REVIEW ARTICLE

Yield of Diagnostic Tests for Celiac Disease in Individuals With Symptoms Suggestive of Irritable Bowel Syndrome

Systematic Review and Meta-analysis

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Background: Individuals with irritable bowel syndrome (IBS) report abdominal pain, bloating, and diarrhea, symptoms similar to those in celiac disease. Studies suggest that the prevalence of celiac disease is increased in individuals with IBS; however, evidence is conflicting, and current guidelines do not always recommend screening for celiac disease in these individuals.

Methods: We conducted a systematic review and meta-analysis to estimate prevalence of celiac disease in unselected adults who met diagnostic criteria for IBS. MEDLINE (1950 to May 31, 2008) and EMBASE (1980 to May 31, 2008) were searched. Case series and case-control studies that used serologic tests for celiac disease were eligible for inclusion. Prevalence of positive serologic indications of celiac disease and biopsy-proved celiac disease were extracted and pooled for all studies and were compared between cases and controls using an odds ratio and 95% confidence interval.

Results: Fourteen studies were identified comprising 4204 individuals, of whom 2278 (54%) met diagnostic criteria for IBS. Pooled prevalence of positive IgA-class antigliadin antibodies, either positive endomysial antibodies or tissue transglutaminase, and biopsy-proved celiac disease were 4.0% (95% confidence interval, 1.7-7.2), 1.63% (0.7-3.0), and 4.1% (1.9-7.0), respectively. Pooled odds ratios (95% confidence intervals) for positive IgA-class antigliadin antibodies, either positive endomysial antibodies or tissue transglutaminase, and biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS compared with controls without IBS were 3.40 (1.62-7.13), 2.94 (1.36-6.35), and 4.34 (1.78-10.6).

Conclusion: Prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS was more than 4-fold that in controls without IBS.

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IRRITABLE BOWEL SYNDROME (IBS) IS a functional disorder of the gastrointestinal tract of unknown origin. The population prevalence in community surveys varies between 5% and 20% depending on the criteria used to define its presence,[1-5] and the condition is more common in female and younger individuals.[2,6-8] The natural history often follows a chronic relapsing-remitting course.[9-11] Affected individuals report symptoms such as lower abdominal pain, diarrhea, and abdominal bloating or distention.[12]

Celiac disease is a chronic enteropathy of the small intestine caused by intolerance to gluten, a constituent of wheat, barley, and rye. Ingestion of gluten by susceptible individuals causes morphologic changes in small intestinal mucosa, leading to villous atrophy and ultimately to malabsorption. The prevalence in the general population of the United States is reported to be almost 1%.[13] Symptoms reported by patients with celiac disease include bloating, abdominal pain, and chronic diarrhea.[14] In contrast to IBS, symptoms may resolve if the disease is recognized and gluten is excluded entirely from the diet.

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Many patients with IBS seek medical advice because of their symptoms,[15,16] and a substantial minority are referred for a specialist opinion and undergo invasive examination to exclude an organic cause before the correct diagnosis is reached.[17-19] Current national guidelines discourage this approach, recommending that the diagnosis of IBS should be made on clinical grounds using symptom-based diagnostic criteria rather than following attempts to exclude all possible organic pathology by exhaustive investigation.[20-23] The American Gastroenterological Association and the British Society for Gastroenterology state that a clini-

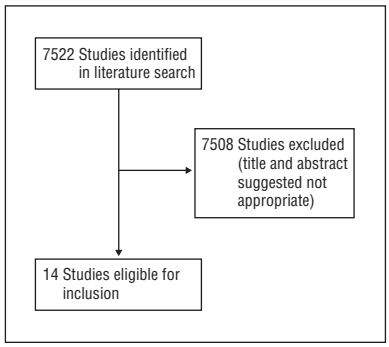

Figure 1. Flow diagram of assessment of studies identified in the systematic review.

cal diagnosis can be supplemented by the ordering of limited laboratory studies including complete blood cell count, erythrocyte sedimentation rate, and thyroid function tests,[20,21] whereas the American College of Gastroenterology position statement does not recommend investigation in patients with symptoms of IBS[22] unless alarming symptoms are present; however, it suggests that testing for celiac disease should be considered in patients with IBS with diarrhea. The routine exclusion of celiac disease in all patients with IBS is recommended only by the National Institute for Health and Clinical Excellence guidelines in the United Kingdom.[23]

