REVIEW

Nonceliac Gluten Sensitivity[1,2]

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ABSTRACT

Nonceliac gluten sensitivity (NCGS) refers to a clinical phenotype in which patients experience intestinal and extraintestinal symptoms related to ingesting a gluten-containing diet after a diagnosis of celiac disease (CD) or wheat allergy has been excluded. CD, an autoimmune disease characterized by villous atrophy triggered by the ingestion of gluten, has increased in prevalence in recent decades, although the majority of patients remain undiagnosed. There is now an increasing public awareness of NCGS and growing interest in the health effects of gluten among health professionals and the lay public. Several randomized controlled trials have explored NCGS but have left many questions unanswered surrounding the pathophysiology, biomarkers, and established diagnostic approach to patients with this condition. Future studies are necessary to establish biomarkers and to elucidate the pathophysiology of this condition because at present, NCGS likely comprises a heterogeneous patient population. In this review, we outline the clinical trials of NCGS as well as the approach to patients with possible NCGS as recommended by an international expert panel. Because maintaining a gluten-free diet has important health, social, and economic consequences, it is necessary for medical professionals to provide practical and evidence-based advice to patients with this condition. *Adv Nutr* 2016;7:1105–10.

Keywords: celiac disease, diet, FODMAP, gluten, sensitivity, wheat

Introduction

Those who do not have celiac disease (CD)[3] or wheat allergy (WA) but who have been identified (by health professionals or by themselves) as being sensitive to gluten are said to have nonceliac gluten sensitivity (NCGS). This entity, which has been described in the literature since as early as the 1980s (1), is distinct from CD. CD is an autoimmune disorder with a worldwide distribution that affects ~1% of the world's population (2) and has a prevalence of 0.7% in the United States (3). It is triggered by the consumption of gluten in genetically susceptible individuals, who are exposed to as-yet-unidentified environmental triggers. In the past few decades, there has been an increase in the prevalence of CD in the United States, and studies of stored serum have confirmed that this observed increase in prevalence is a true increase rather than solely due to an increase in awareness and testing (4).

Along with this increased prevalence of CD, there has been a more recent, broader increase in interest in the gluten-free diet (GFD), which is the primary treatment of CD (5). The GFD has become popular not only among those with NCGS but also in asymptomatic individuals seeking general health benefits from the consumption of this diet. Investigations into the biological basis for NCGS, its prevalence and epidemiology, and the extraintestinal manifestations of the condition have been ongoing for the past decade. This review will explore the recent developments in NCGS, its relation to the more fully characterized entity of CD, and the suggested diagnostic and therapeutic approach to patients with NCGS.

CD

CD is a lifelong, systemic, immune-mediated disease that is triggered by the ingestion of gluten. The disease is characterized by duodenal villous atrophy and can cause a wide variety of intestinal and extraintestinal symptoms. Previously considered to be a rare disease, CD is now recognized as common, with an increasing worldwide prevalence. CD may be associated with abdominal pain and distension, chronic diarrhea, and weight loss, although the majority with the disease present with a variety of nonclassical manifestations, such as anemia, bloating, infertility, or other symptoms. The myriad clinical manifestations can lead to a delay in CD diagnosis (6). CD is also associated with excess mortality (7), lymphoproliferative disease (8), and osteoporotic fractures (9). As such, making the

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[3] Abbreviations used: ATI, amylase trypsin inhibitor; CD, celiac disease; FODMAP, fermentable oligo-di-monosaccharide and polyol; GCD, gluten-containing diet; GFD, gluten-free diet; HLA, human leukocyte antigen; IBS-D, diarrhea-predominant irritable bowel syndrome; NCGS, nonceliac gluten sensitivity; SIBO, small intestinal bacterial overgrowth; WA, wheat allergy.

diagnosis can be crucial for the prevention of morbidity and possibly early mortality. The path to the diagnosis of CD typically starts with clinical suspicion for the disease and is followed by serologic testing, which, in positive cases, prompts esophagogastroduodenoscopy with duodenal biopsy. Although a study from 2012 showed a seroprevalence of CD of 0.7% in the United States (3), most patients in the United States are undiagnosed (10, 11). In response to the underdiagnosis of CD, case-finding initiatives have been advocated (12).

