Sex and racial disparities in duodenal biopsy to evaluate for celiac disease

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Background: Celiac disease (CD) is common but underdiagnosed in the United States. Serological screening studies indicate that, although CD occurs at the same frequency in both sexes, women are diagnosed more frequently than men (2:1). CD is less frequently diagnosed among black patients, though the seroprevalence in this group is not known.

Objective: To measure the rates of duodenal biopsy during EGD for symptoms consistent with CD.

Design: Retrospective cohort study.

Setting: Clinical Outcomes Research Initiative National Endoscopy Database, spanning the years 2004 through 2009.

Patients: Adults undergoing EGD for the indication of diarrhea, anemia, iron deficiency, or weight loss, in which the endoscopic appearance of the upper GI tract was normal.

Main Outcome Measurement: Performance of duodenal biopsy.

Results: Of 13,091 individuals (58% female patients, 9% black patients) who met the inclusion criteria, duodenal biopsy was performed in 43%, 45% of female patients and 39% of male patients ($P < .0001$). Black patients underwent duodenal biopsy in 28% of EGDs performed compared with 44% for white patients ($P < .0001$). On multivariate analysis, male sex (odds ratio [OR] 0.81; 95% CI, 0.75-0.88), older age (OR for 70 years and older compared with 20-49 years, 0.51; 95% CI, 0.46-0.57), and black patients (OR 0.55; 95% CI, 0.48-0.64) were associated with decreased odds of duodenal biopsy.

Limitations: Lack of histopathologic correlation with CD prevalence.

Conclusions: In this multiregional endoscopy database spanning the period from 2004 through 2009, rates of duodenal biopsy increased modestly over time, but overall remained low in patients with possible clinical indications for biopsy. Nonperformance of duodenal biopsy during endoscopy may be contributing to the underdiagnosis of CD in the United States. (Gastrointest Endosc 2012;76:779-85.)

Abbreviations: CD, celiac disease; CORI, Clinical Outcomes Research Initiative; OR, odds ratio.

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Celiac disease (CD) is common, with a seroprevalence of approximately 1% in the United States and Western Europe.[1-3] This autoimmune disease is associated with an increased risk of malignancy[4] and death,[5] risks that diminish in the general population in the years after diagnosis and institution of the only recognized treatment of CD, a gluten-free diet. Despite increasing rates of diagnosis, CD remains underdiagnosed in the United States, with less than 10% of patients with CD having received the diagnosis.[6] The proportion of undiagnosed CD patients in the United States far exceeds that of areas in Western and Northern Europe.[7,8] Because undiagnosed CD is associated with increased mortality,[2] efforts to understand the reasons for these low rates are warranted.

Factors related to the performance of GI endoscopy contribute to the underdiagnosis of CD. A recent analysis of a national pathology database found that among patients undergoing EGD with duodenal biopsy, only 35% had the recommended 4 specimens submitted, despite the finding that adherence to this standard led to a doubling of the CD diagnosis rates.[9] Similarly, an analysis of the Clinical Outcomes Research Initiative (CORI) National Endoscopy Database found that, among individuals undergoing EGD for indications including symptoms of CD, the vast majority (89%) did not undergo a duodenal biopsy during the procedure.[10] However, the time span of the latter study (spanning the years 2000-2003) was before the major seroprevalence study finding that CD is common,[1] and it is unknown whether practice patterns have changed in response to this knowledge.

We aimed to measure whether the performance of duodenal biopsy is increasing over time, by analyzing the CORI database spanning the years 2004 through 2009. We also aimed to identify sociodemographic and medical factors associated with the performance of duodenal biopsy during EGD.

Take-home Message

- Celiac disease (CD) is common but underdiagnosed, and factors related to the performance of duodenal biopsy may contribute to underdiagnosis in the United States.
- During EGD, women are more likely to undergo biopsy than men, despite equal CD seroprevalences; this may contribute to the higher rates of diagnosis among women.

METHODS

We performed a cross-sectional study of the CORI National Endoscopic Database. This database was established in 1995 with the goal of establishing a network of gastroenterologists to prospectively collect data related to endoscopy for clinical and research purposes.[11] Participating sites agree to use a structured computerized report generator to produce all endoscopic reports and comply with quality control requirements. The site's data files are transmitted electronically to a central data repository. The data that are transmitted from the local site to the National Endoscopic Database do not contain most patient or provider identifiers. After completion of quality control checks, data from all sites are merged in the data repository for analysis. Procedure counts are monitored on a weekly basis for atypical activity. The repository is checked for anomalies on a daily basis.

