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ORIGINAL ARTICLE

Psychosocial Factors Are More Important Than Disease Activity in Determining Gastrointestinal Symptoms and Health Status in Adults at a Celiac Disease Referral Center

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Abstract
Background The relative effects of clinical and psychosocial variables on outcome in celiac disease (CD) has not previously been reported. In adult patients with (CD), we studied the relationships among demographics, psychosocial factors, and disease activity with health-related quality of life (HRQOL), health care utilization, and symptoms.
Methods Among 101 adults newly referred to a tertiary care center with biopsy-proven CD we assessed: (a) demographic factors and diet status; (b) disease measures (Marsh score, tissue transglutaminase antibody (tTG) level, weight change and additional blood studies); and (c) Psychosocial status (psychological distress, life stress, abuse history, and coping). Multivariate analyses were performed to predict HRQOL, daily function, self-reported health, number of physician visits, and GI symptoms (pain and diarrhea).
Results Impaired HRQOL and daily function was associated with psychological distress and poorer coping. Self-report of poorer health was associated with poorer coping, longer symptom duration, lower education, and greater weight loss. More physician visits were associated with poorer coping, abnormal tTG levels, and milder Marsh classification. Greater pain scores were seen in those with higher psychological distress and greater weight loss. Finally, diarrhea was associated with greater psychological distress and poorer coping.
Conclusions In patients presenting to a CD referral center, psychosocial factors more strongly affect health status and GI symptoms than disease measures.

Keywords Celiac · Disease · Illness · Outcomes · Psychological

Abbreviations

BMI	Body mass index
BSI	Brief symptom inventory
BSS	Bristol stool scale
CD	Celiac disease
CSQ	Coping strategies questionnaire
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-QOL	Irritable bowel syndrome quality of life scale
LES	Life experiences survey
PHQ	Physician health questionnaire

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SIP	Sickness impact profile
tTG	Tissue transglutaminase antibody
VAS	Visual analog scale

Background

There is considerable heterogeneity in the clinical features of celiac disease (CD) [1]. Disease manifestations (i.e., the observable evidence of structural abnormalities) range widely from normal small-bowel architecture to complete villous atrophy, and from normal blood counts and bone mineralization to anemia and osteoporosis [2]. Illness severity (i.e., the individual's symptoms and subjective assessment of health) is also quite variable; patients with "atypical" celiac disease lack bowel symptoms, whereas those with "classical" celiac disease experience diarrhea, bloating, and, at times, abdominal pain [3].

While it is presumed that the degree of disease activity directly correlates with both symptoms and health status, clinical observations suggest that this is not necessarily true. Our group and others have demonstrated that the severity and extent of underlying villous atrophy do not correlate with clinical presentation [4, 5]. Likewise, in our referral practice we frequently observe patients who despite mild histologic small-bowel injury, report severe symptoms and frequently seek health care. Thus, it is possible that in celiac disease the disease activity does not always relate to the degree of illness severity, and vice versa.

This "disconnect" between disease activity and illness severity/health status may be explained by psychosocial factors, which in other gastrointestinal conditions such as inflammatory bowel disease and irritable bowel syndrome (IBS) predict health care utilization, disability, and health-related quality of life [6, 7]. If the same holds true for celiac disease, then patients with this condition may be better managed using a biopsychosocial approach that considers both biological (i.e., disease) and psychosocial factors [8].

The primary aim of this study was to determine the possible relationships among demographic factors, psychosocial factors (psychological symptoms, coping, abuse, and life events), and measures of disease activity (biological markers) in predicting gastrointestinal symptoms and health status (health-related quality of life and health care utilization) in celiac disease (Fig. 1). We hypothesized that, among patients seen in our tertiary care referral center, psychosocial factors would be the strongest predictors of health status, as well as gastrointestinal symptoms.

