DOI: 10.24996/ijs.2026.67.8.15

ISSN: 0067-2904

Assessment of the Potential Impact of Some Micronutrient Deficiencies on Celiac Disease Severity

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Received: 21/4/2025 Accepted: 3/ 9/2025 Published: xx

Abstract

This study explored the levels of vitamin B12, D3, calcium, zinc, and ferritin in patients with celiac disease (CD) and their clinical relevance. Fifty CD patients (25 males and 25 females: aged 15 to 47) from Baghdad Teaching Hospital and 20 healthy controls were enrolled. Detection of antibodies was performed using ELISA, while micronutrient levels were quantified through photoelectrochemistry and photolysis. CD patients revealed significantly higher levels of anti-gliadin and anti-tissue antibodies ($p < 0.001$) compared to controls. In contrast, significantly reduced levels of vitamin D3, vitamin B12, zinc, calcium, and ferritin were observed ($p < 0.001$). Age-stratified analysis showed that patients aged 15–25 years exhibited reduced levels of ferritin, calcium, and vitamin B12, whereas individuals aged 26–35 years demonstrated the most pronounced deficiency in vitamin D3. These deficiencies correlated negatively with anti-tissue IgA, suggesting a potential contribution to disease severity. The findings propose that micronutrient deficiencies are prevalent in CD and may affect its pathogenesis, emphasizing the importance of initial nutritional assessment and management in individuals affected by the condition.

Keywords: Gluten-related disorders, Micronutrient deficiencies, Vitamin D3, Vitamin B12

تقييم التأثير المحتمل لبعض نقص المغذيات الدقيقة على شدة مرض السيلياك

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الخلاصة

هدفت هذه الدراسة إلى قياس مستويات فيتامين B12 وD3 والزنك والكالسيوم والفيريتين لدى مرضى السيلياك وتحديد أهميتها السريرية. شملت العينة خمسين مريضًا بالسيلياك (25 ذكور و25 إناث، تتراوح أعمارهم بين 15 و47 عامًا) من مستشفى بغداد التعليمي، بالإضافة إلى 20 شخصًا سليمًا كمجموعة ضابطة. تم الكشف عن الأجسام المضادة باستخدام تقنية الإليزا، وقياس مستويات المغذيات الدقيقة عبر الكيمياء الضوئية الكهربائية. أظهر مرضى حساسية الحنطة ارتفاعًا ملحوظًا في مستويات الأجسام المضادة (anti-tissue و anti-gliadin IgA وIgG) مقارنة بالأصحاء (P<0.001)، بينما كانت مستويات فيتامين D3 وB12 والزنك والكالسيوم

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ومخزون الحديد منخفضة بشكل كبير .(P<0.001)وقد أظهرت التحليلات حسب الفئة العمرية أن المرضى الأصغر سنًا (15–25 عامًا) يعانون من نقص أكبر في مخزون الحديد والكالسيوم وB12، في حين كانت أعلى نسبة نقص فيتامين D3 لدى الفئة العمرية (26–35 عامًا). أظهرت النتائج وجود علاقة عكسية بين هذه النواقص ومستويات anti–tissue IgA، مما يشير إلى دور محتمل لها في شدة المرض، ويؤكد على أهمية التقييم الغذائي المبكر لدى المصابين.

