The Microbiota's Intriguing Role in Celiac Disease

By Chris D. Meletis, N.D.
DATE PLACEHOLDER

Celiac disease is characterized by a hereditary response to gliadin, which is a protein fraction of the larger gluten fraction found in wheat. Similar protein fractions are present in rye, barley, triticale, spelt and certain other grains. This response elicits an immune reaction in the gut, leading to inflammation and corresponding symptoms such as diarrhea, abdominal cramping, distention, flatulence, weight loss, fatigue, and malaise.

Once thought to be a rare disorder, celiac disease affects many more people than originally thought. Approximately 1% of Americans with European ancestry (3 million people) may have the disease.[1] There is a dramatic increase in the prevalence from 1:133 in patients not-at-risk, to 1:56 in symptomatic patients, to 1:39 in patients with a second-degree relative with the diagnosis, and to 1:22 in patients with a first-degree relative with celiac disease.[2] Celiac disease usually manifests in early childhood after the first exposures to dietary gluten. However, in an increasing number of individuals, the onset of celiac disease occurs in early and late adulthood.[3] This suggests that additional factors beyond exposure to gluten alone must be involved in the development of the disease.[1]

Patients that have autoimmune diseases such as Hashimoto's thyroiditis, Grave's disease, and type 1 diabetes are at an increased risk of celiac disease.[4] Therefore, it would be advisable to test this group of patients for the disorder. Inflammatory bowel disease

(IBD) is also associated with an increased risk of celiac disease and celiac disease is associated with an increased risk of IBD.[5]

In addition to obvious gastrointestinal manifestations, celiac disease can cause cognitive difficulties. Antibodies produced in celiac patients are damaging to the brain, which can result in symptoms that range in severity from brain fog to outright dementia.[6] In patients with memory problems without any obvious origin, it may be worthwhile to test for celiac disease.

The most common test to screen for celiac disease is the Tissue Transglutaminase IgA antibody test together with testing for IgA antibodies to gliadin. However, this test can be negative even in people who have celiac disease if they also have a selective IgA deficiency, which is common in this population. This means that if IgG antibodies are not also measured many cases of celiac disease can remain undiagnosed.

In this article, I will address the latest research on the connection between celiac disease treatment outcome and the gut microbiota. I will also discuss nutrient deficiencies that occur because of the disease. And finally, I will describe the most effective screening option.

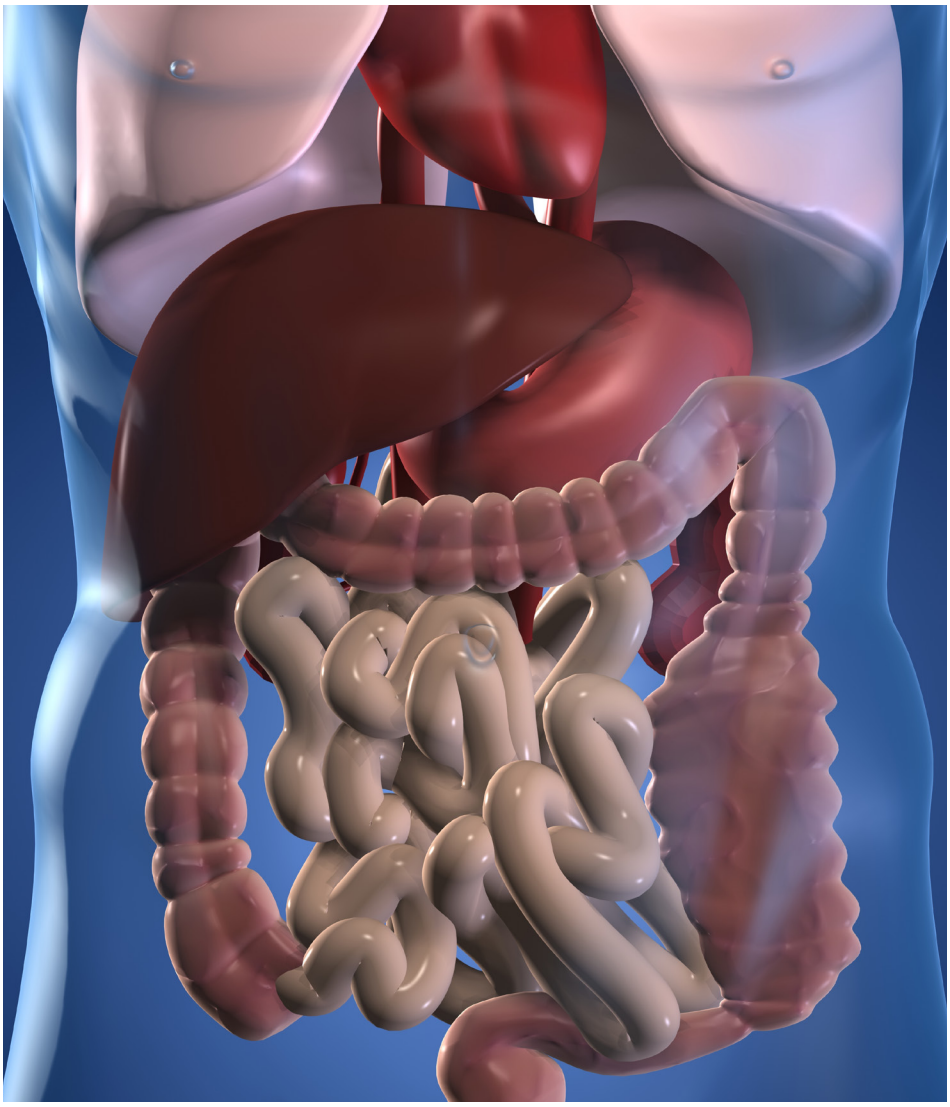
The Gut Microbiota and Celiac Disease Refractory to a Gluten-Free Diet

