ORIGINAL ARTICLE

# Clinical Spectrum of Celiac Disease among Adult Population: Experience from Largest Tertiary Care Hospital in Karachi, Pakistan

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## Abstract

**Introduction:** Celiac disease (CD) is a systemic autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals. Celiac disease affects 0.6–1.0% of the population worldwide. The prevalence of CD in Pakistan is yet unknown due to under diagnosis and lack of awareness.

**Objective:** To determine a vast variety of presenting features in subtypes of CD to overcome the burden of disease.

**Materials and methods:** This was a prospective, comparative, cross-sectional study conducted at Gastroenterology department of Jinnah Postgraduate Medical Center, Karachi from December 2022 till June 2023. This study included all adult patients ≥18 years diagnosed with CD on the basis of clinical presentation, positive IgA and IgG anti-transglutaminase antibodies (value >12 IU/mL detected by ELISA followed by small intestinal biopsy classified as per Marsh criteria. The data obtained were analyzed on the statistical software SPSS version 23. Descriptive statistics were obtained by frequencies and percentages.

**Results:** About 142 patients were enrolled in the study, 103 (91.5%) had classical CD (CCD) whereas 36 (25%) had non-classical (NCCD). About 89 (62.7%) were females and 53 (37.3%) were males. The mean age was found to be 23 ± 6 years. Nutritional deficiencies including anemia, B12, folate, osteopenia and low body mass index (BMI) <18 was found more in CCD group as compared with NCCD group with significant *p*-values. Titers of anti-TTG between CCD and NCCD were not statistically significant. Hypothyroidism and PCOS were the most common associated conditions observed in adult CD patients.

**Conclusion:** In conclusion, CD in adults and has diverse presentations. Adults with unexplained extra-intestinal symptoms like anemia and bone pain should be investigated for CD.

**Keywords:** Chronic diarrhea, Classical celiac disease, Refractory anemia.

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## Introduction

Celiac disease (CD) is a chronic immune-mediated systemic disorder which primarily affects the gastrointestinal tract (GIT) and also has widespread effects on other organ systems which imposes major health problem. Population-based studies worldwide suggest an overall seroprevalence of CD which is of about 1% with prevalence in Asian countries of about 0.5%.[1] This small bowel enteropathy is brought on by dietary gluten consumption and develops in people who are genetically predisposed.[2] Gluten contains gliadin, a glycoprotein that enters the small intestine and binds to human leukocytes antigens (HLA) peptides specially HLADQ2 and HLADQ8 on antigen-presenting cells in submucosa. This causes intraepithelial cell proliferation via helper T-cell activation contributing to pathogenic inflammation which in turn leads to crypt hyperplasia, villous atrophy, and the development of antibodies associated with CD.[3] Celiac disease is diagnosed by combination of histological evidence of villous abnormalities in duodenal biopsy samples and serological findings of disease-related antibodies.[4]

The medical manifestations of CD are diverse, which include a classical presentation with chronic diarrhea, weight loss, and malabsorption of nutrients leading to malnutrition at one end of the spectrum to an incidental finding in an asymptomatic individual at the other.[5] Majority of the patients with non-classical presentation have recurrent oral ulcers, altered bowel habits, short stature, iron deficiency anemia (IDA), irregular menstrual cycle, bone pains and recurrent abdominal pain.[6,7] Diagnoses could be made much later if these presentations are misdiagnosed. The disease's true prevalence, however, appears to be significantly higher than that reported in nations without screening programs. Unfortunately, no research has been conducted to determine the true prevalence of CD in the Pakistani community due to limited resources and dearth of thorough literature on CD that addresses epidemiology, clinical presentation, and treatment.

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**Conflict of interest:** None

Due to the misconceptions that CD only affects people of European descent up until a few decades ago, the disease is not well studied in the majority of Asian nations. Based on the basis of finding evidence that more than half (50%) of newly discovered CD patients have experienced an asymptomatic clinical condition, it is reasonable to extrapolate that the disease burden in nations without screening programs is larger than that is often believed.

