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Original Article

Vitamin B12, Folate, Iron, Ferritin, and Hemoglobin Levels at Diagnosis in Pediatric Celiac Disease: Associations with Clinical, Serological, and Histopathological Features

Pediyatrik Çölyak Hastalığında Tanı Anındaki Vitamin B12, Folat, Demir, Ferritin ve Hemoglobin Düzeyleri: Klinik, Serolojik ve Histopatolojik Özelliklerle İlişkileri

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ABSTRACT

Objective: Celiac disease (CD) is a chronic autoimmune disorder that results from an immune response to gliadin protein. The objective of this study was to identify the underlying causes and risk factors associated with micronutrient deficiencies at the time of diagnosis in children with CD.

Method: This retrospective cross-sectional study included 79 biopsy-proven celiac patients. Age, gender, age at diagnosis, body weight, height, body mass index (BMI), presenting symptoms, tissue transglutaminase IgA (tTGA), serum IgA levels, endoscopic histological findings (Marsh type, presence of *Helicobacter pylori* (*HP*) infection, presence of gastritis), B12, folic acid, iron, ferritin, hemoglobin levels were recorded.

Results: There was an inverse correlation between age at diagnosis and B12 levels (p=0.05). Anorexia was found to be associated with folic acid deficiency (p=0.01). A linear relationship was found between B12, folic acid levels and BMI (p=0.03, p=0.01, respectively). Patients with more severe endoscopic and histopathologic findings (Marsh type 3B and 3C) exhibited lower levels of folic acid and ferritin (p=0.04, p=0.00, respectively). There was no statistically significant association between *HP* infection and levels of vitamin B12, folic acid, iron, ferritin, and hemoglobin (p=0.5, p=0.72, p=0.96, p=0.34, p=0.47, respectively).

Conclusion: Our data suggest that B12 levels are independent of CD. Anorexia and low BMI values are related to low levels of B12 and folic acid. Ferritin levels were low in patients with high tTGA levels and both folic acid and ferritin levels decreased as the severity of villous atrophy increased.

Keywords: Celiac disease, B12, folic acid, micronutrient deficiency, *Helicobacter pylori*

ÖZ

Amaç: Çölyak hastalığı (ÇH), gliadine karşı gelişen immün yanıt sonucu ince bağırsak mukozasında hasara ve buna bağlı mikronutrient malabsorpsiyonuna yol açan kronik bir otoimmün hastalıktır. Bu çalışmanın amacı, ÇH tanısı alan çocuklarda tanı anındaki mikronutrient eksikliklerinin sıklığını ve ilişkili risk faktörlerini belirlemektir.

Yöntem: Bu retrospektif kesitsel çalışmaya biyopsi ile doğrulanmış 79 çocuk çölyak hastası dahil edildi. Demografik ve antropometrik veriler, klinik semptomlar (karın ağrısı, ishal, kusma, kabızlık, anoreksi), dTGA, sIgA düzeyleri, histopatolojik bulgular, *Helicobacter pylori* (*HP*) enfeksiyonu ve gastrit varlığı ile vitamin B12, folik asit, demir, ferritin ve hemoglobin düzeyleri değerlendirildi.

Bulgular: Tanı anında hastaların %20,3'ünde vitamin B12, %20,3'ünde folik asit ve %46,3'ünde demir eksikliği saptandı; %50,6'sında ferritin düzeyleri düşüktü. Anemi yalnızca %15,2 hastada mevcuttu. Tanı yaşı ile vitamin B12 düzeyleri arasında ters yönlü ilişki bulundu (p=0,05). Anoreksi varlığı folik asit eksikliği ile ilişkiliydi (p=0,01). Vitamin B12 ve folik asit düzeyleri ile vücut kitle indeksi (VKİ) arasında pozitif ilişki saptandı (p=0,03 ve p=0,01). Üst normal sınırın 10 katından yüksek tTGA düzeyleri düşük ferritin düzeyleri ile ilişkiliydi (p=0,01). Marsh tip 3B ve 3C hastalarda folik asit ve ferritin düzeyleri anlamlı olarak daha düşüktü (p=0,04 ve p<0,001). *HP* enfeksiyonu ile mikronutrient düzeyleri arasında ilişki saptanmadı.

