ABSTRACT OF ORIGINAL RESEARCH ON COELIAC DISEASE

Disease Burden and Quality of Life Impacts in Patients With Celiac Disease on a Gluten-Free Diet: An Analysis of the iCureCeliac Registry

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Background

Celiac disease (CeD) is an immune-mediated disorder. CeD symptoms and other clinical manifestations are triggered by exposure to dietary gluten, which over time and with poor management can result in long-term health complications.

A gluten-free diet (GFD) is the only management option currently available to patients with CeD, and there is substantial heterogeneity in the clinical manifestations of CeD and in patients' response to a GFD.

Study Objective

To identify patient subgroups with distinct CeD symptom burden profiles and describe corresponding clinical characteristics, as well as the impact of CeD on quality of life (QoL), health status and work productivity, and the effectiveness of a GFD across subgroups.

Methods

Data source

The iCureCeliac® patient registry, hosted by the Celiac Disease Foundation, is the largest geographically diverse registry of US patients diagnosed with CeD and treated in CeD referral centers and community practices.

The registry contains data collected online from 2015 to present. Data collected during the period December 2015 to October 2019 are analyzed here.

Study design

This study was a cross-sectional analysis of iCureCeliac® patient registry data.

Patients were included in the analysis if they reported a biopsy-confirmed diagnosis of CeD and had complete Patient-Reported Outcomes Measurement Information System-Gastrointestinal Symptom (PROMIS-GI) and Celiac Symptom Index (CSI) questionnaire data.

Subgroup identification

Patient subgroups with distinct CeD-related symptom burden profiles (as measured by multiple domains in the PROMIS-GI and CSI questionnaires) were identified using latent class analysis (LCA).

LCA is a model-based clustering method that uses observed indicator variables to identify distinct unobserved patient clusters (i.e. latent classes) in a heterogeneous population, such that the resulting patient clusters are internally homogeneous with regard to their clinical profile and disease experience (e.g. CeD-related symptom burden profile), but distinct from other identified clusters.

The following indicator variables were included in the LCA model.

- ***Eight PROMIS-GI4 domains:*** belly pain, bowel incontinence, constipation, diarrhea, disrupted swallowing, gas and bloating, nausea and vomiting, and reflux – categorized into quintiles assigned values of 1 to 5 (higher values corresponding to higher severity).
- ***Categorical CSI5 score:*** total scores (range: 16–80) were assigned values of 1 to 3, where '1' indicates a low symptom burden (CSI score ≤ 30), '2' indicates a moderate symptom burden (31 ≤ CSI score ≤ 44) and '3' indicates a high symptom burden (CSI score ≥ 45).

Statistical analysis

Latent class analysis

The preliminary number of LCA-defined subgroups was determined using the Bayesian Information Criterion (BIC). The interpretability and meaningfulness of preliminary subgroups identified using this data-driven approach were evaluated, allowing determination of the optimal number of LCA-defined subgroups.

The LCA approach was then re-implemented using the same list of indicator variables, with the optimal number of LCA-defined subgroups pre-specified.

Description of variables

Variables of interest (e.g. demographics, clinical characteristics, QoL as measured by the Celiac Disease Quality Of Life Survey [CD-QOL],6 health status as measured by the RAND 36-item Short-Form Health Survey [SF-36]7 and self-reported adherence to a GFD) were described for the overall population and compared between LCA-defined subgroups.

Continuous variables were described using means and standard deviations (SDs), with analysis of variance (ANOVA) tests for comparisons between LCA-defined subgroups; categorical variables were described using frequencies and proportions, with chi-square tests for comparisons between patient subgroups.

Results

- Of 5,690 patients in the iCureCeliac® registry, 3,699 patients reported a biopsy-confirmed diagnosis of CeD. Of those 3,699 patients, 711 had complete PROMIS-GI data, and 1,351 patients had complete CSI data.
- In total, 376 patients had complete data for both scales and were included in this analysis.
- The LCA identified two distinct subgroups.
- Patients in subgroup 1 (52.4%) had lower PROMIS-GI domain and CSI scores, indicating a lower CeD symptom burden profile.
- Patients in subgroup 2 (47.6%) had higher PROMIS-GI domain and CSI scores, indicating a higher CeD symptom burden profile.
- Descriptive statistics for the indicator variables used in the LCA model are presented in Table 1.
- In the overall population (N = 376; Table 2), most patients were female (82.4%), mean (SD) age at CeD diagnosis was 35.7 (17.2) years and duration of CeD was 5.1 (6.9) years.
- Most patients (93.1%) reported always maintaining a strict GFD, despite almost half (47.3%) reporting CeD symptoms even with adherence to a strict GFD.
- In general, patient demographics were similar between LCA subgroups, and there were no differences in self-reported adherence to a GFD (p = 0.71; Table 2).
- Patients with higher CeD symptom burden generally had a shorter time to onset of symptoms after exposure to gluten (Table 2).

