How Often Do Hematologists Consider Celiac Disease in Iron-Deficiency Anemia? Results of a National Survey

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Abstract: *Background:* Celiac disease (CD) is underdiagnosed, and iron-deficiency anemia (IDA) is a common presentation of CD. No guidelines exist in the literature for screening for CD among those with IDA in the United States. We surveyed hematologists to determine rates of CD screening in patients with IDA. *Methods:* A survey was e-mailed to members of the American Society of Hematology. *Results:* There were 385 complete responses from 4551 e-mails. Most respondents were practicing clinicians (74%), clinical researchers (10%), or laboratory researchers (6%). Specialists in benign hematology accounted for 45% of respondents, oncologists accounted for 33%, and specialists in malignant hematology accounted for 22%. The most common practice types were university-affiliated hospital (43%), private clinic (29%), community hospital (12%), and Veterans Affairs or military hospital (9%). Only 8.6% believed all patients with IDA should be screened for CD. Respondents who had completed their fellowship within 5 years were more likely than more experienced clinicians to believe that all patients with IDA should receive CD screening (OR, 2.8; CI; 1.1-7.5; P=.04). Having a higher volume of IDA patients per month also increased the likelihood of testing (P=.01). In multivariate analysis, specialists in malignant hematology (OR, 3.2; CI, 1.1-9.5; P=.04) and oncologists (OR, 3.5; CI, 1.3-9.5; P=.02) were more likely than specialists in benign hematology to screen all patients for CD, as were those who saw predominately pediatric patients with IDA vs adult patients (OR, 16.9; CI, 3.0-97.0; P=.002). *Conclusions:* Practicing hematologists infrequently screen for CD in IDA. Physicians who have recently finished their fellowship and those who see a high volume of patients with IDA are more likely to screen for CD.

Introduction

Celiac disease (CD) is common, occurring in approximately 1% of the population in the United States,[1,2] although the majority of patients remain undiagnosed. In a recent analysis of National Health and Nutrition Examination Survey data, only 17% of those with CD had received a diagnosis.[1]

Originally considered a pediatric disorder, CD can be diagnosed at any age. It is increasingly recognized among the elderly.[1,3,4] Although the classic presentation of CD is diarrhea and malabsorption, patients may present atypically with nonspecific gastrointestinal (GI) symptoms, osteoporosis, or anemia; the disease also may be detected incidentally at endoscopy for reflux or dyspeptic symptoms.[5] Anemia related to CD is most frequently due to iron deficiency, and in 1 series iron-deficiency anemia (IDA) was the presenting symptom in nearly 10% of patients with CD.[6] In a recent US study, iron-deficient individuals were 28 times more likely to have CD than their non–iron-deficient counterparts.[7]

CD is associated with increased mortality that is reduced to that of the general population over a period of 10 years following diagnosis.[8] Patients with CD are at an increased risk of non-Hodgkin lymphoma.[9] Diagnosing and initiating treatment for CD not only improves GI symptoms, but also may prevent known complications of CD such as the development of other autoimmune diseases.[10,11] Treatment of CD is associated with improvement in quality of life.[12,13]

Similarly to CD, IDA is common in the adult population and occurs in 2% to 5% of adult men and women.[14] IDA is a common reason for referral to gastroenterologists, and loss of blood from the GI tract is the most common cause of IDA.[15] Current recommendations for the GI workup of IDA from the British Society of Gastroenterology (BSG) include CD screening for all patients as well as upper and lower endoscopy for all male patients and postmenopausal women unless there is an obvious cause of non-GI blood loss.[16] If serologic tests are not performed before upper endoscopy or if serologic tests are positive for CD, duodenal biopsies should be performed to aid in diagnosis.[16] The guidelines do not recommend that premenopausal women undergo endoscopic evaluation, although they should still be screened for CD with celiac serologic tests.[16] More recent studies have challenged this recommendation, however, and suggest that premenopausal women may also benefit from endoscopy to aid in the diagnosis of occult GI disease.[17-19]

There are no published guidelines for the evaluation of IDA in the United States. Although hematologists frequently diagnose and treat IDA, it is unknown how often they consider CD in the differential diagnosis and order celiac serologic testing. We therefore developed a survey and distributed it to hematologists to assess their evaluation of patients with newly diagnosed IDA to determine how often hematologists test for CD in these patients. We also sought to determine which characteristics of the patient as well as characteristics of the surveyed hematologists are associated with increased rates of screening for CD in patients with IDA.