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Sonuç: Mikronutrient eksiklikleri, pediyatrik çölyak hastalarında tanı anında sık görülmektedir. Düşük VKİ ve anoreksi, vitamin B12 ve folik asit eksikliği ile ilişkiliyken; ferritin ve folik asit düzeyleri serolojik aktivite ve villöz atrofi şiddeti ile ilişkilidir. Bu nedenle tanı anında kapsamlı beslenme değerlendirmesi önerilmektedir.

Anahtar kelimeler: Çölyak hastalığı, B12, folik asit, mikronutrient eksiklikleri, *Helicobacter pylori*

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disorder that results from an immune response to gliadin protein. It can lead to a deficiency in various micronutrients due to changes in the small intestinal mucosa[1-3].

Patients with CD present with a variety of symptoms, including abdominal distension, chronic diarrhea, chronic abdominal pain, chronic constipation, long-term anorexia, and growth retardation. The severity and frequency of these symptoms can vary significantly from patient to patient. As a result, patients presenting with any of these complaints should be evaluated for CD. In order to diagnose the disease, healthcare professionals frequently utilize a combination of high tissue transglutaminase levels and the endoscopic biopsy method[1].

If CD is not diagnosed and the patient is not put on gluten-free diet, deficiencies of numerous vitamins and minerals, including iron, vitamins B1, B6, and B12, folic acid, vitamin D, zinc, copper, and selenium, have been observed with greater frequency in this patient cohort compared to the general population[1,4-7]. Especially, the risk of developing iron deficiency is significantly elevated in comparison to the general population. Iron deficiency anemia is observed in up to 80% of celiac patients. Similarly, iron or ferritin deficiency without anemia is seen with greater frequency than in the general population[1,2,5,7]. B12 deficiency is observed at a rate of approximately 20%. Folic acid deficiency has been reported with a frequency ranging between 20-80% in various publications[3,4].

It has been reported that micronutrient deficiency in patients with CD may occur for a number of reasons, including the histopathologic severity of the disease, the patient's nutritional status, and the presenting symptoms[1,6,8]. The ESPGHAN recommends screening for vitamin B12, folic acid, iron, ferritin, and vitamin D at the time of diagnosis in patients with CD[2]. Accordingly, this study aimed to evaluate vitamin B12, folic acid, iron, ferritin and hemoglobin status and to identify the underlying causes and risk factors associated with micronutrient deficiencies at the time of diagnosis in children with CD.

MATERIALS and METHODS

This retrospective cross-sectional study included 134 biopsy-proven celiac patients who were followed up in the Department of Pediatric Gastroenterology, Hepatology and Nutrition at University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital between 2018 and 2023. The study was conducted on 134 patients, but 34 were excluded from the final analysis due to lack of data. Additionally, 21 patients were excluded because they had used micronutrient supplementation prior to their diagnosis.

The following variables at the time of diagnosis were recorded: Age, gender, age at diagnosis, body weight, height, BMI presenting symptoms (abdominal pain, diarrhea, vomiting, constipation, anorexia), tissue transglutaminase IgA (tTGA), serum IgA levels, endoscopic histological findings (Marsh type, presence of *Helicobacter pylori* (*HP*) infection, presence of gastritis), B12, folic acid, iron, ferritin, and hemoglobin levels.

Anthropometric data were plotted on growth charts derived from the Centers for Disease Control and Prevention (CDC) using the 2020 QxMD Software Inc. Height-for-age (HFA), weight-for-age (WFA) and body mass index (BMI)-for-age curves were converted into percentiles and Z-scores to identify potential health- or nutrition-related problems. Based on the CDC criteria for stature and weight for age, values less than the 5th percentile, between the 5th and the 95th percentiles, and higher than the 95th percentile were classified as unfavorable, normal, and high, respectively. In addition, BMI values < the 5th percentile, between the 5th and the 85th percentiles, and ≥ the 95th percentile were categorized as underweight, normal weight, and overweight and obese, respectively. Considering the World Health Organizations (WHO) references, height and weight values <-2 Z-score, between -2 to + 2, and ≥+2 were categorized as low, sufficient, and high, respectively[9,10].

In accordance with ESPGHAN guidelines[1], four biopsy specimens were obtained from the duodenum and two from the bulbus. Histopathologic classification was performed using the modified Marsh criteria[11].

