Determinants of Follow-up Care for Patients With Celiac Disease

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Goals: This study aimed to investigate follow-up patterns among celiac disease (CD) patients.

Background: Gender factors are important in CD with women diagnosed more frequently than men despite equal seropositivity in screening studies. To determine if gender influences postdiagnosis care, we performed a retrospective cohort study investigating the impact of gender and mode of presentation on follow-up patterns after diagnosis.

Study: The study included adults with biopsy-proven CD presenting to a single tertiary care center between 2005 and 2014. The primary exposure was at least 1 visit with a CD specialist. The primary outcome was ≥ 2 follow-up visits, including office visits and endoscopic procedures. Data extracted included whether patients had tissue transglutaminase antibodies performed by our laboratory.

Results: We analyzed 708 patients of which 70.5% were female. Follow-up was good with a majority of patients (69%) having at least 1 follow-up visit. On bivariate analysis, patients least likely to follow-up were ages 18 to 29 ($P = 0.03$) and women with atypical presentations ($P = 0.003$). After adjusting for potential confounders, individuals over age 65 were significantly more likely to attend at least 2 follow-up visits (odds ratio, 2.07; 95% confidence interval, 1.21-3.55; $P = 0.0079$). Individuals with an abnormal baseline tissue transglutaminase antibody value in our laboratory were significantly more likely to follow-up (odds ratio, 1.99; 95% confidence interval, 1.39-2.85; $P = 0.0002$).

Conclusions: Gender had no impact on follow-up patterns despite prior studies demonstrating an impact on diagnosis rates. Future attention should focus on retaining young patients and those with atypical modes of presentation.

Key Words: adherence, gluten-sensitivity, gender

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Celiac disease (CD) is a chronic immune-mediated disorder with a worldwide prevalence of around 1%.[1,2] The majority of CD studies have identified that women are diagnosed more frequently than men, typically at rates of 2 to 3 to 1.[3,4] However, in large population-based serological screening studies, there is equal prevalence of CD-specific autoantibodies in men and women.[5,6]

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Prior studies have examined aspects of this gender disparity in hopes that with a better understanding of the factors involved, we can better capture patients that may currently be undiagnosed or undertreated. The existing literature in this realm focuses on patterns in mode of presentation and diagnosis.[7–10] Women appear to have more signs and symptoms of CD at diagnosis[7] and men appear to be particularly underdiagnosed in early adulthood[10] and when presenting with atypical symptoms.[9]

There is a lack of data regarding factors associated with follow-up care. Given the high impact of complications of CD, it is important to ensure that once patients are diagnosed, they remain engaged in care and follow-up with their providers.[11] Frequent follow-up with counseling regarding dietary adherence has been shown to improve patient compliance.[12] The NIH Consensus Development Conference of 2004 recommended "continuous long-term follow-up by a multidisciplinary team."[13] To identify factors associated with obtaining follow-up care, we performed a retrospective cohort study investigating the impact of gender and mode of presentation on follow-up patterns after diagnosis of CD.

MATERIALS AND METHODS

The institutional review board of Columbia University approved this study.

Study Population

The study population consisted of adult patients (18 y old and above) who presented to a single tertiary care center between January 1, 2005 and September 30, 2014. Patients were included if they had biopsy-proven CD and at least 1 visit to a CD specialist. Visits were defined to be either an in-office appointment or appointment for endoscopic procedure with a physician (eg, registered dietitian, advanced nursing visits excluded). Patients were excluded if their first visit to the CD center was outside of the above-specified time period. The latter was specified to ensure that the initial visit was clearly delineated from subsequent follow-up visits and to allow at least 1 year for patients to have a follow-up visit by time of analysis.

