Probiotic Therapy for Celiac Disease

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Celiac disease (CD) is an autoimmune disorder induced by the ingestion of gluten in genetically predisposed individuals who carry the HLA-DQ2 or DQ-8 alleles.[1] This autoimmune disorder affects the small bowel and often produces symptoms of diarrhea, malabsorption, and extraintestinal symptoms.[1] Although CD was once thought to be a disease manifesting during childhood, studies have shown that the prevalence of CD in adults in the United States ranges from 0.7% to 1.1%.[2,3] In addition, several studies have shown that, despite a prevalence comparable to those of European nations, CD remains underdiagnosed in the United States.[3–5]

At this time, the only treatment for CD is lifelong adherence to a gluten-free diet, which involves the elimination of grains containing gluten, wheat, rye, and barley in addition to food products and additives derived from them.[6] Adherence to a gluten-free diet has been shown to improve symptoms, reduce the risk of malignancy, and impart other health benefits such as an improvement in bone mineral density.[7–9] However, studies have shown that dietary transgressions in patients with CD are common and can occur anywhere from 32% to 55%.[10]

Why is it so difficult for patients with CD to adhere to a gluten-free diet? First, the availability of gluten-free products varies among different regions of the United States and the world, especially in developing countries.[11,12] Although more widespread than in the past, gluten-free products in the United States tend to be more readily available online and in upscale food stores as compared with regular grocery stores.[11] Second, gluten-free products tend to be more expensive than their wheat-containing counterparts, which impacts dietary compliance among patients who cannot afford such a diet.[11] Finally, patients who adhere to a gluten-free diet can feel excluded from social activities, such as dining out, travel, and family life, which has a direct negative impact on their quality of life.[13]

Because of the constraints of a gluten-free diet, alternative therapies for CD are being developed, including agents that prevent gluten uptake into the mucosa, decrease immune activation, and reduce gluten exposure by either binding or degrading gluten in the intestinal lumen.[14]

Probiotics, which are live microorganisms that confer a health benefit, may offer benefits to patients suffering from intestinal disorders such as irritable bowel syndrome and CD.[15] One randomized controlled trial evaluating *Bifidobacterium infantis 35624* in patients with irritable bowel syndrome showed a greater reduction in symptom scores for abdominal pain/discomfort, bloating/distention, and bowel movement difficulty compared with placebo.[16] This study also showed normalization of peripheral blood mononuclear cell cytokine levels in patients taking *B. infantis 35624* but not in those taking *Lactobacillus salivarius UCC 4331*, indicating a potential anti-inflammatory effect.[16] Abnormalities in the intestinal microbiome in patients with CD have prompted consideration of their use as a nondietary therapy. Reduced concentrations of *Bifidobacterium* species were observed in the feces of untreated CD patients as compared with healthy adults.[17] A similar study using PCR to identify gut *Bifidobacterium* also showed a reduction in *Bifidobacterium* populations in both active and nonactive CD as compared with healthy controls.[18]

Some probiotics digest or alter gluten. A specific commercially available probiotic, VSL#3 (containing 8 different bacteria), has been shown to reduce the toxicity of gluten when used in a fermentation process.[19] In addition, baked wheat products that are formed by the sourdough fermentation process of wheat gluten by lactobacilli and fungal proteases, are safe for people with CD.[20]

Several studies have also further expanded on the potential anti-inflammatory effects of *B. infantis* on CD. The presence of bifidobacterial strains during intestinal digestion was shown to produce different, less toxic, gliadin peptide sequences in vitro, which could modify the proinflammatory cascade triggered by gliadin-derived peptides in addition to protecting

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epithelial cells from cellular damage by inhibiting increases in epithelial permeability caused by gliadin.[21,22]

In addition to the supplemental role that *Bifidobacterial* species may exert in CD, several studies have also focused on the potential role that it plays in the development of CD later in infancy. Breast milk has been shown to stimulate the growth of *Bifidobacterial* species in the guts of healthy newborns. In 1 prospective study on 164 healthy infants who have at least 1 first-degree relative with CD, reduced numbers of *Bifidobacterium* were found in infants who later had an increased risk for developing CD.[23–25]

