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PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Suspected Nonceliac Gluten Sensitivity Confirmed in Few Patients After Gluten Challenge in Double-Blind, Placebo-Controlled Trials

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A double-blind, placebo-controlled, gluten challenge has been proposed to confirm a diagnosis of nonceliac gluten sensitivity (NCGS) in patients without celiac disease who respond to a gluten-free diet. To determine the accuracy of this approach, we analyzed data from 10 double-blind, placebo-controlled, gluten-challenge trials, comprising 1312 adults. The studies varied in the duration of the challenge (range, 1 d to 6 wk), daily doses for the gluten challenge (range, 2–52 g; 3 studies administered <8 g/d), and composition of the placebo (gluten-free products, xylose, whey protein, rice, or corn starch containing fermentable carbohydrates). Most of the studies found gluten challenge to significantly increase symptom scores compared with placebo. However, only 38 of 231 NCGS patients (16%) showed gluten-specific symptoms. Furthermore, 40% of these subjects had a nocebo response (similar or increased symptoms in response to placebo). These findings reveal heterogeneity and potential methodology flaws among studies of gluten challenge, cast doubt on gluten as the culprit food component in most patients with presumptive NCGS, and highlight the importance of the nocebo effect in these types of studies.

Keywords: Celiac Disease; Wheat Allergy; Irritable Bowel Syndrome; Gluten-Free Diet.

Nonceliac gluten sensitivity (NCGS) was first described in the late 1970s[1,2] and the first series dates back to 1980.[3] However, it has been only since 2009 that rapidly increasing evidence has called our attention to an apparently novel condition.[4] Several epidemiologic studies have suggested that NCGS may affect a variable range (from 0.5% to 13%) of the Western population.[5–9] In line with the advent of NCGS, gluten-free foods among nonceliac patients have grown steadily in popularity, for reasons other than sensitivity, such as eating healthy food or aids in weight loss.[10] A recent survey conducted in the United States showed that almost one third of the adult healthy population were trying to cut down or avoid gluten in their diets.[11]

Currently, NCGS is a syndrome characterized by intestinal and extraintestinal symptoms related to the ingestion of gluten-containing food, in subjects in whom either celiac disease or wheat allergy previously has been ruled out.[12] The clinical spectrum includes irritable bowel syndrome (IBS)-like and other functional gastrointestinal symptoms (bloating, diarrhea, abdominal pain, dyspepsia, and so forth), along with extraintestinal manifestations such as fatigue, headache, numbness, mental confusion, anxiety/depression, and fibromyalgia-like symptoms.[13] Given the lack of a diagnostic biomarker, NCGS mostly remains a self-reported diagnosis for patients and a diagnosis of exclusion for physicians, so a confirmatory test is required. The Salerno experts[14] recently advocated a double-blind, placebo-controlled (DBPC), cross-over, gluten challenge as the gold standard test to discriminate true NCGS patients. First of all, the patient should show at least a 30% decrease in gastrointestinal symptoms after a 6-week gluten-free diet. Then, a DBPC challenge with cross-over should be performed, with a 1-week duration for each challenge and the wash-out period between. The recommended daily doses for gluten are 8 g, whereas the placebo should be gluten-free.[14] It is likely that outcome reports of DBPC in NCGS might be discrepant depending on the selection of patients through previous elimination diets and the challenge methods, including doses and duration for gluten and components for the placebo. The aim of this article is to critically revise the published procedures for DBPC challenge in NCGS trials, to understand potential inconsistent results in trials.