A large number of celiac disease patients continue to have symptoms even after removing gluten from their diet. It has been

suggested that this is due to accidentally ingesting gluten or the presence of another gastrointestinal disease. However, these explanations do not account for symptoms in many of these patients. Instead, researchers have found that an altered gut microbiota is responsible for the lack of improvement on a gluten-free diet in many celiac patients. Wacklin and colleagues analyzed the duodenal microbiota in 18 celiac disease patients who had been following a strict gluten-free diet for several years and yet still suffered from symptoms.[7] The researchers compared these patients with 18 celiac disease patients without symptoms. The patients who continued to suffer from symptoms had improved small bowel mucosa and negative celiac autoantibodies, making their lack of improvement mystifying.

The results indicated that the celiac patients with persistent symptoms had an altered gut microbiota. They were colonized by different duodenal microbiota in comparison with patients without symptoms. In these patients, there was a higher relative abundance of Proteobacteria and a lower abundance of Bacteroidetes and Firmicutes. Additionally, the microbial richness of these patients was reduced. This indicated the presence of intestinal dysbiosis may be the reason why celiac symptoms do not resolve in some patients even while on a strict gluten-free diet.

Many celiac patients who do not improve on a gluten-free diet suffer from small intestinal bacterial overgrowth (SIBO).[8] This provides further evidence that intestinal dysbiosis is involved in celiac disease.



Cause or Consequence?

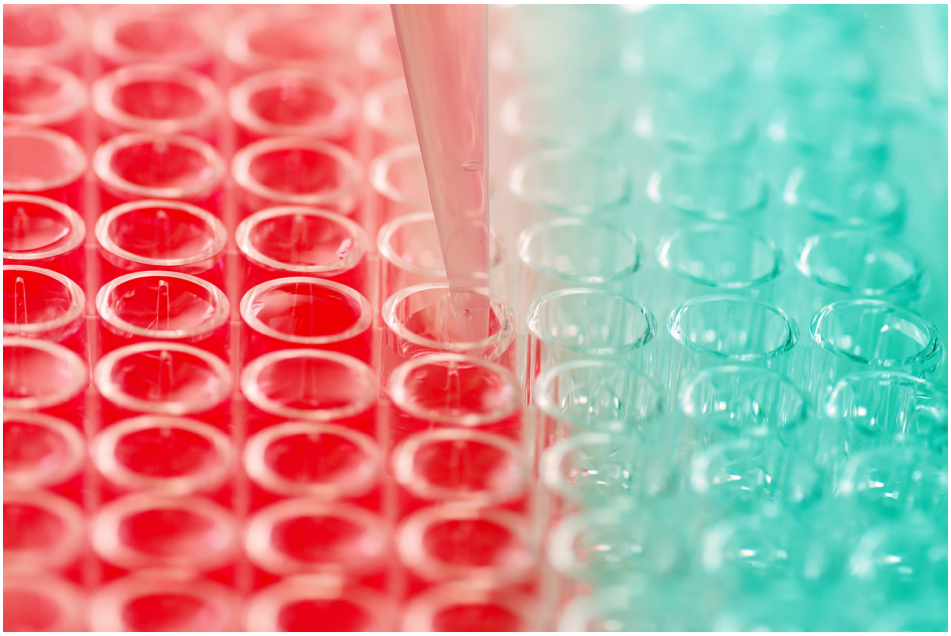
Intestinal dysbiosis may actually predispose patients to the development of celiac disease.[1] The combination of this dysbiosis with environmental factors such as antibiotic exposure could be involved in the development of intolerance to gluten.[1] Dysbiosis of the gut microbiota could lead to an abnormal response to gluten or predispose to infections involved in the pathophysiology of celiac disease.[1]

