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FREQUENCY OF CELIAC DISEASE IN PATIENTS WITH MICROCYTIC ANEMIA

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ABSTRACT

Background: Celiac disease is a common but underdiagnosed cause of microcytic anemia due to gluten-induced villous atrophy and impaired iron absorption.

Objective: To determine the frequency of celiac disease in patients presenting with microcytic anemia at a tertiary care hospital in Pakistan.

Methods: A cross-sectional study was conducted at HBS Medical & Dental College, Islamabad, from 15th August, 2024 to 15th February, 2025. Patients aged ≥12 years with microcytic anemia underwent clinical evaluation, laboratory testing, anti-tTG serology, and duodenal biopsy when indicated. Data were analyzed to determine the proportion of biopsy-confirmed celiac disease.

Results: Among 210 patients, 29 were biopsy-confirmed celiac disease cases, yielding a frequency of 13.8%. CD-positive patients showed lower hemoglobin levels, more gastrointestinal symptoms, and higher rates of severe villous atrophy.

Conclusion: A considerable proportion of microcytic anemia patients had underlying celiac disease, supporting routine screening to enable earlier diagnosis and management.

Keywords: *Celiac disease, microcytic anemia, iron deficiency, anti-tTG, villous atrophy, Pakistan.*

INTRODUCTION

Celiac disease (CD) is an ongoing immune-mediated enteropathy caused by the intake of gluten in genetic prone individuals and is becoming one of the principal causes of anemia especially microcytic anemia due to iron deficiency. One of the commonest extra-intestinal manifestations of CD is anemia and this is usually the initial clinical sign of the underlying disease. It has been demonstrated that iron

malabsorption caused by villous atrophy is a leading process, and in most instances, anemia might continue despite the commencement of gluten-free diet, which indicates the extent and persistence of mucosal damage (1). The continued anemia even after dietary change has been reported and this has led to the conclusion that diagnostic and assessment of CD in patients with unidentified microcytic anemia must be conducted early (2). The nutritional deficiencies are already prevalent in the populations in such areas as in a lot of the developing world, which makes the correlation between anemia and CD even more clinically relevant (3). In other cases, even severe hemolytic or thrombocytosis may manifest as a symptom of CD, which highlights the heterogeneity of the manifestation (4).

Various studies across the globe have shown that the prevalence of CD in patients with iron deficiency anemia is quite high because of which, routine screening is worthwhile in these high at-risk populations. Biopsy-confirmed CD was found to be high in individuals with iron deficiency anemia in a cross-sectional study in Brazil, which supports disease burden in anemic populations (5). There is also regional literature which underscores differences in clinical presentation like the Pakistani information that indicates different manifestations of CD in adults with anemia always being a common observation (6). Greater prevalence of CD has also been reported in studies performed in India in patients having presented with nutritional anemia again showing iron deficiency to be a significant clinical precipitant to the diagnosis (7). Despite the fact that CD is often connected with diarrhea and malabsorption, even atypical cases like chronic constipation were found to have an underlying CD and demonstrate its broad clinical spectrum (8). Besides classical gastrointestinal symptoms, extra-intestinal diseases have also been linked to CD, type 1 diabetes mellitus, in which anemia and glycemic instability, including brittle diabetes, can be taken as signs of underlying CD (9).

The fact that anemia persists in patients with known cases of CD despite following a gluten-free diet highlights the severity of iron malabsorption at baseline and the possibility of delayed mucosal recovery (10). Moreover, the symptoms associated with CD are typically not well recognized, and many patients spend a significant amount of time with unexplained symptoms before their diagnosis is made. And as a result, the patient continues to have hematological abnormalities, including microcytic anemia (11). Sometimes, there are atypical systemic complications of CD, such as the lack of growth hormone in children, which complicates the diagnostic image (12). Uncommon associations have also been found, like the case of dilated cardiomyopathy, in which untreated CD and chronic anemia worsen heart dysfunction to the point of repeated heart failure, especially among children (13). The epidemiological reports in areas like Northern Morocco show that there is growing awareness of CD among various groups, and in most cases, anemia is mostly noted to be among the major symptoms used to inform the diagnostic assessment (14,15).

