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Characterization of Adults With a Self-Diagnosis of Nonceliac Gluten Sensitivity

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Abstract

Background: Nonceliac gluten sensitivity (NCGS), occurring in patients without celiac disease yet whose gastrointestinal symptoms improve on a gluten-free diet (GFD), is largely a self-reported diagnosis and would appear to be very common. The aims of this study were to characterize patients who believe they have NCGS. *Materials and Methods*: Advertising was directed toward adults who believed they had NCGS and were willing to participate in a clinical trial. Respondents were asked to complete a questionnaire about symptoms, diet, and celiac investigation. *Results*: Of 248 respondents, 147 completed the survey. Mean age was 43.5 years, and 130 were women. Seventy-two percent did not meet the description of NCGS due to inadequate exclusion of celiac disease (62%), uncontrolled symptoms despite gluten restriction (24%), and not following a GFD (27%), alone or in combination. The GFD was self-initiated in 44% of respondents; in other respondents it was prescribed by alternative health professionals (21%), dietitians (19%), and general practitioners (16%). No celiac investigations had been performed in 15% of respondents. Of 75 respondents who had duodenal biopsies, 29% had no or inadequate gluten intake at the time of endoscopy. Inadequate celiac investigation was common if the GFD was initiated by self (69%), alternative health professionals (70%), general practitioners (46%), or dietitians (43%). In 40 respondents who fulfilled the criteria for NCGS, their knowledge of and adherence to the GFD were excellent, and 65% identified other food intolerances. *Conclusions*: Just over 1 in 4 respondents self-reporting as NCGS fulfill criteria for its diagnosis. Initiation of a GFD without adequate exclusion of celiac disease is common. In 1 of 4 respondents, symptoms are poorly controlled despite gluten avoidance. (*Nutr Clin Pract*. 2014;29:504-509)

Keywords

celiac disease; gastrointestinal symptoms; irritable bowel syndrome; gluten intolerance; gluten-free diet

Celiac disease is an autoimmune gastrointestinal disease estimated to affect ≥1% of Western populations.[1] It occurs when genetically susceptible patients (HLA-DQ2 and/or HLA-DQ8 haplotype) are exposed to dietary gluten, the major protein in wheat, rye, barley, and related grains, which activates a specific immune response leading to small intestinal villous atrophy, intraepithelial lymphocytosis, and the development of gastrointestinal symptoms.[2] Diagnosis is achieved via serological screening tests followed by typical features on histopathological analysis of endoscopic duodenal biopsies. Treatment is a lifelong, strict, gluten-free diet (GFD). Since adherence to the GFD normalizes serological markers and leads to healing of the small intestine, disease investigation prior to removal of gluten from the diet is essential.

Many of the gastrointestinal symptoms seen in celiac disease (such as diarrhea, bloating, gut pain) can mimic irritable bowel syndrome (IBS), a disorder based on symptom patterns and duration, and characterized by a lack of biomarkers.[3] There is an emerging belief that gluten might mediate IBS symptoms,[4] and the term *nonceliac gluten sensitivity (NCGS)*, defined as a condition in which patients without celiac disease experience improvement of gastrointestinal symptoms while following a GFD, has been recently supported by an expert group.[5] A randomized controlled parallel group trial in which patients fulfilling the definition of NCGS were rechallenged with carbohydrate-deplete gluten or placebo suggested that gluten can specifically induce gastrointestinal symptoms and

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Conflict of interest: SJS has published cookbooks and shopping guides directed toward issues of FODMAPs, irritable bowel syndrome, and celiac disease. PRG has also published a book on a diet for irritable bowel syndrome. There were no conflicts of interest to declare for JRB, EDN, and JGM.

