Numbers and Features of Patients With a Diagnosis of Celiac Disease Without Duodenal Biopsy, Based on a National Survey

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BACKGROUND & AIMS: **According to guidelines, individuals with symptoms of celiac disease should undergo duodenal biopsy analysis to establish a diagnosis, but little is known about physician adherence to these guidelines. We used a patient-powered research network (PPRN) to compare demographics, diagnoses, symptoms, and treatment between groups of patients with celiac disease diagnosed by biopsy analysis and patients with a diagnosis based on results of serology tests.**

METHODS: **We analyzed data from iCureCeliac—a voluntary, PPRN hosted and distributed by the Celiac Disease Foundation, from January 30, 2016, through August 25, 2016. We compared data from adults with a diagnosis of celiac disease (mean age, 43.4 years; 85.6% female) based on biopsy analysis (n = 780) vs patients with a diagnosis based on only serologic analysis (n = 202) using univariate and multivariable analyses. We collected demographic information, as well as data on type of health care practitioner, where patients obtain their primary information about celiac disease, and the Celiac Disease Quality of Life score, nutritionist referral rates, adherence to the gluten-free diet, ongoing symptoms and use of supplements.**

RESULTS: **Among patients with a diagnosis based on serology results, 33.3% were diagnosed by non-gastroenterologists vs 20.7% in the biopsy diagnosed group ($P < .001$). Fewer patients with a diagnosis based on serology results sought nutritional counseling at the time of diagnosis (40.1%) than patients with a diagnosis based on biopsy (58.9%) ($P < .001$). A higher proportion of patients diagnosed by serology without biopsy took dietary supplements to aid in digestion of gluten (19.8%) than patients with a diagnosis based on biopsy (8.9%) ($P < .001$). After we adjusted for age and sex, patients with a diagnosis based on serology were less likely to seek nutritional counseling after diagnosis (odds ratio [OR], 0.45; 95% CI, 0.33–0.63), less likely to receive a diagnosis from a gastroenterologist (OR, 0.16; 95% CI, 0.07–0.37), and more likely to use digestive supplements (OR, 2.61; 95%, CI 1.62–4.19).**

CONCLUSIONS: **In an analysis of data from a PPRN, we found that 21% of adult participants with celiac disease did not have a diagnosis based on a duodenal biopsy. Patients with a diagnosis based on serology results were more likely to be diagnosed by non-gastroenterologists, less likely to seek nutritional counseling, and more likely to use dietary supplements. Patients require more education about management of celiac disease and referral to gastroenterologists for duodenal biopsy confirmation of their disease.**

Keywords: Celiac Disease; Gluten-Free Diet; Biopsy; Dietary Supplement; Gluten Sensitivity; Detection; Small Intestinal Biopsy.

Abbreviations used in this paper: CDQOL, Celiac Disease Quality of Life score; CI, confidence interval; GFD, gluten-free diet; OR, odds ratio; PPRN, patient-powered research network; anti-tTG, anti–tissue transglutaminase.

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Celiac disease is an autoimmune condition characterized by duodenal villous atrophy that is present in nearly 1% of the U.S. population.[1] National gastroenterology authorities, including the American College of Gastroenterology and the American Gastroenterological Association, recommend using a combination of serology and a confirmatory biopsy of the small bowel to diagnose celiac disease in patients with typical signs and symptoms.[2,3] Although biopsy alone may demonstrate the characteristic findings of increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy, serology is an important component of the diagnosis because medication-related villous atrophy, tropical sprue, small-intestinal bacterial overgrowth, and other conditions may have similar histologic findings.[4,5] European guidelines suggest that it may be appropriate to diagnose children without biopsy if anti–tissue transglutaminase (anti-tTG) antibody titers are $\geq$10 times the upper limit of normal in children with a positive genetic test.[6] However, similar guidelines have not been adopted in the United States.

Despite the ongoing debate about the necessity of biopsy in the diagnosis of celiac disease, few studies have looked at the differences in groups who are diagnosed by biopsy versus those who are diagnosed by serology without biopsy. We hypothesize that significant differences exist with regards to demographics, diagnosis, symptoms, and treatment between these 2 groups. We therefore analyzed the Celiac Disease Foundation's iCureCeliac patient-powered research network (PPRN) to compare patients who were diagnosed with celiac disease with versus without a small bowel biopsy.

What You Need to Know

Background

Guidelines recommend that individuals with symptoms of celiac disease undergo duodenal biopsy analysis to establish a diagnosis, but little is known about physician adherence to these guidelines.