Table 1 –

Descriptive statistics for indicator variables used in the LCA model.

Table 1. Descriptive statistics for indicator variables used in the LCA model.

	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
PROMIS-GI				
Domain score, mean (SD)				
Belly pain[a]	50.7 (10.8)	43.6 (6.5)	58.5 (9.1)	< 0.001
Bowel incontinence[b]	4.7 (1.8)	4.2 (0.9)	5.3 (2.4)	< 0.001
Constipation[a]	49.3 (8.0)	46.4 (7.4)	52.5 (7.4)	< 0.001
Diarrhea[a]	49.7 (8.9)	45.0 (6.1)	54.8 (8.7)	< 0.001
Disrupted swallowing[a]	45.4 (7.0)	42.5 (4.4)	48.7 (8.0)	< 0.001
Gas and bloating[a]	52.9 (8.7)	47.5 (6.6)	58.9 (6.4)	< 0.001
Nausea and vomiting[a]	48.6 (7.5)	45.3 (4.7)	52.3 (8.2)	< 0.001
Reflux[a]	45.1 (7.9)	41.0 (5.8)	49.5 (7.6)	< 0.001
CSI[c]				
Total score, mean (SD)	36.9 (10.3)	30.4 (6.9)	44.0 (8.6)	< 0.001
Categorical score, n (%)				
Low burden (16 < CSI ≤ 30)	111 (29.5)	106 (53.8)	5 (2.8)	< 0.001
Moderate burden (31 ≤ CSI ≤ 44)	180 (47.9)	86 (43.7)	94 (52.5)	
High burden (45 ≤ CSI < 80)	85 (22.6)	5 (2.5)	80 (44.7)	

[a]T-score: mean (SD) of 50 (10) for the US general population (higher scores correspond to more of the concept being measured [i.e. higher severity]); [b]Summed score: score range 4–20 (higher scores correspond to more of the concept being measured [i.e. higher severity]); [c]CSI score range: 16–80 (higher scores denote more severe symptoms).
CeD, celiac disease; CSI, Celiac Symptom Index; LCA, latent class analysis; PROMIS-GI; Patient-Reported Outcomes Measurement Information System-Gastrointestinal Symptom; SD, standard deviation.

Compared with patients with a lower symptom burden, patients with a higher symptom burden:

- had a higher mean number of days per year absent from school or work owing to CeD (p < 0.05; Figure 1)
- were more likely to report CeD symptoms despite self-reported adherence to a GFD (p < 0.001) and were less likely to report a GFD as very effective for treating their most significant CeD symptoms (p < 0.001; Table 3)
- had a worse mean (SD) CD-QOL score – lower versus higher CeD symptom burden subgroups, 52.2 (13.4) versus 64.6 (14.5), respectively, p < 0.001 (overall, 58.1 [15.2]; lower scores correspond to better QoL)
- had a higher prevalence of CeD-related health conditions (p < 0.05 in all save one condition [seizure: p = 0.477; Figure 2]) and vitamin and mineral deficiencies (all p < 0.01; Figure 3)
- and had worse general health status as measured by the SF-36 (p < 0.001 in all domains; Figure 4).

Table 2 –

Patient demographic and CeD characteristics for the overall study population and LCA subgroups.

Table 2. Patient demographic and CeD characteristics for the overall study population and LCA subgroups.

Characteristic	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
Age, mean (SD), years				
At survey	40.9 (17.9)	40.0 (18.7)	41.9 (17.0)	0.301
At diagnosis	35.7 (17.2)	34.8 (18.3)	36.8 (15.9)	0.268
Gender, n (%)				
Female	310 (82.4)	154 (78.2)	156 (87.2)	0.067
Male	64 (17.0)	42 (21.3)	22 (12.3)	
Other/unknown	2 (0.5)	1 (0.5)	1 (0.6)	
Race, n (%)				
White	334 (88.8)	184 (93.4)	150 (83.8)	< 0.01
Hispanic	13 (3.5)	7 (3.6)	6 (3.4)	
Other	29 (7.7)	6 (3.0)	23 (12.8)	
Duration of disease, mean (SD), years	5.1 (6.9)	5.5 (7.9)	4.7 (5.5)	0.28
Time between self-reported exposure to gluten and symptom onset, n (%)				
< 2 hours	114 (30.3)	46 (23.4)	68 (38.0)	< 0.001
2–24 hours	143 (38.0)	79 (40.1)	64 (35.8)	
> 24 hours	20 (5.3)	10 (5.1)	10 (5.6)	
Unknown	44 (11.7)	23 (11.7)	21 (11.7)	
Does not develop symptoms	30 (8.0)	25 (12.7)	5 (2.8)	
Missing	25 (6.6)	14 (7.1)	11 (6.1)	
Keeps a strict GFD (self-reported adherence), n (%)				
Never	3 (0.8)	1 (0.5)	2 (1.1)	0.71
Sometimes	4 (1.1)	2 (1.0)	2 (1.1)	
Often	17 (4.5)	7 (3.6)	10 (5.6)	
Always	350 (93.1)	186 (94.4)	164 (91.6)	
Missing	2 (0.5)	1 (0.5)	1 (0.6)	