Variables and Covariates

Data were extracted from the hospital electronic medical record as well as a prospectively maintained database of adults seen at the Celiac Disease Center at Columbia University. The following variables were extracted: age, gender, visits with CD specialists (inclusive of office visits and endoscopic procedures), whether or not the patient was diagnosed at Columbia University Medical Center (CUMC), family history of CD, mode of presentation. The latter was subdivided into classical (diarrhea predominant), atypical (eg, anemia, osteoporosis) or screening (eg, first degree relatives or type I diabetes). In

addition, we obtained whether or not tissue transglutaminase antibody (TTG) testing was performed at our medical center as well as associated TTG values (normal or abnormal per our laboratory's selected cut-off). The first chronological TTG value recorded in our electronic medical record was used as the initial TTG value for comparison. Age was subdivided for analysis into 3 groups: early adulthood (18 to 29 y), adulthood (30 to 64 y), and elderly (65 y and above). Data on whether or not patients were diagnosed at CUMC were obtained as a surrogate marker of which patients were most likely to have CUMC as their primary gastroenterology follow-up. In other words, the authors hypothesize that patients not diagnosed at CUMC may be more likely to have outside hospital follow-up or specialist care.

Outcomes

The primary outcome was ≥ 2 follow-up visits at the CD center with a CD specialist with visits inclusive of office visits and endoscopic procedures. A follow-up visit was defined as any visit occurring after the initial visit and before September 30, 2015. As such, individuals considered to have 1 follow-up visit had a total of 2 visits to the CD center (eg, 1 initial encounter, 1 follow-up encounter).

Statistical Analyses

We used the χ^2 test to assess for associations between categorical variables and used multivariable logistic regression to identify variables independently associated with follow-up. Our multivariable analysis included the following variables a priori: age, gender, mode of presentation, initial TTG value, diagnosed at CUMC and family history. Statistical significance was defined as a 2-sided $P < 0.05$. We used SAS version 9.4 (Cary, NC) for all statistical analyses.

RESULTS

Study Population

In total, 708 patients met eligibility criteria and were included in the final analysis. Patient age ranged from 19 to 93 with a mean age of 49. Over half of the patient cohort was between 30 and 64 years of age. In total, 70.5% of the patient cohort was female. A total of 34.9% had a classical mode of presentation and 17.4% had a family history of CD. The majority (68.8%) of patients had at least 1 follow-up visit, whereas 49.3% had ≥ 2 follow-up visits. Over 80% of patients had a TTG value performed by our laboratory (Table 1). In total, 33% of patients were diagnosed with CD at CUMC. Among those patients diagnosed at CUMC, 72.7% of patients had at least 1 follow-up visit, whereas 50.4% had ≥ 2 follow-up visits.

TABLE 1. Patient Demographics and Characteristics

Patient Characteristics	Patients (N = 708) [n (%)]
Gender	
Male	209 (30)
Female	499 (70)
Age (y)	
18-29	119 (17)
30-64	442 (62)
65 +	147 (21)
Follow-up visits	
No follow-up visits	221 (31)
1 follow-up visit	138 (20)
≥ 2 follow-up visits	349 (49)
Family history	
Yes	123 (17)
No	585 (83)
Mode of presentation	
Classical	247 (35)
Screening	42 (6)
Atypical	419 (59)
Initial TTG [n (%)]	
Normal	371 (52)
Abnormal	221 (31)
No value in laboratory	116 (16)

TTG indicates tissue transglutaminase antibody.

Bivariate Analysis

With regard to the impact of age on follow-up patterns, younger patients (age, 18 to 29) were least likely to follow-up ($P = 0.03$). Within this cohort, men were more likely than women to have ≥ 2 follow-up visits (men, 61.1%; women, 38.6%; Table 2A). With regard to mode of presentation, patients with atypical presentation were the least likely to follow-up ($P = 0.003$; Table 2B). Within this group, men were more likely than women to attend follow-up visits (men, 55.2%; women, 46.2%). TTG value did not show any statistically significant trend in bivariate analysis (Table 2C). Being diagnosed at CUMC did not have a statistically significant impact on follow-up visits ($P = 0.12$).

Multivariable Model

On multivariable analysis, there was no significant difference in follow-up patterns by gender or mode of presentation (Table 3). However, individuals in the older age cohort (eg, 65 +) were significantly more likely to attend at least 2 follow-up visits [odds ratio (OR), 2.07; 95% confidence interval (CI), 1.21-3.55; $P = 0.0079$]. In addition, of those with TTG values performed in our laboratory, individuals with an abnormal baseline TTG value were significantly more likely to follow-up (OR, 1.99; 95% CI, 1.39-2.85; $P = 0.0002$). Those patients with no baseline TTG value performed in our laboratory were significantly less likely to follow-up (OR, 0.18; 95% CI, 0.10-0.31; $P < 0.0001$). Family history of CD did not show any association with likelihood to follow-up. We performed a multivariable analysis restricted to only those patients diagnosed at CUMC. In this cohort (n = 234), there were no significant findings with regard to gender, age, or TTG value on multivariable analysis. Individuals diagnosed by screening for CD were significantly more likely to attend at least 2 follow-up visits (OR, 5.32; 95% CI, 1.65-17.17; $P = 0.005$).