Methods

A literature search was conducted through PubMed, up to March 31, 2016, examining all published articles linked

Abbreviations used in this paper: **ATI, amylase-trypsin inhibitor; DBPC, double-blind placebo-controlled; FODMAP, fermentable oligosaccharides, di-, monosaccharides and polyols; IBS, irritable bowel syndrome; NCGS, nonceliac gluten sensitivity.**

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to the MeSH search terms "non celiac OR nonceliac OR non-celiac OR noncoeliac AND gluten sensitivity" from English language journals. Only randomized DBPC trials evaluating gluten challenge in either NCGS or IBS patients were included. Patients suffering from celiac disease or other gluten-related disorders (gluten ataxia, autism, neurologic symptoms), mostly referenced as "gluten sensitivity," were excluded as well. Duplicate publications were excluded. The reference lists of these articles were reviewed to include further appropriate articles.

Results

The review and selection process is detailed in Figure 1. From a total of 325 eligible articles in our initial search, we finally retrieved 10 DBPC trials with gluten/wheat challenge including a total of 1312 patients with suspected NCGS.[3,15–23] All of these studies were conducted in adult populations. Nine in 10 (90%) studies were published over the past 5 years.

Study Design and Inclusion/Exclusion Criteria

These data are summarized in Table 1. Six of 10 studies had a cross-over DBPC design.[16–18,20–22] All of the studies generally included patients with IBS-like symptoms showing improvement on a gluten-free diet. Celiac disease was ruled out by seronegativity and lack of villous atrophy in duodenal biopsy specimens. Only the 3 studies from the Australian group[15,17,18] used more stringent criteria to exclude celiac disease. Celiac disease was ruled out either by absence of the HLA DQ2/DQ8 haplotypes or by a baseline normal duodenal biopsy (Marsh 0) while on a gluten-containing diet in individuals expressing the HLA DQ2/DQ8 haplotypes. HLA DQ2/DQ8 haplotypes were present in 56%,[15] 53%,[16] 55%,[17] 55%,[18] 57%,[19] 26%,[20] 46%,[21] and 75%[22] of patients, respectively. When reported, wheat allergy was ruled out by specific IgE testing, mostly skin testing. A recent Italian study excluded patients with lactose and fermentable oligosaccharides, di-, monosaccharides and polyols (FODMAP) intolerance,[20] apart from those with celiac disease and wheat allergy.

Gluten Challenge

Only 1 study used wheat instead of gluten for the food challenge.[16] Among the studies using gluten for the food challenge, 3 of the 4 Italian trials used a gluten amount less than 8 g/d,[20–22] which is in disagreement with recent recommendations from the Salerno experts.[14] The remaining studies used a higher gluten amount than that recently recommended: 10 g/d,[23] 16 g/d,[15,17,18] with a low-dose gluten arm in 1 study that used 2 g/d.[17] The study with the longest duration (6 weeks) also used the highest gluten doses (52 g/d),[19] whereas the pioneer study by Cooper et al[3] used 20 g/d for 2 separate days.

Placebo Challenge

All research groups used different placebo components, including gluten-free muffins and bread, xylose, whey protein, or starch. Of note, 2 studies used FODMAP-containing placebo, such as corn starch,[19] and corn starch, lactose, and fructans.[21] The duration of the challenge (from 1 day to 6 weeks) and the wash-out periods between challenges in cross-over studies (from 3 days to a minimum of 2 weeks) also was extremely variable. This information is summarized in Table 2.

