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Modeling Symptom Severity and Estimated Gluten Ingestion in Celiac Disease Patients on a Gluten-Free Diet

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Abstract Introduction: It is common for celiac disease (CD) patients on a gluten-free diet to accidentally consume gluten that can cause symptomatic distress and histologic damage. We present an algorithm to relate the quantity of gluten intake to the severity of episodic symptoms for abdominal pain, bloating and tiredness in CD patients. Methods: This analysis employs a model based on data from the CeliAction study for latiglutenase (ALV003-1221; NCT01917630). A previously estimated average daily quantity of gluten consumed by these trial patients along with the data for frequency and severity of the symptoms for abdominal pain, bloating, and tiredness allowed us to estimate the relationship between episodic inadvertent gluten ingestion and symptom severity. Results: The CD trial patients were previously estimated to consume a mean of 354 mg/day. From the study data, these patients experienced at least one symptom (of six possible) almost every day (6.13/week) and on average experienced 2-3 different symptoms per symptom event. The most common severity (on a 1-5 scale) was 2 for abdominal pain and 3 for bloating and tiredness corresponding to 1.1, 0.9, and 0.7 g gluten consumed per event. The frequency that a severe symptom (4 or 5) occurs during a symptomatic event equates to about 10%, 27%, and 33% for abdominal pain, bloating, and tiredness and correlates to 2.1, 1.2, and 1.0 g gluten consumed per event, respectively. Conclusions: This model suggests that the quantity of ingested gluten varies per event type and likely includes periodic gluten exposures of substantial quantity.

Keywords: *celiac disease, gluten, gastrointestinal symptoms*

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1. Introduction

Accidental gluten exposure is an inevitable consequence of a gluten-free diet (GFD). The complete elimination of gluten from the diet is nearly impossible to achieve no matter the vigilance of the dieter. For celiac disease (CD) patients even ingestion of <100 mg can be harmful [1]. In a recent study, we presented a semi-quantitative model for estimating the quantity of gluten consumed by CD patients on a GFD including distribution of typical daily gluten intake. Though the majority of patients consumed <200 mg/day, a significant fraction consumed far more and the average consumptions were as high as several hundred milligrams for those patients experiencing on average moderate to severe symptoms [2]. Given that a typical Western diet contains about 5-15 g of gluten [3] the elimination of >95% of gluten from the diet is insufficient to ensure long-term health for CD patients.

Here, we extend the understanding of gluten consumption in CD patients by developing an algorithm that relates the quantity of episodic gluten intake to the severity of symptoms experienced for abdominal pain, bloating and tiredness. This work further suggests that symptom distress in CD patients is predominantly caused by episodic gluten ingestion. Although it is now well accepted that accidental gluten consumption occurs on a GFD and that these levels are not unsubstantial, relating these consumption levels to the magnitude of symptom distress to our knowledge has not previously been reported, yet could be of assistance in designing therapeutic candidates that act to negate the effect of gluten in CD patients.

2. Method

This analysis uses data from the CeliAction study for latiglutenase (ALV003-1221; NCT01917630) [4]. We describe the operating equations that relate gluten intake to symptom severity and frequency. The model here makes the following assumptions: (i) The severity of an episodic symptom is linearly proportional to the quantity of gluten intake and (ii) the total gluten intake is

distributed evenly to all symptom frequencies and severities, without a threshold effect. We also address the issue of how much of the reported symptom frequencies and severities are gluten-induced. The validity of these assumptions is challenged in the Discussion section. We define w_s(g) as the quantity (weight) of a gluten intake that would trigger a symptom of severity s and is defined by

$$w_s = s \cdot w_g / F \cdot \sum_{s=1}^{n} s \cdot \nu_s \quad (1)$$

where w_g is the typical rate of gluten intake (per week), $\nu_s$is the frequency of symptom events (per week) for a particular severity s, and F is the fraction of symptom events attributable to gluten. The summation term is the total symptom severity (per week). The right-hand side of Eq. (1) without the term s is then the quantity of gluten that would trigger a single symptom event of s=1. Therefore, the product with $s$is the quantity of gluten that would trigger a single symptom event of severity s. We then plot $f_s$vs. w_s and $\Sigma_S$vs. w_s where f_s is the relative frequency for the occurrence of each symptom severity and Σ_S is the cumulative frequency for symptoms $\geq S$ (cap S) and are given by