In this issue of the *Journal of Clinical Gastroenterology*, Smeucol et al[26] presented their results from the first clinical trial evaluating the effect of *B. infantis* in active, untreated CD patients still consuming gluten-containing products. The study was a placebo-controlled, double-blinded, randomized study comparing *B. infantis* NSL super strain with placebo capsules. A total of 22 patients with positive tissue transglutaminase (tTG) and deamidated gliadin-derived peptides (DGP) were included in this study. Biopsies at the end of the study confirmed CD in all 22 patients. The primary endpoint of the study was to determine the effect of administration of *B. infantis* on intestinal permeability using the lactulose/mannitol fractional excretion ratio at the end of 3 weeks of treatment. Secondary endpoints evaluated included clinical symptom outcomes as measured by the GSRS questionnaire and whether *B. infantis* modified any immunologic and inflammatory markers related to CD.

This study did not meet its primary endpoint. There was no statistically significant difference in intestinal permeability between the *B. infantis* arm and the placebo-controlled arm at the end of the study. Potentially this was not the best primary endpoint to choose for the study, for there is controversy surrounding the use of 5-hour urine collections (as used in this study) as the assessment parameter for small intestinal permeability.[27,28] Urine collection for the first 2 hours reflects small bowel permeability changes, whereas longer duration collections reflect colonic permeability changes. Serum antibody (tTG and DGP) levels were also collected in these patients both at the beginning and at the end of the 3-week trial on probiotics. In the probiotic arm there was a 10% reduction in serum anti-tTG IgA and IgA DGP as compared with a mean increase in the placebo arm; however, these differences did not reach statistical significance. In addition, when looking at proinflammatory cytokines and chemokines, the baseline proinflammatory status persisted in both groups of patients. Finally, this study found that, after 3 weeks of treatment with *B. Infantis*, patients reported improvements in indigestion, constipation, and gastroesophageal reflux as evaluated by the GSRS scale, but not improvements in diarrhea and abdominal pain.

In summary, this is an interesting study that shows a potential for the further study of the use of *B. infantis* probiotic therapy in untreated CD patients. Although the study is limited by its small sample size and variables such as length of treatment duration and dose of probiotic therapy, the treatment arm of the study showed an improvement in symptoms and serum antibody levels (although not statistically significant). Future studies would benefit from enrolling a larger number of patients to further delineate potential benefits of *B. infantis* probiotic therapy as well as from using different doses of probiotic therapy to determine whether an increased benefit is seen with increased doses. Nevertheless, this study provides encouraging and exciting uses of probiotic therapy in a yet unchartered group of patients.

However, before recommending any pharmaceutical therapy for patients with CD, the therapy must be safe and extremely effective, for the gluten-free diet is both. Any therapy needs to protect the CD patient from extremely small amounts of gluten. Although 1 slice of bread contains 3 to 4 gm of gluten, most CD patients react to a small fraction of this value: 50 mg of gluten,[29] and less commonly to as little as 10 mg or even 1 mg.[29,30]

