ABSTRACT

AIM: Screening first-degree relatives of celiac disease (CD) patients offers an opportunity to diagnose CD in a high-risk population. This study aims to determine how frequently CD patients receive a physician-issued recommendation for first-degree relative screening.

MATERIALS AND METHODS: A 12-question survey assessing whether CD patients receive a physician recommendation to screen first-degree relatives for CD, and the impact of such a recommendation, was validated with outpatients in a university gastroenterology practice (“University”). The 12-question survey was then distributed online to members of a celiac organization - the National Foundation for Celiac Awareness (“NFCA”). Results were collected over 3 months. Univariate analysis was used to compare cohort means and assess the association between demographic and diagnostic factors and first-degree relative screening recommendations.

RESULTS: 87 University patients participated in the validation phase. Test-retest reliability of 4 key survey questions was high (Kappa coefficient > 0.80). The main analyses were based on data from 677 NFCA and 82 University respondents. Respondents were predominantly female, with a mean age of 45 years. Significantly more University patients received a recommendation for screening (78% vs 44%, p < 0.001). Ninety-eight percent receiving a screening recommendation (both groups) discussed this with family members, leading to CD screening (University 71%, NFCA 79%) and, ultimately, a CD diagnosis (University 18%, NFCA 27%).

CONCLUSIONS: Physicians of CD patients often do not recommend screening first-degree family members. The high clinical impact of this recommendation suggests that greater physician compliance with screening may increase the diagnosis of CD in high risk individuals.

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Key words: Celiac disease; Screening; First degree relatives; Family

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that is triggered in genetically predisposed individuals by the ingestion of gluten – a protein derived from wheat, barley, and rye. CD is characterized
by small bowel mucosal inflammation, villous atrophy, and crypt hyperplasia, which results from exposure to dietary gluten and improves with the removal of gluten from the diet. Although it was originally thought to be a rare malabsorption syndrome of childhood, CD is now known as a condition that can affect multiple organ systems and can be diagnosed at any age\textsuperscript{11}.

It is estimated that CD affects approximately 0.2-1\% of the adult population in the United States and Europe\textsuperscript{2, 3}. Since CD has a known genetic predisposition, first-degree relatives of patients with CD have a higher prevalence of disease than the general population. Studies in first-degree relatives have shown the prevalence of CD to be 5-11\%\textsuperscript{4-6}. In families with more than one member with CD, the prevalence of CD in first-degree relatives is even higher at 17.2-21.3\%\textsuperscript{6, 7}. Given these findings, the American Gastroenterological Association recommends that all symptomatic first-degree relatives of patients with CD be screened for the disease\textsuperscript{11}, while other organizations, including the National Institute for Health and Clinical Excellence and the World Gastroenterology Organization, recommend screening all first-degree relatives\textsuperscript{8-10}. Additionally, the pediatric literature supports screening of all first-degree relatives\textsuperscript{10-11}.

Despite the rising prevalence of CD, studies indicate that there is still considerable under-diagnosis and delay in diagnosis of the disease\textsuperscript{7, 12-15}. This failure to detect and thus treat CD may lead to increased morbidity and an approximately 4-fold increased risk of mortality\textsuperscript{16}. Factors that may contribute to the under-diagnosis of CD include lack of physician recognition of the clinical spectrum of CD and underuse of diagnostic tests when presented with such patients\textsuperscript{16}. One study identified numerous areas of disagreement between expert and non-expert physicians in the diagnosis and management of CD, including the screening of high-risk groups such as first-degree relatives of CD patients\textsuperscript{16}. This suggests a lack of physician awareness of the increased prevalence of CD in first-degree relatives, which subsequently results in a failure to recommend screening in this population. Failure to screen first-degree relatives of patients with CD may represent a missed opportunity to diagnose CD in a high-risk population. We created, validated, and herein present the findings from a survey aimed at determining if patients with CD are receiving physician recommendations for first-degree relative screening. Further, we aim to determine if patient care at a University GI practice affects the screening rate and diagnosis of CD in first-degree relatives.

**METHODS**

**Study Subjects**

A pilot study population consisted of patients evaluated in the Division of Gastroenterology and Hepatology at Thomas Jefferson University Hospital (TJUH) – a tertiary care medical center in Philadelphia, Pennsylvania, staffed by board certified gastroenterologists. The study was subsequently extended to include members of the National Foundation for Celiac Awareness (NFCA) – a national non-profit CD patient advocacy organization. This study was approved by the TJUH Institutional Review Board (IRB control number 13E-45).

