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Symptoms of functional intestinal disorders are common in patients with celiac disease following transition to a gluten-free diet

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Abstract

Background—Celiac disease and functional intestinal disorders may overlap, yet the natural history of functional symptoms in patients with celiac disease is unknown.

Aim—To investigate the prevalence of irritable bowel syndrome (IBS), functional dyspepsia (FD) and functional bloating (FB) symptoms among patients with celiac disease at diagnosis and during the first year of a gluten-free diet.

Methods—Adults with a new diagnosis of celiac disease were surveyed at baseline, 6 months and 1 year using standardized measures for intestinal symptoms [Rome III diagnostic questionnaire and Celiac Symptom Index (CSI)] and gluten-free diet adherence [Gluten-Free Eating Assessment Tool (GF-EAT) and Celiac Diet Adherence Test (CDAT)].

Results—At diagnosis, two-thirds fulfilled Rome III diagnostic questionnaire symptom criteria for IBS (52%), functional dyspepsia (27%) and/or functional bloating (9%). One year post-diagnosis, there was high adherence to a gluten-free diet as 93% reported gluten exposure less than once per month on the GF-EAT and only 8% had ongoing celiac disease symptoms (CSI score > 45). The rates of those meeting IBS (22%) and functional dyspepsia (8%) symptom criteria both decreased significantly on a gluten-free diet. The prevalence of functional symptoms (any of IBS, FD or FB) at 1 year was 47%.

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Conclusions—Long-term follow-up of patients with celiac disease is necessary because many patients with celiac disease who are adherent to a gluten-free diet have persistent gastrointestinal symptoms.

Keywords

Celiac disease; gluten-free diet; irritable bowel syndrome; functional dyspepsia; functional bloating; prospective cohort study

Introduction

Gastrointestinal symptoms may be non-specific with considerable overlap among conditions. This is especially true for celiac disease, a common immune enteropathy of the small intestine[1], and the even more common functional intestinal disorders, which can also manifest with dyspepsia, bloating, abdominal pain, constipation or diarrhea[2]. The advent of serologic testing for celiac disease facilitated wider screening and it was soon recognized that celiac disease may be more common among patients diagnosed with irritable bowel syndrome (IBS) than among the general population[3] and may be increased in other functional GI disorders, such as functional dyspepsia (FD)[4].

In contrast, much less is known about the prevalence of functional intestinal disorder symptoms in patients with celiac disease or the effects of a gluten-free diet on these symptoms. Case-control and cross-sectional studies suggest that the prevalence of IBS symptoms among patients with celiac disease may be higher than in the general population[5] and celiac disease patients with IBS symptoms report a lower quality of life than those without[6]. Due to the cross-sectional design of these studies, any hypotheses concerning the dynamic effects of a gluten-free diet upon functional symptoms in patients with celiac disease are purely speculative. A better understanding of this relationship would guide the management of patients with celiac disease with persistent symptoms on a gluten-free diet. We therefore prospectively followed a cohort of patients with celiac disease from diagnosis to determine the prevalence of symptoms associated with functional intestinal disorders and the response to a gluten-free diet.

Methods

Study participants

Participants in the Manitoba Celiac Disease cohort were recruited prospectively at the time of diagnosis of celiac disease. Inclusion criteria were: age greater than 16 years; HLADQ genotype associated with celiac disease; and findings of villous atrophy (Marsh IIIa-IIIc[7]) on duodenal biopsy performed while consuming a gluten-containing diet. Persons unable to complete written surveys or oral interviews in English, unable to attend follow-up appointments, or who had been trying to follow a gluten-free diet for greater than six weeks prior to study entry were excluded. The study involved in-person interviews and blood collection at recruitment, and at 6 and 12 months after diagnosis of celiac disease as well as an optional online component which included a more extensive self-report survey in

conjunction with each visit. Results reported are from those participants who elected to complete the online self-report.