Introduction

Celiac disease (CD) is a complex, immune-mediated disorder with a strong genetic predisposition, triggered by gluten and its associated polyamines. Its clinical manifestation involves multiple pathological processes, most notably minor intestinal mucosal injury and the activation of disease-specific immune responses, which are strongly associated with the human leukocyte antigen (HLA) haplotypes DQ2 and DQ8. The autoimmune response targeting tissue transglutaminase (tTG) and environmental exposure to gluten, which is primarily found in wheat, barley, rye, and oats, are the primary factors driving the pathogenesis of celiac disease [1]. Impaired intestinal barrier function, an innate immune response to gluten, dysregulated adaptive immunity, and an imbalance in the gut microbiota are other mechanisms that contribute [2]. *HLA-DQ2* or *HLA-DQ8* genotypes are present in approximately 40% of the general population, indicating an interaction among immunological and environmental factors in the development of celiac disease [3]. Breastfeeding, delivery mode, and gluten introduction timing during infancy have been recommended as possible modifiers of celiac disease risk. However, evidence supporting their impact on disease incidence is limited in retrospective studies [4]. Additionally, celiac disease susceptibility has been linked to gastrointestinal infections, particularly with rotavirus. In infants exposed to gluten before six months of age, early administration of the rotavirus vaccine can significantly reduce this risk [5]. Usually, individuals with CD can develop folate and vitamin B12 deficiency mainly due to malabsorption and villi atrophy [6]. Normal hematopoiesis and neurological function require both folate and B12 vitamins [6]. Up to 41% of newly diagnosed CD patients exhibit vitamin B12 deficiency [7]. Although the cause of vitamin B12 deficiency in CD remains unclear, minor intestinal injury-related complications may be behind this issue. Furthermore, the frequent occurrence of conditions such as intestinal bacterial overgrowth, autoimmune gastritis, impaired intrinsic factor activity, and ileal dysfunction in patients with celiac disease has been related to reduced gastric acidity and consequent cobalamin malabsorption. In children with untreated CD, anemia may increase due to disruptions in folate or vitamin B12 absorption [8]. Untreated CD patients frequently have reduced levels of vitamin D and calcium in their blood, possibly due to malabsorption of nutrients caused by intestinal epithelial damage or exclusion of dairy products from their diet due to lactose intolerance [9]. The CD disorder may be attributed to a deficiency in a calcium-binding protein, which is modulated by vitamin D and contributes to intestinal calcium absorption [10]. The occurrence of osteopenia and osteoporosis in nearly fifty percent of untreated CD patients. Severe vitamin D deficiency in adults can cause osteomalacia [10], these findings could indicate underlying CD. Studies have established that a gluten-free lifestyle and the administration of vitamin D3 play a pivotal role in mitigating the clinical manifestations of osteomalacia and normalizing serum calcium concentrations. In addition, Hypozincemia (low serum zinc levels) was identified in over 50% of patients with untreated CD [11]. The cause of this may be the impaired absorption due to villous atrophy. Other potential causes of zinc deficiency may include chelation by inflammatory proteins, resulting from either excessive loss due to enteropathy, or excessive increased utilization resulting from enhanced enterocyte turnover [12]. Growth retardation, delayed sexual maturation, impaired wound healing, and hypogeusia are all potential consequences of zinc deficiency [13]. CD is associated with ferritin deficiency due to damage to the intestinal villi, which are responsible for iron absorption in the small intestine. Again, when gluten is

consumed, these villi are damaged, impairing absorption and causing iron deficiency anemia. Studies suggest that anemia may be the only symptom in some patients who are not diagnosed with CD [14]. This study aimed to measure the concentrations of vitamin B12, D3, and zinc and investigate their clinical manifestations in CD patients.

Material and methods

Study subjects

Fifty cases (25 females and 25 males) with CD were involved in this pilot study, along with twenty healthy subjects (10 females and 10 males) who served as a healthy control group. Participants' ages ranged between 15 and 47 years. Peripheral blood samples and clinical data were collected from CD patients at the Baghdad Teaching Hospital's Internal Consultation Clinic in Baghdad, Iraq. Disease-specific antibodies and other related diagnostic indicators (anti-tissue IgM and IgG, and anti-gliadin IgM and IgG) were evaluated. Furthermore, the levels of a number of key nutritional parameters (calcium, ferritin, zinc, vitamin D3, and vitamin B12) were assessed in both CD patients and healthy controls. This study followed the Declaration of Helsinki. The University of Baghdad examined and approved the study design on September 20, 2023 (CSES/0921/0054). Written informed consent was obtained.

Blood sample collection

Venous blood (5 ml) was drawn from the studied subjects by intravenous aspiration between 8:30 am and 12:30 pm. The blood samples were then placed in gel tubes for blood clotting at room temperature. Centrifugation at 4000 xg for 10 min was used to collect the serum, which was then transferred to an Eppendorf tube and stored at −20 °C until used for the rest of the analyses.

