

# Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease<sup>1-3</sup>

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## ABSTRACT

**Background:** Atypical presentations of celiac disease appear to be at least as common as is the classic presentation of steatorrhea, diarrhea, and weight loss.

**Objective:** We examined the effect of a gluten-free diet on gastrointestinal symptoms in a cohort of US patients with celiac disease.

**Design:** A follow-up survey was conducted in 215 patients who were evaluated at the University of Iowa from 1990 through 1997 as having biopsy-confirmed celiac disease. The systematic survey asked detailed questions regarding gastrointestinal symptoms before and after the institution of a gluten-free diet in the patients, all of whom had been given the same dietary advice.

**Results:** The group consisted of 160 female and 55 male patients. Although diarrhea was the most frequent symptom in untreated celiac disease, steatorrhea occurred in only one-fifth of patients. Other complaints were common, and most responded to gluten exclusion. The benefit of gluten exclusion was equally apparent in men and women. Diarrhea responded in most patients, usually within days, and the mean time to resolution was 4 wk. Many patients had alternating diarrhea and constipation, both of which were responsive to the gluten-free diet. Most patients had abdominal pain and bloating, which resolved with the diet.

**Conclusions:** Celiac disease causes a wide range of gastrointestinal symptoms. Clinicians must have a high level of suspicion to detect the atypical forms of celiac disease. With a gluten-free diet, patients have substantial and rapid improvement of symptoms, including symptoms other than the typical ones of diarrhea, steatorrhea, and weight loss. *Am J Clin Nutr* 2004;79:669-73.

**KEY WORDS** Celiac disease, gluten-free diet, abdominal pain, enteropathy, irritable bowel syndrome

## INTRODUCTION

Celiac disease, otherwise known as gluten-sensitive enteropathy, is considered a rare disease in the United States (1). The classic syndrome of celiac disease as originally described by Gee (2) consists of steatorrhea, diarrhea, and weight loss in adults and failure to thrive in children and evidence of overt nutritional deficiencies due to small-bowel malabsorption. Subtle presentations of celiac disease were first described > 30 y ago (3). A serum survey of anonymous US blood donors found a high frequency of markers for covert celiac disease (4).

The European experience with celiac disease has provided a perspective that illustrates a broad spectrum of modes of presentation of the disorder and the frequency of monosymptomatic

presentation rather than the classic presentation of malabsorptive symptoms (5-10). Patients who have so-called atypical presentations seem to be at least as common as are those with the classic syndrome. There are few detailed reports of the effectiveness of a gluten-free diet on these atypical symptoms. The aims of the present study were to identify the frequency and nature of gastrointestinal symptoms in a large cohort of patients with diagnosed celiac disease and to determine the effect of a gluten-free diet on these symptoms.

## SUBJECTS AND METHODS

### A systematic survey of subjects with diagnosed celiac disease

The study population consisted of 215 patients in whom celiac disease was diagnosed according to internationally accepted criteria (11). All the patients had an intestinal biopsy specimen compatible with celiac disease and a clinical response to a gluten-free diet. These patients were seen at a single institution in the upper-midwestern region of the United States. The disease was diagnosed in the 215 patients between 1984 and 1998; the disease was diagnosed in 195 of the patients after 1990 and in 188 of the patients after 1995. The age at diagnosis ranged from 1 to 90 y, with a median of 48 y. There was a female-to-male predominance of 3 to 1. The mean age at diagnosis was 55 y. Eighty percent of the patients were adults at the time of diagnosis.

### Identification of subjects

For all subjects, the diagnosis of celiac disease was made at a single institution. Histologic evidence based on duodenal or jejunal biopsy specimens was obtained for all subjects and was interpreted by a single experienced gastrointestinal pathologist. Sixty-two percent of the patients had follow-up biopsies for evaluation of recovery of the duodenal mucosa. Those who did not have a follow-up biopsy had a dramatic, clinically obvious response to a gluten-free diet. All the subjects fulfilled the ac-

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<sup>2</sup> Supported by NIH grant DK 57892-01 (to JAM).