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tiredness.[6] However, this gluten specificity in triggering symptoms was not detected in consecutive crossover studies.[7] Related scientific evidence assessing the effects of gluten outside of celiac disease has focused on animal models or cancer cell lines.[8-10] Regardless of these inconclusive findings, the increased prescription of the GFD for gut and other symptoms may lead clinicians to miss the diagnosis of true celiac disease, for which the risks and associated complications, especially if left untreated, can include higher mortality, increased risk of malignancy, growth impairment in children, infertility, osteoporosis, and autoimmune disease.[11]

Compliance with the GFD is complex. It is generally inappropriate for patients to be on a life-long GFD except for those medically diagnosed with celiac disease or dermatitis herpetiformis. The diet is very restrictive, it can be more expensive than a standard diet,[12] and it is nutritionally inadequate for several nutrients.[13] It has been estimated that in Australia, for every person who has diagnosed celiac disease, there are 20 others eating gluten-free food.[14] In the U.S. lay press, 20% of the general population are reported to associate their symptoms with the ingestion of gluten.[15] There is a paucity of information about why these nonceliac patients choose to follow the GFD and whether they have had celiac disease formally excluded. The present study analyzed data from respondents with self-characterized NCGS who expressed willingness to participate in a clinical trial, and it aimed to characterize the subgroup of people on a GFD who believed they fulfilled criteria for NCGS.

Methods

From January 2010 to February 2011 in metropolitan Melbourne, Australia, flyers distributed through websites and local clinic rooms (including gastroenterology outpatient clinics and dietetic practices) and advertisements in a local newspaper sought adults who believed they had NCGS to participate in a clinical trial. The advertisements clearly stated the inclusion criteria, including living in Melbourne, having had celiac disease ruled out, having currently well-controlled symptoms, following a GFD, and being aged 16 years or older, and stated that participation would involve consuming gluten and providing blood samples and fecal samples. The clinical trial has already been published, and the current study cohort is derived from further analysis of information available from these volunteers and other survey respondents.

Respondents were asked to fill out a questionnaire containing 23 items that were divided into 3 dimensions: symptoms (eg, "Describe your main symptoms," "Do you currently feel in control of your symptoms?"), diet (eg, "Do you follow a strict gluten-free diet?" "How long have you been following a gluten-free diet?" "Where did you find out about a gluten-free diet?"), and celiac disease investigation (eg, "Have you had blood tests [or 'celiac antibodies'] for diagnosis of celiac disease?" "Have you had the gene test for celiac disease?" "Have you had a gastroscopy (endoscopy) for diagnosis of celiac disease?" "If yes, were you consuming gluten in the lead-up to the gastroscopy? How much gluten and for how long before the gastroscopy were you eating gluten? Were you specifically asked to consume gluten in the lead up to the gastroscopy?"). The questionnaire had not been previously validated, and all items were analyzed. Subjects eligible and willing to participate in the research study were evaluated in further detail, by keeping a 7-day food diary and filling in a verified flow chart[16,17] to give a subjective assessment of GFD adherence. This simple flow chart gives a numerical score of adherence to the GFD based on 4 short questions. These subjects were also asked about any additional food intolerances by a registered nutritionist (J.R.B.). The advertising, questionnaire, and protocol were approved by the Eastern Health Research and Ethics Committee.

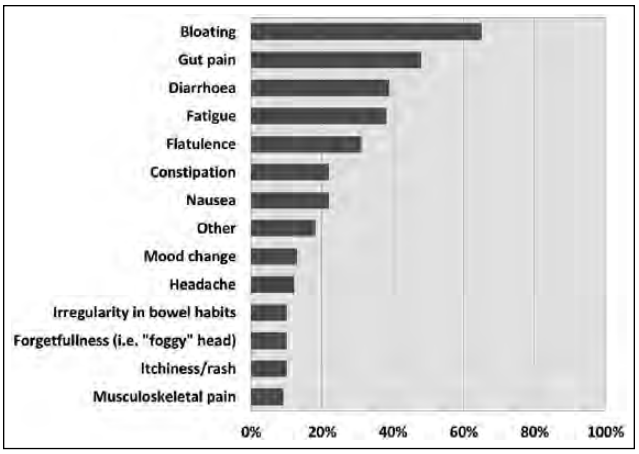

Figure 1. Most common symptoms related to gluten intake reported by participants (N = 147). "Other" refers to descriptions of flu-like symptoms, hot flushes, reflux, dry retching, congestion, mouth symptoms, belching, shivers/shudders, sore throat, sleeplessness, dizziness, poor balance, dry eyes, locomotion, hiccups, and sweats.

