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The prevalence of abnormal celiac antibodies and celiac disease in patients with suspected irritable bowel syndrome: a prospective multi-center US study

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Abstract

Background & Aims—Guidelines recommend that patients with symptoms of non-constipated inflammatory bowel syndrome (NC-IBS) undergo testing for celiac disease (CD). We evaluated the prevalence of CD antibodies and biopsy confirmed CD among patients with NC-IBS in a large US population.

Methods—In a study conducted at 4 sites, from 2003 to 2008, we compared data from 492 patients with symptoms of NC-IBS to 458 asymptomatic individuals who underwent colonoscopy

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BDC conceived and designed the study, was a principal investigator, and is primary author of the manuscript
JHR performed the statistical analysis, and provided critical revision of the manuscript for important intellectual content
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examinations for cancer screening or polyp surveillance (controls). All participants provided blood samples for specific and non-specific CD-associated antibodies. Additionally, patients with IBS were analyzed for complete blood cell counts, metabolic factors, erythrocyte sedimentation rates, and levels of C-reactive protein and thyroid-stimulating hormone. Any subjects found to have CD-associated antibodies were offered esophagogastroduodenoscopy and duodenal biopsy analysis.

Results—Of patients with NC-IBS, 7.3% had abnormal results in tests for CD-associated antibodies, compared to 4.8% of controls (adjusted odds ratio=1.49; 95% confidence interval, 0.76–2.90. *P*=.25). Within the NC-IBS group, 6.51% had antibodies against gliadin, 1.22% against tissue transglutaminase, and 0.61% against endomysium (*P*>.05 vs controls for all antibodies tested). CD was confirmed in 0.41% of patients in the NC-IBS group and 0.44% of controls (*P*>0.99).

Conclusions—Although CD-associated antibodies are relatively common, the prevalence of CD among patients with NC-IBS is similar to that among controls in a large US population. These findings challenge recommendations to routinely screen patients with NC-IBS for CD. More than 7% of patients with NC-IBS had CD-associated antibodies, indicating that gluten sensitivity might mediate IBS symptoms; further studies are needed.

Keywords

celiac disease; celiac antibodies; diarrhea; irritable bowel syndrome; population study; epidemiology; celiac disease incidence; inflammation

Introduction

The presence of gastrointestinal (GI) symptoms suggestive of the irritable bowel syndrome (IBS) is one of the most common reasons for referral to a gastroenterology specialist in the United States. IBS has been estimated to affect approximately 10-20% of the American population (1) and similar prevalence estimates have been reported from other countries. (2-3) The societal impact of IBS is significant, both in terms of direct and indirect costs as well as the impaired health related quality of life that patients with IBS endorse. (4-6)

IBS is one of a group of functional GI disorders, (7) and is characterized by a lack of reproducible or reliable physical abnormalities, biomarkers, or radiologic findings. Multiple symptom-based diagnostic criteria for IBS have been developed in an attempt to simplify and standardize its diagnosis. Manning and colleagues created the first group of diagnostic criteria in 1978. (8) The Rome Committee, a multinational consensus group of experts in functional GI disorders, created another set of criteria, ostensibly to improve the quality of clinical trials in the field of IBS. (9) Since their development, the Rome criteria for IBS have been modified several times, based on evolving evidence regarding the epidemiology, pathophysiology and natural history of the condition. (10-13)

Celiac disease is an autoimmune gastrointestinal disease that can result in symptoms similar to IBS and has an estimated prevalence of 0.7-1% in Western populations. (14) Celiac disease has been linked to other conditions including, but not limited to, diabetes, dermatitis herpetiformis, osteoporosis, infertility, and lymphoma. Celiac disease occurs when genetically susceptible patients are exposed to dietary gluten. The vast majority of individuals with celiac disease possess human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 and these HLA haplotypes appear to be central to the pathophysiologic basis of celiac disease as they are associated with the presentation of gluten peptides to $CD4^+$ T cells in the small bowel mucosa. The presentation of these peptides can result in the activation of intraepithelial lymphocytes via amplifying mechanisms that can ultimately lead to damage to the intestinal epithelium in the form of villous atrophy and eventually the development of

gastrointestinal symptoms, many of which can mimic IBS. While much has been learned about the pathophysiology of celiac disease, much remains to be discovered such as why some individuals with celiac disease fail to develop clinically significant symptoms, despite continued gluten intake