Evolution of serum antibody levels

The automated ELISA (Immunolight Device) system was used to determine the concentration of antibodies (anti-tissue IgM and IgG, and anti-gliadin IgM and IgG) using an ELISA kit.

Assessment of vitamin D3 and B12 levels

The levels of vitamin D3 (V. D3), vitamin B12 (V. B12), and ferritin were determined by electrochemiluminescence using the COBAS e411 device from Roche (Germany), utilizing V. D3, V. B12, and ferritin kits.

Estimation of serum zinc and calcium levels

The zinc and calcium levels were determined using the COBAS C311 device from Roche, Germany, which relies on the photometric method using zinc and calcium kits.

Statistical analysis

The analysis of collected data was conducted utilizing the statistical software packages SPSS (Version 28) by IBM and GraphPad Prism (Version 8). The statistical analyses involved employing an independent t-test. A p-value cutoff of <0.05 was considered significant for differences[15].

Results

Significantly elevated serum antibody levels associated with CD cases

The results of anti-tissue IgA (Au\ml) revealed a highly significant elevation ($P<0.001$) in the patients with CD (145.67±127.22 Au\ml), compared with the healthy control group (4.41±2.23 Au\ml). Regarding the serum levels of anti-tissue IgG (Au\ml), there was a significant increase ($P<0.001$) in patients with CD (54.39±75.26Au\ml) compared to the control

group (5.02±1.90Au\ml). A similar trend of increased serum antibody levels was observed for anti-gliadin IgA (Au/ml), with a mean of 42.48±31.67 Au/ml for patients with CD and 5.46±2.17 Au/ml for the healthy control group. These differences reach significant levels ($p > 0.001$). The serum levels of anti-gliadin IgG (Au\ml) showed a highly significant increase ($p > 0.001$) for patients with CD (46.31±21.01Au\ml) in comparison to those of the healthy control group (4.83±2.68Au\ml), as shown in Table 1.

Table 1: Serum levels of antibodies in the studied CD and healthy control subjects

Antibodies	Groups (Mean ± SD)		
	Healthy control	Celiac disease	P-value
Anti-tissue IgA (Au\ml)	4.41±2.23	145.67±127.22	0.001**
Anti-tissue IgG (Au\ml)	5.02±1.90	54.39±75.26	0.001**
Anti-gliadin IgA (Au\ml)	5.46±2.17	42.48±31.67	0.001**
Anti-gliadin IgG (Au\ml)	4.83±2.68	46.31±21.01	0.001**

** P≤0.01 is statistically significant using independent t-test.

* Data are presented as mean ± standard error (SE). *P<0.05; **P<0.01; NS: Non-Significant.

Levels of the nutritional parameters in the studied subjects

A highly significant decrease ($P < 0.001$) was found in vitamin D3 levels in the CD group (19.66 ± 1.3 ng/dL, Figure 1) compared to the healthy control group (34.23 ± 2.4 ng/dL). Regarding the levels of serum vitamin B12, they were significantly reduced ($P< 0.001$) in patients with CD compared with those of the healthy control group (113.2± 9.7 vs. 374.4 ± 57.56 ng/dl, respectively, Figure 2).