The purpose of this study was to examine individuals who presented with CD in its entirety, from initial presentation to diagnosis and follow-up, in order to close this knowledge gap.

## Materials and Methods

The research was carried out by the Department of Gastroenterology and Hepatology, Jinnah Postgraduate Medical Center, Karachi, from December 2022 to June 2023. Ethical exemption was granted by the Ethical Review Committee (ERC) of our institution on 27th December, 2022 (approval number: 2018-0785-1066).

A sample size of 142 patients was calculated using OpenEpi calculator:

$$N = Z^2 \times (P(100\text{-}P)/d^2,$$

where P is the estimated frequency of fever in CD patients = 10.3%,[8] $Z = 1.96$ and $d = 5.0\%$.

The following inclusion criteria were applied on all adult (age > 18years) patients identified with newly CD as per the criteria supported by American College of Gastroenterology clinical guidelines and were included in the study: Including serological examination of celiac-specific antibodies (anti-transglutaminase IgA and IgG) and at least four mucosal biopsies are collected from the bulb and the second half of the duodenum. Biopsies were analyzed by the same pathologist and were classified according to the Marsh-Oberhuber classification system,[8] which integrated the assessment of intraepithelial lymphocytes (IEL) (the value of 25 T-lymphocytes/100 enterocytes is considered a pathological condition, also called "lymphocytosis"), villous atrophy and crypt hyperplasia. The histological persistence of the aforementioned abnormalities were incorporated and categorized as Marsh 1, Marsh 2, or Marsh 3 (A, B, or C).

Each patient completed a questionnaire that asked about the information regarding demographics and clinical symptoms and signs of the extra-intestinal and intestinal regions.

Clinically CD was classified according to OSLO classification[9] as (1) classical CD (CCD) with gastrointestinal symptoms (including weight loss, diarrhea), (2) non-classical (NCCD) without diarrhea and other extra-intestinal manifestations, and (3) silent (CD) defined as asymptomatic individuals with signs and symptoms below the threshold of detection.

Gastrointestinal symptoms were assessed using standard definitions like diarrhea was defined, as an increase in bowel movements (>3 stools/day) or a reduction in stool consistency (loose or liquid stools, Bristol scale 6–7) for at least 3 months prior to the CD diagnosis.

Rest of the subjective GI symptoms including abdominal pain, bloating, flatulence were considered significant if they lead to hinderance in daily activities.

Laboratory parameters before the diagnosis of CD for all patients included CBC, hemoglobin (anemia was defined as hemoglobin <13.5 gm/100 mL in men and <12 gm/100 mL in women), serum albumin, Ferritin, TIBC, vitamin D levels, serum B12, folate, LFTS, and thyroid function tests, were conducted using conventional laboratory methods, and the results were examined in accordance with the usual ranges anticipated for both the male and female genders. The body mass index (BMI) of each patient was calculated by using both their height and weight. According to the World Health Organization, underweight patients had a BMI of less than 18.5 kg/m$^2$, while overweight patients had a BMI of more than 25 kg/m$^2$.

Bone mineral density was assessed using Dual energy X-ray absorptiometry (DEXA) scan at diagnosis (osteopenia was defined as a T score between –1 and –2.5 SD while osteoporosis was defined as a T score ≤ –2.5 SD as per the WHO criteria).

The exclusion criteria were: (1) people who were previously diagnosed with CD or were currently on a GFD; (2) incomplete records; and (3) patients who were abandoned before a confirmed diagnosis.

The data analysis of this study was carried out using SPSS version 23 software. The mean and standard deviation were calculated for quantitative variables, such as age, hemoglobin, iron, MCV, and WBC. Frequencies and percentages were calculated for qualitative variables, including gender, family history of CD, and clinical spectrum factors such as diarrhea, anemia, unexplained weight loss, abdominal pain, fatigue, nausea, decreased appetite, generalized itching, and pains. Stratification was employed to manage effect modifiers, such as age, gender, and CD duration. The post-stratification Chi-square/Fisher's exact test was used to determine whether these effect modifiers were associated with the clinical spectrum. The results were considered significant if $p \leq 0.05$.

