Relevance of the Gastrointestinal Symptom Rating Scale in Patients With Celiac Disease

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INTRODUCTION

The Gastrointestinal Symptom Rating Scale (GSRS)[1] is a generic patient-reported outcome (PRO) measure that provides a comprehensive assessment of gastrointestinal (GI) symptoms and has been validated for use in clinical trials in patients with irritable bowel syndrome and peptic ulcer disease.[2] The GSRS has also been used in several studies on patients with celiac disease.[3–11]

The GSRS includes 15 items that address a wide variety of GI symptoms. Each item refers to "the past week." This instrument utilizes a 7-point response scale to measure a participant's level of discomfort associated with a given GI symptom, ranging from "No discomfort at all" to "Very severe discomfort." The GSRS items cover five domains that are also called "subscales" for the purposes of obtaining scores (both total and subscale): reflux syndrome, abdominal pain, constipation syndrome, diarrhea syndrome, and indigestion syndrome.

This qualitative study was conducted in order to investigate the relevance of the GSRS in patients with celiac disease and to explore if the GSRS would constitute an appropriate and relevant PRO demonstrating the efficacy of novel treatments for celiac disease.

OBJECTIVES

The objectives were:

(1) To identify items of concern for patients with celiac disease

(2) To determine if the GSRS would be a relevant and appropriate PRO measure for use in clinical trials measuring GI-specific clinical benefits of novel treatments for celiac disease

This study is the first to evaluate the applicability and content validity of the GSRS for use in celiac disease.

METHODS

A qualitative study utilized 21 in-depth individual patient interviews to identify items of concern and determine content validity of the GSRS.

Patient Population

Patients with celiac disease were recruited via local chapters of the Celiac Sprue Association. The screening questionnaire required the following criteria:

- Male or female subjects ≥18 years of whom at least 80% were to be between 18 and 60 years of age
- Diagnosed with celiac disease by a physician
- Diagnosis based on upper endoscopy and biopsy and/or anti-tissue TransGlutaminase (anti-tTG) positivity
- Diagnosed at least 3 months prior
- No concomitant GI disease: peptic ulcer, ulcerative colitis, Crohn's disease, irritable bowel syndrome, gastroesophageal reflux disease (GERD)
- Not participating in a clinical trial at the time of this study

Additionally, screeners were asked to recruit as racially diverse a patient population as possible.

Patient Interviews

Two interviewers experienced in conducting individual patient interviews and focus groups, met with 21 patients who fulfilled the screening criteria and were willing and available to participate. Interviews were conducted in Raleigh, NC and Chicago, IL in October 2007. All subjects signed informed consent prior to the interview. All study materials were reviewed and approved in advance by RTI's Institutional Review Board.

Each interview was performed in two stages:

(1) An open-ended section: subject described all experiences with celiac disease, including symptoms and their impact (see Script 1 on handout).

(2) A "cognitive debriefing" of the GSRS: in response to a set of questions from the interviewer, with follow-up questions or "directed probes," the subject explained what each question meant to him/her, and detailed the relevance and relative importance of each item within his/her personal experience of celiac disease (see Script 2 on handout).

Recording of Patient Interviews

- Interviews were recorded and transcribed; transcriptions were verified through an iterative process of technical and editorial review.
- All responses reported here were verbatim responses provided by interview participants (i.e., the words in the poster ascribed to participants were the words used by the participants). No changes to participant responses were made.

RESULTS

Table 1 describes the interview participants and demonstrates that the screening criteria selected patients with proven celiac disease.

Table 1. Demographics and Screening Criteria of Interview Participants

Characteristic	n (%)
Gender	
Female	16 (76%)
Male	5 (24%)
Age	
Mean (range)	44.6 (20-73)
Race/Ethnicity	
White	20 (95%)
Bi-racial (African-American and white)	1 (5%)
Education	
High school	1(5%)
Some college	2 (10%)
College graduate	12 (57%)
Postgraduate	6 (29%)
Diagnosis by a physician	**21 (100%)**
Diagnosis confirmed with biopsy via upper endoscopy	20 (95%)
Diagnosis confirmed with serum antibody histology test	17 (81%)
Time since diagnosis	
Less than 1 year ago	2 (10%)
Between 1 and 2 years ago	7 (33%)
Between 2 and 5 years ago	4 (19%)
Between 5 and 10 years ago	1 (5%)
10 or more years ago	7 (33%)
Time experiencing celiac disease symptoms	
Mean	
(range)	13.6 years
(1 year and 7 months - 42 years)	
GI comorbidities	
(i.e., peptic ulcer, ulcerative colitis, Crohn's disease, IBS, GERD or acid reflux disease)	0 (0%)
Current participation in clinical trials	**0 (0%)**

IBS = irritable bowel syndrome.

Open-Ended Interviews

The interviews revealed the following:

- A wide range of items of concern with significant variability across participants.
- Twenty of 21 subjects reported having GI symptoms prior to diagnosis and adoption of a gluten-free diet.
- All 21 subjects indicated that they now were likely to develop GI symptoms following gluten exposure.

The number of participants who reported various items of concern is summarized in Table 2.