Both IBS and celiac disease are prevalent conditions that share a common set of symptoms. The median time between seeing a physician because of symptoms and the ultimate diagnosis of celiac disease is 12 months.[14] Previous studies indicate that individuals meeting diagnostic criteria for IBS might be at higher risk of harboring celiac disease compared with controls without IBS. However, data are conflicting.[24-27] In light of this uncertainty, we performed a systematic review and meta-analysis to estimate (1) pooled prevalence of celiac disease in individuals meeting diagnostic criteria for IBS and (2) incremental odds of celiac disease in cases meeting diagnostic criteria for IBS vs matched controls without IBS.

METHODS

DATA SOURCES AND SEARCHES

A search of the medical literature was conducted using MEDLINE (1950 to May 31, 2008) and EMBASE (1980 to May 31, 2008). Studies of IBS were identified using the terms *irritable bowel syndrome* and *functional diseases, colon* (both as Medical Subject Headings and free text terms), and *IBS* and *functional adj5 bowel* (as free text terms). There were no language restrictions, abstracts of the articles identified were assessed for appropriateness to the study question, and all potentially relevant articles were obtained and evaluated in detail. Conference proceedings between January 1, 2000, and December 31, 2007, were hand searched to identify eligible studies published only as an abstract. Bibliographies of all identified relevant studies were used to perform a recursive search of the literature.

STUDY SELECTION

Case series and case-control studies in which unselected adults meeting diagnostic criteria for IBS were recruited and in which serologic tests for celiac disease were conducted in all enrolled individuals were eligible for inclusion. Diagnostic criteria for IBS included a physician opinion, questionnaire data, or specific symptom-based criteria including those of Manning et al[12] and the Rome criteria[28-30] or the scoring system of Kruis et al.[31] These could be supplemented by results of gastrointestinal tract examinations if individual studies performed these. We considered IgA-class antigliadin antibodies (AGAs), endomysial antibodies (EMAs), and tissue transglutaminase antibodies (tTGAs) as valid serologic markers of possible celiac disease. It was not compulsory for studies to include distal duodenal biopsy to confirm celiac disease in individuals with positive results of serologic tests to be eligible for inclusion. Because of a priori concerns about statistical handling of rare events, studies were eligible for inclusion only if they comprised 90 individuals or more. Detailed eligibility criteria for study inclusion were as follows: (1) study participants were adults (90% aged ≥16 years) with a presumed diagnosis of IBS according to physician opinion, questionnaire findings, or normal findings at examination or who met specific diagnostic criteria such as those of Manning et al,[12] Rome I, II, or III criteria, or the scoring system of Kruis et al[31]; (2) the design was a case series or case-control study; (3) participants were not specially selected; and (4) all participants underwent serologic testing for celiac disease and the results were recorded (IgA-class AGAs, EMAs, tTGAs, or any combination of these). Articles were independently assessed by 2 reviewers (A.C.F. and A.M) according to the prospectively defined eligibility criteria.

DATA EXTRACTION

All data were extracted by 2 reviewers (A.C.F. and P.M.) onto a spreadsheet (Microsoft Excel XP Professional Edition; Microsoft Corp, Redmond, Washington), and discrepancies were resolved by consensus. For case series, the number of individuals with positive results of serologic tests for celiac disease was expressed as a percentage of the total number of cases meeting diagnostic criteria for IBS. In case-control studies, this was performed for both cases and controls.

DATA SYNTHESIS AND ANALYSIS

The percentages of individuals meeting diagnostic criteria for IBS with either positive results of serologic tests or biopsy-proved celiac disease were combined for both case series and case-control studies to give a pooled prevalence in these individuals. In addition, for case-control studies, data were pooled for both cases and controls, and the prevalence of positive results of serologic tests and biopsy-proved celiac disease were compared between the 2 groups with an odds ratio (OR). If there were no cases or controls with positive results of serologic tests or biopsy-proved celiac disease in a single study, 0.5 was added to all 4 cells for the purposes of the analysis. We conducted sensitivity analyses according to study setting (population based, primary care, or secondary care), geographic region, diagnostic criteria used to define IBS, and IBS subtype (constipation-predominant, diarrhea-predominant, and alternating symptoms) to examine whether this had any effect on the prevalence or odds of either positive results of serologic tests or biopsy-proved celiac disease. Individual ORs were compared between these subgroups using the Cochran Q test.

