



# Screening for Celiac Disease in Patients with Irritable Bowel Syndrome Fulfilling Rome III Criteria

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## Abstract

**Background** Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. Celiac disease (CD), a treatable autoimmune enteropathy, with varied presentations, may simulate clinically symptoms of IBS. The aim of the present study is to screen for CD in patients with IBS diagnosed based on the Rome III criteria.

**Patients and Methods** A cross-sectional study was conducted at a secondary care gastrointestinal unit in Al-Salam General Hospital in Mosul city, Iraq, from November 2015 to October 2016. All patients fulfilling the Rome III criteria for IBS were screened for CD using antitissue transglutaminase IgA antibodies (anti-tTG). Patients who tested positive were subjected to endoscopic duodenal biopsy to confirm the diagnosis of CD.

**Results** A total of 100 patients were included in the present study (58 female and 42 male), the mean age of the participants was 40.8 years old (standard deviation [SD]  $\pm$  11.57). Ten patients (10/100, 10%) tested positive for anti-tTG antibodies. Five of the seropositive patients (5/10, 50%) showed positive biopsy results according to the Marsh classification, 3 of whom having diarrhea, and 2 with constipation.

**Conclusion** Positive serology and biopsy results suggestive of CD are common among patients with IBS. Screening patients with IBS for CD is justified.

## Keywords

- ▶ irritable bowel syndrome
- ▶ celiac disease
- ▶ anti-tTG antibodies
- ▶ duodenal biopsy

## Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder of unestablished etiology, characterized by recurrent symptoms of abdominal pain, bloating, and altered bowel habit without detectable structural, inflammatory, or biochemical abnormalities.<sup>1</sup> The worldwide prevalence rate is of between 10 and 15%.<sup>2</sup> The diagnosis of IBS is based on clinical symptoms, and investigations are done to exclude

organic diseases simulating IBS rather than to diagnose this disorder.

Reliable diagnostic symptom-based criteria have been established, starting with the criteria of Manning (1978), followed by Kruis et al. (1984), and later on with the emergence of the international working group that developed the Rome I (1992), Rome II (1999), Rome III (2006), and Rome IV (2016) criteria.<sup>3</sup> Organic diseases causing alarm

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**Box 1** Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months with symptom onset at least 6 months before diagnosis, associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stools
3. Onset associated with a change in form (appearance) of stools

**Subtyping IBS by Predominant Stool Pattern**

1. IBS with constipation—hard or lumpy stools (IBS-C).
2. IBS with diarrhea—loose or watery stools (IBS-D).
3. Mixed IBS, diarrhea and constipation (IBS-M).

symptoms must be excluded prior to clinical diagnosis. Management of IBS depends on the amelioration of symptoms rather than on its cure.

Celiac disease (CD) is a chronic immune-mediated disorder of the small bowel initiated by the ingestion of gluten in genetically predisposed individuals.<sup>4</sup> Gluten is a protein found in wheat, rye, and barley. It affects both children and adults, with a prevalence rate in Europe approaching 1%.<sup>5</sup> Similar prevalence rates have been reported from the Middle East, North Africa, and India.<sup>6</sup> Celiac disease is characterized by varied clinical presentations, including intestinal and extraintestinal manifestations. Guidelines recommend that patients suspected of having CD should be screened initially with specific serological tests, and then, the diagnosis is confirmed by duodenal biopsies. Gluten free diet (GFD), which involves the lifelong elimination of wheat, rye, and barley from the diet, is the mainstay of therapy.

Symptoms of IBS may mimic the gastrointestinal symptoms of CD; these similarities between symptoms impart difficulty in clinical differentiation.<sup>7</sup>

It has been shown that testing patients with IBS to detect undiagnosed CD using serology is cost-effective.<sup>8</sup> Alexander et al. did a meta-analysis of 14 studies and reported a prevalence of more than 4-fold of CD in IBS cases compared with control without IBS.<sup>9</sup> However, fewer studies did not show a higher prevalence of CD among IBS patients compared with the general population.<sup>10,11</sup> The aim of the present study is to evaluate the frequency of positive serology and biopsy consistent with CD among patients presenting with symptoms of IBS fulfilling the Rome III criteria.

## Patients and Methods

All patients with symptoms of IBS presenting to the secondary care gastroenterology clinic of the Al-Salam General Hospital in Mosul between November 2015 and October 2016 were attended to and offered standard medical care including clinical interview and physical examination. The patients were requested to complete a questionnaire on symptoms of IBS based on the Rome III criteria (**Box 1**).<sup>12</sup>

The exclusion criteria were: weight loss, anemia, jaundice, bleeding from the rectum, high erythrocyte sedimentation rate (ESR), systemic diseases, endoscopic gastrointestinal lesions, and patients reluctant to perform the serologic test.