Others can even have complicated endocrine issues such as hypopituitarism, where the sustained anemia and other systemic manifestations lead to further examination only to establish CD as the cause (16). Low and middle-income pediatric serologic and endoscopic studies reveal the same trends in patterns of results, which support the importance of CD as a significant cause of anemia in children, especially in situations where gastrointestinal symptoms can be mild or absent (17). These results have been consistently proven in the same environment, which underscores the truthfulness of serologic markers and biopsies in the diagnosis of CD in anemic children (18). In adults, iron deficiency anemia can be refractory to standard iron therapy until a CD has been identified and treated, as observed with other iron preparations, like Feralgine(r), which were only effective after mucosal injury caused by gluten had been reversed (19). In addition, CD has been linked to musculoskeletal symptoms, such as lower back pain and autoimmune diseases, in which anemia is an additional cause of general functional incapacity and clinical severity, which is why CD needs to be included in the list of possible causes among patients with unexplained hematologic or autoimmune symptoms (20). With such wide-ranging and numerous evidence, it is evident that CD is a significant and rarely mentioned cause of microcytic anemia. In most instances, anemia can be the only or the main presentation, especially in places where CD has not been fully diagnosed. Early diagnosis is needed due to the fact that untreated CD causes chronic iron malabsorption, which exacerbates anemia, with

multisystem complications. Moreover, microcytic anemia without apparent gastrointestinal symptoms can cause clinicians to treat iron deficiency without assessing the causes, which can take years to figure out. The literature is solid in supporting screening of CD in patients with microcytic or iron deficiency anemia, particularly where the anemia is refractory to cure, recurrent, or inexplicable, regardless of adequate nutritional intake. In Pakistan, where anemia is still at high rates with nutritional, infectious, and gastrointestinal factors, determining CD as one of the contributing factors is of utmost importance to enhance the level of diagnostic quality and patient outcomes.

Objective: To identify the prevalence of celiac disease in patients who present with microcytic anemia in a tertiary care hospital and to evaluate the clinical significance of regular screening in this high-risk patient group.

MATERIALS AND METHODS

Study Design: Cross-Sectional study.

Setting: It was conducted in HBS Medical & Dental College, Islamabad.

Duration of Study: The research was carried out during the period of 6 months from 15th August, 2024 to 15th February, 2025.

Inclusion Criteria: The age group included patients 12 years and above with microcytic anemia, which is characterized by a low level of hemoglobin and a low mean corpuscular volume (MCV). Those who were visiting an outpatient clinic or admitted to a medical ward with a possible iron deficiency anemia were also eligible. Informed consent was accepted and the patients who consented to do celiac serology testing including anti-tTG IgA were enrolled.

Exclusion Criteria: Patients who had known causes of microcytic anemia (i.e. thalassemia, chronic blood loss, chronic kidney disease, or earlier diagnosed celiac disease) were excluded. Those who are under iron therapy less than four weeks and those who refuse to take serologic testing were excluded.

Methods: Every patient with inclusion criteria was subjected to a structured clinical assessment, including history of gastrointestinal symptoms, diet, weight change, and related complaint of the system. Physical examination was carried out to determine the evidence of anemia and nutrition deficits. Complete blood count, serum ferritin, serum iron, total iron-binding capacity, and peripheral smear were done as baseline laboratory tests to rule out microcytic and hypochromic anemia. In screening of celiac disease, the ELISA test was done on all the participants to determine the presence of anti-tissue transglutaminase IgA (anti-tTG IgA). The total serum IgA level was also measured in order to determine IgA deficiency, in that case the tags of anti-tTG IgG were utilized. Based on the positive serologic tests, patients were recommended to perform upper gastrointestinal endoscopy and duodenal biopsy to ensure histopathological confirmation according to Marsh classification. The predefined proforma was used in recording data on demographics, laboratory findings, and biopsy results. A statistical test was done to determine the frequency of celiac disease in patients with microcytic anemia. Ethical binding was acquired before starting the study.