Results

Of 248 respondents to advertising, 147 (59%) completed and returned the survey; these comprised the study cohort for the present analysis. The mean age of respondents was 43.5 years (range, 16–84 years), and 130 (88%) were female. Forty subjects who met the inclusion criteria of the research study agreed to participate and were enrolled.[7]

The range and frequency of symptoms described by respondents experienced after consuming gluten are shown in Figure 1. Gastrointestinal symptoms were, as anticipated from the advertising, most common. A variety of extraintestinal symptoms were also commonly reported, especially fatigue (also described as tiredness or lethargy). In response to the question whether they currently felt in control of their

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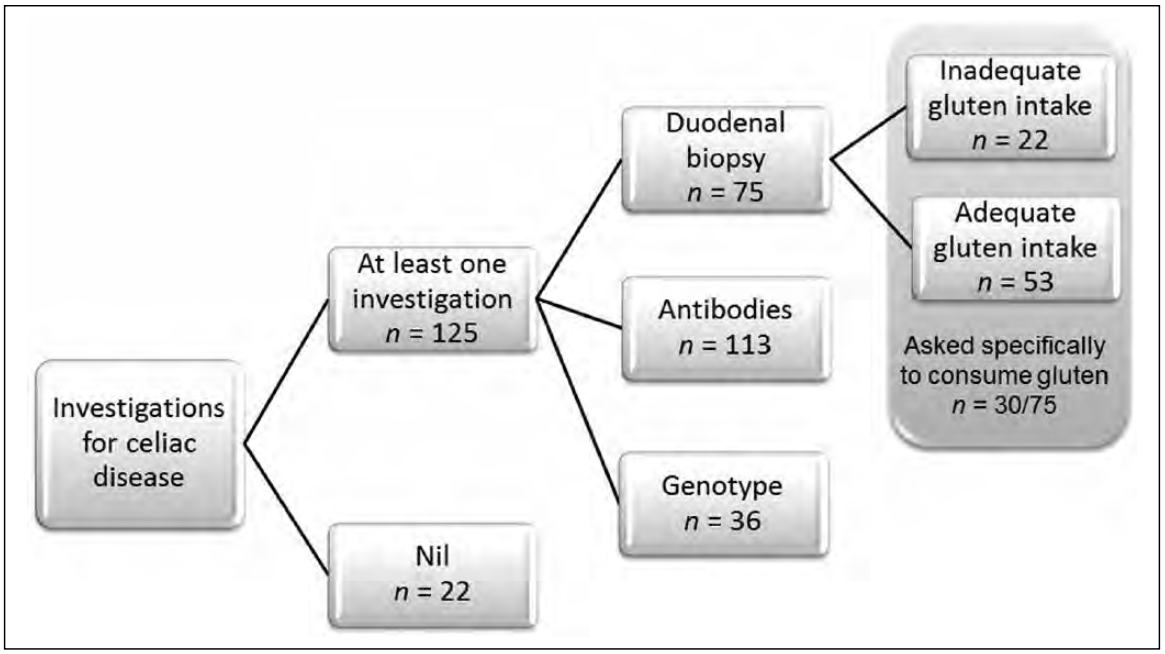

Figure 2. Investigations for celiac disease in participants following a gluten-free diet (N = 147).

symptoms, 22% of participants answered "no," 3% answered "sometimes," 16% answered "mostly," and 59% answered "yes." Just under a third (32%; n = 47) of participants reported having had a hydrogen breath test for sugar malabsorption, 30 (64%) of whom reported positive results for fructose and 14 (30%) for lactose.

Participants were asked whether they believed they follow a strict GFD, answering "no" (22%), "sometimes" (3%), "mostly" (17%), or "yes" (58%). The median time for all respondents to be following a GFD was 36 months (range, 0.25–444 months). The reasons why participants initiated the GFD varied. It was self-initiated in 44% and prescribed by alternative health professionals in 21%, dietitians in 23%, or general practitioners in 12%.

Investigations performed for the diagnosis of celiac disease are shown in Figure 2. No investigation whatsoever (HLA status, antibody testing, or biopsy) had been performed in 15% of the respondents.

For celiac diagnosis, Australian guidelines recommend a gluten challenge as a prerequisite for duodenal biopsies of at least 4 weeks of 16 g of gluten per day.[18] Of the 75 participants who had duodenal biopsies, 30% (n = 22) had an inadequate gluten intake at the time of endoscopy, implying they had already removed gluten from their diet or did not implement an adequate gluten challenge. Only 40% (n = 30) of participants who had duodenal biopsies were asked specifically to consume gluten. Despite this advice, 1 remained gluten-free and 7 gluten-loaded for <4 weeks (consuming daily gluten for an average of 10 days; range, 1–17 days). All biopsies had been performed in the previous 11 years (2000–2011), with only 7 participants reporting having >1 biopsy.

