

Prevalence of a Gluten-free Diet and Improvement of Clinical Symptoms in Patients with Inflammatory Bowel Diseases

Hans H. Herfarth, MD, PhD,* Christopher F. Martin, MSPH,* Robert S. Sandler, MD, MPH,* Michael D. Kappelman, MD, MPH,[†] and Millie D. Long, MD, MPH*

Background: Maintaining a gluten-free diet (GFD) without an underlying diagnosis of celiac disease has enjoyed widespread acceptance in the United States.

Methods: We performed a cross-sectional study using a GFD questionnaire in 1647 patients with inflammatory bowel diseases (IBD) participating in the CCFA Partners longitudinal Internet-based cohort.

Results: A diagnosis of celiac disease and non-celiac gluten sensitivity were reported by 10 (0.6%) and 81 (4.9%) respondents, respectively. Three hundred fourteen (19.1%) participants reported having previously tried a GFD and 135 (8.2%) reported current use of GFD. Overall 65.6% of all patients, who attempted a GFD, described an improvement of their gastrointestinal symptoms and 38.3% reported fewer or less severe IBD flares. In patients currently attempting a GFD, excellent adherence was associated with significant improvement of fatigue ($P < 0.03$).

Conclusions: In this large group of patients with IBD, a substantial number had attempted a GFD, of whom the majority had some form of improvement in gastrointestinal symptoms. Testing a GFD in clinical practice in patients with significant intestinal symptoms, which are not solely explained by the degree of intestinal inflammation, has the potential to be a safe and highly efficient therapeutic approach. Further prospective studies into mechanisms of gluten sensitivity in IBD are warranted.

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Key Words: IBD, gluten, Crohn's disease, ulcerative colitis, celiac disease

The pathogenesis of inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, has only been partly elucidated. The most likely factors involved in promoting the onset and continuation of intestinal inflammation in IBD are an individual genetic predisposition, influence of the host microbiome and still largely undefined environmental triggers. Diet has long been implicated as one of the contributing factors for disease flare-ups of IBD.^{1,2} Accordingly, an elemental diet is a well-established treatment modality in children with IBD. Nevertheless, up to now, clinical trials investigating various diets have failed to yield significant clinical improvement in adult IBD.^{3,4}

Adoption of a gluten-free diet (GFD) without an underlying diagnosis of celiac disease has experienced a rapid and

widespread increase in the United States in recent years. Currently, at least 0.5% of the U.S. population follow a GFD without having a confirmed diagnosis of celiac disease.⁵ Even in the absence of celiac disease, gluten is thought to be associated with bloating, diarrhea, abdominal pain, fatigue, and nausea, leading to the definition of a new entity designated as non-celiac gluten sensitivity (NCGS).⁶ Many of the symptoms associated with gluten exposure in the general population are also common in patients with IBD and may partially be responsible for a diminished quality of life.

A better understanding of patient-reported outcomes is essential to developing new insights into the effectiveness of IBD therapies. Investigating the effects of diet on disease course could open potentially new research avenues.

With this study, we aimed to determine the experience with a GFD in patients with IBD. Specifically, we evaluated the current prevalence of self-reported celiac disease, NCGS and use of GFD, symptomatic improvement while being on GFD, and the degree of adherence to a GFD in a cross-sectional study within the CCFA Partners cohort.

METHODS

CCFA Partners is an ongoing Internet-based cohort study of patients with IBD.⁷ Participants complete a baseline survey, and follow-up surveys occur every 6 months. As a part of this cohort, we administered a 12-question survey on GFD from July 2013

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From the *Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina; and [†]Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina.

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Reprints: Hans H. Herfarth, MD, PhD, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Bioinformatics Building, CB#7080, Chapel Hill, NC 27599 (e-mail: hherf@med.unc.edu).