REFERENCES

1. Green PH, Cellier C. Celiac disease. *N Engl J Med*. 2007;357:1731–1743.
2. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med*. 2003;163:286–292.
3. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538–1544.
4. Murray JA, Van Dyke C, Plevak MF, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. *Clin Gastroenterol Hepatol*. 2003;1:19–27.
5. Virta LJ, Kaukinen K, Collin P. Incidence and prevalence of diagnosed coeliac disease in Finland: results of effective case finding in adults. *Scand J Gastroenterol*. 2009;44:933–938.
6. Green PH, Jabri B. Coeliac disease. *Lancet*. 2003;362:383–391.
7. Murray JA, Watson T, Clearman B, et al. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *Am J Clin Nutr*. 2004;79:669–673.
8. Holmes GK, Prior P, Lane MR, et al. Malignancy in coeliac disease-effect of a gluten free diet. *Gut*. 1989;30:333–338.
9. Meyer D, Stavropolous S, Diamond B, et al. Osteoporosis in a North American adult population with celiac disease. *Am J Gastroenterol*. 2001;96:112–119.
10. Silvester JA, Rashid M. Long-term follow-up of individuals with celiac disease: an evaluation of current practice guidelines. *Can J Gastroenterol*. 2007;21:557–564.
11. Lee AR, Ng DL, Zivin J, et al. Economic burden of a gluten-free diet. *J Hum Nutr Diet*. 2007;20:423–430.
12. Barada K, Bitar A, Mokadem MA, et al. Celiac disease in Middle Eastern and North African countries: a new burden? *World J Gastroenterol*. 2010;16:1449–1457.
13. Lee AR, Ng DL, Diamond B, et al. Living with coeliac disease: survey results from the USA. *J Hum Nutr Diet*. 2012;25:233–238.
14. Tennyson CA, Lewis SK, Green PH. New and developing therapies for celiac disease. *Ther Adv Gastroenterol*. 2009;2:303–309.
15. Chey WD, Maneerattaporn M, Saad R. Pharmacologic and complementary and alternative medicine therapies for irritable bowel syndrome. *Gut Liver*. 2011;5:253–266.
16. O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541–551.
17. Nistal E, Caminero A, Vivas S, et al. Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. *Biochimie*. 2012;94:1724–1729.
18. Collado MC, Donat E, Ribes-Koninckx C, et al. Imbalances in faecal and duodenal *Bifidobacterium* species composition in active and non-active coeliac disease. *BMC Microbiol*. 2008;22:232.
19. De Angelis M, Rizzello CG, Fasano A, et al. Vsl#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for celiac sprue. *Biochim Biophys Acta*. 2006;1762:80–93.

20. Di Cagno R, Barbato M, Di Camillo C, et al. Gluten-free sourdough wheat baked goods appear safe for young celiac patients: a pilot study. *J Pediatr Gastroenterol Nutr*. 2010;51:777–783.
21. Laparra JM, Sanz Y. *Bifidobacteria* inhibit the inflammatory response induced by gliadins in intestinal epithelial cells via modifications of toxic peptide generation during digestion. *J Cell Biochem*. 2010;109:801–807.
22. Lindfors K, Blomqvist T, Juuti-Uusitalo K, et al. Live probiotic *Bifidobacterium lactis* bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. *Clin Exp Immunol*. 2008;152:552–558.
23. Tamara Pozo-Rubio, Marta Olivares, Esther Nova, et al. Immune development and intestinal microbiota in celiac disease. *Clin Dev Immunol*. 2012;2012:654143.
24. Sanchez E, DePalma G, Capilla A, et al. Influence of environmental and genetic factors linked to celiac disease risk on infant gut colonization by *Bacteroides* species. *Appl Environ Microbiol*. 2011;77:5316–5323.
25. DePalma G, Capilla A, Nova E, et al. Influence of milk-feeding type and genetic risk of developing coeliac disease on intestinal microbiota of infants: The PROFICEL study. *PLoS One*. 2012;7:30791.
26. Smeucol E, Hwang HJ, Sugai E, et al. Exploratory, randomized, double-blind, placebo-controlled study on the effects of *Bifidobacterium infantis* natren life start super strain in active celiac disease. *J Clin Gastroenterol*. 2012;47:139–147.
27. Rao AS, Camilleri M, Eckert DJ, et al. Urine sugars for in vivo gut permeability: validation and comparisons in irritable bowel syndrome-diarrhea and controls. *Am J Physiol*. 2011;301: G919–G928.
28. Camilleri M, Nadeau A, Lamsam J, et al. Understanding measurements of intestinal permeability in healthy humans with urine lactulose and mannitol excretion. *Neurogastroenterol Motil*. 2010;22:e15–e26.
29. Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr*. 2007;85:160–166.
30. Biagi F, Campanella J, Martucci S, et al. A milligram of gluten a day keeps the mucosal recovery away: A case report. *Nutr Rev*. 2004;62:360–363.