While celiac disease should be considered in the differential diagnosis of patients with IBS symptoms, it is not clear if the prevalence of celiac disease amongst patients with IBS is high enough to warrant routine screening. A recent systematic review and meta-analysis concluded that biopsy-proven celiac disease was four-fold more prevalent among patients with symptoms suggestive of IBS than in persons without such symptoms. (15) Unfortunately, almost all of the studies included in this analysis were from outside of the United States. This is potentially important as the most recent evidence-based guidance document on the management of IBS offered by the American College of Gastroenterology (ACG) IBS Task Force recommended that patients with clinical features suggestive of IBS with diarrhea (IBS-D) or IBS with a mixed bowel pattern (IBS-M) undergo routine serological screening for celiac disease. (16)

Herein we report the findings from the first prospective, multi-center US study comparing the prevalence of abnormal celiac antibodies and biopsy proven celiac disease in patients with non-constipated IBS to that of healthy volunteers undergoing routine colorectal cancer screening.

Material and Methods

This was a multi-center, prospective, observational cohort study conducted at 4 US sites between August 2003 and August 2008 (National Naval Medical Center Bethesda, MD: Naval Medical Center Portsmouth, VA; Walter Reed Army Medical Center, Washington, D.C.; and the University of Michigan, Ann Arbor, MI). There were two study populations enrolled in this study. An IBS group composed of consecutive patients with symptoms suggestive of non-constipation predominant IBS (NC-IBS) who did not have “alarm features” suggestive of organic disease. Alarm features included symptoms such as unexplained weight loss, fever, significant GI bleeding, or historical features such as a family history of a first degree relative with colon cancer, celiac disease, or IBD. A control group consisted of asymptomatic persons undergoing colonoscopy for colorectal cancer screening or polyp surveillance. The Institutional Review Boards at each site approved this protocol and all patients provided informed consent prior to study participation.

Study Population

Adult patients aged 18-80 years old with symptoms suggestive of IBS were identified in the Gastroenterology clinics at the participating sites. Eligible patients with suspected NC-IBS fulfilled the Rome II criteria for IBS based on their responses to a questionnaire administered in the clinic. (17) Patients who fulfilled criteria for constipation-predominant IBS were not eligible for enrollment due to the design of the study and inclusion of diagnostic evaluations, such as colonoscopy, that were not felt to be clinically appropriate for patients with constipation-predominant IBS.

Patients in the IBS group were referred from their primary or secondary care physicians for a diagnostic evaluation of their IBS symptoms. Patients were excluded from the study if they had been previously diagnosed with co-morbid conditions that could have explained their GI symptoms (e.g. celiac disease, colon cancer, inflammatory bowel disease (IBD), scleroderma, small intestinal bacterial overgrowth, uncontrolled thyroid disease or diabetes). Patients with previous GI or intestinal (large or small bowel) surgery, with the exception of appendectomy or cholecystectomy, were also excluded. Patients reporting “alarm features”

were not eligible for enrollment, nor were women who were pregnant or breast-feeding or patients who had undergone previous diagnostic testing for their IBS symptoms were excluded from enrollment. No participants had been previously tested for celiac disease.

The control group consisted of individuals who were scheduled for screening or surveillance colonoscopy, either due to primary care referrals or self-referral. Controls were recruited from the procedure units of the participating study sites prior to their colonoscopy. All controls completed the same Rome II GI symptom questionnaire to confirm the absence of IBS symptoms. Patients with IBS symptoms, a history of colorectal cancer or other organic gastrointestinal disease were not eligible to serve as controls.

Experimental Protocol

Participants provided blood samples for celiac disease antibody panels and HLA-typing prior to undergoing colonoscopy. The celiac disease antibody panels included the following tests: anti-gliadin IgG ELISA (AGA IgG) with a reference range <10 U/ml, anti-gliadin IgA (AGA-IgA) with a reference range <5 U/ml, anti-human tissue transglutaminase IgA ELISA with a reference range <4 U/ml (TTG), anti-endomysial IgA indirect immunofluorescence assay using monkey esophagus as the substrate (EMA) with a reference range negative, and total serum IgA by nephelometry with a reference range of 44-441 mg/dl. HLA-DQ2 and HLA-DQ8 were determined using PCR amplification and 72 probe hybridizations for the detection of allelic variants using proprietary methods. All testing was performed by Prometheus™ Therapeutics and Diagnostics (Prometheus Laboratories Inc., San Diego, CA). Patients in the IBS group had the following additional blood tests obtained: complete blood count, complete metabolic panel, erythrocyte sedimentation rate, C-reactive protein, and thyroid stimulating hormone.

