

THE PREVALENCE OF CELIAC DISEASE IN PATIENTS WITH IRON-DEFICIENCY ANEMIA IN CENTER AND SOUTH AREA OF IRAN

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ABSTRACT - Background - Celiac disease is an immune-mediated enteropathy due to a permanent sensitivity to gluten in genetically susceptible people. Iron-deficiency anemia is the most widely experienced anemia in humans. Iron-deficiency anemia additionally is a common extra intestinal manifestation of celiac disease. **Objective** - To investigate correlation between tTg levels and histological alterations and then to determine the prevalence of celiac disease in Center and South area patients of Iran with iron deficiency anemia. **Methods** - A total of 402 patients aged 12-78 years who presented with iron-deficiency anemia were included in this study. Hemoglobin, mean corpuscular volume and serum ferritin were determined. Venous blood samples for anti-tissue transglutaminase antibody immunoglobuline A and G were obtained from these patients. Upper gastrointestinal endoscopy was recommended to patients who had positive serology. **Results** - Of 402 patients with iron-deficiency anemia, 42 (10.4%) had positive serology for celiac disease. The small intestine biopsy of all patients with positive serology showed pathological changes (Marsh I, II & III). There was not significant difference in the mean hemoglobin level between iron-deficiency anemia patients with celiac disease and without celiac disease, duodenal biopsy results did not show significant relationship between the severity of pathological changes and levels of anti-tTG IgG (*P*-value: 0/869) but significant relationship was discovered between pathological changes and levels of anti-tTG IgA (*P*-value: 0/004). **Conclusion** - Screening of celiac disease by anti-tissue transglutaminase antibody should be completed as a routine investigation in patients with iron-deficiency anemia. Also physicians must consider celiac disease as a possible reason of anemia in all patients with iron deficiency anemia.

HEADINGS - Celiac disease. Iron-deficiency anemia. Gastrointestinal endoscopy. Transglutaminases.

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy that is caused by a permanent sensitivity to gluten by taking nutrients like wheat, barley, and also rye in genetically sensitive people^(13, 28, 47). CD was historically believed an intestinal disorders of childhood and adult life, characterised by failure to thrive, malabsorption, diarrhea, weight loss, vomiting, unusual stools, and also abdominal distention^(12, 38). On the other hand, only some patients with CD exhibit clinical symptoms, while most of the patients have slight symptoms⁽¹⁹⁾. Consequently, the disease is obviously under diagnosed⁽¹⁸⁾. Clinical appearance may be diarrhea predominance, the so called classical appearance, atypical with patients presenting in most atypical ways or it might be asymptomatic, the so called silent cases^(7, 45).

Celiac disease is a histological diagnosis, and, in patients in whom there is certainly a clinical concern of the problem, small bowel biopsy remains the first diagnostic method. Some assays for the diagnosis of celiac relevant antibodies are available, and, although these serological tests do not exchange the require for small intestinal biopsy for recognition, they could be extremely helpful

as an adjunct to diagnosis. Positive antibody tests might help guide clinicians towards biopsy in patients at high risk of improving celiac disease or inpatients with a low index of suspicion for the disease^(19, 37).

Over the past few years, population dependent serological researches have altered the information on both the clinical pattern and epidemiology of CD. Monosymptomatic, oligosymptomatic, atypical, silent and latent types of CD have been identified^(4, 35) as CD today often presents atypically, it is underdiagnosed. It is recommended that the detection rate might be improved by 12% when serology is employed to determine cases of occult enteropathy^(38, 46). Serologic antibody tests are indicated for all people in whom celiac disease is (even remotely) presumed, and also for all persons considered to be at risk for the disease⁽³³⁾. The enzyme tissue transglutaminase (tTG) was recently defined as the main autoantigen in CD^(1, 29) and the antigenic target recognized by EMA⁽⁸⁾. A human-recombinant kind of tTG was used to develop an ELISA to measure anti-tTG serum antibodies for the diagnosis of CD. Preliminary retrospective studies recommend that the human tTG-based ELISA can identify celiac patients missed by the IgA EMA test^(9, 44).

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Screening studies show a high prevalence of CD (between 1/130-1/300) among both healthy children and adult populations in European countries^(10, 31). In a recent study, the prevalence of CD in 2000 healthy blood donors was found to be 1.3% (1/166- 1/104) in Iran^(2, 42).