Celiac disease was inadequately excluded in 44 of the 65 (68%) participants who self-initiated the GFD, compared with 21 of the 30 (70%) initiated by alternative health practitioners, 12 of the 28 (43%) initiated by dietitians, and 14 of the 24 (58%) initiated by general practitioners (P = .103; chi-square). The only statistically significant difference in intergroup comparisons was for dietitians versus self-initiated (P = .037; Fisher's exact).

Responses in the questionnaire were used to redefine who in this cohort with self-perceived NCGS actually met the defined criteria. Only 28% fulfilled the criteria of NCGS. The remaining had inadequate exclusion of celiac disease (62%), had uncontrolled symptoms despite gluten restriction (24%), or were not following a GFD (27%).

Additional information was sought from the 40 respondents who agreed to participate in the clinical trial. All were found to be adherent with the GFD for a median of 48 months prior to participation (see Table 1). Recorded information (including type and brand of food) from the 7-day food diaries confirmed strict GFD adherence. During the baseline interview, 65% of these participants described some other form of dietary intolerance, allergy, or problem food (detailed in Table 1). Sixty percent described taking regular dietary supplementation, including calcium and/or vitamin D (28%), fish and/or ω-3 oil (28%), and multivitamins (25%). Other reported supplements included B vitamins (10%), magnesium (10%), probiotics (8%), folate (5%), and biotin (5%). Less common supplements taken by 2% of participants included melatonin-5, glucosamine, protein, sage, iron, vitamin E, liver support (supplement powder consisting of N-acetyl cysteine, milk thistle, acetyl carnitine, alpha lipoic acid, and vitamin E), zinc, St John's Wort, and horsetail.

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Table 1. Dietary Adherence to the Gluten-Free Diet (GFD) and Other Food Intolerances Described by Participants (n = 40): Baseline Dietary Information.

Median time spent following GFD (range)	48 months (2–444 months)	
Subjective assessment of GFD adherence	Do not follow a strict GFD	0%
	Follow a GFD but with errors that require correction	8%
	Follow a strict GFD	92%
Additional intolerances to gluten sensitivity	Nil	35%
	Single	38%
	Multiple	27%
Reported problem foods	FODMAP-containing foods[a]	43%
	Dairy (including lactose, casein, whey)	17%
	Food chemicals (eg, amines, sulfites, benzoates)	8%
	Tomatoes	5%
	Other[b]	22%

[a]FODMAPs comprise fructose in excess of glucose, sorbitol, mannitol, fructans and galacto-oligosaccharides.
[b]Caffeine, corn, ginger, chili, psyllium, capsicum, nuts, cinnamon, balsamic, gums, preservatives, spices.

Discussion

Although understanding of celiac disease has considerably improved both clinically and pathologically during recent decades, the evidence regarding NCGS remains incomplete. This survey has provided the first data to characterize adults with a self-diagnosis of NCGS, targeting those who use a GFD for relief of their gastrointestinal symptoms.

Several key findings were revealed by the survey. First, only 58% of respondents believed that they were strictly gluten-free, and therefore the remaining respondents could not be considered to be following a GFD. Of those who believed they were gluten-free, detailed assessment of the food intake of the subgroup who entered the clinical trial showed excellent adherence to the GFD. This was despite 44% of the whole cohort and 33% of the clinical trial participants having self-initiated the GFD without dietetic supervision or education. Perhaps this reflects the high standards of information widely available with regard to gluten content of foods.

