A Validated Disease-Specific Symptom Index for Adults With Celiac Disease

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BACKGROUND & AIMS: Although the incidence of celiac disease (CD) is increasing, studies have been hampered by the lack of validated outcome measures. We sought to create a disease-specific Celiac Symptom Index (CSI) to reliably assess relevant symptoms. **METHODS:** A 36-item questionnaire was created after design by an expert committee and review/revision by patient focus groups. The survey, covering domains of CD-related symptoms and general health, was initially administered to 154 individuals with biopsy-proven CD; immunoglobulin (Ig)A tissue transglutaminase titers were determined, and gluten-free diet adherence was evaluated by a dietitian. The questionnaire was then revised to exclude questions with poor test characteristics and administered to a second, independent group of 52 individuals, to ensure validity. **RESULTS:** The subscales of "specific symptoms" and "general health" had excellent psychometric qualities that consisted of 11 and 5 items, respectively. The additive score based on these items was correlated with current general health, as measured by a visual analog scale and short form 36 general health subscale ($P \leq .001$ for both), as well as degree of adherence to the gluten-free diet ($P = .008$), lending external validity to the CSI. The resulting 16 questions make up the first CD-specific symptom index. **CONCLUSIONS: The CSI allows for disease-specific monitoring of symptoms as an independent outcome measure or as part of a surrogate for disease activity in individuals with CD. The CSI might be an important tool for future clinical CD research.**

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Celiac disease (CD) is an increasingly important clinical ailment with a prevalence of between 1:250 and 1:67 in many populations.[1–5] The number of patients diagnosed with CD has rapidly increased due largely to greater clinical awareness and improvement in diagnostic modalities.[6] Currently, the only accepted treatment for CD is lifelong adherence to a strict gluten-free diet (GFD). Gluten avoidance has been shown to lead to improvement in the majority of related problems including osteoporosis/osteopenia,[7] anemia,[8] risk of malignancy,[9] gastrointestinal symptoms,[8] and in some studies, quality of life.[10–13] Although the majority of patients do quite well with a GFD, treatment is burdensome in terms of increased cost,[14] reduced nutritional value,[15] and social constraint.[16–18] Further, it is clear that adherence to the GFD is imperfect, with 20% to 50% of patients not sustaining dietary restriction.[19,20] The result of this is that the leading cause of nonresponsive CD, estimated to occur in 10%–30% of celiac patients, is persistent gluten exposure.[21,22]

The combination of an increasing patient population and the recognition that dietary restriction is not completely efficacious in a significant percentage of individuals with CD is driving clinical research and, in particular, the search for novel nondietary therapeutic modalities. Studies to date investigating either maintenance of disease remission with gluten challenge or induction of remission in nonresponsive patients have been hampered by the lack of a widely accepted outcome measure other than intestinal biopsy, which is severely limited by expense, invasiveness, and potential sampling variability.[23–25]

For many gastrointestinal diseases, it is symptomatology which drives therapy and provides the foundation of validated activity indices such as the Crohn's Disease Activity Index,[26] the gastroesophageal reflux disease Impact Scale,[27] or the Gastrointestinal Symptom Rating Scale (GSRS).[28] These tools are of proven value in clinical research and allow clinicians to compare patient populations and objectively assess outcomes in a standardized fashion.

It is widely recognized that CD has a unique symptom profile distinct from those of other gastrointestinal disorders, such as inflammatory bowel disease or irritable bowel syndrome. For example, potential manifestations of CD are quite diverse and symptoms, such as fatigue can be severe in the absence of localizing symptoms, such as diarrhea or abdominal pain. Although there is certainly some degree of overlap, it is likely that "off the shelf" tools created for use in another disorder will have limitations when applied to CD. For instance, the GSRS, which has been used most often in CD, includes 5 domains: abdominal discomfort, diarrhea, indigestion, constipation, and reflux. It would be expected that, for the typical patient with CD, abdominal discomfort and diarrhea will improve with treatment, while typically constipation worsens (due to improved absorption and low fiber content of the GFD[15]), and reflux is unchanged. Indeed, this exact pattern was seen in a recent clinical trial in CD. Although a true validation study of the GSRS in CD has not been described, the inclusion of unrelated and divergent domains likely detracts from the reliability of this instrument in CD. This may be 1 reason why there has been disparity between and within studies using these measures.[10,29]

Abbreviations used in this paper: BIDMC, Beth Israel Deaconess Medical Center; CD, celiac disease; CSI, Celiac Symptom Index; EQ-5D, Euroqol-5D; GFD, gluten-free diet; GSRS, Gastrointestinal Symptom Rating Scale; IgA, immunoglobulin A; SF, short form; tTG, tissue transglutaminase.

