



## Original article

# The prevalence of celiac disease in patients fulfilling Rome III criteria for irritable bowel syndrome

Esin Korkut<sup>a</sup>, Mehmet Bektas<sup>a</sup>, Erkin Oztas<sup>b</sup>, Mevlut Kurt<sup>b,\*</sup>, Hulya Cetinkaya<sup>a</sup>, Ali Ozden<sup>a</sup>

<sup>a</sup> Department of Gastroenterology, Ankara University Medical School, Ankara, Turkey

<sup>b</sup> Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, Ankara, Turkey

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## ABSTRACT

**Background and aims:** Celiac disease shares several symptoms which constitute some of the ROME criteria used for the diagnosis of irritable bowel syndrome (IBS), and as such many patients with underlying Celiac disease may be mistakenly diagnosed as having IBS. The aim of the present study was to determine the prevalence of Celiac disease in patients with IBS fulfilling ROME III criteria.

**Materials and methods:** Patients who fulfilled ROME III criteria for irritable bowel syndrome were screened for Celiac disease using the Biocard™ Celiac Disease Stick test, and patients who tested positive had their serum samples analyzed for anti-gliadin IgA and IgG, and anti-tissue transglutaminase IgA antibodies. Patients with detectable antibody levels underwent endoscopic duodenal biopsy to confirm a diagnosis of Celiac disease.

**Results:** Two of 100 patients who were diagnosed as having irritable bowel syndrome as per the Roma III criteria were found to have elevated levels of serum anti-gliadin IgA and IgG, and anti-tissue transglutaminase IgA antibodies, with histological evidence of Celiac disease on examination of duodenal biopsy. Both patients were started on a gluten-free diet, showing significant improvement in their symptoms on follow-up.

**Conclusions:** Celiac disease is a common finding among patients labeled as IBS. Celiac disease must be considered in differential diagnosis of IBS especially in the therapy refractory group.

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## 1. Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by symptoms of abdominal pain or discomfort that is associated with disturbed defecation. IBS is one of the common problems that a gastroenterologist encounters in daily practice [1]. Reported prevalence rate for IBS was above 15% in western society [2,3]. A diagnosis of IBS is mainly symptom based, since there is no objective physical examination, laboratory or radiological findings specific to this disorder. Many of the symptoms on the list, including diarrhea, abdominal cramps, and symptom relief after defecation and bloating, are also shared by Celiac disease (CD). Despite this, serologic testing for CD and duodenal biopsy are not routinely obtained in patients with suspected IBS, which may easily result in a missed diagnosis, particularly in case of an atypical presentation of CD. Many gastroenterologists support the inclusion of CD screening tests as part of routine testing for IBS; however this has yet to become a universally accepted recommendation. The aim of this study was to establish the

frequency of CD in investigated patients diagnosed with IBS based on the Rome III criteria.

## 2. Materials and methods

All patients presenting to the Gastroenterology clinic of Ankara University Hospital between October 2006 and January 2007, regardless of their complaints, where approached for enrollment in this study. After informed consent was obtained, patients fulfilling the Roma III criteria for IBS were evaluated for inclusion in the study. Exclusion criteria were advanced age ( $\geq 65$  years), presence of one or more alarming symptom (weight loss, onset at advanced age, having a family history of inflammatory bowel disease or cancer, fever, abnormal physical examination findings, arthritis, dermatitis, malabsorption, anemia, leucocytosis, high sedimentation rate, presence of occult blood in stool), abnormal upper and lower gastrointestinal system endoscopic studies, presence of any kind of gastrointestinal system malignancy, having concomitant metabolic or endocrine diseases (diabetes mellitus, hyper- and hypo-thyroidism, adrenocortical disorders) heart failure, chronic obstructive pulmonary disease, liver cirrhosis, renal failure, severe depression, having history of continuous drug use.

Laboratory tests conducted for each patient were a complete blood count, erythrocyte sedimentation rate, fasting blood glucose, urea,

\* Corresponding author. Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, Kizilay Sk. No:2, 06100, Sıhhiye, Ankara, Turkey. Tel.: +90 505 2762812; fax: +90 312 3124120.

E-mail address: [dr.mevlutkurt@gmail.com](mailto:dr.mevlutkurt@gmail.com) (M. Kurt).

creatinine, aminotransferases, thyroid hormones (free T4, free T3 and thyroid-stimulating hormone), microscopic stool examination, occult blood test in stool, digestion tests in stool and serum IgA levels. Patients with selective IgA deficiency were also excluded from the study.