Table 2. Number of Participants Reporting Items of Concern[a]

Item of Concern	N = 21 n (%)
Diarrhea/loose stools	16 (76.2)
Bloating, gas, pressure, burping/belching, flatulence	12 (57.1)
Fatigue/exhaustion/lethargy	12 (57.1)
Weight loss	12 (57.1)
Anemia/low iron	10 (47.6)
Abdominal/stomach pain; cramping	10 (47.6)
Constipation	10 (47.6)
Nausea/vomiting	9 (42.9)
Excessive illness: viruses, infections, bronchitis, sinusitis, seasonal allergies, etc.	9 (42.9)
Headaches/migraines	8 (38.1)
"Brain fog,"(described as difficulty with normal thought processes); concentration or attention problems	8 (38.1)
Blurred, reduced, or impaired eyesight	6 (28.6)
Skin symptoms: itching, rash, dermatitis herpetiformis, eczema, psoriasis, dry patchy skin or lips, etc.	6 (28.6)
Irritability, moodiness	5 (23.8)
Stools/gas with strong odor	5 (23.8)
Sleep problems: interrupted, insomnia, or too much sleep	5 (23.8)
Cramping, stiffness, or pain in extremities or joints	4 (19.0)
Hunger/gnawing hunger pains	3 (14.3)
Osteoporosis/osteopenia	3 (14.3)
Oral symptoms: mouth ulcers, teeth enamel problems	2 (9.5)
Depression, "blues"	2 (9.5)
Dizziness/vertigo	2 (9.5)
Hair loss	1 (4.8)
Edema	1 (4.8)

[a]All items of concern were verbatim reports.

Table 2 shows the following:

- The items of concern expressed were highly variable and covered almost all items reported in the literature as expressed by patients with celiac disease[12] (infertility and still births, sometimes mentioned in the literature, were not mentioned).
- These findings confirm the protean manifestations of celiac disease and are representative of the general celiac population.
- GI symptoms (e.g., diarrhea, bloating, gas) were reported by the greatest number of participants. Following GI symptoms, fatigue and weight loss were reported by the greatest number of participants.

Additionally,

- Over half of all participants indicated that items such as excessive illnesses (e.g., colds, flu), "brain fog," fatigue, anemia, weight loss, vision problems, sleep problems, osteopenia, and depression would only be relevant among newly diagnosed patients or patients who have difficulty maintaining a gluten-free diet.
- Around a quarter of participants explained that they thought many of these symptoms were largely related to malnutrition due to chronic gluten exposure. This was done by recall (an often lengthy period prior to diagnosis).
- For participants considering themselves "well-controlled," GI symptoms, which they attributed to accidental ingestion of gluten, were clearly considered the most relevant.
- Twenty of the 21 participants stated that GI symptoms would be the first to appear if they accidentally ingested gluten (most commonly bloating/gas, abdominal pain/discomfort, diarrhea, or vomiting) and that these symptoms would develop within a matter of minutes or hours.
- For two-thirds of participants, even ingesting minute amounts of gluten would be sufficient to bring on GI symptoms.
- Almost three-quarters reported experiencing non-GI symptoms (e.g. lethargy, mild depression, illnesses [colds, flu, etc.] itching) prior to following a gluten-free diet.
- While the majority of participants said that they would not suffer any additional ill effects due to accidental gluten exposure, a small minority reported that accidental gluten exposure could cause non-GI symptoms, such as headaches/migraines, fatigue, or irritability/moodiness, generally AFTER the onset of GI symptoms.

GSRS Cognitive Debriefing

Subjects rated the relevance and importance of each of the 15 GSRS items using the following scale:

0 = Totally irrelevant

1 = Relevant but not important

2 = Moderately important

3 = Very important

Higher scores indicate greater severity.

Results from this rating task are summarized in Table 3. To facilitate interpretation, the topics covered by GSRS items are arranged in order of importance to participants, and the average rating for each item related to that topic is provided.

Table 3. Importance Ratings for GSRS Questions

Item	GSRS Question No.	Average Ranking Mean (Median)
Diarrhea	11	2.73 (3)
Bloating	7	2.65 (3)
Passing gas or flatus	9	2.63 (3)
Pain or discomfort in the upper abdomen/pit of stomach	1	2.55 (3)
Constipation	10	2.55 (3)
Urgent need to have a bowel movement	14	2.43 (3)
Loose stools	12	2.33 (3)
Sensation of not completely emptying bowel	15	2.33 (3)
Nausea	5	2.25 (3)
Hard stools	13	1.78 (3)
Acid reflux	3	1.58 (2)
Burping	8	1.48 (1)
Rumbling in the stomach	6	1.43 (1)
Heartburn	2	1.33 (1)
Hunger pains	4	1.28 (2)

Results confirmed the following impressions from the open-ended interviews:

- Lower GI symptoms were among the most important concerns, reflected by responses to Questions 1, 3, 5, 7, 9, 10, 11, 12, 13, 14, and 15.
- Upper GI symptoms, reflected by responses to Questions 2, 4, 6, and 8, were less relevant.
- Participants reported diarrhea, loose stools, and constipation.

CONCLUSIONS

1. **Celiac disease was diagnosed by a physician for all participants; in 20 of 21 participants, celiac disease was diagnosed by upper endoscopy and biopsy.**
2. **Open-ended interviews showed a wide variability in items of concern. This range is consistent with the literature and clinical consensus.**
3. **Almost all subjects reported that GI symptoms would be the first to appear on accidental ingestion of gluten.**
4. **Cognitive debriefing interviews confirmed and extended the results of open-ended interviews.**
5. **Eleven of 15 questions in the GSRS were reported as relevant and applicable to the participants' experience of celiac disease, while 4 questions relating to burping, stomach rumbling, heartburn, and hunger pains were described as the least relevant.**
6. **The results support the face and content validity of the GSRS for use in clinical trials of celiac disease; however, the GSRS does not contain all items of concern reported by participants.**

These results suggest that relevant subscales of the GSRS may be used in clinical trials of novel treatments for celiac disease. Further work on validating relevant subscales of the GSRS in this population or development of a new instrument addressing all the items of concern according to the FDA guidance on PRO development may be considered.

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