CeD, celiac disease; GFD, gluten-free diet; LCA, latent class analysis; SD, standard deviation.

Table 3 –

Patient perception of GFD effectiveness in overall symptom management.

Table 3. Patient perception of GFD effectiveness in overall symptom management.

n (%)	Overall N = 376	Lower CeD symptom burden n = 197	Higher CeD symptom burden n = 179	*p* value
CeD symptoms despite adherence to a strict GFD				
Yes	172 (47.3)	56 (29.3)	116 (67.1)	< 0.001
No	131 (36.0)	99 (51.8)	32 (18.5)	
Unknown	61 (16.8)	36 (18.8)	25 (14.5)	
GFD treats the most significant symptoms				
Not at all	9 (2.4)	4 (2.0)	5 (2.8)	< 0.001
Moderately[a]	62 (16.5)	10 (5.1)	52 (29.1)	
Very much[b]	248 (66.0)	147 (74.6)	101 (56.4)	
Unknown	17 (4.5)	8 (4.1)	9 (5.0)	
Missing	40 (10.6)	28 (14.2)	12 (6.7)	

[a]'Moderately' includes the responses 'A little bit' and 'Somewhat'. [b]'Very much' includes the responses 'Quite a bit' and 'Very much'.
CeD, celiac disease; GFD, gluten-free diet.

Figure 1 – Absenteeism due to CeD.

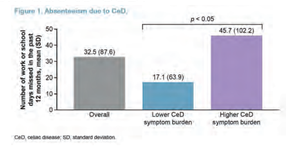


Figure 2 – Prevalence of CeD-related health conditions.

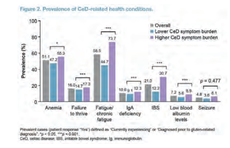
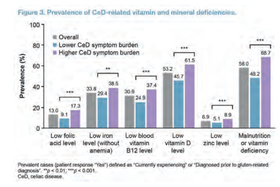


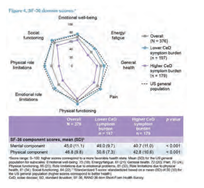
Figure 3 – Prevalence of CeD-related vitamin and mineral deficiencies.



Limitations

- The registry contains US patient data only, which may not be representative of other countries.
- Patients who are willing to fill out the survey may differ from the general CeD population.
- Of the patients included in the registry, only a small proportion had complete data for both the CSI and PROMIS-GI questionnaires.
- Information on clinical metrics (e.g. biomarkers of enteropathy, laboratory measures) that may aid in distinguishing symptom burden profiles was not available.

Figure 4 – SF-36 domain scores.



Conclusions

- This study indicates that most patients (94%) report always adhering to a strict GFD.
- Despite adherence to a GFD, many patients still experience CeD symptoms, which have a substantial impact on their day-to-day lives.
- Using LCA, patients with two distinct symptom burden profiles were identified, as captured by the PROMIS-GI and CSI questionnaires.
- Higher CeD symptom burden was associated with decreased QoL, increased CeD-related health conditions and nutritional deficiencies, and increased absenteeism (lending to the high level of absenteeism in theoverall population, with patients reporting an average of approximately 33 days of work or school missed in the preceding year).
- Patients with lower symptom burden were less likely to report many CeD-related health conditions or vitamin deficiencies and are more likely to believe that a GFD treats their symptoms.
- These data underscore the heterogeneity of CeD and the need for therapeutic options beyond a GFD to mitigate disease burden in patients with CeD.

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Disclosures

K. Chen was an employee of Takeda Pharmaceutical Company Limited at the time of the research. M. Geller is an employee of Celiac Disease Foundation, a nonprofit organization that received funding from Takeda to conduct this study. D. Leffler and L Meckley are employees of Takeda Pharmaceutical Company Limited. F. Mu, K. Kponee-Shovein and E Swallow are employees of Analysis Group, Inc., a consultancy that received funding from Takeda to conduct this study.

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