



ORIGINAL ARTICLE

# Anemia in celiac disease is multifactorial in etiology: A prospective study from India

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## Introduction

Celiac disease (CD) is a unique autoimmune disease, with a known environmental predisposition factor in the form of gluten, in genetically predisposed individuals.<sup>1</sup> It is the most common cause of malabsorption syndrome.<sup>2</sup> Over the past two decades, CD has emerged as a common health-care problem in Asian countries, with current seroprevalence (using antitissue transglutaminase [tTG] or anti-endomysial antibodies) of 1.6% and prevalence (confirmed by histology) of 0.5%.<sup>3</sup> The prevalence of CD is increasing worldwide and in India (0.6% in India).<sup>3</sup>

Typical CD presents with chronic diarrhea and malabsorption. However, nearly 50% of adult patients present with atypical

## Abstract

**Background and Aims:** Anemia is one of the most common extraintestinal manifestations of celiac disease (CD), with iron deficiency anemia (IDA) being the predominant cause. However, anemia in CD can have varied etiologies, including mixed nutritional deficiency. We aimed to study the prevalence and etiology of anemia in CD in a north Indian population.

**Methods:** In this prospective observational study, consecutive patients with documented CD between January 2012 and December 2013 were included, and all patients underwent detailed clinical assessment; hematological investigations including iron profile, serum folate, and vitamin B<sub>12</sub> levels; and esophageoduodenoscopy with duodenal biopsies for histopathological examination. Prevalence of anemia and different deficiencies were calculated, and a correlation between hematological parameters and histological findings was found.

**Results:** Of the 103 patients studied, anemia was detected in 96 patients, giving a prevalence of 93.2% with a baseline hemoglobin of  $8.94 \pm 2.54$  g/dL. Overall, iron deficiency was seen in 84 (81.5%) patients, followed by vitamin B<sub>12</sub> deficiency in 14 (13.6%) and folate deficiency in 11 (10.7%) patients; 17 (16.5%) patients had anemia due to mixed nutritional deficiencies, and 4 (3.9%) patients had anemia of chronic disease. The mean hemoglobin and median ferritin levels were significantly lower in patients with severe villous atrophy compared to those with mild atrophy.

**Conclusion:** Anemia in patients with CD is multifactorial. Even though iron deficiency is the most common cause, other nutrient deficiencies should always be explored.

presentations like anemia, short stature, and osteopenia.<sup>4</sup> Anemia is one of the most common extraintestinal manifestations of CD, reported to occur in 5–40% of patients in the West and in more than 80% patients in developing countries, with a higher prevalence in Asian countries.<sup>4–7</sup> Iron deficiency anemia (IDA) is the most common form of anemia in CD.<sup>8</sup> However, studies have shown that anemia in CD is actually multifactorial and can have varied etiologies, including mixed nutritional deficiency, anemia of chronic disease (ACD), and aplastic anemia.<sup>8</sup> With increasing prevalence of CD in developing countries, it is important to know the contributing factors of anemia in different populations. The aim of this study was to find the prevalence and etiology of anemia in patients with CD in a north Indian population.

## Methods

**Subjects.** We conducted a prospective observational study at a tertiary care referral center in north India from January 2012 to December 2013. Consecutive patients of CD (age > 12 years) were included after giving written informed consent. The diagnosis of CD was based on modified European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria.<sup>9</sup> Patients who were already on a gluten-free diet, those with coexistent diseases causing anemia (renal disease, chronic liver disease), and patients with overt gastrointestinal bleed were excluded from the study. The study was approved by the ethical committee of the hospital and was conducted in compliance with the guidelines of good clinical practice of the World Medical Assembly Declaration of Helsinki.<sup>10</sup>

**Celiac disease work-up.** A complete clinical assessment, including the duration of symptoms, detailed clinical examination, and baseline tests (hemogram and biochemical parameters), was conducted in all patients. IgA tTG antibody levels were measured in all patients using an indirect solid-phase enzyme immunoassay (ELISA) kits (Celikey, Phadia GmbH, Freiburg, Germany). Esophagogastroduodenoscopy using an Olympus GIF 180 H endoscope was performed under conscious sedation using intravenous midazolam to evaluate morphological changes in duodenal mucosa, and four to six biopsies were taken from the second part of duodenum for histopathological examination. The histological examination was carried out by a single histopathologist, and the histological severity was graded according to modified Marsh grading.<sup>11</sup>

