A Novel Patient-Derived Conceptual Model of the Impact of Celiac Disease in Adults: Implications for Patient-Reported Outcome and Health-Related Quality-of-Life Instrument Development

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ABSTRACT

Background: Celiac disease is a chronic inflammatory condition with wide ranging effects on individual’s lives caused by a combination of symptoms and the burden of adhering to a gluten-free diet (GFD).

Objectives: To further understand patients’ experience of celiac disease, the impact it has on health-related quality of life (HRQOL), and to develop a conceptual model describing this impact. Methods: Adults with celiac disease on a GFD reporting symptoms within the previous 3 months were included; patients with refractory celiac disease and confounding medical conditions were excluded. A semi-structured discussion guide was developed exploring celiac disease symptoms and impact on patients’ HRQOL. An experienced interviewer conducted in-depth interviews. The data set was coded and analyzed using thematic analysis to identify concepts, themes, and the inter-relationships between them. Data saturation was monitored and concepts identified formed the basis of the conceptual model.

Results: Twenty-one participants were recruited, and 32 distinct gluten-related symptoms were reported and data saturation was reached. Analysis identified several themes impacting patients’ HRQOL: fears and anxiety, day-to-day management of celiac disease, physical functioning, sleep, daily activities, social activities, emotional functioning, and relationships. The conceptual model highlights the main areas of impact and the relationships between concepts.

Conclusions: Both symptoms and maintaining a GFD have a substantial impact on patient functioning and HRQOL in adults with celiac disease. The conceptual model derived from these data may help to design future patient-reported outcomes as well as interventions to improve the quality of life in an individual with celiac disease.

Keywords: celiac disease, conceptual model, patient-reported outcome, quality of life.

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Introduction

Celiac disease is a systemic immune disorder in which the sentinel lesion is an enteropathy triggered by ingestion of gluten proteins from wheat, rye, and barley [1]. Gluten proteins are partly digested to gluten peptides that are able to enter the intestinal submucosa where they are presented by antigen-presenting cells expressing the celiac-permissive human leukocyte antigen molecules DQ2 or DQ8 [2,3]. These molecules are able to present gluten peptides that have been deamidated by the enzyme tissue transglutaminase [4]. In individuals with celiac disease, gluten presentation leads to T-cell activation and subsequently intestinal inflammation and a spectrum of gastrointestinal (GI) symptoms, malabsorption, and systemic manifestations including malignancy [5]. The past decade has witnessed a remarkable increase in awareness of celiac disease partly because of the availability of simple and accurate serologic screening in the form of anti-tissue transglutaminase antibody testing. Using serologic assays, the prevalence of celiac disease in the United States and Europe has been determined to be approximately 1% (range 1:250 to 1:67) [6–8].

Currently, the only accepted therapeutic option for celiac disease is lifelong adherence to a gluten-free diet (GFD), defined as strict avoidance of foods, beverages, medications, and...
supplements containing gluten. Treatment improves most symptoms and can lead to normalization of all standard diagnostic tests including serologic tests and histological findings [9-13]. Despite good overall prognosis, it is clear that celiac disease has a persistent significant impact on patients’ lives, in terms of both ongoing symptoms [14,15] and psychosocial burden [16-19]. There is also increasing evidence that intermittent symptomatic gluten exposure is a common occurrence in individuals with celiac disease, despite attempts to maintain a GFD [20-24].

Several studies have investigated the impact of celiac disease on health-related quality of life (HRQOL); findings have, however, been inconsistent. Some studies have found that patients with celiac disease have a similar or better HRQOL than the general population [25,26], whereas others have found that they have a poorer HRQOL than the general population or healthy controls [27-29]. Previous research has also explored the factors that influence HRQOL [28,30], with failure to adhere to a GFD, symptomatic status, female sex, and younger age at diagnosis all found to be associated with lower HRQOL.