Any celiac disease antibody (AGA IgG, AGA IgA, TTG, or EMA) above the reference range was considered to be an abnormal (positive) test result. All patients (regardless of indication for colonoscopy) with any positive celiac disease antibody test were offered esophagogastroduodenoscopy (EGD) with at least 4 duodenal biopsies to confirm the diagnosis of celiac disease. These biopsies were obtained from the second and third portions of the duodenum using a forward viewing endoscope and additional biopsies, including from the duodenal bulb, were left to the discretion of the endoscopist. All biopsies were placed in 10% formalin, processed in accordance with each participating center's standard anatomic pathology specimen processing protocol, stained with hematoxylin and eosin, and examined by staff pathologists at each institution. A blinded expert GI pathologist subsequently reviewed all duodenal biopsies obtained from individuals who had abnormal celiac antibodies Patients were considered to have celiac disease if they had abnormal celiac antibody test results and also demonstrated small intestinal biopsy findings of villous atrophy and/or increased intraepithelial lymphocytes (IELs) based on the interpretation of the expert GI pathologist.

Statistical analysis

A priori sample size calculations were based on published existing data regarding the prevalence of celiac disease. The sample size of 1000 was based on the suspected prevalence of celiac disease being 1% in the general population and 5% in the IBS population. Recent epidemiological studies using blood donor analysis indicate that the prevalence of celiac disease in the US population is approximately 0.75%. (20) If the prevalence of celiac disease in patients with uninvestigated IBS symptoms is as high as 5% as suggested in the UK literature, (21) then 416 patients would be required in both the control and experimental arms to achieve 90% power to detect a two-sided alpha of 0.05. Formal data analysis comparing prevalence rates of celiac disease in the IBS group and the control group were

performed at the University of Michigan. Statistical comparisons of findings between the IBS and control groups are reported by t-test for normally distributed parameters. For categorical comparisons, Chi-square was used unless cells had expected counts less than 5, in which case Fisher's exact test was used. Logistic regression was performed to estimate the odds of celiac disease or a positive serology, adjusted for age and sex. A p-value of less than 0.05 was considered statistically significant. Additional analyses stratified by age (dichotomized at 50 years), sex and different definitions of biopsy-proven celiac disease were performed. All analyses were carried out using SAS 9.2 (SAS Institute Inc., Cary, NC)

Results

Study Population

Four hundred and ninety-two patients with symptoms suggestive of IBS and 458 healthy volunteers were enrolled in this study. The demographic characteristics of the IBS and control groups are shown in Table 1. Patients with suspected IBS were significantly younger and more likely to be female compared to the control group (mean age 40.72 years vs. 54.44 years, $p<0.0001$, 70% vs. 41% female, $p<0.0001$, respectively). There were no significant differences in the races of the two groups with the largest proportions of study participants being Caucasian (81.16%) or African-American (10.32%).

Serologic and Histologic Findings

The prevalence of abnormal celiac disease antibody tests in the IBS and control groups are shown in Table 2. The prevalence of low IgA levels was 0.63% (6/950) and was not different between the two study groups ($p=0.93$). No participants were found to have complete absence of IgA. Overall 6.11% (58/950) of the study population had at least one abnormal celiac disease antibody level. Among IBS patients, 7.32% (36/492) had at least one abnormal celiac disease antibody test result compared to 4.80% (22/458) of the controls (adjusted odds ratio (aOR) = 1.49; 95% confidence interval, CI = 0.76, 2.90, $p = 0.25$, adjusted for age and sex). The most common abnormal celiac test in study participants was elevated AGA IgG with an overall prevalence of 4.0% (38/950). In the IBS group the prevalence of abnormal AGA IgG was 4.88% (24/492) compared to 3.06% (14/458) in controls (aOR = 1.19; 95% CI = 0.50, 2.79; $p=0.70$). Abnormal AGA IgA was identified in 1.68% (16/950) of the study population; 1.63% (8/492) in the IBS group and 1.75% (8/458) in controls (aOR = 1.41; 95% CI = 0.47, 4.22; $p = 0.54$). The overall prevalence of abnormal TTG was 0.85% (8/950) and was more common in IBS patients (1.22%; 6/492) compared to controls (0.44%; 2/458) but this difference was not statistically significant (aOR = 3.87; 95% CI = 0.61, 24.74; $p=0.15$). Abnormal EMA was the least common abnormal celiac disease antibody test observed, occurring in only 0.53% (5/950) of the study population and was not different between the IBS patients (0.61%; 3/492) or controls (0.44%; 2/458) (aOR = 1.65; 95% CI = 0.17, 15.42; $p=0.66$).