Anti-tTGA and IgG were measured using a Euroimmun microELISA assay; values >10 IU/mL were considered positive, and quantitative measurement was not performed for values above 200 IU/mL.

Anemia status was determined according to WHO recommendations: https://www.who.int/publications/i/item/9789240088542

Serum vitamin B12, folic acid, iron, and ferritin levels were measured using an immunoassay method on a Roche Cobas c8000 automated biochemical analyzer. The lower limit for B12 deficiency was 200 ng/L, for folic acid deficiency 3.89 mcg/L, for iron deficiency 50 mcg/dL and for ferritin deficiency 7 mcg/L[12].

The Marsh classification was employed for the endoscopic histopathologic assessment of CD. The presence of *HP* infection was confirmed through Gram-Giemsa staining. The diagnosis of gastritis was based on the histopathologic findings.

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2024/06-11, date: 16.05.2024) approved this study. Our study is a retrospective study without human intervention. Therefore, patient consent is not required.

Statistical Analysis

The statistical analysis was conducted using the SPSS v26.0 (IBM, Chicago, USA®) software package for Windows. The data distribution was determined to be mean and standard deviation or median and interquartile range, which is defined as the range between the 25th and 75th percentiles. Categorical variables were expressed as numbers and percentages. For the comparison of numerical data between paired groups, the Student's t-test was used for normally distributed group comparisons, and the Mann-Whitney U test was used for non-normally distributed group comparisons. Nominal and ordinal variables were compared with the chi-square test of independence. The chi-square test of independence was employed to assess the relationship between nominal and ordinal variables. In the event that the comparison of numerical variables was parametric according to the distribution, a paired-sample t-test was employed; conversely, if non-parametric, a Wilcoxon's related two-sample test was utilized. In the case of comparisons between more than two independent groups, the Kruskal-Wallis test was employed. Similarly, when comparing more than two dependent groups, the Friedman test was utilized. The relationship between the two variables was evaluated using the Pearson and Spearman correlation tests. A logistic regression analysis was conducted to ascertain the factors associated with micronutrient deficiency. The predictive factors were reported using multivariate odds ratios (ORs) adjusted with 95% confidence intervals and a significance level.

RESULTS

The study included 79 patients diagnosed with biopsy-proven CD. The female-to-male ratio was 1.19:1. The mean age at diagnosis was 7.5 years (Table 1). Abdominal pain was the most common presenting complaint (Figure 1). Twenty-seven patients presented with no symptoms at the time of initial diagnosis. Of these patients, 12 were diagnosed as a result of family screening, while 15 were diagnosed as a result of screening while being followed up with Type 1 diabetes mellitus (DM).

Fifteen patients were classified as Marsh type 2, 18 as Marsh type 3A, 36 as Marsh type 3B and 10 as Marsh type 3C. The evaluation of the relationship between BMI and Marsh type revealed that BMI values decreased as histopathologic findings worsened (p=0.02).

At the time of diagnosis, 20.3% of patients had B12 deficiency, 20.3% folic acid deficiency, and 46.3% iron deficiency. Additionally, 50.6% of patients exhibited low ferritin levels. On the other hand, anemia was present in only 15.2% of patients.

Table 1. Characteristics of patients

		Number (N %)
Sex	Female	43 (54.4%)
	Male	36 (45.6%)
Age at diagnosis (years)	Mean (SD)	7.51 (4.43)
Weight Z-score	Mean (SD)	-0.84 (1.31)
Height Z-score	Mean (SD)	-0.66 (1.44)
Weight for height*	Mean (SD)	87.07 (6.68)
BMI Z-score	Mean (SD)	-0.65 (1.20)
	<-2 SDS	13 (16.5%)
BMI Z-score	>-2 SDS	66 (83.5%)

*: W/H was used only for patients younger than 5 years, BMI: Body mass index, SD: Standard deviation, SDS: Standard deviation score

