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Interest in medical therapy for celiac disease

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Abstract

Objectives: A gluten-free diet is the treatment for celiac disease, but pharmaceutical agents are being developed. The level of interest amongst patients in using a medication to treat celiac disease is unknown. This study examined the level of interest amongst patients in medication to treat celiac disease.

Methods: A questionnaire was distributed to celiac disease patients and data were collected on demographics, presentation, and interest in medication. Three validated celiac disease-specific instruments were incorporated: Celiac Disease Associated Quality of Life, the Celiac Symptom Index, and the Celiac Dietary Adherence Test.

Results: Responses were received from 365 individuals with biopsy-proven celiac disease. Respondents were 78% ($n = 276$) female, 48% ($n = 170$) over 50 years of age, and experienced a classical (diarrhea predominant) presentation in 44% ($n = 154$). Of the 339 individuals answering the question regarding use of a medication to treat celiac disease, 66% were interested. Interest was greatest in older individuals (71% >50 years of age *versus* 60% <50 years of age, $p = 0.0415$), men (78% men *versus* 62% women, $p = 0.0083$), frequent restaurant customers (76% *versus* 58%, $p = 0.0006$), those dissatisfied with their weight (73% *versus* 51%, $p = 0.0003$) and those concerned with the cost of a gluten-free diet (77% *versus* 64%, $p = 0.0176$). Length of time since diagnosis, education, presentation, and symptoms with gluten exposure did not demonstrate any effect. Interest in medication was associated with a worse quality of life (CD-QOL 69.4 *versus* 80.1, $p < 0.0001$).

Conclusions: Most individuals with celiac disease are interested in using a medication. Interest was highest among men, older individuals, frequent restaurant customers, individuals dissatisfied with their weight or concerned with the cost of a gluten-free diet, and those with a worse quality of life.

Keywords: celiac disease, survey, therapy

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Introduction

Celiac disease is a common autoimmune disorder triggered by the ingestion of gluten, a protein component of wheat, rye, and barley. The prevalence of celiac disease has increased over the past 50 years and affects approximately 1% of the population [Rubio-Tapia *et al.* 2009; Fasano *et al.* 2003; Mustalahti *et al.* 2010]. The treatment for celiac disease, a lifelong strict gluten-free diet (GFD), is effective and improves symptoms in the majority of patients [Murray *et al.* 2004]. Adherence to the diet, however, is variable. Adherence is increased in patients

involved in support groups and in those with a thorough understanding of the GFD diet [Leffler *et al.* 2008]. The GFD presents numerous difficulties since it is inconvenient, relatively expensive, and may be lacking in certain nutritional components, such as fiber [Lee *et al.* 2007; Thompson *et al.* 2005]. Approximately 30% of celiac patients experience persistent symptoms on a GFD and the most common cause is continued gluten exposure [O'Mahony *et al.* 1996; Abdulkarim *et al.* 2002]. Some celiac patients following a GFD do not have complete histological healing and have persistent villous atrophy,

crypt hyperplasia, and/or intraepithelial lymphocytosis [Rubio-Tapia *et al.* 2010]. The etiology of persistent histologic abnormalities is unknown but may be related to small amounts of continued gluten exposure. According to CODEX standards, a food may be considered gluten-free if it contains less than 20 parts per million (ppm) gluten (see http://www.codexalimentarius.net/web/index_en.jsp). Gluten ingestion may not be intentional, but inadvertent via contamination of grains and other foods. The availability of expert dietary counseling is limited and may contribute to difficulties maintaining a strict GFD [Nelson *et al.* 2007].

Advances in understanding celiac disease pathogenesis have fostered research and development in several prospective pharmaceutical agents to treat the disorder. As the disease is so common worldwide, a large potential market exists. Nondietary approaches to celiac disease treatment include reducing gluten exposure, decreasing intestinal permeability, and modulating immune activation [Mukherjee *et al.* 2012]. Genetically engineered grains, enzymatic degradation, probiotics, and synthetic polymers are potential means to reduce gluten exposure [Stoven *et al.* 2012; Tye-Din *et al.* 2010; Smecuol *et al.* 2013; Pinier *et al.* 2009]. Larazotide, a regulator of tight junctions, has been examined in celiac disease patients following gluten exposure [Kelly *et al.* 2013]. Anticytokine agents, vaccines, enzyme inhibition, HLA DQ2/8 blockade, and helminth infection, have been studied as potential immune-modulating therapeutic agents [McSorley *et al.* 2011; Sollid and Khosla, 2011].