Most studies exploring the impact of celiac disease symptoms and a GFD on patients’ quality of life have used a cross-sectional quantitative design and have evaluated quality of life using either generic instruments, such as the six-dimensional health state short form [28,31,32] and the EuroQol five-dimensional questionnaire [26,30,33,34], or celiac-specific measures, such as the Celiac Disease Questionnaire [28], the Celiac Symptom Index [35], and the Celiac Disease Quality of Life (CD-QOL) [36]. Little qualitative research has focused on the impact of celiac disease on patients’ HRQOL. Qualitative methods using open-ended questions allow for the issues of importance to patients to be explored. Therefore, qualitative research is required to fully understand the impact of specific symptoms and of adhering to a GFD. Conceptual models can be developed from qualitative data to illustrate the areas of impact in a condition and the inter-relationships between them. These models can then be used in de novo instrument development to consider the appropriateness of existing instruments for patient populations with celiac disease or to identify meaningful patient-centered endpoints in clinical trial and/or health technology appraisal settings.

The objective of this work was to help inform and improve future celiac disease research by conducting qualitative interviews with patients with celiac disease to explore the symptoms experienced and the impact of these symptoms on patients’ HRQOL to develop a patient-centered conceptual model of celiac disease. Given the potential application of this research to the development of de novo celiac disease instruments to measure appropriate clinical trial end points, this study adhered to the US Food and Drug Administration’s (FDA’s) Patient-Reported Outcome (PRO) Measures Guidance for Industry (2009) and informed the development of three celiac-specific outcome measures: the Celiac Disease Symptom Diary (CDSD), the Impact of Celiac Disease Symptoms Questionnaire (ICDSEQ), and the Impact of Adhering to a Gluten-Free Diet Questionnaire (IGFDQ).

**Methods**

**Design**

A cross-sectional, qualitative study was designed to gather information on the symptoms of celiac disease and the impact of symptoms and adhering to a GFD on patients’ lives and functioning.

**Recruitment**

To reflect the adult celiac population in the United States [37], a nonprobabilistic purposive sampling strategy was applied. As is recommended in qualitative research, the sample size was guided by data saturation (the point at which no new information is obtained from additional qualitative data) [38] rather than a predetermined sample size. Patients were recruited from a celiac disease clinical center at Beth Israel Deaconess Medical Center in Boston, MA. Patients’ medical charts were reviewed to identify potential participants meeting the inclusion criteria. Eligible patients were then contacted to ascertain their interest in taking part in an interview. All patients were 18 years or older with a history of biopsy-proven celiac disease and following a GFD with at least one previous visit with a dietitian for gluten-free counseling, who reported GI or non-GI symptoms felt to be related to gluten exposure within the previous 3 months. This population is consistent with that recommended in meetings with the FDA as amenable for targeting with novel therapies [39]. All gluten exposure episodes were reported to be inadvertent and there was no minimum or maximum symptom threshold for inclusion. The a priori goal was 65% to 75% females, 90% to 95% Caucasian, and a mean age of 35 to 45 years, consistent with reported US celiac disease demographic characteristics [37,40]. Patients with known or suspected refractory celiac disease or significant concomitant GI or extraintestinal disease were excluded.

**Procedures**

Interviews were conducted one-on-one, in-person when possible, or by telephone if needed (one participant was unable to travel for the interview and therefore took part by telephone). All interviews were conducted by the same experienced qualitative interviewer. Interviews followed a semistructured interview guide that included open-ended questions to allow participants to spontaneously report their symptoms as well as probing questions to elicit further detail. Each participant was asked to describe the symptoms he or she experiences and the effect celiac disease had on different areas of their life. Adherence was determined through both review of the medical record and participant recall.

**Analysis**

The entire data set was coded and analyzed by experienced qualitative researchers. The data were analyzed using thematic analysis according to the methodology described by Braun and Clarke [41]. The analysis consisted of an initial reading and rereading of the data to identify themes and categories emerging from the data. The analysis also aimed to identify relationships between symptoms and impacts. A qualitative analysis software tool, Atlas.ti (ATLAS.ti Scientific Software Development GmbH, Germany), was used to facilitate the analysis process. The themes and concepts emerging from the analysis were recorded in a saturation grid and saturation was monitored in accordance with the methods described by Kerr et al. [42]. Coding concordance was rigorously assessed by a second coder who independently analyzed all the transcripts after which both coders met with another member of the project team to discuss and reconcile any coding issues. Participant enrollment was ongoing until concept saturation was reached.