The prevalence of either the DQ2 or DQ8 haplotype among IBS patients (46.34%; 228/492) was lower compared to controls (52.62%; 241/458) (aOR = 0.71; 95% CI = 0.51, 0.97; $p = 0.03$). This was due to a lower prevalence of the DQ2 haplotype among IBS patients than controls (33.3% vs. 39.3%; aOR = 0.61; 95% CI = 0.44, 0.86; $p = 0.004$). The prevalence of the DQ8 haplotype was less common, occurring in 17.6% of the study population, with similar frequencies in IBS patients (16.46%; 81/492) and controls (18.12%; 83/458) (aOR = 1.14; 95% CI = 0.76, 1.70; $p = 0.54$).

Celiac disease, defined as any abnormal celiac disease antibody test result and duodenal mucosal histology demonstrating villous atrophy and/or increased intraepithelial lymphocytes (IELs), was confirmed in 4 study participants (0.42%). The prevalence of

confirmed celiac disease in the IBS group of 0.41% (2/492) was similar to that in the control group (0.44%; 2/458; p > 0.99, Fisher's exact test). The celiac antibody and HLA profiles of study patients identified with celiac disease are shown in Table 3. All subjects diagnosed with celiac disease had abnormal EMA and TTG as well as the DQ2 haplotype and all were Caucasian. Duodenal biopsies from the 2 patients with suspected IBS diagnosed with celiac disease demonstrated villous atrophy and increased IELs while the biopsies from the 2 controls diagnosed with celiac disease demonstrated only increased IELs. (Table 3) The percentage of patients with an abnormal celiac disease antibody test result, positive HLA DQ2 or DQ8 haplotype, but no histologic evidence of celiac disease was similar in the 2 study groups (2.18% of controls (10/458) and 1.83% of IBS patients (9/492, aOR = 0.92; 95% CI = 0.31, 2.72; p = 0.88). In these participants, the most common abnormal celiac antibody test result was AGA IgG. None of the patients found to have a positive AGA IgG test result had a histological diagnosis of celiac disease.

Stratification of comparisons by age or sex did not result in meaningfully different results. In subjects < 50 years of age, the prevalence of celiac disease was 0.53% (2/376) in IBS patients vs. 1.79% (1/56) in controls (p=0.34) and in those ≥ 50 years of age, 0 patients in the IBS group compared to 0.25% (1/393) of controls were diagnosed with celiac disease (p>0.99). Among men, 0.69% (1/145) with IBS were diagnosed with celiac disease compared to 0.75% (2/266) of controls (p>0.99). When the definition of celiac disease was made to require the presence of abnormal celiac disease antibodies and duodenal biopsies with increased IELs AND villous atrophy, no patients in the control group fulfilled celiac disease criteria and, using a 1/2 count correction per cell, the estimated OR = 4.73 for the diagnosis of celiac disease in the IBS group vs. controls, with a 95% CI 0.23 - 98.81, indicating significant estimate inaccuracy.

Discussion

This study represents the first large-scale, prospective comparison of celiac disease prevalence between patients with symptoms suggestive of IBS and healthy controls from the US. This study used a comprehensive antibody panel to screen for, and small bowel biopsies to confirm, the diagnosis of celiac disease, and failed to demonstrate statistically significant differences in the prevalence of abnormal antibody tests or biopsy-proven celiac disease between the two groups. The prevalence of biopsyproven celiac disease in patients with IBS (0.41%) was similar to the prevalence of 0.20% to 1.15% described in other US and non-US populations. (20-25) El-Salhy and colleagues recently reported a 0.4% prevalence of biopsy proven celiac disease in 968 IBS patients from Norway, all of whom fulfilled the Rome III criteria for IBS-D. (26)

