

## Prevalence of Celiac Disease Among Patients with Refractory Iron Deficiency Anemia in North-Western Saudi Arabia

Rasha I. Ibrahim<sup>1</sup>, Omer B. Sulieman<sup>2</sup>, Mahmoud K. Mansour<sup>3</sup>,  
Mahmoud R. Abdelmotaleb<sup>4</sup>, Noor K. ALJarba<sup>2</sup>

<sup>1</sup> Department of Internal Medicine, Clinical Hematology and Oncology Unit,  
Faculty of Medicine, Ain Shams University, Egypt.

<sup>2</sup> Department of Internal Medicine, King Salman Specialist Hospital, Hail, Saudi Arabia

<sup>3</sup> Department of Clinical Microbiology, Faculty of medicine, Suez Canal University, Egypt

<sup>4</sup> Department of Gastroenterology, King Salman Specialist Hospital, Hail, Saudi Arabia

\*Corresponding author: Rasha Ibrahim Ibrahim, Mobile: 00201126537107-00966533840914  
, Email: rashaibraheem@med.asu.edu.eg, ORCID Id: 0000-0001-7118-8395

### ABSTRACT

**Background:** Celiac disease (CD) is an immune-mediated intestinal disease caused by a hypersensitivity to gluten in genetically susceptible people. The most frequent type of anemia in the world is iron-deficiency anemia (IDA), which is also thought to be the most typical extra intestinal symptom of celiac disease.

**Aim:** This study aimed to determine the prevalence of CD in patients with unexplained refractory IDA by using anti-tissue transglutaminase (anti-tTG) antibodies or by endoscopic biopsy in North-Western Saudi Arabia (Hail Province)

**Design and Methods:** This is a cross-sectional discipline that was done at the King Salman Specialist Hospital, Hail, Saudi Arabia during the period from January 2019 to December 2021. We evaluated two thousand four hundred adult Saudi patients with IDA for etiology. Of those, 270 patients (11.25%) were found to have refractory IDA. IgA and IgG tissue transglutaminase (tTG) antibodies were tested in sera from patients with IDA of unknown cause using an ELISA test. Intestinal endoscopic biopsies were taken from the second part of the duodenum in these patients. Histopathologic examination results of patients categorized based on Marsh classification.

**Results:** In 16 patients (5.9%) with refractory IDA, anti-tTG antibodies were found to be positive; histopathologic evidence of CD was seen in 15 patients (5.5%). The mean age of the diagnosed patients was  $28.6 \pm 8.1$  years and all of them were females.

**Conclusions:** Celiac disease was more common in patients with refractory iron deficient anemia. In individuals with refractory iron deficiency anemia, we advise serological testing for early detection of celiac disease.

**Keywords:** Anti-tissue transglutaminase antibodies, Celiac disease, Iron Deficiency Anemia.

### INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that affects small intestine. Exposure to dietary gluten worsens CD in people with a genetic predisposition <sup>(1)</sup>. The pathophysiology basics of CD involve abnormal interaction between gluten, immune system and the gut leading to destruction of villi that will lead to ineffective absorption of various nutrients. Iron, B<sub>12</sub>, folic acid and fat-soluble vitamin deficiencies are particularly noticeable <sup>(2)</sup>.

Numerous serological techniques have been described for CD diagnosis, serum IgA-endomysial antibodies (IgA-EMA) and tissue transglutaminase IgA (IgA-tTG) testing provide the best levels of diagnostic accuracy, with a sensitivity of 95% and a specificity that is nearly 100% <sup>(3)</sup>. Furthermore, CD patients frequently exhibit IgA insufficiency. As a result, an IgG test against tTG is used for CD screening in patients who are at risk. Furthermore, genetic testing can aid in the diagnosis <sup>(4)</sup>.

A third of the world's population is affected by anemia, which has several distinct etiologies and is a major cause of morbidity globally <sup>(5)</sup>. One of the most prevalent nutritional issues worldwide, iron deficiency

anemia (IDA), has a significant negative influence on health and quality of life. Increased iron loss or inadequate iron absorption are the usual culprits <sup>(6)</sup>. Screening for CD, autoimmune gastritis, Helicobacter pylori infection, and hereditary form of IDA is advised in patients with unexplained or refractory IDA. Patients with refractory IDA had CD in between 4% and 6% of cases. In 100% of patients with CD, refractoriness to oral iron therapy was discovered <sup>(7)</sup>. Studies in the late 1990's identified CD as a possible cause of IDA unresponsive to oral iron treatment without other manifestations of malabsorption syndrome <sup>(8)</sup>. It has been estimated that IDA is present in up to 80 - 90% of patients with CD <sup>(9)</sup>. Impaired absorption of iron and other minerals, such as folate and cobalamin, is the most obvious cause of anemia in CD. It has been noted that there is also occult gastrointestinal blood loss <sup>(10)</sup>.

