see related article on page 508

Can Gluten Contribute to Irritable Bowel Syndrome?

Elena F. Verdu, MD, PhD[1]

Abstract: Functional gastrointestinal disorders are the most common gastroenterological problem in our society. Changes in gut function, including pain perception, motility, and intestinal permeability, and low-grade inflammation have been described in patients with irritable bowel syndrome (IBS). The triggering factors for the described immunity and gut functional changes in patients with IBS are not completely understood. Similarly to post-infective IBS, some patients with IBS symptoms exhibit immunological evidence of gluten sensitivity but have no overt intestinal mucosal injury. They have symptoms that meet the diagnostic criteria for IBS and respond symptomatically to exclusion of gluten from the diet. Thus, gluten sensitivity may be involved in the pathogenesis of a subgroup of IBS patients. Unfortunately, there remain many unanswered questions regarding the mechanistic link between gluten sensitivity and functional gastrointestinal symptoms.

Am J Gastroenterol 2011; 106:516–518; doi:10.1038/ajg.2010.490

INTRODUCTION

Irritable bowel syndrome (IBS) is a clinically defined entity, characterized by a gastrointestinal symptom complex, in the absence of any discernible organic cause. Rome III diagnostic criteria define IBS as recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (1). Thus, the definition of IBS is based on a *clinical description*, and likely involves many pathophysiological pathways that are not currently well understood (2,3). Infectious gastroenteritis can trigger long-lasting alterations in gut immunity and function and is considered to be the strongest environmental risk factor for IBS (4,5). Others have proposed certain food components as triggers of symptoms in IBS (6–8). Thus, similarly to the entity of "post-infectious IBS," gastrointestinal (GI) symptoms may develop because of abnormal immune responses to dietary components. In this issue of the *American Journal of Gastroenterology*, Biesiekierski *et al.* (9) provide evidence that gluten, the storage proteins in wheat that cause celiac disease in genetically predisposed persons, can induce functional symptoms in subjects without celiac disease. The mechanisms through which gluten induces symptoms in humans without celiac disease remain unclear. However, the concept that gut dysfunction and symptom generation can arise from abnormal host responses to gluten (10) is underpinned by results of basic scientific studies showing that gluten sensitivity in mice results in subtle changes of mucosal immunity, and marked changes in neuromuscular and epithelial GI function (11,12).

SYMPTOM GENERATION IN IBS: FOCUS ON BOTTOM-UP MECHANISMS

A number of mechanisms have been proposed to underlie symptom generation in IBS. These include psychological illnesses, abnormal gastrointestinal motility and permeability, visceral hyperalgesia, altered central perception of visceral events, and low-grade gut inflammation (13–15). Thus, the current model for functional gut disorders includes the bi-directional communication between the gut and the brain (16). Bottom-up mechanisms refer to those that originate from alterations in the gut tissue or lumen. A large number of studies have focused on the role of altered motility as an underlying mechanism for symptom generation in patients with IBS. Manometric and electrophysiological abnormalities have been described in the colon and small intestine of patients with IBS, frequently occurring in response to stressful stimulation or after meal ingestion (17,18). Visceral hypersensitivity has also been proposed as a mechanism for symptom generation in IBS patients (19–21). Similarly to dysmotility, the sensory abnormalities are present only in a proportion of patients with IBS. The exact cause and mechanisms of neuromotor, epithelial and visceral perception abnormalities in patients with IBS are unknown.

[1]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada. **Correspondence:** Elena F. Verdu, Farncombe Family Digestive Health Research Institute, McMaster University, 1200 Main Street West, HSc 3N8, Hamilton, Ontario, Canada L8N 3Z5. E-mail: verdue@mcmaster.ca
Received 12 October 2010; accepted 28 November 2010

LOW-GRADE INFLAMMATION IN IBS: IS GLUTEN A TRIGGER?

It is now well accepted that low-grade inflammation and immune activation are present in patients with IBS, even in those without a history of infectious gastroenteritis. Biopsy specimens from patients with IBS without a history of gastroenteritis have shown increased numbers of neutrophils and mast cells in the colonic mucosa (22) and chronic inflammatory infiltrate with neuronal degeneration in the myenteric plexus of the jejunum (23). Activated mast cells have been found in close proximity of enteric nerves in IBS patients (24–26). Recent studies have suggested that immune alterations are not confined to the gut and that increased levels of circulating inflammatory cytokines, T-cell activation, and cytokine gene polymorphism are present in patients with IBS (27–30). In the absence of previous GI infection, other unidentified environmental factors could trigger low-grade inflammation in IBS. This could constitute a *common pathway* through which a large array of luminal antigens, including GI pathogens (31), dysbiosis (32), and food components (8), lead to symptom generation. Studies in animal models have shown that mucosal inflammation alters gut sensory-motor function (33,34) and that deeper layers of the gut wall, including muscle and nerves, actively participate in the inflammatory response to luminal stimuli (33).