In the current study, testing for celiac disease with a comprehensive antibody panel that included AGA, TTG, and EMA antibodies as well as HLA typing ultimately altered the diagnosis in only 2/492 patients with suspected IBS. While our results indicated that patients with suspected IBS might be 49% more likely to have abnormal celiac antibody tests than healthy controls, this discrepancy appeared to be primarily due to a non-statistically significant increased frequency of abnormal AGA IgG. All study subjects who were diagnosed with celiac disease in the current trial demonstrated elevated TTG and EMA antibodies. This observation is similar to several recent studies that evaluated the population prevalence of celiac disease in different settings. (27-28). In the study by Katz et al, the prevalence of celiac disease in a predominantly Caucasian population from a geographically isolated area in the US was 0.8%, (27) while Walker and colleagues found a prevalence of celiac disease of nearly 2% in a Swedish, population-based study. (28) Both of these studies used a sequential testing technique, with TTG as the first test followed by EMA confirmation and showed that this diagnostic approach optimized the sensitivity of TTG

screening. Neither employed testing for anti-gliadin antibodies. Additionally, in both of these studies, the presence of gastrointestinal symptoms did not demonstrate strong correlation to the presence of celiac antibodies or biopsy-proven celiac disease. (27-28)

We found the prevalence of celiac disease in our patient population to be lower than that described in a recent systematic review/meta-analysis describing the prevalence of celiac disease in patients with suspected IBS. (15) This review identified seven case-control studies of 2,978 individuals (1,052 with IBS) which used EMA or TTG antibodies to screen for celiac disease. (21, 29-34) Three percent of the IBS cohorts, compared with 0.70% of controls, were found to have a positive EMA or TTG antibody, or both (OR = 2.94, 95 % CI=1.36-6.35). More importantly, in a separate analysis of five studies (21, 30, 32-34), 34 of 952 IBS patients compared with 12 of 1,798 controls were found to have both serologic (AGA, EMA or TTG antibodies) and small bowel biopsy evidence of celiac disease (3.57% vs. 0.67%; OR=4.34, 95 % CI=1.78-10.61). Of note, the populations in these reports, with the exception of the preliminary findings associated from the current study (33), did not include a US population.

We believe that the frequency with which abnormal AGA IgG antibodies were identified in the patients with suspected IBS in our study may be an important observation, despite the fact that the differences between the two groups was not statistically significant. While no longer considered a standard celiac disease screening test due to its relatively low sensitivity and specificity, (35) patients with suspected IBS in our study were nearly twice as likely as controls to have an elevated AGA IgG antibody. However, this might be due to effects of age or sex rather than directly related to IBS. Even though none of the IBS patients with abnormal AGA IgG levels fulfilled the histologic criteria for celiac disease, one wonders whether elevated AGA IgG might be related to the generation of IBS-like symptoms in a susceptible individual. Certainly, some patients diagnosed with IBS relate symptom onset to the ingestion of a meal. More specifically, a subset of IBS sufferers link their symptoms to the ingestion of gluten containing foods and report that gluten exclusion results in substantial symptom improvement. Such patients are frequently described as “gluten sensitive” and have been the subject of recent clinical studies and reviews. (36-37) A recent report from Sapone et al. compared and contrasted clinical and laboratory features among patients with gluten sensitivity, celiac disease, and healthy, gluten tolerant controls. (38) These investigators found that gluten sensitivity, characterized by intolerance to gluten-containing foods without evidence of small intestinal damage, was more likely to be associated with activation of innate, rather than adaptive, immune responses seen with celiac disease. Intestinal permeability was preserved in gluten sensitive patients as was expression of tight junction proteins. Interestingly, gluten sensitivity was associated with a greater degree of increased IELs compared to celiac disease and gluten tolerance. Importantly, none of the gluten sensitive patients in the Sapone study had abnormal anti-TTG or EMA antibodies, but 46.15% had elevated AGA IgA and 50% had elevated AGA IgG.

