

# Epidemiology of Celiac Disease in Iran: A Review

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## ABSTRACT

Celiac disease (CD) was traditionally believed to be a chronic enteropathy, almost exclusively affecting people of European origin. Celiac disease is the permanent intolerance to dietary gluten, the major protein component of wheat. The availability of new, simple, very sensitive and specific serological tests has shown that CD is as common in Middle Eastern countries as in Europe, Australia and New Zealand where the major dietary staple is wheat. A high prevalence of CD has been found in Iran, in both the general population and the at-risk groups, i.e. patients with type 1 diabetes or irritable bowel syndrome (IBS).

In developing countries, serological testing in at risk groups is necessary for early identification of celiac patients. Clinical studies show that presentation with non-specific symptoms or a lack of symptoms is as common in the Middle East as in Europe. Wheat is a major component of the Iranian diet and exposure to wheat proteins induces some degree of immune tolerance, leading to milder symptoms that may be mistaken with other GI disorders. The implementation of gluten free diet (GFD) is a major challenge for both patients and clinicians in Iran, especially since commercial gluten-free products are not available in this area.

## KEYWORDS

Celiac disease; Epidemiology; Iran

## INTRODUCTION

In the last few years, considerable changes in the epidemiology of celiac disease (CD) have been observed.

A marked increase in CD prevalence and incidence has been reported, which can be at least partially explained by both the development of more sensitive serological tests and a higher degree of disease suspicion.<sup>1,2</sup> Although screening programs may discover some of the asymptomatic CD cases,

a high proportion of under diagnosed patients may be detected an appropriate clinical approach is undertaken.<sup>3</sup>

CD is the result of both environmental (gluten) and genetic factors (HLA and non-HLA genes).

Distribution of these two components can probably be used to predict at risk areas of the world for gluten intolerance.<sup>4</sup> In this respect, the world geographical distribution of CD seems to have

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followed the spread of wheat consumption and migratory flows of mankind. Cultivation of wheat and barley, first exploited and intensively developed in Levant and western Zagros (Iran), slowly spread westward across northern Europe to reach Britain by circa 4000 B.C.<sup>5,6</sup> The aim of this review is to investigate the epidemiology, different clinical presentations and management of CD in Iran.

### Epidemiology of CD in the World

Age of presentation and prevalence of CD appears to have changed dramatically over the last 30-40 years.<sup>7</sup> Until a few years ago, gluten intolerance was thought to be a disorder almost exclusively affecting Europeans or people of European origin and they described typical features of celiac patients. Until a decade ago, CD was considered to be very rare in Middle Eastern countries.

A comparison of recent studies in European and Middle Eastern countries has shown that CD is common in both areas, with an almost similar prevalence (Table 1).<sup>8-17</sup> This discovery can be attributed to the judicious use of serological screening tests which measure anti-gliadin antibodies (AGA) anti-endomysial antibody (EMA), and more recently anti-transglutaminase antibody (anti-tTG) which has permitted the diagnosis of many silent and subclinical CD cases that otherwise would not have been recognized.<sup>18,19</sup>

**Table 1: Prevalence of CD in Europe compared to Middle East population based on serological screenings.<sup>8-17</sup>**

| Europe         | Prevalence | Asia                           | Prevalence     |
|----------------|------------|--------------------------------|----------------|
| Italy          | 1:106      | Iran                           | 1:166          |
| Czech          | 1:218      | Israel                         | 1:157          |
| Norway         | 1:262      | Syria                          | 1.5:100        |
| Portugal       | 1:134      | Turkey                         | 1:87           |
| Sweden         | 1:190      | Anatolian adults               | 1:100          |
| Netherlands    | 1:198      | Kuwait (Chronic diarrhea)      | 1:18           |
| United Kingdom | 1:100      | Saudi Arabia (Type 1 diabetes) | 12:100         |
| Switzerland    | 1:132      | Japan                          | 1:20,000       |
| Spain          | 1:118      | India                          | 1:500-1:20,000 |

Nowadays, the map of CD prevalence in different areas of the world is much more

detailed than in the past. However, there is limited data about the prevalence of CD in Middle Eastern countries. Prevalence of CD varies among different populations worldwide and the actual prevalence of CD has been shown to be higher than before. For instance, recent studies of serum markers in blood donors have shown a prevalence of 1:250 in Sweden, 1:524 in Denmark, 1:333 in Holland, 1:157 in Israel, 1:250 in the USA and 1:681 in Brasil.<sup>20-24</sup>