Data were pooled using a random-effects model[32] to give more conservative estimates. Commercially available software (StatsDirect version 2.4.4; StatsDirect Ltd, Cheshire, England) was used to generate forest plots of pooled prevalences and pooled ORs with 95% confidence intervals (CIs). We assessed for evidence of publication bias for case-control studies by applying the Egger test to funnel plots.[33]

RESULTS

The search identified 7522 potentially relevant citations (**Figure 1**). From these, we identified 14 studies[24-27,34-43] comprising 4204 individu-

Table 1. Characteristics of Included Studies

Source	Type of Study	Country	Consecutive Patients Recruited	Setting	Diagnostic Tests for Celiac Disease	Diagnostic Criteria for IBS	Sample Size	No. of Individuals Meeting Diagnostic Criteria for IBS
Hin et al,[41] 1999	Case series	UK	Unclear	Primary care	EMA	Primary care physician diagnosis	132	132
Agréus et al,[34] 2000	Case-control	Sweden	NA	Population based	IgA-class AGA and EMA	Questionnaire based	100	50
Sanders et al,[25] 2001	Case-control	UK	Yes	Secondary care	IgA-class AGA, EMA, and distal duodenal biopsy	Rome II	600	300
Wahnschaffe et al,[37] 2001	Case series	Germany	Yes	Secondary care	IgA-class AGA, EMA, and tTGA	Organic disease excluded after intensive investigation	102	102
DeMarchi et al,[38] 2002	Case series	Italy	Yes	Secondary care	AGA, EMA, and distal duodenal biopsy[a]	Rome II	257	257
Sanders et al,[35] 2003	Case-control	UK	NA	Population based	IgA-class AGA, EMA, and distal duodenal biopsy	Rome II	1200	123
Shahbazkhani et al,[26] 2003	Case-control	Iran	Yes	Secondary care	IgA-class AGA, EMA, and distal duodenal biopsy	Rome II supplemented by investigation	210	105
Funka et al,[42] 2004	Case series	Latvia	Unclear	Secondary care	EMA	Physician diagnosis	191	191
Locke et al,[24] 2004	Case-control	US	NA	Population based	EMA and tTGA	Manning et al	128	50
Kennedy et al,[36] 2006	Case series	UK	Unclear	Primary care	AGA (class not stated) and EMA	Primary care physician diagnosis	138	138
van der Wouden et al,[27] 2007	Case series	Holland	Unclear	Secondary care	EMA	Rome II	148	148
Catassi et al,[43] 2007	Case series	US and Canada	Unclear	Primary care	tTGA and distal duodenal biopsy	Primary care physician diagnosis	255	255
Chey et al,[39] 2007	Case-control	US	Unclear	Secondary care	IgA-class AGA, EMA, tTGA, and distal duodenal biopsy	Rome II	640	364
Ozdil et al,[40] 2008	Case-control	Turkey	Unclear	Secondary care	IgA-class AGA, EMA, tTGA, and distal duodenal biopsy	Rome II supplemented by investigation	100	60

Abbreviations: AGA, antigliadin antibody; EMA, endomysial antibody; IBS, irritable bowel syndrome; NA, not applicable; tTGA, tissue transglutaminase antibody; UK, United Kingdom; US, United States.

[a] Did not provide separate data for positive AGAs and EMAs; therefore, only included in analyses for prevalence of biopsy-proved celiac disease after positive celiac serology.

als that used serologic tests for celiac disease in 2278 subjects (54%) meeting diagnostic criteria for IBS. There was 100% agreement between the 2 reviewers (A.C.F. and A.M.) when assessing study eligibility.