Methods

Survey Design

A survey was developed by 4 gastroenterologists, a hematologist, and 2 medical residents using the website surveymonkey.com. After the survey was completed, it was tested on several hematologists for content and ease of use and changes were made accordingly. There were 3 sections to the survey, and respondents were unable to return to a previous section after it had been completed. The first section collected demographic information, including primary job function (eg, clinical, research, administration), subspecialty (eg, benign hematology, oncology), years in practice, patient volume, practice setting (eg, university-affiliated hospital, private office), region of practice, number of patients with IDA, and average age of patients with IDA.

The second section contained 6 hypothetical patients: a 30-year-old woman, a 45-year-old postmenopausal woman, a 55-year-old premenopausal woman, a 55-year-old postmenopausal woman, a 45-year-old man, and a 55-year-old man. Ages and menopausal status were selected to reflect BSG recommendations that men and all postmenopausal woman with IDA have serologic testing for CD as well as upper endoscopy and colonoscopy, and current recommendations that people at average risk for colon cancer begin screening at age 50 years.[16,20] Respondents were asked which tests they would order or perform for the initial workup of IDA in each of the patients. Possibilities included office hemoccult/rectal examination, outpatient hemoccult test × 1, outpatient hemoccult test × 3, upper endoscopy, colonoscopy, urine hemosiderin, urine cytology, analysis of CD55 and CD59, serologic testing for CD, and a trial of iron repletion; several of these tests were included to minimize response bias (ie, no listing only the potential workup of CD).

The third section was a series of statements regarding the GI workup of IDA. Respondents were asked if they strongly agreed, agreed, were neutral, disagreed, or strongly disagreed with each of the statements.

Response Collection

The e-mail addresses of members of the American Society of Hematology were extracted from the American Society of Hematology Membership Directory. A link to the survey was e-mailed each month for 4 consecutive months. Responses were incentivized with a raffle for an iPod Touch. The e-mails were sent from the address irondefanemia@columbia.edu from members of the department of internal medicine. There were no references to gastroenterology or CD. Responses were collected via surveymonkey.com.

Data Analysis

The data were imported into SAS version 9.2 (SAS Institute, Cary, NC) for analysis, and the percentages

of respondents ordering each test for each hypothetical patient were calculated. Chi-squared analyses were performed for each hypothetical patient and each procedure or test in comparison to the responses for the hypothetical 30-year-old female patient. Univariate analyses were performed with the dependent variable as the response to the statement "All patients with IDA should have celiac serologies ordered." Independent variables included primary job, subspecialty, years in practice, patient volume, practice setting, geographic region of practice (Northeast, Midwest, West, South), number of patients with IDA, and average age of patients with IDA. Chi-squared values were calculated for all analyses except for number of patients with IDA. For this analysis, a Cochran-Armitage 2-sided trend test was performed. Multiple regression was performed with the same dependent response and independent responses, including practice subspecialty, years in practice, patient volume, practice region, number of patients with IDA, and average age of patients with IDA. Odds ratios (ORs) and confidence intervals were calculated. Statistical significance was defined as 2-sided *P* values of <.05 for all tests. Graphs for figures were created in Microsoft Excel.

Results

Respondent Demographics

There were 385 complete responses from 4551 e-mail addresses, for a response rate of 8.5%. Demographic characteristics of the respondents are shown in Table 1 and the figure. Most respondents were practicing clinicians seeing patients (74%), with the majority classifying themselves as specialists in benign hematology. The most common practice types were university-affiliated hospital (43%), private office or clinic (29%), and community hospital (12%). Most respondents had been in practice for more than 20 years (58.2%); 3.4% were current fellows (Figure, A). All geographic areas of the country were well represented.

Most respondents saw 21 to 50 or 51 to 100 patients monthly (both 32%), while 25% saw fewer than 21 and 10% saw more than 100. On average, respondents saw 3 to 5 (31%) or 6 to 10 (28%) patients with IDA per month, although there was a wide spread of the number of patients seen: 4% saw no patients with IDA, while 8% saw more than 20 (Figure, B). The most common average age of patients with IDA was 31 to 50 years (47%), followed by 51 to 70 years (34%). Fewer patients were children, younger adults, or elderly adults.