We queried the database for all adults (age 20 years and older) undergoing EGD during the period spanning January 1, 2004, through December 31, 2009, that listed 1 of the following indications in the primary indication field: anemia, iron deficiency, diarrhea, or weight loss. We included only those EGDs in which no focal abnormality anywhere in the upper GI tract was noted. These inclusion criteria were the same as those of the previous analysis during the earlier time period,[10] with the rationale that these indications can be manifestations of CD and that a normal-appearing duodenum is a common endoscopic finding in CD.[12]

The primary outcome was the performance of duodenal biopsy. We assessed the following variables for possible association with the primary outcome: year of the procedure, indication, patient age, sex, race (black vs white), ethnicity (Hispanic vs non-Hispanic), and region, as divided into Northeast (Massachusetts, New York, New Jersey, Ohio, Vermont), North Central (Indiana, Minnesota, Nebraska, North Dakota), Northwest (Oregon, Washington), Southeast (Florida, Georgia, Kentucky, North Carolina), South Central (Mississippi, Oklahoma, Tennessee, Texas), and Southwest (Arizona, California, Colorado, New Mexico, Nevada).

We used the χ^2 test for univariate analysis and the Cochran-Armitage test to assess for a temporal trend in biopsy performance. We performed multiple logistic regression to assess for independent associations with the performance of small-bowel biopsy. The following covariates were included a priori in the multivariate model: year of the procedure, age group, sex, race (categorized as white, black, and other), Hispanic ethnicity, practice setting, region, and indication for the procedure.

All statistical tests were performed by using SAS version 9.2 (SAS Institute, Cary, NC). The Institutional Review Board of Columbia University Medical Center reviewed this protocol and deemed it exempt because the data did not contain any patient identifiers when provided to the investigators.

RESULTS

We identified 13,091 individuals who underwent EGD who met the inclusion criteria during this 6-year period

Table 1. Characteristics of adult patients undergoing EGD for the indications of weight loss, diarrhea, iron deficiency, or anemia, 2004-2009 (N = 13,091)

Characteristic	No. (%) of patients
Year of procedure	
2004	2343 (18)
2005	2380 (18)
2006	2490 (19)
2007	2413 (18)
2008	1919 (15)
2009	1546 (12)
Sex	
Male	5515 (42)
Female	7576 (58)
Age group, y	
20-49	3539 (27)
50-69	5281 (40)
≥70	4270 (33)
Race	
White	11,489 (88)
Black	1141 (9)
Other	456 (3)
Ethnicity	
Hispanic	1006 (8)
Non-Hispanic	12,080 (92)
Practice type	
Community/health maintenance organization	8490 (66)
University	2580 (20)
Veterans Affairs medical center	1713 (13)
Region	
North Central	1611 (12)
Northeast	2464 (19)
Northwest	1494 (11)
South Central	2016 (15)
Southeast	1622 (12)
Southwest	3884 (30)
Indication	
Anemia	9074 (69)
Iron deficiency	377 (3)
Diarrhea	2039 (16)
Weight loss	1601 (12)

(Table 1). The majority of patients (7576; 58%) were female, and 11,489 (88%) were white. The majority of examinations (8490; 66%) were performed in a community or health maintenance organization setting. Anemia was the most common indication for endoscopy (9074; 69%), followed by diarrhea (2039; 16%), weight loss (1601; 12%), and iron deficiency (377; 3%).

Duodenal biopsy was performed in 43% of all patients (Table 2). The rate of biopsy increased each year of the observation period, from 35% in 2004 to 51% in 2009 (P for trend $<.0001$). Female patients were more likely than male patients to undergo duodenal biopsy (45% vs 39%, $P < .0001$). Biopsies were performed more frequently in younger patients (age, 20-49 years, 54%; age 50-69 years, 43%; age 70 and older, 33%; $P < .0001$). Only 28% of black patients underwent duodenal biopsy during EGD compared with 44% of white patients ($P < .0001$). There was marked regional variability in biopsy rates, with the highest rates in the Northwest (59%) and the lowest in the North Central region (19%, $P < .0001$). Biopsy rates were lower in academic settings (38%) than in community/health maintenance organization settings (43%) or Veterans Affairs medical centers (44%, $P < .0001$). The differences between the sexes, age groups, whites, and blacks and among the various indications remained stable over the 6-year period (Fig. 1); during this time, all groups had a modest increase in biopsy rates, but the disparities between these groups persisted.

