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Reprint requests

Address requests for reprints to: Nicholas J. Shaheen, MD, MPH, Professor of Medicine and Epidemiology, Director, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, CB#7080, Chapel Hill, NC 27599-7080.

Conflicts of interest

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Gluten Sensitivity: Not Celiac and Not Certain

See "No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly-absorbed, short-chain carbohydrates," by Biesiekierski JR, Peters SL, Newnham ED, et al on page 320.

The current working definition of nonceliac gluten sensitivity (NCGS) is the occurrence of irritable bowel syndrome (IBS)-like symptoms after the ingestion of gluten and improvement after gluten withdrawal from the diet after exclusion of celiac disease based on negative celiac serologies and/or normal intestinal architecture and negative immunoglobulin (Ig)E-mediated allergy tests to wheat.[1–3] Symptoms reported to be consistent with NCGS are both intestinal (diarrhea, abdominal discomfort or pain, bloating, and flatulence) and extra-intestinal (headache, lethargy, poor concentration, ataxia, or recurrent oral ulceration).[2] These criteria strongly and conveniently suggest that NCGS is best understood as a subset of IBS or perhaps a closely related but distinct functional disorder. Although the existence of NCGS has been slowly gaining ground with physicians and scientists, NCGS has enjoyed rapid and widespread adoption by the general public. It has been suggested in the lay press that ≥20% of the general population reports symptoms in association with the ingestion of gluten[4] and can be regarded as having "gluten sensitivity."[5] Strikingly, and for many in the celiac field depressingly, in the general US population more people are aware of NCGS than they are of celiac disease.[6]

The concept of NCGS was first introduced into the literature as case reports,[7,8] but the first controlled study was published in this journal 30 years ago conducted in 8 nonceliac patients with chronic diarrhea and abdominal pain in whom symptoms were relieved on a gluten-free diet and exacerbated with gluten challenge.[9] This was before the advent of accurate serologic tests, and we cannot be certain that these patients would not now be classified as mild enteropathy celiac disease.[10] These reports documented the potential for clinical effects of gluten outside of traditional celiac disease. In recent years, a number of disparate attempts have been made to better understand and classify this disorder. Although the modern era of celiac disease was ushered in by the availability of widely available accurate serologic testing, the authors of "No effects of gluten in patients with self-reported non-celiac gluten sensitivity following dietary reduction of low-fermentable, poorly-absorbed, short-chain carbohydrates" in this edition of GASTROENTEROLOGY may be attributed with starting the modern era of NCGS, which their landmark study published in 2011.[11]

In their prior study, Biesiekierski et al[11] conducted a double-blind, randomized trial in 34 patients diagnosed with IBS in whom celiac disease was excluded, and who were symptomatically controlled on a gluten-free diet. Participants were randomized to consume in a blinded fashion either 16 g/d of gluten or gluten-free bread and muffins. Participants exposed to gluten experienced

significant exacerbation of overall intestinal symptoms ($P = .047$), pain ($P = .016$), bloating ($P = .031$), satisfaction with stool consistency ($P = .024$), and tiredness ($P = .001$). There were no changes in fecal lactoferrin, levels of celiac antibodies, C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2/DQ8. Although moderate in size, this study was the first on NCGS to utilize rigorous randomized, double-blind, controlled clinical trial methodology. The striking differences in gastrointestinal and extra-intestinal symptoms seen in the gluten and placebo arms of this study did much to convince the medical and scientific community that NCGS was a real entity, studiable using standard research methodologies.

The past few years have seen a flurry of clinical and basic research studies targeting NCGS, the results of which seem determined to thwart any attempt to come to broad consensus regarding what NCGS is or is not, what causes it, and who it might affect.