Findings

In an analysis of patients in iCureCeliac we found that 21% of patients received a without biopsy analysis. There were no demographic differences between patients with a diagnosis based on biopsy vs. serologic analysis, but patients diagnosed without biopsies were more likely to be diagnosed by a non-gastroenterologist or non-physician healthcare practitioner, and use supplements to aid in digestion of gluten. Patients diagnosed without a biopsy were less likely to seek nutritional counseling at the time of diagnosis.

Implications for patient care

Patients require more education about management of celiac disease and referral to gastroenterologists for duodenal biopsy confirmation of their disease.

Methods

Study Design

We performed a cross-sectional analysis using questionnaire data from iCureCeliac, a voluntary PPRN. Beginning in January 2016, the questionnaire was distributed to patients via the Celiac Disease Foundation Web site. Patients had the option to enter as much or as little data as they desired on an entirely voluntary basis with no financial incentive offered. Informed consent was obtained from each patient before completion of the survey. We included patients 18 years or older who indicated a diagnosis of celiac disease in the questionnaire and who answered questions regarding symptoms, the mode of diagnosis, and treatment that applied to our study between the inception of the PPRN on January 30, 2016, and August 25, 2016.

All coauthors had access to study data and have reviewed and approved the final version of the manuscript. This study was approved by the institutional review board of Columbia University Medical Center on September 22, 2016.

Data Collection

We collected basic demographic information including age, gender, age at diagnosis, and region within the United States. Data regarding patients' diagnosis were also extracted from the survey, including which diagnostic tests were used, which type of physician or nonphysician health care practitioner made the diagnosis, where patients obtain their primary information about celiac disease, and the Celiac Disease Quality Of Life score (CDQOL).[7] We also examined information about treatment, such as nutritionist referral rates, adherence to the gluten-free diet (GFD), ongoing symptoms, and use of supplements.

Statistical Analysis

We used SAS version 9.4 (SAS Institute Inc, Cary, NC) for all calculations. We measured associations using chi-square and Fisher exact tests for categorical values and Student *t* tests for continuous variables. We then analyzed data via multiple logistic regression, reporting odds ratios (OR) and 95% confidence intervals (CIs) to identify variables that were independently associated with a biopsy-free diagnosis of celiac disease after adjusting for age and gender.

Results

We identified 982 patients who met criteria for inclusion in the study, as shown in Figure 1. The demographic and baseline characteristics of our study population are shown in Table 1. The subjects were predominantly female (86%) and predominantly white (91%). The mean age was 43.4 years (standard deviation $\pm$ 15.3). A plurality of patients was diagnosed between

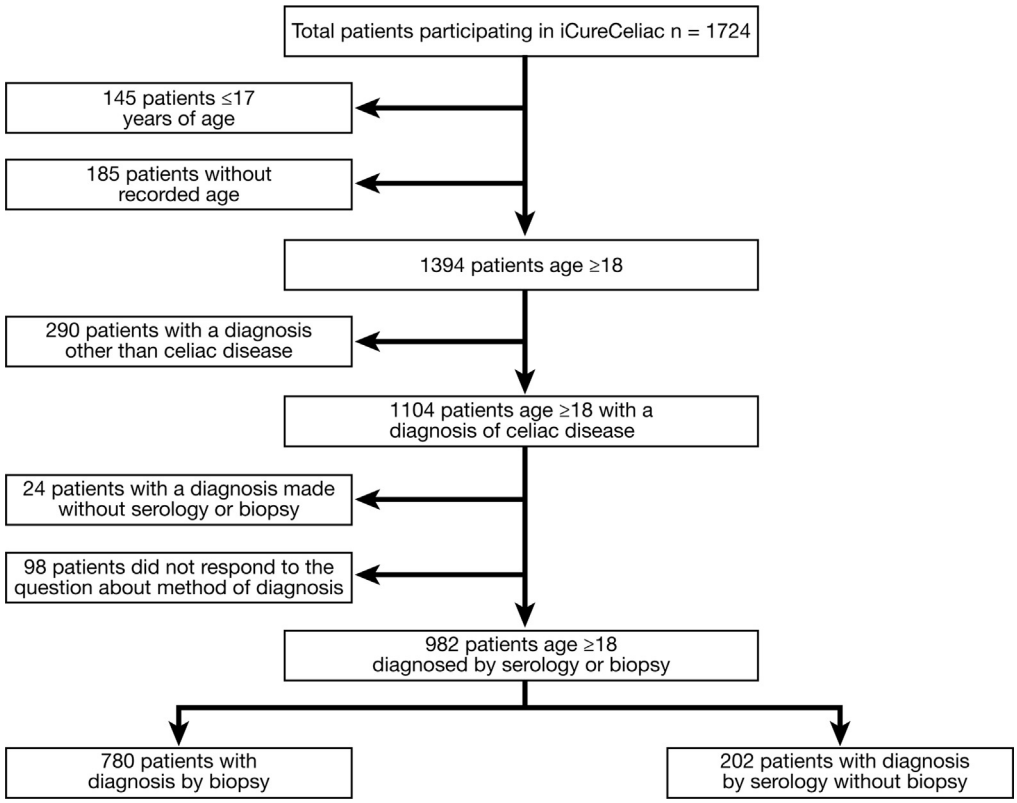

Figure 1. Study participants.