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Due to the limitations of existing symptom assessment tools, we hypothesized that a CD-specific symptom index would cover a spectrum of symptoms distinct from existing surveys. In this paper we describe the creation and initial validation of the Celiac Symptom Index (CSI). We anticipate that the CSI will be an important new tool in the accurate measurement of clinical status in patients with CD.

Methods

Outline of Study Methods

In the development of the CSI, standard survey techniques were utilized as discussed in detail below. Items were derived by an expert panel and submitted to evaluation and revision by sequential focus groups. In the initial cohort, we then evaluated test-retest reliability It is expected that item responses should change minimally over a short time frame such as 1 week. Items that show low reliability (low Pearson product-moment correlation coefficient) are suggestive of random answering by participants and generally unsuitable. Next, individual items were evaluated for appropriate response spread across the response choices. Items for which participants almost always chose the highest answer (ceiling effect) or the lowest answer (floor effect) do not allow for discrimination between individuals and are thus typically removed. Item-total correlation allows evaluation for item redundancy (eg, fatigue and low energy level), and is related to the Cronbach α statistic, which is used to assess domain groupings with higher numbers suggesting a closer relationship between questions. High Cronbach α results are generally reassuring for surveys that address a specific issue, for example, gastrointestinal symptoms. The final step in the development of the CSI was principal component analysis, a test related to factor analysis which is used to confirm domain groupings.[30]

Initial Questionnaire Design

Our first step in creating the CSI was the assembly of an expert panel consisting of gastroenterologists, dieticians, psychologists, and individuals with CD to discuss the symptoms central to CD. Over a series of meetings, questions eliciting specific symptoms were created and segregated into distinct domains. From these domains, a bank of items was developed which was felt to be representative of the areas in question.

Next, 2 sequential focus groups of individuals with CD were held. During these, the domains decided upon by the expert panel were discussed and the derived items were presented. The focus groups clarified question intent and added items in areas felt to be deficient. In order to achieve saturation, or nearly complete coverage of relevant symptoms, any item suggested by an individual in 1 of the focus groups was added to the initial derivation questionnaire. The final question bank consisted of a 17-question demographics section, and 36 questions making up the initial CSI. The 36 questions were divided into 2 domains; (1) CD-related symptoms (28 items); and (2) general health (8 items).

First Validation Study

This 36-question survey was administered to an initial group of 154 individuals with biopsy-proven CD. Advertisements for the study were placed in regional CD support group publications, and individuals with biopsy-proven CD visiting the skilled celiac dietician at our institution were sent targeted invitations.

Individuals were asked to complete a 3-day food record prior to assessment. During the research visit, participants would complete the questionnaire, have blood drawn for immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody titer, and undergo evaluation for gluten exposure by a highly skilled dietician with over 10 years of experience working with CD.

The nutritional evaluation was done in a standardized fashion as we have previously described using analysis of 3-day food records, a food ingredient quiz, and a dynamic interview.[31,32] Global GFD adherence was recorded on a 6-point Likert scale ranging from 1 ("excellent adherence: consuming gluten less than 3 times per year") to 6 ("not currently following a gluten - free diet") (Supplementary Table 1). Analysis of tTG titers was done by enzyme-linked immunosorbent assay (ELISA) with recombinant human antigen (INOVA Quanta Lite human-tTG IgA, San Diego, CA; sensitivity 94%, specificity 99%).

Test-Retest Reliability

A subset of 32 participants completed the initial questionnaire a second time 1 week after the initial appointment and returned it by mail. These were used to calculate test-retest reliability using Pearson product-moment correlation coefficients. Domains were considered stable over time with Pearson product-moment correlation coefficients >0.60. The final selection of items was correlated with the standard health status instruments, short form (SF) 36 general health subscore, and Euroqol-5D (EQ-5D) visual analog scale to insure the relevance of the items to health status. Items not correlated with these instruments were excluded from the questionnaire.

Second Validation Study

For questions that showed adequate reliability, item-total correlations within expected domains were calculated. Items with $r < 0.40$ were discarded and the Cronbach α calculated. Domain groupings were considered valid with an α of $>$ 0.70. Interitem correlation was also assessed at this time and items with a correlation of > 0.70 were considered redundant. In these cases, the item less well correlated with the SF-36 general health subscore and EQ-5D visual analog scale was discarded. Finally, the revised CSI, consisting of 16 questions (Supplementary Table 2) was administered to 52 additional subjects who underwent dietician evaluation identical to the initial cohort.

Overall symptom scores were calculated in a simple additive fashion with higher scores denoting more severe symptoms. Correlation of CSI score with demographic factors, dietician evaluation, and quality of life scores was assessed using the Fisher exact test, and Pearson and Spearman correlations. Statistical analysis was completed using SPSS for Windows (Rel. 13.0. 2004; SPSS Inc, Chicago, IL).

This study was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations.

Results

Study Population

The demographic characteristics of the initial study population and the validation cohort were not significantly different than that of the overall CD population seen at Beth