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through August 2013. Participants were asked if they (1) were ever on a GFD, and if yes if they were still on a GFD; (2) had been diagnosed with celiac disease or gluten sensitivity by a health care provider; (3) if GFD improved each of the following symptoms: bloating, diarrhea, abdominal pain, fatigue, nausea; (4) if GFD led to less severe or fewer flares of their IBD; and (5) if fewer medications were needed to control disease activity while on a GFD. Respondents, who still were on a GFD at the time of the survey, were asked to complete a validated 7-item GFD adherence survey.⁸

Statistical Analyses

Descriptive statistics were used to characterize the population, including proportions and 95% confidence intervals, medians, and interquartile ranges, and means and standard deviations as appropriate. Bivariate statistics were used to compare reduction in flares by IBD subtype (Crohn's disease versus ulcerative colitis) and by other factors. These statistics included Pearson's chi-square test statistic, Fisher's exact test, Wilcoxon rank sum test, and Student's *t* test as appropriate. STATA version 10.0 (College Station, TX) was used for all analyses and *P* < 0.05 was considered statistically significant. The Institutional Review Board at the University of North Carolina at Chapel Hill approved the study protocol.

RESULTS

A total of 1647 patients, who completed both a baseline survey and the specific GFD questionnaire, were included in the study. Ten (0.6%) and 81 (4.9%) patients had been diagnosed with celiac disease and gluten sensitivity by their health care provider, respectively. Three hundred fourteen (19.1%) participants reported ever having tried a GFD and 135 (8.2%) reported current use of a GFD. No differences were found between the GFD and non-GFD groups with regard to disease type, duration of disease, concomitant medication, educational status, and other baseline characteristics (Table 1). In a subanalysis, clinical baseline characteristics of individuals who completed the GFD questionnaire were compared with individuals within the CCFA Partners cohort who were not asked to complete a GFD questionnaire. There were no clinical significant differences in disease type or baseline characteristics between both groups (data not shown).

Improvement of Symptoms on a GFD

Of the 314 patients, who have ever followed or were still following a GFD, 206 (65.6%) reported that they experienced an improvement of at least 1 specific clinical symptom which has been associated with gluten exposure (Fig. 1). Furthermore 38.3% also recounted fewer and less severe flares while being on a GFD and 23.6% stated that they required fewer medications to control the disease. There were no significant differences pertaining to baseline characteristics between patients with or without improvement of clinical symptoms on a GFD (data not shown).

TABLE 1. Baseline Characteristics of the Inflammatory Bowel Disease Population in CCFA Partners, Stratified by Ever or Current Attempted GFD and Never on GFD for Symptom Control

Characteristic	GFD (n = 314)	Non-GFD (n = 1333)	<i>P</i>
Age, yr	46.5 (15.4)	46.2 (15.4)	0.88
Sex, %			
Female	74	74	0.99
Type of IBD, %			
Crohn's disease	61	63	0.62
Ulcerative/indeterminate colitis	39	37	
Duration of disease, yr	17.4 (13.4)	16.5 (12.8)	0.25
Ostomy, % yes	6.9	7.8	0.60
Medications, %			
5-ASA	74.5	71.4	0.27
Corticosteroids	27.7	23.6	0.12
Immunomodulators	45.9	47.0	0.70
Biologic anti-TNF	55.4	54.7	0.82
Education, %			
High school or less	7.4	6.4	0.51
College and higher	92.6	93.6	
Disease activity			
sCDAI	148.8 (97.3)	142.5 (90.0)	0.35
SCCAI	3.2 (2.5)	3.1 (2.6)	0.73
Quality of life SIBDQ	5.0 (1.2)	5.1 (1.1)	0.70
BMI	25.7 (6.7)	26.0 (7.2)	0.60

Values are expressed as mean ± SD unless otherwise specified.

BMI, body mass index; SCCAI, simple clinical colitis activity index; sCDAI, short Crohn's disease activity index; SIBDQ, short inflammatory bowel disease questionnaire.

Adherence to GFD and Correlation with Symptom Improvement

In those patients who were still following a GFD (n = 135), adherence was found to be excellent in 41.5%, average in 34.1%, and fair/poor in 24.4%. Excellent adherence to a GFD was associated with reduced fatigue, as compared with fair/poor adherence (*P* < 0.03). Adherence was not associated with significant differences in other clinical symptoms.