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Received July 22, 2003.

Accepted for publication October 2, 2003.

cepted criteria for establishing the diagnosis of celiac disease (11). All the subjects received similar dietary instruction on a gluten-free diet, and this instruction was provided by the same dietitian, who was experienced in the dietary treatment of celiac disease. Identical written material was used to aid in the education of each patient. Every effort was made to see that the patients adhered to a strict gluten-free diet. All the patients were seen routinely by the same dietitian for at least one follow-up visit and were actively encouraged to join local or national support groups for celiac disease. Just one patient openly acknowledged eating gluten-containing foods on a regular basis. All the others denied deliberately consuming gluten more than once a month. Except for the one noncompliant patient, all the subjects showed substantial improvement on follow-up biopsy, if performed. The noncompliant patient, however, had persistently positive endomysial antibodies and villous atrophy. Two other patients could not be interviewed because they died before the survey.

### Telephone survey

A scripted telephone interview was carried out by trained, experienced gastrointestinal nurses who were not involved in the care of the patients. The interviews were done between 1997 and 1998,  $\geq 6$  mo after the diagnosis of celiac disease and the start of a gluten-free diet. Detailed questions were asked concerning 1) the presence of gastrointestinal symptoms at the time of diagnosis, 2) the patient's perspective on how the gluten-free diet had affected each of these symptoms, and 3) the duration, frequency, severity, and features of the patient's bowel movements at diagnosis and  $\geq 6$  mo after the start of a gluten-free diet. On the basis of a search of the records of the Departments of Pathology, Gastroenterology, and Dietetics and the hospital diagnostic index, the 215 patients who participated in the present study constituted all the patients in whom celiac disease was diagnosed between 1984 and 1997. The study was approved by the Institutional Human Research Board of the University of Iowa.

### Statistical analysis

McNemar's chi-square test was used to compare paired categorical variables. The sign test was used to examine trends in the frequency of symptoms over time. A  $P$  value  $< 0.05$  was considered significant. An analysis of variance test based on ranks was used to test for any significance of sex on outcomes of the gluten-free diet. Statistical analyses were performed by using SAS (version 6; SAS Institute Inc, Cary, NC).

## RESULTS

### Weight change and body mass index

The median ( $\pm$  SEM) body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) of the women ( $21.3 \pm 6.2$ ) was not significantly different from that of the men ( $23.4 \pm 5.1$ ). Two-thirds of the patients reported weight loss in the 6 mo before diagnosis. One-half of these patients had a BMI  $< 20$ , and of the 23% who had a BMI  $\geq 25$ , 11% were obese (BMI  $\geq 30$ ) (Table 1). The same proportions of males and females gained or lost weight after the institution of a gluten-free diet (for the males, 31% gained and 41% lost; for the females, 36% gained and 35% lost). Ninety-one patients gained weight between the time of diagnosis and 6 mo after starting a gluten-free diet, and the weight gain ranged from 0.5 to 46 kg (average of 7.5 kg). In the same period, 25 patients lost an average of

**TABLE 1**

Effect of a gluten-free diet on BMI in patients with celiac disease<sup>1</sup>

Patients	At diagnosis	After 6 mo of a gluten-free diet
Male		
BMI category (%)		
Underweight	28	24
Normal	41	51
Overweight	16	16
Obese	15	9
BMI ( $\text{kg}/\text{m}^2$ )	$24.2 \pm 7.1^2$	$25.7 \pm 7.3$
Female		
BMI category (%)		
Underweight	33	26
Normal	32	48
Overweight	14	17
Obese	12	10
BMI ( $\text{kg}/\text{m}^2$ )	$22.6 \pm 10$	$21.9 \pm 4.9$
All patients		
BMI ( $\text{kg}/\text{m}^2$ )	$22.9 \pm 9.4$	$22.8 \pm 5.7$

<sup>1</sup>  $n = 215$ . Underweight, BMI (in  $\text{kg}/\text{m}^2$ )  $< 20$ ; normal, BMI = 20–24.9; overweight, BMI = 25–29; obese, BMI  $\geq 30$ .