**Development of the Conceptual Model**

The conceptual model was developed using the codes and concepts identified during the analysis of the interview data from all participants. The model was developed and reviewed by
Results

In total, 21 patients participated in the study. The saturation grid indicated that data saturation had been reached. The mean age was 42 years, 71% were women, and 91% were Caucasian. Patients’ demographic characteristics and clinical profiles are presented in Table 1.

Qualitative analysis identified several themes relating to the impact of celiac disease on patients’ HRQOL that make up the conceptual model (Fig. 1): fears and anxiety, day-to-day management of celiac disease, physical functioning, sleep, daily activities, social activities, emotional functioning, and relationships. The arrows in the figure indicate the direction of influence; for example, the arrows at the bottom of the model indicate that celiac disease symptoms can affect the six areas of HRQOL. The dotted arrow represents the moderating influence of time since diagnosis on the extent to which GFD management impacts patients’ lives.

We now present detailed descriptions of the areas of impact, with example quotations from participants provided in Table 2 to illustrate each impact.

Symptoms

Overall, 32 distinct gluten-related symptoms were reported, 13 of which were reported by at least four patients (or ~20% of the sample), and were considered reliably attributable to celiac disease. Table 3 presents the most commonly reported and most troublesome symptoms. These symptoms fall into two main categories: GI and non-GI symptoms. The common GI symptoms included the following: diarrhea, constipation, abdominal pain, bloating, nausea, gas, and weight loss/inability to gain weight. The common non-GI symptoms and concerns included fatigue, anemia, headache, muscle/joint pain, skin rash, and memory/thinking problems. Most symptoms were scored on 5-point scales aside from abdominal pain and headache, which were scored on 10-point scales. Using 1 as mild, 2 to 3 as moderate, and more than 3 as severe for the 5-point scales, and 1 to 3 as mild, 4 to 7 as moderate, and more than 7 for severe for the 10-point scales, we found that 17% had only mild symptoms, 24% had mild and moderate symptoms, and 59% had at least one severe symptom. Although some patients reported having been previously diagnosed with comorbid conditions potentially causing similar symptoms, including irritable bowel syndrome, gastroesophageal reflux, and lactose intolerance, all patients reported being able to identify their celiac disease symptoms and differentiate them from those of other conditions.

Fears and Anxiety

Participants commonly reported experiencing fears and anxiety after being diagnosed with celiac disease, relating predominantly to the possibility of ingesting gluten and thus experiencing symptoms, the possibility of passing the disease onto future generations, and the long-term outcomes of the disease. More specifically, patients reported being apprehensive when eating outside of the home because they feared they would ingest gluten unknowingly and experience symptoms. Female patients with children expressed their concern about passing celiac disease on to their children and one patient reported that her child had been diagnosed with the disease already, and she often would worry about the long-term implications for her child. Patients also mentioned the fear about possible complications and the risk of cancer associated with celiac disease.

Lifestyle Impacts of Adhering to a GFD

Participants reported various inconveniences associated with adhering to a GFD, including the need to plan ahead to ensure they always had gluten-free food and the increased difficulty of having to check product labels when shopping for food or checking ahead with restaurants to ensure they have gluten-free options. Nevertheless, in addition to the inconveniences associated with following a GFD, some patients reported a positive effect on their lives because of their increased focus on a healthier lifestyle.

HRQOL Impacts

Physical functioning

Participants reported celiac disease symptoms having a negative impact on their physical activities. Specifically, symptoms such as fatigue, headaches, and joint pain limit participants’ participation in sports or exercise. One participant reported that experiencing flatulence stopped her from going to the gym.