$$f_s = \nu_s / \sum_{s=1}^{n} \nu_s \quad (2)$$

$$\Sigma_S = \sum_{s=S}^{n} \nu_s \quad (3)$$

The value n in Eqs. (1) - (3) represents the high-end (most severe) of the severity scale for a specific symptom. The data used in this paper were based on abdominal pain (0 to 10 scale), bloating (0 to 5 scale) and tiredness (0 to 5 scale), where 0 is for no symptom, 1 is for very mild symptom severity and the high-end value is for very severe symptom severity. The middle of the scale is for moderate symptom severity. For consistency of severity scale, we renormalized the severity values for abdominal pain from a 1 to 10 scale to a 1 to 5 scale, by mapping the values of severity 1 and 2 into 1, 3 and 4 into 2 and so on to 9 and 10 into 5. [Therefore n=5 in Eq. (1)-(3).] The values for the key variable ν_s are obtained directly from the ALV003-1221 CeliAction Phase 2b data [4,5,6] and were recorded using the Celiac Disease Symptom Diary (CDSD©) patient-reported outcome (PRO) instrument [7,8]. The determination of w_g has been reported before where we performed a semi-quantitative analysis of the quantity of gluten that CD patients on a GFD consume inadvertently [2]. We determined this quantity based on stool and urine analysis [9,10,11] against standard measurements for gluten challenges with the mean consumptions determined to be about 244 mg and 363 mg, respectively, per day. Based on another determination using the histology improvements for placebo in the ALV003-1221 study (NCT01255696), we determined the quantity of gluten-removed from the diets of CD trial from which we estimated about 456 mg/day normally consumed. The average of these values is 354 mg/day or 2.48 g/wk, which we use in the following analysis.

3. Results

From the ALV003-1221 CDSD data we determined the frequency of each severity level for abdominal pain, bloating, and tiredness. These values are tabulated in Table 1 for placebo (PBO) and 600 mg and 900 mg latiglutenase arms for the pre-treatment run-in period that spanned 4 weeks. We present this level of detail to show that each pre-randomization arm gives consistent results. The results were for seropositive subjects (n=103 for the total of these arms); however, subsequent analysis with seronegative subjects gave results that were numerically consistent. The weighted average frequency ν_s is also presented and is used in the subsequent calculations. The weekly frequency for each symptom (also including diarrhea and nausea for comparison) are given in Table 2 along with the total of these symptoms and also the frequency of experiencing at least one symptom. The latter is important because we assume this value represents the frequency of ingesting sufficient gluten to trigger a symptom event. The fraction of the time that a particular symptom occurs during a symptomatic event, Ω, is given by the ratio of the frequency of the symptom to the frequency of experiencing at least one symptom and is also presented in Table 2.

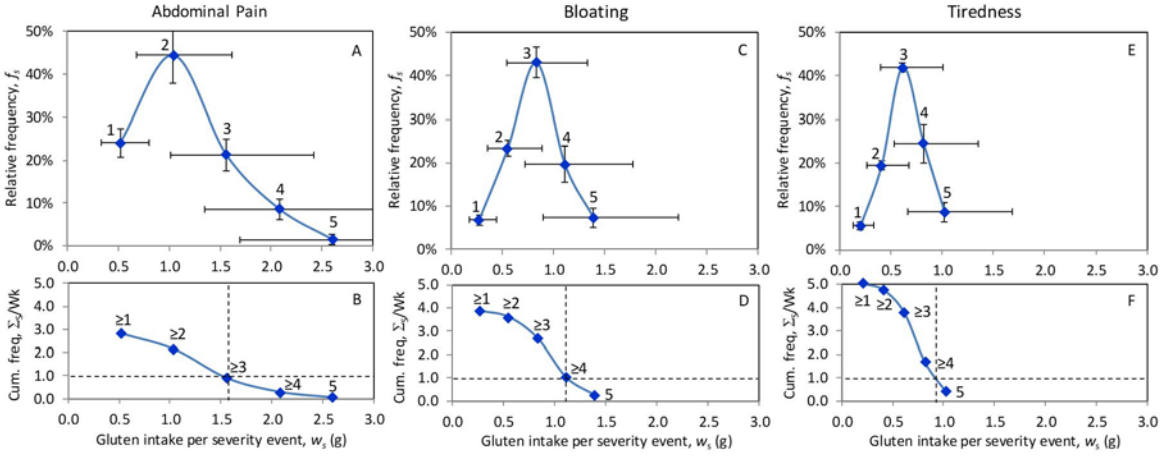

Figure 1. Plot of relative frequency f_s (A, C, E) and cumulative frequency Σ_S (B, D, F) vs. gluten intake w_s for each severity level for abdominal pain, bloating and tiredness. Each point is labeled by the severity value on a 1-5 scale. The vertical dotted line in B, D, and F denotes the episodic gluten ingestion that occurs on an average of once per week for this patient population. Uncertainty limits are discussed in the text and shown only for plots A, C, and E

Table 1. Average frequency ν_s, relative frequency f_s, cumulative frequency Σ_S (all frequencies per week) and gluten intake w_s for severity level s (pre-treatment period)