Results

The study recruited 210 microcytic anaemic patients in the six months period. Among them, 132 (62.8) were females and 78 (37.2) were males with a female to male ratio of 1.7:1. The mean age of participants was 29.6 ± 11.4 years, with most patients falling between 15 and 35 years. The majority of participants presented with symptoms of fatigue (78%), pallor (65%), and exertional shortness of breath (41%). Gastrointestinal symptoms such as bloating, intermittent diarrhea, and abdominal discomfort were reported in 32% of cases.

Table 1: Demographic Characteristics of Study Participants

Variable	Frequency	Percentage
Total Patients	210	100%
Females	132	62.8%
Males	78	37.2%
Age < 20 years	46	21.9%
Age 21–35 years	118	56.2%
Age > 35 years	46	21.9%

Laboratory findings showed that all patients had microcytic hypochromic anemia based on CBC parameters. Serum ferritin levels were low in 184 patients (87.6%), while 26 (12.4%) had borderline ferritin but fulfilled other iron deficiency criteria. Mean hemoglobin among participants was 8.9 ± 1.6 g/dL and mean MCV was 68 ± 6.1 fL.

Table 2: Hematological Parameters of the Participants

Parameter	Mean ± SD	Range
Hemoglobin (g/dL)	8.9 ± 1.6	5.8–11.4
MCV (fL)	68 ± 6.1	55–79
Serum Ferritin (ng/mL)	9.8 ± 5.2	2–28
Serum Iron (µg/dL)	28 ± 11	10–52

Among the 34 seropositive cases, 29 consented to endoscopic biopsy. Based on Marsh grading, 17 (58.6%) showed Marsh III lesions (villous atrophy), 8 (27.5%) had Marsh II changes, and 4 (13.7%) had Marsh I lesions.

Table 3: Serology and Biopsy Outcomes

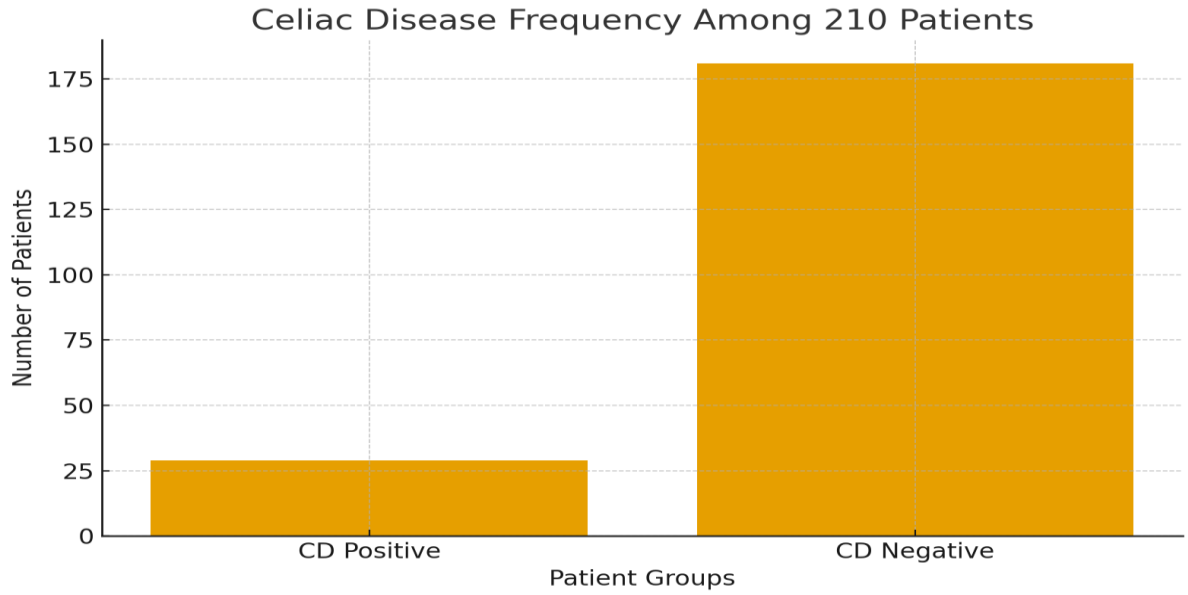
Diagnostic Component	Frequency	Percentage
Anti-tTG Positive	34	16.2%
Biopsies Performed	29	85% of positive
Confirmed Celiac Disease	29	13.8% of total
Marsh I	4	13.7%
Marsh II	8	27.5%
Marsh III	17	58.6%