ages 41 and 50 years. A total of 31% of respondents resided in the Midwest United States. A total of 55% of patients sought nutritional counseling at the time of diagnosis and the mean CDQOL score was 58.4 (standard deviation ± 14.5), correlating with a good quality of life.[7] Overall, 11% of patients reported using dietary supplements "to aid in the digestion of gluten." The self-reported strict adherence to a GFD ("I always keep a strict GFD") in the cohort was 86.6%. Of the 225 patients who answered the question about ongoing symptoms, 46% remained symptomatic despite adhering to a GFD. Of the 982 patients, 202 (20.6%) were diagnosed by serology without biopsy.

Table 2 describes the additional tests (n = 108) that were reported by the 202 patients who were diagnosed by serology without biopsy. The most frequently used test was a gluten challenge, but HLA testing and stool tests were also common.

We compared patients whose diagnosis included a biopsy (n = 780; "biopsy group") with those who were diagnosed by serology without biopsy (n = 202; "serology group") in Table 3. There were no significant differences between the 2 groups in current age, gender, age at diagnosis, or region. Patients in the biopsy group were more likely to be diagnosed by gastroenterologists (65.7% vs 31.3%; $P < .001$) and patients in the serology group were more likely to be diagnosed by non-gastroenterologist physicians (33.3% vs 20.7%; $P < .001$) and nonphysician health care practitioners (35.4% vs 13.6%; $P < .0001$). Patients whose diagnosis included a biopsy were significantly more likely to have sought nutritional counseling at the time of diagnosis (58.9% vs 40.1%; $P < .001$). Although there were no differences in GFD adherence ($P = 1.00$), patients who were diagnosed by serology without biopsy showed a trend toward remaining symptomatic despite maintaining adherence to a GFD (65% vs 51%; $P = .11$). Additionally, patients who were diagnosed by serology only were more than twice as likely to use supplementation to "aid in the digestion of gluten" (19.8% vs 8.9%; $P < .001$). We performed a subsequent analysis on the subset of respondents who answered questions regarding ongoing symptoms and having sought nutritional counseling (n = 225) to evaluate the high percentage of patients who reported remaining symptomatic despite adhering to a GFD. Among patients who were diagnosed by biopsy, those who saw a dietitian showed a trend toward being less likely to report persistent symptoms (36%) compared with those who did not see a dietitian (55%; $P = .20$). Among those diagnosed by serology alone, the overall prevalence of persistent symptoms was higher, and those who saw a dietitian trended toward being more likely to report persistent symptoms (68%) than those who did not see a dietitian (48%; $P = .17$).

We performed multiple logistic regression analysis on the same variables, shown in Table 4, adjusting for age and gender. Patients diagnosed by serology without biopsy were half as likely to seek nutritional counseling after diagnosis (OR, 0.45; 95% CI, 0.33–0.63) and about one-sixth as likely to have been diagnosed by a gastroenterologist (OR, 0.16; 95% CI, 0.07–0.37). Furthermore, patients diagnosed by serology only were more likely to