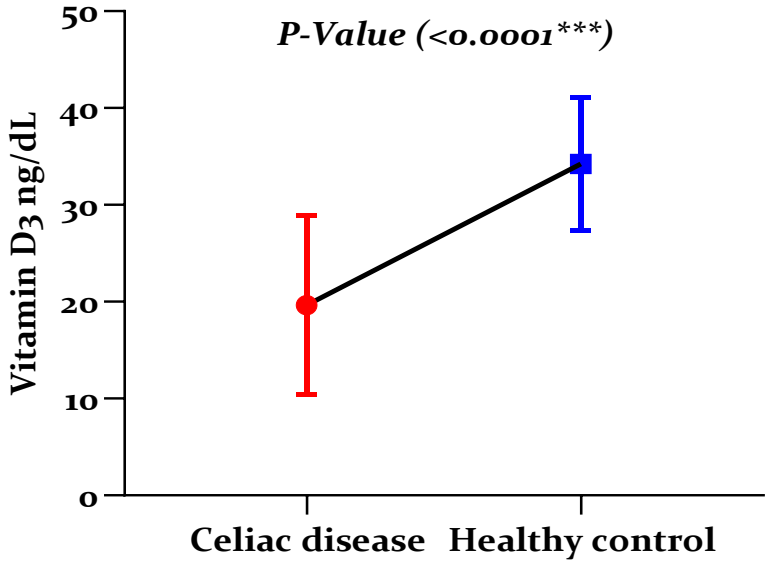

Figure 1: Levels of serum vitamin D3 in study subjects

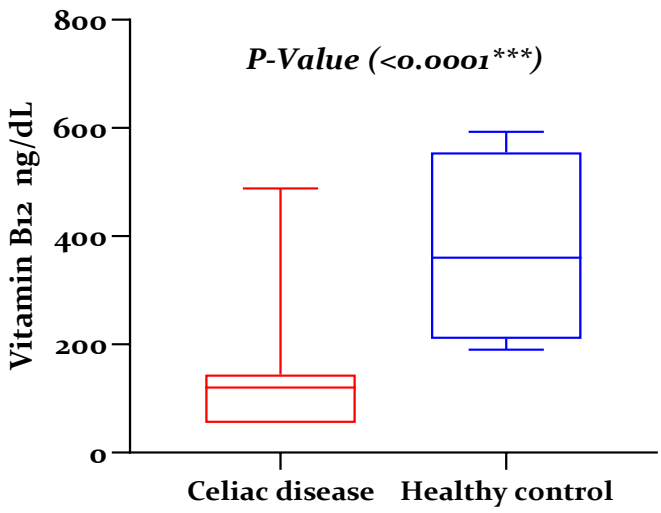

Figure 2: Levels of serum vitamin B12 in study subjects

Regarding the serum zinc status, these findings also revealed a statistically significant (P > 0.001) decrease in zinc levels in patients with CD (27.55 ± 2.34 mg/dL, Figure 3) compared to the healthy control group (76.35 ± 7.084 mg/dL).

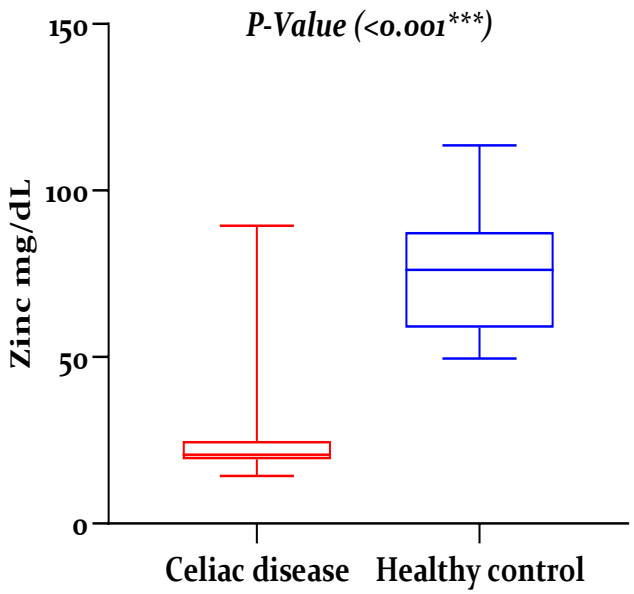

Figure 3: Serum levels of zinc in CD patients in comparison to their healthy controls

Similarly, these findings also revealed a statistically significant (P > 0.001) drop in serum ferritin levels in patients with CD (11.16 ± 0.697 mg/dL) compared to those of the healthy control group (66.55 ± 7.04 mg/dL, Figure 4).

