Gluten-Free Diet Response Flagged

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Celiac disease–associated serum antibodies and the expression of the human leukocyte antigen complex (HLA) DQ2 genotype can identify individuals with diarrhea-dominant irritable bowel syndrome (IBS-D) who are likely to respond to a gluten-free diet, investigators reported in an article appearing in the July issue of Clinical Gastroenterology and Hepatology.

Although the presence of villous atrophy in the small intestine together with gluten sensitivity are the typical diagnostic criteria for classical celiac disease in patients with diarrhea, gluten sensitivity may also cause abdominal symptoms in the absence of villous atrophy, wrote Dr. Ulrich Wahnschaffe of Ernst-Moritz-Arndt Universität, Greifswald (Germany) and his colleagues.

In a previous study, the investigators found that a subgroup of patients with IBS-D without villous atrophy benefitted from a gluten-free diet; the patients were identified by the expression of HLA-DQ2 (A1*0501/B1*0201) and increased antibodies against gliadin and/or tissue-transglutaminase in duodenal aspirate.

The investigators in the current study sought to determine whether these serum antibodies, in association with HLA-DQ2 expression, are markers for gluten sensitivity. They measured HLA-DQ2 expression and celiac disease–associated IgA and IgG serum antibodies against gliadin and tissue-transglutaminase in 145 patients with IBS-D, 74 celiac patients (30 untreated and 44 treated), 57 patients with active inflammatory bowel disease (IBD) who were used as the disease control group, and 62 healthy controls.

Each patient underwent abdominal ultrasound, upper and lower endoscopy, distal duodenal biopsies, and blood and stool tests.

Of the IBS-D patients, 41 participated in a nonrandomized evaluation of a gluten-free diet for 6 months. Follow-up antibody levels, stool frequency, and gastrointestinal symptom scores were collected for these patients.

Expression of HLA-DQ2 was observed in all of the patients with untreated celiac disease, 93% of those with treated celiac disease, and 39% of the IBS-D patients. "HLA-DQ2 expression was significantly more frequent in IBS-D patients, compared [with IBD] patients and controls," the authors wrote.

IgA antibodies against gliadin and/or tissue-transglutaminase were observed in 93% of the untreated celiac disease group, 7% of those with treated celiac disease, 2% of those with IBS-D, and no patients with IBD, confirming the significance of these IgA antibodies as a marker for active celiac disease.

In contrast, "increased serum IgG against gliadin and/or tissue transglutaminase were present not only in most patients with untreated [celiac disease], but also in the majority of patients with treated celiac disease and may therefore represent markers for gluten sensitivity," the authors wrote.

About one-third of the IBS-D patients were positive for this marker, and the proportion of patients with the marker was significantly higher in IBS-D than in IBD patients.

In the extended gluten-free diet study, those IBS-D patients who were HLA-DQ2 positive had significant improvement in diarrhea in response to the diet. In addition, "a symptom score covering typical gastrointestinal symptoms of IBS, …like abdominal pain or bloating, improved to normal values in most patients expressing HLA-DQ2 or with celiac disease–associated serum IgG antibodies after gluten-free diet," they wrote, noting that this association supports the presence of gluten sensitivity in a subgroup of approximately 17% of IBS-D patients.

The investigators determined that expression of HLA-DQ2 in combination with serum IgG against gliadin and/or tissue-transglutaminase was a predictor of response to a gluten-free diet in IBS-D patients.

"Sensitivity to predict the response to gluten-free diet was higher for HLA-Dq2 expression, whereas specificity was higher for celiac disease–associated IgG; both parameters combined yielded positive and negative predictive values of 56% and 88%, respectively," they wrote.

These values, although not ideal, are acceptable, because the gluten-free diet is a nontoxic, relatively inexpensive treatment option, they added.

"Our findings, which require confirmation by randomized studies, suggest that screening for HLA-DQ2 and/or celiac disease–associated IgG [in patients with IBS-D] could identify an additional larger subgroup of patients without villous atrophy or celiac disease–associated IgA who will benefit from gluten-free diet," the authors concluded. ■

ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Probiotics for Irritable Bowel Syndrome

History and Rationale for Use

The concept of probiotics as beneficial for intestinal health began with Nobel Prize–winning Russian scientist Ilya Ilyich Mechnikov. He viewed the large intestine as a vestigial organ that harbored dangerous, putrefaction-inducing bacteria, and believed that introducing lactobacilli into the body would promote health. The longevity of Balkan peasants, he wrote in "The Prolongation of Life: Optimistic Studies" in 1907, was likely a result of their consumption of fermented milk products.

