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Symptomatic suspected gluten exposure is common among patients with coeliac disease on a gluten-free diet

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Abstract

BACKGROUND—A gluten-free diet is the only recommended treatment for coeliac disease.

AIM—To determine the prevalence and characteristics of reactions to gluten among persons with coeliac disease on a gluten-free diet.

METHODS—Adults with biopsy proven, newly diagnosed coeliac disease were prospectively enrolled. A survey related to diet adherence and reactions to gluten was completed at study entry and 6 months. The Celiac Symptom Index (CSI), Celiac Diet Assessment Tool (CDAT) and Gluten-Free Eating Assessment Tool (GF-EAT) were used to measure coeliac disease symptoms and gluten-free diet adherence.

RESULTS—Of the 105 participants, 91% reported gluten exposure <1 per month and median CDAT score was 9 (IQR 8-11), consistent with adequate adherence. A suspected symptomatic reaction to gluten was reported by 66%. Gluten consumption was unsuspected until a reaction occurred (63%) or resulted from problems ordering in a restaurant (29%). The amount of gluten consumed ranged from cross-contact (30%) to a major ingredient (10%). Median time to symptom onset was 1 hour (range 10 min to 48 h), and median symptom duration was 24h (range 1 h to 8 days). Common symptoms included abdominal pain (80%), diarrhea (52%), fatigue (33%), headache (30%) and irritability (29%).

CONCLUSION—Reactions to suspected gluten exposure are common among patients with coeliac disease on a gluten-free diet. Eating at restaurants and other peoples' homes remain a risk for unintentional gluten exposure. When following individuals with coeliac disease, clinicians

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should include questions regarding reactions to gluten as part of their assessment of gluten-free diet adherence.

Keywords

Coeliac disease; Diet, gluten-free; Coeliac disease/diet therapy; Coeliac disease/complications; Prospective cohort study

Introduction

Coeliac disease is a chronic autoimmune condition involving the small intestine which is triggered by gluten ingestion. Thus, the mainstay of therapy is strict avoidance of all sources of dietary gluten, rather than pharmacologic therapies, which play significant roles in the management of other autoimmune conditions[1]. While diet adjustment may appear to be a straightforward intervention, adhering to a gluten-free diet is challenging nonetheless. Inaccurate or incomplete labelling of food ingredients, cross-contact with gluten containing foods and the need to rely upon others to help determine if food is safe may all lead to gluten ingestion. Awareness of the intricacies of a gluten-free diet is sub-optimal, even among chefs and food industry workers[2] and foods which are represented as gluten-free may contain clinically significant amounts of gluten[3–5].

Based upon patient self-report, ingestion of gluten by persons trying to follow a gluten-free diet appears to be fairly common. In cross-sectional studies, up to 50% of patients with coeliac disease trying to follow a gluten-free diet report consuming gluten, either intentionally or unintentionally[6,7], and a similar proportion may have persistent mucosal damage[8,9]. In case series and cohort studies, unrecognised gluten consumption is the most commonly identified cause of non-responsive coeliac disease[10,11].

During clinical follow-up visits, many patients with coeliac disease anecdotally report adverse effects of gluten exposure while trying to follow a gluten-free diet. The nature of these ‘reactions to gluten’ has not been well-described. There are isolated reports of persons with coeliac disease on a gluten-free diet developing minor to significant symptoms after supervised administration of a single dose of gluten in a clinical trial setting[12,13], and only one cross-sectional study reporting reactions to gluten in a cohort of patients with coeliac disease[14].

The aim of this study was to describe clinical symptoms thought to be associated with suspected gluten exposure among newly-diagnosed patients with biopsy-confirmed coeliac disease who are trying to follow a gluten-free diet. A secondary aim was to explore the circumstances contributing to symptomatic suspected gluten exposure. A greater understanding of these reactions would aid the practitioner when assessing patient adherence to a gluten-free diet, and may help those with celiac disease to better recognize occurrences of actual gluten exposure.

Methods

Participants were recruited prospectively at the time of diagnosis of coeliac disease. In Manitoba, all testing for coeliac disease-associated antibodies is performed at a central laboratory. This facilitated a population-based approach to reduce recruitment bias. Specifically, a list of physicians with patients who tested positive for anti-tissue transglutaminase antibodies was generated on a weekly basis throughout the enrollment period (December 2012 to September 2015). These physicians were contacted to inform them of the study, and were provided with materials to invite their patients to participate. Secondary recruitment methods included referral by the surgeon or gastroenterologist at the time of diagnostic endoscopy, and advertisements at retailers of gluten-free products and in the newsletter of the Manitoba Chapter of the Canadian Celiac Association. The study was approved by the University of Manitoba Research Ethics Board.