Table 1. Baseline Demographics

Gender (n = 981)	
Male	141 (14.4)
Female	840 (85.6)
Age (mean ± SD, n = 982)	43.4 (± 15.3)
18–29	214 (21.8)
30–39	225 (22.9)
40–49	184 (18.7)
50–59	184 (18.7)
60–74	158 (16.1)
≥75	17 (1.7)
Age at diagnosis (n = 972, mean ± SD, n = 933)	37.1 (± 13.5)
<10 *y*	21 (2.2)
11–20 *y*	101 (10.4)
21–30 *y*	213 (21.9)
31–40 *y*	213 (21.9)
41–50 *y*	214 (22.0)
>51 *y*	210 (21.6)
Race (n = 963)	
Asian	2 (0.2)
Black	6 (0.6)
Latino	22 (2.7)
White	880 (91.4)
Other	55 (5.7)
Highest education level (n = 299)	
High school diploma or less	25 (8.4)
Some college, less than a college degree	53 (17.7)
Vocational, trade school, or associate degree	43 (14.4)
Bachelor's degree	88 (29.4)
Graduate degree	72 (24.1)
Doctorate	18 (6.0)
I currently live in this region of the United States (n = 862)	
Northeast	238 (27.6)
South	156 (18.1)
Midwest	272 (31.6)
West	196 (22.7)
The tests used to diagnose me were	
Biopsy of the intestine or small bowel during EGD	780 (79.4)
Serology without biopsy	202 (20.6)
At the time of diagnosis, I sought nutritional counseling (n = 963)	
Yes	528 (54.8)
No	431 (44.8)
Do not know	4 (0.4)
Where do you obtain your primary information about celiac disease? (n = 870)	
Health care provider (eg, physician, dietitian)	246 (28.3)
Social media/Internet Web page	410 (47.1)
Other media (book, magazine)	47 (5.4)
Foundation or support group	98 (11.3)
Do not use information source	69 (7.9)
Mean CDQOL score (n = 742)	58.4 (± 14.5)
I am just as healthy as anybody I know (n = 922)	
Strongly/somewhat disagree	375 (40.7)
Neither agree or disagree	140 (15.2)
Somewhat/strongly agree	407 (44.1)
Do you use supplements to aid in the digestion of gluten? (n = 828)	
Yes	92 (11.1)
No	736 (88.9)
I keep a strict GFD (n = 837)	
Always/often	818 (97.7)
Sometimes/rarely/never	19 (2.3)
I am still symptomatic despite keeping a GFD (n = 225)	
Yes	103 (45.8)
No	88 (39.1)
Do not know	34 (15.1)

NOTE. Values are n (%) or mean ± SD.
CDQOL, Celiac Disease Quality of Life score; EGD, esophagogastroduodenoscopy; GFD, gluten-free diet; SD, standard deviation.

use supplements to aid in the digestion of gluten (OR, 2.61; 95% CI, 1.62–4.19).

We also found that patients diagnosed by serology showed a trend toward improved quality of life, because they were more likely to have a CDQOL score above the median ($P = .07$). To further explore this finding, we broke down the CDQOL by the 4 factors proposed by Dorn et al[7] (Table 5). Although there was no statistically significant difference between the 2 groups, patients diagnosed by serology without biopsy showed a trend toward improved CDQOL scores in the domains of "Limitations" ($P = .21$) and "Health Concerns" ($P = .20$). However, when broken down by individual question (Supplementary Table 1), for CDQOL question 19 ("I feel like I think about food all of the time") those diagnosed by serology only were significantly more likely to agree with that statement ($P = .01$).

Discussion

In this cross-sectional study of 982 patients with celiac disease, participating in a PPRN, we found several significant differences when comparing patients diagnosed by serology without confirmatory biopsy with those whose diagnosis included a biopsy in accordance with current guidelines. To our knowledge, this is the first such comparison between these groups. Notably, 21% of the participants in our study did not undergo

Table 2. Tests Used in the Diagnosis of Celiac Disease in Those Who Did Not Undergo Duodenal Biopsy

Additional tests used for diagnosis in serology group (total n = 108 tests reported by 202 patients)	Number of additional tests (%)
HLA (genetic) testing	20 (9.9)
Skin biopsy	12 (5.9)
Gluten challenge	21 (10.4)
ALCAT food sensitivity test	5 (2.5)
Stool test	15 (7.4)
Saliva test	7 (3.5)
Allergy skin test	9 (4.5)
Other tests	13 (6.4)
No tests but responded well to a gluten-free diet	6 (3.0)

Table 3. Comparison of Patients With Biopsy-Diagnosed Celiac Disease Versus Those Diagnosed by Serology Without Biopsy