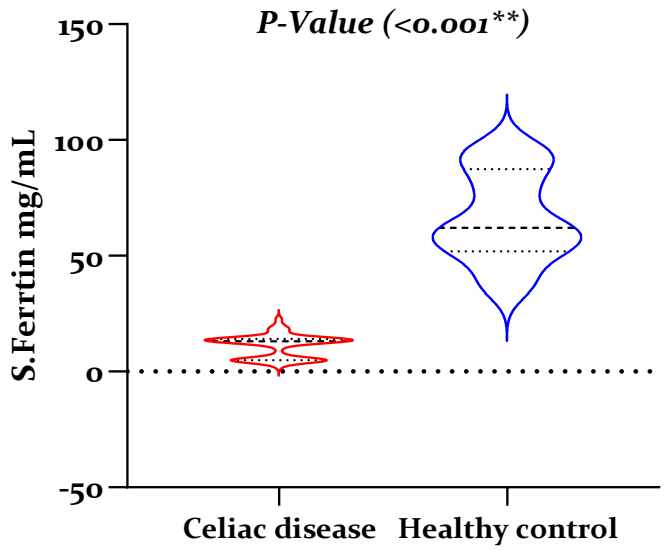

Figure 4: Serum levels of ferritin in CD patients in comparison to their healthy counterparts

Additionally, serum calcium levels were significantly decreased (P< 0.0002) in CD patients (6.32 ± 0.23) compared to the healthy control group (8.6 ± 0.31, Figure 5).

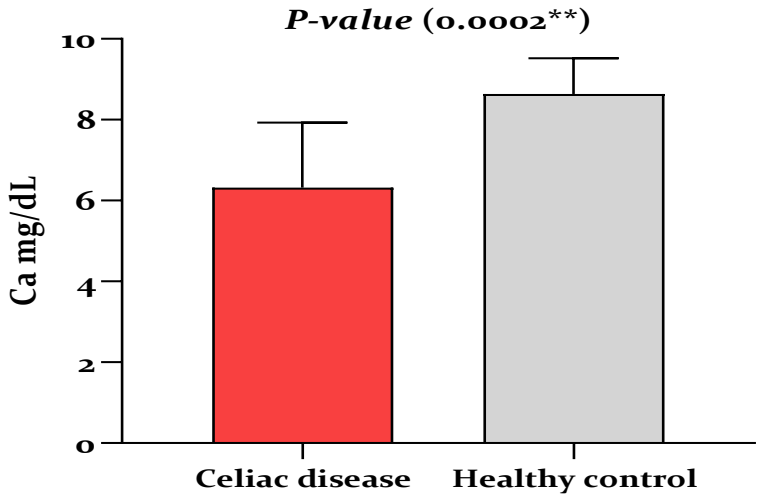

Figure 5: Serum calcium levels in CD patients in comparison to their healthy controls

Effect of some descriptive data on the biochemical markers (Age and Gender) in patients

Table 2 illustrates how age affects biochemical indicators in people with CD. Three age groups were distinguished: 15–25, 26–35, and 36–47 years. Ferritin levels in the 15–25 age group were substantially lower (7.8 ± 1.2 mg/dL) than in the 26–35 and 36–47 years age groups (14.485 ± 0.59 and 12.4 ± 0.89 mg/dL, respectively) (P < 0.001). Furthermore, the calcium levels in the 15–25 age group showed a significant decrease (5.052 ± 0.33 mg/dL, P < 0.001). In comparison to the 26–35 and 36–47 age groups (7.445 ± 0.26 and 6.9 ± 0.25 mg/dL, respectively). The 15–25 age group had substantially lower vitamin B12 levels (80.7 ± 10.6 ng/dL) (P = 0.019) than the 26–35 and 36–47 age groups (141.12 ± 21.01 and 128.71 ± 8.3 ng/dL, respectively). In the 15–25 age group, vitamin D levels were significantly lower (18.47 ± 1.5 ng/dL) than in the 26–35 and 36–47 age groups (14.25 ± 0.75 and 26.65 ± 3.2 ng/dL, respectively; P < 0.001). No statistically significant difference was observed (P = 0.341) in zinc levels among the three age groups (26.464 ± 2.34, 22.812 ± 2.64, and 31.17 ± 3.2, respectively).