Outcome measures

At recruitment, and at 6 and 12 months after diagnosis of celiac disease, intestinal symptoms were assessed using the Celiac Symptom Index (CSI)[8] and Rome III diagnostic questionnaire items for irritable bowel syndrome (IBS), functional dyspepsia (FD) and functional bloating (FB)[2]. CSI scores range from 16 to 80 with scores of 30 or less associated with good quality of life and excellent GFD adherence whereas scores of 45 or greater are associated with poor quality of life and worse GFD adherence[8]. Participants were considered to "fulfil Rome III diagnostic questionnaire criteria" using the scoring algorithm for the relevant questionnaire items. Participants were also asked about previously diagnosed chronic medical conditions, including irritable bowel syndrome, at recruitment and at each follow-up visit.

Adherence to a gluten-free diet was assessed using the Gluten-Free Eating Assessment Tool (GF-EAT)[9] and the Celiac Diet Adherence Test (CDAT)[10]. The GF-EAT is a self-report measure for participants to estimate the frequency of gluten exposure (either intentional or unintentional). The CDAT is a 7 item instrument with scores ranging from 7 to 35. A CDAT score of 12 or less is considered "adequate adherence".

At each visit, serum was collected for assay for anti-tissue transglutaminase IgA antibodies (tTG) in the Immunology Laboratory at St Boniface Hospital, Winnipeg, Canada. In May 2015, the assay was changed from Immulisa (Immco Diagnostics Inc, Buffalo NY) to Bioplex 2200 (Biorad Laboratories (Canada) Inc, Montreal QC). All results are reported as multiples of the upper limit of normal (ULN) for the assay used (Immulisa 20, Bioplex 15).

Data analysis

Data analysis was performed using RStudio Version 0.99.903[11] with R software version 3.3.1[12]. Prevalence estimates are presented as mean with 95% confidence interval. This study was reviewed by the University of Manitoba Research Ethics Board and all activities were conducted in accordance with the Tri-Council Policy Statement (TCPS2) of the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada.

Results

Participants

Between December 2012 and June 2015, 179 persons were screened for eligibility and 119 participated in the study, 109 of whom participated in the optional online component. Reasons for exclusion were: not interested/no time (48), on gluten-free diet greater than 6 weeks (9), hospitalization (1) and language barrier (2). Each individual participant provided written informed consent prior to participation in the study. There were 5 participants who dropped out of the study: 2 too busy, 2 moved away and 1 lost to follow-up. Another 19 participants continued in the study but did not complete the 6 and/or 12 month online

component. Thus, we report the 85 participants who completed all study visits (3 interviews and 3 online surveys). The median age was 36 years (IQR 27-54), two-thirds were female and all subjects were HLADQ2 and/or HLADQ8 positive (Table 1).

Gastrointestinal symptoms

There was a trend towards resolution of celiac disease symptoms following adoption of a gluten-free diet (Table 2). By 12 months, only 7 participants (8%) had a CSI score above 45, which is associated with poorer adherence and decreased quality of life[8].

The prevalence of symptoms associated with functional intestinal disorders also decreased with a gluten-free diet (Table 3). At diagnosis, 66% met Rome III symptom criteria for any of the functional disorders [(IBS (52%), FD (27%) or FB (9%); sum of individual categories is greater than 66% because some participants reported symptoms of both FD and IBS, which are not mutually exclusive]. This decreased to 47% at 12 months (IBS 22%; FD 8%; FB 16%). In contrast to the overall trend and either IBS or FD, the prevalence of FB symptoms increased following adoption of a gluten-free diet. All 6 HLADQ2^{-}/DQ8^{+} participants met Rome III symptom criteria for IBS at diagnosis, only one of whom did not report functional symptoms at 12 months [3 IBS, 1 FD, 1 FB].