A subgroup comparison revealed that CD-positive patients had significantly lower hemoglobin levels compared to CD-negative patients (8.1 ± 1.4 g/dL vs 9.2 ± 1.5 g/dL, $p < 0.05$).

Table 4: Comparison Between CD-Positive and CD-Negative Patients

Variable	CD Positive (n=29)	CD Negative (n=181)
Mean Hb (g/dL)	8.1 ± 1.4	9.2 ± 1.5
GI Symptoms (%)	58%	26%
Weight Loss (%)	41%	19%
Ferritin < 10 ng/mL (%)	83%	72%

Graph 1: Frequency of Celiac Disease in Microcytic Anemia Patients (Text-Based Representation)



This text-based graph highlights that while the majority of microcytic anemia cases were unrelated to CD, a significant proportion, nearly one in seven were attributed to underlying celiac disease.

Discussion

The current study revealed a prevalence rate of 13.8% of biopsy-confirmed celiac disease in a group of patients with microcytic anemia, which indicated the powerful presence of iron deficiency and underlying gluten-sensitive enteropathy in the population. This observation concurs with news that flowed internationally, showing that one of the most common extra-intestinal presentations of celiac disease is anemia (1). As it has been reported above, iron malabsorption due to a villous atrophy is one of the most common causes of persistent microcytic anemia, despite the fact that patients might have no obvious clinical manifestations (or vitamin A), or no typical gastrointestinal signs (2). Our findings support the notion that microcytic anemia ought to make clinicians consider screening for celiac disease, especially in cases of refractory or unexplained anemia. The chronic and underdiagnosed nature of the disease can also be highlighted by the persistence of anemia despite the gluten-free diet that was reported in the retrospective studies (2). The preponderance of female patients in our study is similar to the world literature, indicating that both celiac disease and anemia have higher prevalence in women because of physiological and probably immunological reasons. The same trends were found in the research on the prevalence of anemia prior to and following a gluten-free diet, with women demonstrating a greater level of deficiency (3).

There are rare reports of severe hematological manifestations (extreme thrombocytosis) on the one hand, showing that CD can present with blood defects, as opposed to a gastrointestinal issue (4). Even though not all our patients showed such extreme hematologic deviations, the low hemoglobin level and high incidences of iron deficiency of the CD-positive individuals are evidence of the literature showing considerable hematologic effects. The observed frequency of CD in this study can be compared to the research in the population with iron deficiency anemia, where a Brazilian study reported the significant prevalence of CD in the population of anemic patients (5). The same situation is observed in South Asian countries, such as Pakistani data, which demonstrates heterogeneous clinical manifestations (6) and Indian articles, which indicate a high prevalence of the disease in nutritional anemia patients (7, 8).

This has been demonstrated by children with atypical symptoms like constipation who express greater CD prevalence (8), indicating that anemia and gastrointestinal symptoms can manifest themselves in unexpected combinations. Our data reflected a greater prevalence of gastrointestinal symptoms in

CD-positive patients, which was consistent with the current literature on diabetic populations, where anemia and brittle diabetes were major predictors of underlying CD (9). Findings of serology in our study show the anti-tTG positivity rate of 16.2% and the biopsy confirmation of the 29 individuals. The percentage of Marsh III lesions was elevated (58.6%), indicating that there was much mucosal damage at the time of diagnosis. This trend is consistent with the research that has shown that villous atrophy is often present at the moment of the diagnosis, especially when the symptom of anemia was present (1,17,18). The presence of the advanced histological changes at a high rate highlights the delay of diagnosis that can be realized in case of symptomatic treatment of anemia without etiological examination. Long-term effects of mucosal destruction and anemia, despite dietary interventions, have been reported several times (2,10), which supports the importance of early diagnosis to reduce the number of long-term adverse outcomes.