Variable	Biopsy-diagnosed celiac disease (n = 780)	Serology only (no biopsy) (n = 202)	*P* value
Gender			
Male	109 (14.0)	32 (15.8)	
Female	670 (86.0)	170 (84.2)	.50
Age (mean ± SD)	43.4 (± 15.6)	43.5 (± 14.4)	.99
18–39	354 (45.4)	85 (42.1)	
40–59	282 (36.2)	86 (42.6)	
60–74	128 (16.4)	30 (14.9)	
≥75	16 (2.1)	1 (0.5)	.22
Age at diagnosis (mean ± SD)	36.8 (± 13.6)	38.1 (± 13.2)	.24
>10 *y*	18 (2.3)	3 (1.5)	
11–20 *y*	81 (10.5)	20 (10.1)	
21–30 *y*	179 (23.1)	34 (17.2)	
31–40 *y*	162 (20.9)	51 (25.8)	
41–50 *y*	168 (21.7)	46 (22.2)	
>50 *y*	166 (21.5)	44 (22.2)	.42
I currently live in this region of the United States			
Northeast	192 (28.0)	46 (21.1)	
South	125 (18.2)	31 (17.6)	
Midwest	219 (31.9)	53 (30.1)	
West	150 (21.9)	46 (26.1)	.69
I was diagnosed by this type of physician (n = 246)			
Gastroenterologist (pediatric or adult)	130 (65.7)	15 (31.3)	
Nongastroenterologist physician	41 (20.7)	16 (33.3)	
Other health care practitioner	27 (13.6)	17 (35.4)	**<.0001**
Where do you obtain your primary information about celiac disease?			
Health care provider (eg, physician, dietitian)	198 (28.6)	48 (27.1)	
Social media/Internet Web page	321 (46.3)	89 (50.3)	
Other media (book, magazine)	38 (5.5)	9 (5.1)	
Foundation or support group	76 (11.0)	22 (12.4)	
Do not use information source	60 (8.7)	9 (5.1)	.54
Sought nutritional counseling at time of diagnosis			
Yes	449 (58.9)	79 (40.1)	
No	313 (41.1)	118 (59.9)	**<.0001**
I am just as health as anybody I know			
Strongly/somewhat disagree	306 (41.7)	69 (36.7)	
Neither agree or disagree	108 (14.7)	32 (17.0)	
Somewhat/strongly agree	320 (43.6)	87 (46.3)	.43
I use supplements to aid in the digestion of gluten?			
Yes	59 (8.9)	33 (19.8)	
No	602 (91.1)	134 (80.2)	**<.0001**
I keep a strict GFD			
Always/often	655 (97.8)	163 (97.6)	
Sometimes/rarely/never	15 (2.2)	4 (2.4)	1.00
I am still symptomatic despite keeping a GFD			
Yes	77 (51.0)	26 (65.0)	
No	74 (49.0)	14 (25.0)	.11
Mean CDQOL score (± SD)	58.2 (± 14.6)	59.6 (± 14.4)	.29

NOTE. Values are n (%) or mean ± SD. Boldface denotes significant *P* values (<.05).
CDQOL, Celiac Disease Quality of Life score; GFD, gluten-free diet; SD, standard deviation.

duodenal biopsy as a means of establishing the diagnosis of celiac disease, which is inconsistent with guidelines set forth by the American Gastroenterological Association and American College of Gastroenterology.[2,3] This is similar to findings in 1 study from the United States (21.6%).[7] Furthermore, although the percent of patients undergoing a biopsy-free diagnosis made by non-gastroenterologists in our study was similar to another study from Switzerland (30.6%),[8] the percentage of biopsy-free diagnosis by gastroenterologists was significantly higher in our study (31.3% vs 3.6%). These findings support that biopsy-free diagnoses are common in the United States and elsewhere. This has the potential to inappropriately subject patients to a lifelong GFD, which is burdensome socially, economically, and with regards to quality of life.[1,9–11]

The option of forgoing a duodenal biopsy has been codified in European pediatric guidelines,[6] but has not been adopted in the United States. A 2017 study by Liu et al[12] followed a cohort of 1339 high-risk patients

Table 4. Factors Independently Associated With a Diagnosis of Celiac Disease by Serology Without Biopsy

Variables	Adjusted OR[a]	95% CI	*P* value
Region			
Northeast	0.99	0.59–1.65	.97
South	1.00	—	—
Midwest	0.98	0.60–1.62	.95
West	1.23	0.73–2.06	.44
Age group at diagnosis			
<10 *y*	1.00	—	—
11–20 *y*	1.46	0.39–5.51	.58
21–30 *y*	1.10	0.31–3.99	.88
31–40 *y*	1.77	0.47–6.76	.40
41–50 *y*	1.68	0.42–6.78	.47
>51 *y*	2.37	0.55–10.23	.25
Where do you obtain your primary information about celiac disease?			
Health care provider (eg, physician, dietitian)	1.00	—	—
Social media/Internet Web page	1.15	0.77–1.70	.50
Other media (book, magazine)	0.96	0.43–2.12	.92
Foundation or support group	1.25	0.70–2.25	.45
Do not use information source	0.61	0.28–1.31	.20
I am just as health as anybody I know			
Strongly/somewhat disagree	1.00	—	—
Neither agree or disagree	1.32	0.82–2.12	.26
Somewhat/strongly agree	1.20	0.84–1.71	.32
Sought nutritional counseling, at time of diagnosis	**0.45**	**0.33–0.63**	**<.0001**
I use supplements to aid in the digestion of gluten?			
Yes	**2.61**	**1.62–4.19**	**<.0001**
No	1.00	—	—
I keep a strict GFD			
Always/often	0.95	0.31–2.90	.92
Sometimes/rarely/never	1.00	—	—
I am still symptomatic despite keeping a GFD			
Yes	1.52	0.72–3.20	.28
No	1.00	—	—
Do not know	0.96	0.33–2.80	.94
Diagnosed by this type of physician			
Gastroenterologist (pediatric or adult)	**0.16**	**0.07–0.37**	**<.0001**
Nongastroenterology physician	1.00	—	—
Other health care practitioner	0.54	0.23–1.27	.16
Median CDQOL Score			
≥Total sample median (58)	1.41	0.98–2.03	.07
<Total sample median (58)	1.00	—	