<sup>2</sup>  $\bar{x} \pm \text{SD}$  (all such values).

12.5 kg (range: 1–63 kg). This weight loss was most pronounced in the patients who were obese at diagnosis. However, 12 patients who had normal or low weight at diagnosis actually lost weight despite a gluten-free diet. This was largely due to excessive food restriction rather than persistent disease.

### Bowel habits

The prevalence of various gastrointestinal symptoms before the diagnosis of celiac disease is shown in Table 2. Seventy-five percent of the patients said that they had had diarrhea, which was defined as liquid or unformed stools at least monthly, before the diagnosis of celiac disease. However, only 47% of the patients reported daily diarrheal stools before diagnosis (Figure 1). More than one-half of the patients with diarrhea had buoyant and malodorous stools suggestive of steatorrhea. Not surprisingly, only 12% reported bloody diarrhea. Sixty-one percent complained of frequent flatulence, and 64% had urgency. Thirty-one percent complained of significant tenesmus, and 38% had experienced fecal incontinence. Just over one-half of the patients reported

**TABLE 2**

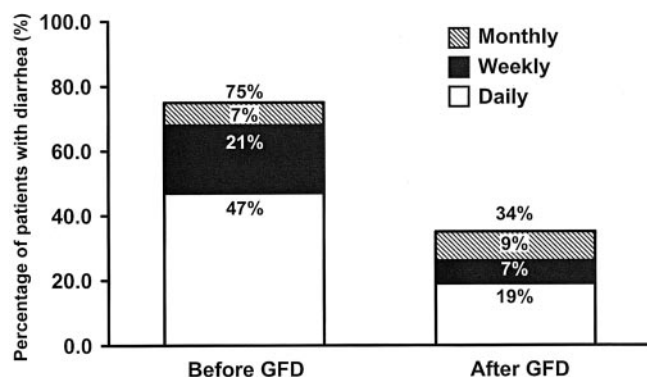
Gastrointestinal symptoms before and after a gluten-free diet in patients with celiac disease<sup>1</sup>

Symptom	Before	After
	<i>n</i> (%)	
Diarrhea	163 (75)	73 (34) <sup>2</sup>
Constipation	83 (39)	64 (30) <sup>3</sup>
Abdominal pain	171 (79)	6 (3) <sup>2</sup>
Abdominal bloating	157 (73)	9 (4) <sup>2</sup>
Nausea or vomiting	96 (44)	19 (9) <sup>4</sup>
Lactose intolerance	85 (39)	27 (13) <sup>2</sup>

<sup>1</sup>  $n = 215$ .

<sup>2,3</sup> Significantly different from before diet (McNemar's chi-square test): <sup>2</sup>  $P < 0.001$ , <sup>3</sup>  $P < 0.02$ .

<sup>4</sup> Significantly different from before diet,  $P < 0.01$  (binomial proportions comparison).



**FIGURE 1.** Change in frequency of diarrhea in patients with celiac disease ( $n = 215$ ) before and 6 mo after starting a gluten-free diet (GFD).

postprandial diarrhea (**Figure 2**). The effect of a gluten-free diet was dramatic in most patients, with resolution of the symptoms related to diarrhea. The prevalence and frequency of diarrhea dropped substantially ( $P < 0.001$ ) after the institution of a gluten-free diet (Figure 1). Sixty-six percent of the subjects who had diarrhea initially had complete resolution of the diarrhea by 6 mo. In the subjects who reported persistent diarrhea after the gluten-free diet, most had a dramatic reduction in the frequency of diarrhea ( $P < 0.001$ ). Fecal incontinence became very uncommon after treatment ( $P = 0.004$ ). When asked to estimate when the diarrhea started to subside after they began using a gluten-free diet, most of the patients reported significant improvement within 31 d; only 23% said that  $> 31$  d were needed for significant improvement (**Figure 3**).