Considering the wide range of clinical characteristics of CD, like anemia, osteoporosis, dermatitis herpetiformis, and neurologic problems and critical problems like non-Hodgkin's lymphoma, small bowel adenocarcinoma, esophageal cancer, and melanoma, early analysis of CD is crucial, because it is otherwise related to increased mortality^(26, 40, 43).

Iron-deficiency anemia (IDA) is an extremely generally encountered anemia in humans (2%-5% of adults) and is usually attributable to either increased iron loss or impaired absorption of iron⁽⁵⁾. Iron is absorbed in the proximal small intestine and the absorption depends upon many factors, such as an intact mucosal surface area and also bowel acidity. The iron deficiency in celiac disease mainly results from impaired absorption of iron however there could also be occult blood loss in the gastrointestinal tract⁽³²⁾.

Iron deficiency anemia is a generally observed symptom in CD. Only a minority of CD patients present with classical malabsorption symptoms, while most patients have subclinical or silent forms in which IDA may be the sole appearance⁽⁶⁾. Studies using serologic tests as well as small-bowel biopsies in patients referred for assessment of IDA have documented CD in 0% to 8.7% of patients⁽²⁵⁾.

To our information, there is no published study from Center and South of Iran about prevalence of CD in patients with IDA of unknown source. The aim of this study was to investigate correlation between tTg levels and histological alterations and then to define the prevalence of CD in Center and South area patients of Iran with IDA.

METHODS

Patients

In a cross-sectional study, we approved patients with a diagnosis of IDA who were referred to the Gastroenterology and hematology Departments of Yazd Shahid Sadoughi University School of Medicine, Research and Training Hospital. At first, IDA detection was restored to all 402 patients. IDA was defined as: hemoglobin level less than lower limits (13.5 g/dL for male adult, 12.0 g/dL for female adult), ferritin level <30 ng/mL (normal 20-300 ng/mL), transferrin saturation lower than 20%, and mean corpuscular volume (MCV) less than 80 fL. From April 2012 – March 2014, patients aged between 12 and 78 years old were examined. Patients with obvious blood loss, such as those with a history of melena, hematochezia, hemoptysis, recurrent epistaxis, hematuria, trauma, pregnancy, serious respiratory or cardiac disorders, hypermenorrhea (periods ≥ 7 days), menometrorrhagia, gastric surgery, known chronic diseases and hematologic diseases were excluded from the study. The Ethics Committee of the Yazd Shahid Sadoughi University of Medical Sciences approved the study and informed

consent was attained from all patients after explaining the aims and also protocol of the study.

Serological and assessment for CD

Venous blood samples for tissue transglutaminase antibody (tTG) were obtained from all patients. Samples were tested for IgA and IgG anti-tTG antibodies using a commercially available enzyme-linked immunosorbent assay (AESKU 7503, Germany); the tTG IgA value greater than 18 IU/mL was considered positive. Upper gastrointestinal endoscopy and small intestine biopsy was recommended to patients who had positive serology.

Statistical analysis

Data are presented as mean \pm SD or percentage. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 17.0, *t*-test for comparison of the means of quantitative variables, chi-Square test for comparison of qualitative variables and pearson's chi-square test for determine correlation of between two categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

From the 402 patients with IDA of obscure origin, 348 were females (86.6%), and 54 were males (13.4%). Totally, 42 patients (25 F, 17 M) with IDA of obscure origin were found to be positive for at least one of the anti-tTG antibodies.

There was no significant difference between those with and without CD in hemoglobin (Hb), MCV or ferritin level of CD ($P > 0.05$). IgA anti-tTG antibody was found to be positive in 8 (19%) patients with IDA of obscure origin. IgG anti-tTG antibody was found to be positive in 10 (24%) patients with IDA of obscure origin. 24 patients were positive for both IgA and IgG anti-tTG antibodies (57%). All subjects who were positive for anti-tTG IgA and IgG had histopathological findings of CD on duodenal biopsy, which were classified as Marsh I, Marsh II and Marsh III in patients with IDA. Duodenal biopsy results did not show significant relationship between the severity of pathological changes and levels of anti-tTG IgG (P -value: 0/869) but significant relationship was discovered between pathological changes and levels of anti-tTG IgA (P -value: 0/004) (Table 1). It was not significant relationship between levels of anti-tTG IgA and anti-tTG IgG. ($r^2=0.047$) (Figure 1).