Detailed characteristics of all included studies are given in **Table 1**. Seven were case-control studies[24-26,34,35,39,40]; the controls were healthy individuals from the general population in 5 studies,[24,25,34,35,40] healthy siblings in 1 study,[26] and asymptomatic individuals undergoing colorectal cancer screening in 1 study.[39]

YIELD OF IgA-CLASS AGA-TESTING IN INDIVIDUALS MEETING DIAGNOSTIC CRITERIA FOR IBS

Seven studies[25,26,34,35,37,39,40] reported data on IgA-class AGAs in 1104 subjects. The percentage of individuals meeting diagnostic criteria for IBS who tested positive ranged from 0% to 18.0%, with a pooled prevalence of positive IgA-class AGAs of 4.0% (95% CI, 1.7%-7.2%) (**Table 2**). Five studies[25,26,35,39,40] offered duodenal biopsy to individuals who tested positive, and findings were consistent with celiac disease in 8 of 27 individuals (30%) with positive IgA-class AGAs.

Six studies[25,26,34,35,39,40] reported the number of cases meeting diagnostic criteria for IBS and controls without IBS testing IgA-class AGA positive. A positive IgA-class AGA was noted in 36 cases (3.6%) compared with 19 controls (1.0%). The OR (95% CI) for positive IgA-class AGA in cases compared with controls was, therefore, 3.40 (1.62-7.13), with no evidence of funnel plot asymmetry (**Figure 2**). No statistically significant differences were detected in ORs for posi-

Table 2. Pooled Prevalence and ORs (Compared With Controls Without IBS) for Positive Celiac Serology and Biopsy-Proved Celiac Disease in Cases Meeting Diagnostic Criteria for IBS According to Study Country, Setting, and Diagnostic Criteria Used to Define IBS

Variable	No. of Studies	No. of Individuals Meeting Diagnostic Criteria for IBS	Pooled Prevalence (95% CI)	No. of Studies	No. of Cases and Controls	OR (95% CI)
IgA-class AGAs						
All studies	7	1104	4.0 (1.7-7.2)	6	2850	3.40 (1.62-7.13)
North American studies	1	364	NA[a]	1	640	NA[a]
European studies	4	575	4.6 (0.8-11)	3	1900	4.38 (1.74-11)
Middle Eastern studies	2	165	4.7 (1.7-9.2)	2	310	6.80 (0.84-55)
Population-based/primary care–based studies	2	173	11 (2-26)	2	1300	3.89 (1.06-14)
Secondary care–based studies	5	931	2.3 (1.0-4.1)	4	1550	2.74 (0.92-8.12)
Studies using symptom-based diagnostic criteria	5	952	3.3 (1.8-5.3)	5	2750	4.10 (1.64-10)
Studies using physician opinion/questionnaire/ investigation to exclude organic disease	2	152	6 (2-35)	1	100	NA
EMAs or tTGA						
All studies	13	2021	1.63 (0.7-3.0)	7	2978	2.94 (1.36-6.35)
North American studies	3	669	2.3 (0.9-4.0)	2	768	1.55 (0.42-5.65)
European studies	8	1187	1.0 (0.2-2.1)	3	1900	3.67 (1.28-10.5)
Middle Eastern studies	2	165	4.4 (0.5-22)	2	310	5.53 (0.13-237)
Population-based/primary care–based studies	6	751	1.5 (0.6-3.0)	3	1428	1.97 (0.60-6.43)
Secondary care–based studies	7	1270	1.7 (0.4-4.1)	4	1550	3.99 (1.04-15)
Studies using symptom-based diagnostic criteria	7	1150	2.6 (0.8-5.3)	6	2878	3.07 (1.33-7.08)
Studies using physician opinion/questionnaire/ investigation to exclude organic disease	6	871	0.9 (0.03-1.9)	1	100	NA[a]
Biopsy-proved celiac disease						
All studies	7	1464	4.1 (1.9-7.0)	5	2750	4.34 (1.78-11)
North American studies	2	619	1.8 (0.9-3.0)	1	640	NA[a]
European studies	3	680	5.6 (3.3-8.6)	2	1800	5.45 (2.13-14)
Middle Eastern studies	2	165	4.4 (0.5-22)	2	310	5.53 (0.13-237)
Population-based/primary care–based studies	2	378	3.1 (1.6-5.1)	1	1200	NA[a]
Secondary care–based studies	5	1086	4.4 (1.4-8.9)	4	1550	4.26 (1.06-17)
Studies using symptom-based diagnostic criteria	6	1209	4.3 (1.7-8.0)	5	2750	4.34 (1.78-11)
Studies using physician opinion/questionnaire/ investigation to exclude organic disease	1	255	NA[a]	0	NA[a]	NA[a]

Abbreviations: AGAs, antigliadin antibodies; CI, confidence interval; EMAs, endomysial antibodies; IBS, irritable bowel syndrome; NA, not applicable; OR, odds ratio; tTGA, tissue transglutaminase antibody.
[a]No studies to combine for analysis.

tive IgA-class AGAs in European vs Middle Eastern studies or for population-based and primary care–based studies vs secondary care–based studies (Table 2).