Inclusion criteria for the Manitoba Coeliac Disease Cohort were: age greater than 16 years; HLA genotype associated with coeliac disease; and findings of villous atrophy (Marsh IIIa-IIIc[15]) 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.

Each participant completed an in-person interview and self-report survey at study entry (diagnosis of coeliac disease) and 6 months thereafter. These included items related to medical history, symptoms, diet and food choice. Symptom severity was assessed using the Celiac Symptom Index (CSI)[16]. The Celiac Diet Assessment Tool (CDAT)[17], a 7-item self-report measure with questions about symptoms and personal traits, and Gluten-Free Eating Assessment Tool (GF-EAT)[6], which also includes items related to gluten consumption during the past four weeks, were used to evaluate adherence to a gluten-free diet.

Suspected reactions to gluten were characterized using the REAC-G (Reactions Experienced After Consuming Gluten), a self-administered measure developed specifically for this study by a panel which included gastroenterologists, health psychologists, and persons with coeliac disease. The content was further revised by adding other potential symptoms following pretesting for readability and face validity by three members of the Canadian Celiac Association. The final version included 10 items related to the timing (3), quantity (2), symptoms (2), and circumstances (2) of the most recent gluten exposure and changes in these factors over time (1) (see Supplementary Material for full details).

Serum levels of anti-tissue transglutaminase antibodies (TTG) were determined using a standard ELISA kit (EUROIMMUN US, New Plains, New Jersey).

Data analysis was performed using RStudio Version 0.99.467[18] with R software version 3.1.2[19]. Descriptive statistics were used to characterize the group at baseline and the group who reported a symptomatic reaction to gluten. At baseline, those who experienced a symptom “often”, “very often” or “always” were considered symptomatic and those who “never” or “rarely” experienced the symptom were considered asymptomatic.

Results

There were 182 eligible patients invited to participate in the study of whom 50 declined to participate and 4 did not attend any scheduled study visits. Of the remaining 128 potential participants, 9 elected not to participate in the online surveys (but did complete other aspects of the study), 3 moved out of the study area and 4 dropped out between the initial (diagnosis) and six month follow-up visit. There were 7 participants who continued in the study but did not complete the 6 month online survey. Thus, 105 participants (69% female) completed the recruitment and 6 month follow-up visits (Table 1). Median age was 37 years (IQR 27-54 years). The predominant genotype was HLA DQ2 (82%) with 10% HLA DQ8 positive and 8% heterozygous for HLADQ2 and HLADQ8. Overall, self-reported gluten-free diet adherence at 6 months was high (Table 2). That is, on the GF-EAT, 26% reported no gluten exposure and 66% reported infrequent gluten exposure (less than once per month). The median CDAT score of 9 (IQR 8-11) is consistent with “adequate” adherence. The 9 participants who indicated they consumed gluten more than once per month were considered not to be following a gluten-free diet, thus they were excluded from further analyses related to suspected gluten exposure. This group included persons not following a gluten-free diet for lifestyle reasons as well as persons generally restricting gluten intake who nonetheless chose to consume gluten several times per month. Serum TTG IgA levels decreased in all but two participants, one who reported following a strict gluten-free diet and one who reported gluten exposure more than once per week. Of those following a gluten-free diet at the six month follow-up visit, 57% had TTG IgA antibody levels within the normal range and the rate did not differ between those who reported a symptomatic reaction to gluten (56%) and those who did not (55%). As expected, at 6 months CDAT scores correlated more closely with CSI scores (r^2 = 0.49, 95% CI 0.33-0.63) than with decrease in serum TTG IgA levels (r^2 = 0.20, 95% CI 0.01-0.38). All patients were referred to a dietitian with specialist training in gluten-free diets and 82% reported receiving gluten-free diet information from a dietitian. The dietitian consultation rate was similar among those with and without a symptomatic suspected gluten exposure [70% (95% CI 51-89%) vs. 87% (95% CI 79-95%)].

At the six-month follow-up, there were 69 participants (72%) who reported “having had a reaction to gluten” while trying to follow a gluten-free diet of whom only 68% reported having a reaction every time they consumed gluten. Of these reactions, 74% occurred in the month immediately preceding the survey. The median time from suspected gluten ingestion to first symptom experienced was one hour (interquartile range 0.6-8 hours). A small proportion (13%) reported delayed onset of symptoms 12 hours or longer after suspected gluten ingestion. The age, gender, and rate of normal TTG antibody levels did not differ significantly from those who reported more immediate symptoms. The median duration of symptoms was 24 hours (interquartile range 6-48 hours).