NCGS

Along with the increase in the incidence of CD, there has been a growing interest over time in the GFD among patients without CD. Patients who do not have CD or WA but who experience intestinal and extraintestinal symptoms related to the ingestion of gluten-containing foods are said to have NCGS (13). There is uncertainty with regard to the prevalence of gluten avoidance, and varying estimates are likely due to differing definitions and measurements (e.g., point prevalence compared with recent practices; strict GFD compared with low-gluten diet, etc.). An analysis of the NHANES in 2009–2010 found that the majority of patients who maintain a GFD were not diagnosed with CD (3). Furthermore, a market research study found that 30% of Americans reported that they have decreased their intake or are avoiding gluten completely (14). A questionnaire in England found that >25% of patients with inflammatory bowel disease have tried a GFD (15).

Like CD, the clinical picture of NCGS is variable and diverse and includes intestinal symptoms such as diarrhea, constipation, bloating, and abdominal pain as well as extraintestinal symptoms including anxiety, fatigue, fibromyalgia, foggy mind, and headache (16). However, unlike CD, there are no known serologic markers for NCGS and there is no agreed-upon diagnostic approach. Patients with NCGS do not have duodenal villous atrophy, the histologic hallmark of CD. Although susceptibility to CD is dependent on the human leukocyte antigens (HLAs) DQ2 and DQ8, there is no established genetic marker identified for NCGS. Although gluten has been shown to induce an adaptive immune response in patients with CD, intestinal tissue of patients with NCGS has been suggested to show reduced numbers of T-regulatory cells, which may indicate that the innate immune system is involved in patients who develop NCGS (17). Wheat amylase trypsin inhibitors (ATIs), rather than gluten, have been proposed as major stimulators of these innate immune cells (18). A comparison of CD and NCGS is shown in **Table 1**.

Despite the uncertainty with regard to diagnosis and pathophysiology, public awareness of NCGS is growing. In a 2011 study in chefs and the general public, both groups exhibited a greater awareness of the term "gluten sensitivity" than the term "celiac disease." (19) A similar study in the United Kingdom from 2013 showed that awareness among the general public and among chefs was higher for gluten sensitivity than for CD, although the awareness for both had increased substantially over time (5). The analysis of NHANES found that 49 of the 7762 nonceliac individuals interviewed reported adherence to a GFD, yielding a weighted prevalence of NCGS of 0.55% (20).

TABLE 1 Comparison of CD and NCGS[1]

	CD	NCGS
Prevalence	1%	Unknown
Symptoms	Variable, diverse	Variable, diverse
Genetic markers	DQ2/DQ8	None known
Serologic markers	TTG, gliadin antibodies, deamidated gliadin, endomysial antibodies	None (gliadin antibodies)
Duodenal histology	Villous atrophy	Normal
Malignancy risk	Yes	None known
Osteoporosis risk	Yes	None known
Diagnostic approach	Established	Not established
Duration	Lifelong	Unknown

[1] CD, celiac disease; NCGS, nonceliac gluten sensitivity; TTG, tissue transglutaminase.

NCGS and Diarrhea-Predominant Irritable Bowel Syndrome

A 2007 German study by Wahnschaffe et al. (21) sought to investigate a connection between gluten and diarrhea-predominant irritable bowel syndrome (IBS-D). In that study, 41 patients with IBS-D were enrolled and prescribed a GFD for 6 mo. Overall scores of gastrointestinal symptoms significantly improved from the start of the study compared with scores at the end of 6 mo ($P < 0.01$). Of the 41 patients, 20 had gastrointestinal scores that improved into the normal range along with improvements in stool frequency. Patients with IBS-D who were positive for HLA-DQ2 and for CD-associated IgG serologies (anti-tissue transglutaminase and anti-gliadin) were more likely to have symptomatic improvement with the GFD ($P < 0.01$). These results suggested that ≤50% of patients with IBS-D could have NCGS and that HLA-DQ2 positivity may be predictive of a clinical response. These striking findings were tempered by the fact that this study was not blinded and had no control group to validate and further quantify the effect of the intervention.

NCGS: Controlled Trials

To further address the question of NCGS in patients without a diagnosis of CD, a series of randomized, placebo-controlled trials have been performed and will be reviewed here. A summary of the trials is shown in **Table 2**.