In our study, we sought to determine the prevalence of CD in adult Saudi patients with unexplained refractory IDA in northwestern Saudi Arabia (Hail Province), who had been identified by anti-tissue transglutaminase (anti-tTG) antibodies and intestinal endoscopic biopsies.

## PATIENTS AND METHODS

This is a cross-sectional study that was done at King Salman Specialist Hospital, which is tertiary specialized hospital in Hail province in North western of Saudi Arabia during the period from January 2019 to December 2021.

**Inclusion criteria:** Adult Saudi patients aged 18 to 55 years who had hemoglobin (Hb) levels below 12 g/dL for men and 11.0 g/dL for women, ferritin levels below 24 ng/mL for men and 11 ng/mL for women, and transferrin saturation below 15% (according to WHO criteria of IDA) made up the study's target population <sup>(11)</sup>.

**Exclusion criteria:** Patients with recognized causes of IDA (such as a chronic bleeding) as well as women who were pregnant or nursing. Failure to respond to treatment (hemoglobin increases of less than 1 g/dL) at a dose of at least 100 mg of elemental iron daily after 4 to 6 weeks of therapy is considered as refractoriness to oral iron <sup>(7)</sup>.

Our electronic records identified 2400 patients with IDA in total, of whom 270 patients (11.25%) matched the inclusion criteria. Testing for anti-tissue transglutaminase (tTG) antibodies was done after taking a blood sample from a peripheral vein. IgA and IgG tissue transglutaminase (tTG) antibodies were detected by ELISA using cutoff values of 15 IU/mL. All cases that tested positive for the anti-tTG antibody had endoscopic samples collected from the second part of the duodenum. Histopathologic examination were categorized based on the Marsh classification.

### Ethical Approval:

**Our study conformed to the stipulations of declaration of Helsinki of 1975, and its amendments in 2008. The Ethics Committee of King Salman Specialist Hospital approved the study and all patients gave their informed consents.**

### Statistical analysis

Statistical Package for the Social Sciences (SPSS), Version 23.0 (IBM SPSS Inc., Chicago, IL, USA) were used for data analysis. Quantitative data were reported as mean±SD, while qualitative data were reported as frequencies and percentages.

## RESULTS

During the period from 2019 to 2021, 270 patients (11.25%) with refractory IDA were found out of 2400 adult Saudi patients with IDA. Two hundred fifty were females (92.5%), and 20 were males (7.5%). Out of 270 patients, 16 individuals (5.9%) tested positive for anti-tTG IgA and IgG class antibodies, respectively, in 14 and 4 patients with iron deficiency anemia of unknown etiology. Anti-tTG IgA and IgG were present in two

cases. The histopathological findings of CD on duodenal biopsy in 15 people who tested positive for anti-tTG were categorized as Marsh IIIc in 3 cases, Marsh IIIb in 11 cases, and Marsh II in 1 patient. All diagnosed patients with CD were females, the mean age  $28.6 \pm 8.1$  years, the mean Hb level was  $10.4 \pm 1.4$  g/dL (range: 8.1–10.5), Serum ferritin level was  $4.1 \pm 1.7$  µg/L (range: 1.0–13.0), MCV level was  $70 \pm 6.6$  fL (range: 65–78 fL), MCH level was  $20 \pm 2$  pg (range: 18–28 pg). (Tables 1 & 2).

**Table (1):** Refractory IDA patients' characteristics

Patients Characteristics	N=270(%)
Mean age ± SD	26 ±7.4 years
Mean Hb ± SD	8 ± 3.5 gm/dl
Males / Females	20/250
tTG IgA (n, %)	14 (5.1%) IU/mL
tTG IgG (n, %)	4 (1.5%) IU/mL
Positive Intestinal biopsy	15 (5.5%)

**Table (2):** Characteristics of 16 patients with CD

Patient no	Sex (M/F)	Age (years)	Anti-tTG IgA	Anti-tTG IgG	Duodenal biopsy (modified Marsh)
1	F	21	45	11	IIIb
2	F	22	84	8	IIIb
3	F	18	25	8	II
4	F	25	179	5	IIIb
5	F	35	288	8	IIIc
6	F	39	381	7	IIIc
7	F	43	0	41	IIIb
8	F	39	200	13	IIIb
9	F	35	55	18	IIIb
10	F	18	48	4	IIIb
11	F	22	179	3	IIIc
12	F	30	339	0	IIIb
13	F	33	44	7	IIIb
14	F	22	99	22	IIIb
15	F	21	0	60	negative
16	F	36	112	0	IIIb

Modified Marsh classification: I= intraepithelial lymphocytosis, II: crypt hyperplasia, IIIa=mild villous atrophy, IIIb= moderate villous atrophy, IIIc= total villous atrophy.