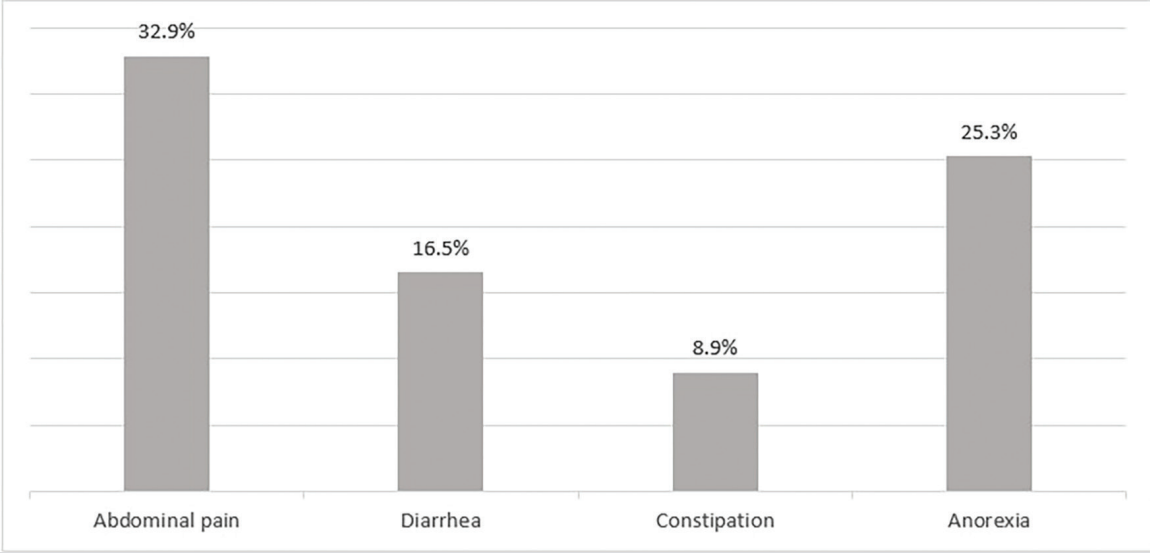

Figure 1. Symptoms of the patients at admission

There was no correlation between gender and B12, folic acid, iron and ferritin levels (p=0.47, p=0.76, p=0.53, p=0.24, respectively).

There was an inverse correlation between age at diagnosis and B12 levels (p=0.05). However, no correlation was found between age at diagnosis and folic acid, iron and ferritin levels. (p=0.34, p=0.64, p=0.59, respectively).

A comparison of the micronutrient levels of the patients with their presenting symptoms revealed that those with anorexia exhibited lower levels of B12 and folic acid (p=0.04, p=0.01, respectively). Upon evaluating the relationship between anorexia and micronutrient deficiency, it was determined that anorexia and folic acid deficiency were the only two variables associated in a regression analysis (p=0.01) (Table 2, Supplementary Table S1). No association was identified between other symptoms and micronutrient levels.

When the relationship between anthropometric measurements and micronutrient levels was evaluated, a linear relationship was found between WFA standard deviation score and folic acid levels (p=0.03). There was no correlation between WFA and B12, iron and ferritin levels (p=0.62, p=0.18, p=0.51, respectively).

There was no correlation between HFA and B12, folic acid, iron and ferritin levels (p=0.6, p=0.45, p=0.27, p=0.88, respectively).

On the other hand, a linear relationship was found between B12, folic acid levels and BMI (p=0.03, p=0.01, respectively), (Figure 2). There was no correlation between BMI and iron and ferritin levels (p=0.42, p=0.3, respectively).

Tissue transglutaminase levels higher than 10-fold were found to be associated with low ferritin levels (p=0.01). Patients with tTGA levels greater than 10 times the upper limit of normal had significantly higher odds of iron deficiency [OR: 3.54, 95% confidence interval (CI): 1.20-10.44; p=0.022] (Supplementary Table S2). No significant correlation was identified between tissue transglutaminase levels and levels of vitamin B12, folic acid, iron, and hemoglobin (Table 3).

Patients with more severe endoscopic and histopathologic findings (Marsh type 3B and 3C) exhibited lower levels of folic acid and ferritin (p=0.04, p=0.00, respectively). And also, more severe histopathological involvement (Marsh 3B-3C) was significantly associated with increased odds of ferritin deficiency (OR: 2.72, 95% CI: 1.08-6.86; p=0.034) (Supplementary Table S3).