The amount of gluten consumed at the time of most recent reaction ranged from cross-contact (29%) to a major ingredient (10%, Table 3); however, 36% were uncertain how much gluten they had consumed because they suspected gluten exposure only after the reaction occurred. Uncertainty regarding gluten exposure increased with the time to onset of symptoms; 50% of those who first experienced symptoms ≥12 hours after exposure were

uncertain of the amount of gluten consumed, compared to 32% of those who first experienced symptoms within 1 hour (OR 2.1, 95% CI 0.66-6.4).

Retrospectively suspected gluten exposure (i.e., once a reaction occurred) was both the most common feature of suspected gluten exposure and the most commonly endorsed ‘most important’ factor contributing to suspected gluten exposure (Table 4). Problems ordering in restaurants contributed to 30% of suspected gluten exposuress. Other factors, such as frustration (7%), not wanting to offend the host (6%), embarrassment (6%), anger (3%), and a desire to fitin (1%) occurred rarely. Beliefs that ‘gluten containing food tastes better’ or ‘a little gluten is not harmful’ were not reported as contributing to symptomatic suspected gluten ingestion. Other practical difficulties, such as forgetting to check labels, relying on another person who indicated the food was gluten-free, and foreign language barriers while travelling, were also identified as contributing to suspected gluten exposure. There were five participants (7%) who reported experiencing symptoms after intentionally consuming gluten because no gluten-free food was available.

Abdominal pain (80%) and diarrhea (52%) were the most commonly reported symptoms of suspected gluten exposure (Table 5). A broad range of systemic and extra-intestinal symptoms were also reported, including fatigue (33%), headache (30%), bloating (30%) and irritability (29%). Overall, symptoms of suspected gluten exposure reflected the range of symptoms reported at diagnosis.

Participants reported that their reaction to gluten changed over time (Table 6). Following adoption of a gluten-free diet, 29% reported experiencing fewer symptoms and 34% reporting experiencing more symptoms with suspected gluten exposure. Over 40% reported that the intensity of their symptoms increased while 28% experienced less intense symptoms and the remainder reported no change in symptom intensity. Sensitivity to gluten tended to increase, with the perceived amount of gluten ingestion which triggered a reaction becoming less (19%) or much less (32%) for the majority, 24% reporting no change and only 6% reporting that much more gluten ingestion was necessary to evoke a reaction.

Discussion

While a gluten-free diet has been the only recommended treatment for coeliac disease for more than half a century, surprisingly, neither the frequency nor the effects of gluten ingestion by patients with coeliac disease trying to follow a gluten-free diet have been carefully evaluated. Participants in this study were genetically susceptible patients with a biopsy confirmed diagnosis of coeliac disease who had been trying to follow a gluten-free diet for six months. The majority had experienced symptoms during the previous month which they attributed to suspected gluten ingestion. For most, these reactions occurred within one hour of suspected gluten ingestion, and resolved within 48 hours.

The range of symptoms of suspected gluten exposure while following a gluten-free diet was similar to symptoms experienced at initial diagnosis, and included extraintestinal symptoms, such as headache and non-specific rashes, as well as systemic symptoms, such as fatigue and

irritability. While diarrhea was the most common gastrointestinal symptom experienced by individuals exposed to gluten, 28% of respondents experienced constipation.

Gluten challenge studies have demonstrated that symptomatic and histologic relapse of coeliac disease may take months to years[20]; however, most participants in the present study reported symptomatic reactions to gluten within hours of exposure, which corroborates the one other report regarding symptomatic gluten reactions[14]. Interestingly, this study also appeared to show a biphasic pattern, with the majority of respondents experiencing immediate symptoms and a subgroup experiencing a more delayed reaction. Symptomatic relapse has been found to precede the development of villous atrophy[21]. Further, villous atrophy does not correspond to reported symptoms at diagnosis[22,23], suggesting that the acute symptoms experienced in response to gluten ingestion are not mediated by villous atrophy. Rapid onset of transient symptoms of abdominal discomfort, bloating and vomiting has been reported in the context of open-label gluten challenge[24–27]. Possible mechanisms for the relatively rapid onset of systemic symptoms include direct effects of gliadin peptides[28,29], T-cell activation, an immune complex mediated reaction or release of serotonin in response to gluten ingestion[30].