Vazquez-Roque et al. (22) conducted a randomized controlled trial in Rochester, Minnesota, in 45 patients with IBS-D who tested negative for CD by serology and who were currently maintaining a regular (gluten-containing) diet. These patients were randomly assigned to ingest either a gluten-containing diet (GCD) or a GFD for a period of 4 wk. Subjects who consumed the GFD had significantly fewer bowel movements per day than those who consumed the GCD (95% CI: −0.652, −0.015; $P = 0.04$). Those who consumed the GCD who were HLA-DQ2/8-positive had a greater increase in their bowel movements per day than did those who were HLA-DQ2/8-negative ($P = 0.019$). The GCD was also associated with higher small bowel permeability [as measured by both cumulative mannitol excretion ($P = 0.028$) and lactulose-to-mannitol

TABLE 2 Summary of randomized controlled trials[1]

Study (ref)	Country	Patients, *n*	Duration, wk	Patient population	Intervention	Placebo arm	Main findings	HLA effect
Vazquez-Roque et al. (22)	USA	45	4	IBS-D with a GCD	GCD vs. GFD	No	GCD was associated with an increase in bowel movements per day and higher small bowel permeability	Yes, effects of GCD greater in HLA-DQ2/8-positive patients
Biesiekierski et al. (23)	Australia	34	6	IBS reporting symptomatic improvement with a GFD	Gluten (2 bread slices and 1 muffin/d) vs. placebo along with GFD	Yes	68% of patients had inadequately controlled symptoms with gluten vs. 40% with placebo	None
Biesiekierski et al. (24)	Australia	37	3	IBS reporting symptomatic improvement with a GFD	2-wk run-in period with low-FODMAP diet, then randomly assigned to high-gluten, low-gluten, or GFD for 1 wk, and finally, 3-d rechallenge trial in 22 patients	Yes	Low-FODMAP diet reduced symptoms; there was no specific gluten effect on symptoms	None
Di Sabatino et al. (25)	Italy	61	5	NCGS with a GCD for ≥2 mo	1-wk crossover gluten challenge with gluten capsules (4.375 g) vs. placebo	Yes	Only 3 patients met the cutoff for being truly gluten-sensitive; most patients had no significant change in symptom score between the trial phases	None
Elli et al. (16)	Italy	101	3	GFD-responsive during phase 1 of study	1-wk crossover gluten challenge with gluten capsules (5.6 g) vs. placebo	Yes	14% of patients had a symptomatic relapse during the blind gluten challenge	Not assessed

[1] FODMAP, fermentable oligo-di-monosaccharide and polyol; GCD, gluten-containing diet; GFD, gluten-free diet; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; NCGS, nonceliac gluten sensitivity; ref, reference.

excretion ratios ($P = 0.0012$)], and this outcome was greater in HLA-DQ2/8-positive patients than in HLA-DQ2/8-negative patients. The results suggest that gluten may have an effect on bowel barrier function in IBS-D, especially in those patients with HLA haplotypes associated with CD. These results supported the findings by Wahnschaffe et al. that gluten plays a prominent role in IBS-D.

Two studies by Biesiekierski et al. (23, 24) addressed the common phenomenon of patients who consume a self-prescribed GFD for improvement in intestinal and/or non-intestinal symptoms. Their first double-blind, randomized, placebo-controlled trial, published in 2011 (23), consisted of patients with irritable bowel syndrome who had already reported a symptomatic improvement with a GFD despite having tested negative for CD (determined by the absence of HLA-DQ2/DQ8 or a normal duodenal biopsy while following a GCD). In that study, conducted in Australia, 34 participants received either gluten or placebo (in the form of gluten-free or gluten-containing slices of bread and muffin) daily along with a GFD for up to 6 wk. Of the patients randomly assigned to receive gluten, 68% reported inadequate control of symptoms, including gastrointestinal symptoms and tiredness, compared with only 40% of the placebo group. Notably, those in the gluten group reported worsening of their symptoms within 1 wk of starting the intervention diet. Patients in both groups were tested for HLA haplotypes DQ2/DQ8 and for the induction of anti-gliadin antibodies, but neither test proved to be predictive of a worsening of symptoms with gluten. The results supported the notion that NCGS is a distinct clinical entity that could no longer be attributed to placebo, but a clear physiologic mechanism remained lacking.

Biesiekierski et al. (24) then published a follow-up study in 2013 in 37 patients with self-diagnosed gluten-induced symptoms who were treated for 2 wk with a diet with a reduced content of fermentable oligo-di-monosaccharides and polyols (FODMAPs) and who were then randomly assigned to receive a high-gluten diet, a low-gluten diet, or a GFD with whey protein for 1 wk. Patients were excluded from having CD by either negative HLA-DQ2/8 testing or normal duodenal biopsy on endoscopy while following a GCD. Overall gastrointestinal symptom scores improved during the 2-wk run-in period consisting of a low-FODMAP diet ($P < 0.0001$), but all symptoms significantly worsened ($P = 0.001$) while receiving the dietary treatments, irrespective of the diet. In contrast to their earlier study, the investigators now found no specific effect of a GCD on patients with NCGS; rather, there was an improvement in symptoms with a diet with a low-FODMAP content. The results of this second trial by Biesiekierski et al. suggested the possibility that the clinical response to a GFD by patients with NCGS may not be due to gluten itself in some or most cases but due to the fact that a GFD shares some features with a low-FODMAP diet, and that the latter is driving the effect.