Some studies suggest that NCGS generally belongs on the spectrum of functional bowel disorders.[11–13] Other studies are more suggestive that NCGS may actually fit better within the spectrum of celiac disease. For example, in contrast with the studies by Biesiekierski et al[11] and Saponi et al,[14] a number of studies have reported that nonceliac individuals with gluten-responsive symptoms are more likely to carry human leukocyte antigen (HLA)-DQ2/8.[12,15] Taking a somewhat different tack, Carroccio et al[13] reported that NCGS patients with negative wheat IgE allergy testing developed greater symptoms with wheat exposure compared with placebo ($P < .0001$). The presence of anemia, weight loss, self-reported wheat intolerance, history of food allergy in infancy, and coexistent atopic diseases were more frequent in wheat-sensitive patients than in non–gluten-responsive IBS controls. There was also a higher frequency of positive serum assays for IgG/IgA anti-gliadin and greater association with DQ2 or DQ8 haplotype than controls.

Similar discrepancies have been reported in biophysical measures after gluten exposure in NCGS patients. Gluten has been shown to induce low-grade intestinal inflammation in experimental models as well as in human studies.[3,12,16] However, small intestinal permeability has been reported to increase with gluten exposure in some studies,[12] and be unchanged in others.[11,14] Gluten-containing diet has been reported to induce proliferation of peripheral blood monocytes and enhance cytokine production independent of DQ status[12] and to induce basophil activation.[17] These findings contrast with other recent studies, which in 1 case was unable to find any gluten-induced inflammation in NCGS,[18] and in the other found that eosinophil infiltration of the duodenal and colon mucosa was the major abnormality induced by wheat.[13] Further, although some studies have suggested that NCGS may be characterized by selective activation of the innate immunity with increased expression of Toll-like receptors-2 and -4 and FOXP3,[19,20] this contrasts with the association with HLA-DQ genotypes characteristic of adaptive immunity noted. It should also be noted that gluten may not, in reality, be the culprit in NCGS. Rather, other wheat proteins or carbohydrates may be the major etiologies of gastrointestinal distress in otherwise healthy individuals who eat wheat.[21] IgE-mediated wheat allergy[22] and opiate-like activity of gluten[23] have also been proposed. Finally, a nocebo effect of wheat ingestion might explain the much of the current prevalence of NCGS as patients who believe themselves to be food sensitive are preconditioned to avoidance.[24]

In this issue of Gastroenterology, Biesiekierski et al[25] return with another double-blind, randomized, controlled trial on NCGS. Although in many ways this work seems to have been designed as a more thorough follow-on study to their prior work, the most significant variation from the prior study was the recommendation that participants restrict to low-fermentable, poorly absorbed, short-chain carbohydrates (FODMAPs) throughout the study. With the changing patterns of food intake and dietary behaviors over the last 20 years so-called westernization, FODMAPs have constituted significant proportion in food consumption.[26] FODMAPs have been identified as important triggers for functional gut symptoms in people with visceral hypersensitivity or abnormal motility responses, largely by inducing luminal distension via a combination of osmotic effects and gas production related to their rapid fermentation by bacteria in the small and proximal large intestines.[27,28] This seems to have been the rationale behind the addition of a low FODMAP diet in the current study, limiting alternate dietary triggers that could confound results. In the current study, 37 subjects with NCGS defined as "IBS fulfilling Rome III criteria that self-reportedly improved with a GFD" after exclusion of celiac disease were enrolled into the trial. All participants were continued on their gluten-free diet and after a 1-week baseline, started on a low FODMAP diet for a 2-week run in period. Participants were then randomly assigned to 1 of 3 study arms, received high-gluten (16 g gluten per day), low-gluten (2 g gluten per day and 14 g whey protein per day), or control (16 g whey protein per day) diets for 1 week, followed by a washout period of $\geq$2 weeks. Participants then crossed over to the next randomly assigned treatment arm and repeated this a third time until all participants had received all 3 treatments. Finally, at a substantially later time (8–17 months after initial study) 22 subjects then participated in a crossover study and to groups given gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 days. The clinical, serologic, and immunologic parameters were evaluated at 7- and 3-day rechallenge periods.