It is striking that over 60% of participants did not suspect that they had consumed gluten until they experienced a reaction. This may relate to unidentified sources of gluten. In Canada, up to 10% of naturally gluten-free starches and 1% of those labelled gluten-free[4] may contain gluten in excess of the 20 ppm upper threshold determined by the CODEX Alimentarius Commission [31]. Alternatively, the symptoms experienced may have been unrelated to gluten consumption or coeliac disease and may be a manifestation of another condition, such as viral gastroenteritis, foodborne illness, irritable bowel syndrome or lactose intolerance. However, the sporadic nature of these symptoms, their short duration and their temporal association with greater risk of gluten exposure (e.g., at a restaurant or eating at another person's home) support that they may reflect a reaction to actual gluten ingestion rather than a chronic condition, such as irritable bowel syndrome. The prevalence of reactions to suspected gluten exposure is also much greater than the estimated prevalence of irritable bowel syndrome among patients with celiac disease[32]. As in other clinical contexts, it is much more difficult to ascertain whether the reaction is to some non-gluten component of a gluten-containing food, e.g., FODMAPs, wheat amylase-trypsin inhibitors[33].

Diet adherence appeared to be most challenging in the social realm where a patient must self-identify and/or rely upon others, such as when ordering at a restaurant or eating at another person's home. These situations were most commonly implicated in contributing to suspected gluten exposure and have been identified in other surveys[34]. Conversely, the belief that a little gluten is not harmful, anger and frustration with a gluten-free diet and dissatisfaction with the taste and quality of gluten-free food were rare and not highlighted as important factors contributing to suspected gluten exposure, perhaps reflecting the recent increases in availability and variety of specialty gluten-free products.

Given that symptomatic reactions are experienced by many persons on a gluten-free diet and may be markers of gluten ingestion, follow-up by health care professionals should include

assessment of reactions to suspected gluten exposure in addition to diet review. As well, it may be helpful when educating patients about the gluten-free diet to inform them about common symptoms and reactions to gluten ingestion after a period on a gluten-free diet.

This study has several important limitations that need to be clarified in future studies. First and foremost, while inadvertent gluten ingestion may be common, and similar rates have been reported in other cross-sectional studies[7], our study is limited by the use of self-report to ascertain gluten exposure. The quantity of gluten consumed was not verified through direct measurement and was often suspected retrospectively. Reliance upon self-report as a proxy for gluten ingestion is common in clinical studies of patients with coeliac disease[35]. Few studies include objective measures, such as duodenal histology or serology. Moreover, these measures are impractical and do not provide real-time information regarding gluten consumption[36]. There are limited reports of measuring gluten excretion directly as a proxy for gluten ingestion[37,38]. This reflects the predicament of persons with coeliac disease who must navigate the omnipresent risk of cross-contact with gluten containing foods without access to objective tools to verify or quantify gluten content. In this void, symptoms may become the most important source of feedback regarding adherence to a gluten-free diet.

Another limitation is the use of an observational design with retrospective reporting of suspected gluten exposure. Ideally, a study of reactions to gluten among patients with celiac disease would be performed in a randomized double-blind fashion similar to that proposed for studies of nonceliac gluten sensitivity[39]. This would provide the benefit of being able to confirm and quantify gluten ingestion; however, it would not provide data regarding circumstances which contribute to suspected gluten exposure and may itself be confounded by inadvertent gluten exposure if baseline gluten-free diet is not appropriately controlled.

Finally, participants in this study were relative neophytes who had followed a gluten-free diet for only six months. Arguably, this may not be the most appropriate population in which to study reactions to gluten as it is possible that with experience of a gluten-free diet, the rate of suspected gluten exposure may decrease and/or awareness of gluten ingestions and association of reaction with gluten exposure would be more accurate. It is equally possible that the social contexts that contribute to suspected gluten exposure may be unavoidable. Intermittent gluten exposures have been found to occur even after many years on a gluten-free diet[6,34,35]. In a study of community dwelling adults and children with celiac disease on a long-term gluten-free diet, nearly 50% had detectable levels of gluten immunogenic peptides in their urine[38]. This suggests that gluten exposure is likely a very common phenomenon even with experience with a gluten-free diet. Nevertheless, a longer follow-up period and verification of suspected gluten ingestion would facilitate evaluation of the dynamics of factors contributing to gluten exposure in relation to duration of a gluten-free diet and how these relate to persistent mucosal damage.