Table 2: The potential impact of age on the different assessed nutritional parameters

	Age categories (Mean ± SE)				
Parameters	15-25	26-35	36-46	*Eta squared*	*P-value*
Ferritin	7.8 ± 1.2	14.485 ± 0.59	12.4 ± 0.89	0.351^{M}	<0.001**
Zinc	31.17 ± 3.2	22.812 ± 2.64	27.464 ± 2.34	0.045^{s}	0.341 NS
Ca	5.052 ± 0.33	7.445 ± 0.26	6.9 ± 0.25	0.441^{L}	<0.001**
V.B12	80.7 ± 10.6	141.12 ± 21.01	128.71 ± 8.3	0.156^{M}	0.019*
V.D3	18.47 ± 1.5	14.25 ± 0.75	26.65 ± 3.2	0.286^{M}	<0.001**

*Data are presented as mean ± standard error. A one-way ANOVA test was performed to compare age categories

* ANOVA Effect Sizes (Small size= 0.01, medium size= 0.06, large size= 0.14)

*Significance levels: P<0.05**; P<0.01; NS: Non-Significant

Regarding the potential influence of gender on the different assessed biochemical parameters, Table 3 illustrates how gender may affect ferritin, zinc, calcium, vitamin B12, and vitamin D3 levels, among other biochemical markers, in patients with celiac disease. Across all measured parameters, the results show that no statistically significant difference was observed ($P > 0.05$) between males and females, indicating that gender has a minimal effect on these bio-parameters in the investigated cohort.

Table 3: The potential effect of gender on biochemical assessed parameters

	Gender (Mean ± SE)			
Parameters	Female	Male	*Cohen's d*	*P-value*
Ferritin	10.83 ± 1.2	11.5 ± 0.59	-0.135	0.634 NS
Zinc	27.7 ± 3.2	27.4 ± 2.64	0.019	0.948 NS
Calcium	6.5 ± 0.33	6.24 ± 0.26	0.098	0.730 NS
V.B12	122.45 ± 10.6	104.01 ± 21.01	-0.277	0.351 NS
V.D3	18.4 ± 1.5	20.94 ± 0.75	.267	0.332 NS

* Data are presented as mean ± standard error (SE). *P<0.05; **P<0.01; NS: Non-Significant.

*Cohen's d t-test effect size (Small size=0.2, medium size= 0.5, large size= 0.8)

Correlation between studied parameters in patients with CD

The correlation between the investigated bio-parameters is depicted in Figure 6. Anti-tissue IgA and anti-gliadin IgG (r=0.66), and anti-tissue IgG and anti-gliadin IgA were found to be significantly positively correlated (r=0.58). This suggests a heightened immunological response leading to an increase in CD-associated antibody production. The anti-tissue IgA, however, shows a significant negative correlation with ferritin (r= -0.28), zinc (r= -0.31), and vitamin D (r=-0.49). Anti-tissue IgG and vitamin B12 showed a weak positive correlation (r=0.42). Remarkably, there was no association between the biochemical parameters and anti-gliadin IgG. In terms of the relationship between vitamins and minerals, zinc showed a weakly positive association with vitamin D and vitamin B12 (r=0.29).