NOTE. Boldface denotes significant *P* values (<.05).
CDQOL, Celiac Disease Quality of Life score; CI, confidence interval; GFD, gluten-free diet; OR, odds ratio.
[a]Adjusted for age and gender.

(associated HLA genotypes or those with type 1 diabetes mellitus), and found that more than 5% developed evidence of autoimmunity to gluten, defined as persistence of anti-tTG antibodies for more than 3 months or the development of celiac disease. In 46% of these patients, however, the evidence of autoimmunity resolved spontaneously, suggesting that there may be transient elevations of anti-tTG that do not correspond to true disease activity.[12] A case report by Mahadev et al[13] details an adult with a transient rise in anti-tTG, antiendomysial antibodies, and antideamidated gliadin peptide that were found as part of a work-up for another condition, all of which resolved within 9 months. These studies suggest that diagnoses made by serology without confirmatory biopsy should be interpreted with caution because patients may be committed to a life-long GFD unnecessarily. In addition to biopsy and serology, there are commercially available tests of various specimen types (eg, stool and saliva) marketed to aid in the diagnosis of celiac disease without any proven benefit. Guidelines, therefore, recommend against the routine use of intestinal permeability tests, or stool or salivary tests for celiac disease diagnosis.[2]

We found that patients diagnosed by serology only were less likely to be diagnosed by a gastroenterologist and more likely to be diagnosed by a non-gastroenterologist physician or a nonphysician health care provider. It stands to reason that patients diagnosed by a gastroenterologist are more likely to proceed to biopsy because this is a gold standard for diagnosis, set forth by major gastroenterology organizations and performed relatively simply via upper endoscopy. This disparity may be caused by failure in education to health care providers about the proper diagnosis of celiac

Table 5. CDQOL Domains in Biopsy-Diagnosed Celiac Disease Versus Serology Only Diagnosed Celiac Disease

Factors of CDQOL (15)	Overall (n = 742)	Biopsy-diagnosed celiac disease (n = 591)	Serology only (no biopsy) (n = 151)	*P* value
Limitations (CDQOL 1, 5–7, 14–17, 19) Mean ± SD Range, 0–45	26.0 ± 7.8	25.8 ± 7.8	26.7 ± 7.6	.21
Dysphoria (CDQOL 10–13) Mean ± SD Range, 0–20	14.9 ± 3.6	14.84 ± 3.6	14.9 ± 3.8	.85
Health concerns (CDQOL 2–4, 18, 20) Mean ± SD Range, 0–25	12.2 ± 4.7	12.1 ± 4.7	12.6 ± 4.6	.20
Inadequate treatment (CDQOL 8–9) Mean ± SD Range, 0–10	5.5 ± 1.9	5.5 ± 1.9	5.4 ± 1.9	.55

CDQOL, Celiac Disease Quality of Life score; SD, standard deviation.

disease or by challenges referring patients to gastroenterologists for upper endoscopy with biopsy. Moreover, we found that patients diagnosed by serology without biopsy were less likely to seek nutritional counseling at the time of diagnosis. This finding may be explained by the fact that as more gastroenterologists diagnose patients by biopsy, they are therefore more likely to be referred to a dietitian, in keeping with standard of care for celiac disease recommended by the American College of Gastroenterology.[2] However it also suggests that the patients who are being diagnosed by non-gastroenterologist physicians and nonphysician practitioners are not only not referred for the appropriate diagnostic procedures, but also not referred for appropriate treatment interventions.

This sample was comprised of a highly adherent population (almost 98% reported keeping a strict GFD "always" or "often") that remained relatively symptomatic despite this excellent adherence (45.8% of all patients remained symptomatic despite GFD). Although there was not a significant association, 65% of patients in the serology group remained symptomatic despite reporting adherence to a GFD as compared with 51% of those in the biopsy group ($P = .11$). The relatively high rates of nonresponse to GFD in our study may call into question the accuracy of the celiac disease diagnosis. However, those diagnosed by biopsy did show a trend toward benefit from dietary counseling, with nonresponse rates similar to those previously reported in the literature.[14,15] In contrast, patients diagnosed by serology only showed a trend toward having more persistent symptoms after consultation with a dietitian. This may further suggest that patients diagnosed without a biopsy are being misclassified as having celiac disease and as such are not responding to dietary modification.