The analysis of the endoscopic histopathologic findings revealed that 40 patients exhibited gastritis, while 14 patients also demonstrated a concomitant *HP* infection. The results of the single regression analysis indicated that there was no statistically significant association between *HP* infection and levels of vitamin B12, folic acid, iron, ferritin, and hemoglobin (p=0.5, p=0.72, p=0.96, p=0.34, p=0.47, respectively). No association was observed between gastritis and B12, folic acid, iron, ferritin, and hemoglobin levels (p=0.5, p=0.65, p=0.15, p=0.15, p=0.13, p=0.07, respectively) (Table 4).

Table 2. Assessing the association between symptoms and micronutrient levels				
Micronutrient level	**Symptom**	**B coefficient (95% CI)**	**R^2**	**p-value**
Vitamin B12 (ng/L)	Abdominal pain	-34.07 (-108.57 to 40.44)	0.011	0.365
	Diarrhea	15.36 (-80.39 to 111.12)	0.001	0.750
	Constipation	-53.32 (-177.75 to 71.12)	0.009	0.396
	Anorexia	-74.03 (-157.05 to 8.99)	0.039	0.080
Folate (mcg/L)	Abdominal pain	0.02 (-1.73 to 1.77)	0.000	0.981
	Diarrhea	0.17 (-2.06 to 2.41)	0.000	0.877
	Constipation	0.33 (-2.58 to 3.25)	0.001	0.821
	Anorexia	-2.45 (-4.34 to -0.55)	0.079	**0.012***
Iron (mcg/dL)	Abdominal pain	-4.65 (-17.15 to 7.86)	0.007	0.462
	Diarrhea	-1.76 (-17.81 to 14.29)	0.001	0.828
	Constipation	-8.28 (-29.14 to 12.59)	0.008	0.432
	Anorexia	-0.28 (-14.47 to 13.92)	0.000	0.969
Ferritin (mcg/L)	Abdominal pain	-1.67 (-6.82 to 3.47)	0.005	0.519
	Diarrhea	-1.44 (-8.04 to 5.15)	0.002	0.664
	Constipation	-5.01 (-13.54 to 3.53)	0.017	0.247
	Anorexia	-1.56 (-7.39 to 4.27)	0.004	0.595
Hemoglobin (g/dL)	Abdominal pain	-0.49 (-1.18 to 0.20)	0.025	0.161
	Diarrhea	-0.50 (-1.39 to 0.39)	0.016	0.266
	Constipation	0.46 (-0.70 to 1.62)	0.008	0.431
	Anorexia	0.24 (-0.54 to 1.03)	0.005	0.540

B is the unstandardized coefficient from univariable linear regression and represents the mean difference associated with the presence of each symptom. CI: Confidence interval, R^2: Coefficient of determination, *: $p<0.05$