## Results

A total number of 142 patients were enrolled in the research study. The gender distribution of patients showed that 53 (37.30%) were males and 89 (62.70%) were females. In terms of marital status, 62 (43.70%) were married and 80 (56.30%) were unmarried. Majority had CCD 103 (72.6%) whereas others had 36 (25%) NCCD and 3 (2%) had silent CD.

Abdominal bloating was the most prevalent digestive complaint reported, 117 (82.4%), followed by abdominal pain 100 (70.3%); others included diarrhea 92 (64%), steatorrhea 15 (10%), and unexplained weight loss 14 (9.9%). The most common extra-intestinal signs and symptoms experienced were fatigueability 116 (81%), anemia 99 (69.7%) with IDA being the most common type, found in 69 (49.3%) of patients followed by folate deficiency anemia 30 (21.8%) while B12 deficiency was present in 23 (16.2%) patients. Dexa scans showed that 51 (35.9%) patients had normal bone density, while 8 (56.3%) had osteopenia and 11 (7.7%) had osteoporosis. Others included oral ulcers in 59 (41.0%), shortness of breath (SOB) in 59 (41%), bone pain in 54 (38%), and fever in 35 (24%).

Laboratory findings showed that the mean hemoglobin level was 8.911 ± 2.787, iron level was 41.361 ± 36.772 µg/dL, MCV was 64.4 ± 19.357 fL, WBC count was $17.700 \times 10^3$/mL ± $6.13902 \times 10^3$/mL, PLT count was 5,56,000 ± 19091.876, calcium level was 8.235 ± 0.942 and VITB-12 level was 277.378 ± 295.573 in Table 1.

The most common comorbidities observed in adult CD patients were 12 (8.5%) hypothyroidisms being the most common followed by 11 (8.0%) PCOS and 4 (2.8%) type 1 DM shown in Figure 1.

The analysis was done between groups of CCD and NCCD which showed anemia and B12-deficiency were more common in the classical group compared with the non-classical group, while there were no significant differences in IgA and IgG levels among the groups ($p > 0.05$) in Table 2.

**Table 1:** Characteristics of the patients enrolled in the study

| *Demographics* | *n* | *%* |
|---|---|---|
| Gender | | |
| Male | 53 | 0.373 |
| Female | 89 | 0.627 |
| Marital status | | |
| Married | 62 | 0.437 |
| Unmarried | 80 | 0.563 |
| Age* | 23.86 | 6.105 |
| *Symptoms* | *n* | *%* |
| Folate deficiency | | |
| Yes | 31 | 21.8 |
| No | 111 | 78.2 |
| B12 -deficiency | | |
| Yes | 23 | 16.2 |
| No | 119 | 83.8 |
| Dexa | | |
| Normal | 51 | 35.9% |
| Osteopenia | 80 | 56.3% |
| Osteoporosis | 11 | 7.7% |
| Iron deficiency | | |
| Yes | 70 | 49.3 |
| No | 72 | 50.7 |
| *Labs* | *Mean* | *Standard deviation* |
| Hemoglobin | 8.911 | 2.787 |
| Iron | 41.361 | 36.772 |
| MCV | 64.4 | 19.357 |
| WBC | 17.700 | 6.13902 |
| PLT | 556000 | 19091.876 |
| Calcium | 8.235 | 0.942 |
| VITB-12 | 277.378 | 295.573 |

*Age in years and also presented as mean and SD

In addition, there were significant associations between different BMI categories and CD types ($p = 0.014$). Specifically, a higher percentage of CCD patients have a BMI < 18 compared with non-classical and silent CD patients. Furthermore, also significant associations between abdominal pain ($p < 0.001$), diarrhea ($p < 0.001$), noc diarrhea ($p = 0.001$), watery diarrhea ($p < 0.001$), fatigue ($p < 0.001$), SOB ($p = 0.039$), bone pain ($p = 0.008$), and fever ($p = 0.004$) with CD types. Majority of stool samples were classified as normal ($n = 90$, 63.4%). In addition, there were associations between steatorrhea ($p = 0.042$) and mucus in stool ($p = 0.084$) with CD types, but they were not statistically significant.