**Survey: Development, Pilot, and Validation Analysis**

A 12-question online survey was created using the SurveyMonkey® program (Survey Monkey, Inc., USA). The survey questions were designed to assess demographic information, CD status, method of CD diagnosis (including testing and type of physician to make the diagnosis), physician recommendation for CD screening in first-degree relatives, and discussion with and ultimate diagnosis of CD in first-degree relatives. The full survey is given as Supplementary Document 1.

For the pilot study, the billing records of the Division of Gastroenterology and Hepatology at TJUH were queried to identify 300 consecutive patients seen in the division (from April 2012 to April 2013) whose records included the billing code for “Celiac Disease” (ICD-9 code 579.0). These patients were contacted via telephone and provided with a thorough description of the study and opportunity to have their questions answered. Patients without an email account, or those unwilling to share this, were excluded. Patients providing verbal consent for study participation were emailed the link to the full survey.

Survey responses were collected in a secure, de-identified database. Two weeks after completion of the survey, patients were sent four key questions from the survey for the purpose of validation. These questions focused on CD diagnosis, receiving physician recommendation for first-degree relative screening, discussing the recommendation with first-degree relatives, and whether such discussion with first-degree relatives resulted in CD screening. Responses were again collected. Patients under the age of 18 years and those not answering the four validation questions were excluded from the analysis.

Validation analyses were performed for the four questions to determine whether patients provided consistent answers. For each question, the marginal rates (percent of patients providing one specific answer at each of the two time points, i.e. “Yes” or “No”) and agreement (percent of patients providing any two consistent answers at each of the two time points, i.e. “Yes-Yes” or “No-No”) were calculated. Using this information, kappa (K) coefficients were calculated for each question to account for the agreement occurring by chance. Any question having $K > 0.8$ was considered as providing consistent and reliable patient answers. We hypothesized that when responding to the same survey questions at two separate time points, patients would provide consistent answers.

**Survey: National Distribution**

After completion of survey validation, the link to the full online survey was distributed via email and social media (Facebook® and Twitter®) to members of the NFCA. Results were collected via SurveyMonkey® during a 3 month study period. Patients under the age of 18 years and those not answering all of the survey questions were excluded from the analysis.

**Survey: Measures and Statistical Analysis**

The main analysis compared the pilot (University) and national (NFCA) populations with self-reported CD. Univariate statistics were used to evaluate cohort means and calculate frequencies for: receiving a recommendation from any physician to have first-degree relatives screened for CD; type of physician offering the recommendation; discussing physician recommendations with first-degree relatives; and diagnosis of CD in first-degree relatives undergoing screening.

Additional statistical analyses (chi-square and two-tailed Fisher’s exact test, as appropriate) were used to compare means/frequencies between the cohorts and to determine within each cohort if there was any relationship between demographic or diagnostic factors and the likelihood of receiving the first-degree relative screening recommendation.

Our main hypotheses were that patients with CD do not uniformly receive recommendations from their physicians to have first-degree
relatives screened for CD, and those patients being cared for in a University GI practice are more likely to receive this recommendation than those belonging to a national CD patient advocacy organization.

**RESULTS**

**Pilot Study for Survey Validation**

Of the 300 patients contacted at TJUH, 153 gave verbal consent for study participation and were emailed the survey link. Of the 147 patients who declined, 7 (4.8%) did so because of a lack of an email account. A total of 100 entries were collected for the first survey. After excluding patients with incomplete surveys, 93 patients remained. Each of these patients was emailed the link to the second validation survey two weeks after completion of the first survey. A total of 87 patients responded to the second survey – giving a follow-up response rate of 93.5%. Figure 1 illustrates full patient enrollment details.

The test-retest reliability (i.e. the study participant providing a consistent answer at both time points) for the four key questions was generally high (test-retest agreement > 90% and K > 0.80). The exact wording, number of respondents, agreement, and K coefficients for each validation question are listed in Table 1.