There is a lack of data on perception of pharmaceutical agents to treat celiac disease amongst individuals with the disease. We used a questionnaire to obtain information from a large number of adults with celiac disease and attempted to identify overall interest in medication to treat the disease. We also examined which factors were associated with an interest in a pharmaceutical agent, including quality of life, GFD adherence, and celiac disease activity.

Materials and methods

The study was approved by the Institutional Review Board of Columbia University Medical Center.

A survey was designed and included information on demographics, celiac disease presentation,

symptoms, and interest in medication to treat celiac disease. Three validated celiac disease specific instruments were included to assess quality of life, disease activity, and GFD adherence respectively [Dorn *et al.* 2010; Leffler *et al.* 2009a, 2009b]. Respondents were also asked several specific questions including questions regarding the frequency of restaurant meals, concern about cost of a GFD, and satisfaction with current body weight. The questionnaire was initially tested on a group of 10 patients with celiac disease and was modified to ensure the clarity of the questions.

Adults (≥ 18 years of age) with celiac disease were asked to participate in a health survey on celiac disease. The questionnaire was distributed by the Celiac Disease Center of Columbia University via an electronic format to an email list of 477 patients and in a paper format to individuals during an office visit or support group meeting. The questionnaire was distributed via support groups in Iowa, California, and New York. The electronic surveys were completed using Survey Monkey, an Internet survey program. Responses were collected between November 2010 and March 2011. Responses consisted of a multiple choice format except for height and weight. Patients were specifically asked whether they would take a medication to treat celiac disease, if available. The questions were graded on a five-point Likert scale with responses: not at all, slightly, moderately, quite a bit, and a great deal. For analysis, respondents who answered 'a great deal' and 'quite a bit' were considered to have a positive response (for example, interested in medication) while responses 'not at all', 'slightly', and 'moderately' were considered to be negative response (for example, not interested in medication). Patients who reported nonceliac gluten intolerance were excluded from analysis. Patients were also excluded from analysis that did not have biopsy-proven celiac disease, and those who did not provide gender, age, or answer the question on interest in medication.

Quality of life was assessed using the celiac disease-related quality of life instrument (CD-QOL) [Dorn *et al.* 2010]. The CD-QOL is a reliable and valid celiac disease specific instrument with 20 questions across four clinically relevant subscales (celiac disease related limitations, dysphoria, health concerns, and inadequate treatment). The instrument assesses the respondent's feelings to particular celiac disease-associated symptoms over the previous 30 days. The questions consist

of a five-point Likert scale labeled 1 through 5, where 1 is not at all, 2 is slightly, 3 is moderately, 4 is quite a bit, and 5 is a great deal. For analysis, the responses are reverse coded and totaled. A higher score, with a maximum value of 100, may mean a higher quality of life and a decreased degree of celiac disease symptoms.

The disease activity of the respondents was assessed using the Celiac Symptom Index (CSI), a validated instrument for monitoring celiac disease-specific symptoms [Leffler *et al.* 2009a]. The CSI consists of 16 questions using a five-point Likert scale. While cutoff levels for disease activity do not exist, scores of ≤ 30 and ≥ 45 are suggestive of clinical remission and ongoing active disease, respectively.

Adherence to a GFD was assessed using the Celiac Dietary Adherence Test (CDAT). The CDAT is a validated seven-question instrument, using a five-point Likert scale, providing a standardized assessment of GFD adherence in celiac disease patients [Leffler *et al.* 2009b]. Scores are additive from 7 to 35, with higher scores associated with worse adherence. A score < 13 is associated with excellent or very good GFD adherence. A score > 17 is associated with fair to poor adherence to the GFD.