Di Sabatino et al. (25) enrolled 61 patients with suspected NCGS in Italy in a double-blind, placebo-controlled, crossover gluten-challenge trial. Patients following a GCD for ≥2 mo before screening underwent serologic testing for CD and WA as well as upper endoscopy with duodenal biopsies to exclude CD. Patients then began a strict GFD for 1 wk and were randomly assigned to receive either 1 capsule of 4.375 g purified wheat gluten or rice starch as a placebo each day for 1 wk. After a 2-wk washout period, the groups were subsequently crossed over for an additional 1 wk. Most of the patients showed no difference in symptom score during the gluten phase compared with the placebo phase, although 3 patients did meet symptom scores high enough to be identified by the authors as truly gluten-sensitive. No biomarker was predictive of identifying those few patients who had a much greater symptomatic response to gluten compared with placebo. This trial raises the possibility that the response to gluten over placebo in those with NCGS may be driven by a large effect in a small proportion of patients.

Most recently, Elli et al. (16) published a double-blind, placebo-controlled gluten-challenge trial in Italy. A total of 134 patients without CD or WA (confirmed with serologic testing and, in cases of high suspicion for CD, with duodenal biopsy) who reported gastrointestinal symptoms with gluten were enrolled and completed phase 1 of the study, in which they followed a strict GFD for 3 wk. Of the 134 phase 1 patients, 101 (75.3%) were deemed responsive to the GFD on the basis of symptom evaluation. These patients moved on to phase 2 of the trial in which they were randomly assigned to receive gluten or placebo for 1 wk in the form of capsules. As was the case for the trial by Di Sabatino et al., the placebo capsule contained rice starch. However, the dose of gluten in this trial was higher, at 5.6 g. After 1 wk, there was a 1-wk washout, after which the groups were crossed over for 1 more week. Overall, study subjects reported a greater worsening of their well-being during gluten administration than during placebo administration ($P = 0.05$). Of the 97 patients who completed the second phase of the study, only 14% had a symptomatic relapse during the blind administration of gluten, again suggesting that a minority proportion of patients respond negatively to gluten, at least in the doses given in these trials.

Overall, these trials have variable and, in some cases, conflicting results. But 1 recurrent theme in these trials is that patients who responded symptomatically to dietary gluten exhibited both intestinal and extraintestinal symptoms. This prominence of extraintestinal symptoms distinguishes NCGS from IBS-D. Among patients who presented to a CD research center in Maryland and who were classified as having NCGS, the most common symptoms reported aside from abdominal pain were eczema and/or rash, headache, foggy mind, fatigue, and depression (26). One study by the Australian group specifically examined neuropsychiatric outcomes. Peters et al. (27) studied 22 patients with irritable bowel syndrome, who improved after being maintained on a GFD, and who were randomly assigned to receive a short-term diet of gluten, whey protein, or placebo, followed by a washout period and crossover. Gluten ingestion was associated with higher overall depression scores than placebo but not when compared with whey protein. Gastrointestinal symptoms were induced similarly across all of the dietary

challenges. More studies are needed that focus specifically on each of these extraintestinal manifestations of NCGS to parse out their importance and pathophysiology.

Approach in the Patient

Given the lack of predictive biomarkers and the large placebo effect shown in these trials, there remains great uncertainty and controversy surrounding the nature of NCGS. As such, when a patient shows an improvement with a GFD but CD has been excluded, he or she faces a condition with an unknown pathophysiology. As public awareness of NCGS and popularity of the GFD grows, gastroenterologists and primary care physicians alike will be seeing more patients who avoid gluten. A 2014 study (28) in 84 patients who avoid gluten despite having ruled out CD reported that 79% of the patients were female and 30% of patients were found to have an alternative diagnosis. The most common of these alternative diagnoses were small intestinal bacterial overgrowth (SIBO), fructose or lactose intolerance, microscopic colitis, and gastroparesis. Patients who avoid gluten commonly reported additional food intolerances beyond lactose and fructose.