DISCUSSION

Follow-up medical management of CD by specialty clinics is recommended[13]; however, there are little data concerning whether patients have follow-up care and factors associated with its occurrence. In the current study, about 50% of patients were seen ≥ 2 times. There were only 2 significant factors associated with increased likelihood of follow-up. Patients over age 65 were significantly more likely to attend follow-up visits within a CD specialty center. In addition, patients with a baseline elevated TTG value in our laboratory were significantly more likely to attend follow-up visits. Mode of presentation and gender did not have a statistically significant impact on follow-up patterns on multivariable analysis.

TABLE 2. Bivariate Analysis: Predictors of Follow-Up

Patient Characteristics	Follow-up Visits	n (%) Males	n (%) Females	*P*
A. Univariate analysis: follow-up by gender and age				
All patients	Total	209 (29.52)	499 (70.48)	0.18
	No follow-up	67 (32.06)	154 (30.86)	
	1 follow-up	32 (15.31)	106 (21.24)	
	2 + follow-up	110 (52.63)	239 (47.90)	
Age 18-29	Total	36 (30.25)	83 (69.75)	0.03
	No follow-up	12 (33.33)	33 (39.76)	
	1 follow-up	2 (5.56)	18 (21.69)	
	2 + follow-up	22 (61.11)	32 (38.55)	
Age 30-64	Total	119 (26.92)	323 (73.08)	0.52
	No follow-up	41 (34.45)	93 (28.79)	
	1 follow-up	24 (20.17)	72 (22.29)	
	2 + follow-up	54 (45.38)	158 (48.92)	
Age 65 +	Total	54 (36.73)	93 (63.27)	0.46
	No follow-up	14 (25.93)	28 (30.11)	
	1 follow-up	6 (11.11)	16 (17.20)	
	2 + follow-up	34 (62.96)	49 (52.69)	
	Mode of Presentation	**Males**	**Females**	
B. Univariate analysis: follow-up by mode of presentation				
Classical	Total	73 (29.55)	174 (70.45)	0.67
	No follow-up	21 (28.77)	54 (31.03)	
	1 follow-up	18 (24.66)	34 (19.54)	
	2 + follow-up	34 (46.58)	86 (49.43)	
Atypical	Total	116 (27.68)	303 (72.32)	0.003
	No follow-up	42 (36.21)	95 (31.35)	
	1 follow-up	10 (8.62)	68 (22.44)	
	2 + follow-up	64 (55.17)	140 (46.20)	
Screening	Total	20 (47.62)	22 (52.38)	1.00
	No follow-up	4 (20.00)	5 (22.73)	
	1 follow-up	4 (20.00)	4 (18.18)	
	2 + follow-up	12 (60.00)	13 (59.59)	
	Initial TTG	**Males**	**Females**	
C. Univariate analysis: follow-up by TTG value				
Initial TTG normal	Total	105 (28.30)	266 (71.70)	0.22
	No follow-up	34 (32.38)	75 (28.20)	
	1 follow-up	15 (14.29)	59 (22.18)	
	2 + follow-up	56 (53.33)	132 (49.62)	
Initial TTG abnormal	Total	68 (30.77)	153 (69.23)	0.29
	No follow-up	11 (16.18)	30 (19.61)	
	1 follow-up	8 (11.76)	29 (18.95)	
	2 + follow-up	49 (72.06)	94 (61.44)	
No TTG in our laboratory	Total	36 (31.03)	80 (68.97)	0.92
	No follow-up	22 (61.11)	49 (61.25)	
	1 follow-up	9 (25.00)	18 (22.50)	
	2 + follow-up	5 (13.89)	13 (16.25)	

TTG indicates tissue transglutaminase antibody.