Quality of life, adherence, and disease activity were calculated for respondents who answered each respective instrument and also completed the question on the use of medication. We assessed for factors associated with interest in medication for celiac disease, as indicated by a response of 'quite a bit' or 'a great deal' to the question gauging interest. The chi-squared and Fisher's exact test were used to compare proportions of categorical variables. The Mann-Whitney *U*-test was used to compare continuous variables. *p*-values were two sided and a value < 0.05 was considered significant. All statistical calculations were performed with SAS 9.2 (Cary, NC, USA).

Results

General characteristics of the respondents

Responses were received from 465 individuals with celiac disease. Respondents were 78% ($n = 276$) female and 48% ($n = 170$) were over 50 years of age. Celiac disease was diagnosed by biopsy in 79.2% of these individuals ($n = 365$). Since biopsy is considered the gold standard in

diagnosis, only this group was included for analysis. After excluding those respondents who did not report age or sex, 352 respondents with celiac disease were analyzed (Table 1). Surveys were completed electronically in 54.5% ($n = 192$), during a clinic visit in 32.7% ($n = 115$), and in a support group in 9.4% ($n = 33$).

Disease characteristics of the respondents

Respondents reported a classical (diarrhea predominant) presentation in 44% ($n = 154$), an atypical presentation in 50% ($n = 177$), and no symptoms in 5% ($n = 18$). A response to the GFD was reported in 72% ($n = 255$).

Interest in using medication

Analysis was performed on the responses of 339 individuals answering the question on medication use. Of these, 66% ($n = 222$) were interested in medication to treat celiac disease.

Factors associated with interest in a celiac disease medication

Factors associated with an interest in using a celiac disease medication are displayed in Tables 2 and 3. Older individuals were more interested in medication than younger individuals (71% of those > 50 years of age *versus* 60% of those ≤ 50 years of age, $p = 0.0415$). Men were more interested than women in medication (78% men *versus* 62% women, $p = 0.0083$). Interest in medication to treat celiac disease was significantly higher with frequent restaurant use (76% frequent restaurant customers *versus* 58% infrequent restaurant customers, $p = 0.0006$), those dissatisfied with their weight (73% dissatisfied with weight *versus* 51% satisfied with weight, $p = 0.0003$), and those concerned with the cost of a GFD (77% concerned with cost *versus* 64% not concerned with cost, $p = 0.0176$) (see Table 3). Length of time since diagnosis, education, extent of counseling by a dietician, response to a GFD, presentation, and symptoms with gluten exposure did not demonstrate any effect.

Quality of life, adherence to a GFD, and disease activity

The CD-QOL, CDAT, and CSI scores are displayed in Table 4. The CD-QOL instrument was completed by 302 respondents with a mean score of 73. Interest in medication was associated with

Table 1. Characteristics of patients with biopsy-proven celiac disease ($n = 352$).

	N [%]
Age group	
18–20	17 (5)
21–30	45 (13)
31–40	51 (14)
41–50	69 (20)
51–60	78 (22)
61–70	63 (18)
71–80	24 (7)
>80	5 (1)
Gender	
Male	76 (22)
Female	276 (78)
Education	
Grade school	2 (0.6)
Middle school	1 (0.3)
High school	37 (11)
College	168 (48)
Graduate school	142 (40)
[No response]	3 (0.8)
Years since diagnosis	
< 1 year	36 (10)
1–4	123 (35)
5–10	100 (28)
>10	92 (26)
[No response]	1 (0.3)
Presentation	
No symptoms	18 (5)
Classical	154 (44)
Atypical	177 (50)
[No response]	3 (0.9)
Years of symptoms prior to diagnosis	
<1 year	48 (14)
1–4 years	93 (26)
5–10	56 (16)
>10 years	115 (33)
[No response]	3 (0.9)
Response to gluten-free diet	
Yes	255 (72)
Somewhat	61 (17)
No	22 (6)
[No response]	14 (4)
Seen by a dietician	
Never	72 (20)
One time	133 (38)
Two or three times	126 (36)
Regularly	17 (5)
[No response]	4 (1)

a significantly decreased quality of life (CD-QOL 69.4 *versus* CD-QOL 80.1, $p < 0.0001$). The CDAT instrument was completed by 328 respondents with a mean score of 12.2, indicating good or excellent adherence. Mean CDAT scores were 12.6 and 11.4 for those interested and those not interested in using a medication respectively ($p = 0.0062$). The CSI instrument was completed by 310 respondents with a mean score of 32.9. Mean CSI scores were 34.2 and 30.4 ($p = 0.0044$) for those interested and not interested in using a medication, respectively.