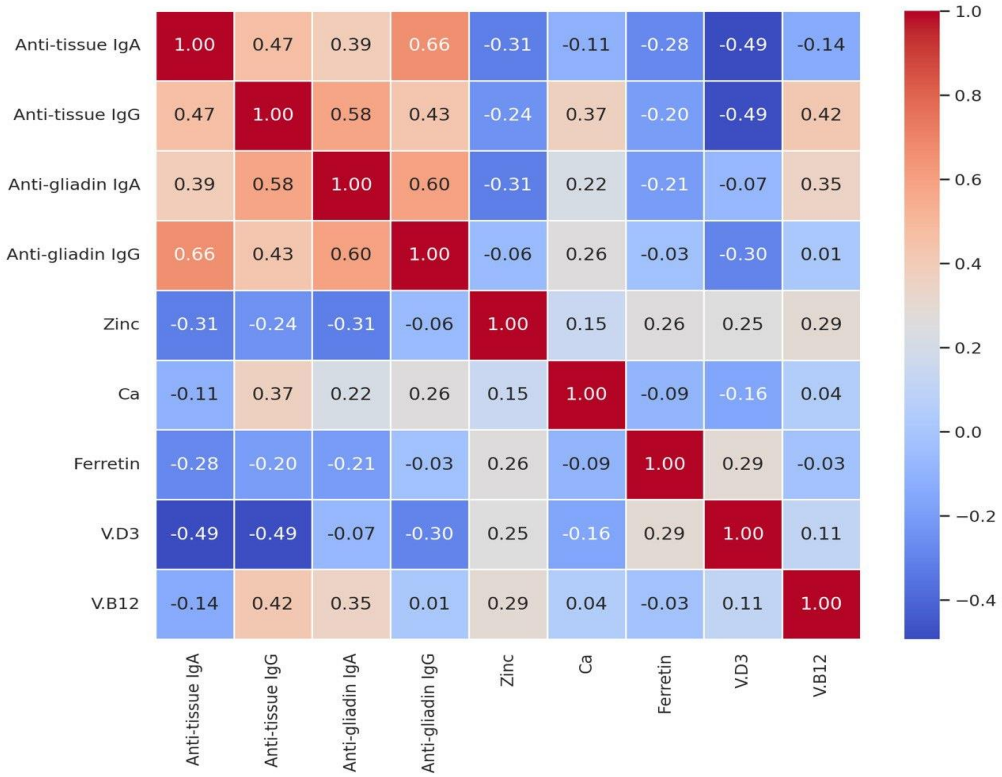

Figure 6: Correlation between studied parameters in patients with CD

Discussion

Celiac disease is characterized by villous atrophy, which causes mucosal injury in the small intestine due to gluten intolerance, leading to impaired nutrient absorption [16]. The study demonstrated a significant increase in IgA and IgG antibody levels in patients with CD compared to the healthy control group. These antibodies are key biomarkers in the diagnosis of CD, and this finding aligns with a study conducted by Rubio-Tapia *et al.,* [17], which identified anti-tissue transglutaminase IgA and anti-gliadin IgA antibodies as the most sensitive markers for detecting CD, making them effective tools for diagnosing the condition in affected patients. The study findings are also consistent with Kulik *et al.,* [18], who suggested that elevated levels of "anti-tissue IgG" may be useful in diagnosing patients with IgA deficiency, a common condition among individuals with CD. They confirmed that combining different antibody tests improves diagnostic accuracy. On the other hand, monitoring the levels of these antibodies over time is essential to assess patients' response to the gluten-free diet, as explained by Mulder *et al.,* [19]. The gradual decrease in antibody levels indicates an improvement in the patients' condition and their compliance with the diet. A comprehensive literature review reveals the influence of celiac disease on vitamin D3 homeostasis. For instance, a study conducted by Dragland [20] found that 76.5% of patients with CD had insufficient vitamin D3 levels [20]. Moreover, meta-analytic data reported by Vici *et al.,* [21] demonstrated that patients with celiac disease exhibited significantly lower levels of vitamin D3 compared to healthy controls. Furthermore, a study by Whiting *et al.,* [22] clarified that celiac disease patients had a lower rate of intestinal absorption of vitamin D3, which can exacerbate deficiency [23]. Moreover, cross-sectional studies by Sun *et al.,* [24] also highlighted a negative association between vitamin D3 and CD levels. Another study conducted by Hansen *et al.,* [25] revealed that patients with celiac disease exhibiting reduced vitamin D3 levels were found to be at an increased risk of developing osteoporosis and sustaining fractures [26]. Vitamin B12 deficiency is commonly observed in untreated celiac disease. This deficiency may result from multiple

