline and increasing to a maximum of 25 around the 120-minute mark. This is just one example of how IMO may be represented on the SIBO breath test. It's also common to see a high baseline methane value from the start. We'll review some of those results later on in this presentation.