### Epidemiology of CD in Iran

CD was considered uncommon in Iran until a decade ago, but following the application of simple serological tests for diagnosis of CD in Western countries, several studies have been published on the prevalence and importance of CD in Iran. This prevalence varies in different subgroups and ranges from 0.5% among schizophrenia patients<sup>25</sup> to 12% in patients with irritable bowel syndrome (IBS).<sup>26</sup> For instance, prevalence of CD in low risk subjects was reported to be even higher than that of Western countries (1 out of 166 healthy Iranian blood donors).<sup>27</sup> Recent screening studies performed by means of simple, sensitive and specific tests (AGA, EMA and tTG) in the general population and at-risk groups in different geographical areas in Iran with a large consumption of wheat have shown that the prevalence of gluten sensitivity is similar to that of Western countries. However, there might be a different prevalence of CD between the northern versus the southern areas in Iran.<sup>28</sup>

The first study on CD ran from November 1998 through February 1999 in 2000 healthy blood donors in Tehran. Total serum AGA was measured and analyzed in all donors by an ELISA test and those with positive results were tested for EMA. All donors who had a positive serology for both AGA and EMA underwent small intestinal biopsies. Of 2000 healthy blood donors, 49 were positive for IgA

AGA (38 males, 11 females) and 12 were EMA positive. Gluten sensitive enteropathy was found in all subjects who had positive serology as follows: Marsh I (3), Marsh II (4) and Marsh IIIa (5) lesions. The results of this study showed that the prevalence of CD in this group was 1/166 and these results were similar to that of Western countries.<sup>27</sup>

In a study on apparently healthy blood donors in Northern Iran (Sari), CD was detected in 13 out of 1438 individuals. Small bowel biopsies were consistent with Marsh 0 (1), Marsh I (8), Marsh II (2) and Marsh IIIa (2). At the same time, out of 1361 blood samples collected from apparently healthy blood donors in Southeastern Iran (Kerman), 16 had positive CD serology. The histology of the small bowel was consistent with Marsh 0 (1), Marsh I (8), Marsh II (2) and Marsh IIIa (2) which represented an overall prevalence of 1:120 and 1:91 for these two cities, respectively.<sup>29</sup>

Saberi-Firouzi et al. also screened 1440 healthy individuals for EMA and tTG antibodies in Shiraz, Iran. Only 7 were positive for tTG antibody, of these 2 were also EMA positive. Five subjects with positive serology agreed to undergo upper GI endoscopy. Small bowel abnormalities that included Marsh I-IIIc were noted in all patients with positive tTGA assays. The prevalence of CD in this study was less than 0.5% which was much lower than reports from other areas of the country.<sup>30</sup>

A seroprevalence study of 2547 healthy blood donors in Golestan Province showed 28 (1.1%) tTG positive cases.<sup>31</sup> This study had the same results as a study by Akbari et al.<sup>29</sup>

A case control study by Shahbazkhani et al. was undertaken at a university clinic in Tehran to determine the frequency of CD among patients diagnosed with IBS and consisted of 105 cases in each arm. Twelve IBS cases and no controls were diagnosed with CD. The result of this evaluation showed a prevalence of CD greater than 11% among IBS patients.<sup>27</sup>

On the other hand, Emami et al. did not find any cases of CD based on serum IgA t-TG in a much larger sample of IBS patients in Isfahan.<sup>28</sup>

Two different studies evaluated the prevalence of CD in iron deficiency anemia (IDA) patients in Iran. In a study by Nikpour and Hosseini, 126 patients with IDA underwent D2 biopsies during endoscopy. The average Hb level was 8.8 mg/dl. Serology was evaluated (AGA and EMA) for those who had a positive histopathology for CD. The researchers found that duodenal biopsies revealed histological features of CD in 8 (6.3%) patients according to modified Marsh criteria (6 Marsh IIIa; 2 Marsh IIIc). Six (75%) had positive serology for CD (2 positive EMA; 3 positive AGA; 1 positive for both).

In another study by Zamani et al., 206 patients were found to have IDA of obscure origin. Serology tests showed 31 positive tests (tTG and/or EMA). Thirty cases (14.6%) had abnormal duodenal histology of which 16 had Marsh III, 12 had Marsh II, and 2 had Marsh I lesions. After 4 to 6 months of gluten-free diet (GFD), the mean hemoglobin concentration of the patients rose from 8 mg/dl to 13 mg/dl. Both studies showed a high prevalence of CD in IDA of obscure origin and the efficacy of a GFD in patients who have mild to severe villous atrophy was demonstrated.<sup>32,33</sup>

Behcet's disease (BD) is a chronic, relapsing inflammatory disease characterized by recurrent oral and genital aphthous lesions whose presentation is similar to CD. Based on a possible association, the sera of 288 patients with BD were screened with EMA and tTG antibodies for CD and D2 biopsies were taken from seropositive subjects.<sup>34</sup> Fourteen patients had positive tTG (2 positive EMA) but only 4 had compatible histology with CD (1, Marsh III; 3, Marsh I). The patients with CD were placed on a GFD to evaluate its efficacy on the improvement of their lesions. All 4 cases responded to the GFD. Although there seems to be a high

percentage of false positive tTG results in BD, CD is approximately twice as common as seen in the general population.