Discussion

This study provides important information on the interest amongst celiac disease patients in the United States in medication to treat the disease. Most individuals with celiac disease appear enthusiastic about a potential pharmaceutical agent. The treatment for celiac disease has been limited to the strict removal of gluten from the diet, and the potential market for pharmaceutical agents is vast as millions worldwide are affected. To the best of the authors' knowledge, this is the first study that has examined interest in a medication amongst individuals with celiac disease in the United States and also the first to examine disease characteristics, including the use of three validated celiac disease-specific instruments. In a recent questionnaire study in England by Aziz and colleagues, all celiac patients were interested in using alternative therapies with vaccines, anti-zonulin agents, and peptidases being the most popular [Aziz *et al.* 2011]. Importantly in our study, not all patients were interested in using a medication. Patient concerns about a potential medication to treat celiac disease include cost, efficacy, and potential side effects or safety.

It is not surprising that interest in a medication was highest amongst older respondents. Older patients may be more likely to accept use of a medication as they are accustomed to taking medications to treat other diseases. Younger patients may not take medications for other conditions and thus feel more comfortable utilizing a dietary approach alone. Men were also more interested in medication use. The survey did not include marital status, but it would be interesting to know whether marital status or involvement in home food preparation would affect interest in a drug. Length of time since diagnosis, presentation, symptoms, and response to a GFD did not appear to have any effect on interest in therapy.

Table 2. Factors associated with interest in celiac disease medication.

	Interested in medication (%)	p-value
Age group		0.0415
<50 (<i>n</i> = 177)	107 (60)	
≥50 (<i>n</i> = 162)	115 (71)	
Gender		0.0083
Male	58 (78)	
Female	164 (62)	
Education		0.7872
College or greater (<i>n</i> = 300)	196 (65)	
Less than college (<i>n</i> = 37)	25 (68)	
Years since diagnosis		1.0
<1 year (<i>n</i> = 35)	23 (66)	
1–4 (<i>n</i> = 119)	79 (66)	
5–10 (<i>n</i> = 96)	63 (66)	
>10 (<i>n</i> = 88)	57 (65)	
Presentation		0.4785
No symptoms (<i>n</i> = 15)	12 (80)	
Classical (<i>n</i> = 149)	96 (64)	
Atypical (<i>n</i> = 173)	113 (65)	
Years of symptoms prior to diagnosis		0.9456
<1 year (<i>n</i> = 47)	31 (66)	
1–4 years (<i>n</i> = 91)	61 (67)	
5–10 (<i>n</i> = 53)	33 (62)	
>10 years (<i>n</i> = 111)	72 (65)	
No symptoms (<i>n</i> = 34)	24 (71)	
Response to gluten-free diet		0.7050
Yes (<i>n</i> = 248)	158 (64)	
Somewhat (<i>n</i> = 59)	41 (69)	
No (<i>n</i> = 20)	13 (65)	

Table 3. Attitudes of patients with celiac disease and interest in using medication.