Only 55% of our cohort sought nutritional counseling at the time of diagnosis. This finding is similar to a previous study in which 60% of respondents reported seeing a dietitian either once or not at all.[14] It is unclear if patients were provided with dietary information by other means or did not remember being referred for dietary counseling at the time of diagnosis. Regardless, this is inconsistent with guidelines suggesting that all patients be referred to a dietitian at the time of diagnosis. When further evaluating the patients who remain symptomatic, those diagnosed by biopsy were less likely to remain symptomatic after seeing a dietitian as compared with those who did not. Although the result was not statistically significant, it suggests that patients diagnosed by biopsy may be more likely to benefit from dietary counseling, further supporting the importance of confirmatory biopsy in making an accurate diagnosis.

Interestingly, patients who were diagnosed by serology were more likely to use dietary supplements. Because there are currently no Food and Drug Administration–approved supplements that are proven to aid in the digestion of gluten, this again suggests that those diagnosed by serology without biopsy (who are more likely to be diagnosed by nongastroenterologist physicians and nonphysician health care providers) are not being educated about the correct management of celiac disease. Probiotics and over-the-counter gluten-degrading enzymes were both included under "supplements" in the questionnaire and the data to support the use of probiotics[16] and over-the-counter enzymatic therapies[17,18] in celiac disease remain equivocal at best. Given these findings, patients are possibly being misdiagnosed by nongastroenterologists, in part because of false-positive serologies or during times of transient celiac disease autoimmunity, suggested by Liu et al,[12] and because they are not being referred for biopsy, are being incorrectly labeled as having celiac disease. This causes them to remain symptomatic despite good adherence to a GFD, and may lead them to seek additional therapy to

treat symptoms, such as enzymatic supplementation or probiotics, when they are not being properly treated for their true underlying diagnosis.

We examined the difference in quality of life, defined as the CDQOL score between patients who were biopsied and those who were not biopsied. At baseline, the mean CDQOL score for all participants was 58.4, which suggests a relatively good health-related quality of life in our cohort. There was no difference in health-related quality of life between patients who were biopsied and those who were not. There were no significant differences between the 2 groups in any of the 4 domains that make up the CDQOL: (1) disease-related limitations, (2) dysphoria, (3) health concerns, and (4) inadequate treatment.

Our study has several limitations, some of which were inherent to its retrospective and observational nature. The relationships we identify are associations and inferring causality should be done with caution. The study was compiled from a voluntary questionnaire in a PPRN. Although there was no financial incentive to complete the questionnaire, the study population still represents a self-selected cohort of patients who may be more symptomatic or more aware of their disease and possibly more likely to adhere to a GFD. To our knowledge, there has been no study validating a self-reported diagnosis of celiac disease in this or other cohorts. However, previous studies characterizing celiac disease in both the United States[19,20] and Canada[21] have also relied on self-report. The high percentage of patients who remain symptomatic despite adherence to a GFD may call the diagnosis of celiac disease into question; however, the trend that fewer patients remain symptomatic in the biopsy group (51% vs 65%), suggest that these patients may be more likely to be correctly identified as having celiac disease as compared with the serology group. The study cohort was primarily female (86%). A prior national survey suggested roughly a 3:1 female to male predominance in the United States[20] and another survey reports that of new celiac disease cases diagnosed between 2000 and 2010, a total of 63% were female.[22] Furthermore, 91% of patients self-identified as being white, and 60% reported achieving a bachelor's degree or higher, which is much higher than the percentage of U.S. adults holding a bachelor degree: 33%.[23] Although these characteristics may limit the generalizability of our findings, this study nevertheless reflects a population of celiac disease that is not typically studied, such as those not attending large academic celiac disease centers, and those diagnosed without the involvement of a gastroenterologist. We also adjusted for age and gender to reduce the probability that these variables were driving the differences between the biopsy and serology group.

In summary, in this analysis of 982 adults in a celiac disease PPRN, we found that 21% of participants were diagnosed by serology without biopsy and those patients were more likely to be diagnosed by health care practitioners other than gastroenterologists, less likely to seek nutritional counseling for their celiac disease, and more likely to take supplements to aid in the digestion of gluten. These patients may be falsely diagnosed with celiac disease and instead have another untreated gastrointestinal illness. Furthermore, those with true celiac disease may not be properly educated on maintaining a GFD by dietitians. Future studies are warranted to further characterize this population regarding the long-term consequences of forgoing the duodenal biopsy, and to develop educational interventions to promote evidence-based diagnosis and management of celiac disease.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.09.006.