Relationship between intestinal symptoms and gluten exposure

At 12 months, those who reported no gluten ingestion had similar rates of Rome III functional symptoms to those who consumed any gluten (50% vs. 47%; p = 0.73). The nature of the functional symptoms experienced differed according to reported gluten exposure, but this was not statistically significant. Those who were gluten exposed reported greater IBS symptoms (25% vs. 8%; p = 0.28) and lower rates of FD symptoms (5% vs 25%; p = 0.06) than those who reported adherence to a strict gluten-free diet (no reported accidental or intentional gluten exposure). The rate of FB symptoms was 17% in both groups. Neither prevalence nor quality of functional symptoms differed based upon tTG positivity or CDAT score.

Relationship between functional intestinal symptoms and celiac disease symptoms

There was a strong correlation between CSI scores and functional intestinal symptoms. Using a cut-off of 30 or less for well-controlled celiac disease, 85% of those with any functional intestinal symptoms did not have well-controlled celiac disease (Odds ratio 21, 95% CI 7-67). Conversely, only 15% of those with well-controlled celiac disease reported functional intestinal symptoms. At 12 months, 5 of the 6 participants with celiac disease symptoms (CSI > 45) reported gluten exposure. All patients with celiac disease symptoms at 12 months also fulfilled Rome III diagnostic questionnaire criteria for a functional intestinal disorder [1 IBS, 4 FD, 2 FB].

Non-celiac disease gastrointestinal diagnoses

At recruitment, only one person reported having previously received a diagnosis of IBS and no participants reported a diagnosis of inflammatory bowel disease. At the 6 month visit, one participant reported receiving a physician diagnosis of IBS since the recruitment visit. This participant reported Rome III symptoms of IBS at recruitment, but only fulfilled Rome

III diagnostic symptom questionnaire criteria for FB at the 6 and 12 month visits. At 12 months, 5 participants reported new gastrointestinal diagnoses of gastroesophageal reflux disease (2), silent reflux (1), lactose intolerance (1) or microscopic colitis (1). The patient with lactose intolerance and one patient with GERD did not report Rome III functional intestinal symptoms at any time point. One patient with GERD reported symptoms of FD at 6 months and symptoms of IBS at 12 months. The patient with silent reflux reported symptoms of FD at 6 months and symptoms of FB at 12 months. The patient with microscopic colitis reported symptoms of FB at 6 months and symptoms of IBS at 12 months.

Discussion

When the diagnosis of celiac disease is made, it is often assumed that gastrointestinal symptoms will resolve if gluten can be successfully eliminated from the diet. This prospective cohort study demonstrates that many individuals with celiac disease may have persistent gastrointestinal symptoms one year after diagnosis despite apparent good adherence to a gluten-free diet and normalized serum tTG levels. Symptoms compatible with functional intestinal disorders were common among patients with celiac disease at the time of diagnosis. After 12 months, overall frequency of self-reported Rome III symptoms of IBS and FD decreased significantly to approach that of the general population[13,14], but the proportion of patients with FB increased. Neither adherence to gluten-free diet nor serum tTG antibody levels correlated with fulfilling Rome III symptom criteria.

The high rate of IBS symptoms at time of celiac disease diagnosis likely reflects the lack of specificity for Rome III criteria in the setting of untreated celiac disease. The rate of Rome III symptoms of IBS 12 months after diagnosis of celiac disease was 22%, which is similar to the 24% pooled prevalence among previous studies of patients with celiac disease strictly adherent to a gluten-free diet[5] and at the upper limit of the range of previous estimates of the prevalence of IBS among Canadians (6-25%[13]). Nevertheless, 22% is double the estimated global prevalence of IBS (11.2%)[15].

In comparison to this epidemiologic data, our results demonstrate that patients with celiac disease who recently adopted a gluten-free diet may have a higher prevalence of IBS symptoms than the general population. The reason for this is unknown; however, resolution of other inflammatory intestinal disorders, such as enteric infections[16] and inflammatory bowel disease[17], is also associated with an increased prevalence of symptoms associated with IBS. Symptoms of functional intestinal disorders have been reported to fluctuate in individuals; however, the profile of symptoms in the general population is relatively stable with a gradual increase in IBS symptoms with age[18]. This pattern contrasts with the overall decrease in symptoms of functional intestinal disorders and significant decrease in prevalence of symptoms of IBS observed in this study.