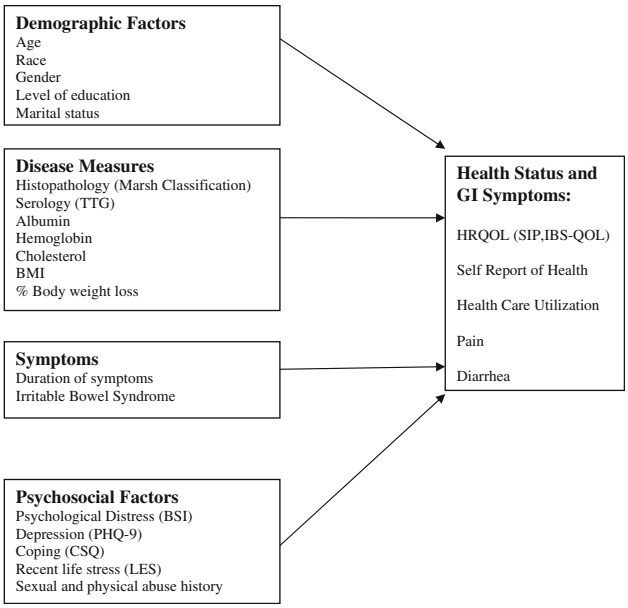

Fig. 1 Overview of model for analyzing the relationships among demographic factors, psychosocial factors, and disease measures with gastrointestinal symptoms and health status (see text for details)

Methods

Study Subjects

We studied consecutively 101 adults (≥18 years old) who were newly self- or physician-referred for the management celiac disease to the Columbia University Celiac Disease Center between January 2006 and January 2009. All had biopsy proven celiac disease (confirmed by expert review of prior and/or current histopathology) and most had moderate to severe symptoms and/or disease-related consequences. Patients with evidence for other structural GI diseases (e.g., IBD, recurrent small-bowel obstruction, neoplasia, chronic pancreatitis, gastrectomy, or bowel resection) or who were referred for screening based only on a positive family history (i.e., otherwise asymptomatic with normal laboratory tests) were excluded. The study was approved by the Institutional Review Boards of both Columbia University (site of patient recruitment and assessment) and the University of North Carolina at Chapel Hill (site of data management and analysis).

Clinical Assessment

At initial presentation, subjects who agreed to participate either released histopathologic results of prior duodenal biopsies or underwent a subsequent endoscopy with duodenal biopsies. All patients underwent a standardized health care provider assessment and laboratory testing (including IgA tissue transglutaminase levels (tTG)

antibody unless recent results were available), and completed a series of psychosocial questionnaires. The following data were obtained from all patients.

Demographic Factors

1. The *Demographic Medical Questionnaire* has been used by the UNC group in its NIH treatment trial and in other studies [9]. The questions address baseline demographic features (*age*, *race*, *gender*, *educational level*, *marital status*, *and health care utilization*) gastrointestinal symptoms (including *diarrhea*, *pain*, and the Rome III Modular Questionnaire), and other background variables of interest as related to the study aims.

Disease Measures

i. *IgA tissue transglutaminase antibody titer (tTG)* was measured using direct enzyme-linked immunosorbent assay (ELISA). tTG titer levels correlate with the levels of intestinal injury [10, 11]. While the majority of tTG levels were obtained from a single laboratory, four total laboratories were used. Because different laboratories used different scales for standardization all analyses of tTG levels were dichotomized into normal versus abnormal.
ii. *Routine blood studies* including *hemoglobin*, *total cholesterol*, *and albumin*, which can be used to assess malabsorption of iron, fats and protein, respectively, were measured by standard automated lab techniques.
iii. *Histopathology for diagnosis and classification* was obtained from duodenal biopsies from the most recent or post enrollment endoscopies that were reviewed by a Columbia Presbyterian Medical Center attending pathologist together with one of the authors, a gastroenterologist (PG) and classified based on *Marsh Criteria* [2, 5]. This is a direct measure of the degree of intestinal damage and is classified as *Type I*, *II*, *III and IV* in increasing order of disease severity. For all analyses, Marsh scores were dichotomized into mild/moderate (Marsh I, II, IIIa) correlating with normal villous architecture with intraepithelial lymphocytosis to partial villous atrophy or severe (Marsh IIIb, IIIc), correlating with subtotal or total villous atrophy.
iv. *Body mass index measurement (BMI)* was calculated from the patient's *height* and *weight* that was measured by a study nurse. A low BMI may be the result of intestinal malabsorption.