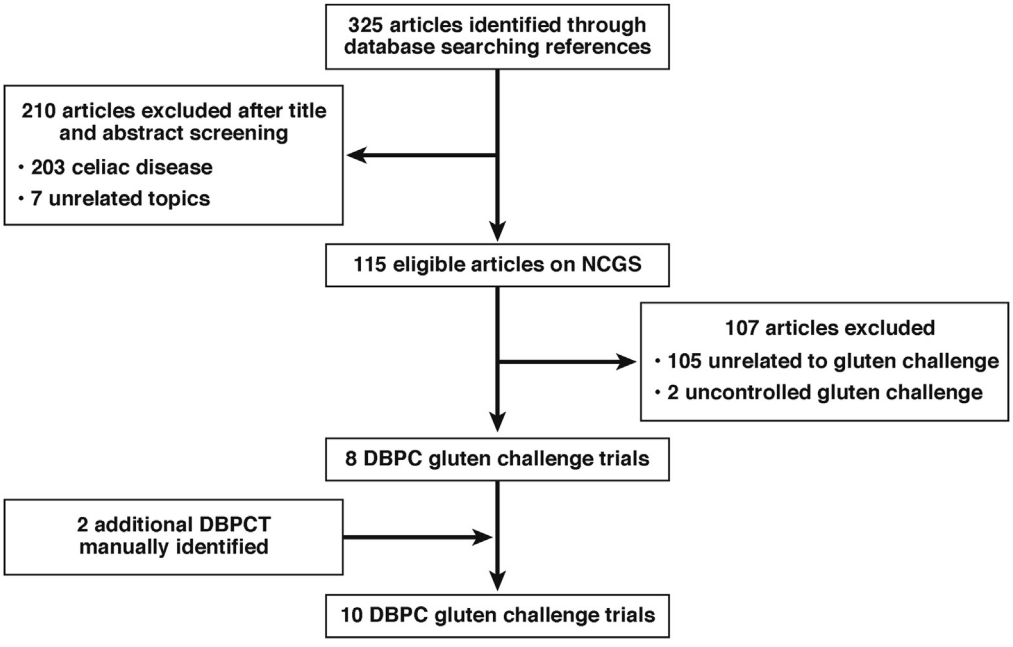

Figure 1. Flow chart of literature search performed for this systematic review. DBPCT, double-blind, placebo-controlled trial

Table 1. Detailed Analysis of Methodology for Patient Selection and Primary End Points in the Ten Randomized, Double-Blind, Placebo-Controlled Trials Evaluating Gluten Challenge to Date in NCGS Patients

Study, year of publication, country	Sample size, design	Inclusion criteria	Criteria for exclusion of celiac disease	Criteria for exclusion of wheat allergy	Primary end points
Cooper et al,[3] 1980, England	6, DBPCT	Severe diarrhea responsive to empiric GFD	Lack of villous atrophy	NS	Remission of diarrhea
Biesiekierski et al,[15] 2011, Australia	34, DBPCT	Self-reported NCGS	Negative HLA DQ2/DQ8 or duodenal Marsh 0 biopsy if positive haplotypes	NS	Proportion of patients responding with "no" on more than half of the symptom assessments to the following question, "Over the last week were your symptoms adequately controlled?"
Carroccio et al,[16] 2012, Italy	920, cross-over DBPCT	IBS and self-reported NCGS patients	Negative antibodies and lack of villous atrophy	Negative skin and serum IgE testing	Resolution of symptoms on elimination diets and recurrence after DBPC challenge
Biesiekierski et al,[17] 2013, Australia	37, cross-over DBPCT	IBS and self-reported NCGS patients	Negative HLA DQ2/DQ8 or duodenal Marsh 0 biopsy if positive HLA	NS	Change in overall symptoms (visual analogue scale) >20 mm from the run-in period (low FODMAP) to the end of the study (gluten vs placebo)
Peters et al,[18] 2014, Australia	22, cross-over DBPCT	Self-reported NCGS patients	Negative HLA DQ2/DQ8 or duodenal Marsh 0 biopsy if positive haplotypes	NS	Mental state (STPI)
Shahbazkhani et al,[19] 2015, Iran	73, DBPCT	IBS patients	Negative antibodies and lack of villous atrophy	Negative IgE testing	Change in overall symptoms (visual analogue scale)
Di Sabatino et al,[20] 2015, Italy	61, cross-over DBPCT	Self-reported NCGS patients	Negative antibodies and lack of villous atrophy	Negative IgE testing	Change in overall symptoms (visual analogue scale)
Zanini et al,[21] 2015, Italy	35, cross-over DBPCT	Self-reported NCGS patients	Negative antibodies and lack of villous atrophy	Negative IgE testing	Symptom worsening while taking gluten compared with placebo
Elli et al,[22] 2016, Italy	98, cross-over DBPCT	Patients with functional symptoms, including IBS and functional dyspepsia	Negative antibodies and duodenal biopsy specimens if high suspicion	Negative skin and blood IgE testing	Symptom worsening while taking gluten compared with placebo
Picarelli et al,[23] 2016, Italy	26, DBPCT	Self-reported NCGS patients	Negative antibodies and histologic and organ culture of duodenal biopsy specimens	Negative IgE testing	Change in overall gastrointestinal and extraintestinal symptoms (visual analogue scale)

