

# Is Routine Duodenal Biopsy Necessary for the Detection of Celiac Disease in Patients Presenting with Iron Deficiency Anemia?

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## ABSTRACT

**Backgrounds:** Iron deficiency anemia (IDA) is one of the well recognized presentations of celiac disease (CD). According to the lack of data from our population in this regard, we determined the prevalence of CD in patients presenting with IDA to see if it is worthwhile to do a precise screening for CD in such patients.

**Methods:** This cross-sectional study was conducted on patients referred with IDA to Poursina Hakim Gastroenterology Clinic, Isfahan (IRAN). All included patients underwent upper gastrointestinal endoscopy and duodenal biopsy. Histopathological changes were assessed according to the Marsh classification. Also, patients were evaluated for IgA anti-tissue transglutaminase (t-TG) antibody with enzyme-linked immunosorbent assay (ELISA) technique. CD was defined as having Marsh II or above histopathology or being seropositive with Marsh I histopathology and having a good response to gluten free diet (GFD).

**Results:** During the study, 130 patients with the mean age of  $35.5 \pm 13.7$  (67.7% female [20.4% post-menopausal]) were undergone seropathological studies. According to histopathological study and a clinical response to GFD, 13 patients (10%) were ultimately diagnosed with CD. Nine patients (6.9%) were seropositive, from which, five patients (3.8%) were ultimately diagnosed as CD cases. IgA anti-tTG became negative in all of these patients after six months of GFD.

**Conclusion:** CD should be considered in any adult patient presenting with unexplained IDA, even if not accompanied with gastrointestinal symptoms. Routine duodenal biopsy performed during diagnostic upper gastrointestinal endoscopy is worthwhile in order to investigate for CD as an underlying cause of IDA in adult patients.

**Keywords:** Celiac disease, diagnosis, iron deficiency anemia

## INTRODUCTION

Iron deficiency is the most common cause of microcytic, hypochromic anemia worldwide<sup>[1,2]</sup> and is frequently caused by either overt or occult chronic blood loss from the gastrointestinal

tract. Therefore, the standard evaluation of a patient presenting with iron deficiency anemia (IDA) includes a complete evaluation of the gastrointestinal tract to identify a source of bleeding.<sup>[3,4]</sup> Once gastrointestinal blood losses have been excluded, intestinal malabsorption syndromes should be investigated as the IDA may be the only presenting sign of malabsorption due to the presence of intestinal villous atrophy.<sup>[5]</sup>

Celiac disease (CD) is a malabsorption syndrome that was thought to be rare in the past.<sup>[6-8]</sup> Recent screening studies using valuable screening tools showed that CD is one of the most frequent genetically based diseases which occur worldwide with a prevalence ranging from 1:85 to 1:500 in different populations.<sup>[9-12]</sup> The study that performed in our area showed that its prevalence is 0.6%<sup>[13]</sup> to 0.8%<sup>[14]</sup> among healthy blood donors and 0.5%<sup>[15]</sup> to 0.9% in general population.<sup>[16]</sup>

It is known that CD has a wide clinical heterogeneity from typical malabsorption syndrome to atypical intestinal complaints or extra intestinal mono-symptomatic presentation, such as short stature or IDA.<sup>[17]</sup> CD was first described with classic symptoms of malabsorption syndrome such as diarrhea, steatorrhea, and weight loss, but nowadays, IDA is one of the well recognized presentations of CD in any age, sex, or ethnic group. Despite such a high prevalence of CD among these patients, CD is often unrecognized in IDA.<sup>[18]</sup> The prevalence of CD in patients with IDA has been estimated to be approximately 2.8% in a prospective study by Karnam *et al.*<sup>[19]</sup> Studies in Europe using anti-gliadin and anti-endomysial antibodies have shown a prevalence of 5%.<sup>[20-22]</sup>

According to the lack of data from our population on the prevalence of CD in patients presenting with IDA, we determined the prevalence of CD in patients presenting with IDA to see if it is worthwhile to do a routine precise screening for CD in such patients.