Of the 1380 patient approached, some of which were previously evaluated and treated in primary and secondary clinics, 100 were deemed suitable for inclusion in the final analysis (Fig. 1). All 100 patients were screened for CD using the commercially available *Biocard*<sup>TM</sup> Celiac test. Capillary fingertip blood is first diluted with a blood buffer (0.09% sodium azide) after which three drops of blood are applied onto the test card. After a waiting period of 3–5 min as per manufacturer instructions, the appearance of red line in both of the control and test fields indicates a positive result, while a red line in the control field alone indicates a negative one (Fig. 2).

Test-positive patients would be subject to further testing to confirm a diagnosis of CD, including serum anti gliadin IgA, IgG and tissue transglutaminase Ig G and after confirmation total of four biopsies taken from the second part of the duodenum were sent to for histopathological examination in formaldehyde solution. All specimens were evaluated by a designated pathologist. Findings were interpreted based on the MARSH criteria (Stage 0–4) based on the presence of intraepithelial lymphocytes, crypt hyperplasia and villous atrophy [4]. Those found to have CD would be started on a gluten-free diet and followed-up in our department. This study was conducted with approval by the local ethics committee at Ankara University.

### 3. Results

Of the 100 patients who fulfilled the Rome III criteria for IBS, 75 were female (mean age  $40.65 \pm 12.49$ ) and 25 were male (mean age  $37.5 \pm 13.69$ ) (Table 1). While 59 of the patients had at least 3 of the

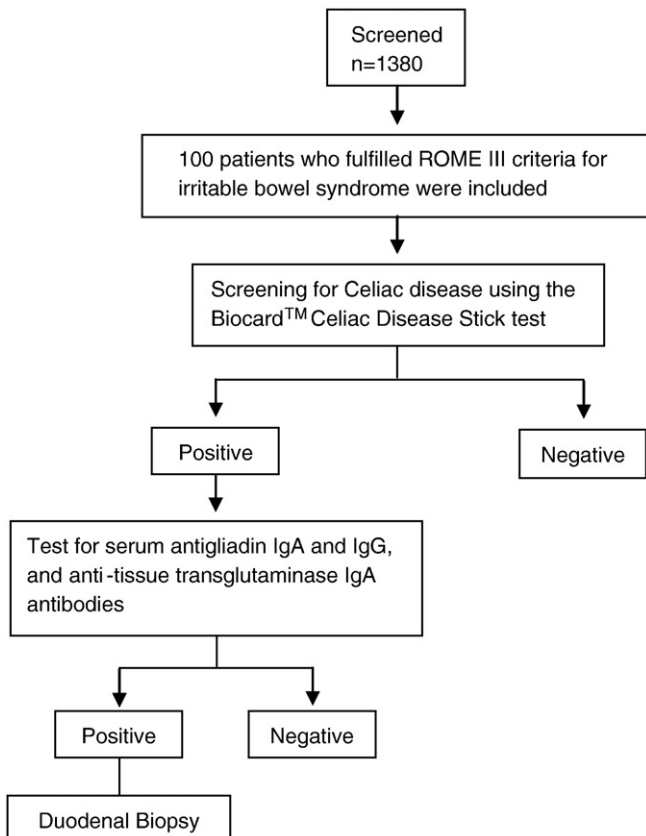


Fig. 1. Disposition of patients.



Fig. 2. *Biocard*<sup>TM</sup> coeliac test a) negative, b) positive.

described symptoms, 41 of them only had 2 symptoms. Duration of symptoms ranged from 6 months to 20 years (mean 63 months). Based on stool consistency as described in the Rome III criteria, patients were subdivided into 3 groups: 63 as IBS with constipation, 21 as IBS with diarrhea and 16 as mixed IBS.

Two patients, both female, tested positive for CD using the *Biocard*<sup>TM</sup> Celiac test. Subsequent serological testing confirmed the presence of high titers of anti gliadin and tissue transglutaminase antibodies. Histopathological examination of duodenal biopsy specimens revealed typical findings consistent with CD (both patients with Marsh type 3a histology). While one of the patients predominantly had diarrhea, the other mainly complained of constipation. Both patients responded well to a gluten-free diet and are currently under follow-up.