factors, including reduced gastric acid secretion, bacterial overgrowth, and damage to the small intestinal mucosa. Impaired vitamin B12 absorption in CD is also thought to include the presence of autoantibodies targeting intrinsic factor (IF) and gastric parietal cells [27]. A study found that 21% of patients with CD had low vitamin B12 levels, and 8% had elevated homocysteine levels, indicating vitamin B12 insufficiency. On the other hand, a study showed that 41% of children with celiac disease had low levels of vitamin B12 before starting a gluten-free lifestyle. In the same study, after 1 year of a gluten-free lifestyle, 30% of children still had low vitamin B12 levels [2, 26]. A recent review article has determined that vitamin B12 deficiency in CD patients can be a result of impaired IF production, reduced pancreatic enzyme secretion, and alterations in the gut microbiome. Supplementation with vitamin B12 is recommended for individuals with CD, especially those with active disease or those who have not responded to a gluten-free [28]. Zinc deficiency was found in 0–40% of individuals after a Gluten-Free-Diet and in over 50% of adult CD patients upon diagnosis [11]. Mineral deficiency is associated with malabsorption disorders, which are also influenced by the level of mucosal inflammation. According to research by Mazzola *et al*., [29], they advocated measuring serum zinc levels in CD patients at diagnosis and again after 3 months, until the level is normal, then every 1-2 years for symptoms. They also prescribed 25 to 40 mg/day zinc supplementation until zinc levels were normal [30]. Studies indicate that iron deficiency is a prevalent symptom in patients with CD, even in the absence of obvious gastrointestinal symptoms. In a study by Zingone and Zanini [31], approximately 46% of undiagnosed celiac disease patients had iron deficiency as a first symptom. This deficiency can be attributed to chronic malabsorption resulting from damage to the small intestine mucosa. Patients with CD suffer from intestinal villus atrophy due to an immune reaction against gluten, which leads to a reduction in the intestinal absorption area of iron, as shown to be reduced in patients, which is consistent with previous studies [32, 33]. In addition, chronic inflammation associated with CD may contribute to disrupting iron absorption by increasing levels of hepcidin, a key regulator of iron metabolism, which is consistent with the proposal by Kamal and Kadhim [33]. This decrease in calcium levels is attributed to damage to the intestinal mucosa due to the autoimmune response induced by gluten, which depletes other essential minerals. This finding is consistent with that reported by Çamtosun *et al.,* [34], which confirmed that approximately 30–60% of newly diagnosed CD patients had low bone mineral density, while 18–35% of them were diagnosed with osteoporosis, reflecting the chronic effect of calcium deficiency. In addition, vitamin D is a key regulator of calcium uptake and absorption, as well as maintaining mineral balance in the body. The current results showed that patients with CD participating in the study suffer from vitamin D deficiency. This finding is consistent with previous study by Di Stefano *et al.,* [9], which proposed that vitamin D deficiency is common in patients with CD, as it is directly associated with decreased calcium absorption and an increased risk of skeletal complications. Following a gluten-free diet may improve nutrient absorption in celiac patients. However, the risk of calcium and vitamin D3 deficiency may persist due to the presence of an immunological response and synthesis of antibodies that attack the mucosal layer in the small intestine, similar to what was reported by Gorini and Tonacci [35].

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Conclusion

The results indicate significant immune activation and nutritional deficiencies in patients with CD. There were increased levels of anti-tissue and anti-gliadin antibodies, suggesting heightened immune responses. This was associated with significant decreases in vitamin D, vitamin B12, zinc, calcium, and ferritin, as well as a negative correlation between anti-tissue IgA and these micronutrients, indicating impaired absorption. Additionally, younger CD patients (15-25 years) were more vulnerable to deficiencies in these nutrients. These findings underscore the importance of comprehensive monitoring and supplementation with vitamins

and minerals, particularly in younger CD patients, to address both immune and nutritional imbalances.

Acknowledgments

The authors would like to express their sincere thanks and gratitude to all the staff of the Internal Medicine Consultation Clinic at Baghdad Teaching Hospital, Medical City, Baghdad, Iraq.

Competing interests

The authors state that they have no known competing financial interests or personal relationships that could have influenced the work described in this paper.

Funding

This study received no outside funding

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