All subjects underwent esophagogastroduodenoscopy (EGD). Typical findings suggestive of CD were present in 86 (60%) patients. Gross findings on EGD were visible fissuring and scalloping 120 (84%), atrophic mucosa 18 (12.6%) and nodularity 2 (2.8%). Biopsy results as per MARSH classification showed increased IEL 135 (95%), villous atrophy 74 (52%), and crypt hyperplasia 60 (42%), with type 3A MARSH 74 (52%) being the most common type. Endoscopic findings with respect to biopsy marsh classes were presented in Figure 2.

## Discussion

Celiac disease is a chronic debilitating disease affecting individuals from infancy to adulthood, with no specific age group due to high variability in presenting symptoms ranging from classic disease presenting with chronic diarrhea traditionally taught as malabsorption syndrome to no symptoms at all like in non-classical CD (NCCD) which is diagnosed incidentally thus it remains heavily underdiagnosed.

The incidence of CD detection is rising globally as a result of a significant shift in how individuals with CD appear in recent years, with a drop in the frequency of the disease's classic presentation. The majority of our patients had conventional CD, but 36 (or 25%) of them also had non-classical symptoms. Recent investigations have shown that non-classical diversity is becoming more common like in an adult cohort study conducted on 101 CD patients, 49 patients had non-classical presentation with a mean 24 months delay in diagnosis as compared with CCD diagnosed within 2.3