The total number of evaluated patients was 210, and only 100 patients were eligible to be included in the study. The age

range was between 13 and 65 years old, with a mean age of 40.8 years old ( $SD \pm 11.57$ ). Antitissue transglutaminase IgA (Anti-tTG IgA) antibody test was used to screen the selected patients for CD by measuring IgA antibodies to human recombinant tTG through the commercial kit Aeskulisa tTG-A 3503, a new generation of a solid phase enzyme immunoassay using human recombinant tTG crosslinked with gliadin-specific peptides. A positive test should exceed a cutoff value of 15 U/ml. Other investigations included complete blood count, ESR, blood sugar, blood urea, microscopic stool examination, and, for selected patients, thyroid function test, abdominal sonography, and bone profile. All patients > 50 years old were offered colonoscopic examination to exclude underlying organic disease. Patients with positive tTG-IgA test were subjected to upper gastrointestinal endoscopy; two biopsies were taken from the duodenal bulb and four from more distal areas. All biopsy specimens were subjected to a histopathological examination performed by expert pathologists and the results were reported based on the modified Marsh criteria.<sup>13</sup>

Data were analyzed (**Box 2**) using IBM SPSS Statistics for Windows, Version 18.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied to calculate the mean, median, range, percentage, p-value, and SD wherever appropriate.

The study protocol was approved by the Medical Ethics Committee of the Ninevah University and Mosul health directorate; all participants agreed to sign the written informed consent form.

## Results

Out of the 100 patients diagnosed with IBS based on the Rome III criteria, 58 were female (mean age: 40.4 years old;  $SD \pm 12.34$ ), and 42 were male (mean age: 41.5 years old;

**Box 2** Marsh-Oberhuber classification

Type	Mucosal description
0	Normal mucosa
1	Infiltrative lesion with more than 25 lymphocytes/100 epithelial cells.
II	Crypt hyperplasia.
III a,b,c	Partial, subtotal, total villous atrophy.

**Table 1** Distribution of patients according to gender and bowel habit type

Gender	IBS-D n; %	IBS-C n; %	IBS-M n; %	No. of patients Total 100
Female	36/58; 62.1%	12/58; 20.7%	10/58; 17.2%	58/100
Male	20/42; 47.6%	16/42; 38.1%	6/42; 14.3%	42/100

Abbreviation: IBS, irritable bowel syndrome.

SD  $\pm$  10.54). Their bowel habit characteristics are shown in (►Table 1).

The duration of symptoms ranged from 1 to 32 years (mean: 10.3 years). Ten patients (7 female and 3 male) out of the of the total 100 (10%) tested positive for tTG-IgA antibody ( $p < 0.00001$  compared with a CD seroprevalence rate of 2% in some normal populations).<sup>6</sup> Five patients (3 female, 2 male) of the 10 seropositive (5/100, 5%) showed abnormal histopathological changes according to the modified Marsh criteria (2 Marsh I, 1 Marsh II, and 2 Marsh IIIc), and 3 patients displayed Marsh 0 (negative biopsy result). Two seropositive patients refused to undergo duodenal biopsy. Five of the 10 seropositive patients (5/10; 50%) had predominantly diarrhea, 3 (3/10; 30%) had predominantly constipation, and 2 (2/10; 20%) had a mixed pattern. The characteristics of the seropositive patients are shown in (►Table 2).

## Discussion

Despite being a common gastrointestinal disorder and the development of symptom-based parameters to diagnose IBS, there is no clinical criterion or result of investigation that is pathognomonic of IBS.<sup>14</sup> Further confusing the issue, symptoms of IBS frequently overlap and may coexist with symptoms of other gastrointestinal and nongastrointestinal disorders.<sup>15</sup>

In the present study, patients were selected according to the Rome III criteria, which are more suitable for the definition of the symptoms of our patients compared with other

criteria, considering the duration of symptoms and subtyping of bowel habits.

Patients were screened serologically by IgA-tTG antibody test alone to detect CD. It is an enzyme-linked immunoassay (ELISA) test, operator independent, and is recommended as a screening test for CD, with a sensitivity of 94% and a specificity of 97%.<sup>16</sup>

Reports from different regions in the world showed mostly an increased prevalence of CD in patients with IBS compared with the general population, and fewer reports showing no such increase (►Table 3).<sup>10,17-23</sup>

A large meta-analysis by Irvine et al. involving 36 studies found a higher prevalence of positive serology and biopsy for CD in patients with IBS compared with healthy controls.<sup>24</sup> Another study, by Almazar et al., conducted in a USA tertiary care center and recruiting 533 patients and 531 controls, found no difference in the prevalence of CD between patients with IBS and controls.<sup>25</sup> Recently, Mohammad et al. from Iraq detected 5 seropositive patients for CD (7.1%) in a sample of 70 patients with IBS fulfilling the Rome III criteria.<sup>26</sup> This variation in results might be ascribed to different geographical locations, racial differences, study characteristics, sample size, and selection bias.