**Anemia work-up.** All patients underwent complete hemogram, which included hemoglobin, total leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and peripheral blood smear examination; the iron profile including serum ferritin, serum iron, total iron binding capacity, and transferrin saturation; serum levels of vitamin B<sub>12</sub>; and folate. Anemia was diagnosed according to World Health Organization (WHO) criteria: hemoglobin level < 12 g/dL in females and < 13 g/dL in males.<sup>12</sup> Iron deficiency was defined as serum ferritin < 30 ng/mL, serum iron < 30 µg/dL, total iron binding capacity > 400 µg/dL, and percentage saturation < 15%.<sup>13</sup> ACD was defined as reduced transferrin saturation < 16% and serum ferritin > 100 ng/mL.<sup>14</sup> Serum folate and B<sub>12</sub> levels were measured using a competitive immunoassay. Folate deficiency was designated as decreased serum folate levels (< 4.0 ng/mL) and vitamin B<sub>12</sub> deficiency as low serum B<sub>12</sub> levels (< 200 pg/mL).<sup>15,16</sup> Hematological parameters (hemoglobin, ferritin, RDW, serum folate, and vitamin B<sub>12</sub>) were correlated with histological severity. All patients with anemia were started on a gluten-free diet, and nutritional supplementation was carried out with iron, folic acid and B<sub>12</sub>, all orally administered, supplemented in those found to be deficient in these parameters.

**Statistical analysis.** The hematological parameters, including baseline hemogram, iron profile, serum folate, and vitamin

**Table 1** Clinical presentation of patients enrolled in the study (N = 103)

Clinical presentation	No of patients (%)
Fatigue, shortness of breath	74 (71.8%)
Diarrhea	35 (34%)
Short stature	25 (24.3%)
Pain abdomen	20 (19.4%)
Dyspepsia	19 (18.4%)
Delayed puberty	17 (16.5%)
Menstrual irregularities	16 (15.5%)
Diabetes mellitus	11 (10.7%)
Thyroid dysfunction	11 (10.7%)
Bone pains	11 (10.7%)
Constipation	8 (7.8%)
Infertility	2 (1.9%)
Diabetes mellitus	11 (10.7%)

B<sub>12</sub> levels, were analyzed for all patients. The descriptive data were presented as percentages for categorical variables and mean ± standard deviation (SD) for quantitative variables. The continuous variables were compared using student's t-test, whereas the categorical variables were compared using the Chi-squared test. A *P*-value of < 0.05 was considered significant. Pearson's or Spearman's correlation coefficient was applied to study correlations between hematological parameters and villous atrophy. All statistical testing was performed using the SPSS version 17 software.

## Results

**Clinical characteristics.** A total of 103 consecutive patients of CD were studied, of whom 48 (46.6%) were males, and 55 (53.4%) were females. The mean age at the time of presentation was 26.15 ± 13.3 years, with a median duration of symptoms of 4.5 years before presentation. The clinical presentation was typical in 35 (34%) patients with diarrhea and malabsorption, whereas the majority of patients, 68 (66%), presented with atypical symptoms, anemia being the most common (Table 1). The baseline hemoglobin in the study group was 8.94 ± 2.54 g/dL, with an MCV of 70.18 ± 10.52 and RDW of 21.17 ± 4.20. A total of 68 patients (66%) had a microcytic hypochromic picture, 25 (24.3%) normocytic normochromic, and 10 (9.7%) mixed micro and macrocytic picture on peripheral smear. The median serum ferritin level was 8 ng/mL (IQ range: 5–30 ng/mL), with a mean serum folate of 18.89 ± 12.42 ng/mL and median serum vitamin B<sub>12</sub> of 311 pg/mL (IQ range: 213–510) (Table 2).

**Anemia.** Symptoms of anemia (fatigue, shortness of breath) were the most common presenting feature seen in 74 patients (71.8%). However, on laboratory evaluation, anemia was detected in 96 patients, with a prevalence of 93.2%. The mean hemoglobin level was 8.9 ± 2.6 g/dL. Overall, iron deficiency in the study group was seen in 84 patients (81.5%), followed by vitamin B<sub>12</sub> deficiency in 14 (13.6%) and folate deficiency in 11 (10.7%) patients. On etiological evaluation, anemia was a