Symptoms

i. *Health care provider assessment*: The health care provider identified the predominant clinical presentation of the celiac disease, either *classical* (i.e., with GI symptoms) or *atypical* (without GI symptoms but possibly with other disease manifestations), determined the *duration of symptoms* and ascertained the patient reported *degree of weight loss* over the prior 3 months and from a baseline that preceded gastrointestinal symptoms (if any) or the celiac diagnosis [12].

Psychosocial Assessment

i. *Brief Symptom Inventory (BSI-18)*: This 18-item questionnaire commonly used in research of patients with gastrointestinal disorders was used to quantify overall psychological distress [13]. For each question, responses ranged from 0 (not at all) to 18 (extremely). The scores were summed to derive a general severity index (GSI), the most sensitive indicator of the respondent's overall distress level. Subjects with GSI scores greater than 59 are considered to have significant psychological distress.
ii. *Patient Health Questionnaire (PHQ-9)*: a nine-item scale that measures depressive symptoms and functional impairment [14].
iii. *Coping Strategies Questionnaire (CSQ)*: The six-item Catastrophizing subscale and two questions related to the patient's ability to control or reduce symptoms were used to assess coping style [15]. We have found this brief questionnaire to be strongly predictive of pain symptoms, health status, and 1-year health outcome of our gastroenterology patients.
iv. *Life Experiences Survey (LES)*: a 50-item questionnaire that assesses both negative and positive life stress experienced over the past 6 months [16].
v. *Abuse Severity Questionnaire*: This 13-item questionnaire has been used for survey and screening purposes in our previous studies and has been validated to the Structured Abuse and Trauma Interview [17].

Outcome Assessment

i. *Sickness Impact Profile (SIP)*: a 136-item generic measure of health-related functional status. Items are group into 12 categories; each category relates to an aspect of daily living. Summary scores for *Physical subscale (three categories)*, *Psychosocial subscale (four categories)* and Overall score (all 12 categories) are calculated [18]. Notably, there is a high degree of overlap between the psychosocial questionnaires that were utilized and the SIP Psychosocial subscale. Therefore, for all analyses, the four categories in the Psychosocial subscale were excluded, leaving the overall score to include the remaining eight categories.

Based on a prior study, we considered SIP scores ≥ 2.75 to represent significant functional impairment [19].

ii. *IBS quality of life (IBS-QOL)*: This 34-item item validated, condition specific measure of health-related quality of life for IBS [20]. Due to the fact that a celiac disease-specific instrument did not yet exist when the study was started, the IBS-QOL was used to assess gastrointestinal symptom-related health status for subjects with celiac disease.

iii. *Self-Report of Health*: at study entry each subject was asked, "In general, how would you describe your health?" Responses fell along a five-point Likert scale that included: excellent, very good, good, fair, or poor.

iv. *Health Care Utilization Questionnaire*. This questionnaire, which has also been used previously in IBS research [21], assessed the *number of health care visits*, number of days spent in bed, number of telephone calls to health care providers, the number of hospitalizations (medical and psychiatric) and surgeries, the type and number of medications taken, and the type of diagnostic procedures performed. The time frame for most questions is within the previous 3 or 6 months, a time frame that ensures reliability.

v. *Pain:* subjects were asked to rate their daily level of abdominal pain using a Visual Analog Scale (VAS) (100 mm; 0 = "none", 100 = "very severe"). The daily scores averaged over 2 weeks were used to calculate an overall (2-week) average daily pain score.