YIELD OF EMA OR tTGA-TESTING IN INDIVIDUALS MEETING DIAGNOSTIC CRITERIA FOR IBS

Thirteen studies[24-27,34-37,39-43] used either EMAs or tTGAs in 2021 individuals, 41 (2.0%) of whom tested positive. The percentage of individuals testing positive ranged from 0% (in 5 studies) to 11.4%, and the pooled percentage (95% CI) testing positive in all 13 studies was 1.63% (0.7%-3.0%) (Table 2). Five studies[25,26,35,39,43] provided data on duodenal biopsy results in those testing positive, with 37 of 1147 individuals (3.2%) testing positive and being offered duodenal biopsy; 36 accepted. Of these, 33 individuals (92%) had histologic changes in keeping with celiac disease; therefore, 33 of 1147 individuals (2.9%) in these 5 studies had biopsy-confirmed celiac disease.

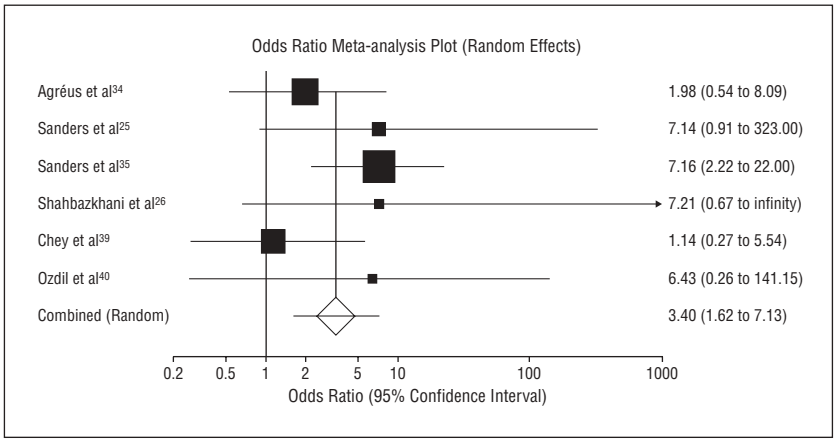

Figure 2. Pooled odds ratio for positive IgA-class antigliadin antibodies in case participants meeting diagnostic criteria for irritable bowel syndrome vs control participants. The solid squares indicate the individual study result; the size of the squares, the weight that each study contributes to the overall meta-analysis; and the diamond, the 95% confidence interval for the pooled odds ratio when all study results are combined.

Seven case-control studies[24-26,34,35,39,40] used EMAs or tTGAs in 2978 individuals, 1052 (35%) of whom met diagnostic criteria for IBS. The number of cases testing positive for EMAs or tTGAs was 32 (3.0%) compared with 13 of 1926 controls (0.7%). The percentage of cases testing positive in each study ranged from 0% to 11.4% compared with 0% to 2.6% of controls. The OR (95% CI) for testing positive for EMAs or tTGAs in cases meeting diagnostic criteria for IBS compared with controls was 2.94 (1.36-6.35) (**Figure 3**), with no evidence of funnel plot asymmetry. No statistically significant differences were detected in ORs for positive EMAs or tTGAs in US vs European or Middle Eastern studies or for population-based and primary care–based studies vs secondary care–based studies (Table 2).