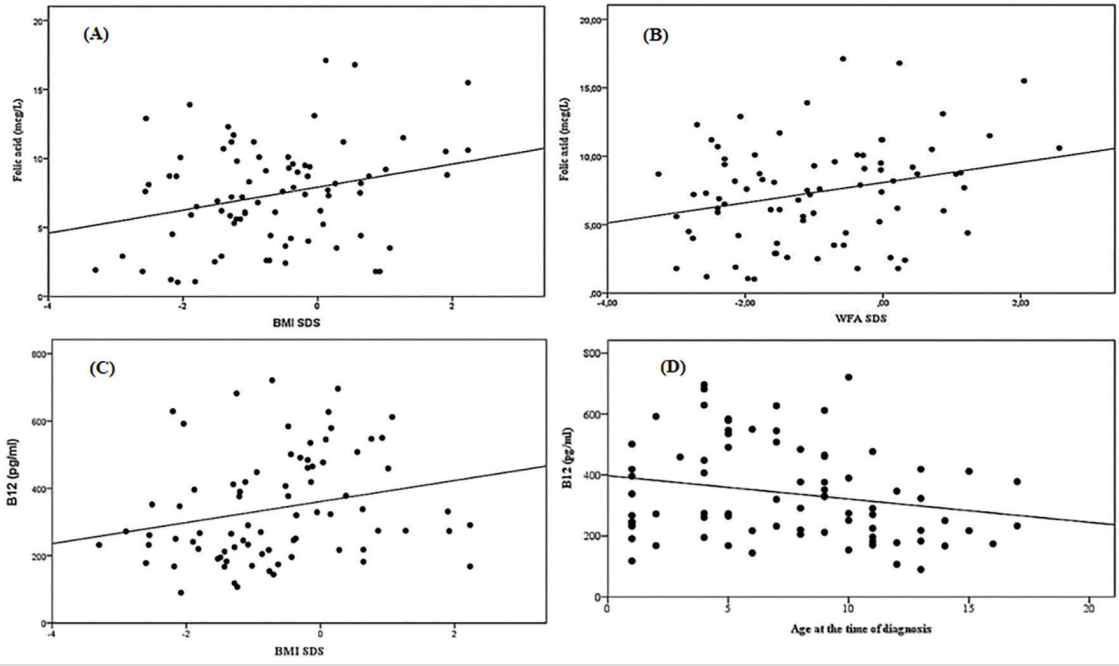

Figure 2. Relationship between (A) BMI and folic acid levels, (B) WFA SDS and folic acid levels, (C) BMI and B12 levels and (D) age at the time of diagnosis and B12 levels

BMI: Body mass index, WFA: Weight-for-age, SDS: Standard deviation score

Table 3. Assessing the association between tissue transglutaminase IgA levels and micronutrient levels					
Micronutrient level	**tTGA <10x, median (IQR)**	**tTGA >10x, median (IQR)**	**B coefficient (95% CI)**	**R^2**	**p-value**
Vitamin B12 (ng/L)	419.0 (218.0-508.0)	273.5 (217.8-404.3)	-56.72 (-136.11 to 22.66)	0.026	0.159
Folate (mcg/L)	8.7 (5.3-11.2)	7.3 (4.3-9.5)	-1.32 (-3.18 to 0.53)	0.026	0.158
Iron (mcg/dL)	64.3 (36.0-78.6)	40.2 (26.2-66.7)	-10.76 (-24.02 to 2.49)	0.033	0.110
Ferritin (mcg/L)	18.0 (3.9-29.6)	6.8 (4.0-13.6)	-6.93 (-12.25 to -1.62)	0.081	**0.011***
Hemoglobin (g/dL)	12.2 (11.7-12.6)	12.1 (11.1-12.9)	-0.17 (-0.92 to 0.58)	0.003	0.649

The tTGA <10x and >10x groups included 21 and 58 patients, respectively. B is the unstandardized coefficient from univariable linear regression and represents the mean difference for tTGA >10x compared with tTGA <10x. IQR: Interquartile range, CI: Confidence interval, R^2: Coefficient of determination, *: p<0.05, tTGA: Tissue transglutaminase IgA

Table 4. Assessing the association between endoscopic and histopathological features and micronutrient levels				
Micronutrient level	**Endoscopic/histopathological feature**	**B coefficient (95% CI)**	**R^2**	**p-value**
Vitamin B12 (ng/L)	Marsh type 3B-3C (vs. type 2-3A)	-36.46 (-108.02 to 35.10)	0.013	0.314
	Gastritis	-23.78 (-94.64 to 47.08)	0.006	0.506
	Helicobacter pylori infection	32.01 (-60.75 to 124.77)	0.006	0.494
Folate (mcg/L)	Marsh type 3B-3C (vs. type 2-3A)	-1.67 (-3.30 to -0.03)	0.051	**0.046***
	Gastritis	-0.37 (-2.03 to 1.28)	0.003	0.656
	Helicobacter pylori infection	-0.38 (-2.55 to 1.79)	0.002	0.727
Iron (mcg/dL)	Marsh type 3B-3C (vs. type 2-3A)	-6.92 (-18.89 to 5.05)	0.017	0.253
	Gastritis	-8.40 (-20.16 to 3.35)	0.026	0.159
	Helicobacter pylori infection	-0.32 (-15.91 to 15.28)	0.000	0.968
Ferritin (mcg/L)	Marsh type 3B-3C (vs. type 2-3A)	-6.86 (-11.58 to -2.15)	0.098	0.005*
	Gastritis	-3.69 (-8.52 to 1.13)	0.029	0.132
	Helicobacter pylori infection	-3.03 (-9.40 to 3.35)	0.011	0.347
Hemoglobin (g/dL)	Marsh type 3B-3C (vs. type 2-3A)	-0.22 (-0.89 to 0.45)	0.005	0.517
	Gastritis	-0.43 (-1.08 to 0.23)	0.021	0.198
	Helicobacter pylori infection	-0.45 (-1.31 to 0.41)	0.014	0.301

B is the unstandardized coefficient from univariable linear regression. Reference categories were Marsh type 2-3A and absence of gastritis or *Helicobacter pylori* infection. CI: Confidence interval, R^2: Coefficient of determination. *: p<0.05

Fifteen patients were diagnosed with Type 1 DM. Patients with Type 1 DM exhibited milder endoscopic and histopathologic findings compared to other patients (p=0.00). No correlation was observed between B12 levels and the presence of Type 1 DM (p=0.39). Conversely, an inverse correlation was identified between the presence of Type 1 DM and folic acid and ferritin levels (p=0.01, p=0.04, respectively).