► *Theoretical reasons why probiotics could be beneficial in irritable bowel syndrome include anti-inflammatory effects and immune modulation in the gut.*
► *Clinical trial data remain sparse, and quality control is problematic.*

A century later much is known about gut function, the 400 species of bacteria that reside in the colon, and host-flora interactions, including communication between intestinal microbes and the immune system. For instance, the host's immune system can differentiate between pathogenic bacteria and commensals through pattern recognition receptors and Toll-like receptors (TLRs). TLR2 triggers an immune response to gram-positive bacteria and yeasts, TLR4 mediates responses to lipopolysaccharides from gram-negative bacteria, and TLR9 recognizes certain sequences of bacterial DNA (Dig. Dis. 2006;24:137-47).

The currently accepted definition of probiotics is "nonpathogenic microorganisms, which, when ingested as living cells, exert a positive influence on host health or physiology" (Dig. Dis. 2006;24:137-47). The *Lactobacillus* and *Bifidobacterium* genera of bacteria are the most widely tested and commonly used probiotics.

There are several reasons why certain probiotic organisms could have beneficial effects in irritable bowel syndrome (IBS). Many have antiviral and antibacterial effects, which could be important in the 15%-25% of patients whose IBS dates from an episode of infectious gastroenteritis. Also, probiotics have anti-inflammatory effects on mucosal surfaces. By reducing gut mucosal inflammation, these organisms could decrease immune-mediated activation of enteric neurons and thus alter neural traffic between the gastrointestinal tract and the central nervous system. Moreover, probiotics could quantitatively and qualitatively alter the gut flora, change the volume and composition of stool and gas, and increase secretion of intestinal mucus (Gastroenterology 2005;128:541-51).

Clinical Trials

Two studies done at the Mayo Clinic, Rochester, Minn., used a composite probiotic (VSL#3, manufactured by VSL Pharmaceuticals). The first study included 25 patients with diarrhea-predominant IBS who received VSL#3 powder (450 billion lyophilized bacteria per day) or placebo twice daily for 8 weeks. There was a borderline significant difference between the active and placebo groups on abdominal bloating, but no differences in gastrointestinal transit time, bowel function scores, or global symptom relief (Aliment. Pharmacol. Ther. 2003;17:895-904).

In the second trial, 48 patients were randomized to receive either the active treatment or placebo for up to 8 weeks. Mean post-treatment scores for symptoms including abdominal pain, flatulence, and bloating were numerically lower in the active treatment group, but only the score for flatulence achieved statistical significance. A total of 46% of patients in the active treatment group and 33% of patients in the placebo group had satisfactory relief for half of the weeks (J. Clin. Gastroenterol. 2006;40:264-9).

Another research group, led by Dr. Eamonn Quigley, professor of medicine at University College Cork (Ireland), randomized 362 women with IBS of any subtype to receive either placebo or one of three doses of encapsulated *B. infantis* (1×10^6, 1×10^8, or 1×10^{10} colony-forming units per milliliter) each day for 4 weeks.

On the primary end point, abdominal pain/discomfort at week 4, only the 1×10^8 group had significant improvements, compared with baseline. Patients in this group also had significant improvements on the secondary outcomes of bloating/distention, sense of incomplete evacuation, passage of gas, straining, and bowel habit satisfaction (Am. J. Gastroenterol. 2006;101:1581-90).

A Role for Inflammation

In another study, 75 patients were randomized to receive either 1×10^{10} of *L. salivarius* or *B. infantis* in a malted milk drink or a malted milk placebo for 8 weeks. On the three cardinal symptoms of IBS—abdominal pain/discomfort, bloating or distention, and bowel movement difficulty, the *Bifidobacterium* was superior to the *Lactobacillus,* and the therapeutic gain of 20%-25% over placebo was equivalent to that reported for tegaserod (Gastroenterology 2005;128:541-51).

In this study, the investigators also measured peripheral blood cytokine levels and reported that, compared with normal controls, baseline levels of interleukin (IL)-10 were low and levels of IL-12 were increased, a ratio that is skewed toward a proinflammatory cytokine profile. This ratio returned to normal among patients in the *B. infantis* group, but not in the *L. salivarius* group or the normal controls.

The authors wrote that in this study, "by demonstrating a normalization of the IL-10/IL-12 ratio in the bifidobacteria-fed subjects alone, and in parallel with symptomatic improvement, we provide the first evidence for efficacy for an anti-inflammatory approach in IBS."

Advice From an Expert

Much confusion exists regarding the use of probiotics for IBS, with many substandard studies and exaggerated claims, according to Dr. Quigley, who is also vice president of the World Gastroenterology Organisation. In an interview, he noted that few probiotics have been subjected to high-quality clinical trials. He also pointed out that quality control is a real issue.

"Many of the probiotics on the shelf cannot be validated in terms of constituents, dose, viability, properties, efficacy, lack of contamination, and shelf-life," he noted. Finally, he cautioned that probiotics differ: "No two are exactly the same. Extrapolations from one, even if closely related, cannot and should not be made."

—Nancy Walsh

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