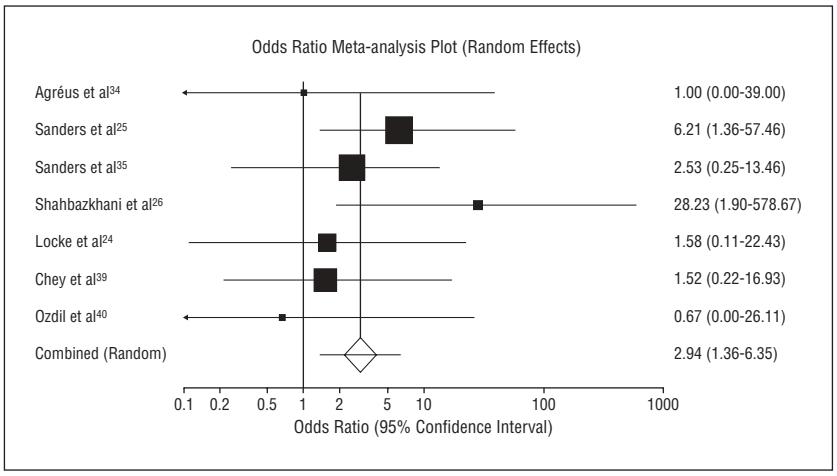

Figure 3. Pooled odds ratio for positive endomysial or tissue transglutaminase antibodies in case participants meeting diagnostic criteria for irritable bowel syndrome vs control participants. The solid squares indicate the individual study result; the size of the squares, the weight that each study contributes to the overall meta-analysis; and the diamond, the 95% confidence interval for the pooled odds ratio when all study results are combined.

YIELD OF DISTAL DUODENAL BIOPSY AFTER POSITIVE CELIAC SEROLOGIC FINDINGS IN INDIVIDUALS MEETING DIAGNOSTIC CRITERIA FOR IBS

Seven studies[25,26,35,38-40,43] followed positive celiac serology screening of any type with the offer of duodenal biopsy in 1464 individuals. There were 62 (4.2%) subjects with biopsy-proved celiac disease after initial screening using serology followed by duodenal biopsy, with percentages ranging from 0% to 11.4%. The pooled prevalence (95% CI) of biopsy-proved celiac disease in individuals in these 6 studies was 4.1 (1.9-7.0) (Table 2). Two studies[25,26] reported prevalence of biopsy-proved celiac disease according to IBS subtype, with a pooled prevalence of 7% (1.4%-17%) in constipation-predominant IBS, 8% (2%-17%) in diarrhea-predominant IBS, and 8% (3%-14%) in those with alternating symptoms.

Five case-control studies[25,26,35,39,40] followed positive celiac serologic tests with the offer of duodenal biopsy in 2750 individuals, of whom 952 (35%) met diagnostic criteria for IBS and 1798 were controls. Thirty-four cases (3.6%) had biopsy-proved celiac disease after antibody testing and distal duodenal biopsy compared with 12 controls

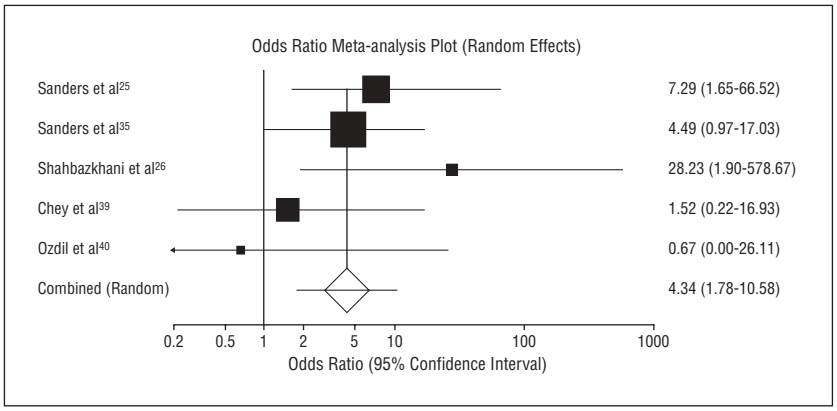

Figure 4. Pooled odds ratio for biopsy-proved celiac disease in case participants meeting diagnostic criteria for irritable bowel syndrome vs control participants. The solid squares indicate the individual study result; the size of the squares, the weight that each study contributes to the overall meta-analysis; and the diamond, the 95% confidence interval for the pooled odds ratio when all study results are combined.