Although the effects of food allergy on gut function have been well studied, the role of non-allergic, immune hypersensitivity reactions to specific food components is less understood. Recently, attention has been given to "gluten sensitivity," which can present with IBS or dyspepsia-like symptoms in the absence of overt enteropathy, or positive tissue transglutaminase antibodies (10–12). GI symptoms in these patients seem to improve after exclusion of gluten from the diet. The study by Biesiekierski *et al.* (9), however, shows that IBS patients, diagnosed according to the Rome III criteria and in whom celiac disease had been excluded, exhibit more symptoms upon a gluten re-challenge than those receiving placebo. Thus, gluten can cause symptoms in some patients with IBS. The burning question is, *by which mechanism*? In their study, Biesiekierski *et al.* investigated this possibility by measuring fecal lactoferrin, as a marker of injury, and intestinal permeability. Despite worsening of symptoms after gluten re-challenge, no changes in intestinal permeability or fecal lactoferrin were identified. However, the role of small-intestinal low-grade inflammation triggered by gluten re-challenge cannot be ruled out. The measurement of permeability in the clinical setting is complex, highly dependent on the probes used and the underlying intestinal transit, and does not necessarily correlate with low-grade mucosal inflammation. Low-grade inflammation may be difficult to detect, and, as shown in studies in IBS patients, immune activation may be confined to the mucosal or neuromuscular layers. Although no changes in fecal lactoferrin were observed in the study by Biesiekierski *et al.*, it is important to highlight that there was no indication of intestinal injury in these patients, and that subtle changes in mucosal immune activation, such as those described in IBS patients (22,23), could have been present.

SHOULD PHYSICIANS SUGGEST "GLUTEN SENSITIVITY" AS A POSSIBLE CAUSE OF FUNCTIONAL SYMPTOMS?

When a certain food component has been identified to aggravate symptoms in a patient with IBS, physicians often advise on lifestyle and dietary changes. It is still unclear whether "gluten sensitivity" should be discussed with IBS patients who have not self-identified gluten as a trigger for their GI symptoms. The results from Biesiekierski *et al.* (9) support the fact that IBS symptoms can be triggered by gluten in a proportion of patients with IBS, but the condition clearly remains multifactorial. Thus, gluten may be one of a multitude of triggers of low-grade inflammation and/or gut dysfunction in IBS. Wahnschaffe *et al.* (7) have proposed that the presence of genetic markers for celiac disease predicts responsiveness to a gluten-free diet among patients with IBS. Similarly, in the absence of tissue transglutaminase antibodies, positive anti-gliadin antibodies could indicate immunological activation to gluten, without celiac disease. Positive anti-gliadin antibodies are non-specific, and occur in a variety of inflammatory conditions. The use of celiac-associated biomarkers, such as anti-gliadin antibodies, may, however, represent a useful case-finding strategy in unselected IBS patients. "Gluten sensitivity" could be raised as a possible cause of functional symptoms in patients with positive anti-gliadin antibodies, and gluten restriction advised as a therapeutic trial.

CONCLUSION

Evidence is accumulating suggesting that hypersensitivities, or abnormal gut functional responses to specific food components, and in particular gluten, could be involved in symptom generation in gut functional disorders. Gluten sensitivity may be involved in the pathogenesis of a subgroup of IBS patients, but there are gaps in our understanding of the mechanistic pathways through which gluten can contribute to functional bowel disorders. Gluten sensitivity does not, by any means, explain all intolerance to food in IBS patients. However, it provides a basis for constructing a model linking a specific food component with dysfunction in the gut, and for devising new management strategies for gut functional disorders. Identification of serological biomarkers indicating "gluten sensitivity" and whether they predict responsiveness to gluten restriction in IBS patients would significantly enhance the clinical management of this common GI disorder.

CONFLICT OF INTEREST

Guarantor of the article: Elena F. Verdu, MD, PhD.

Financial support: None.

Potential competing interests: None.