Endoscopy finding show the scalloping of folds in the duodenum in 39 IDA patients (92.9%) while 3 IDA patients (7.1%) did not show this change.

In Table 2, the mean levels of Hb, MCV, and serum ferritin and age in IDA patients with CD are compared with the levels in IDA patients without CD. There was no significant difference in the mean Hb level between IDA patients with CD and without CD ($P=0.317$).

Mean hemoglobin ($P=0.802$) and ferritin levels ($P=0.81$) in the IDA patients with celiac disease does not have significant relationship with the severity of pathological changes and level of iron according to marsh classification (Table 3).

TABLE 1. Serologic features of patient, Relationship between the severity of pathological changes and levels of anti-tTG IgA and IgG according to duodenal biopsy in IDA patients with CD

Histology	Marsh I		Marsh II		Marsh III		Total	
	IgG	IgA	IgG	IgA	IgG	IgA	IgG	IgA
<18	3 (37.5%)	6 (60%)	1 (12.5%)	1 (10%)	4 (50%)	3 (30%)	8	10
≥18	9 (26%)	6 (18/7%)	5 (14/7%)	5 (15/6%)	20 (58/8%)	21 (65/6%)	34	32
Total	12 (28.9)	12 (28.6%)	6 (14.3%)	6 (14.3%)	24 (57.1%)	24 (57.1%)	42	42

IDA: iron-deficiency anemia; CD: celiac disease. Modified Marsh classification: Marsh I (intraepithelial lymphocytosis >40/100 epithelial cells), Marsh II(intraepithelial lymphocytosis + crypt hyperplasia) and Marsh III (villous atrophy) in patients with iron-deficiency anemia.

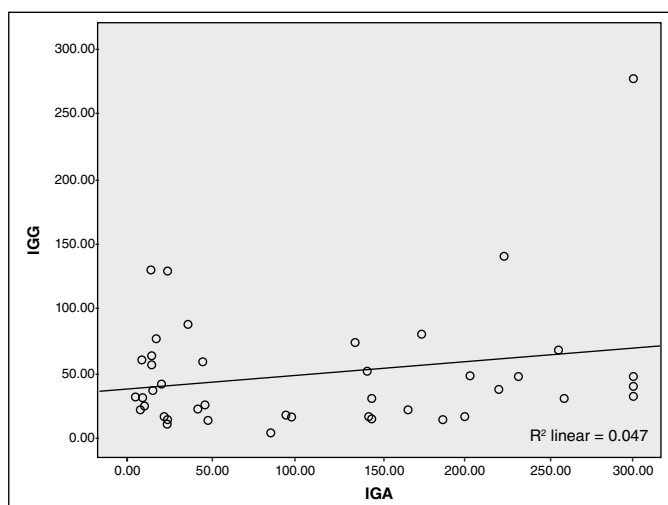


FIGURE 1. It was not significant relationship between levels of anti-tTG IgA and anti-tTG IgG according to $r^2 = 0.047$

TABLE 2. Demographic and hematological parameters in IDA patients with and without CD

Index	CD patients	Non-CD patients	P-value
Age	25.76 ± 12.24	36.66 ± 10.53	<0.001
Hb (g/dL)	9.89 ± 1.56	10.18 ± 1.83	>0.05 (0/31)
MCV (fL)	72.57 ± 6.22	72.76 ± 6.64	>0.05 (0/85)
Ferritin (ng/mL)	11.13 ± 8.71	11.13 ± 9.06	>0.05 (0/99)

IDA: iron-deficiency anemia; CD: celiac disease; MCV: mean corpuscular volume.

TABLE 3. Level of hemoglobin and ferritin in IDA patients with CD

Index	CD patients	Hb (g/dL)	Ferritin (ng/mL)
Marsh I	12	10.13 ± 1.4	13.67 ± 11.12
Marsh II	6	9.7 ± 0.5	8.41 ± 4.41
Marsh III	24	9.7 ± 1.85	10.57 ± 8.47
P-value	-	0.802	0.466

Modified Marsh classification: Marsh I (intraepithelial lymphocytosis >40/100 epithelial cells), Marsh II(intraepithelial lymphocytosis + crypt hyperplasia) and Marsh III (villous atrophy) in patients with IDA. IDA: Iron-deficiency anemia; CD: celiac disease.