**Patient Characteristics**

In the main analysis, only University and NFCA patients with self-reported CD were included (n = 82/87 and 677/1011, respectively). Patient demographic characteristics are shown in Tables 2 and 3. The average age of the University patients was 44.4 years (range 18-86), with 74% being female. Seventy-eight percent of the patients were diagnosed by a gastroenterologist (GI), with small bowel biopsy being the most commonly used diagnostic test (82%). The average age of the University patients was 44.4 years (range 18-86), with 91% being female. Fifty-nine percent of the patients were diagnosed by a GI, with small bowel biopsy being the most commonly used diagnostic test (68%). The average number of first-degree relatives for each NFCA patient was 5.6 (4.9 living).

When comparing the University and NFCA cohorts, there was statistically more female NFCA respondents (91% vs 74%, p < 0.001), and NFCA patients had, on average, more first-degree relatives (5.6 vs 5, p = 0.03). Compared to the NFCA, University respondents were more likely to report a diagnosis of CD by a GI physician (78% vs 59%, p < 0.001) and use of small bowel biopsy as a diagnostic test (82% vs 68%, p = 0.011). The use of serologic and genetic testing was similar in both populations (p > 0.05).

**Physician Recommendation for Relative Screening**

Compared to the NFCA patients, patients at the University were more likely to receive the recommendation from a physician to have their first-degree relatives screened for CD (78% vs 44%, p < 0.001). Similarly, University patients were more likely to receive this recommendation from a GI physician (92% vs 67%, p < 0.001).

In both the University and NFCA populations, there was no relationship between receiving the recommendation for screening and CD patient age (< 45 years vs ≥ 45 years; p = 1.0 University, p = 1.0 NFCA), sex (p = 0.77 University, p = 0.69 NFCA), or specialty of physician diagnosing CD (GI vs non-GI; p = 0.75 University, p = 0.69 NFCA). Although a CD diagnosis which included small bowel biopsy was associated with a higher rate of recommendation for first-degree relative screening in the NFCA population (p = 0.047), this was not the case in the University patients (p = 0.73). Table 4 summarizes these results.
In both the University and NFCA populations, a majority of recommendations for first-degree relative screening were provided by GI physicians. Approximately one-fifth of patients in each cohort were originally diagnosed by a non-GI (22% University, 20% NFCA).

**Impact of Physician Recommendation for Relative Screening**

Of the patients receiving a physician recommendation for first-degree relative screening, 98% in both the University and NFCA cohorts discussed the recommendation with at least one family member (*p* = 0.01). Often, the recommendation was discussed with more than one family member, as 63 University patients and 294 NFCA patients reported discussing the recommendation with a total of 143 and 862 first-degree relatives, respectively. In both populations, approximately three-quarters of these discussions resulted in at least one family member being screened (71% University, 79% NFCA, *p* = 0.183). Ultimately, 18% and 27% of screenings led to a diagnosis of CD in the University and NFCA populations, respectively (*p* = 0.069). These results are shown in Table 5.

When evaluating the total number of family discussions and living first-degree relatives for the University population, 11.1% of discussions resulted in a family member diagnosis, and 4.4% of total living first-degree family members were diagnosed with CD. Similarly, in the NFCA cohort, 17.4% of discussions resulted in a family member diagnosis, and 4.5% of total living first-degree family members were diagnosed with CD.

**DISCUSSION**

 Preventing the long-term morbidity and mortality associated with untreated CD is amplified by recognizing undiagnosed CD in the population. Since the clinical symptoms of CD are variable and often non-specific, with only 50% of adults diagnosed with CD having the “classic” symptom of diarrhea[17], targeted screening of high-risk populations offers an opportunity to increase diagnosis and treatment. First-degree relatives of patients with CD represent one such high-risk population.

Our study is important in that we have developed and validated a patient survey that reliably assesses whether patients with CD receive a physician recommendation to screen first-degree relatives, and we have used this survey to assess the frequency and efficacy of this physician issued recommendation.

In our validation analysis, four key survey questions focused on the main outcomes had high test-retest reliability with K-coefficients greater than 0.8 – generally agreed upon as “substantial” or “excellent” agreement[18, 19]. The validation of our survey prior to national distribution increased the likelihood of reliable, reproducible answers and adds strength to the findings in the main study analysis.

Our study design provides the opportunity to compare the care of CD patients within a University GI practice to those managed by a presumably more heterogeneous group of health care providers. Our findings suggest greater rigor in establishing a diagnosis of CD at the University GI practice, where small bowel biopsy was utilized significantly more often. Compliance with recommending screening for first-degree relatives was also greater in CD patients cared for at the University and, not surprisingly, this recommendation was more likely to come from a GI physician. In fact, there was a marked disparity in the rate of screening recommendation between the University and NFCA populations, with over three-quarters of University patients receiving this recommendation versus fewer than half of the NFCA patients.