The results of the multivariate analysis are shown in Table 3. Later year (odds ratio [OR] for 2009 vs 2004 1.97; 95% CI, 1.71-2.28) was associated with increased odds of duodenal biopsy, whereas male sex (OR 0.81; 95% CI, 0.75-0.88), older age (OR for 70 years and older compared with 20-49 years, 0.51; 95% CI, 0.46-0.57), black race (OR 0.55; 95% CI, 0.48-0.64), and Hispanic ethnicity (OR 0.69; 95% CI, 0.59-0.80) were associated with decreased odds of duodenal biopsy. Differences between regions, practice types, and clinical indication remained significant on multivariate analysis (Table 3).

DISCUSSION

In this analysis of a national endoscopy database encompassing a broad spectrum of endoscopy settings during the period 2004 through 2009, duodenal biopsy was performed in 43% of patients undergoing EGD for anemia,

TABLE 2. Variables associated with the performance of small intestinal biopsy during EGD

Characteristic	Biopsy performed, no. (%)	*P* value
Year of procedure		<.0001
2004	822/2,343 (35)	
2005	904/2,380 (38)	
2006	1,063/2,490 (43)	
2007	1,062/2,413 (44)	
2008	942/1,919 (49)	
2009	783/1,546 (51)	
Sex		<.0001
Male	2162/5515 (39)	
Female	3414/7576 (45)	
Age group, Y		<.0001
20-49	1904/3539 (54)	
50-69	2247/5281 (43)	
≥70	1424/4270 (33)	
Race		<.0001
White	5087/11,489 (44)	
Black	318/1,141 (28)	
Other	168/456 (37)	
Ethnicity		.7688
Hispanic	424/1006 (42)	
Non-Hispanic	5149/12,080 (43)	
Practice type		<.0001
Community/health maintenance organization	3665/8490 (43)	
University	988/2580 (38)	
Veteran's Administration medical center	751/1713 (44)	
Region		<.0001
North Central	311/1611 (19)	
Northeast	852/2464 (35)	
Northwest	874/1494 (59)	
South Central	919/2016 (46)	
Southeast	496/1622 (31)	
Southwest	2124/3884 (55)	
Indication		<.0001
Anemia	3449/9074 (38)	
Iron deficiency	188/377 (50)	
Diarrhea	1382/2039 (68)	
Weight loss	557/1601 (35)	

iron deficiency, diarrhea, or weight loss. Although the rate of biopsy increased over time, even in the last year of the analysis (2009), only 51% underwent duodenal biopsy. Older individuals, males, blacks, and Hispanics were less likely to undergo biopsy than younger individuals, women, and white individuals.

This is the first study to measure duodenal biopsy rates nationally since the report in 2003 that the prevalence of CD is nearly 1% in the United States,[1] significantly greater than previously thought.[13] Diagnosis rates appear to be increasing, based on data from Olmsted County[6] and from a large insurance claims database.[14] Despite these increasing diagnosis rates, there is evidence that CD remains underdiagnosed in this country. The prevalence of diagnosed CD in Olmstead County in 2001 was measured to be 0.04%, one twentieth of the true prevalence as measured by serological screening.[1,2,6] There are multiple potential steps along the path of a patient's symptomatic presentation during which a CD diagnosis may be missed, and there is evidence that appropriate testing and referral by the patient's primary care provider is crucial.[15] The recent study of biopsy practices, in which only 35% of EGDs with duodenal biopsy included the recommended number of specimens (≥4), suggests that factors related to the performance of endoscopy are, in part, responsible for low diagnosis rates.[9]

Our current study found that men undergoing EGD are less likely to undergo a duodenal biopsy than women. Most seroprevalence studies of CD found a similar prevalence among men and women,[1,2,16] but multiple epidemiological studies in the United States and elsewhere found that women are more likely to be diagnosed with CD,[5,6] and multiple studies of patients with CD have a female-to-male ratio of approximately 2:1.[17,18] This may be attributed to increased health care seeking by women, but, alternatively, this may be attributed to unproven beliefs among patients and physicians that CD predominantly affects women. Low rates of duodenal biopsy among men will lead to fewer diagnoses of CD among men, further reinforcing the notion that CD is less likely to develop in men.