vi. *Diarrhea*: using the Rome III Modular Questionnaire, subjects were asked whether over the prior 3 months they had either hard or lumpy (Bristol Stool Scale types 1 or 2) or loose and/or watery stool (Bristol Stool Scale types 6 or 7) over 25% of the time. Diarrhea alone was defined as loose and/or watery stool $\geq$ 25% of the time and hard and/or lumpy stool $\leq$ 25% of the time [22]. We also identified a group with diarrhea mixed with constipation (i.e., loose and/or watery stool $\geq$ 25% of the time and hard and/or lumpy stool $\geq$ 25% of the time).

Data Analysis

Statistical Analyses

We developed regression models to determine associations between independent variables (demographics, psychosocial factors, disease severity measures) with the following outcomes: (1) SIP (score <2.75 vs. ≥ 2.75 [19]) (logistic regression); (2) IBS-QOL (linear regression); (3) self-report of health (linear regression); (4) health care utilization (≤ 1 vs. ≥ 2 physician visits for gastrointestinal problems over prior 6 months) (logistic regression); (5) pain (repeated measures linear regression); and (6) diarrhea (yes or no) (logistic regression). First, we performed bivariate analyses (correlations, *t* tests, or Chi square tests depending on the type of variables) between the independent variables and outcome variables. Second, we chose those independent variables that were associated with the outcome ($p < 0.2$) for entry into the regression model. If the number of significantly associated variables exceeded the capacity of the model (based on sample size), we chose variables based on both the relative strength of their association and the following pre-specified hierarchy of variable importance: (1) demographic factors; (2) life stress and abuse; (3) disease based measures; and (4) overall psychological symptoms, catastrophizing and depression. Third, we ran each model. Finally, any independent variable that did not appear to be strongly associated with the outcome was removed from the model, and likelihood ratio tests were used to compare the new "reduced" model to both the prior model and original model.

Eighteen percent of the tTG levels were determined more than 3 months prior to the clinical assessment. Because tTG levels can change over time, we first analyzed the data with all tTG samples and then repeated the analyses using only those with samples obtained within 3 months. There were no differences in the findings for all analyses with one exception (prediction of diarrhea). Therefore the results presented below are for the entire set of tTG samples unless otherwise indicated.

Results

Demographic, Disease, Psychosocial, and Clinical Features

A total of 136 subjects were approached to participate. Twenty-four patients did not meet inclusion criteria and 11 declined to participate due to time constraints. Thus, a total of 101 subjects participated. The characteristics of the study population are presented in Table 1. At the time of the study, 19 patients had Marsh I and Marsh II pathology. Among these subjects, at diagnosis two had Marsh II (both also had elevated tTG serology), six had Marsh IIIa, four Marsh IIIb, and two Marsh IIIc disease. For the remaining five patients, we could not ascertain histopathology results from the time of diagnosis.

For patients with negative tTG and ongoing symptoms, additional tests were performed when indicated. These revealed microscopic colitis (two subjects), non-specific proctitis (one subject), and small-intestinal bacterial overgrowth (one subject). Subjects were not assessed for

Table 1 Descriptive statistics ($n = 101$)

