Digestive Diseases and Sciences (2023) 68:1084–1085
https://doi.org/10.1007/s10620-022-07802-3

INVITED COMMENTARY

Non-celiac Gluten Intolerance: A Call to Clarify

Jacqueline Jossen[1] · **Benjamin Lebwohl**[1]

Accepted: 16 December 2022 / Published online: 20 January 2023

Interest in consuming a gluten-free diet (GFD) among people who do not carry the diagnosis of celiac disease has risen substantially in the past decade [1]. The many reasons for this increase, which include perceptions that the diet is healthier, promotes weight loss, improves acne, alleviates gastrointestinal symptoms, or is effective as an adjunct treatment for autoimmune diseases, [2, 3] are either unproven or have been refuted [4]. A disease entity termed non-celiac gluten sensitivity (NCGS) was devised to include individuals who perceived a benefit from consuming a GFD. Unlike celiac disease, with well-defined serologic and histologic biomarkers, NCGS is a heterogeneous and poorly-understood condition with diagnostic criteria that can be challenging to measure or confirm in clinical practice [5]. Though very little is known about the contribution of the gluten protein in the pathogenesis of NCGS, there is accumulating evidence that other grain components may be the true culprit in symptom development.

In the face of this uncertainty, a new study by Jansson-Knodell et al. published in this issue of *Digestive Diseases and Sciences* assesses this widespread phenomenon [6]. In this study, the investigators report an additional analysis of a survey conducted many of the same authors distributed in 2019 to more than 2000 respondents via Amazon's crowdsourcing marketplace Mechanical Turk, the principal results of which were published in 2021 [7]. The prior publication reported on the demographics of those with self-reported food intolerances overall, whereas the present analysis focuses specifically on wheat and gluten. They found that a self-reported intolerance to wheat, rye, barley, flour, or pasta was present in 5.1% of respondents overall, but that respondents were selective in terms of the gluten-containing foods to which they were intolerant; reports of sensitivity to *all* gluten-related items was reported in only 5.6% of those reporting an intolerance to any given gluten-containing food, suggesting that gluten itself may not be the common denominator for perceived gluten intolerance.

The study has strength in its large numbers, but several important limitations in its design. Participants with celiac disease and wheat allergy, for whom a gluten-free diet is a necessity, were not distinguished from individuals without celiac disease who reported intolerance. There is also ambiguity in the terms "flour" and "pasta," since a growing share of the marketplace offers gluten-free varieties of these products. Additional limitations exist in participants' self-reporting, since one of the challenges with self-reported diagnosis is that the full medical context and prior workup is unknown. Alternative etiologies including small intestinal bacterial overgrowth, and fructose and lactose intolerance are likely responsible for symptoms in 30% of people who avoid gluten (PWAG) and were not accounted for in this survey of self-reported food intolerances [8].

The Salerno Criteria for NCGS recommend a double-blind, placebo-controlled, crossover gluten challenge as the gold standard for its diagnosis [5]. In a clinical setting, a blinded gluten challenge is difficult to execute, prompting a laxity in making the diagnosis in clinical practice. In research settings, however, randomized clinical trials performing this sort of gluten challenge reveal few with true NCGS and a strong nocebo (subjects who report worse symptoms when receiving placebo) effect [9, 10]. As such, investigations to better understand the pathophysiology underlying symptoms currently attributed to NCGS are ongoing.

NCGS and irritable bowel syndrome (IBS) share a similar semiology in that though both lack specific biomarkers for diagnosis, they both carry strong associations and both may be triggered by dietary components. There is growing support for the contribution of fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) in patients with IBS and possibly those with NCGS. For instance, almost a decade ago, Biesierkierski, et al. showed that a low FODMAP diet improved symptoms in patients with NCGS. Though symptoms worsened in the groups receiving gluten or placebo,

✉ Benjamin Lebwohl
bl114@cumc.columbia.edu

[1] Departments of Medicine and Pediatrics, The Celiac Disease Center at Columbia University, 180 Fort Washington Avenue, Suite 936, New York, NY 10032, USA

the symptoms experienced in those receiving placebo were worse, demonstrating a strong nocebo effect [9]. A moderately-low FODMAP diet has also been effective in symptom management of celiac disease patients treated with a GFD with healed villi and persistent symptoms, highlighting the value of this diet outside of IBS, and among those with a clear indication for gluten avoidance [11].