Hypothetical Patient Evaluations

When respondents were asked for the initial evaluation of IDA, serologic tests for CD were ordered at similar rates, in only 11% to 18% of patients, across various sample patients (Table 2). Compared with 30-year-old women, patients significantly less likely to have celiac serologic tests ordered were 55-year-old premenopausal women (*P*=.024), postmenopausal women (*P*=.069) and 55-year-old men (*P*=.042). There was no significant difference in

Table 1. Respondent Demographic Information

	Respondents, No. (%) (N=385)
Primary Work	
Seeing patients	285 (74)
Clinical research	38 (10)
Laboratory research	25 (6)
Administrative	24 (6)
Other	13 (3)
Subspecialty	
Benign hematology	174 (45)
Malignant hematology	84 (22)
Oncology	127 (33)
Practice Setting	
University-affiliated hospital	165 (43)
Private office or clinic	111 (29)
Community hospital	46 (12)
VA/military hospital	33 (9)
Public hospital	12 (3)
Managed care organization	10 (3)
NA	8 (2)
Region of Practice	
South	125 (32)
Northeast	116 (30)
West	76 (20)
Midwest	68 (18)
Patients Per Month	
0-20	95 (25)
21-50	125 (32)
51-100	125 (32)
≥100	40 (10)
Average Age of IDA Patients	
<18	13 (3)
18-30	49 (13)
31-50	180 (47)
51-70	129 (34)
≥70	14 (4)

IDA, iron-deficiency anemia; NA, not available; No., number; VA, Veterans Affairs.

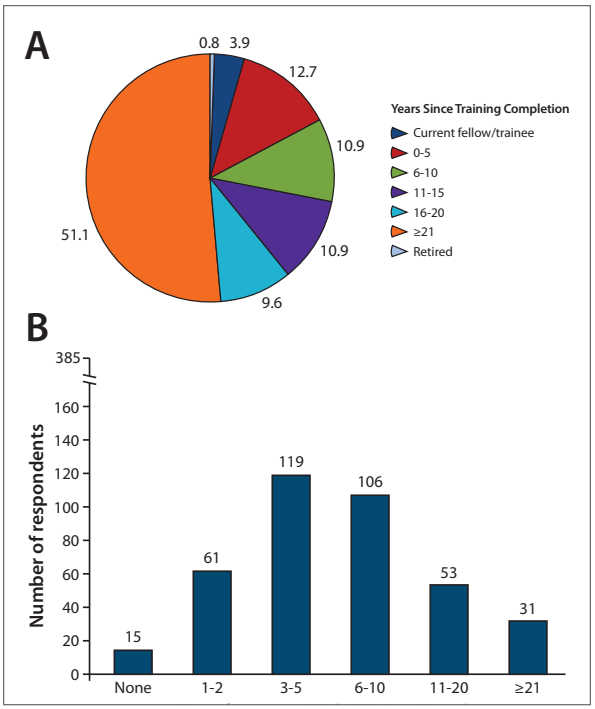

Figure. The demographic characteristics of the 385 respondents included (A) the number of years since completion of training and (B) the number of patients with IDA seen per month.

IDA, iron-deficiency anemia; No., number.

the rate of ordering celiac serologic testing between that for a 30-year-old woman and that for postmenopausal women or a 45-year-old man (all $P>.05$).

The rate of upper endoscopy varied across hypothetical patients. Thirty-year-old women were the least likely of all the patients to have an esophagogastroduodenoscopy (EGD) ordered as initial workup (all $P<.001$). Similarly to upper endoscopy, colonoscopy rates differed greatly among potential patients. Only 9% of 30-year-old women would receive colonoscopies, whereas percentages for other patients ranged from 60% to 88% (all $P<.001$). A trial of iron supplementation was ordered frequently for 30-year-old women (80%), and was ordered significantly less frequently for other hypothetical patients (all $P<.001$).