The current study was not designed to address the issue of gluten sensitivity and additional studies are needed to better understand this interesting and poorly understood group of patients. While it is possible that some of these patients have latent celiac disease and that others might suffer from an as yet undefined immunological response to gluten, another possibility is that patients with gluten sensitivity share features with persons affected by carbohydrate malabsorption/maldigestion. An underappreciated fact is that wheat serves as one of main dietary sources of fructans. (39) Fructans are indigestible, nonabsorbed carbohydrates that upon reaching the colon are fermented by the bacterial flora and recent data suggests that fructan ingestion can cause GI symptoms (40) and that dietary exclusion can improve GI symptoms in some patients with IBS. (41)

There are several limitations to our study. The ages and genders of the IBS and control groups were not matched. These differences were recognized *a priori* but deemed unavoidable given our selection of a convenience sample of healthy persons undergoing colonoscopy for colorectal cancer screening or polyp surveillance to serve as controls. We do not feel that the demographic differences identified between the study groups significantly influenced our results and stratified analysis by age and sex did not alter our findings significantly.

Another potential limitation is that our study population did not include patients with IBS-C. Because constipation is a relatively infrequent complaint of patients with celiac disease, we were concerned that the inclusion of patients with IBS-C might compromise our ability to fully appreciate the overlap between celiac disease and IBS. As this study failed to identify a difference in the prevalence of celiac disease between NC-IBS and controls, we doubt that the inclusion of patients with IBS-C would have altered our results. Furthermore, the clinical data collected at patient enrollment did not allow for the reliable division of the NC-IBS cohort into diarrhea-predominant IBS (IBS-D) or mixed bowel habit IBS (IBS-M). The inability to reliably subgroup the NC-IBS patients was related to our focus on excluding IBS-C patients and use of the Rome II criteria which provide a definition for IBS-D but not for IBS-M. (19) The Rome II criteria were chosen for this study because they were the prevailing symptom-based criteria for IBS at the time that this study was conceived. This is a potentially important point as it is possible that the prevalence of celiac disease may have been higher had we enrolled only patients with IBS-D.

The power calculation was based on an expected prevalence of celiac disease of 5% in the IBS group versus 1% in the control group. The low prevalence of celiac disease observed in this study may have compromised the statistical power of the study and the reliability of our estimates. The estimated prevalence of 5% of celiac disease in the IBS group used in the power analysis was based on estimates published in the medical literature at the time that the study was designed (2004). Departing from 3% or 3.6% versus 0.7% in controls would have resulted in a required sample size of 600-800 per group. Basing the power calculation on an expected difference in prevalence of 1% versus 0.5% would have resulted in a study requiring more than 6000 participants per group, which is unlikely to be feasible.

It is possible that our study underestimated the true prevalence of biopsy-proven celiac disease in IBS patients since the protocol required the endoscopist to obtain only 4 biopsies from the second and third portions of the duodenum. The optimal number and location of small bowel mucosal biopsies needed to diagnose celiac disease remains controversial. A recent study found that 90% of celiac disease patients could be identified with as few as 2 small intestinal biopsies and 100% with 4 biopsy specimens. (42) Nonetheless, patchy histologic abnormalities have been reported in celiac disease and the possibility of sampling error during the procurement of small bowel biopsies in patients with abnormal celiac antibody tests should be considered. (43-45) Additionally, interobserver variability regarding histological evaluation of small bowel biopsies in patients with celiac disease has been reported. (46) We attempted to minimize this by having all biopsy specimens from patients with abnormal celiac antibodies interpreted by a single expert GI pathologist. Furthermore, there was no difference in the proportion of subjects with abnormal serology in conjunction with HLA-DQ2 or DQ8 between the IBS and control groups, making it unlikely that our negative findings are due to misclassification of celiac disease histologically. We note that no information regarding diet was collected prior to serological testing or upper endoscopy. It is possible that some patients either voluntarily or unconsciously avoided foods containing gluten prior to testing. This could have caused us to underestimate the prevalence of celiac disease in either study cohort. Nonetheless, our study mimics clinical practice where patients are rarely queried about their diet prior to diagnostic testing for

celiac disease. Finally, our study did not include a formal evaluation of the response to a gluten-restricted diet in patients with abnormal celiac antibody testing. Therefore, the clinical significance of abnormal antibody test results and the likelihood of a response to a gluten-restricted diet in the absence of histologic changes of celiac disease remains unclear.