This is the first study to focus on patterns of follow-up by age, gender, and mode of presentation. Prior studies have analyzed how these factors influence diagnosis rates although results have been inconclusive. The largest study in this field, by Dixit et al,[10] examined 1682 patients with CD within a wide age range and found the largest disparity of diagnoses in young men (age, 18 to 29). These findings were thought to be potentially related to greater symptom burden in women or greater health care exposure in young women compared with men. On the basis of these prior studies, we had theorized that these patterns might continue after diagnosis; namely, that men or young men might be less likely to follow-up with their providers. The results of our current study, however, suggest this does not occur and that older age and serologic results may be a larger determinant in follow-up patterns.

In our study, patients in the oldest age cohort (65 +) were more likely to attend follow-up visits. There is an extensive body of literature examining patient adherence and follow-up patterns in other disease states. Factors that have been shown to strongly influence adherence include health literacy and health beliefs, cognitive factors (eg, memory), interpersonal aspects of the patient-physician relationship, shared decision making, patients' attitudes and concurrent mental health diagnoses (eg, anxiety, depression).[14] Studies on follow-up in a variety of other disease states, including malignancy, alcohol use disorder and cystic fibrosis, have shown higher rates of loss to follow-up and lower adherence in younger patients.[15–17] As such, our findings in CD are concordant. One possible etiology of this finding is the fact that the dietary changes required for adherence in CD affect

TABLE 3. Multivariate Analysis: Predictors of Follow-up

Patient Characteristics	Odds Ratio for At Least 1 Follow-up Visit (95% CI)	*P*	Odds Ratio for ≥2 Follow-up Visits (95% CI)	*P*
Gender				
Male	0.90 (0.62-1.31)	0.59	1.16 (0.82-1.65)	0.41
Female	1.0 (ref)	—	1.0 (ref)	—
Age (y)				
18-29	1.0 (ref)	—	1.0 (ref)	—
30-64	1.64 (1.04-2.59)	0.03	1.31 (0.84-2.03)	0.24
65 +	1.96 (1.12-3.44)	0.019	2.07 (1.21-3.55)	0.008
Mode of presentation				
Classical	1.0 (ref)	—	1.0 (ref)	—
Atypical	0.83 (0.58-1.18)	0.29	0.94 (0.67-1.32)	0.72
Screening	1.76 (0.74-4.17)	0.20	1.54 (0.72-3.29)	0.27
Family history				
No	1.0 (ref)	—	1.0 (ref)	—
Yes	1.05 (0.66-1.66)	0.85	1.29 (0.83-2.00)	0.26
Initial TTG				
Normal	1.0 (ref)	—	1.0 (ref)	—
Abnormal	2.06 (1.35-3.14)	0.0009	1.99 (1.39-2.85)	0.0002
Not in laboratory	0.26 (0.17-0.41)	< 0.0001	0.18 (0.10-0.31)	< 0.0001

CI indicates confidence interval; Ref, reference; TTG, tissue transglutaminase antibody.

all aspects of life, including social interactions. Young patients may feel a particularly high burden and face difficulty with adherence as a result, although our study did not assess potential underlying factors in full. In addition, age-related follow-up patterns may be influenced by health insurance availability. Finally, patients in the older age cohort may follow-up more due to greater prevalence of refractory CD, which may require ongoing tertiary care.[18]

Our study also found that individuals whose initial TTG value in our laboratory was abnormal were more likely to follow-up with their provider in a specialty center. Prior studies have shown that TTG immunoglobulin A is the most efficient serological test for CD diagnosis and correlates well with degree of intestinal damage.[19–21] Moreover, a 2014 study by Bhattacharya et al[22] found that mean TTG titers were significantly higher in patients with classic symptoms of CD as compared with those with nondiarrheal disease ($P = 0.02$). One potential explanation for our findings is that those patients with baseline abnormal TTG values had more severe symptoms and, as such, were more motivated to attend follow-up visits compared with those with clinically silent or mild disease. We were unable to assess subjective symptom burden in the patient cohort to correlate this with follow-up patterns.