Constipation, which was defined as the infrequent passage of firm stool associated with a sense of discomfort, was reported in 38.6% of the subjects before diagnosis (Table 2). Most of these patients reported resolution of the constipation within 6 mo of adapting to a gluten-free diet ( $P < 0.02$ ). The patients reported a significant reduction in the need for straining ( $P = 0.003$ ), the need for laxatives ( $P = 0.001$ ), and subjective problems with hemorrhoids ( $P = 0.001$ ). Patients frequently reported the pres-

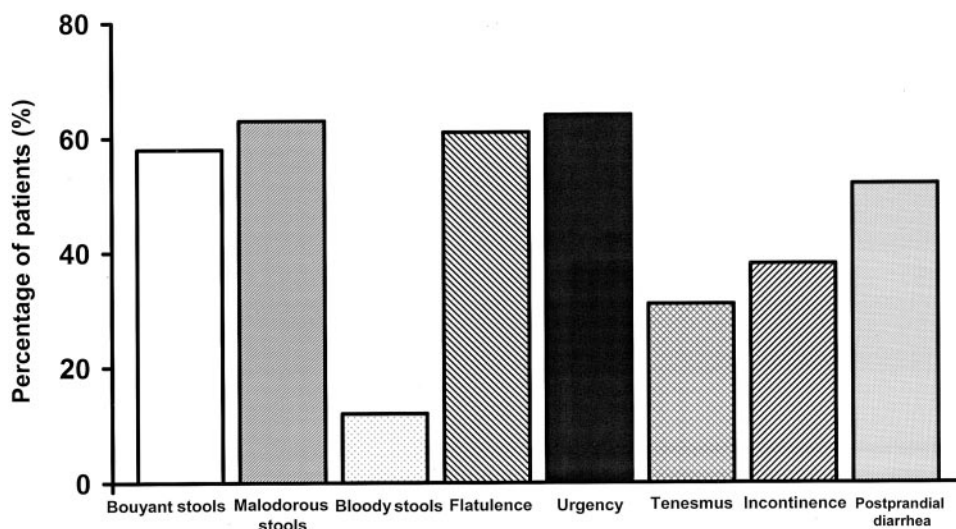
ence of both diarrhea and constipation before diagnosis of celiac disease (chi-square = 0.002).

**Abdominal pain**

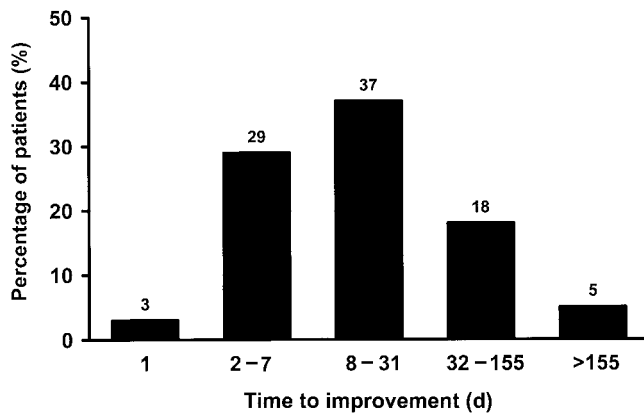
Seventy-nine percent of all the subjects reported having had significant recurrent abdominal pain before the diagnosis of celiac disease. Although the pain could be present in any part of the abdomen, it was most commonly reported in the lower part or diffusely throughout the abdomen. A substantial minority of patients cited the right upper quadrant or epigastrium as the primary site of abdominal pain. Forty-six percent of the patients indicated that the pain was worse with eating. Sixty percent said the pain improved after defecation. The pain was described as cramping and intermittent or, less commonly, sharp. Most of the patients described it as being severe. Fully 48% of the reported symptoms were consistent with the Rome II criteria for irritable bowel syndrome. After 6 mo of consuming a gluten-free diet, just 2 patients still met these criteria ( $P < 0.0001$  for comparison with the number who met the criteria before diagnosis of celiac disease), and  $> 95\%$  of the patients had substantial relief or complete resolution of their pain, usually within days of the introduction of a gluten-free diet. Postprandial pain decreased significantly after a gluten-free diet ( $P = 0.001$ ).