Previous studies have not evaluated the prevalence of FD or FB symptoms in treated celiac disease. We observed a significant decrease in functional dyspeptic symptoms 12 months after starting a gluten-free diet which paralleled the decrease in IBS symptoms. In contrast, rates of FB symptoms fluctuated and the relative proportion of participants reporting

symptoms of FB increased after celiac disease diagnosis. FB is a residual diagnosis which requires exclusion of other functional disorders, including IBS and FD. Many participants who fulfilled Rome III IBS symptom criteria at diagnosis subsequently fulfilled criteria for FB or FD. These findings suggest that celiac disease may be a useful model to study the effects of inflammation (and its resolution) on intestinal motility and symptoms of functional intestinal disorders. Another possible reason for these increased symptoms is that a gluten-free diet itself may be associated with bloating. In a small study of 12 healthy participants who did not have a Rome III functional intestinal disorder who consumed standardized meals with varying gluten content, post-prandial transverse colon volume measured by MRI was inversely related to gluten content and perceived bloating was greatest with gluten-free bread[19].

In the absence of reliable biomarkers, distinguishing symptoms of celiac disease (and gluten ingestion) from functional intestinal symptoms is a common clinical challenge. Not only do the symptoms overlap, but also both conditions may respond to the same dietary management strategies. Adopting a gluten-free diet typically improves celiac disease related symptoms, but it is not possible to differentiate the effects of gluten withdrawal from changes in fiber intake[20] and/or FODMAP ingestion[21,22] associated with this intervention. The latter two interventions may have significant therapeutic benefit in IBS and future studies should include detailed information regarding intake of these dietary constituents. Any patient-reported outcomes may be confounded by the tendency to attribute many symptoms to unrecognized gluten ingestion[9], which would appear to strengthen the relationship between functional intestinal symptoms and GFD non-adherence. Thus, the observed difference in type of functional symptoms reported based upon dietary adherence may reflect perceptions that gluten exposure causes abdominal pain or diarrhea. In fact, in our cohort, many gluten exposures were accidental and more thorough examination revealed that most of these were unsuspected until after symptoms were experienced[9]. This highlights the clinical need for a reliable non-invasive biomarker of gluten exposure among patients with celiac disease.

The relative excess of IBS symptoms among patients with celiac disease could also be attributable to the HLA immunophenotype[23]. In our cohort, IBS symptoms were more frequent and more persistent among individuals who were HLADQ2^{-}DQ8^{+}. In studies of IBS-D patients who do not have celiac disease, those who are HLADQ8^{+} have faster small intestinal transit[24]. HLADQ2/DQ8 carriers who do not have celiac disease have more severe IBS symptoms and a greater response to a gluten-free diet than those who are HLADQ2^{-}8^{-} [25]. The numbers in these subgroups are small and the effect of immunophenotype on development of IBS symptoms requires further testing.

Studies of patients with celiac disease are constrained by the unavailability of objective measures of gluten ingestion[26]. Assessment of GFD adherence by a trained dietitian is a commonly used metric in research studies, yet this process is not standardized. The CDAT is highly correlated with expert dietitian evaluation and performs better than tTG [9]. In our study, there was a high concordance between the CDAT and GF-EAT and at 12 months tTG antibody levels decreased in all participants apart from two who had levels above the upper limit of the assay at diagnosis. It is known that those with higher antibody levels at diagnosis

take longer to normalize and this is not necessarily a sign of persistent villous atrophy[27]. As well, at 12 months, CSI scores were below threshold for 92% of participants, suggesting that symptoms experienced were not those typically associated with celiac disease.