Sleep

Sleep is affected by symptoms; patients may wake up at night because of symptoms such as abdominal pain, or they may feel the need for more sleep because of fatigue. One participant who experienced dermatitis herpetiformis as a symptom of celiac disease reported that it negatively impacted sleep because of the itching it caused.
Daily activities
Many of the symptoms experienced by participants had a negative impact on their daily activities. Experiencing diarrhea caused for participants the need to stay near a bathroom and therefore prevented them from engaging in certain daily activities. Symptoms such as abdominal pain, nausea, headaches, or muscle/joint pain affected participants’ ability to do grocery shopping or housework they would usually do. Several symptoms also interfered with participants’ work or study. Cognitive symptoms caused participants to miss appointments and prevented them from working effectively. Bloating meant that clothes did not fit and affected the clothes participants could wear.

Social activities
Social activities are affected by several symptoms of celiac disease. Diarrhea causes for some participants the need to stay close to a bathroom and some participants reported that it can prevent them from going out in the evening. Other GI symptoms such as constipation, abdominal pain, nausea, and gas often interfered with the enjoyment of social activities or caused participants to avoid social events. Fatigue impacted participants’ willingness to go out in the evening or to make social plans.

Adhering to a GFD also had a negative impact on social activities. Participants reported that being involved in food-related social events, such as eating at restaurants, was difficult, because it would cause worry about whether gluten-free food would be available or whether meals were being prepared in a gluten-free kitchen. Participants sometimes avoided social outings for these reasons.

Emotional functioning
Participants reported many emotional effects associated with experiencing celiac disease symptoms. Depression and anxiety were associated with many of the symptoms, including diarrhea, abdominal pain, fatigue, and cognitive problems. Participants also reported several symptoms causing them to feel frustrated. Symptoms such as constipation and gas caused embarrassment for participants. Other emotional impacts included feeling angry, annoyed, distressed, or irritable because of symptoms.

Adhering to a GFD also caused negative emotions for participants. Participants reported that they often felt like a bother or burden to others who have to accommodate their dietary requirements, which makes social activities less enjoyable. They also reported feeling guilty and embarrassed about being an inconvenience to others. Having to disclose their disease to others also was reported to be awkward and uncomfortable at times.

Relationships
For some participants, being unable to participate in or enjoy activities because of symptoms had a negative impact on participants’ relationships with their family or friends.

Participants also reported that needing to adhere to a GFD sometimes caused a strain on their relationships with family or friends. Participants discussed about others having to accommodate them in terms of ensuring there were gluten-free options if they went to a restaurant or to other social events. Some patients reported that friends and family were very understanding and did not mind accommodating, whereas others mentioned that friends and family would get annoyed, which would negatively affect their relationship. Some participants felt that their family or friends did not understand their disease and therefore the need to adhere to a GFD. Participants reported that adhering to a GFD required planning ahead to ensure they always had gluten-free food, which made it difficult for some to participate in spontaneous activities with friends or family.

Discussion
This is the first patient-centered qualitative study to explore the effect of celiac disease on quality of life and to illustrate the impact through a conceptual model while also adhering to the US
The development of the CD-QOL included focus groups with 12 patients; nevertheless, the qualitative results are not reported in the development article. Other celiac-specific instruments such as the Celiac Symptom Index [35] and the CD-QOL [36] were developed using items generated from literature reviews or clinical experts rather than from qualitative research with patients and therefore would not meet US FDA guidelines for PRO development. Furthermore, the present study is the first to explore the specific impact of experiencing celiac disease symptoms on HRQOL as well as the impact of adhering to a GFD. The conceptual model illustrates the domains of HRQOL that are affected specifically by symptoms (physical functioning, daily activities, and sleep) in addition to the domains affected by both symptoms and adherence to a GFD.