DBPCT, double-blind, placebo-controlled trial; GFD, gluten-free diet; NS, not stated; STPI, state trait personality inventory.

Table 2. Detailed Analysis of Gluten and Placebo Composition, Duration of Challenges and Wash-Out Periods, Along With Outcome Reports in the Eight Randomized, Double-Blind, Placebo-Controlled Trials Evaluating Gluten Challenge to Date in NCGS Patients

	Gluten/wheat challenge doses and duration	Placebo challenge composition	Washout period	Primary end point, outcome report	Ability to adequately distinguish gluten from placebo or comparison between the clinical response to gluten or to placebo
Cooper et al,[3] 1980, England	Gluten 20 g/d for 4 wk (sachets were taken the first 3 days of weeks 2 and 4)	Gluten-free flour	–	Significant overall worsening of intestinal symptoms for gluten-containing group ($P = .0025$)	NR
Biesiekierski et al,[15] 2011, Australia	Gluten 16 g/d 6 wk	Gluten-free muffins and bread	–	Symptoms control on gluten-free diet, (1) 68% of symptoms were not adequately controlled in the gluten arm (2) 40% of symptoms were not adequately controlled in the placebo arm	NR
Carroccio et al,[16] 2012, Italy	Wheat-containing capsules 20 g for 2 wk	Xylose	1 wk	Increase >30% in symptoms on wheat challenge, 30% of challenged patients were diagnosed as nonceliac wheat sensitivity	NR
Biesiekierski et al,[17] 2013, Australia	Gluten High: 16 g/d Low: 2 g/d 2 wk	16 g whey protein	At least 2 wk	Increase in overall abdominal symptoms of >20 mm, (1) 8% correctly identified and developed symptoms with gluten, but not with placebo (2) 30% were symptomatic in the placebo arm	NR
Peters et al,[18] 2014, Australia	Gluten 16 g/d for 3 d	16 g whey protein or placebo	A minimum of 3 d	Effect of gluten ingestion on mental state, state of depression was significantly higher in the gluten group compared with placebo, but not with whey protein	NR
Shahbazkhani et al,[19] 2015, Iran	Gluten 52 g/d for 6 wk	Corn starch, quantity not specified	–	Symptom control during a 6-wk challenge, 74% were symptomatic in the gluten arm at week 6; 17% were symptomatic in the placebo arm at week 6	NR

Di Sabatino et al,[20] 2015, Italy	Gluten 4.735 g/d for 1 wk	4.735 g/d rice starch	1 wk		Change in overall symptoms, compared with placebo, gluten resulted in a significantly higher severity of the overall symptom score	31 of 61 (52%) showed similar symptoms with gluten or placebo 21 of 61 (33%) showed more symptoms on placebo compared with gluten 9 of 61 (15%) showed symptom relapse after gluten challenge, but not after placebo
Zanini et al,[21] 2015, Italy	Gluten 7.9 g/d for 10 d	76.7 g corn starch, 6.8 g lactose, 0.16 fructans	2 wk		Participants' ability to correctly identify the gluten based on symptom recurrence, 33% correctly identified and developed symptoms with gluten	33% correctly identified and developed symptoms with gluten, but not with placebo; 49% erroneously identified placebo as gluten-containing
Elli et al,[22] 2016, Italy	Gluten 5.6 g/d for 7 d	Rice starch	1 wk		Identify patients with NCGS from those reporting an improvement of gastrointestinal symptoms after GFD through a DBPC, 14% of patients responding to gluten withdrawal showed a symptomatic relapse during the gluten challenge	69 of 98 (70%) did not show symptom relapse after gluten challenge; 14 of 98 (14%) showed symptom relapse after both gluten and placebo challenge; 14 of 98 (14%) showed symptom relapse after gluten challenge (NCGS), but not after placebo
Picarelli et al,[23] 2016, Italy	10 g/d for 1 d	Gluten- and lactose-free croissant		–	Change in overall symptoms, 61% developed symptoms on gluten	61% developed symptoms on gluten with gluten-containing croissants, 46% developed symptoms with gluten-free croissants