In summary, this prospective cohort study has demonstrated that among individuals with coeliac disease trying to follow a gluten-free diet, symptomatic reactions to suspected gluten exposure were common, of short duration, occurred soon after suspected gluten exposure, and were frequently experienced in the context of eating at restaurants or other peoples'

homes. These findings reflect the unavailability of practical tools for persons trying to adhere to a strict gluten-free diet to objectively assess whether a food contains gluten or if they have consumed gluten. Further studies are needed to determine the mechanism of these acute reactions to gluten. Until then, a history of patient experience of suspected reactions to gluten should be routinely elicited during the monitoring of patients with coeliac disease following a gluten-free diet.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of study participants (n=105)

Female	69% (72)
Age [years; mean (IQR)]	37 (27-54)
Genotype	
HLADQ2	82% (86)
HLADQ8	10% (11)
HLADQ2/DQ8	8% (8)
TTG positive [%(n)]	95% (100)
Marsh Classification at diagnosis	
IIIa	33% (35)
IIIb	49% (45)
IIIc	18% (21)

Table 2

Coeliac disease symptoms and measures of gluten-free diet adherence at diagnosis and 6 months thereafter

Celiac Symptom Index [median (IQR)][1]	
Initial study visit	35 (29-44)
At 6 months	32 (27-39)
TTG IgA positive %(n)	
At diagnosis	95% (100)
At 6 months	43% (44)
Gluten-Free Eating Assessment Tool [% (n)] (n=105)	
Frequent gluten (>1/week)	<1% (1) *
Occasional gluten (1-3/month)	8% (8) *
Usually gluten-free rare intentional gluten (<1/month)	10% (10)
Usually gluten-free, rare accidental gluten (<1/month)	56% (59)
No gluten	26% (27)
Celiac Diet Adherence Test score[2]	
[median (IQR)] (n=95)	9 (8-11)
Symptomatic reaction to suspected gluten exposure (n=96) *	72% (69)

[1] Celiac Symptom Index scores range from 16 to 80, scores <30 are associated with clinical remission and scores >45 are associated with poor quality of life and worse gluten-free diet adherence.

[2] Celiac Diet Adherence Test scores range from 7 to 35, scores > 12 predict inadequate gluten-free diet adherence.

* Participants with frequent gluten exposure were excluded from further analyses

Table 3

Reactions Experienced After Consuming Gluten (REAC-G) among patients with coeliac disease who reported symptomatic suspected gluten exposure after trying to follow a gluten-free diet for 6 months (n=69)

	%(n)
Reaction every time gluten consumed	68%(46)
Amount of gluten consumed	
Cross-contact only	30%(20)
Crumbs	4%(3)
Minor ingredient	16%(11)
Moderate ingredient	4%(3)
Major ingredient	10%(7)
Unsure	36%(25)
Number of symptoms experienced [median (IQR)]	3 (2-4)
Time to onset of symptoms, hours [median (IQR)]	1 (0.6-8)
Duration of symptoms, hours [median(IQR)]	24 (6-48)

Participants who were trying to follow a gluten-free diet were asked to recall their last symptomatic to gluten.

Table 4

Factors contributing to suspected gluten ingestion among patients with coeliac disease who reported symptomatic suspected gluten exposure after trying to follow a gluten-free diet for 6 months (n=69)

	Contributing factors	Most important factor
Did not know/suspect until reaction	63%(43)	55%(38)
Problems ordering in restaurant	29%(20)	17%(12)
No gluten-free food available	7% (5)	3%(2)
Frustration with gluten-free diet	7%(5)	3%(2)
Did not want to offend host	6%(4)	4%(3)
Embarrassed to ask	6%(4)	4%(3)
Did not want to draw attention to lack of GF food	4%(3)	--
Anger towards coeliac disease	3% (2)	--
To fit in with others	1%(1)	1%(1)
Other	5%(3)	12%(8)

Table 5

Symptoms of gluten reaction and relationship to symptoms reported at diagnosis

Symptom	Reported reaction to gluten (n=69)	At diagnosis	
		Symptomatic reaction (n=69)	Entire cohort (n=105)
Abdominal pain	80%	54%	51%
Diarrhea	52%	48%	41%
Fatigue/low energy	33%	70%	59%
Bloating	30%	58%	44%
Headache	30%	29%	33%
Irritability	29%	67%	55%
Constipation	28%	54%	46%
Vomiting	19%	10%	9%
Mouth ulcers	7%	28%	24%
Non-specific skin rash	4%	55%	52%

Table 6

Change in symptomatic response to suspected gluten exposure following adoption of a gluten-free diet (n=69)

	Much Less	Less	Unchanged	More	Much more
Number of symptoms	13%	16%	37%	22%	12%
Symptom intensity	10%	18%	31%	19%	22%
Symptom duration	10%	22%	37%	16%	15%
Amount of gluten that evokes a reaction	32%	19%	24%	19%	6%