**Table 2** Baseline laboratory parameters of 103 patients

Parameter	Mean $\pm$ SD
Hemoglobin (g/dL)	8.94 $\pm$ 2.54
Total leukocyte count (cells/cumm)	7210 $\pm$ 2459
Platelet (lakh/mcl)	3.04 $\pm$ 1.48
Mean corpuscular volume (fL/red cell)	70.18 $\pm$ 10.52
Mean corpuscular hemoglobin (pg/cell)	20.87 $\pm$ 4.52
Red blood cell distribution width (%)	21.17 $\pm$ 4.20
Serum ferritin (median) (ng/mL)	8.00 (5.0–30.0)
Serum iron (ug/dL)	81.23 $\pm$ 51.60
Total iron binding capacity (ug/dL)	493.20 $\pm$ 139.97
Percentage transferrin saturation	16.65 $\pm$ 10.68
Serum folate (ng/mL)	18.89 $\pm$ 12.42
Serum vitamin B <sub>12</sub> (median) (pg/mL)	311.00 (213.0–510.0)
Serum bilirubin	0.64 $\pm$ 0.31
Aspartate aminotransferase/ Alanine aminotransferase (U/L)	42.87 $\pm$ 36.30/ 43.62 $\pm$ 43.63
Alkaline phosphatase (IU/L)	169.79 $\pm$ 103.17
Serum protein/albumin (g/dL)	(7.7 $\pm$ 0.8)/(4.2 $\pm$ 0.7)

**Table 3** Etiology of anemia in 103 patients

Etiology	N (%)
Iron deficiency alone	66
Folate deficiency alone	3.9
Vitamin B <sub>12</sub> deficiency alone	2.9
Iron + folate deficiency	5.8
Iron + vitamin B <sub>12</sub> deficiency	7.8
Vitamin B <sub>12</sub> + folate deficiency	1
Iron + vitamin B <sub>12</sub> + folate deficiency	1.9
Anemia of chronic disease	3.9

result of isolated nutritional deficiency in 75 (72.8%) patients: iron deficiency alone in 68 (66%), folate deficiency alone in 4 (3.9%), and vitamin B<sub>12</sub> deficiency alone in 3 (2.9%) patients. However, 17 patients (16.5%) had anemia due to mixed nutritional deficiencies (Table 3). ACD was present in four patients (3.9%).

**Correlation of hematological parameters with disease severity.** A total of 50 (48.5%) patients had mild villous atrophy (Marsh grade 3A), and 53 (51.5%) had severe villous atrophy (Marsh grade 3 B and C) on histopathology. The mean hemoglobin levels were significantly higher in patients with mild villous atrophy when compared to patients with severe villous atrophy (9.6 vs 8.2 g/dL,  $P = 0.004$ ). The mean RDW in patients with mild villous atrophy was 19%, whereas in severe villous atrophy, it was 21.75%, which was significantly higher ( $P = 0.02$ ). The median serum ferritin levels were also significantly higher in patients with mild villous atrophy when compared to patients with severe villous atrophy (20 ng/mL vs 5 ng/mL,  $P = 0.002$ ). No significant difference was seen in serum folate levels (20.28 ng/mL vs 17.58 ng/mL,  $P = 0.323$ ) and serum vitamin B<sub>12</sub> levels (307 pg/mL vs 311 pg/mL,  $P = 0.522$ ) in patients with mild and severe villous atrophy.

## Discussion

The results of our study confirm that atypical symptoms are more common in patients with CD compared to typical presentation (66% vs 34%). Anemia was the most common presenting feature in our study and was multifactorial. On laboratory evaluation, anemia was prevalent in 96 patients (93.2%), with IDA being the most common. Our study also shows that anemia due to mixed nutritional deficiencies was seen in 16.5% and ACD in 3.9% patients. The degree of anemia increased with the severity of villous atrophy.

The prevalence of anemia in CD is highly variable in different age groups and geographic locations. The prevalence is higher in developing countries (>80%) compared to developed ones (5–40%), and the prevalence is higher in adults than in children.<sup>4,8</sup> In population-based studies from North America and Europe, anemia was seen in 35 and 53% patients of CD, respectively, and in 20–80% patients from Middle Eastern and North African populations.<sup>6,7,17,18</sup> However, studies from India have reported an even higher prevalence of anemia in patients with CD.<sup>4,19–21</sup> In our study, symptoms suggestive of anemia were the presenting feature in 74 patients (71.8%), but on investigation, anemia was seen in 96 patients (93.2%).

In our study, IDA was seen in 84 (81.5%) patients, with isolated IDA in 68 (66%) patients. The median serum ferritin levels of the whole study group were low at 8 ng/mL (5–30 ng/mL), with 68 (66%) patients having a microcytic hypochromic picture on peripheral smear. IDA in patients with CD has been reported less often in studies from the West compared to Asia and Africa. In recent studies, it has been seen in up to 21.6% patients in a European cohort and in 8–40% patients in American cohorts.<sup>5,22,23</sup> In the Middle Eastern and North African populations, IDA was seen in over 50% patients with CD.<sup>24,25</sup> The major mechanism of IDA in CD is malabsorption.<sup>17</sup> Another proposed mechanism is occult gastrointestinal blood loss, seen in up to 54% patients in one study.<sup>18,26</sup> Small bowel capsule endoscopy and double-balloon enteroscopy have been used to identify alarming endoscopic features, such as ulcerations, raised patches, and in polyps in patients of CD and refractory IDA.<sup>27,28</sup> Refractory IDA that is unresponsive to iron supplementation alone is another manifestation of CD, seen in 18–22% patients with CD.<sup>29,30</sup> A previous study from our center<sup>31</sup> reported CD in up to 58% patients with refractory IDA.