A variety of neurological disorders such as epilepsy, ataxia and neuropathy have been reported in association with CD. Emami et al. studied 108 consecutive idiopathic epileptic patients.<sup>35</sup> The diagnosis of CD was determined by tTG antibodies and small intestinal biopsy. Histopathologic changes were interpreted according to the modified Marsh classification criteria.<sup>36</sup> The results of this study showed that 4 out of 108 (3.7%) epileptic patients were positive for IgA anti t-TG while the known prevalence of CD in the study area was 0.6%. Intestinal biopsies showed Marsh I lesions in all cases. The prevalence of CD is increased among patients with epilepsy of unknown etiology, justifying evaluation for CD in any patient with idiopathic epilepsy even in the absence of digestive symptoms.

To assess the prevalence, related symptoms, endoscopic and histologic gastric features of CD in patients with *Helicobacter pylori* (HP), Rostami Nejad et al. investigated 450 dyspeptic patients by routine D2 biopsies.<sup>37</sup> HP was positive in 411 (91.3%) cases. Duodenal histology was normal in 385 (85.6%) patients, and positive in 28 (6.2%) who had Marsh I-IIIc lesions. In those with positive histology, 23 (82.1%) were also HP positive and 31 had positive CD serology. Serological analysis indicated that 12 out of 31 (38.7%) positive patients had abnormal histology (Marsh I -IIIc). The prevalence of CD in this group of patients was 2.6% and this finding indicated a false positive histology or low sensitivity of tTG in HP infection.

Celiac disease is a common chronic intestinal disease frequently associated with dyspeptic symptoms. It fulfill many of the disease criteria required for a screening program. From November 2007 to October 2008, 407 patients who underwent endoscopy for dyspeptic symptoms were studied.<sup>38</sup> The results of this

study showed that 10 out of 33 tTGA positive patients had abnormal histology (Marsh I-IIIc). In this study around 2.5% had small bowel mucosal abnormalities and positive CD serology. This may support routine serological screening for CD in dyspeptic patients.

We are probably far from an ideal screening serologic tool which relies on the antibody test as the sole method of screening for CD since the overall sensitivity and specificity of the IgA anti-tTG antibody has been determined to be 38% and 98%, respectively, in one Iranian study. The positive and negative predictive values for the anti-tTG antibodies were 57% and 96%, respectively. The sensitivity was 80% in patients with Marsh IIIc, which contrasts other reports that suggest a diagnostic accuracy of over 90% for anti-tTG antibody.

Therefore serologic screening could result in many missed diagnoses, particularly in patients with lesser degrees of mucosal abnormalities.<sup>39</sup>

Rostami Nejad et al. evaluated 496 pregnant women for CD by serology. Thirteen (2.6%) cases had a positive serology for tTGA; 2 had low birth weight babies and 2 had a previous history of miscarriage.<sup>40</sup> This study showed a high incidence of unfavorable outcomes in pregnancy associated with positive serology for CD.

Different studies show that CD is the most common cause of chronic non-bloody diarrhea in adults and children in Iran, ranging from 6.5-19%.<sup>41,42</sup> Thus routine testing for CD is necessary in all patients who present with chronic non-bloody diarrhea.

Another study in 827 pregnant women showed 3.26% positive tTGA<sup>43</sup> which is much higher than the general population. Since we expect a lower pregnancy rate in CD cases, further evaluation is needed with other well designed studies.

EMA antibody was positive in 6 (2.4%) of 250 consecutive type I diabetes mellitus cases.

D2 histology was compatible with Marsh I (2), Marsh II (3) and Marsh IIIb (1).<sup>44</sup> In another study by Fallahi et al., 96 children with type 1 diabetes mellitus were tested for tTG antibody.<sup>45</sup> Six (6.25%) were seropositive, and histopathological changes were compatible with CD in intestinal biopsies of all (5, Marsh IIIa; 1, Marsh IIIb). Results of both studies show that the prevalence of CD in Iranian patients with type I diabetes mellitus is relatively high, justifying screening for CD in all patients with type I diabetes mellitus regardless of the presence or absence of symptoms. Patients should be screened at the onset of diabetes mellitus diagnosis and at regular intervals during follow up.