## METHODS

### Patients and setting

This study was done from 2003 to 2008 in Poursina Hakim Research Institute, a tertiary referral gastrointestinal center in Isfahan, IRAN. All patients who were referred to the endoscopic unit of the institute for evaluation of IDA were the

target population of our study. Primary evaluation of anemia was done by the hematologist who referred the patients for exclusion of gastrointestinal causes of anemia. IDA was defined as hemoglobin <12g/dl in women (normal, 12.0–16.0 g/dl) and <14g/dl in men (normal, 14.0–18.0 g/dl), and ferritin <15 µg/L (normal, 25–300 µg/L). Those with prior gastrointestinal surgery, ulcerative disease of the gastrointestinal tract, known gastrointestinal malignancy, chronic diseases, and known cases of CD were not included. The ethics committee of the Isfahan University of Medical Sciences approved the study and informed consent was obtained from all patients after explaining the aims and protocol of the study.

### Serological assessment for CD

Serum level of IgA was measured in all patients to find cases with selective serum IgA deficiency. IgA anti-tissue transglutaminase (anti-tTG) antibody was determined in all patients using an enzyme-linked immunosorbent assay (ELISA) technique by a commercially available kit (ORG540 A, ORGENTEC Diagnostica GmbH). IgA anti-tTG antibody above 10 Au/ml was considered positive, as determined by the manufacturer.

### Pathological assessment for CD

All included patients underwent upper gastrointestinal endoscopy. After oropharyngeal anesthesia, a “Pentax EPM-3300” EG2940 scope was used for the endoscopy procedure. Patients with an obvious source of gastrointestinal bleeding were excluded from the study. The second part of duodenum was observed carefully in all patients and at least four spike biopsies were taken from the second part of duodenum (D2). Biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, cut in 4 µm sections, and stained with hematoxylin-eosin for histopathologic examination. Biopsy specimens were evaluated according to Marsh 1992, revised and validated in 1997 as Marsh I to III (Marsh IIIA, Marsh IIIB, and Marsh IIIC).<sup>[23]</sup>

### Definition of CD

Patients with Marsh II or above histopathology or seropositive patients with Marsh I histopathology and an expected good response to gluten free diet

(GFD) were considered to have CD. We classified patients with villous atrophy and a negative antibody profile as having antibody negative CD only if they had good response to GFD. IgA anti-tTG antibody was re-tested after GFD every three months.

### Statistical analyses

Data are presented as mean $\pm$ SD or percentage. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 16.0, *t*-test for comparison of the means of quantitative variables and Chi-Square test for comparison of qualitative variables.  $P < 0.05$  was considered statistically significant.

## RESULTS

During the study, 130 patients with the mean age of  $35.5 \pm 13.7$  (88 [67.7%] female [20.4% post-menopausal]) were included in our study after exclusion of patients with obvious source of IDA in endoscopy. In all 130 patients, D2 biopsies were taken. According to histopathological study and a clinical response to GFD, 13 patients (10%) were ultimately diagnosed with CD. Also, IgA anti-tTG antibody was determined in all patients and nine patients were seropositive. From these patients, five patients were ultimately diagnosed as CD cases based on histopathological study. IgA anti-tTG became negative in all of the five patients after six months of GFD [Table 1].

There was no significant difference between those with and without CD in age, gender, Hb or ferritin level, or family history of CD ( $P > 0.05$ ). However, abdominal pain and diarrhea were more prevalent in CD patients ( $P < 0.05$ ); [Table 2].