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD *et al.* Functional bowel disorders. Gastroenterology 2006;130:1480–91.
2. Mearin F. IBS: new Rome III criteria. Med Clin (Barc) 2007;128:335–43.
3. Gwee KA. Irritable bowel syndrome and the Rome III criteria: for better or for worse? Eur J Gastroenterol Hepatol 2007;19:441–7.
4. Rodríguez LA, Ruigómez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. BMJ 1999;318:565–6.

5. Ruigómez A, García Rodríguez LA, Panés J. Risk of irritable bowel syndrome after an episode of bacterial gastroenteritis in general practice: influence of comorbidities. Clin Gastroenterol Hepatol 2007;5:465–9.
6. Wahnschaffe U, Ullrich R, Riecken EO *et al.* Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastreonterology 2001;121:1329–38.
7. Wahnschaffe U, Schulzke JD, Zeitz M *et al.* Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol 2007;5:844–50.
8. Atkinson W, Sheldon TA, Shaath N *et al.* Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004;53:1459–64.
9. Biesiekierski JR, Newnhham ED, Irving PM *et al.* Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double blind randomized placebo controlled trial. Am J Gastroenterol 2011;106:508–14 (this issue).
10. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. Am J Gastroenterol 2009;104:1587–94.
11. Verdu EF, Huang X, Natividad J *et al.* Gliadin-dependent neuromuscular and epithelial secretory responses in gluten-sensitive HLA-DQ8 transgenic mice. Am J Physiol Gastrointest Liver Physiol 2008;294:G217–25.
12. Natividad JM, Huang X, Slack E *et al.* Host responses to intestinal microbial antigens in gluten-sensitive mice. PLoS One 2009;4:e6472.
13. Quigley EMM. Disturbances of motility and visceral hypersensitivity in irritable bowel syndrome: biological markers or epiphenomenon. Gastroenterol Clin N Am 2005;34:221–33.
14. Miller V, Hopkins L, Whorwell PJ. Suicidal ideation in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2004;2:1064–8.
15. Chitkara DK, van Tilburg MA, Blois-Martin N *et al.* Early life risk factors that contribute to IBS in adults: a systematic review. Am J Gastroenterol 2008;103:765–74.
16. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology 2009;136:2003–14.
17. Drossman DA, Camilleri M, Mayer EA *et al.* AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108–31.
18. Quigley EM. Disturbances in small bowel motility. Baillieres Best Pract Res Clin Gastroenterol 1999;13:385–95.
19. Mertz H, Naliboff B, Munakata J *et al.* Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40–52.
20. Schmulson M, Chang L, Malakoff B *et al.* Correlation of symptom criteria with perception thresholds during rectosigmoid distension in irritable bowel syndrome patients. Am J Gastroenterol 2000;95:152–6.
21. Accarino AM, Azpiroz F, Malagelada JR. Mechanosensitive intestinal afferents in irritable bowel syndrome. Gastroenterology 1995;108:636–43.
22. Chadwick VS, Chen W, Shu D *et al.* Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 2002;122:1778–83.
23. Tornblom H, Lindberg G, Nyberg B *et al.* Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002;123:1972–9.
24. Guilate M, Santos J, de Torres I *et al.* Diarrhea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2007;56: 203–9.
25. Ohman L, Isaksson S, Lindmark AC *et al.* T-cell activation in patients with irritable bowel syndrome. Am J Gastroenterol 2009;104:1205–12.
26. Barbara G, Stanghellini V, De Giorgio R *et al.* Activated mast cells in proximity to colonia nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693–702.
27. van der Veek PP, van den Berg M, de Kroon YE *et al.* Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. Am J Gastroenterol 2005;100:2510–6.
28. Dinan TG, Quigley EM, Ahmed SM *et al.* Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology 2006;130:304–11.
29. Liebregts T, Adam B, Bredack C *et al.* Immune activation in patients with irritable bowel syndrome. Gastroenterology 2007;132:913–20.
30. 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;128:541–51.
31. Spiller RC. Role of infection in irritable bowel syndrome. J Gastroenterol 2007;42 (Suppl 17): 41–7.
32. Mättö J, Maunuksela L, Kajander K *et al.* Composition and temporal stability of gastrointestinal microbiota in irritable bowel syndrome—a longitudinal study in IBS and control subjects. FEMS Immunol Med Microbiol 2005;43:213–22.
33. Collins SM, McHugh K, Jacobson K *et al.* Previous inflammation alters the response of the rat colon to stress. Gastroenterology 1996;111: 1509–15.
34. Bercík P, Wang L, Verdú EF *et al.* Visceral hyperalgesia and intestinal dysmotility in a mouse model of post infective gut dysfunction. Gastroenterology 2004;127:179–87.