The prospective longitudinal design and use of standardized and validated measures of intestinal symptoms and gluten-free diet adherence are methodological strengths of this study. As well, the diagnosis of celiac disease was confirmed by intestinal biopsy in all participants and the HLADQ genotype was positive for HLA DQ2 and/or DQ8. Data regarding additional gastrointestinal diagnoses were also available. Notably, only one participant reported lactose intolerance and one participant reported microscopic colitis. A limitation of our study is that we do not have biopsy data available to determine whether there was persistent epithelial injury in those with the persistent symptoms. We follow current practice guidelines that outline recommended investigations for evaluation of patients with non-responsive celiac disease (persistent symptoms after 12 months adherence to a gluten-free diet)[1] and further follow-up of this cohort is planned to document causes of persistent symptoms.

The current study highlights the high prevalence of symptoms of functional intestinal disorders among patients with biopsy-confirmed celiac disease who have been following a gluten-free diet for one year. This underscores the importance of adequate follow-up of patients who have been diagnosed with celiac disease, and the need to ensure full and thorough evaluation of those with persistent symptoms after adoption of a gluten-free diet. Longer longitudinal follow-up studies that include histologic evaluation are needed to determine the prevalence of functional disorders in treated celiac disease.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Table 1
– Participant characteristics at baseline (n=85)

Age [years (IQR)]	**36 (27-54)**
Female [% (n)]	66% (56)
HLA Genotype [% (n)]	
DQ2	86% (73)
DQ8	7% (6)
DQ2/DQ8	7% (6)
Marsh classification [% (n)]	
3a	35% (30)
3b	43% (36)
3c	22% (19)
Celiac serology [median(IQR)]	
tTG IgA level multiples of upper limit of normal	5.7 (2.1- >10)
Other GI Diagnoses	
Lactose intolerance	5% (5)
Peptic ulcer	1% (1)
Irritable bowel syndrome	1% (1)
Inflammatory bowel disease	0

Table 2

Celiac disease symptoms, gluten-free diet (GFD) adherence and serology in patients with celiac disease during the first 12 months on a GFD (n=85)

	Diagnosis	6 months GFD	12 months GFD
Celiac Symptom Index (CSI)			
	36	32	31
Median [IQR]	(29-44)	(27-38)	(25-37)
Above symptom threshold[1] [%(n)]	18% (16)	9% (8)	8% (7)
Gluten-free diet adherence			
Celiac Diet Adherence Test (CDAT)[2]			
Median [IQR]	---	9 (8-11)	9 (8-11)
Adequate adherence [%(n)][3]	---	92% (76)	96% (82)
Gluten-Free Eating Assessment Tool (GF-EAT) [% (n)]			
Gluten unrestricted	---	4% (3)	1% (1)
Occasional gluten (1-4 /month)	---	2% (2)	6% (5)
Rare intentional gluten (<1 /month)	---	12% (10)	13% (11)
Rare accidental gluten (<1/month)	---	73% (62)	65% (55)
No Gluten	---	9% (8)	14% (12)
Celiac serology [median(IQR)]			
tTG IgA level	5.7	0.8	0.6
[multiples of ULN; median (IQR)]	(2.1- >10)	(0.4-1.7)	(0.4-1.3)

[1] CSI scores > 45 are associated with poorer adherence and lower quality of life (possible score range 16 to 80);

[2] Persons not restricting gluten were considered non-adherent and CDAT scores were not calculated;

[3] Scores of 13 or less are associated with adequate adherence (possible score range 7 to 35); ULN - upper limit of normal.

Table 3

Prevalence of symptoms fulfilling Rome III questionnaire criteria for IBS, FD and FB in celiac disease patients during the first 12 months on a GFD (n=85)

Rome III criteria symptoms [%(95% CI)]	Diagnosis	6 months GFD	12 months GFD
Irritable bowel syndrome (IBS)	52% (41-63%)	32% (22-43%)	22% (14-33%)
Functional dyspepsia (FD)	27% (18-38%)	11% (5-20%)	8% (4-17%)
Functional bloating (FB)	9% (4-18%)	21% (13-32%)	16% (10-26%)
Any of IBS, FD or FB	66% (55-75%)	58% (46-69%)	47% (36-58%)