The overall effect on detecting undiagnosed CD was compounded by the fact that NFCA patients had more total (statistically significant) and living (not statistically significant) first-degree family members than the University celiac patients. The lower rate of recommendation in the NFCA population may be explained to some extent by the fact that those without small bowel biopsy were less likely to receive the recommendation. Perhaps patients without this diagnostic criterion were thought by their physicians to not have a definitive diagnosis of CD. However, the recommendation rate was less than 50% even in those NFCA patients reporting small bowel biopsy as a diagnostic test establishing CD.

With regards to the actual recommendation to screen first-degree family members, approximately 20% of both University and NFCA patients receiving this recommendation from a GI physician had been diagnosed by a non-GI physician. Thus, it is likely that some non-GI physicians who diagnose CD do not routinely advise family screening. Whether due to a lack of awareness among non-GI’s about the high prevalence of CD in first-degree family members or other factors, the likely result is a delay or failure to screen family members of those with CD.

The importance of recognizing CD in a timely fashion cannot be understated. Although the prevalence of CD has increased fourfold in US over the last 50 years[14, 15], population based-studies suggest that only a small proportion of CD cases are clinically recognized – just 21% in a recent European study employing mass serologic screening[20]. The potential health risks of unrecognized CD are multifold. In addition to the nutritional deficiencies (including iron, vitamin B12, folate, copper, and zinc), bone disease (osteopenia and osteoporosis), and reproductive disorders (including preterm birth and intrauterine growth restriction) associated with undiagnosed CD, there appears to be a direct correlation between gluten exposure

**Table 4** Association between demographic and diagnostic characteristics on recommendation to screen.

<table>
<thead>
<tr>
<th>Recommendation n (%), University</th>
<th>P-value</th>
<th>Recommendation n (%), NFCA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 years</td>
<td>30/38 (79)</td>
<td>1.0</td>
<td>117/360 (44)</td>
</tr>
<tr>
<td>Age ≥ 45 years</td>
<td>34/44 (77)</td>
<td>0.77</td>
<td>156/351 (44)</td>
</tr>
<tr>
<td>Male</td>
<td>16/21 (76)</td>
<td>0.77</td>
<td>30/64 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>48/61 (79)</td>
<td>0.77</td>
<td>270/613 (44)</td>
</tr>
<tr>
<td>Celiac diagnosed by GI</td>
<td>49/64 (77)</td>
<td>0.75</td>
<td>181/402 (45)</td>
</tr>
<tr>
<td>Celiac diagnosed by non-GI</td>
<td>15/18 (83)</td>
<td>0.75</td>
<td>119/275 (43)</td>
</tr>
<tr>
<td>Diagnosis including small bowel biopsy</td>
<td>53/67 (79)</td>
<td>0.73</td>
<td>236/460 (51)</td>
</tr>
<tr>
<td>Diagnosis NOT including small bowel biopsy</td>
<td>11/15 (73)</td>
<td>0.73</td>
<td>84/217 (39)</td>
</tr>
</tbody>
</table>

**Table 5** Discussion of recommendation to screen with first-degree relatives, subsequent screening, and new CD diagnoses.

<table>
<thead>
<tr>
<th>n (%)</th>
<th>University</th>
<th>NFCA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD patients receiving the recommendation who ultimately discussed it with ≥1 family member</td>
<td>63/64 (98)</td>
<td>294/300 (98)</td>
<td>1.0</td>
</tr>
<tr>
<td>Discussions resulting in ≥1 family member being screened</td>
<td>45/63 (71)</td>
<td>233/294 (79)</td>
<td>0.183</td>
</tr>
<tr>
<td>Family member screenings leading to a diagnosis of CD</td>
<td>16/90 (18)</td>
<td>150/353 (22)</td>
<td>0.069</td>
</tr>
</tbody>
</table>

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**Roy A et al.** Recommendation for family screening in celiac...
and the incidence of autoimmune disorders and lymphoproliferative malignancy in patients with CD\textsuperscript{21–25}. Conversely, compliance with a gluten free diet has direct benefits, and studies have demonstrated that autoimmune antibody levels and the risk of malignancy and mortality are reduced in the years subsequent to diagnosis of CD and the institution of a gluten free diet\textsuperscript{26–27}.