DISCUSSION

CD is a chronic autoimmune enteropathy triggered by gluten-containing food intake and causes micro- and macronutrient deficiencies. These deficiencies should be identified at the time of diagnosis, and supportive therapies should be planned if necessary[1,2]. Micronutrient deficiency may occur due to malabsorption associated with the small intestine's involvement in the disease and the severity of that involvement. Conditions such as decreased food intake caused by the symptoms of the disease, chronic diarrhea, or accompanying gastritis may increase micronutrient deficiency. In the present study, the underlying causes of micronutrient deficiencies in celiac patients at the time of diagnosis were investigated.

Micronutrient deficiencies are frequent in children with CD. Iron deficiency without anemia is observed in approximately 20% of patients with CD[7,13]. The prevalence of iron deficiency anemia has been reported to range from 14.1% to 70%[7,14,15]. The frequency of B12 deficiency has been documented to vary from 12% to 40%, while folic acid deficiency has been reported in approximately 20% of cases, as evidenced in various published studies[3,15,16]. The frequencies observed in our study were comparable to those reported in the literature.

There is no reported significant association between micronutrient deficiency and gender in general population. On the other hand, some studies have reported conflicting data between hemoglobin levels and gender[17,18]. There is even less data about this issue in celiac patients. One study revealed no correlation between gender and micronutrient deficiency in celiac patients[3]. Our results are consistent with this.

The relationship between age and micronutrient deficiency was evaluated, and no correlation was identified with regard to iron, ferritin, and folic acid levels. However, an inverse correlation was identified between B12 levels and age at time of diagnosis. There is a paucity of data evaluating the relationship between age and B12 deficiency in the pediatric population, particularly in patients with CD. In the NHANES III data set, it was reported that the prevalence of B12 deficiency increased significantly between the ages of 12 and 19[19,20]. In a study conducted by Eroglu et al.[21] with a large patient data set in Turkish children, an inverse correlation between age and B12 levels was reported. These data suggest that the inverse correlation between age at diagnosis and B12 levels in our patient group is independent of CD.

The most prevalent presenting symptoms among celiac patients are chronic abdominal discomfort, chronic diarrhea, and abdominal distension. The incidence of growth failure is particularly elevated during adolescence[6,16]. Frequency of our patients' presenting symptoms were consistent with literature. Abdominal pain was experienced by 33.3% of patients, while diarrhea occurred in 13.3% and growth failure in 13.7%[22].

Upon evaluating the relationship between the patients' symptoms and micronutrient deficiency, a correlation was identified between folic acid levels and anorexia. There was no relation between presenting symptoms and other micronutrient levels. Despite the dearth of data in this domain, no correlation was identified between symptoms and micronutrient levels in an adult study[8]. In pediatric patients, it was reported that the hemoglobin and ferritin levels of symptomatic patients were significantly lower than those of asymptomatic patients[6]. We could not find any data supporting this relation. There was no other data regarding the relation of symptoms and other micronutrient levels in literature.

In the present study, 26.62% of patients exhibited low WFA, 21.5% low HFA, and 16.5% low BMI. A study conducted by Taskin and Ata[23] on Turkish children revealed that low WFA was present in 21.8%, low HFA in 19.4%, and low BMI in 35.5%. In a study conducted by Setavand et al.[24] on Iranian children, low WFA, low HFA and low BMI were found to be 28.8%, 18% and 25.8%, respectively. Similarly, in a study by Almahmoud et al.[25] on paediatric patients in Kuwait, the rates were 20.3%, 31% and 20.8%, respectively. In the present study, a relationship was identified between low BMI and low B12 and folic acid levels; however, no relationship was observed with iron and ferritin levels. The study by Wierdsma et al.[3] revealed no association between B12 and folic acid levels and low HFA and low BMI. Similarly, the study by McGrogan et al.[4] found no association between ferritin and low BMI. The limited number of cases in both studies may have resulted in different outcomes. As low BMI is related to more severe histopathological findings in our study, this may be leading to low levels of some micronutrients.