DISCUSSION

This is the largest survey analyzing patient-reported data about the prevalence of a GFD in a Western IBD population. In this Internet-based cohort, nearly 20% of all patients reported having tried a GFD and 8% were currently attempting a GFD. This is a significantly higher percentage than the current GFD prevalence of 0.5% among individuals without celiac disease in the United States.⁵ More than half of the patients reported symptom improvement and nearly 40% fewer flare-ups of IBD while

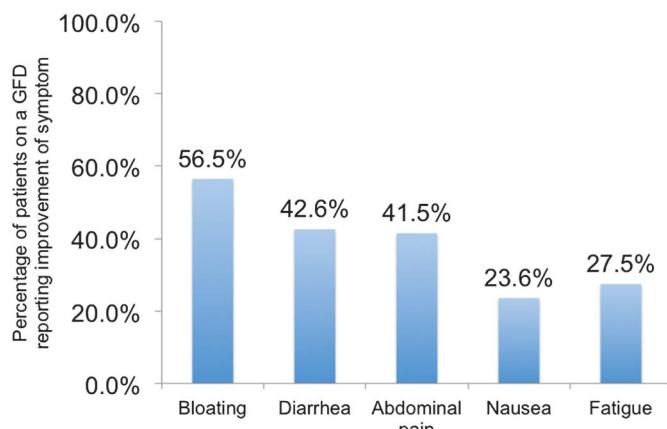


FIGURE 1. Reported symptom improvements in patients with IBD attempting a GFD ($n = 314$).

being on a GFD. This observation suggests that in a subgroup of patients with IBD, gluten may cause intestinal (diarrhea, bloating, abdominal pain) and extraintestinal (fatigue, nausea) symptoms. Similar effects of a GFD have been described in patients with irritable bowel syndrome (IBS) indicating a potential trigger effect of gluten-containing foods in gluten susceptible patients.^{9–11}

NCGS is defined by the exclusion of celiac disease including negative celiac serologies and/or normal intestinal architecture and negative immunoglobulin E-mediated allergy tests to wheat. Additionally, to meet criteria for NCGS, the clinical symptomatology of IBS type of symptoms has to improve after gluten withdrawal and worsen after the ingestion of gluten. A specific reaction to gluten in patients with NCGS is currently debated.¹² Biesiekierski et al¹³ recently showed that gluten by itself might be not the culprit for the IBS type symptoms in patients with previously diagnosed NCGS, but rather the intake of low-fermentable, poorly absorbed short-chain carbohydrates (fermentable, oligo-, di-, monosaccharides, and polyols; FODMAPs) may be responsible for these effects. Also, gluten does not elicit an inflammatory response in the duodenum in patients with NCGS.¹⁴ The diagnosis of NCGS was reported by nearly 5% of the respondents in our survey. Thus far, studies in patients with IBD investigating inflammatory responses to gluten in duodenal or colonic biopsies have not been performed. Theoretically, gluten could create a proinflammatory environment in the intestine, leading to more frequent disease flares and the need for more intensified therapies, similar to patients with IBD and concurrent celiac disease.¹⁵ However, we cannot exclude that a GFD leads to a significant reduction of dietary FODMAPs, which as shown by Biesiekierski et al,¹³ leads to an improvement of the gastrointestinal symptoms of the patients. Of note, an exploratory study has demonstrated that dietary reduction of FODMAPs leads to significant amelioration of symptoms including abdominal pain, bloating, gas, and diarrhea in patients with IBD.¹⁶

Those patients maintaining a GFD at the time period of the survey were asked to fill out a recently validated 7-item Celiac Dietary Adherence Test.⁸ The additive scores of this test reflect the adherence to a GFD and correlate highly with a standardized dietitian evaluation and seem to outperform serological testing.