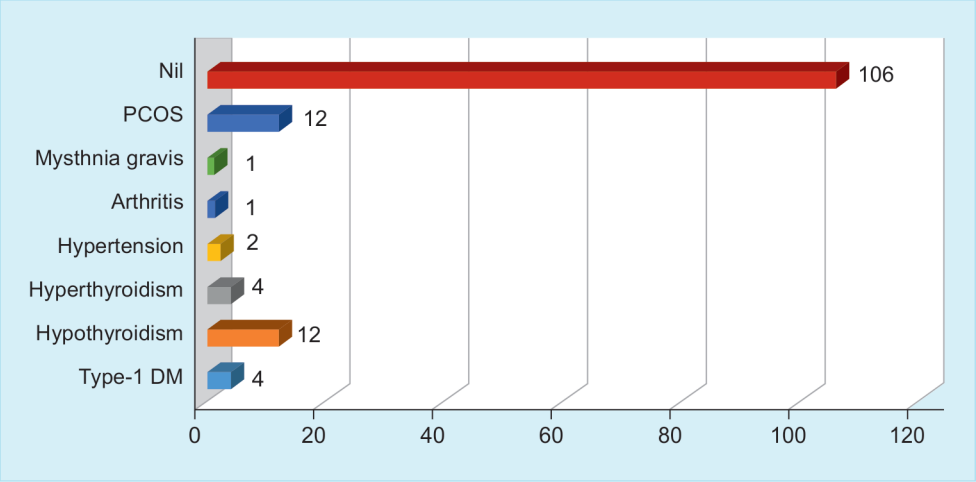


**Fig. 1:** Presentation of comorbidities

**Table 2:** Association of celiac disease types with study variables

| *Study variables* | *Classical (n = 103)* | *Non-classical (n = 36)* | *Silent (n = 3)* | *p-value* |
|---|---|---|---|---|
| BMI | | | | |
| <18 | 11 (10.7%) | 4 (11.1%) | 0 (0.0%) | 0.014* |
| 18–25 | 92 (89.3%) | 28 (77.8%) | 3 (100.0%) | |
| 26–32 | 0 (0.0%) | 4 (11.1%) | 0 (0.0%) | |
| Abdominal pain | | | | |
| Yes | 81 (78.6%) | 16 (44.4%) | 3 (100.0%) | <0.001* |
| No | 22 (21.4%) | 20 (55.6%) | 0 (0.0%) | |
| Diarrhea | | | | |
| Yes | 91 (88.3%) | 1 (2.8%) | 0 (0.0%) | <0.001* |
| No | 12 (11.7%) | 35 (97.2%) | 3 (100.0%) | |
| Noc diarrhea | | | | |
| Yes | 35 (34.0%) | 1 (2.8%) | 0 (0.0%) | 0.001* |
| No | 68 (66.0%) | 35 (97.2%) | 3 (100.0%) | |
| Steatorrhea | | | | |
| Yes | 15 (14.6%) | 0 (0.0%) | 0 (0.0%) | 0.042* |
| No | 88 (85.4%) | 36 (100.0%) | 3 (100.0%) | |
| Watery diarrhea | | | | |
| Yes | 57 (55.3%) | 3 (8.3%) | 0 (0.0%) | <0.001* |
| No | 46 (44.7%) | 33 (91.7%) | 3 (100.0%) | |
| Bleeding PR | | | | |
| Yes | 6 (5.8%) | 0 (0.0%) | 0 (0.0%) | 0.305 |
| No | 97 (94.2%) | 36 (100.0%) | 3 (100.0%) | |
| Mucus | | | | |
| Yes | 12 (11.7%) | 0 (0.0%) | 0 (0.0%) | 0.084 |
| No | 91 (88.3%) | 36 (100.0%) | 3 (100.0%) | |
| Fatigue | | | | |
| Yes | 89 (86.4%) | 27 (75.0%) | 0 (0.0%) | <0.001* |
| No | 14 (13.6%) | 9 (25.0%) | 3 (100.0%) | |
| SOB | | | | |
| Yes | 49 (47.6%) | 10 (27.8%) | 0 (0.0%) | 0.039* |
| No | 54 (52.4%) | 26 (72.2%) | 3 (100.0%) | |
| Bone pain | | | | |
| Yes | 47 (45.6%) | 7 (19.4%) | 0 (0.0%) | 0.008* |
| No | 56 (54.4%) | 29 (80.6%) | 3 (100.0%) | |
| Proximal myopathy | | | | |
| Yes | 14 (13.6%) | 1 (2.8%) | 0 (0.0%) | 0.161 |
| No | 89 (86.4%) | 35 (97.2%) | 3 (100.0%) | |
| Fever | | | | |
| Yes | 33 (32.0%) | 2 (5.6%) | 0 (0.0%) | 0.004* |
| No | 70 (68.0%) | 34 (94.4%) | 3 (100.0%) | |
| Anemia | | | | |
| Yes | 72 (70.6%) | 27 (75.0%) | 0 (0.0%) | 0.024* |
| No | 30 (29.4%) | 9 (25.0%) | 3 (100.0%) | |
| B12-deficiency | | | | |
| Yes | 22 (21.4%) | 1 (2.8%) | 0 (0.0%) | 0.025* |
| No | 81 (78.6%) | 35 (97.2%) | 3 (100.0%) | |
| IgA | | | | |
| Increase | 72 (69.9%) | 23 (63.9%) | 2 (66.7%) | 0.799 |
| Normal | 31 (30.1%) | 13 (36.1%) | 1 (33.3%) | |
| IgG | | | | |
| Increase | 71 (68.9%) | 19 (52.8%) | 2 (66.7%) | 0.217 |
| Normal | 32 (31.1%) | 17 (47.2%) | 1 (33.3%) | |

*p*-value calculated by Chi-square/Fisher's exact test. *Significant if $p \leq 0.05$