**Other gastrointestinal symptoms**

Nausea was reported by 42% of the patients before the diagnosis of celiac disease; vomiting occurred in just over one-fifth of these patients. These symptoms usually resolved with a gluten-free diet (Table 2). Lactose intolerance was self-reported in 39% of the patients before diagnosis of celiac disease. Seventy-two percent of these patients had a formal laboratory or medically confirmed diagnosis of lactose intolerance before the diagnosis of celiac disease. Interestingly, less than one-half of the patients with lactose intolerance before the diagnosis of celiac disease reported that they had successfully incorporated lactose into their diet after starting a gluten-free diet. It is possible that this was an underestimate because it took a mean of 8 mo (range: 1–36 mo) for a complete resolution of lactose intolerance to occur.



**FIGURE 2.** Percentage distribution of specific bowel features or symptoms at diagnosis in patients with celiac disease ( $n = 215$ ).



**FIGURE 3.** Time required for alleviation of diarrhea after patients with celiac disease ( $n = 215$ ) started a gluten-free diet.

Seventy-three percent reported abdominal bloating, which was usually described as generalized abdominal distention that usually occurred after eating. Almost all of these patients reported complete relief of bloating with the institution of a gluten-free diet ( $P < 0.0001$ ) (Table 2). Seven subjects (4 females and 3 males) had no specific gastrointestinal symptoms; among these patients, 2 males had weight loss and the other patients had unexplained anemia.

#### Onset of new symptoms after introduction of a gluten-free diet

After starting a gluten-free diet, 6.2% of the patients who had not had diarrhea before the diagnosis of celiac disease experienced diarrhea. Constipation occurred in 18.6%; in many cases, it responded to a subsequent increase in fiber intake.

#### DISCUSSION

This detailed report in a cohort of US patients with diagnosed celiac disease illustrates the broad spectrum of gastrointestinal symptoms and the efficacy of intervention with a gluten-free diet. Celiac disease has traditionally been thought of as a diarrheal illness. However, although most of our patients had some diarrhea before diagnosis, less than one-half of them had daily diarrhea; a substantial portion of them had constipation after consuming the gluten-containing diet. These results are consistent with the symptoms reported in a large questionnaire study (12); however, unlike that study, all the patients in the present study were from a specific geographic location and received uniform dietary intervention. In many cases the diarrhea was not the feature that precipitated medical evaluation. Indeed, many patients with long-standing, undiagnosed celiac disease regarded their bowel movements as normal or even as typical of constipation, and only on direct questioning was the symptom elicited. However, direct questioning about the nature of the stools and the frequency of diarrhea may provide useful information in the evaluation of patients who have other features of the disease.

Celiac disease has been regarded as a malabsorptive condition that results in weight loss in adults and in failure to thrive in children. Our patients showed substantial differences in BMI at the time of diagnosis: one-half of the patients were underweight; yet a substantial minority was overweight, and some were even obese. These differences may be accounted for by differences in

the amount of small intestine affected by the disease. Interestingly, many of those who were obese at diagnosis lost weight on the gluten-free diet. Micronutrient deficiencies may have driven specific food cravings, as occurs in pica, which has been reported in iron-deficient children with celiac disease (13).