Abdominal Pain							
s	**PBO**	**600 mg**	**900 mg**	**ν_s**	**f_s**	**Σ_S**	**w_s(g)**
1	0.64	0.67	0.81	0.67	24%	2.80	0.53
2	1.10	1.41	1.43	1.25	45%	2.13	1.06
3	0.55	0.71	0.52	0.60	21%	0.88	1.60
4	0.29	0.19	0.17	0.24	9%	0.28	2.13
5	0.06	0.03	0.00	0.04	1%	0.04	2.66
Total	2.64	3.00	2.92	2.80	100%		
Bloating							
s	**PBO**	**600 mg**	**900 mg**	**ν_s**	**f_s**	**Σ_S**	**w_s(g)**
1	0.28	0.22	0.31	0.26	7%	3.86	0.31
2	0.90	0.86	0.99	0.90	23%	3.60	0.62
3	1.60	1.80	1.54	1.66	43%	2.70	0.93
4	0.85	0.71	0.53	0.76	20%	1.04	1.24
5	0.33	0.26	0.15	0.28	7%	0.28	1.54
Total	3.96	3.85	3.52	3.86	100%		
Tiredness							
s	**PBO**	**600 mg**	**900 mg**	**ν_s**	**f_s**	**Σ_S**	**w_s(g)**
1	0.30	0.27	0.21	0.28	6%	5.00	0.24
2	0.94	1.00	1.05	0.97	19%	4.72	0.48
3	2.14	2.03	2.11	2.10	42%	3.75	0.72
4	1.38	0.96	1.30	1.23	24%	1.65	0.96
5	0.50	0.39	0.29	0.43	9%	0.42	1.20
Total	5.26	4.65	4.95	5.01	100%		

Table 2. Total relative frequency $\Sigma\nu_s$ (per week) and fractional frequency from the CDSD for PBO patients during the pre-treatment period

	Ab pain	**Bloating**	**Tiredness**	**Diarrhea**	**Nausea**	**Total**	**At least one**
$\Sigma\nu_s$	2.64	3.96	5.26	2.32	1.52	15.73	6.13
Ω	0.43	0.65	0.86	0.38	0.25		

The values of w_s, f_s and Σ_S can be computed by Eqs. (1) - (2) and are given in Table 1 and Figure 1. The key observations are:

- The most common severity (on a 1-5 scale) was 2 for abdominal pain (mild to moderate) and 3 for bloating and tiredness (moderate) and corresponds to about 1.1, 0.9, and 0.7 g, respectively of gluten consumed per event.
- The frequency that a severe symptom ($s \geq 4$ out of 5) occurs during a symptomatic event computes to about 10%, 27%, and 33% for abdominal pain, bloating, and tiredness respectively, corresponding to 2.1, 1.2, and 1.0 g of gluten consumed per event.
- The plot of cumulative frequency Σ_S vs. gluten consumed w_s indicates that these moderately to severely symptomatic patients episodically consume at least1 g of gluten on average once per week.

We call attention to a number of other observations evident in Table 2. The most frequent symptom is tiredness (5.26/week) followed by bloating (3.96/week) and then abdominal pain (2.64/week). Part of tiredness, a non-gastrointestinal symptom, can be attributed to non-gluten causes. These surprisingly high frequencies reflect the frequent occurrence of mild symptoms that may be due to high sensitivity to gluten or to causes other than gluten. A symptom event, however, is typically accompanied by multiple symptom responses (2-3 per event) as evidenced by the frequency of total symptoms (15.73/week) vs. at least one symptom (6.13/week) in Table 2 suggesting that, for example, tiredness frequency typically accompanies other symptoms, which in turn may reflect a gluten exposure.

4. Discussion

The source and extent of accidental gluten intrusion is hard to identify and varies with individuals on a GFD depending on their diet habits and diligence. But persistent gluten exposure can lead to persistent histologic damage and episodic symptomatic distress. In this study, we develop a model for relating quantity of gluten ingestion to episodic symptom severity. We critique the following assumptions for the model stated in the Methods section, namely (i) the severity of an episodic symptom is linearly proportional to the quantity of gluten intake and (ii) the total gluten intake is evenly distributed among all symptom frequencies and severities.

Regarding the first assumption, there is certainly a positive correlation of symptom severity to gluten consumption based on prior gluten-challenge (GC) studies [12,13] and for lack of a better indication, a linear function is chosen for simplicity. We point out that in one GC study mucosal damage as measured by Vh:Cd was observed to be linear with gluten consumption [13]. However, there is also evidence suggesting that symptom severity does not correlate with histologic damage [14,15]. So, the assumption for linearity may be influenced by other factors.