Second, 1 in 4 participants who judged themselves to be gluten-sensitive remained markedly symptomatic despite gluten avoidance. This suggested either that the symptoms were improved from a very high level while participants were eating gluten or that gluten had little to do with the symptoms. One explanation is that by markedly reducing gluten intake, patients concomitantly eliminate a major source of other triggers of gastrointestinal symptoms. Other potential triggers in gluten-containing cereals include fermentable, poorly absorbed, short-chain carbohydrates (collectively termed FODMAPs—fermentable oligo- di-, and mono-saccharides and polyols)[19] and other wheat proteins.[20] Indeed, in the more detailed analysis of the 40 patients who entered the clinical trial, nearly one-half had identified noncereal foods that contain high levels of FODMAPs as additional triggers of symptoms. FODMAPs are found in a wide variety of foods,[21-23] including grains and cereals, and wheat- and rye-derived products contain the highest FODMAP content, predominantly fructans. Cereal products with the lowest FODMAP content are mostly gluten-free, based on rice, oat, quinoa, and corn ingredients.[21] It is likely, therefore, that "gluten restriction" will automatically reduce a patient's dietary FODMAP intake.

Third, almost 2 out of 3 respondents appeared not to have adequately excluded celiac disease. The failure to exclude celiac disease was not confined to those who self-initiated the diet or to alternative health practitioners but also included general practitioners (although these were few in number). Dietitians seemed the best informed. Duodenal biopsy remains the gold standard in the diagnosis of celiac disease and best clinical practice, although new European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommendations suggest that this may not always be the case.[24] False-negative results can occur in association with gluten restriction prior to testing since gluten withdrawal is associated with improvement of duodenal histology and reduction in serum levels of celiac-specific antibodies.[11] Hence, patients should not commence a GFD and, ideally, should be gluten-loaded prior to being tested for celiac disease. There is yet to be consensus on the optimum dose of gluten needed and the length of time of such loading,[25] although recent data show that lower doses and shorter challenge duration may be efficacious.[26] However, for the purpose of this study, recommendations from the Australian Therapeutic Guidelines were used where an adequate challenge protocol is the equivalent of 4–6 slices of wheat bread (16–24 g gluten) per day for at least 4 weeks.[18] More than 1 in 4 patients in the present study had inadequate gluten intake at the time of endoscopy. Forty percent of the patients who underwent endoscopic assessment were instructed to increase gluten intake prior to assessment. No data were collected on the patients' gluten intake at the time of serological testing, nor did we determine the timing or possible delay between serological/genetic testing and endoscopy. The only test independent of gluten intake is HLA typing, but this can only exclude celiac disease. Twenty-nine percent of the patients having any investigation of celiac disease had such testing.

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Fourth, the survey results indicate that patients with self-perceived NCGS are highly heterogeneous in the levels and standards of healthcare they had received. A major observation was that the importance of a definitive diagnosis or exclusion of celiac disease was poorly appreciated. The confusion and controversy have arisen in part from a failure to distinguish clearly between the protein (gluten) and carbohydrate (fructan) components of wheat. Indeed, patients who believe they have NCGS are likely to benefit from lowering their dietary intake of FODMAPs.[7] Interestingly, a low number (27% of the 40 clinical trial participants) reported multiple food intolerances, compared with previous data showing that 50% of IBS patients identified 2–5 foods and 31% identified 6–10 foods as causes of their intolerances.[27] Regular use of dietary and herbal supplements was more frequent in this study (60%) than that reported for the general adult Australian population (16%–45%).[28] More recent data from the United States show that 55% are multiple supplement users.[29]

There are several limitations to the study. The context of the advertising was recruitment for an international clinical trial, and this may have attracted a biased sample of those with NCGS. Hence, the results can only apply to this cohort, made up predominantly of women of mean age 43.5 years, and the applicability of the results to the NCGS population as a whole cannot be assessed. In addition, just over one-half of the respondents to the advertising completed the questionnaire, a response rate that indicates a risk of a sampling. However, the notion that a lower response rate means lower survey accuracy has been strongly challenged over recent years.[30] The results were based on participant interpretation, and verification of aspects such as the diagnostic test performed and their findings was limited to a subset of participants who fulfilled the criteria.

Two relevant and important issues that arise from this survey deserve further discussion. First, the importance of diagnosing celiac disease cannot be underplayed. Being definitively diagnosed with celiac disease creates the opportunity for optimal outcomes and ensures ongoing monitoring for associated conditions, memberships to support groups, health fund assistance, and, in many European countries, a subsidy for the GFD. Celiac disease demands serious adherence to the GFD, something not done in about half of the patients in the present study. Furthermore, the diagnosis has implications for family screening. The difficulty in excluding this diagnosis is considerable after the GFD has been instituted as outlined above. This message needs to be disseminated to patients and primary care health professionals; a proportion of each group failed to have adequate celiac disease exclusion in the present cohort.