Agree/Disagree Statements Regarding IDA Workup

When asked whether all patients with IDA should have various diagnostic procedures, only 26% of respondents agreed or strongly agreed that colonoscopy should be performed, while even fewer (18%) believed that EGD should be performed (Table 3). While a small minority of respondents believed that a negative colonoscopy effectively ruled out GI blood loss as a cause of IDA (3%), or negative upper endoscopy ruled out malabsorption as a cause of IDA (5%), substantially more respondents believed that a negative celiac serologic test result sufficiently ruled out CD as a cause of IDA (25%). Roughly half of respondents (49%) stated that they routinely referred IDA patients to gastroenterologists for evaluation. However, only 9% agreed with the statement that patients with IDA should have serology testing for CD.

Demographic variables were utilized for univariate analysis with the dependent variable being the response to the statement, "All patients with IDA should have celiac serologies ordered." The more patients with IDA respondents saw monthly, the more likely they were to agree with the above statement ($P=.01$). No other demographic information reached statistical significance.

Multiple logistic regression was performed with various demographic information using the same dependent variable as in the previous univariate analyses. In this model, controlling for other variables, both specialists in malignant hematology (OR, 3.2; CI, 1.1-9.5; $P=.04$) and oncologists (OR, 3.5; CI, 1.3-9.5; $P=.02$) were significantly more likely than specialists in benign hematology to agree with the statement that all patients with IDA should have celiac serologic testing. Clinicians who had completed their fellowship within 5 years were more likely than more experienced clinicians to agree with the statement (OR, 2.8; CI; 1.1-7.5; $P=.04$), as were respondents who saw predominantly pediatric patients as compared with those who saw primarily adult patients (OR, 16.9; CI, 3.0-97; $P=.002$).

Discussion

By surveying practicing hematologists, we were able to determine the awareness of CD as a potential cause of IDA. In general, patients with CD have a long duration of symptoms and see many physicians prior to diagnosis.[21,22] Our study indicates that hematologists rarely include celiac serologic testing as part of the initial workup for IDA. This may be a contributing factor to the underdiagnosis of CD in the United States.

To our knowledge, there are no recommended guidelines for the evaluation of iron deficiency in the United States. However, our results show that for any theoretical patient, the rates of screening for CD via serologic testing are well below the recommended rates in BSG guidelines.[16] There was no substantial difference in rates of ordering celiac serologic testing based on the patient's sex, age, or menopausal status. The ordering rate of 11% to 18% for the various hypothetical patients suggests that undiagnosed CD is not high on the differential diagnosis of IDA for many hematologists.

Although the rates of upper endoscopy are more encouraging, as reflected in the fact that 55% of respondents would order an EGD in a 55-year-old man, endoscopy alone is inadequate workup for CD and the diagnosis may be missed despite endoscopy.[23] Men and selected racial groups were even less likely to undergo biopsy.[23] Even when

Table 2. Hypothetical Patient Evaluations[a]

	Tests That Would Be Ordered							
Patient Characteristics	**EGD, No. (%)**	***P* Value**	**Colonoscopy, No. (%)**	***P* Value**	**Celiac Serologies, No. (%)**	***P* Value**	**Trial of Iron, No. (%)**	***P* Value**
30-year-old woman	39 (10)	[b]	35 (9)	[b]	67 (17)	[b]	309 (80)	[b]
45-year-old postmenopausal woman	151 (39)	<.001	232 (60)	<.001	68 (18)	1.0	175 (45)	<.001
55-year-old premenopausal woman	137 (36)	<.001	260 (68)	<.001	44 (11)	.024	207 (54)	<.001
55-year-old postmenopausal woman	196 (51)	<.001	329 (85)	<.001	48 (12)	.069	164 (43)	<.001
45-year-old man	199 (52)	<.001	282 (73)	<.001	56 (15)	.33	157 (41)	<.001
55-year-old man	210 (55)	<.001	340 (88)	<.001	46 (12)	.042	152 (39)	<.001

EGD, esophagogastroduodenoscopy; No., number.

[a] Based on responses from 385 clinicians.

[b] The 30-year-old woman was used as reference for comparison.

Table 3. Agree/Disagree Statements Regarding IDA Workup[a]

Statement	Strongly Agree or Agree, No. (%)	Neutral, No. (%)	Disagree or Strongly Disagree, No. (%)
IDA patients should have colonoscopy performed	99 (26)	54 (14)	232 (60)
IDA patients should have EGD performed	69 (18)	63 (16)	253 (66)
IDA patients should have celiac serologies ordered	33 (9)	80 (21)	272 (71)
Negative colonoscopy rules out GI loss as cause of IDA	10 (3)	13 (3)	362 (94)
Negative EGD rules out malabsorption as cause of IDA	21 (5)	24 (6)	340 (88)
Negative celiac serologies rule out CD as cause of IDA	98 (25)	82 (21)	205 (53)
Routine referral to gastroenterologist for patients with IDA	187 (49)	66 (17)	132 (34)

EGD, esophagogastroduodenoscopy; IDA, iron-deficiency anemia; No., number.