### 4. Discussion

IBS symptoms have been reported in 10–20% of adolescents and adults worldwide, with the disorder more prevalent in women [5]. Studies from Turkey utilizing the Rome II criteria have estimated the prevalence of IBS in the general population as ranging from 7.4–19.1% [6,7]. IBS is best viewed as an interaction of biological and psychosocial factors. Disturbance of brain-gut interaction, abnormal central processing, altered motility, visceral hyperalgesia, autonomic and hormonal events, genetic and environmental factors, postinfectious sequela, and psychosocial disturbance are variably involved, depending on the individual [8]. In light of all the different mechanisms implicated in the pathophysiological process, it is no surprise that the treatment of IBS poses a great challenge to clinicians, as well as resulting increased treatment costs [9,10].

In our study we preferred to utilize the Rome III criteria for IBS. Core differences from the Rome II criteria include a redefinition of the duration and frequency of symptoms required for a diagnosis of IBS, as well as the inclusion of relief of symptoms after defecation as a diagnostic criterion. Subtypes of IBS were also updated [5]. The main aim of the Rome III study group was to offer a more comprehensive

Table 1

Demographic and clinical characteristics of the study population.

	Female (n = 75)	Male (n = 25)
Age	40.65 ± 12.49	37.5 ± 13.69
IBS subtypes		
IBS with constipation (IBS-C)	54 (72.0%)	9 (36.0%)
IBS with diarrhea (IBS-D)	10 (13.3%)	11 (44.0%)
Mixed IBS (IBS-M)	11 (14.7%)	5 (20.0%)
Duration of IBS symptom (years)		
<1	11 (14.7%)	1 (4.0%)
1–5	29 (38.7%)	14 (56.0%)
5–10	18 (24.0%)	5 (20.0%)
>10	17 (22.6%)	5 (20.0%)
<i>Biocard</i> <sup>TM</sup> celiac disease stick test		
Positive	2 <sup>a</sup>	–
Negative	73	25

<sup>a</sup> One patient had IBS-C, other had IBS-D.

model to help guide clinical practice, epidemiological and therapeutic studies as well as research into pathophysiology [5]. As with the preceding set of criteria, review of symptoms and clinical evaluation were deemed sufficient to make a diagnosis of IBS based on the Rome III criteria. In patients with typical IBS symptoms in the absence of any alarming symptoms, further laboratory testing is not warranted [5].

The prevalence of CD in the general population lies between 0.02–1% [11–16]. Data on the prevalence of the disorder in Turkey is limited, estimated at 0.99–1.3% [17,18]. To date, in studies investigating the prevalence of CD in patients diagnosed with IBS based on the Rome I, II and Manning criteria, the prevalence has been reported between 0–11.4% [19]. In a study from England by Sanders et al. [20], 300 patients who were referred for secondary care with a suspicion of having IBS met the Rome II criteria for the disorder. They used antigliadin (AGA) and anti endomesium antibodies (EMA) to screen for CD. Sixty-six of the patients were found to be positive for EMA, while 14 patients (4.7%) had CD confirmed by biopsy (11 EMA positive, 3 EMA negative). In another primary care cross-sectional study by the same team, out of 1200 patients 123 met the Rome II criteria for IBS. Again AGA and EMA were used as screening tests, and 3.3% of the patients had histopathological findings consistent with CD [21].

In the USA, Fasano et al. [22] conducted a large comprehensive study on 5073 patients presenting to primary and secondary clinics with IBS symptoms. In a subgroup of patients who had chronic diarrhea (n:1848), the prevalence of CD was 3.85%, while in patients complaining mainly of abdominal pain (n:1695) and constipation (n:1539), frequency of CD was 3.32% and 2.6%, respectively. Recently, Jadallah et al. [23] from Jordan detected antiTG antibodies in 24 out of 742 previously uninvestigated patients who fulfilled the Rome II criteria for IBS. Duodenal biopsies confirmed the presence of CD in 3.23% of patients, an outcome similar to our study. In all of the aforementioned studies, as in our own, symptomatic relief was achieved with a gluten-free diet.