Demographic features	
Age (mean, SD)	41 (14.8)
Race	
Caucasian	90.1%
African American	2.0%
Hispanic	6.9%
Other	1.0%
Female	69.3%
Education level (mean, SD)	16.9 years (2.5)
Married	55.4%
Disease-based measures	
Marsh diagnosis	
Marsh I	5.9%
Marsh II	12.9%
Marsh IIIa	44.6%
Marsh IIIb	26.7%
Marsh IIIc	9.9%
tTG (% abnormal)	28.7%
Albumin (mean, SD)	4.3 (0.4) g/dl
Hemoglobin (mean, SD)	13.4 (1.6) g/dl
Cholesterol (mean, SD)	174 (36.0) mg/dl
BMI	
% Weight loss in past 3 months	1.8% (3.0%)
Physician classification	
Classical [% with IBS 65.3%]	79.2%
Atypical [% with IBS 30.0%]	19.8%
Symptoms	
Duration of symptoms (mean)	10.5 years
Gluten-free diet	83.2%
Pain (VAS 0–100 range) (mean, SD)	18 (16)
Diarrhea	40%
Diarrhea alone	37%
Diarrhea with constipation	3%
Irritable bowel syndrome	58.4%
	Of those with IBS:
IBS-C	18.7%
IBS-D	47.5%
IBS-M	5.1%
IBS-U	28.8%
Psychosocial factors	
Recent life stress [LES mean negative items (SD)]	3.5 (8.1)
% Abuse (any)	21.8
Psychological symptoms (BSI) (mean, SD)	53.2 (10.1)
% with significant psychological distress (BSI)	31.6
Depression (PHQ-9) (mean, SD)	1.3 (4.3)
% with minor or major depression (PHQ-9)	8.0
Coping (CSQ)	
Catastrophizing sum score	5.1 (6.6)
Degree of control over symptoms	4.0 (1.5)
Ability to decrease symptoms	3.6 (1.6)
IBS-QOL (mean, SD)	81.4 (18.3)
SIP (mean, SD)	
Overall excluding psychosocial dimension	4.6 (5.4)
% Impairment (>2.75)	49.5
Self-rating of health	
Poor	4.0%
Fair	14.9%
Good	41.6%
Very good	29.7%
Excellent	9.9%
Health care utilization: times seeking care gastrointestinal condition over prior 6 months	
≤1	63.5%
≥2	36.5%

lactose intolerance and none had previously been diagnosed with IBS.

Multivariate Analyses

As described, a series of regressions were performed to determine associations with the specified outcome measures described above. The results are summarized in Table 2 and individually discussed below.

Daily Function (Sickness Impact Profile: Table 2)

The final model showed a moderate effect, explaining 39% of the overall variance. All predictor variables were in the expected direction. Greater psychological distress (BSI) (OR = 1.1; 95%CI = 1.04–1.19) and a greater tendency to catastrophize (CSQ) (i.e., to view the illness in a pessimistic and negativistic manner) (OR = 1.21; 95%CI = 1.07–1.37) were associated with impaired daily functioning. Of note, earlier in the model no history of abuse and a shorter duration of disease were associated with poorer function, though these variables were eliminated in the final model.

Health-Related Quality of Life (IBS-QOL: Table 2)

The final model showed a strong effect, explaining 53% of the overall variance. All predictor variables were in the expected direction. As found with daily function, poorer health-related quality of life was best explained by greater catastrophizing ($\beta = -0.48$; $p < 0.0001$) and greater psychological distress ($\beta = -0.30$; $p = 0.001$). Initially, the presence of IBS was predictive of a lower IBS-QOL,

Table 2 Summary of multivariate analyses

$n = 101$	Label	SIP		IBSQOL		SR health		MD visits		VAS pain		Diarrhea	
		OR (95% CI)	*p* value	STB	*p* value	STB	*p* value	STB	*p* value	STB	*p* value	OR (95% CI)	*p* value
Demographics	Education (years in school)					0.20	0.01						
Disease	Marsh classification, mild versus severe							0.88	0.03				
	tTG: Normal versus Abnormal							−1.59	<.0001				
Symptoms	Weight Loss:% of body weight					−0.17	0.03			0.93	0.05		
	IBS (yes/no)			−0.11	0.18								
	Duration of symptoms (months)					−0.29	0.0005						
Psychosocial	Baseline BSI	1.1 (1.04,1.19)	0.003	−0.30	0.001					0.77	<.0001	1.05 (0.998, 1.15)	0.0580
	CSQ: Degree of control over symptoms											0.72 (0.51, 1.02)	0.0640
	CSQ: Ability to decrease symptoms					0.35	0.0002	−0.26	0.005	−1.83	0.05		
	CSQ: Catastrophizing sum score	1.21 (1.07, 1.37)	0.002	−0.48	<.0001	−0.22	0.02						
	R-square	0.39		0.53		0.44				0.45		0.14	