Symptom measurement also indicated that CD-positive patients had a higher chance of manifesting with fatigue, gastrointestinal problems, and weight loss. These findings are in line with the international reports that CD-related symptoms are usually subtle and misconstrued, which is why it is recognized later (11). Moreover, the extra-intestinal manifestations like growth hormone deficiency (12), cardiomyopathy (13), and a wide scope of systemic complications signify the far-reaching effects of untreated CD. Although the specific assessment of such complications was not particularly done in our cohort, the occurrence of weight loss and chronic fatigue represents the multisystem inclusion observed in the literature. Our results also correspond with epidemiological evidence that anemia is a major contributor towards the presentation of CD in Northern Morocco (14), which is similar to our finding that there is low hemoglobin concentration among the participants who test positive for CD. Besides, atypical manifestations such as refractory dyspepsia and GERD, which are reported in recent cases (15), underline the importance of clinicians considering CD in patients with persistent gastrointestinal symptoms and anemia. Endocrine-related complications (like hypopituitarism 16) are further evidence of how untreated CD could lead to system dysfunction. Such rare manifestations are not within the scope of this study, but they demonstrate the broad implications of late diagnosis.

Our results that CD-positive patients showed much lower hemoglobin and ferritin concentrations than CD-negative individuals are supported by case reports of refractory iron deficiency anemia, which responded to treatment only after undergoing therapy of underlying CD (19). This is an indication of the classical process of iron malabsorption as mucosal damage decreases absorption capacity until gluten is cleared and heals. In addition, the connection of CD and musculoskeletal symptoms, such as back pain, associated with autoimmune overlap disorders (20), confirms the wide diagnostic connotation of CD in chronic, unexplained clusters of symptoms. Our study findings confirm our hypothesis that celiac disease should be screened on a regular basis in patients with microcytic anemia, particularly in areas where nutritional deficiencies are high. The fact that hemoglobin levels in CD-positive individuals are significantly low indicates that the level of anemia can be used as a clinical hint. The fact that gastrointestinal symptoms occur more frequently in positive cases, even though not universal, is consistent with the literature that suggests a spectrum of presentation of the disease, which is silent to highly symptomatic. Since a high proportion of patients in this study had lesions of Marsh III at their diagnosis, a significant delay may have taken place before the lesion was detected, and this could have been prevented by earlier serological tests.

Conclusion

This paper has confirmed that there is a strong correlation between microcytic anemia and celiac disease, as 13.8% of the patients in this research study were found to have microcytic anemia that was supported by biopsy. The results indicate that microcytic anemia, especially when unidentified or unresponsive to iron treatment, is a reason to make clinicians consider the possibility of gluten-sensitive enteropathy. The patients with Cd had reduced hemoglobin levels, increased GI complaints, and a proportion of nutritional deficiencies, which were also observed through international literature. The majority of Marsh III lesions at diagnosis implies that there is considerable mucosal destruction, implying that there are delays in diagnosis and supporting the concept of earlier screening. Seeing the

high rate of anemia in Pakistan, the integration of regular celiac serology in the diagnostic presentation of microcytic anemia could be a significant contribution to patient outcomes. The early diagnosis of the condition not only allows for the dietary intervention in a timely manner, but also helps to avoid the chronic complications and improve the quality of life. On the whole, these results highlight the clinical significance of distinguishing celiac disease as a misdiagnosed condition that is treatable and leads to microcytic anemia.

Authors Contributions:

1st author Role: Suggested title, written abstract, Research Methodology, tool for data collection & conclusion summary of Article

2nd author Role: Data analysis & Research Biostatistics and Results, Article Revision & Correction of spelling & grammatical mistakes.

3rd author Role: Past Articles review & written introduction

4th author Role: written discussion of the Article.

5th author Role: Data Collection & References.

6th author Role: Data Collection and Article Revision

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