In the present study, three seropositive patients had negative biopsy results (Marsh 0) and two showed Marsh grade I, which is nonspecific for CD. Both grades are regarded as potential CD, which means that these patients are at increased risk of developing overt CD in the future.<sup>27</sup> Also, Marsh grade II lacks diagnostic support for CD, while villous atrophy, which was identified in two of the seropositive

**Table 2** Characteristics of seropositive patients

Patient no.	Age (years old)	Gender	IBS subtype	tTG-IgA U/ml cutoff: 15	Marsh type	Duration of symptoms (years)
1	23	F	IBS-D	18.6	0	8
2	48	F	IBS-M	35	0	8
3	48	F	IBS-C	16	0	6
4	34	F	IBS-D	17.9	I	5
5	45	F	IBS-D	17.1	I	10
6	51	M	IBS-C	41.16	II	13
7	28	M	IBS-C	98.88	III c	15
8	46	F	IBS-D	166.8	III c	20
9	30	M	IBS-M	18.2	Refused biopsy	5
10	34	F	IBS-D	100	Refused biopsy	1

Abbreviations: F, female; IBS, irritable bowel syndrome; M, male.

**Table 3** Studies of celiac disease in patients with irritable bowel syndrome

Authors (Ref.)	Country	Number of patients	Prevalence of CD
Sanders et al. <sup>17</sup>	UK	300	4.7%
Sanders et al. <sup>18</sup>	UK	123	3.3%
Fasano et al. <sup>19</sup>	USA	5073	3.85% with diarrhea 2.6% with constipation
Shahbazkhani et al. <sup>20</sup>	Iran	105	11.4%
Jadallah et al. <sup>21</sup>	Jordan	742	3.2%
Korkut et al. <sup>22</sup>	Turkey	100	2%
El-Sahly et al. <sup>23</sup>	Norway	968	0.4%
Hin et al. <sup>10</sup>	UK	132	0%

Abbreviation: CD, celiac disease.

patients, is more typical of CD.<sup>28</sup> These two patients with total villous atrophy displayed a very high titer of tTG-IgA antibody level. Studies in children and adults with CD have concluded that serum tTG antibody level correlates positively with the severity of small intestinal histopathology.<sup>29</sup> One female patient, 34 years old, with high tTg- antibody titer (100 U/ml) did not undergo endoscopy and biopsy, and it is highly expected that this patient has CD.

The classic presentation of adult CD is diarrhea, which was identified in 5 of the seropositive patients (50%). Constipation is not an uncommon symptom in adult CD<sup>30</sup> and it was present in 3 seropositive patients (30%).

Four of the seropositive patients (4/10; 40%) (1 with Marsh grade II, 2 with Marsh grade IIIc, and 1 female patient with an antibody titer of 100 U/ml who refused biopsy) responded to GFD within a period of 4 weeks, with improvement in the general well-being and intestinal symptoms. Improvement of clinical symptoms on GFD is not enough to confirm the diagnosis of CD, since a subset of patients with IBS may also improve on GFD.<sup>31</sup> To be more stringent in the diagnosis of CD, an improvement on diet should be supported by serial measurements of serum antibody level and possibly repeated duodenal biopsy after a reasonable follow-up period (between 3 and 6 months). It was not possible to confirm the actual prevalence of CD in all seropositive patients in our sample, as many of them are noncompliant with extended future follow-up and doing necessary tests. Anyway, we can roughly estimate the prevalence of CD in the IBS patients included in the present study to be not less than 3% ( $p=0.02$  compared with a 1% prevalence rate in normal populations), which is comparable with the results of many other studies.

The patients included in the present study were referred from primary care health centers and represent more severe and chronic conditions of IBS, which may have an impact on the ultimate prevalence of CD in patients who manifested symptoms of IBS.

## Conclusion

In the present study, the frequency of positive anti-tTG antibody test in patients with IBS based on the Rome III

criteria was of 10%, and the likelihood of CD in these patients was high (at least 3%).

Antibody testing for CD in patients who fulfill the IBS diagnostic criteria is recommended in Mosul, Iraq.

Further well-controlled studies including larger samples of patients are needed and follow-up of seropositive and biopsy-positive patients to ascertain the diagnosis of CD is required, which includes GFD, repeated serology tests, and duodenal biopsy.

### Ethical Approval

Ethical approval was granted by the Medical Ethics Committee of the Ninevah University.

### Informed Consent

All participant agreed to sign an informed written consent form.

### Note

Hospital-based study supported by Iraqi ministry of health. The patients were not charged, and no charge was received by the author.

### Conflict of Interests

The author has no conflict of interests to declare.

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