High tTGA levels suggest more severe damage to intestinal mucosa[1]. This may contribute to micronutrient deficiencies. However, there is limited data about this effect. A study demonstrated a significant association between elevated tTGA levels and diminished vitamin A and vitamin B1 levels. However, this correlation was not found to exist with ferritin levels[4]. On the contrary, another study showed that tTGA levels were not associated with any vitamin or mineral levels. In our study, we only found that tTGA levels were inversely correlated with ferritin levels. The inverse correlation between tTGA and ferritin levels observed in our study may reflect the fact that ferritin levels decrease with increasing mucosal damage, whereas tTGA levels increase in parallel with the severity of mucosal injury.

In our study, a decrease was found in ferritin and folic acid levels as the histological findings of the disease worsened. When compared with the literature data, a correlation was found between ferritin levels and the degree of villous atrophy in the study of Al-Hussaini et al.[6]. In the study of Deora et al.[5] no relation was found between ferritin levels and the degree of villous atrophy. When the same study was analysed, it was observed that iron and ferritin levels were found to be lower compared to similar studies. The difference in the results may be due to the difference in the populations in which the studies were performed, the difference in nutritional status or the use of iron supplementation beforehand.

Some publications suggest a potential link between *HP* infection and gastritis with various micronutrient deficiencies. Celiac patients may also have concomitant *HP* infection and gastritis. Therefore, we evaluated whether these pathologies lead to any additional risk of micronutrient deficiency in celiac patients. In various

studies, the prevalence of *HP* infection in individuals with CD ranges from 18% to 50%, with gastritis being observed in approximately 50% of cases[26-30]. In our study, 18.9% of the patients were found to be infected with *HP*, while 50.9% exhibited gastritis findings. In some adult studies, it has been reported that there is a significant relation between iron deficiency anemia and *HP* infection in celiac patients, therefore, every patient undergoing endoscopy should be screened for *HP* infection[31-33]. The relationship between *HP* infection and micronutrient deficiency was examined by Agin et al.[30], who identified a correlation between folic acid deficiency and *HP* infection. Conversely, some studies did not reveal a relationship between *HP* infection and micronutrient levels[34,35]. The findings of the present study revealed no correlation between *HP* infection and the levels of B12, folic acid, iron, and ferritin. According to the extant data, it appears unlikely that *HP* infection is associated with an increased risk of micronutrient deficiency, particularly in cases of childhood CD. Consequently, there is no evidence to support the routine screening for *HP* infection in these patients.

Study Limitations

The retrospective study design, the single-center setting, and the lack of information on patients' dietary habits prior to diagnosis appear to be the main limitations of this study.

CONCLUSION

In conclusion, micronutrient deficiency is a common condition in CD. B12 deficiency was found to increase with age, which was in concordance with the general population data suggesting that B12 levels are independent of CD. On the other hand, we demonstrated that, anorexia and low BMI values are related to low levels of B12 and folic acid. Besides that, ferritin levels were low in patients with high tTGA levels and both folic acid and ferritin levels decreased as the severity of villous atrophy increased. We may conclude that ferritin seems to be affected only by intestinal damage. However, oral intake seems to be more effective on folic acid levels as they are lower in anorexic and underweight children.

Ethics

Ethics Committee Approval: The Human Investigation Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 2024/06-11, date: 16.05.2024) approved this study.

Informed Consent: Our study is a retrospective study without human intervention. Therefore, patient consent is not required.

Declaration of AI Use: AI was used to assist with language editing and to improve the clarity and presentation of the manuscript. All scientific content, analyses, and interpretations were critically reviewed and verified by the authors, who take full responsibility for the final manuscript.

Footnotes

Authorship Contributions

Concept: M.Ö., Design: M.Ö., Data Collection or Processing: Ş.P., D.D., S.Ç., G.E.E., Ç.Ö.E., Analysis or Interpretation: M.Ö., Ö.B.S., Writing: M.Ö., Ö.B.S., Ş.P., D.D., S.Ç., G.E.E., Ç.Ö.E.

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