On a different note, an American study by Locke et al. [24] on 50 primary care patients diagnosed with IBS using Manning criteria, TTg antibody positivity was reported at 4%. Interestingly, they discovered that this rate was not different in patient with dyspeptic symptoms compared to those who were asymptomatic. They suggested that CD did not explain the presence of either IBS or dyspepsia in these subjects. In the Netherlands, van der Wouden et al. [25] published a study on 163 patients presenting for secondary care and who met the Rome II criteria from IBS. EMA was not detected in any of the 148 patients who were tested. Furthermore, none of the 32 patients in whom duodenal biopsies were indicated had histopathological findings consistent with CD.

In a Turkish study by Ozdil et al on 60 patients completely fulfilling the Rome II criteria for IBS, antigliadin IgA positivity was observed in 4 patients [7]. However, normal findings on histopathological examination of duodenal biopsies excluded a diagnosis of CD [7].

It is obvious from the above-mentioned studies that there is no consensus on routine testing for CD in IBS patients [5,19–25]. Unfortunately, it is not always possible to identify patients with CD who present with IBS-like symptoms based on history and clinical evaluation alone. In an intriguing study by O'Leary et al, while 30 out of 150 patients (20%) with CD fulfilled the Rome criteria for IBS, only 8 individuals out of 162 controls (5%) were found to have IBS [26].

In two recent cost-effectiveness analyses it has been postulated that serologic testing for CD in a population with a prevalence of around 1% would be cost-effective [9,10]. For our study, we preferred to use the commercially available *Biocard*<sup>TM</sup> Celiac Test as a simple, rapid, and reliable home test kit for the detection of tissue transglutaminase IgA autoantibodies from a fingertip blood sample [27,28]. For this test, Raivio et al. [28] reported a sensitivity and specificity of 82% and 100%, respectively. Both patients who tested positive were eventually proven to have CD after histopathological examination of duodenal biopsies. Of course, since not all the patients

in the study group were subject to histopathological evaluation, it is not possible to comment on whether the prevalence of this disorder might actually be greater than 2%. On the other hand, our study population consisted of patients previously investigated in primary and secondary clinics, most of which had already undergone endoscopic and colonoscopic evaluation without any ascertainable pathology, including iron deficiency anemia. It would not be prudent to obtain duodenal biopsies from all patients with IBS just to exclude a diagnosis of CD, particularly if they have already been investigated before and had negative Biocard tests.

The fact that a majority of patients in our study population had constipation-predominant IBS may have contributed to a lower prevalence of the disorder.

To date, several presentations of CD have been identified: typical, atypical, latent and potential [29,30]. It is widely believed that most patients with CD have obscure clinical and functional characteristics, labeling them as having latent disease or as potential Celiac patients [31,32]. Missed diagnosis poses a risk for potential complications such as osteoporosis, infertility and malignancies [33–35]. A gluten-free diet has been shown to decrease mortality and improve quality of life, even in symptomatic patients [36].

Whether the Rome III criteria offer any added advantage over previous editions with regards to the correct identification of organic diseases such as CD is not clear. On the other hand, the only differences from the Rome II criteria being changes to the duration of symptoms and redefinition of subtypes, it would be unfair to place judgment on whether exclusion of CD is possible or not based on these criteria alone. Our study is the first of its kind to investigate the frequency of CD in patients with IBS using the latest Rome III criteria.

To conclude, in our study population of IBS patients diagnosed using the Rome III criteria; we established the prevalence of CD as 2%. The prevalence of CD in patients diagnosed with IBS using the Rome III criteria is not different from previous studies using other diagnostic criteria for IBS. In previously investigated patients who have received prior treatment for IBS, the Biocard finger test offers an easy to use, rapid and cheap option for screening for CD. Of course, a larger cohort would be required to establish the actual benefit of this test. The sensitivity and specificity of this screening test also needs to be evaluated by further studies on patients with histopathologically proven CD.

## 5. Learning Points

- Celiac disease must be considered in differential diagnosis of IBS especially in the therapy refractory group.
- The main aim of the Rome III study group was to offer a more comprehensive model to help guide clinical practice, epidemiological and therapeutic studies as well as research into pathophysiology.
- There is no consensus on routine testing for Celiac disease in IBS patients.
- Our study is the first of its kind to investigate the frequency of Celiac disease in patients with IBS using the latest Rome III criteria.
- We established the prevalence of Celiac disease as 2% in our study population of IBS patients using the Rome III criteria.
- Biocard<sup>TM</sup> Celiac Test as a simple, rapid, and reliable home test kit for the detection of tissue transglutaminase IgA autoantibodies from a fingertip blood sample.

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