GFD, gluten-free diet; NR, not reported.

Primary End Points and Outcome Report

The main findings of the included studies are shown in Table 2. Measurement of the primary end point was performed in 9 studies by means of overall change in symptoms after both challenges.[3,15–20,22–23] The studies by Biesiekierski et al[17] and Di Sabatino et al[20] reported the ability to adequately distinguish gluten from placebo as a secondary end point of the study. After these studies, 2 more Italian studies also included the distinction between gluten and placebo as a primary[21] or secondary[22] end point.

When overall symptoms were reported quantitatively (sum of symptom scores in all patients), gluten or wheat was shown to trigger significantly more symptoms compared with placebo in 7 trials studies.[3,15,16,18–20,22] However, only 4 studies[17,20–22] also reported the challenge outcome qualitatively, aiming at differentiating patients with specific-gluten symptoms or patients with similar or more symptoms on placebo than with gluten (nocebo effect). These data are summarized in Table 3. Only 38 of 231 (16%) NCGS patients showed gluten-specific symptoms.[17,20–22] Of note, a nocebo response (similar or higher symptom worsening with placebo) was observed in 94 of 231 (40%) patients. When the only study using a FODMAP-containing placebo was excluded,[21] the nocebo effect remained unaltered (77 of 196; 39%). Interestingly, using wheat instead of gluten for the food challenge, which was conducted in 1 single study,[16] resulted in identification of 30% of patients with nonceliac wheat sensitivity.

Discussion

The present review shows that more than 80% of nonceliac patients, labeled as suffering from NCGS after a favorable response to a gluten-free diet, cannot reach a formal diagnosis of NCGS after a double-blind, placebo-controlled gluten challenge. Double-blind, placebo-controlled, cross-over trials currently represent the gold standard for confirming dietary factors involved in functional gastrointestinal symptom generation. Accordingly, several conclusions can be drawn from our results. To

Table 3. Comparison of Quantitative and Qualitative Outcome Report After Double-Blind, Placebo-Controlled Gluten Challenge in Five Studies on NCGS Patients

	Outcome report after placebo-controlled gluten challenge			
	Quantitative	Qualitative		
		Gluten-specific symptoms (symptoms triggered with gluten but not with placebo)	Nocebo effect (similar or higher symptoms with placebo compared with gluten)	No symptoms with either gluten or placebo
Biesiekierski et al,[17] 2013, Australia	Similar symptom worsening with gluten or whey protein diet	3 of 37 (8%)	11 of 37 (29%)	NR
Di Sabatino et al,[20] 2015, Italy	Significant symptom worsening with gluten compared with placebo (56.9 vs 43.7; $P = .034$)	9 of 61 (15%)	52 of 61 (85%)	NR
Zanini et al,[21] 2015, Italy	NR	12 of 35 (34%)	17 of 35 (49%)[a]	6 of 35 (17%)
Elli et al,[22] 2016, Italy	Borderline significant symptom worsening with gluten vs placebo (6.1 vs 5.3; $P = .05$)	14 of 98 (14%)	14 of 98 (14%)	70 of 98 (71%)
Picarelli et al,[23] 2016, Italy	Nonsignificant symptom worsening with gluten vs placebo (61% vs 46%; $P = .6$)	NR	NR	NR
Overall results		38 of 231 (16%)	94 of 231 (40%)	76 of 133 (57%)