(0.7%). The OR (95% CI) for biopsy-proved celiac disease in cases compared with controls was, therefore, 4.34 (1.78-10.58) (**Figure 4**), with no evidence of funnel plot asymmetry. No statistically significant differences were detected between ORs for biopsy-proved celiac disease in European vs Middle Eastern studies (Table 2). Two studies compared the prevalence of biopsy-proved celiac disease with the prevalence in controls and reported data according to IBS subtype,[25,26] with a pooled OR of 8.82 (1.59-49) in constipation-predominant IBS, 10.9 (2.46-48) in diarrhea-predominant IBS, and 10.8 (2.7-43) in those with alternating-symptoms. No statistically significant differences were detected between these ORs.

COMMENT

This study has provided an estimate of the prevalence of positive celiac antibodies and biopsy-proved celiac disease in individuals meeting diagnostic criteria for IBS. The prevalence of positive serologic findings of celiac disease was as high as 4% depending on the serologic test used, and the prevalence of biopsy-proved celiac disease was more than 4%. The positive predictive value of serology in diagnosing biopsy-proved celiac disease was 92% for EMAs or tTGAs compared with only 30% for IgA-class AGAs, although because individuals testing negative were not subjected to duodenal biopsy, the accuracy of these tests

in enabling diagnosis of celiac disease will have been overestimated owing to verification bias. In addition, we found that individuals with symptoms suggestive of IBS were almost 3 times as likely to test positive for EMAs or tTGAs compared with controls without IBS and more than 4 times as likely to have biopsy-proved celiac disease. The latter remained the case if only secondary care–based studies were included in the analysis but is of a smaller magnitude than that reported by Sanders et al[25] in their case-control study in secondary care where the OR for biopsy-proved celiac disease in those meeting Rome II criteria for a diagnosis of IBS was 7.0.

These data are relevant because the pretest likelihood of underlying celiac disease in suspected IBS has important health economic implications as established by previous decision models. Two economic analyses have examined a strategy of routinely testing for celiac disease in suspected IBS, with serologic markers followed by distal duodenal biopsy in those individuals testing positive.[44,45] Both used conservative estimates of any potential future cost savings if a diagnosis of celiac disease was confirmed and a gluten-free diet initiated, and deliberately made other assumptions that weighted the decision analysis models in favor of empirical therapy for IBS rather than screening for celiac disease. In the first model, if the prevalence of celiac disease in individuals with symptoms suggestive of IBS was assumed to be 3%, there was only a 1% increase in lifetime costs with testing for celiac disease using tTGAs over usual management, and the cost per quality-adjusted life-year gained by the diagnosis of celiac disease was $7400.[44] If the prevalence of celiac disease in suspected IBS was 5%, close to the estimate in the present meta-analysis, the cost per quality-adjusted life-year gained decreased to $4900. The second model assumed a similar prevalence of celiac disease and reported that testing for celiac disease with EMAs or tTGAs cost $11 000 per patient cured of symptoms, which could be cost-effective depending on the willingness to pay.[45] The strategy became dominant (ie, more effective but less expensive) over empirical therapy for IBS when prevalence of celiac disease in suspected IBS exceeded 8%, close to the upper limit of the estimated prevalence of biopsy-proved celiac disease in individuals meeting diagnostic criteria for IBS in the present study.

Potential limitations of meta-analyses of studies evaluating the accuracy of diagnostic tests arise as a result of problems with the method of the type of studies included. Case-control studies are subject to spectrum bias because the study design often excludes mild cases that are difficult to diagnose, which leads to overestimation of the diagnostic performance of the test being examined, compared with studies that use a clinical cohort.[46] Inasmuch as 7 of 14 studies included in this systematic review were case-control studies, this should be borne in mind when interpreting the results.

The quality of the studies included has implications for the results of a systematic review. Because of the types of study eligible for this review, a formal quality assessment according to existing recommended criteria was impossible. However, most studies explicitly stated that they were prospective, and 8 used recommended symptom-based diagnostic criteria to define the presence of IBS, with 7 studies using Rome II criteria, which at the time many of these studies were conducted were considered the standard for making the diagnosis of IBS by experts in the field.[30]