DISCUSSION

Celiac Disease or gluten-sensitive enteropathy is an autoimmune enteropathy attributable to food gluten intolerance in genetically susceptible individuals⁽³⁴⁾. It consists of a large spectrum from overt malabsorption or usual gastrointestinal symptoms to clinically silent conditions⁽²²⁾. IDA may be found in CD patients even in the lack of diarrhea or steatorrhea. The loss of iron in the bowel enterocytes, malabsorption of daily iron, and also rarely gastrointestinal bleeding may lead to the pathogenesis of IDA in CD⁽³⁰⁾. Due to the development in diagnostic methods for determining CD, asymptomatic cases are actually the most common form of the disease, and are seven times more usual compared to clinically discovered patients⁽²⁷⁾. Studies utilizing serologic tests and also small-bowel biopsies in patients referred for analysis of IDA have reported CD in 1.8%-14.6% of patients^(20, 47).

Applying a highly sensitive screening test (tTG antibody test) and also duodenal histological examination, this is the study considering the prevalence of CD in patients with IDA of unclear cause in a Iranian population.

Our study showed that the prevalence of CD in IDA patients in the Center and South area of Iran was 10.4% according to tTG (IgA and IgG) titer and biopsy results. Various rates of prevalence of CD in IDA patients have been reported among different studies^(11, 17, 24, 39). The prevalence of CD in patients presenting with IDA varies range. In a prospective study of 130 patients from Isfahan (Iran), Emami et al. (2012) diagnosed thirteen patients (10%) with CD⁽¹⁷⁾. In a study of 4120 patients with IDA, conducted in the Tehran (Iran), 14.6% of these patients had CD⁽⁴⁷⁾. In another study in Iran, CD was present in 6.3% of patients with IDA⁽¹¹⁾. In studies from USA and Turkey, show prevalence 8.7% and 8.33%, respectively^(11, 24). This disparity of prevalence could possibly be related to differences in local prevalence of CD as well as patient selection criteria. In this study, a large number of patients referred from different cities of the, Central and Southern regions of Iran and ethnic differences is the causes of disparity of prevalence of CD in IDA patients.

The clinical spectrum of CD is wide and includes classic presentation of malabsorption with diarrhea, no classical extra intestinal features, subclinical or asymptomatic forms, and potential disease characterized by positive serology with a normal intestinal mucosa on biopsy^(36, 41).

Clinicians might fail to consider CD as a cause of IDA while gastrointestinal symptoms are absent or nonspecific. In this study, a large amount of IDA patients (54.8%) with CD did not report any specific gastrointestinal symptoms, in accordance with earlier reports showing that most cases of CD in IDA appear to be atypical or silent, determined only by a screening procedure^(16, 47, 39). This is significantly less than the value of 73.3 % reported by Zamani et al. in their clinical study⁽⁴⁷⁾. The outcomes of long-standing unestablished CD in IDA are that these patients are at risk of preventable problems. The majority of patients (59.5%) were female, a finding comparable to previous studies conducted in the other area of Iran, United States, Europe and the Middle East^(14, 23). Such a higher frequency rate of CD amongst women might be attributed to the higher incidence of autoimmune diseases found in the female population.

In our study, there were no differences in hematological indices- including MCV, hemoglobin and ferritin levels- between CD patients and other patients with anemia of obscure origin to help distinguishing them (Tables 2 and 3). In CD patients, there was not significant relationship between hemoglobin and ferritin levels with marsh pathological Criteria, these finding were similar to Ganji et al., but Zamani et al. showed that the hemoglobin level had significant relationship with the severity of duodenum injury, and this difference in results is presumably because of different criteria inserted in their study^(21, 47).