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Supplementary Table 1. CDQOL in Biopsy-Diagnosed Celiac Disease Versus Serology Only Diagnosed Celiac Disease by Individual Question

CDQOL Question	Overall (n = 742)	Biopsy-diagnosed celiac disease (n = 591)	Serology only (no biopsy) (n = 151)	*P* value
1. I feel limited by this disease				
Yes	321 (43.3)	251 (42.5)	70 (46.4)	
No	421 (56.7)	340 (57.5)	81 (53.6)	.38
2. I feel worried that I will suffer from this disease				
Yes	347 (56.8)	271 (45.9)	76 (50.3)	
No	395 (53.2)	320 (54.2)	75 (46.7)	.33
3. I feel concerned that this disease will cause other health problems				
Yes	260 (35.0)	204 (34.5)	56 (37.1)	
No	482 (65.0)	387 (65.5)	95 (62.9)	.55
4. I feel worried about my increased risk of cancer from this disease				
Yes	359 (43.4)	283 (47.9)	76 (50.3)	
No	383 (51.6)	308 (52.1)	75 (49.7)	.59
5. I feel socially stigmatized having this disease				
Yes	434 (58.5)	343 (58.0)	91 (60.3)	
No	308 (41.5)	248 (42.0)	60 (39.7)	.62
6. I feel like I am limited in eating meals with coworkers				
Yes	223 (30.1)	178 (30.1)	45 (29.8)	
No	519 (70.0)	413 (69.9)	106 (70.2)	.94
7. I feel like I am not able to have special foods like birthday cake and pizza				
Yes	277 (37.3)	225 (38.1)	52 (34.4)	
No	465 (62.7)	366 (61.9)	99 (65.6)	.41
8. I feel that the diet is sufficient treatment for my disease				
Yes	311 (41.9)	247 (41.8)	64 (42.4)	
No	431 (58.1)	344 (58.2)	87 (57.6)	.90
9. I feel that there are not enough choices for treatment				
Yes	300 (40.4)	240 (40.6)	60 (39.7)	
No	442 (59.6)	351 (59.4)	91 (60.3)	.85
10. I feel depressed because of my disease				
Yes	599 (80.7)	476 (80.6)	123 (81.5)	
No	143 (19.3)	115 (19.5)	28 (18.5)	.80
11. I feel frightened by having this disease				
Yes	653 (88.0)	519 (87.8)	134 (88.7)	
No	89 (12.0)	72 (12.2)	17 (11.3)	.76
12. I feel like I do not know enough about the disease				
Yes	629 (84.8)	502 (84.9)	127 (84.1)	
No	113 (15.2)	89 (15.1)	24 (15.9)	.80
13. I feel overwhelmed about having this disease				
Yes	599 (80.7)	481 (81.4)	118 (78.2)	
No	143 (19.3)	110 (18.6)	33 (21.9)	.37
14. I have trouble socializing because of my disease				
Yes	642 (86.5)	513 (86.8)	139 (85.4)	
No	100 (13.5)	78 (13.2)	22 (14.6)	.66
15. I find it difficult to travel or take long trips because of my disease				
Yes	475 (64.0)	379 (64.1)	96 (63.6)	
No	267 (36.0)	212 (35.9)	55 (36.4)	.90
16. I feel like I cannot live a normal life because of my disease				
Yes	586 (79.0)	470 (79.5)	116 (76.8)	
No	156 (21.0)	121 (20.5)	35 (23.2)	.47
17. I feel afraid to eat out because my food may be contaminated				
Yes	501 (67.5)	392 (66.3)	109 (72.2)	
No	241 (32.5)	199 (33.7)	42 (27.8)	.17
18. I feel worried about the increased risk of one of my family members having celiac disease				
Yes	394 (53.1)	313 (53.0)	81 (53.6)	
No	348 (46.9)	278 (47.0)	70 (46.4)	.88

Supplementary Table 1. Continued

CDQOL Question	Overall (n = 742)	Biopsy-diagnosed celiac disease (n = 591)	Serology only (no biopsy) (n = 151)	*P* value
19. I feel like I think about food all the time				
Yes	446 (60.1)	342 (57.9)	104 (68.9)	
No	296 (39.9)	249 (42.1)	47 (31.1)	**.01**
20. I feel concerned that my long-term health will be affected				
Yes	315 (42.5)	248 (42.0)	67 (44.4)	
No	427 (57.6)	343 (58.0)	84 (55.6)	.59

NOTE. Values are n (%) or mean ± standard deviation.
CDQOL, Celiac Disease Quality of Life score.