The finding that those patients without a baseline TTG value in our system were significantly less likely to attend follow-up visits may be related to the fact that our hospital is a tertiary care referral center. Patients may be referred for 1-time visit for consultation with a CD specialist while receiving the majority of their care with a community physician. Those patients without a TTG value in our system during time of initial visit may have brought records from another institution or come for a specific consultation question that did not require further laboratory testing.

In an effort to further assess this, we analyzed patients based upon whether or not their initial CD diagnosis was made by a physician at our medical center, hypothesizing that these patients may be more likely to follow-up at our medical center. Patients diagnosed at our medical center had slightly more follow-up visits compared with those diagnosed elsewhere but the difference was not statistically significant. We theorize that this is related to the small sample size of the cohort diagnosed at our institution. Of note, patients diagnosed at CUMC were more likely to attend follow-up visits when they were identified by screening for CD—a finding that was not seen in the full study cohort. We theorize that this is because those patients who were screened at CUMC might have other medical conditions, psychosocial-related or family-related factors linking their care to our medical center and thus influencing their likelihood of attending follow-up appointments.

Recently, there has been an interest in evaluating the types of referrals and, more specifically, the diagnostic accuracy of referrals to tertiary care centers for CD.[23–25] As community and media interest and excitement surrounding the gluten-free diet has increased,[26] patients are often self-diagnosing CD or being diagnosed by community physicians. In CD, there is therefore a potential problem with both under diagnosis and over diagnosis.[23] Moreover, our research group previously performed a study reviewing the pathologic diagnosis of CD rendered by pathology departments other than our own. Although there was a good degree of agreement with original pathology interpretation when performed in a university-based pathology department, there was less agreement with the original pathology interpretation when it originated from a community hospital or private pathology service.[27] Similarly, a recent study by Ianiro et al[24] evaluated 198 patients newly referred to their tertiary care celiac center and found that diagnosis of CD was only confirmed in 60% of the patient cohort. This suggests an important role for tertiary care referral centers and a need for these centers to assist with both diagnosis and management of CD. Our study found that the majority of patients did follow-up with providers at our center and those with abnormal TTG values suggestive of CD were more likely to follow-up.

In recent years, there has been an increasing worldwide prevalence of CD and, in particular, an increase in prevalence among adults in a disease once thought to be child-predominant.[11,28] Adults are more likely to present with atypical symptoms and complications of CD.[9] Adherence

to a gluten-free diet is a key component of management in CD and is necessary to help reduce the risk of complications. Studies have shown that one of the most effective methods of improving dietary adherence is consistent, repetitive counseling for patients.[12,29] As such, it is very important to focus on ensuring proper follow-up visits with CD specialists after diagnosis to maximize dietary adherence and reduce complication rates.

The current study suggests that patients in early adulthood and adulthood are less likely to follow-up with their care providers. In addition, patients with normal or no serologic testing in a tertiary care facility are less likely to follow-up. Providers should focus additional attention on retaining these patient cohorts in the future.

There are limitations to this study. The study was performed at a tertiary care referral center. In assessing patient follow-up patterns, there is a possibility for bias as some patients may have only come to our center for a 1-time referral visit while continuing regular CD follow-up with a physician outside of our system. These data (eg, outside hospital appointments or laboratory values) were not possible to capture retrospectively through our hospital electronic medical record. In addition, our study focused on CD specialists within our hospital system and did not include visits with general gastroenterologists. Some general gastroenterologists may diagnose or follow patients with CD, however, and these visits were not captured. We were unable to obtain sufficient data regarding patient demographics such as race, ethnicity or insurance status, or time between follow-up visits to include this in our analysis and this is another limitation to the current study. With regard to TTG testing, some patients may have had testing performed outside of our medical record system and thus are not captured in our analysis although reassuringly, over 80% of our cohort had an initial TTG value reported in our system. Finally, we were not able to obtain subjective data regarding symptom control to correlate this with follow-up patterns but this would be an interesting avenue to study in future research.

Overall, CD is a chronic condition with increasing prevalence and a high burden of complications, including potentially fatal conditions like lymphoma. When one considers the recommendations of the NIH Consensus Conference on Celiac Disease, our data reveals that not all patients receive regular follow-up. This applies especially to younger patients. In the future, efforts should be made to focus on this clinical cohort to try to improve follow-up patterns.

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