Recent studies have reported that iron deficiency is not the only contributing factor to the causation of anemia but that it is multifactorial.<sup>8,32</sup> In our study, folate deficiency in combination with other deficiencies was present in 11 patients (10.7%) and isolated folate deficiency in 4 patients (3.9%). Studies by Harper *et al.*<sup>8</sup> and Wierdsma *et al.*<sup>33</sup> have reported folate deficiency in 12 and 20% patients of CD, respectively, and described it to be the most common cause of megaloblastic anemia in such patients. However, folate deficiency in CD is not very common, possibly due to a higher prevalence of small intestinal bacterial overgrowth in CD, which increases serum folate levels due to bacterial synthesis of folate.<sup>34–36</sup>

In our study, vitamin B<sub>12</sub> deficiency was found in 14 patients (13.6%), with isolated vitamin B<sub>12</sub> deficiency in 3 patients (2.9%). The prevalence of vitamin B<sub>12</sub> deficiency is variable in different studies and ranges from 8 to 41% of

patients.<sup>37,38</sup> Bode *et al.*<sup>39</sup> and Wierdsma *et al.*<sup>33</sup> reported B<sub>12</sub> deficiency in 11% and 19% of adult patients with CD, respectively. The mechanism of vitamin B<sub>12</sub> deficiency in CD is not well established. Various postulated mechanisms are ileal villous atrophy,<sup>40,41</sup> pancreatic insufficiency in CD,<sup>42,43</sup> autoimmune gastritis,<sup>44</sup> small intestinal bacterial overgrowth,<sup>34</sup> and decreased efficiency of mixing with transfer factors in small intestine.<sup>37</sup>

ACD was seen in four (3.9%) of our patients with CD. The prevalence is lower than what is reported by Bergamaschi *et al.*,<sup>45</sup> who found 17% of patients with ACD. Harper *et al.*<sup>8</sup> reported that 13% patients with CD had elevated serum ferritin (more than 50th percentile for age) and ESR levels and were diagnosed with ACD. Increased levels of pro-inflammatory cytokines, including interleukin-1 $\beta$ , interleukin-6, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ , and the defective production of endogenous erythropoietin in patients with untreated CD are said to cause both decreased iron absorption and macrophage iron release, thereby leading to anemia.<sup>45</sup>

The novel finding of our study is mixed nutritional deficiency in 17 (16.5%) of the patients, which has not been highlighted in earlier studies. A study by Wierdsma *et al.*<sup>33</sup> reported various nutrient deficiencies in untreated CD: vitamin A in 7.5%, vitamin B<sub>6</sub> in 14.5%, folic acid in 20%, vitamin B<sub>12</sub> in 19%, zinc in 67%, and low iron stores in 46% patients. This suggests that a significant proportion of patients may have anemia due to mixed nutritional deficiency, which will not be corrected with iron supplementation alone. There is a need for further evaluation of etiology of anemia in those patients who do not improve on iron supplementation and gluten withdrawal. The mean hemoglobin and median ferritin levels in our study were significantly lower in patients with severe villous atrophy compared to those with mild atrophy. Recent studies have also established that patients with anemia have more severe villous atrophy, with higher levels of inflammatory markers and tTG antibodies than in patients with diarrhea.<sup>20,46</sup>

Our study is the first one from Southeast Asia on the profile of anemia in patients with CD and the largest to date. It highlights the multifactorial nature of anemia in CD and that patients with severe enteropathy have more severe anemia. However, our study has a few limitations. We have not evaluated the D-xylose test as a measure of malabsorption. We have also not studied other trace elements and vitamins, which have been reported to be deficient in some patients with CD. We measured serum folate and vitamin B<sub>12</sub> levels, which do not always corroborate actual deficiency states. We have attributed IDA to malabsorption due to CD and have not taken into account other factors like menstrual losses and parity in women and worm infestation in our patients. Our study was a one-time study on causative factors of anemia and did not take into account follow up after gluten withdrawal and nutritional supplementation.

## Conclusion

To conclude, 93% of patients with CD in our study had anemia, with IDA being the most common cause (81.5%). Other causes included folate deficiency (10.7%), vitamin B<sub>12</sub> deficiency (13.6%), mixed nutritional deficiency (16.5%), and ACD (3.9%). There was a correlation between the severity of anemia and the degree of villous atrophy.

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