Fructans are a FODMAP that naturally occur in many foods, including wheat products. They are rapidly fermented to form intraluminal gas and metabolites that attract excess luminal water. These fermentation products contribute to the bloating, diarrhea, and abdominal pain typical of IBS. Gluten challenge performed with wheat products thus may provoke symptoms secondary to fructan fermentation rather than to gluten sensitivity. A recent study that used purified gluten, fructan, and placebo in müsli (muesli) bars to assess the contribution of fructans to NCGS reported that the overall symptom score, and especially bloating, was highest during fructan challenge, whereas symptom scores during gluten challenge were even lower than those during placebo [12].

Further complicating this issue is the possible contribution of amylase trypsin inhibitors (ATI), components of wheat protein that defend the living wheat plant against pathogens. In vitro studies have examined the innate immune systemic response via the pro-inflammatory chemosensor Toll-like receptor 4 following activation by ATI [13]. Association with other diseases including baker's asthma has led to the hypothesis that oral ingestion of wheat proteins containing ATI may be a trigger for NCGS via the induction of intestinal inflammation. Though intriguing, there are not enough available in vivo data to definitively characterize how ATI contributes to NCGS.

Gluten avoidance continues to loom large, in particular in populations susceptible to adopting current dietary trends. As clinicians, it behooves us to be curious and continue to investigate patients with these symptoms. Thus far, the data suggest that the term NCGS used to describe the population with perceived gluten sensitivity in the absence of diagnosed celiac disease is a misrepresentation of the true nature of this syndrome. Rather, there is considerable heterogeneity in this population in terms of dietary triggers that should be accounted for when diagnosing and counseling patients.

Gastroenterologists and celiac disease specialists are uniquely situated to help clarify symptom etiology, identify alternative triggers of symptoms, and personalize care. Along with our dietitian colleagues, we can help educate patients about dietary sensitivities while also ensuring no nutritional deficit or maladaptive eating behaviors emerge.

References

1. Reilly NR. The gluten-free diet: recognizing fact, fiction, and fad. *J Pediatr* 2016;175:206–210.
2. Arslain K, Gustafson CR, Baishya P, Rose DJ. Determinants of gluten-free diet adoption among individuals without celiac disease or non-celiac gluten sensitivity. *Appetite* 2021;1(156):104958.
3. Passali M, Josefsen K, Frederiksen JL, Antvorskov JC. Current evidence on the efficacy of gluten-free diets in multiple sclerosis, psoriasis, type 1 diabetes and autoimmune thyroid diseases. *Nutrients* 2020;12(8):2316.
4. Lerner BA, Green PHR, Lebwohl B. Going against the grains: gluten-free diets in patients without celiac disease-worthwhile or not? *Dig Dis Sci* 2019;64(7):1740–1747. https://doi.org/10.1007/s10620-019-05663-x.
5. Catassi C, Elli L, Bonaz B et al. Diagnosis of non-celiac gluten sensitivity (NCGS): The Salerno experts' criteria. *Nutrients* 2015;7(6):4966–4977.
6. Jansson-Knodell CL, White M, Lockett C, Xu H, Rubio-Tapia A, Shin A. Self-reported gluten intolerance is prevalent, but not all gluten-containing foods are equal. *Dig Dis Sci*. 2022. https://doi.org/10.1007/s10620-022-07800-5.
7. Jansson-Knodell CL, White M, Lockett C, Xu H, Shin A. High prevalence of food intolerances among US internet users. *Public Health Nutr* 2021;24(3):531–535.
8. Tavakkoli A, Lewis S, Tennyson C, Lebwohl B, Green PHR. Characteristics of patients who avoid wheat and/or gluten in the absence of celiac disease. *Dig Dis Sci* 2014;59(6):1255–1261.
9. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology* 2013;145(2):320–8.e1-3.
10. Molina-Infante J, Carroccio A. Suspected nonceliac gluten sensitivity confirmed in few patients after gluten challenge in double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol.* 2017;15(3):339–348.
11. van Megen F, Skodje GI, Lergenmuller S et al. A low FODMAP diet reduces symptoms in treated celiac patients with ongoing symptoms-a randomized controlled trial. *Clin Gastroenterol Hepatol* 2022;20(10):2258-2266.e3.
12. Skodje GI, Sarna VK, Minelle IH et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology* 2018;154(3):529-539.e2.
13. Zevallos V, Raker V, Tenzer S, Schild H, Steinbrink K, Schuppan D. Nutritional wheat amylase-trypsin inhibitors promote intestinal inflammation via activation of myeloid cells. *Gastroenterology* 2017;152(5):1100–1113.