CI 95% confidence intervals, *OR* odds ratio, *95% STB* standardized beta coefficient, *CSQ* coping strategies questionnaire, *IBS* irritable bowel syndrome, *IBSQOL* IBS quality of life instrument, *SIP* sickness impact profile, *SR Health* self-reported health, *tTG* tissue transglutaminase antibody

though IBS was later eliminated from the final model since it was explained by the psychosocial variables.

Self-Reported Health (Table 2)

The final model showed moderate to strong effects, explaining 44% of the overall variance. Again, all predictor variables were in the expected direction with the strongest effects related to poor coping, that is, less perceived ability to decrease symptoms ($\beta = 0.35$; $p = 0.0002$) and greater catastrophizing ($\beta = -0.22$; $p = 0.02$). Additionally, a longer duration of GI symptoms ($\beta = -0.29$; $p = 0.0005$), lower educational attainment ($\beta = 0.20$; $p = 0.01$), and a greater weight loss ($\beta = -0.17$; $p = 0.03$) were associated with poorer self-rating of health. Of note, in the initial model, those with IBS had a lower self-report of health, though this variable was later eliminated from the final model, which was presumably due to the stronger effect of the psychosocial variables that were entered later.

Physician Visits (Table 2)

Those with abnormal tTG levels ($\beta = -1.59$; $p < 0.0001$) and milder Marsh scores ($\beta = 0.88$; $p = 0.03$) were significantly more likely to have sought treatment for their gastrointestinal condition at least twice over the prior 6 months. Additionally, those with less perceived ability to decrease symptoms ($\beta = -0.26$; $p = 0.005$) sought more physician visits.

Gastrointestinal Symptoms (Table 2)

The final model that predicted pain showed moderate to strong effects, explaining 45% of the overall variance with all predictor variables were in the expected direction. The strongest predictors for greater pain reporting were higher psychosocial distress ($\beta = 0.771$; $p < 0.0001$), decreased perceived ability to decrease symptoms ($\beta = -1.8$; $p = 0.05$), and greater percentage of weight loss ($\beta = 0.93$; $p = 0.05$).

The final model that predicted diarrhea showed minimal effects, explaining 14% of the overall variance. There were borderline significant effects for both decreased perceived ability to control symptoms (OR = 0.72; $p = 0.06$) and for psychological distress (BSI) OR 1.05; $p = 0.06$) to explain diarrhea.

Table 3 summarizes those factors predicting the various health status and symptom measures. At a glance, it is evident that disease factors, except for an abnormal tTG and a milder Marsh score being associated with more physician visits, were not predictive of the outcome measures. Conversely psychosocial measures, specifically psychological distress (BSI) and maladaptive coping

Table 3 Summary of results: factors predicting health status in celiac disease and symptom measures

Variable	Daily function (SIP) $R^2 = 0.39$	HRQOL (IBS-QOL) $R^2 = 0.53$	Health (self-report) $R^2 = 0.44$	MD visits	Pain (VAS) $R^2 = 0.45$	Diarrhea (Rome III) $R^2 = 0.14$
Demographic	O	O	+ Education	O	O	O
Disease						
Marsh (mild/severe)	O	O	O	++ (mild)	O	O
tTG	O	O	O	+++	O	O
Other blood work	O	O	O	O	O	O
Symptoms						
% wt. loss	O	O	+	O	++	O
Symptom duration	O	O	+++	O	O	O
Psychosocial						
Psychological distress	++	++	+++	O	+	±
Poor coping (CSQ)	++	+++	+	++	+	±
Abuse	O	O	O	O	O	O
Life stress	O	O	O	O	O	O

It is noted that psychosocial factors more than disease-related or clinical measures are significantly associated with the health status measures noted at the top. n 101

O = p-value > 0.1; ± = 0.1–0.5; + = 0.05–0.01; ++ = 0.01–0.001; +++ = <0.0001

(catastrophizing and decreased perceived ability to control symptoms), are most significantly associated with all the outcome measures.