The high frequency of abdominal pain was unexpected. It almost certainly contributes to the misery of patients with untreated celiac disease. The relation of pain to meals suggests a maldigestive component to the pain. Among children with celiac disease, abdominal pain was found to be more common in those who tested positive for *Helicobacter pylori* than in those who did not (14). However, because the abdominal pain resolved with the gluten-free diet, it is possible that a combination of celiac disease and the effects of *H. pylori* infection caused the pain. In many patients with celiac disease, the disease is initially diagnosed as irritable bowel syndrome. In this cohort of patients, fully 46% would have met the symptomatic criteria for irritable bowel syndrome laid down by the Rome II system, namely, frequent abdominal pain associated with a disordered bowel habit (15).

The variety of symptoms experienced by patients who ultimately prove to have celiac disease is a major impediment to diagnosis. Many of these features are nonspecific and are more often seen as manifestations of other diseases, such as irritable bowel syndrome. Before the diagnosis was made, the physicians of many of these patients assumed that functional causes were to blame for the symptoms. However, the dramatic response of these symptoms to restriction of dietary gluten implies that those symptoms were not due to a coexistent irritable bowel syndrome. The frequent misdiagnosis of irritable bowel syndrome in patients with celiac disease may in part be due to a low degree of suspicion for celiac disease, but it may also be attributable to the erroneous assumption that abdominal pain is a rare symptom in celiac disease. Indeed, a study from the United Kingdom reported a 5% prevalence of celiac disease among patients referred by their general practitioner for irritable bowel syndrome (16). Serologic screening tests may be useful for the primary care practitioner in identifying patients with celiac disease (17).

One of the strengths of the present study was the very high response rate ( $> 98\%$ ) of the subjects, probably because  $> 90\%$  of the patients had routine follow-up with the same gastroenterologist and dietitian. The benefit of a gluten-free diet was clearly established in this group of patients and is not surprising. However, not all the patients had complete resolution of their symptoms. Although symptoms may persist or recur after 6 mo, they are usually much less severe. Quality of life was not directly measured in this study but probably improved substantially with the dramatic reduction in symptoms. In the small proportion of patients who continue to have diarrhea or constipation or in whom such symptoms develop with treatment, these persistent symptoms may be associated with a lower quality of life, especially in female patients (18). Fine et al (19) systematically investigated persons with celiac disease who had persistent diarrhea and identified lymphocytic colitis, disaccharidase deficiency, and pancreatic exocrine insufficiency as causative factors, all of which may be amenable to treatment. The new onset of constipation after the introduction of a gluten-free diet probably reflects a decrease in fiber intake, and many such patients respond to the addition of dietary fiber. In other patients, the new onset of constipation may reflect a return of a predisposition to constipation after resolution of the malabsorptive disease.

Is it likely that these results can be replicated in other populations? The subjects in the present study constituted a midwestern US population, who generally tend to be very compliant. Another feature that may have increased the likelihood of compliance was the fact that this group included few adolescents. The presence of a very active support group to which most of the cohort belonged also may have had an effect on improving compliance. Nevertheless, the study illustrates the efficacy of the diet in a large cohort of patients.

The weaknesses of the study included the lack of correlation between symptomatic improvement and any histologic or serologic measures; such measurements were not systematically performed in concert with the symptom survey. The study also measured the benefit only on an intention-to-treat basis.

We described a broad spectrum of gastrointestinal symptoms in patients with diagnosed celiac disease. These patients had a surprisingly high prevalence of abdominal pain. The prescribed gluten-free diet was shown to have a dramatic, but not universally beneficial, effect on the patients' gastrointestinal symptoms. 

JAM undertook the design and execution of the study, wrote the manuscript, and was primarily responsible for the research presented here. TW participated in the design of the methods, undertook data collection, oversaw the trained interviewers, undertook the data analysis, and edited the manuscript. BC undertook dietary counseling, including follow-up, of the subjects; was involved in the design of the instruments used for questioning; and provided commentary on the draft of the manuscript. FM undertook pathologic examinations, verified the diagnosis in the cohort, and provided commentary on the methods and the draft of the manuscript. None of the authors had any conflicts of interest.

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