It has also been found that genes associated with celiac disease susceptibility alter microbial colonization of the infant's gut, indicating that individuals predisposed to celiac disease may have a weakened ability to develop a microbiota that protects against the disease.[9] Furthermore, studies have shown that the same environmental factors that alter early life gut microbiota composition such as cesarean vs. vaginal birth, lack of breastfeeding, intestinal infections, and antibiotic intake are also associated with an increased risk of celiac disease.[10,11,12,13,14]

This evidence indicates that dysbiosis of the gut microbiota may predispose to celiac disease in susceptible individuals.[1] It also suggests that resolving dysbiosis through modification of the microbiota may help alleviate celiac disease symptoms or reduce the risk of developing the disease in the first place.[1]

The Vicious Cycle of Celiac-Induced Nutrient Depletion

Patients with celiac disease are often deficient in key nutrients due to both low dietary intake and malabsorption. Vitamin D has been found to be deficient in 70% of children recently diagnosed with celiac disease.[15] Low serum ferritin levels were found in 34.5% of children with celiac disease and 18.6 of these children had low zinc levels.[15] Folate insufficiency has



also been detected in celiac patients.[16] Furthermore, gluten-free foods have been found to be low in fiber, vitamin D, vitamin B12, folate, iron, zinc, magnesium, and calcium.[17]

Deficiencies in nutrients like zinc can lead to increased intestinal permeability due to zinc's role in maintaining the integrity of tight junctions.[18,19] This increased intestinal permeability can result in dysbiosis of the gut microbiota, which can create a vicious circle whereby celiac disease is associated with nutrient deficiencies and these deficiencies in turn lead to "leaky gut," which further exacerbates celiac symptoms. Furthermore, vitamin D deficiency can contribute to intestinal dysbiosis due to its ability to influence the composition of the gut microbiota.[20]

The Most Accurate Celiac Disease Testing

US BioTek Celiac Antibody Panel measures for serum tissue transglutaminase (tTG) IgA and IgG in addition to IgA and IgG antibodies specific for deamidated gliadin peptide (DGP). tTG has 94% sensitivity and 98% specificity in detecting untreated celiac disease in an IgA competent person. As noted earlier in this article, not all celiac disease patients test positive for tTG IgA autoantibodies or DGP IgA antibodies. If a patient is suspected to have celiac disease but still tests negative, it may be because the patient has a selective IgA deficiency, which commonly occurs in this population.[21] Therefore, tTG IgG autoantibodies and DGP IgG antibodies can assist with the detection of celiac disease in those patients with a selective IgA deficiency. Anti-gliadin IgA and anti-gliadin IgG can also be used to monitor whether a patient has adhered to a gluten-free diet.

Conclusion

Celiac disease is a disorder that is far more common than previously thought with a substantial number of individuals suffering from the condition. Recent evidence indicates that alterations in the gut microbiota may be involved in ongoing symptoms in celiac patients who do not experience improvement even after following a gluten-free diet. Celiac disease is associated with a number of nutrient deficiencies that can exacerbate symptoms of the disease. A celiac antibody panel measuring serum tTG IgA and IgG in addition to IgA and IgG antibodies specific for DGP is an effective way to ensure patients are accurately diagnosed.

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