[a] Based on responses from 385 clinicians.

the duodenum is biopsied, the recommended number of biopsies are infrequently performed.[24]

CD is ultimately diagnosed by endoscopic biopsy of the duodenum.[25] The rates of referral for upper endoscopy ranged from 10% to 55% among the different clinical scenarios, indicating knowledge of the need to exclude an upper-GI cause of IDA that may include CD as well as ulcers or tumors. However, this in itself does not ensure that patients receive the necessary duodenal biopsy to diagnose CD. In a study of a national endoscopic database, we found that anemic or iron-deficient patients undergoing upper endoscopy had duodenal biopsy performed only 38% and 50% of the time, respectively.[23]

Similarly to the responses for the individual theoretical patient cases, the majority of respondents did not believe that all patients diagnosed with IDA should have a basic GI workup performed. Previous guidelines and studies had suggested that all patients with IDA should have serologic testing for CD, men and postmenopausal women should have upper and lower endoscopy, and even premenopausal women may benefit from serologic testing and/or endoscopy.[3,7,16-18]

On univariate analysis, the only significant predictor for whether clinicians believed that all patients with IDA should have celiac serologic testing was the number of patients with IDA that they saw monthly. Perhaps these clinicians encountered more patients in their practices who were ultimately diagnosed with CD as the cause of IDA, which is why they considered testing for it more frequently. The BSG guidelines for investigating IDA estimate the pretest probability of CD in patients with IDA to be roughly 5%, and a recent study of a cohort of young men supports this.[26]

When several demographic variables were analyzed simultaneously, statistically significant predictors of screening for CD included subspecialty, patient age (pediatric vs adult), and years of clinical experience. Specialists in pediatric hematology were significantly more

likely than those in adult hematology to screen for CD in patients with IDA, perhaps because CD was formerly considered predominantly a disease of childhood.[27] Interestingly, the hematologists most likely to screen for CD based on experience were those with 0 to 5 years of experience since their fellowship, possibly owing to the recent increasing recognition of the frequency and danger of underdiagnosis of CD.[1,3] In addition, evidence exists that the true prevalence of CD has increased 4-fold over the last 50 years,[3] indicating that it is an emerging disease. It is counterintuitive that both oncologists and specialists in malignant hematology were more than 3 times as likely to screen for CD compared with specialists in benign hematology. Also of note, the majority of respondents worked at a university-affiliated hospital, indicating that they were likely interacting with hematology trainees and students. This further emphasizes the need for dissemination of knowledge about the prevalence of CD and the use of serologic testing in diagnosis.

The clearest limitation of our study is the relatively low response rate of 8.5%. Although a low response rate has the potential to introduce nonresponse bias, we were still able to acquire 385 complete responses with a broad range of demographics (Table 1). Possible causes for the low response rate include the use of an e-mail–based survey as opposed to an in-person survey, and the use of either incorrect or obsolete e-mail addresses. Another limitation is the use of a survey to assess clinical practice, as what hematologists actually order for patients may differ significantly from their survey responses. It is also difficult to draw substantial conclusions about pediatric hematologists given the small sample size included in our study.

It would be informative to collect data on hematologists' ordering practices to assess whether their survey responses correspond to clinical practice. Collecting data on other subspecialists, including gastroenterologists as well as primary care physicians, could reveal additional groups of physicians who are contributing to the underdiagnosis of CD and could potentially be targeted for education in the future.

Conclusion

Our study suggests that hematologists do not routinely screen patients with IDA for CD regardless of the characteristics of the patient. Certain demographic factors, such as years in practice and number of patients with IDA seen monthly, may increase the frequency of screening. The underdiagnosis of CD has serious health implications for affected individuals, and patients with newly diagnosed IDA present an opportunity for accurate diagnosis that should not be overlooked.

Disclosures

The authors have no real or apparent conflicts of interest to report.

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