## DISCUSSION

IDA, as the only presenting feature of CD, is not uncommon in adult or even in elderly patients. As the prevalence of CD is high in the community, it should therefore be considered as a potential cause in any patient presenting with IDA. Recent guidelines from the British Society of Gastroenterology recommended that duodenal biopsies should be taken during endoscopy if no obvious cause of iron deficiency could be found.<sup>[24]</sup> In our study, we evaluated the patients with IDA that were referred by hematologists after primary

**Table 1:** CD patients' characteristics ( $n=13$ )

Age (years)	35.3 $\pm$ 14.3 [16-67]
Gender (female/male)	7 (53.8%)/6 (46.1%)
Hb (g/dl)	10.2
Ferritin ( $\mu$ g/L), mean $\pm$ SD	7.2
Positive tTG	5 (38.4%)
Villous atrophy	
Marsh II	6 (46.1%)
Marsh IIIA	1 (7.6%)
Marsh IIIB	2 (15.3%)
Marsh IIIC	4 (30.7%)

Data are shown as mean $\pm$ SD [range] or number (%)

**Table 2:** Hemoglobin and ferritin levels in CD compared with other patients

	CD patients $n=13$	Other IDA patients $n=117$	<i>P</i>
Age (year)	35.5 $\pm$ 13.7	36.0 $\pm$ 14.6	0.886
Gender (female/male)	7(53.8%)/ 6(46.1%)	81(71.6%)/ 36(31.8%)	0.206
Hb (g/dl)	10.22 $\pm$ 1.12	9.65 $\pm$ 1.42	0.16
Ferritin ( $\mu$ g/L)	7.29 $\pm$ 2.51	8.41 $\pm$ 3.13	0.21
Family history	1 (7.6%)	0	0.10
Abdominal pain	9 (69.2%)	43 (36.7%)	0.02
Diarrhea	5 (38.4%)	12 (10.2%)	0.01

Data are shown as mean $\pm$ SD or number (%)

evaluations. Patients with an obvious origin of bleeding in upper gastrointestinal endoscopy were excluded from our study. We found CD as the cause of IDA of obscure origin in a significant proportion (10%) of the patients. In a study by Zamani *et al.*, they also have found that there is a high prevalence (14%) of CD in patients with IDA of obscure origin. In their study, the prevalence of CD was amongst the highest rates reported. One possible reason was that they evaluated CD among highly selected patients in whom the cause of IDA could not be identified after extensive evaluations. Also, they considered patients with positive serological tests and milder degrees of duodenal mucosal lesions (e.g. Marsh I or II) as having CD.<sup>[8]</sup> Lower rates (2-3%) of the prevalence of CD in IDA patients have been reported among different studies.<sup>[19,25-27,24]</sup> This disparity could possibly be related to differences in local prevalence of CD as well as patient selection criteria. Umapprasanna *et al.* prospectively evaluated all patients presenting with IDA without excluding other gastrointestinal



(GI) disorders and found the prevalence of CD to be 2.8% in these patients. Their results comparing to our study could be due to that they did not exclude other IDA patients with an obvious site of bleeding at upper and lower endoscopy.<sup>[19]</sup>

In our study, the prevalence of abdominal pain and diarrhea was significantly higher in CD than in non-CD cases that could be a clue to case finding. However, a significant proportion of CD patients did not report any gastrointestinal symptoms which showed that CD should be considered in any patient with unexplained IDA, even if they do not have any gastrointestinal symptoms. In this study, we used a human recombinant protein based tTG test, which has a higher sensitivity and accuracy than a guinea pig protein-based tTG test. However, anti-tTG antibody test is not 100% sensitive, as 8 out of 13 CD patients (61.5%) had negative serology but high levels of villous atrophy (M II to M III). Thus, we recommend a routine duodenal biopsy among patients presenting with unexplained IDA.

## CONCLUSION

According to the high prevalence of CD among adult patients presenting with IDA, routine duodenal biopsy, performed during diagnostic upper gastrointestinal endoscopy, and seropathological studies for diagnosing CD is recommended. CD should be considered in any patient with unexplained IDA, even if they do not have typical or atypical gastrointestinal symptoms suggesting the disease.

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