[a]This study used a FODMAP-containing placebo.

begin with, they hint at the possibility that gluten may not be responsible for gastrointestinal and extraintestinal symptoms in the vast majority of patients with self-reported NCGS. Second, they suggest that the accuracy of a DBPC trial may be far from perfect for diagnosing NCGS. Most of the enrolled patients are highly motivated and would expect that the disease can be controlled by dietary modifications and this likely may promote both a precebo (before the intervention) and placebo effect (during the intervention). Conversely, some others may show negative expectations irrespective of the consumed food, and experience symptoms with a placebo, namely, the nocebo effect. It is noteworthy that up to 40% of patients with suspected NCGS in this systematic review undergoing a DBPC challenge showed a nocebo response. Beyond negative expectations, potential reasons responsible for a nocebo effect are discussed later. Combining the aforementioned considerations and our present findings, a DBPC food challenge currently remains as the imperfect gold standard for NCGS, until we have diagnostic biomarkers available.

As for the gluten challenge procedure, a literature search in the present review drew marked heterogeneity in doses and duration for gluten and placebo challenges. The NCGS diagnostic protocol recommended by the Salerno experts[14] in 2015 included an 8 g/d gluten challenge for 1 week, followed by a wash-out period for 1 week, and then a cross-over to placebo for 1 week. It is important to acknowledge that these are not evidence-based recommendations, but expert committee recommendations. Furthermore, some aspects of the challenge procedure may be questionable and should be validated in prospective studies. A 1-week duration for the gluten challenge might be short for patients showing mild or fluctuating symptoms. If tolerated, the challenge might be prolonged to at least 2 weeks or beyond to ensure detection of the whole spectrum of patients. Likewise, the diagnostic yield of the gluten challenge may be increased with higher gluten doses. The current recommendation of 8 g/d is lower than the average daily intake of gluten in Western countries (10–15 g).[14] By using a gluten dose of 7.9 g/d for 10 days, the study by Zanini et al[21] diagnosed twice as many patients with gluten-specific symptoms (34%) compared with the studies by Di Sabatino et al[20] (17%) and Elli et al[22] (14%), which used lower gluten doses (4.7 and 5.6 g, respectively) for 1 week. As proposed by the Australian research group,[15,17,18] 16 g/d may be more accurate doses for a diagnostic gluten challenge, although tolerability might be a concern for high doses. With regard to the wash-out period, it also is relevant to underscore that 1 week may be too short to avoid carry-over effects (the possibility that effects from previous challenge still may be present in a cross-over trial). Finally, the placebo substance must be completely gluten-free,[14] but we detected 2 studies using FODMAP-containing corn starch.[19,21] Symptoms related to this placebo substance might have been misinterpreted as a nocebo effect and potentially prevented a diagnosis of NCGS.

Beyond optimization in the food challenge procedure, the key question is: what diagnosis should be given to the majority of symptomatic patients who feel better on a gluten-free diet but cannot be diagnosed formally with NCGS? As brilliantly suggested in a recent editorial, "the strange world of NCGS is complex and will not give up its secrets easily."[24] The potential inclusion of different cohorts of patients with wheat- (and maybe other cereal-) related symptoms under the common umbrella of NCGS might explain this enormous diagnostic gap for the gluten challenge. This melting pot hypothesis is shown in Figure 2. First, inclusion of misdiagnosed celiac patients as NCGS patients may blur our understanding of this new entity, therefore adequately ruling out celiac disease is essential.[24] A survey characterizing