The findings of this study demonstrate that both the experience of symptoms and the requirement to adhere to a GFD have a negative impact on HRQOL. In addition, celiac disease can coexist with other disorders, such as gastroesophageal reflux and lactose intolerance, among others, patients reported to be able to readily differentiate their gluten exposure–related celiac disease symptoms from symptoms with other etiologies. Recent studies have shown that adults with celiac disease experience ongoing symptoms, enteropathy, and treatment-related burden, which are all significant problems. Thus, there is clearly unmet need in the celiac population, and the goal of optimizing the quality of life for patients with celiac disease has not been achieved. There is a great deal of ongoing effort on novel therapies for celiac disease as well as educational approaches to a GFD. Nevertheless, all these must be considered within the complex relationship between symptoms, disease risk, and treatment burden in celiac disease. A review of end points for phase 2 and 3 trials of drugs for celiac disease concludes that “a PRO instrument will probably be required” in phase 3 trials as either a primary or a coprimary end point [43]. Therefore, a robust conceptual model of how different factors impact the lives of patients with celiac disease is vital for the development of instruments to measure outcomes in celiac disease as well as to develop evidence-based strategies to improve quality of life. The conceptual model we present in this article is a useful tool for informing a PRO measurement strategy to be used in the evaluation of new treatments. These data, along with the qualitative data, were used to inform the development of three celiac-specific questionnaires (CDSD, ICDSQ, and IGFDQ). Recent reviews of PRO measures suitable for use in celiac disease have discussed the CDSD as a potential instrument for use in clinical trials [44,45]; the lack of development information, however, has also been highlighted [45]. Therefore, the present study provides important information on the development of these celiac-specific instruments. The model highlights domains of importance to patients and potential relationships between concepts.

Adults with celiac disease interviewed in this study reported a highly variable range of gluten-related symptoms, which had a substantial effect on their physical and social functioning, emotional well-being, and HRQOL. Symptoms affect physical functioning, such as the ability to exercise, as well as daily activities including work inside and outside the home. When patients have symptoms, they feel physically unwell and are often distracted and less productive in their daily activities. Patients commonly report that gluten-related symptoms lead to disrupted sleep and avoidance of activities, both of which may have significant adverse effects on relationships with family and friends and can lead to feelings of frustration, guilt, and depression. Even when social activities are not avoided, patients tend to report less enjoyment from their activities. The emotional effects of gluten-related symptoms are considerable and include feelings of embarrassment, anxiety, anger, depression, and feeling like a burden. Thus, symptoms can have a profound effect on all GFD, gluten-free diet.

### Table 2 – Example participant quotations.

<table>
<thead>
<tr>
<th>Concept</th>
<th>Example quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fears and anxiety</td>
<td>“It was not so much actively now, but initially fairly anxiety-provoking, (...) reading about, you know, long-term, are there autoimmune risks? Are there, you know long-term increased cancer risk? (...) and those were, sort of, things that I had not learned about in Medical School and I found surprising and anxiety-provoking early on in the diagnosis.”</td>
</tr>
<tr>
<td>Lifestyle impacts</td>
<td>“It impacts what I eat, where I eat, when I eat, if I can eat, so everything has to be first minimally planned out, so I’m coming to meet you today and before I can come here I pack up a lunch because we’re going to be done at 12:30 and I don’t know if the cafeteria would have food that I would know was safe.”</td>
</tr>
<tr>
<td>Physical activities</td>
<td>“Things like that I was, you know, sleeping a lot more, you know, nine, ten hours a day instead of the usual seven or eight and yeah, that and coupling that with trying to exercise, that was kind of non-existent ‘cause after five, ten minutes I would just be dead tired.” [impact of fatigue on physical activities]</td>
</tr>
<tr>
<td>Sleep</td>
<td>“When it was most severe over the winter it was like most intolerable, like I could never go to sleep ‘cause it was like so irritating at night. Like, I wouldn’t stop itching, it like bled a little bit.” [impact of skin rash on sleep]</td>
</tr>
<tr>
<td>Daily activities</td>
<td>“If it happens during working, then I, you know, again, I miss another half an hour or another hour or whatever it is, of work, you know, so I can’t bill and I can’t, you know, I lose the money.” [impact of abdominal pain on daily activities]</td>
</tr>
<tr>
<td>Social activities</td>
<td>“Sometimes we’d be out at dinner I’d be getting up three or four times in the middle of the meal to go to the bathroom, which then again, you’re beginning to feel embarrassed because why am I getting up and going and leaving and coming back.” [impact of constipation on social activities]</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>“There was a time where I’d have say, ‘I can’t go, I’m not going,’ to wherever we were going, so I’d feel guilty, I’d feel anxious and then I’d feel depressed about the fact that I had to miss out on something that I wanted to do.” [emotional impact of diarrhea]</td>
</tr>
<tr>
<td>Relationships</td>
<td>“We keep a generally gluten-free house, so that impacts her. She can’t eat the kind of foods that she’s used to and that she wants to eat, at least around the house, and so sometimes that causes a little bit of strain on our relationship.” [impact of adhering to a GFD on relationships]</td>
</tr>
</tbody>
</table>