	Interested in medication (%)	p-value
I eat in restaurants		0.0006
Frequently (<i>n</i> = 135)	103 (76)	
Not frequently (<i>n</i> = 201)	117 (58)	
Cost of gluten-free diet		0.0176
Is an issue (<i>n</i> = 124)	96 (77)	
Is not an issue (<i>n</i> = 139)	89 (64)	
I am satisfied with my weight		0.0003
Yes (<i>n</i> = 85)	43 (51)	
No (<i>n</i> = 168)	123 (73)	
I am glad I was diagnosed with CD		0.1087
Yes (<i>n</i> = 143)	89 (62)	
No (<i>n</i> = 123)	88 (72)	
I feel sick if I eat gluten		0.3725
Yes (<i>n</i> = 177)	114 (64)	
No (<i>n</i> = 99)	69 (70)	

Table 4. Celiac Disease–Quality of Life (CD-QOL), Celiac Dietary Adherence Test (CDAT), and Celiac Symptom Index (CSI) scores among all biopsy-proven celiac disease patients.

Score	Overall mean (standard deviation)	Interested in medication versus not interested	<i>p</i> -value
CDQOL (<i>n</i> = 302)	73.2 (15.5)	69.4 versus 80.1	<0.0001
CDAT (<i>n</i> = 328)	12.2 (3.5)	12.6 versus 11.4	0.0062
CSI (<i>n</i> = 310)	32.9 (10.5)	34.2 versus 30.4	0.0044

Those who are concerned about the cost of a GFD, are frequent restaurant customers, or are dissatisfied with their weight appeared more interested in using medication as well. Restaurant eating, availability of gluten-free foods, and cost are all barriers to GFD adherence so this is not unexpected. Medications may be used on an intermittent basis, specifically when dining outside the home. In the Canadian Celiac Health Survey of 2681 patients with celiac disease, 81% reported avoiding restaurants and 94% brought gluten-free food when traveling [Cranney *et al.* 2007]. While there has been an increase in the availability of gluten-free food in markets and restaurants, the availability of gluten-free food in the United States is still limited [Lee *et al.* 2007]. Gluten-free food is often more than twice the price of similar gluten-containing foods [Lee *et al.* 2007]. In some European countries subsidies are provided for gluten-free food, but celiac patients in the United States bear a substantial economic burden.

Individuals interested in medication to treat celiac disease had a decreased quality of life. Those that experience disease-related limitations, dysphoria, health concerns, and feelings of inadequate treatment as assessed by the CD-QOL are more likely to want drug therapy. The symptom index instrument (CSI) and dietary adherence instrument (CDAT) scores were significantly different among respondents interested in medication and those not interested in medication. The symptom CSI scores were 34.2 and 30.4 ($p = 0.0044$) for those interested and not interested in medication; however, the clinical significance of this is unclear. Respondents in both groups did not meet criteria for clinical remission (CSI <30) or active disease (CSI >45). The mean for those not interested in medication nearly approached the cutoff score for clinical remission. This may suggest that patients in remission on a GFD alone may be less inclined to use a medication. The mean CDAT scores for the groups were 12.6 and 11.4, both consistent

with good or excellent dietary adherence. While there was a statistically significant difference, this does not appear clinically significant as both groups had excellent or very good GFD adherence as indicated by a score of less than 13.

This study has several limitations. Patients were recruited via the Celiac Disease Center of Columbia University, a tertiary referral center, as well as support groups, and may be more educated about the disease. These individuals may be more receptive to medical care, including the use of a medication. A large percentage of respondents completed college or graduate school and may be more willing to consider medical therapy. This survey did not assess which classes or types of medications respondents would be most willing to use or in which situations, such as daily or on an intermittent basis. The survey also did not assess how much patients would be willing to pay for a medication. If a medication is approved to treat celiac disease, but it is not covered by an individual's particular prescription plan, it is unclear whether interest in the drug would remain significant.

The majority of patients with celiac disease expressed an interest in using a medication to treat the disease. A pharmaceutical agent would be particularly helpful in certain situations for individuals with celiac disease, such as eating outside the home or during travel. Medical therapy could be utilized in conjunction with dietary therapy. Any medication should be safe with limited side effects, similar to a GFD.

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Conflict of interest statement

PG was a paid consultant for Alba Therapeutics and advisory board member for Alvine Pharmaceuticals and ImmusanT. CT, BL, SL have participated in preliminary drug-related trials for Alvine Pharmaceuticals and Alba Therapeutics but are not paid consultants or advisors. SS has no conflicts of interest to declare.

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