Less is known about the prevalence of CD among black and Hispanic patients in the United States. Black patients in the United States have been included in 2 prevalence studies. Not et al[19] screened 2000 healthy blood donors for

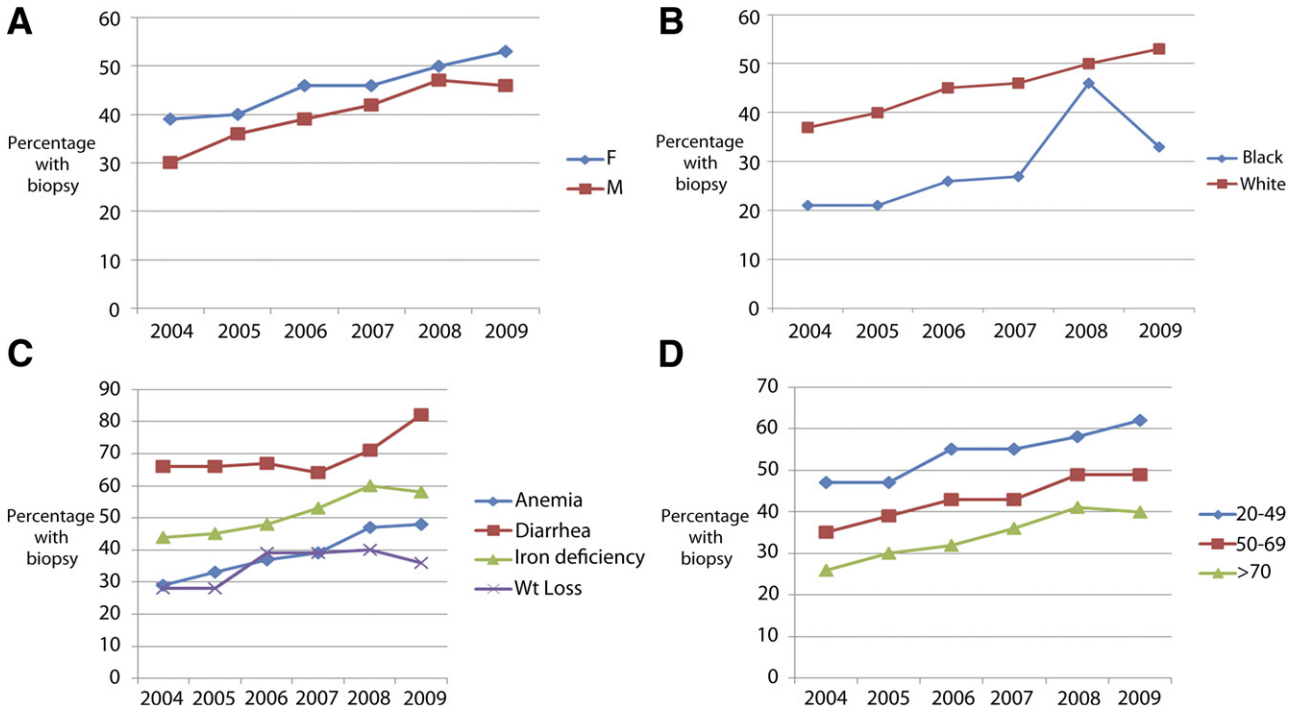

Figure 1. Temporal trends in small intestinal biopsy stratified by **(A)** sex, **(B)** race, **(C)** indication, and **(D)** age.

CD, and this cohort included 230 black patients. One of 230 patients (0.4%) had a positive endomysial antibody. In the multicenter study of CD prevalence by Fasano et al,[1] blacks comprised 3% of 13,145 screened individuals (n = 395). The prevalence of CD among asymptomatic black individuals was not reported, but among symptomatic black individuals, it was reported as 1:48, similar to that of white individuals. The overall prevalence of CD among all asymptomatic minorities (blacks, Hispanics, and Asians) was reported as 1:236. Apart from these 2 studies, there are no investigations of the prevalence of CD among black or Hispanic individuals in the United States. Black individuals are underrepresented among patients with diagnosed CD because they comprise only 1.3% of patients in the Celiac Disease Center at Columbia University (9 of 700 patients with biopsy-proven CD).[20] Although the prevalence of CD among black and Hispanic individuals in the United States is unknown, there are several studies from South America and the Caribbean reporting on CD, either prevalence or case series.[21-28] In a prevalence study in Argentina, 12 of 2000 healthy adults (0.6%) in Buenos Aires screened positive; given the large proportion of patients of Italian ancestry, that population may not be generalizable to the Hispanic population in the United States.[29] A study of healthy blood donors in Mexico found a seroprevalence of approximately 2%.[22] This study demonstrates that physicians are less likely to search for a diagnosis of CD in black and Hispanic patients, which may perpetuate the unproven notion that CD is rare in these groups.