## DISCUSSION

Anemia due to iron deficiency is a common sign of CD. Classic malabsorption symptoms are only present in a small percentage of CD patients, for the majority, IDA may be the only symptom <sup>(12)</sup>.

Up to 62% of adult patients with CD have extraintestinal manifestations <sup>(13)</sup>. One of the most common extraintestinal symptoms of CD is believed to be IDA without overt clinical evidence of intestinal

malabsorption<sup>(14)</sup>. Conversely, in patients with unexplained IDA, CD accounts for 5% to 6% of the anemia<sup>(15, 16)</sup>.

Few researches have been done to determine the prevalence of CD in the Arab community. In meta-analysis study done by **El-Metwally et al.**<sup>(17)</sup> that explored the epidemiology of CD in Arab countries, Saudi Arabia reported having the greatest frequency of CD in the general population (3.2%), with women showing a greater prevalence compared to men. In Saudi Arabia, CD is a frequent condition, with prevalence (in normal populations) of biopsy-proven of 1.4% and seroprevalence of 2.7%<sup>(18)</sup>. In a different meta-analysis of CD in at-risk groups in Saudi Arabia, the prevalence of seropositive-CD was 15.6%, whereas the prevalence of biopsy-proven was 10.6%<sup>(19)</sup>.

In Hail Province, the prevalence of CD in adult Saudi patients with refractory IDA is being reported for the first time in our study. We found that out of 2400 adult Saudi patients with IDA, 270 patients (11.25%) were identified to have refractory IDA and we reported a 5.9% prevalence of CD serology in patients with IDA of unknown etiology, while tissue proved diagnosis was about 5.5%. Our results are supported by **Mahadev et al.**,<sup>(20)</sup> that found 3–5% of people with IDA who were evaluated also have CD, as shown by research from Europe, USA and Middle East. Our results are also consistent with **Zamani et al.**<sup>(21)</sup> who investigated the prevalence of CD in patients with IDA of unknown cause, of the 4120 IDA patients, 206 patients were found to have IDA of unknown origin. Out of a total of 206 patients (14.6%), 30 had CD. This also is in concordance with study done in Oman, where they discovered about 8% frequency of CD serology in Omani people with IDA of unknown etiology<sup>(22)</sup>. In individuals with IDA, CD was shown to be present in 11% and 10.4%, respectively, of Indian and Iranian patients<sup>(8, 23)</sup>. While in studies from USA and Turkey, the prevalence was around 8%<sup>(24, 25)</sup>. According to **Pelkowski and Viera**<sup>(26)</sup> CD was highly associated with refractory IDA, as 10% of the research group had CD. In a study conducted in western Saudi Arabia, they found that 50% of CD patients suffered from either Osteomalacia or iron deficiency anemia<sup>(27)</sup>.

The mean age of the patients in our study was  $28.6 \pm 8.1$  years, which is slightly younger than the  $34.12 \pm 11.23$  years in the Omani study and those of **Kavimandan et al.**<sup>(22, 8)</sup> ( $32.1 \pm 13.1$  years).

ALL patients diagnosed with CD in our study were females, which is consistent with **Baghbanian et al.**<sup>(23)</sup> The majority of the participants in his study (59.5%) were females, which is comparable to earlier research done in Iran, the US, Europe, and the Middle East<sup>(28, 29)</sup>. The higher prevalence of autoimmune illnesses in the female population may be the cause for the higher frequency of celiac disease in women.

Mean Hb observed in our study was  $10.4 \pm 1.4$  g/dL. This is quite similar to the value reported by **Shahzad et al.**<sup>(30)</sup> who reported a mean Hb of  $8.81 \pm 1.23$  g/dL.

Most of patients in our study (93.3%) had been classified as Marsh III, this can be explained by that the most severe anemia was found in patients with Marsh 3 lesions, which is consistent with the etiology of IDA being characterized by decreased intestine absorption.<sup>(31)</sup>

Recovery from IDA in CD usually occurs within a year of beginning a strict gluten-free diet, in most cases without additional iron supplementation. Therefore, it is important to evaluate any patient with anemia who does not seem to be responding to routine treatment<sup>(32)</sup>.

## CONCLUSION

Patients with celiac disease frequently present with IDA, which is typical in this population. We advise screening celiac disease in people with iron-deficit anemia.

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