A total of 670 cases with non-specific GI symptoms were tested for serum IgA levels and tTG antibodies. Positive IgA tTG and IgG tTG were found in 22 cases as well as in 3 out of 8 IgA-deficient individuals. The prevalence of CD antibodies in serologically screened samples, excluding IgA-deficient cases, was 3.3% and 3.7% when IgA-deficient cases with positive tTG-IgG were included. This study indicated a high prevalence of CD antibodies among patients with non specific GI symptoms (3.7%). More awareness regarding the atypical presentation of CD could be the key step in identifying asymptomatic patients.<sup>46</sup>

Short stature is one of the most common causes of referrals to pediatric endocrinologists and is a well-known feature of pediatric CD.<sup>47</sup> Hashemi et al. studied 104 children with idiopathic short stature (49 males, 55 females). All patients were investigated by serology and D2 histopathology. IgA tTG antibodies and IgA AGA were positive in 36 and 35 cases, respectively. Histological abnormalities compatible with CD were seen in 31 IgA tTG antibody positive and 28 IgA AGA positive subjects [26.9% (28 were positive for both anti-tTG and anti-AGA)].<sup>48</sup> This figure is very high and needs confirmation with other well designed studies. High wheat consumption has been a

major component of the Iranian diet for thousands of years<sup>49</sup> and the presence of about 57.6% frequency of HLA DQ2 and DQ8 in the general population suggests that a high percentage of our community could be susceptible to different presentations of CD.<sup>50</sup> There seems to be a lower prevalence of CD in Isfahan and Shiraz.<sup>28,30,39</sup>

The current wheat consumption per capita per year in Iran and other Middle Eastern countries is shown in Table 2. As this table shows, Iranians rank as one of the top wheat-consuming populations in the Asia–Pacific region with a per capita consumption of up to 150 kg/year.<sup>51,52</sup>

**Table 2:** Wheat consumption (kg) per person per year for countries in the Asia–Pacific region.<sup>19,27,51</sup>

| < 25 kg/year | 25-74 kg/year | 75-150 kg/year | > 150 kg/year |
|--------------|---------------|----------------|---------------|
| Thailand     | India         | China          | Iran          |
| Singapore    | Nepal         | Saudi Arabia   | Turkey        |
| Indonesia    | Malaysia      | Oman           | Kazakhstan    |
| Myanmar      | North Korea   | Yemen          | Turkmenistan  |
| Bangladesh   | Japan         | Afghanistan    | Iraq          |
| Malaysia     | Philippines   | Pakistan       | Syria         |
|              | Sri Lanka     | Mongolia       | Jordan        |
|              | Taiwan        | South Korea    | Uzbekistan    |
|              | Cambodia      |                | Tajikistan    |
|              | Laos          |                | Kyrgyzstan    |

## CONCLUSION

Celiac disease was presumed to be rare in Iran because of low awareness and a low index of suspicion. However new epidemiological data show that CD is a common disorder in Middle Eastern countries, particularly Iran. Table 3 shows the current primary list of CD frequency in Iran.<sup>53-57</sup> This suggests a need for a more uniformly designed evaluation of CD for the entire country and a mapping of HLA DQ in the same areas along with a gluten consumption assessment, since a variable frequency of CD in different parts of Iran may exist as is the case for India.<sup>58</sup>

Although the prevalence of CD in some areas in Iran such as Shiraz Province is very low, a summary of the reviewed studies suggests a prevalence of 1% in the remaining areas of Iran which is similar to the frequency of this

disorder in Western European countries.<sup>27,29,59,60</sup>

Since commercial gluten-free products are not readily available and significantly more expensive than their gluten-containing products in this area, therefore the main concern is the implementation of a GFD for Iranian patients. This information will be useful to dietitians and gastroenterologists who counsel celiac patients, and to celiac advocacy groups for seeking financial support from the government.

**Table 3: Prevalence of celiac disease among at risk groups in Iran (serological screenings).**

| Disease groups                           | Prevalence (%) | References |
|--|----------------|------------|
| Normal population                        | 0.6            | 27         |
| Chronic diarrhea (children)              | 6.5-20         | 41,42      |
| Inflammatory bowel disease               | 7.8            | 53         |
| Autoimmune hepatitis                     | 3.6-10         | 54         |
| Chronic psychiatric disorders            | 1.5            | 25         |
| Irritable bowel syndrome                 | 1-11.4         | 26         |
| Short stature                            | 4-33.6         | 48         |
| Type 1 diabetes mellitus                 | 2.4            | 44         |
| Epilepsy                                 | 2.7            | 35         |
| Dyspepsia                                | 2.5            | 47         |
| Infertility                              | 1.5            | 55         |
| Patients with non-specific GI symptoms   | 3.3            | 46         |
| Mental retardation                       | 1              | 56         |
| Recurrent aphthous stomatitis            | 2.84           | 57         |
| Behcet's                                 | 1.32           | 34         |
| Iron deficiency anemia of unknown origin | 14.6           | 58         |

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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