Younger age was predictive of duodenal biopsy, with patients in the oldest category (70 years and older) nearly half as likely to have a biopsy compared with patients ages 20 to 49 years (multivariate OR 0.51; 95% CI, 0.46-0.57). Previously thought to primarily present in childhood, a CD diagnosis can be made at any age and is most commonly diagnosed during the fourth through sixth decades.[30] However, CD can present in the elderly, either as long-standing mild/subclinical disease[31] or as a de novo development.[32] Diagnosis and treatment of CD in the elderly may be especially important because this age group is most at risk of the subsequent development of refractory CD and enteropathy-associated T-cell lymphoma.[33,34] Although our knowledge regarding CD in the elderly increased in the previous decade, the low rates of duodenal biopsy in the oldest age group relative to the youngest have not changed over time (Fig. 1).

The reasons for the modest increase in biopsy rates over time are not obvious, but this is likely attributed in part to greater awareness of CD; this analysis begins in 2004, shortly after publication of the first national prevalence study in the United States, establishing the seroprevalence rate of 0.8%.[1] It could also reflect knowledge of low biopsy rates as established by a previous study.[10] This change could also be patient driven, given increased patient awareness of CD. Regardless of this cause, it is congruent with the modest annual increase in the number of specimens submitted during duodenal biopsy in a separate database study.[9]

This study has a number of limitations. The CORI database is not linked to pathology results, and although rates of duodenal biopsy could be measured, the results of said biopsies were not available. As such, the rate of CD

TABLE 3. Multiple logistic regression identifying variables associated with the performance of small intestinal biopsy during EGD

Characteristic	Odds ratio	95% CI	*P* value
Year of procedure			
2004	1.0	[ref]	[ref]
2005	1.15	1.01-1.31	.0336
2006	1.36	1.20-1.55	<.0001
2007	1.41	1.24-1.61	<.0001
2008	1.89	1.65-2.16	<.0001
2009	1.97	1.71-2.28	<.0001
Sex			
Male	.81	.75-.88	<.0001
Female	1.0	[ref]	[ref]
Age group			
20-49 y	1.0	[ref]	[ref]
50-69 y	.72	.66-.80	<.0001
≥70 y	.51	.46-.57	<.0001
Race			
White	1.0	[ref]	[ref]
Black	.55	.48-.64	<.0001
Other	.56	.46-.69	<.0001
Ethnicity			
Hispanic	.69	.59-.80	<.0001
Non-Hispanic	1.0	[ref]	[ref]
Practice type			
Community/ health maintenance organization	1.0	[ref]	[ref]
University	.54	.48-.60	<.0001
Veterans Affairs medical center	.78	.68-.89	.0002
Region			
North Central	.42	.36-.49	<.0001
Northeast	1.0	[ref]	[ref]
Northwest	2.69	2.33-3.11	<.0001
South Central	1.36	1.18-1.56	<.0001
Southeast	.82	.71-.94	.0061
Southwest	2.23	1.99-2.49	<.0001
Indication			
Anemia	1.0	[ref]	[ref]
Iron deficiency	1.42	1.14-1.78	.0018
Diarrhea	3.25	2.89-3.67	<.0001
Weight loss	.85	.75-.96	.007

diagnosis was not measured in this study, and so the impact of nonperformance of duodenal biopsy on CD diagnosis rates could not be quantified. Moreover, important clinical information that would have an impact on the pretest likelihood of CD, such as positive serology results or a family history, was lacking in this database. Because the aim of this study was to quantify endoscopist behavior in scenarios in which duodenal biopsy was likely indicated, the inclusion criteria were chosen to be most applicable to a patient who may have CD. Most patients undergoing EGD for the indication of anemia, iron deficiency, diarrhea, or weight loss would potentially benefit from duodenal biopsy to diagnose or exclude CD, especially if no obvious explanatory lesion is identified in the rest of the upper GI tract. Even a patient with negative serological study results should undergo duodenal biopsy if EGD is being performed, given the imperfect sensitivity of serology, which in some studies was less than 80%.[35] Race/ethnicity may be subject to misclassification because it was entered by the endoscopist and not by the patient. Strengths of this analysis include its multicenter national setting, representing a broad spectrum of practice types throughout the United States, the 6-year time span to evaluate for temporal trends, and the presence of racial and ethnic minorities that have been underrepresented in the study of CD.

We conclude that physicians performing EGD in the United States for a variety of indications that are compatible with CD presentation (anemia, iron deficiency, diarrhea, and weight loss) perform duodenal biopsy at variable rates and are less likely to perform duodenal biopsy on patients who are male, black or Hispanic, or elderly. Although biopsy rates have increased over time, the overall rate of duodenal biopsy during EGDs done for the indications mentioned was only 51% in 2009, lending further support to the notion that endoscopic practice is in part responsible for the underdiagnosis of CD in the United States. Future efforts should focus on increasing duodenal biopsy rates in the appropriate context and increasing the rate of CD diagnosis in symptomatic individuals.

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