The second issue involves the risks in committing to the GFD in the absence of celiac disease. Apart from making diagnosis of celiac disease difficult, the GFD is potentially nutritionally inadequate. A dietitian-taught GFD strives to ensure adequate intake of all nutrients. Even with excellent teaching, inadequacies of intake do occur and include fiber, thiamin, folate, and calcium intakes.[13] It is likely that self-taught patients may not always understand the fundamentals of successfully identifying nutrient-dense gluten-free foods, which include wholegrain foods (fortified where possible), legumes, fruits, vegetables, lean meat, fish, and eggs. Compounding this is the finding of the present study that 65% of the clinical trial subgroup described avoidance of other foods that were perceived to be a problem. The health implications of following long-term restrictive diets require investigation. This area is especially significant given the evidence for the important roles of fiber and prebiotics (such as fructans) in grain- and cereal-derived carbohydrates in relation to bowel health.[31]

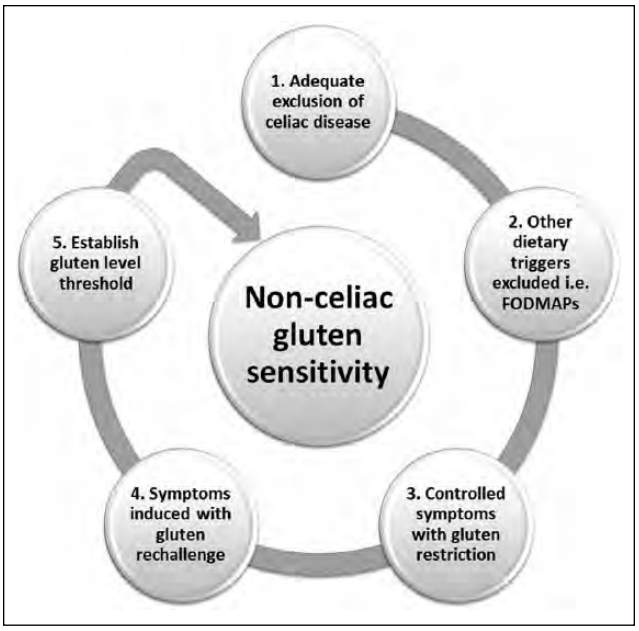

Figure 3. Suggested flow chart for defining nonceliac gluten sensitivity: Step 1: Definitive exclusion of celiac disease done by either absence of the celiac-associated HLA-DQ genotype or negative celiac serology and a normal duodenal biopsy on a gluten-rich diet. Step 2: After testing for celiac disease, other possible dietary triggers should be investigated, importantly fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs), by initiating and trialing the low-FODMAP diet for 6 weeks. Skilled dietetic input is imperative. Step 3: If the patient experiences no or partial symptom improvement in response to the low-FODMAP diet, it is then worth considering gluten. Patients should exclude dietary gluten for 4 weeks and record symptom response. Step 4: Provided there is marked improvement in symptoms with the GFD, blinded challenges (ie, monitored reintroduction of gluten) can be subsequently undertaken. Step 5: Following a positive challenge, the amount of gluten tolerated should be established by systematic rechallenges beginning with small amounts of gluten.

Much research is needed to fulfill our understanding of NCGS; an important issue is identification of the clinical phenotype, which would allow prevalence to be determined. However, in the meantime, a pathway for clinical application and diagnosis of NCGS has been suggested, as shown in Figure 3. After

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celiac testing, other possible dietary triggers should be investigated (such as FODMAPs), and the amount of gluten tolerated should be established.

In conclusion, initiation of a GFD without adequate exclusion of celiac disease is common. In 1 of 4 patients, symptoms are poorly controlled despite gluten avoidance, but most patients appear to be well versed in the GFD. Better definition and definitive characterization of this patient group are needed.

Author Note

Authorship for this article is as follows: Planning and conducting the study, JRB and EDN; collecting and interpreting data, JRB; drafting the manuscript and approval of the final draft, all authors. Jessica R. Biesiekierski is currently with the Translational Research Centre for Gastrointestinal Disorders, KU Leuven, Leuven, Belgium. Susan J. Shepherd is currently with the Department of Dietetics and Human Nutrition, La Trobe University, Melbourne, Australia.

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