We used a human recombinant protein-based anti-tTG test, which has higher sensitivity and accuracy than a guinea pig protein-based tTG test. However, neither IgA anti-tTG nor IgG anti-tTG was 100% sensitive. We found no direct correlation between serum IgG anti-t levels and histological severity according to the Marsh classification, while there was a significant relationship between serum IgA anti-t and histological severity. Donaldson et al. investigated IgA anti-tTG levels ≥ 100 units were almost exclusively in adults and children with Marsh grade 3 duodenal histopathology⁽¹⁵⁾, in other study Bhattacharya et al. showed a significant correlation between IgA anti-tTG titers and anthropometric parameters and severity of duodenal histopathology⁽³⁾.

These studies highlight the importance of the prevalence of CD in different patient groups.

The relatively small sample size may be considered a limitation of our study. Studies with larger populations would provide more accurate results. Also, human leukocyte antigens (HLA)-DQ2 and HLA-DQ8 have been implicated in confirmation of CD and a diagnosis of CD in patients with both negative HLA-DQ2 and HLA-Dq8 is really implausible. In the study, no HLA test was performed to strongly exclude a diagnosis of CD. Thus, it is possible that an additional number of patients might be diagnosed as having CD.

CONCLUSION

By serological test, we found that the prevalence of CD in IDA patients was 10.4% in this study, this outcomes was obtained in conditions that the majority of patients had not gastro intestinal symptoms. Therefore, serological screening is recommended for early detection of CD in all patients with u IDA. There are some important benefits of CD screening in patients with IDA. It may prevent the need for other often useless tests, treatment failure, and intestinal lymphoma, since CD may easily be treated with a gluten-free diet.

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Authors' contributions

Baghbanian M: study design; performing most of the procedures on patients, revision of the article writing, Farahat A: statistical analysis; manuscript writing; responsible for the process of submitting the article; data recollection, Vahedian HA: manuscript writing; study design. Sheyda E: data recollection, Zare-Khormizi MR: manuscript writing; responsible for the translation into English and text formatting.

Baghbanian M, Farahat A, Vahedian HA, Sheyda E, Zare-Khormizi MR. A prevalência da doença celíaca em pacientes com anemia por deficiência de ferro no Centro e zona Sul do Irã. *Arq Gastroenterol.* 2015;52(4):xxx.

RESUMO - Contexto - A doença celíaca é uma enteropatia imunomediada, devido a uma sensibilidade permanente ao glúten em pessoas geneticamente suscetíveis. A anemia por deficiência de ferro é a anemia mais frequente em seres humanos e, além disso, é uma manifestação extra intestinal comum da doença celíaca. **Objetivo** - Investigar a correlação entre níveis de imunoglobulina de anticorpos anti-transglutaminase tissular A (anti-tTG IgA) e G (IgG anti-tTG) e alterações histológicas e, em seguida, determinar a prevalência de doença celíaca no Centro e Sul do Irã em pacientes com anemia por deficiência de ferro. **Métodos** - Foram incluídos neste estudo um total de 402 pacientes com idades entre 12-78 anos, que apresentavam anemia por deficiência de ferro. Hemoglobina, volume corpuscular médio e ferritina sérica foram determinados. Amostras de sangue venoso para imunoglobulina de anti-tTG IgA e IgG anti-tTG foram obtidas nestes pacientes. Endoscopia gastrointestinal foi recomendada para pacientes que tiveram sorologia positiva. **Resultados** - Dos 402 pacientes com anemia por deficiência de ferro, 42 (10,4%) tiveram sorologia positiva para doença celíaca. A biópsia do intestino delgado de todos os pacientes com sorologia positiva mostrou alterações patológicas (Marsh I, II e III). Não houve diferença significativa no nível de hemoglobina média entre os pacientes com deficiência de ferro com ou sem a doença celíaca. O resultado da biópsia duodenal não mostrou relação significativa entre a gravidade das alterações patológicas e níveis de IgG anti-tTG (*P*-valor: 0/869), mas descobriu-se relação significativa entre as alterações patológicas e níveis de anti-tTG IgA (*P*-valor: 0/004). **Conclusão** - A pesquisa de doença celíaca por dosagem de anticorpo anti-transglutaminase tissular deve ser completada como investigação de rotina em pacientes com anemia por deficiência de ferro. Os clínicos devem considerar a doença celíaca como um possível causa de anemia em todos os pacientes com anemia ferropriva.

DESCRITORES - Doença celíaca. Anemia ferropriva. Endoscopia gastrointestinal. Transglutaminases.

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