Discussion

Within the practice of medicine, we often use the terms disease and illness synonymously. In actuality, these terms connote fundamentally different concepts. Disease describes dysfunction in the structure or function of body systems. It can be measured in the laboratory or by endoscopy. Illness is an individual's experience related to changes in states of being [23]. When evaluating patients with gastrointestinal disorders, we often see that the observable measures of disease and the patient's perception of ill health are dissociated. For example, patients with severe peptic ulcer disease or ulcerative colitis may have no symptoms until they present with gastrointestinal hemorrhage. Conversely, patients with Crohn's disease who have minimal disease activity or those with functional GI disorders who lack overt disease may have severe symptoms and marked disability. These observations led us to assess the biological and psychosocial factors that contribute to disease and illness among patients with celiac disease, and to determine their predictive effects on health status and symptoms.

Among 101 patients seen in a tertiary care celiac disease referral center, psychosocial factors strongly predicted health status: those with more psychological distress and/or poorer coping strategies had poorer daily function, health-related quality of life, and self-reported health, as well as greater healthcare utilization. In contrast, the disease-related factors were generally not associated with these outcome variables. In fact, milder, rather than more severe, disease activity as measured by the Marsh histopathological classification predicted more physician visits. We think it logical that those with abnormal tTG levels would have more physician visits since a major reason for referral to a celiac disease center would be the presence of gastrointestinal symptoms associated with an elevated tTG. These findings are notable and confirmatory for a biopsychosocial model of illness [8, 24] where the understanding of illness and disease is based on the integrated effects of biological and psychosocial processes.

Furthermore, we found that psychological distress—and not disease-based measures—was closely associated with pain and less so diarrhea. In fact, the significant influence of these gastrointestinal symptoms (e.g., IBS) on predicting health-related quality of life (Table 2) became no longer significant when the psychological variables entered the model, thus suggesting their stronger effect on HRQOL. This is consistent with recent findings that neither the severity [4] nor the extent [25] of underlying mucosal celiac disease explains the clinical features.

We believe that the inability of celiac disease measures to explain the various clinical outcomes studied reflects a change in the profile of patients seen in our health care system, especially at celiac disease referral centers. Over the last few decades, screening for this disease has increased dramatically, and today the majority of patients are seen prior to the development of the "classical" disease manifestations [26]. As a result, the pool of patients seen have milder disease, and thus the gastrointestinal

symptoms reported by the patients are not necessarily related to the malabsorption typically associated with "classical" celiac disease [27]. Instead, the patients are more likely to present with the common symptoms of IBS and other functional GI disorders and as seen in this study, these symptoms are closely associated with psychosocial influences. Indeed, clinicians seeing patients with a positive tTG or even a small-bowel biopsy for celiac disease need to be cautious in attributing the clinical presentation solely to the underlying disease without proper consideration of the concurrent psychosocial factors that affect the patient's health status. This may be even more relevant for patients who despite adherence to a gluten-free diet continue to have symptoms and seek health care at referral centers such as ours. Similarly, in a Boston referral center among patients on a strict gluten-free diet, the most common reason for refractory symptoms was IBS [28].