According to the international expert panel at the Salerno conference on nonceliac gluten sensitivity (13), before an investigation for alternative diagnoses there must first be a proper evaluation for the presence of CD or WA with the use of serologic markers. Serologic markers for CD will normalize once a GFD is started, with normalization typically preceding recovery of duodenal histology (2). Therefore, some patients who appear to have NCGS may actually have CD that remains undetected because testing was performed after the GFD was already started. A current survey (29) in 147 patients believed to have NCGS found that 62% had inadequate exclusion of CD. Of the 75 patients who underwent esophagogastroduodenoscopy with biopsy, only 29% had adequate gluten intake at the time of duodenal biopsy to exclude CD. In 15% of the patients surveyed, no serologic, HLA, or endoscopic testing had been conducted. This study highlights the fact that patients who present with apparent NCGS often have not had an adequate investigation for CD or alternative diagnoses. In addition to undiagnosed CD or WA, other possible etiologies of symptoms in patients with suspected NCGS may be innate immunity to ATIs (18) or FODMAPs (24) rather than gluten itself. As per the Salerno experts' 2-step diagnostic protocol, patients with suspected NCGS following a GCD in whom CD and WA have been excluded should first be assessed for clinical responsiveness with a GFD followed by a gluten challenge to measure the effects of the reintroduction of gluten to the diet (13). The gluten that is reintroduced to the diet should have a defined ATI content and be free of FODMAPs. If the gluten challenge is negative, patients should then be evaluated for other possible diagnoses as described above, such as SIBO, FODMAP intolerance, or other food intolerances.

Although both conditions are treated with a GFD, there are compelling reasons for initiating an investigation to determine whether a patient has NCGS or CD. For patients with CD, the GFD is a lifelong prescription with both economic and social consequences (2). In contrast, the duration and degree of gluten avoidance necessary for patients with NCGS have not been established. Gluten-free products are more expensive and less commercially available than their wheat counterparts (30), and it is particularly difficult to eat outside of the home and at restaurants while conforming to a GFD (4, 20). The GFD is also often deficient in fiber and in certain nutrients, including B vitamins (31). A diagnosis of CD also has implications for family members, who may need screening for the disease. Finally, an investigation of the cause of the patient's symptoms may uncover alternative diagnoses, including SIBO, microscopic colitis, or other food intolerances, which may obviate the need for a long-term GFD.

Gluten and General Health Effects

Although the literature on NCGS primarily concerns individuals with a symptomatic adverse response to dietary gluten, a GFD has also become popular as a method to improve overall health and well-being, even among apparently asymptomatic individuals. In a 2014 questionnaire-based study (32) in 942 athletes without CD, >40% of subjects reported following a GFD ≥50% of the time. Reasons for following a GFD included the belief that the diet would decrease systemic inflammation and improve athletic performance. To further explore this concept, Lis et al. (33) designed a randomized, controlled, double-blind crossover study in 13 nonceliac cyclists. Subjects were randomly assigned to receive either 1 wk of a GCD or a GFD and then crossed over after a 10-d washout period. Data on gastrointestinal symptoms as well as athletic performance on timed trials were collected at the end of each diet and there were no significant differences found between the short-term GFD compared with the GCD. Future studies will be needed to further explore if this trend of athletes using a GFD is sustained, and whether this diet makes any significant difference in athletic performance or overall well-being.

Future Directions

Because there is still great uncertainty around the entity known as NCGS, more investigation is necessary to determine the pathophysiology behind both the gastrointestinal and extraintestinal manifestations of NCGS. In future studies, we suggest that there be strong consideration for a placebo run-in phase to better parse out the degree to which the symptomatic response is due to the placebo; patients with a strong placebo response could then be excluded from the remainder of the trial. The existing trials are limited by their short durations; thus, future trials may benefit from longer study periods. We also suggest studies focused on specific extraintestinal symptoms of NCGS (e.g., a study that uses fMRI to explore the cognitive symptom commonly referred to by patients as "brain fog"). Finally, investigation of the effect of gluten on the duodenal and colonic microbiome may help elucidate biomarkers and the mechanism by which gluten induces symptoms in select individuals.

Conclusions

CD is an immune-mediated, chronic disease with a growing prevalence. NCGS appears to be a distinct entity that has

emerged more recently and that contributes to the growing popularity of the GFD. There are no known biomarkers associated with NCGS and no established diagnostic approach at this time, but blinded, randomized, crossover dietary-challenge trials have suggested that there is a subset of individuals without CD who experience both gastrointestinal and extraintestinal manifestations when exposed to dietary gluten. Future studies are needed to further clarify the pathophysiology of NCGS and to be able to predict which patients will benefit from following a GFD.

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