In summary, the prevalence of celiac disease in our large, prospective evaluation of US patients with NC-IBS was 0.41%. This prevalence was similar to that observed in healthy controls (0.44%). Previous decision analytic models have found that screening for celiac disease is cost-effective when the prevalence of celiac disease in a specific population is 1% or greater. (47-48) Therefore our findings challenge recommendations to routinely screen for celiac disease in patients with NC-IBS (16, 49-50) Our study cannot address the cost effectiveness of routinely screening for celiac disease in patients with IBS-D and there are clearly situations in which screening for celiac disease in patients with IBS symptoms should be pursued. For example, patients with IBS symptoms who also have a family history of celiac disease or a personal history of type I diabetes mellitus, autoimmune thyroiditis, infertility, unexplained iron deficiency anemia, and premature osteoporosis, could be reasonably expected to have a higher pretest probability of celiac disease and should be tested. Finally, the finding of elevated levels of celiac antibodies in nearly 7% of patients with IBS in our study underscores the need to more fully understand the concept of gluten sensitivity. While we did not identify a statistically significant difference in the prevalence of celiac antibodies in NC-IBS patients compared to controls and the presence of AGA antibodies did not correlate to histologic changes consistent with celiac disease, the possible role of these antibodies in IBS requires additional study.

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Table 1
Demographic characteristics of participating subjects

Variable	Suspected IBS (492)	Healthy controls (458)	*P* value
Age (+/- SD)	40.72 (12.94)	54.44 (7.81)	< 0.0001
Female (%)	344 (69.92)	189 (41.27)	< 0.0001
Race (%)			
Caucasian	391 (79.47)	380 (82.97)	0.17
African American	48 (9.76)	50 (10.92)	0.56
Hispanic	21 (4.27)	7 (1.53)	0.01
Asian	11 (2.24)	12 (2.62)	0.70
American Indian	2 (0.41)	0 (0)	0.17
Other	4 (0.81)	7 (1.53)	0.30
Unknown	15 (3.05)	2 (0.44)	0.002
Marital status (%)			
Married	317 (64.43)	343 (74.89)	0.001
Divorced/Separated	40 (8.13)	33 (7.21)	0.56
Single	109 (22.15)	66 (14.41)	0.001
Other/Unknown	26 (5.28)	16 (3.49)	0.72

Table 2

Prevalence of abnormal celiac disease serum tests amongst among evaluable samples for participants in the IBS and control groups

Test	Suspected IBS (n=492), n(%)	Healthy controls (n=458), n(%)	*P* value	aOR (95% CI)
Any abnormal celiac disease test	36 (7.32)	22 (4.8)	0.25	1.49 (0.76, 2.90)
AGA IgG	24 (4.88)	14 (3.06)	0.70	1.19 (0.50, 2.79)
AGA IgA	8 (1.63)	8 (1.75)	0.54	1.41 (0.47, 4.22)
EMA	3 (0.61)	2 (0.44)	0.66	1.65 (0.17, 15.42)
TTG IgA	6 (1.22)	2 (0.44)	0.15	3.87 (0.61, 24.74)
Total IgA (low)	3 (0.61)	3 (0.66)	0.93	0.93 (0.19, 4.62)
DQ2	164 (33.33)	180 (39.30)	0.004	0.61 (0.44, 0.86)
DQ8	81 (16.46)	83 (18.12)	0.54	1.14 (0.76, 1.70)

CD= celiac disease, AGA= antigliadin antibody, EMA=anti-endomysial antibody, TTG= anti-tissue transglutaminase antibody, IgG=immunoglobulin G, IgA=immunoglobulin A, aOR = adjusted odds ratio (for age and sex), CI = confidence interval

Table 3

Laboratory characteristics of patients diagnosed with celiac disease

Group	Study site	Abnormal (Yes/No)				Present (Yes/No)		Duodenal histology
		AGA IgG	AGA IgA	EMA	TTG IgA	DQ2	DQ8	
Control	Bethesda	No	Yes	Yes	Yes	Yes	No	Increased IELs
Control	Bethesda	No	No	Yes	Yes	Yes	No	Focally increased IELs
IBS	Bethesda	No	No	Yes	Yes	Yes	No	Villous atrophy and increased IELs
IBS	Michigan	No	No	Yes	Yes	Yes	No	Villous atrophy and increased IELs

AGA= antigliadin antibody, EMA=anti-endomysial antibody, TTG= anti-tissue transglutaminase antibody, IgG=immunoglobulin G, IgA=immunoglobulin A IELs=intraepithelial lymphocytes

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