Fears and anxiety and dietary impacts were related to sleep and daily activities, and sleep) in addition to the domains affected by both symptoms and adherence to a GFD.
aspects of patients’ lives. In addition to symptoms, adherence to a GFD was shown to have a negative effect on patients’ social and emotional functioning. Although there seems to be many negative aspects related to celiac disease and its symptoms, several patients mentioned positive effects of knowing the cause of their symptoms since being diagnosed with celiac disease including feeling “healthier” and living a healthier lifestyle.

These data were used to derive the conceptual model outlined in Figure 1. In this model, celiac disease is mediated by two major themes: 1) lifestyle effects related to following a GFD and 2) gluten-related symptoms. Both these major themes directly affect physical functioning and daily activities as well as social and emotional functioning. Although unique in that this model is derived directly from patient report, it is consistent with previous reports [16,18] providing the model with face validity.

Although data saturation was achieved, suggesting that increasing the number of interviews would not have led to different conclusions [42], we recognize that the sample size is limited and that results may vary in different populations. Nevertheless, the results elicited are consistent with what are currently published on symptoms of gluten exposure [20,22,23,46,47], and demographic characteristics of the study population are similar to those of the North American adult celiac population in general [25,37]. Furthermore, work using much larger number of participants for development and validation of the PRO instruments has confirmed this findings. We also note that although some of the concepts elucidated may seem apparent to clinicians and investigators well versed in celiac disease, past observations have largely come from clinicians rather than directly from patients in the setting of a formal concept elucidation interview. These data, derived from direct, unprompted patient interview, coded and evaluated using rigorous qualitative research methods, provide the necessary foundation for the development of a new patient-reported instrument following regulatory guidelines. Conceptual models are valuable tools that permit the illustration of complex inter-relationships between concepts in a clear and succinct way and are important for measurement strategies and identification of patient-reported end points for clinical studies assessing novel treatments for celiac disease. The model presented was developed entirely from patient-reported symptoms and concepts and therefore includes only concepts of importance to patients. The relationships between concepts differentiate areas of functioning that may be improved if a treatment reduces symptoms, and those that are likely to continue to be affected to some extent by continued adherence to a GFD.

Finally, we acknowledge that these data were derived only from patients with one or more symptomatic gluten exposure episode in the previous 3 months, and as such may not be applicable to asymptomatic patients or patients with very good disease control. Given the acute need for validated PROs for use in pivotal clinical trials, for which the present primary aim is to improve control of celiac disease in patients with persistent symptoms related to gluten exposure despite earnestly following a GFD, a primary aim of this work was to develop instruments to measure celiac symptoms and disease impact. To best achieve this goal, we opted to focus on a population with at least one recognized symptomatic gluten exposure in the last 3 months. Although this does exclude asymptomatic patients, it is worth noting that recent literature reports that most patients have intermittent gluten exposure despite attempts to remain gluten-free, suggesting that the studied population is actually typical [20–24]. Nevertheless, responsiveness and generalizability of this work will require further evaluation in large cross-sectional and prospective studies across diverse populations.

### Conclusions
We present the results of a rigorously conducted cross-sectional qualitative study of the effects of celiac disease on patients’ HRQOL in a cohort of adults with celiac disease demographically similar to that of the overall North American celiac population. These data provide an improved understanding of the myriad ways that celiac disease and specifically gluten-related symptoms and the need of adhering to a GFD affect the lives of adults with celiac disease. Although further study is needed, this work helps to define the range of symptoms reported by patients and the way in which these symptoms interact with psychosocial factors to better design studies and interventions to improve overall HRQOL in adults with celiac disease. The conceptual model described in this report forms the basis for the development and clinical validation of uniquely celiac disease-specific PRO instruments designed to assess patient symptoms and quality of life in clinical and research settings.