We feel that the second assumption does not require much discussion as we are using the observed distribution of symptom total severity in Table 2.

The other issue to address is the proportion of symptoms that are gluten-induced and the estimates of *F* determined in the Results section. One approach is to compare symptom scores for a GC trial before (baseline) and after controlled gluten is consumed. However, it is not known how much baseline symptom severity is due to inadvertent gluten consumption in addition to persistent symptoms due to chronic intestinal damage. Nevertheless, such measurements can be used to estimate a lower limit to the proportion of symptoms due to gluten ingestion. The only published GC trials that reported gastrointestinal symptom scores (based on the Gastrointestinal Symptom Rating Score, GSRS) showed less than 50% increases in symptom severity upon the start of the GC period [13,14]. An unpublished study using the more specific CDSD (ALV003-1121, NCT01560169) showed abdominal pain increasing by greater than 2-fold for total severity upon initiation of a 2 g/day gluten ingestion and greater than 5-fold for moderate to severe symptom severity. Other pain domains showed less difference but were still significant for moderate to severe severity, such as greater than 3-fold for nausea and diarrhea. This study also used sham gluten run-in and run-out so these effects are not due to anticipation of taking gluten. It should be noted that other gastrointestinal (GI) ailments, such as functional GI syndromes (e.g., irritable bowel syndrome) are common in CD patients [16].

We now address the uncertainties to the data in Figure 1. For the abscissa w_s, which is based on the average gluten consumption of 354 mg/day of gluten, we use the relative standard deviation ±%RSD of the three values leading to this estimate, which is ±30%. For the uncertainty in the ordinate, we use the ±%RSD for the f_s values for the three arms that were used in this model (i.e., placebo, 600 mg, and 900 mg doses in Table 1).

Finally, we note that the work presented here represents average or typical symptom responses to gluten ingestion, but in fact, the symptom response is highly variable not just between patients, but for the same patient on different days. For example, in a larazotide acetate study (NCT00492960) the standard deviations for the change in symptom severity with gluten ingestion (2.7 g per day) were typically greater than the change itself for the entire population [14]. In the unpublished ALV003-1121 study(NCT01560169) the standard deviation for symptom severity for an individual patient from day to day for a fixed 2 g/day gluten consumption was similarly greater than the average symptom severity over the GC period. Further, in this trial for any given ingestion of 2 g of gluten, symptoms were reported in only 30% of the patient days.

The results in Figure 1 show that the lowest severity symptoms are triggered by gluten ingestion as low as 200 mg and the highest severity symptoms by gluten ingestion of up to 2.6 g. These determinations have relevance for drug treatments, such as latiglutenase that are based on degrading gluten in the stomach [4,5,6]. These results indicate that a 2-g gluten intrusion occurs in <10% of symptomatic events and about once per month (Figure 1A, B) therefore a treatment that protects to this level will safeguard patients in >90% of symptomatic gluten intrusion and significantly reduce the severity for the remaining events.

In conclusion, these results may be useful to clinicians and dieticians monitoring the health of CD patients as well as to drug developers for CD, particularly in designing gluten-challenge studies. It is our hope that this work will spur future efforts to more directly measure the symptomatic effect of gluten ingestion, perhaps using an intermittent and random gluten challenge using sham and real gluten daily ingestions.

List of Abbreviations

CD - Celiac disease
CDSD© - Celiac Disease Symptom Diary
GC - Gluten challenge
GFD - Gluten-free diet
GI - Gastrointestinal
GSRS - Gastrointestinal Symptom Rating Score
PRO - Patient reported outcome
RSD - Relative standard deviation
Vh:Cd - Villous height to crypt depth ratio

Ethics Approval and Consent to Participate

The protocol, patient informed consent form (ICF), and amendments to these documents were reviewed and approved by IECs/IRBs.The study was conducted in accordance with the International Conference on Harmonization (ICH) guidelines E6 Good Clinical Practice (GCP), the Declaration of Helsinki, European Union Directives, and with applicable local regulations governing clinical trials. The principal investigator (PI) agreed to adhere to the basic principles of “Good Clinical Practice”, as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, “Responsibilities of Sponsors and Investigators”, 21 CFR, Part 50, 1998, and 21 CFR,Part 56, 1998.

Consent for Publication

The authors JAS and PTL give consent for publication.

Availability of Data and Material

Data and material will be made available upon request to the lead author JAS.

Competing Interests

JAS is a founder of and owns stock in ImmunogenX.
PTL is a consultant to ImmunogenX.

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Authors' Contributions

JAS; Conception
JAS, PTL; Design of the work
JAS; Acquisition, analysis
JAS, PTL; Interpretation of data
JAS; Drafted the work
JAS, PTL; Substantially revised it

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