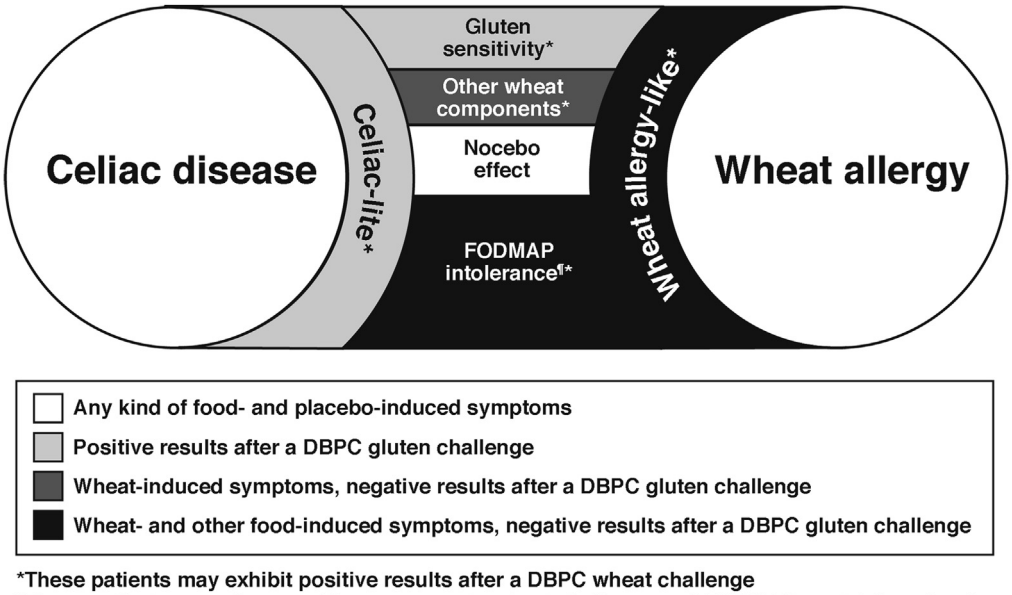

Figure 2. The melting pot hypothesis for NCGS, with different patients lumped together under a common label. Although a gluten challenge might not identify patients intolerant to FODMAP or sensitive or allergic to nongluten proteins, a wheat challenge likely may identify these patients along with patients suffering from gluten-specific symptoms.

147 adults with self-reported NCGS showed that celiac disease had been ruled out inadequately in 61% of patients.[25] In a recent systematic review, up to 20% of NCGS patients in the literature who showed HLA haplotypes and lymphocytic enteritis eventually were relabeled as celiac patients, after advanced diagnostic techniques (including the HLA-DQ2–gliadin tetramer test and anti-endomysium antibodies in duodenal cell culture) or re-evaluation after gluten challenge.[26] Consequently, more sensitive assays[27–30] than those commonly used for celiac disease should be considered for patients with gluten-related symptoms who carry the DQ2 and/or the DQ8 haplotypes.

Second, Carroccio et al[16] explored a subset of NCGS patients showing a high prevalence of concomitant atopic disease, multiple food hypersensitivity, and duodenal and colon eosinophilic infiltration. These findings suggest the existence of a different cohort of NCGS patients with a wheat allergy–like profile. In these patients, a wheat allergy likely may be driven by a non-IgE mechanism and therefore may be overlooked with currently recommended skin and blood testing.[31] In this respect, there are very recent data that suggest a wheat-dependent Th1 immunologic activation in the rectal mucosa of NCGS patients.[32] Third, aside from gluten, wheat may have at least 2 components that may trigger or exacerbate gastrointestinal symptoms: carbohydrates (primarily fructans, included in the FODMAP list), and proteins different from gluten, such as amylase-trypsin inhibitors (ATIs) and wheat germ agglutinin.[33] The efficacy of a low FODMAP diet for IBS symptoms is out of the question and supported by high-quality evidence.[17,34,35] Consequently, FODMAP intolerance likely may play an important role in the NCGS grey zone between celiac disease and wheat allergy (Figure 2). Further studies comparing gluten-free and low FODMAP diet in patients with a presumptive diagnosis of NCGS definitely are warranted. On the other hand, nongluten proteins contained in wheat deserve further attention. ATIs are strong activators of innate immune responses in monocytes, macrophages, and dendritic cells,[36] and wheat germ agglutinin, which has epithelial-damaging and immune effects at very low doses in vitro, also might contribute to both intestinal and extraintestinal manifestations of NCGS.[37] ATIs conceivably might induce symptoms in a subset of NCGS patients with concomitant autoimmune[38] or allergic diseases[31] because those clinical conditions can be exacerbated by a high ATI ingestion. It is noteworthy that commercially available gluten is not purified, therefore nongluten proteins are not removed specifically for the challenge. This issue makes it difficult to discern whether gluten-specific symptoms in challenges ultimately are triggered by either gluten or nongluten proteins, such as ATIs. Furthermore, ATI effects are dose-dependent and a great variability in ATI activity has been reported in different wheat varieties,[39] so this could be another important factor to consider when designing gluten challenges.