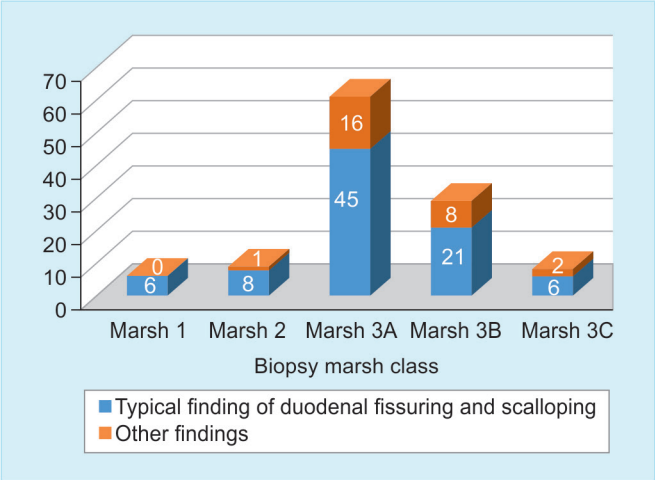


**Fig. 2:** Endoscopic findings

months.[9] Delays in diagnosis of CD have been observed in the past, as the study by Green et al. revealed a significant linear positive trend among patients who presented as asymptomatic adults at screening with 11-year diagnostic delay on average.[10] Due of these reasons, diagnosing non-classic CD might be difficult. The mean age of diagnosis was 22.9 ± 5 years in CCD group and 27 ± 6 years in NCCD. These data show that the average age of diagnosis in Pakistan ranges between the 20s and 30s which is in accordance with previous studies conducted in Pakistan which showed median age at diagnosis was 26 years (mean 29.9 ± 12.7 years).[11] However, in contrast to global studies from Europe and USA adult CD was usually diagnosed around fourth and fifth decades of life.[12,13]

The prevalence, severity, and manifestation of CD varies among different parts of world based on a person's gender and sex. In our study majority were females which was similar to the meta-analysis conducted recently by Jansson-Knodell et al.[14] showing female–male ratio of about 2–2.5:1, in European countries. However, in China, most patients with adult CD were males.[15] Some studies suggest no significant gender differences among patients diagnosed in late 50s.[16]

Our study revealed that abdominal bloating was common primary gastrointestinal complaint in both groups; however, this is in contradiction with earlier studies that highlighted diarrhea about 69%, as the most common intestinal symptom among Pakistani population.[17] Numerous other digestive symptoms, such as decreased appetite, steatorrhea, constipation, nausea, vomiting, weight loss were also recorded.

Anemia is a common clinical manifestation of CD typically as a result of iron, folic acid, and vitamin B12 malabsorption. As the proximal part of the duodenum is commonly damaged in CD, there is a decrease in iron absorption leading to IDA. Iron deficiency anemia was the most common nutrient deficiency found in our study among both groups, similar results were achieved in a local study done at KPK, in which 5.8% of patients with IDA were positively screened for IgA tTG.[18]

A recent cohort of 572 adult Americans with biopsy proven CD, 78% had anemia at diagnosis with iron 50.8% having IDA.[19] Several other studies also supported the fact of IDA as the most common extra-intestinal manifestation of CD.[20] Similarly, in a recent meta-analysis among young patients with refractory IDA without gastrointestinal symptoms, when tested were found to

have positive serological test for CD.[21] Thus, IDA might be the initial presentation of CD and must be ruled out in asymptomatic patients with anemia without overt loss.

Metabolic bone disease is a frequent extra-intestinal symptom of CD which may have disastrous effects due to low bone mass and high fracture susceptibility. In our study, most patients had osteopenia 80 (56%), followed by osteoporosis in 11 (7%) among both men and women, which was similar to study conducted by Kotze et al.[22] among Brazilian CD patients which revealed osteopenia in 56.1% and osteoporosis in 29.2% of patients on initial visit, later on 25% of osteoporotic patients developed low impact fractures. In other systemic literature review, when newly diagnosed young patients between ages 20 and 35 years were assessed for BMD status as compared with controls, they had low bone mineral density.[23] However, in a recent study, the sole presentation of CD was osteoporosis without any gastrointestinal symptom.[24] Thus, many researchers now advise to screen patients with refractory osteoporosis for underlying CD. Although the precise relationship between CD and excessive bone loss is unknown, as the condition affects the intestines, the absorption of calcium and vitamin D gets difficult; both of which are crucial for preserving bone density. Bone problem was not a frequent presenting complaint in our patients, it was a frequent finding during patient screening.