We examined the effect of study setting, country of origin, IBS definition used, and IBS subtype on the OR for positive serologic test results and biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS compared with controls without IBS, although in some cases, there were too few studies to allow meaningful pooling of data, and conclusions are, therefore, limited. It would be presumed that the ORs would be higher in studies based in secondary care. This could occur as a result of selection bias because patients with more severe symptoms and, therefore, a greater probability of underlying organic disease, are more likely to be referred by their primary care physician for a specialist opinion. However, pooled ORs for positive IgA-class AGAs and positive EMAs or tTGAs were similar between population-based and primary care–based studies and those conducted in secondary care. This implies that the findings of this systematic review are not limited to secondary care and that primary care physicians managing patients who meet symptom-based diagnostic criteria for IBS should also consider screening for celiac disease. Insofar as geographic setting, no significant differences were detected in ORs for studies conducted in North America, Europe, or the Middle East when there were sufficient studies to pool and compare. It has been a traditionally held belief that the prevalence of celiac disease is lower in North America than in Europe. In our meta-analysis, there were 3 North American studies, and the pooled prevalence and pooled ORs for testing positive for EMAs or tTGAs were similar between North American and European studies. In terms of diagnostic criteria for IBS, when only studies that used Rome II criteria were pooled, the ORs again were similar, which suggests that increasing the stringency of the criteria used has little effect on prevalence of positive celiac serology or biopsy-proved celiac disease in individuals with symptoms suggestive of IBS. The prevalence of biopsy-proved celiac disease was similar between the IBS subtypes, and no significant differences were detected in ORs for the presence of biopsy-proved celiac disease compared with controls without IBS according to IBS subtype. These ORs were higher than those for our other sensitivity analyses; however, this probably reflects that the 2 studies reporting these data had the highest prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS. These limited data suggest that celiac disease may be an alternative diagnosis to consider in those with constipation-predominant IBS and those with alternating symptoms, as well as diarrhea-predominant IBS.

Because IBS is more prevalent than celiac disease, there remains the possibility that some of these individuals may truly have IBS with undiagnosed celiac disease and that the diagnosis of celiac disease is inci-

dental. In this situation, the symptoms will not be truly attributable to celiac disease and may not improve with the patient's adherence to a gluten-free diet. Only 2 of the included studies reported the effect of instituting a gluten-free diet on symptoms subsequently, and the number of included individuals was small; however, most of those who commenced a gluten-free diet reported that their symptoms were improved or resolved.[26,35] However, for several reasons, the studies included in this systematic review could also have underestimated the true prevalence of biopsy-proved celiac disease in individuals meeting diagnostic criteria for IBS. Serologic test results for celiac disease can be falsely negative in IgA deficiency, for which most of the studies did not screen. In addition, none of the studies assessed whether individuals were already excluding gluten from their diet in an attempt to alleviate symptoms before serologic testing or duodenal biopsy. Only participants with positive celiac serology underwent distal duodenal biopsy. A recent article demonstrated that in individuals undergoing distal duodenal biopsy who had histologic findings in keeping with celiac disease, the sensitivity of tTGAs was substantially reduced in those without total villous atrophy.[47]

Studies have shown that almost half of the patients with celiac disease have evidence of osteoporosis when bone mineral density is measured[48,49]; however, whether this translates into an increased risk of osteoporotic fracture in patients compared with the general population is controversial.[50-52] Despite this, bone mineral density improves with adherence to a gluten-free diet.[49] There is also evidence that the risk of gastrointestinal malignant neoplasms, in particular, non-Hodgkin lymphoma, is increased in celiac disease[53,54] and that adherence to a gluten-free diet ameliorates this.[55] Other potential sequelae include anemia, short stature, infertility or recurrent fetal loss, and vitamin D deficiency. Even if the diagnosis of celiac disease is incidental and, therefore, a gluten-free diet is unlikely to have any effect on symptoms, there may be other benefits to screening for celiac disease in individuals meeting diagnostic criteria for IBS in terms of preventing long-term complications of the condition.

In conclusion, this systematic review and meta-analysis demonstrate that the prevalence of biopsy-proved celiac disease in individuals meeting diagnostic criteria for IBS is in the region of 4%, and the odds for biopsy-proved celiac disease in these individuals is more than 4-fold that in healthy controls. If screening is to be undertaken, then EMA or tTGA testing should be preferred to IgA-class AGA testing because of a higher positive predictive value, although the yield will depend on the prevalence in the population being studied.

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