However, the test does not quantify the amount of gluten intake, but rather points to the likelihood of gluten contamination. More than 40% of the respondents were strictly maintaining to a GFD, whereas roughly 25% of the patients were found to be fair or poorly adherent. Intriguingly, of all clinical symptoms, only fatigue improved significantly with good adherence. Fatigue in the absence of iron deficiency anemia is a leading symptom in many patients with IBD.¹⁷ It is possible that fatigue conversely influenced adherence in our cohort, but coincidentally, the worsening of fatigue was also the most significant finding in a gluten challenge study conducted in patients with NCGS.⁹

The class II MHC haplotype HLA-DQ2 and HLA-DQ8 are present in almost all patients with Crohn's disease and interestingly can be also found in 50% of the patients who are improving on a GFD, which is higher than can be expected in the general population.⁶ Studies in patients with IBS with predominant diarrhea have also shown that carrier of HLA-DQ2 respond favorably to a GFD. In fact in 60% of the patients with IBS with predominant diarrhea HLA-DQ2 positivity, but no signs of overt celiac disease (negative tissue transglutaminase antibodies and no signs of active celiac disease on biopsies obtained in the duodenum), symptoms such as diarrhea and bloating improved on a 6-month GFD compared with only 12% in patients without HLA-DQ2 positivity.¹⁸ As it is speculated in patients with NCGS, gluten might have a direct impact on intestinal barrier function and the mucosal immune system in patients with IBD with the HLA-DQ2 or HLA-DQ8 genotype.¹⁹ In a recent study by Vazquez-Roque et al,¹¹ the small intestinal permeability was significantly increased in patients with IBS with predominant diarrhea with HLA-DQ2 or HLA-DQ8 positivity on a gluten-containing diet, but this was not the case in HLA-DQ2 and HLA-DQ8-negative patients. Also RNA expressions of several proteins associated with the epithelial barrier in the colonic mucosa (zonula occludens-1, occludin, and claudin) were generally lower in participants on a gluten-containing diet compared with those on a GFD. However, diet-associated changes of RNA expression reached only statistical significance in study participants, who were found to have an HLA-DQ2- or HLA-DQ8-positive status. HLA-DQ2 or HLA-DQ8 is not found in higher frequencies in patients with IBD, but it would be fascinating to evaluate the associations of these haplotypes with the response to a GFD in patients with IBD in prospective studies.²⁰ Moreover, the degree of intestinal inflammation in patients with non-celiac IBD could be influenced by the recently identified non-gluten α -amylase/trypsin inhibitors, which can be found in wheat and related cereals. These amylase/trypsin inhibitors are strong activators of the innate immune response through the Toll-like receptor 4, leading to the upregulation of proinflammatory cytokines in vitro and in vivo.²¹

Patient-reported data based from the CCFA Partners cohort have several limitations as outlined recently.²² CCFA Partners is a volunteer sample of patients, and thus the above-described findings may not reflect similar diet habits in all patients with IBD. To address the possibility of selection bias within the sample completing the GFD questionnaire, we compared the characteristics of

those who completed the questionnaire to those of the CCFA Partners cohort in general and found no clinical significant differences. Since the study was based on a single questionnaire without collecting blood samples, we could neither rule out occult celiac disease with serological tissue transglutaminase testing nor could determine the HLA-DQ2 or HLA-DQ8 status. Previous studies have shown that the prevalence of celiac disease in patients with IBD is comparable to the prevalence in the non-IBD population.^{15,23} The finding that 0.6% of patients reported to be diagnosed with celiac disease is comparable with the currently reported 0.7% prevalence of celiac disease (including diagnosed and undiagnosed cases) in the United States.²⁴ Currently, the majority of celiac disease patients in the United States are undiagnosed, but because patients with IBD suffer from similar gastrointestinal symptoms as many celiac disease patients, it is very likely that in the setting of the diagnostic work-up for IBD, concurrent celiac disease is diagnosed either by serologic testing or by endoscopy.

In conclusion, the high prevalence of a GFD in the CCFA Partners cohort strongly suggests a potential role of this diet in the adjunctive therapeutic management of subgroups of patients with IBD. Testing GFD in clinical practice in patients with significant intestinal symptoms, which are not solely explained by the degree of intestinal inflammation, has the potential to be a safe and highly efficient therapeutic approach after appropriate testing for celiac disease. Further research into investigating possible mechanisms of gluten-mediated worsening of intestinal inflammation in susceptible patients with IBD is also warranted.

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