Autoimmunity and genetic predisposition may be linked to the extra-intestinal involvement in CD. In our study, thyroid disorder (hypothyroidism 12% and hyperthyroidism 4%) was the most common associated autoimmune disease. This was supported by past international studies which showed that those with autoimmune thyroid diseases had a greater prevalence of subclinical CD. A recent review article consolidated most relevant literature between the relationship of CD and AITD concluded that despite the fact that people with AITD must be regarded as being at high risk for CD, routine screening may not be necessary given cost-effectiveness and the paucity of instances documented in earlier screening trials. Furthermore, it can be difficult to recognize the simultaneous emergence of both of these diseases precociously due to the prevalence of asymptomatic presentations of CD and AITD.[25] Atrophic mucosa and apparent fissuring/scalloping were the most frequent EGD results with predominant histopathological finding of increased IELS with villous atrophy, this falls in MARSH class 3A category. However, apart from villous atrophy, various other features can also be noted in duodenal biopsy specimens including goblet cell depletion, pseudostratification of nuclei, and loss of normal shape of enterocytes.[26] According to the study by Moran et al.,[27] significant duodenal neutrophilia (including foci of cryptitis and crypt abscesses) was found among 56% of pediatric and 28% of adult CD patients. Thus, CD can manifest in a variety of ways, but duodenal biopsy still remains a crucial part of the diagnosis of CD. There are several conditions that might closely resemble CD, such as tropical sprue, chronic viral disease, *H. pylori* gastritis, bacterial overgrowth, NSAIDS. Despite the fact that the classic findings of increased IEL, villous atrophy and crypt hyperplasia are quite distinctive, they are only one of many classic findings. Therefore, a diagnosis cannot be made just based on histology; it also requires a high degree of clinical suspicion, expert pathologist assessment, and expert review. In our analysis, there was no discernible relationship between MARSH class and CD type. We require additional large-scale research to advance our understanding of this underdiagnosed illness since this study only included uni-center data.

Celiac disease overall negatively impacts the social, psychological, functional and economic life of individuals, specially in low-income countries where lack of knowledge and limited resources for obtaining gluten-free food supplementation is another problem as these products are expensive as compared with standard food products, this makes adherence to GFD even more poor and follow-up of such patients becomes difficult. Recent data had also supported the idea that low-income countries had worst CD-related issues due to above-mentioned factors.[28]

As Pakistan is a low-income country with heavy burden of such patients presenting to tertiary care government setups its seems crucial to understand need of the hour, ongoing health education and treatment should be established and offered with reference to socioeconomic factors, this will help to identify patients with non-classical presentation, as delay in diagnosis increases morbidity and mortality. Large-scale research should also be done on patients' knowledge about various presentations of CD and importance of adherence to GFD and the difficulties encountered by patients to acquire them.

As our government setup caters non-affording population, our study had some limitations, genetic testing, further metabolic workup and familial screening could not be done at our setup due to cost issues.

## Conclusion

While CD is predominantly observed as CCD in our system, there is a significant underdiagnosis of certain CD cases, particularly those categorized as non-CCD (NCCD). Our study aimed to comprehensively identify the diverse manifestations of CD in our population, with a specific focus on the non-classical variety. As a result, we recommend that patients presenting with extra-intestinal symptoms, particularly anemia, should be approached with a high level of suspicion and undergo testing for CD. Implementing this approach will facilitate early detection of the disease, ultimately reducing both short- and long-term morbidities. Moreover, this will serve as a valuable resource for clinicians in low-income nations, enhancing their understanding of CD's epidemiology and enabling them to provide accurate information to their patients.

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