We found that the recommendation for first-degree family screening was highly impactful. Nearly all in both cohorts (98%) acted on this information through discussions with family members. Subsequently, a high percentage of screened family members were diagnosed with CD (18% University, 27% NFCA). This is greater than the estimated prevalence of CD in first-degree relatives\textsuperscript{2–5} and may have resulted from selection bias. Family members at higher risk for CD based on history or symptoms may have been more likely to receive a recommendation from an affected family member and/or proceed with screening. We adjust for this potential bias by reporting the diagnostic yield of the screening recommendation in all first-degree relatives regardless of whether screening was recommended or pursued. The 4.5% rate of CD diagnosis in all first-degree relatives, in both the University and NFCA groups, more closely approximates the range reported in the literature. It is important to point out, however, that in prior studies that involved more generalized screening for CD among first-degree relatives, the rates of CD detection were similar to what we observed in our study. One study from Brazil, for example, reported that 15.7% of first-degree relatives of CD patients were positive for antiendomysial antibodies IgA\textsuperscript{28}.

The study reported herein has additional limitations to those already mentioned. First, the validation data was taken from a relatively small sample size. Higher numbers of university survey responders would likely have yielded kappa values with more narrow confidence intervals. Although the patient numbers were adequate to conclude that patients were providing consistent, reliable answers to our key survey questions, even a small number of patients giving conflicting answers could have greatly impacted the ultimate validation calculations. Second, a survey based study is vulnerable to recall bias. For instance, patients may answer questions based on how they believe they or their physicians “should” have behaved (regarding diagnostic studies, recommendations for screening, and passing along this recommendation to family members) rather than accurately reporting these events. Thus, it is possible that there is some degree of inflation in all of the results. Third, despite the overall demographic similarities between our two study populations, there was a significant female predominance – especially in the NFCA cohort which was comprised of 91% women. This is likely a representation of the fact that CD is twice as frequent among females\textsuperscript{29}, the membership characteristics of the NFCA (91% of social media members are female), and behavior characteristics of this national organization (90% of respondents on two recent NFCA-sponsored online surveys were female).

Selection bias may have been present in both study groups. In the University group, one-third of contacted patients completed an initial survey. Furthermore, only patients with active email accounts were eligible to participate in the survey. Fortunately, only a minority of patients (<5%) were excluded due to lack of email capabilities. In the NFCA group, there was a smaller fraction of respondents to a widely distributed survey. Thus, the results of both groups may not be generalizable with one being a University GI practice and the other a national support group for CD whose membership is voluntary.

Additional inherent limitations of survey-based investigations are the accuracy associated with self-reporting and greater granular details of the study population. It was not possible to specifically characterize each NFCA patient regarding the type of practice setting in which they were diagnosed and managed. Further, there were no means by which to verify the diagnosis of CD. Some NFCA patients reporting CD would not meet stringent diagnostic criteria and may have had alternative diagnoses such as gluten sensitivity. A small but statistically significant fraction of NFCA patients reported response to a gluten free diet as a diagnostic tool. Our survey does not reveal how many of these patients considered themselves diagnosed as CD based on the response to a gluten free diet alone versus in conjunction with specific antibodies and/or small bowel biopsy. It is important to note, however, that the rate of receiving a physician recommendation for CD screening in first-degree relatives was below 50% even in those NFCA patients who reported a diagnosis based on small bowel biopsy.

In summary, physicians often do not recommend CD screening for first-degree family members of affected patients. Fewer than 50% of a national sample of patients with self-reported CD received such a recommendation – far below that observed for patients with a diagnosis code of CD being cared for at a University GI practice. The recommendation for screening has a large downstream effect with CD patients nearly always passing along the message to family members. We found the diagnostic yield in those screened consistent with the reported incidence of CD in first-degree relatives. Thus, failure to recommend screening represents a missed opportunity to target a population at high-risk for CD. Future avenues of research should focus on measures to improve physician compliance with recommending screening, understanding the delay between patient diagnosis and the recommendation to screen, developing optimal strategies for presenting the screening recommendation to facilitate family discussions, and further evaluation of the diagnostic yield of screening all first-degree relatives, both symptomatic and asymptomatic.

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CONFLICT OF INTERESTS

The authors state that they have no conflict of interest.

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