Furthermore, a noteworthy recent study using confocal endomicroscopy in the duodenum after duodenal infusion of foods, including wheat, showed early (5 minutes) epithelial breaks, dilation of intervillous spaces, and increased intraepithelial lymphocytes after food challenge.[40] This could evoke an innate immune mechanism, which has been suggested repeatedly in NCGS pathogenesis,[41–43] but an adaptative response in previously sensitized patients also must be considered. Over the past 5 years, active research in pursuit of a diagnostic biomarker for NCGS has been developed, including antigliadin antibodies,[44] chemokine secretion from peripheral blood mononucleated cells,[45] in vitro cytometric basophil activation tests,[46] and fecal assays.[47] Although promising, these tools have not been replicated unequivocally by others,[48,49] therefore an accurate diagnostic biomarker remains an unmet goal.

This confusing uncertainty on the true culprit(s) for NCGS has opened a scenario of different semantic definitions, including nonceliac gluten sensitivity or nonceliac wheat sensitivity[50] to nonceliac wheat protein sensitivity.[33] According to the results of the present review, it is questionable to continue including gluten in the name of the disease when a high proportion of patients with suspected NCGS do not seem to have gluten-specific symptoms in a double-blind, placebo-controlled challenge. Nonceliac wheat sensitivity might be a more accurate term to cover the whole spectrum of patients. One drawback of changing gluten for wheat is that barley and oats may be excluded inappropriately. However, wheat is by far the most common source of gluten. Likewise, some investigators have advocated to distinguish between carbohydrates (causing food intolerance as a result of carbohydrate fermentation by the colonic microbiota) and nongluten proteins (causing food sensitivity owing to an immune response to nutrient-derived antigens).[33,43] Albeit this distinction might be necessary from a physiopathologic standpoint, we believe that the term *wheat* should prevail within nomenclature and food challenge for these patients in clinical practice. Nonceliac wheat sensitivity might be a more accurate term to cover the whole spectrum of patients, including patients intolerant to carbohydrates, showing sensitivity, and allergic to wheat through a non-IgE mechanism.[43,50]

Conclusions

In conclusion, more than 80% of patients with suspected NCGS cannot be diagnosed formally after a double-blind, placebo-controlled, cross-over gluten challenge. Many doubts arise from these findings, including the appropriateness of including gluten in the name of the disease, the methodologic flaws of the currently recommended double-blind, placebo-controlled, cross-over trials as the gold standard diagnostic tool for NCGS, along with the possibility of NCGS being a melting pot made up of different patients lumped

together under a common label. The nocebo effect was detected in up to 40% of patients, possibly related to several factors including negative expectations, carry-over effect in cross-over trials, or use of FODMAP-containing placebo. Further research should assess several optimizations proposed for the currently accepted double-blind, placebo-controlled trial, aside from deciphering whether using wheat instead of gluten for the food challenge may increase the diagnostic yield of food challenge in patients with suspected NCGS.

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Conflicts of interest
The authors disclose no conflicts.