We might speculate that patients with celiac disease who report diarrhea and/or abdominal pain are more likely suffering from "celiac-IBS" much like "IBD-IBS," [7], which relates more to brain-gut dysregulation and/or abnormal serotonin activity than malabsorption [29]. Furthermore, as in post-infectious IBS [30] as well as IBD-IBS [31], these symptoms and behaviors are strongly influenced by psychosocial factors. In fact, in this referral-based population, over one-half of the patients met Rome III criteria for IBS and yet, almost 80% were considered to have "classic" celiac disease due to their IBS-like symptoms. This high prevalence exceeds a community-based estimate (23%) [32] and is close to referral population estimates for IBS [33, 34].

That psychological distress was a strong predictor of health status is consistent with data from Fera et al. [35], who reported that high anxiety and depression in celiac disease is associated with a decreased quality of life. Psychological distress was seen in one-third of our patients, and similar findings are reported in celiac practices in the USA and Italy [35–38] as well as with other medical disorders [8, 39]. Additionally, the important role of maladaptive cognition termed catastrophization (i.e., an exaggerated negative response to physical symptoms that is characterized by helplessness and pessimism) in determining health status has also been demonstrated across medical conditions in general [40] as well as for all gastrointestinal disorders [41]. It is also consistent with the way patients living with celiac disease conceptualize and cope with their disorder [42].

This study had several limitations. First, it was not possible to obtain repeat duodenal biopsies and tTG levels in a sub-group of patients at the time of study enrollment. Thus the values may not have accurately reflected the degree of underlying disease at the time of study entry. Therefore, we controlled for the age of the Marsh scores. We also performed a sub-analysis that only included patients whose tTG levels were obtained within 100 days of assessment. The reults were no different. We also recognize that Marsh severity may have varied depending on the extent of tissue sampling [43]. Second, the study enrolled patients with both newly developed and long-standing disease who were both on and off a gluten-free diet. Therefore, we controlled for duration of disease and the use of gluten-free diet. Third, as a cross-sectional study, we were able to establish association, not causation. Others have noted that within the first year of diagnosis there is a high prevalence of anxiety and depression [44], which in many patients improves with time [45]. While such "reactive" psychological symptoms are possible in our study population, the average duration of symptoms was over 10 years, and the vast majority of patients were already on a gluten-free diet. Finally, because our study included a highly select group of patients referral to a specialty center, the results may not applicable to patients seen in other clinical practices, patients who are diagnosed solely based on screening, or for those with celiac disease not seeking health care. However, by design we sought a group of patients who had persistent symptoms despite prior evaluations and therapy. That a high percentage of these patients had referred themselves to our clinic is in line with referral patterns to other specialized clinics within US tertiary care facilities. While studies are needed in other populations, our findings are applicable to those patients who clinicians, particularly at referral centers, treat for their ongoing symptoms.

These findings highlight the limits of the biomedical model and suggest greater utility from a biopsychosocial approach to patients with celiac disease [23]. For instance, some of the patients in this study had persistent symptoms and high health care utilization despite a gluten-free diet and negative serology. From a biomedical perspective, these patients are considered nonresponsive, and have no underlying mucosal disease to treat. Yet from the biopsychosocial perspective, successful treatment for these patients requires attention to the psychosocial distress, maladaptive coping, and a possible co-existing functional gastrointestinal disorder. In addition to a gluten-free diet, treatment may include [46], psychological support possibly to improve dietary compliance [36] and to also reduce psychological distress and improve coping skills, thus improving overall health status [9]. In addition, centrally acting pharmacologic agents, such as tricyclic antidepressants or selective serotonin norepinephrine reuptake inhibitors, may help in reducing the GI symptoms and psychological distress [47]. These potential treatment methods warrant further investigation for the treatment of CD.

In conclusion, this study demonstrated that in a US celiac disease referral population in which most patients

were already on a gluten-free diet, psychosocial factors more than disease-based measures predict a variety of health status measures, including daily functional status, quality of life, self-perception of health, and GI symptoms. These findings are consistent with emerging data relating the role of psychosocial factors in health status not only for functional GI disorders but also structural diseases like IBD and celiac disease. Understanding the disorder and its treatment is best served by a biopsychosocial approach.

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