

# The Role of Gluten-Free Diet in Rebalancing Micronutrient Deficiencies in Children With Celiac Disease

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## Abstract

**Introduction:** Celiac disease (CD) is one of the most common reasons for malnutrition. This study aimed to determine the status of the micronutrients, including vitamins and minerals in children with CD.

**Methods:** The participants of this study included children <18 years old newly diagnosed with CD from January 2016 to December 2017 in the Clinic of Gastrointestinal and Digestive Diseases affiliated with Shiraz University of Medical Sciences. The diagnosis of CD was based on serological and pathologic findings. Finally, the data was analyzed using SPSS 22.

**Results:** In the present study, 78 children with CD were evaluated, including 30 (38.5%) males and 48 (61.5%) females. The levels of hemoglobin and iron significantly improved after 6 months of treatment ( $P=0.001$ ). In the present study, the level of calcium was below the normal range in 5 (6.4%) patients at diagnosis. However, its level was within a normal range in all patients 6 months after the treatment. Based on the results, the level of phosphorus was low in 24 (30.7%) and 5 (6.4%) patients before and after the treatment, respectively ( $P=0.001$ ). Further, the vitamin D level was below a normal range in 66 (84.6%) and 15 (19.2%) patients at diagnosis and 6 months after the treatment, respectively ( $P=0.001$ ). On the other hand, the mean level of folic acid increased from 16.5 at diagnosis to 22.39 after 6 months of treatment ( $P=0.001$ ). Finally, the mean level of zinc also increased from 73.3 at diagnosis to 81.6 after 6 months of treatment ( $P=0.001$ ).

**Conclusion:** In general, the levels of iron, folate, vitamin D, and zinc reduced in patients with CD. In most patients, these deficiencies improved by receiving a gluten-free diet (GFD). Monitoring patients with CD is recommended for the diagnosis of micronutrient deficiencies.

**Keywords:** Celiac disease, Iron, Folate, Vitamins, Micronutrients

## Introduction

Celiac disease (CD) is an autoimmune disease that is presented with gluten hypersensitivity and varying degrees of enteropathy.<sup>1</sup> In addition, the CD is one of the most frequent reasons for malnutrition.<sup>2</sup> In CD, damage to the small intestine reduces the production of digestive enzymes and the absorption of micronutrients.<sup>3</sup> The global prevalence of CD has been increased in recent years.<sup>2</sup> In a study conducted in our center, the prevalence of CD in children was estimated at 0.6%.<sup>3</sup>

The clinical symptoms of CD may be mild and non-specific symptoms include diarrhea, malnutrition, and weight loss, and constipation.<sup>4</sup> In some cases, a mild microcytic anemia or folate deficiency may be the sole presentations.<sup>5</sup> The diagnosis of CD is typically made by serological (anti-tissue transglutaminase IgA) and histopathological tests.<sup>6</sup>

Patients with CD are prone to deficiencies in the absorption of nutrients.<sup>7</sup> In a study on children with CD, 81.6% and 64.1% of patients had iron and zinc deficiencies, respectively.<sup>8</sup> In another study,

the deficiencies of magnesium, calcium, iron, vitamins D, B12, and folate were reported in patients with CD.<sup>9</sup> Considering the high prevalence of malnutrition in children with CD, and the lack of a previous study on the status of micronutrients in our center, this study aimed to determine the level of nutrients, including vitamins and minerals in children with CD before and after treatment with a gluten-free diet (GFD).

### Methods

The present prospective study was performed on children <18 years old newly diagnosed with CD from January 2016 to December 2017. These patients referred to the Clinic of Gastrointestinal and Digestive Diseases affiliated with Shiraz University of Medical Sciences Shiraz, Iran.

The diagnosis of CD was based on the elevated titer of antibodies to tissue transglutaminase immunoglobulin A (anti-tTG IgA) and duodenal biopsy. The patients were managed by GFD. At the time of diagnosis, blood samples were taken to measure routine laboratory parameters, followed by recording patients' information including age, gender, weight, height, body mass index, clinical symptoms, and a family history of CD. The titer of IgA anti-tTG was determined by enzyme-linked immunosorbent assay. All the measurements were performed at the diagnosis and 6 months after receiving GFD. Moreover, the biopsy samples of the duodenum were examined for definite diagnosis and Marsh classification. It should be noted that patients did not consume any mineral and vitamin supplements during the 6-month follow-up.

The data were analyzed using SPSS 22 and descriptive statistics, mean, and standard deviation were used to present the data. Additionally, the Wilcoxon test, paired Student's *t* test, and chi-square test were used as inferential statistical tests. Eventually, the Kolmogorov-Smirnov test was applied to assess normal distribution.

### Results

The present study investigated 78 children with CD including 30 (38.5%) males and 48 (61.5%) females. The mean age of the patients was  $8.7 \pm 3.4$  years old and the youngest and oldest children aged 3 and 18 years old, respectively. Of these patients, 18 (23.1%) had diabetes and 5 (4.1%) of them suffered from thyroid problems. Table 1 presents the comparisons of demographic and laboratory parameters at diagnosis and 6 months following a GFD.

Although there was no significant difference comparing serum calcium, phosphorous, and vitamin B12, the levels of zinc, magnesium, folate, and vitamin D significantly improved following 6 months of GFD (Table 2). The normal ranges of micronutrients are provided in Table 3.

### Discussion

In the present study, the levels of hemoglobin, serum iron, and ferritin significantly improved in patients with

CD after 6 months of treatment with GFD ( $P=0.001$ ). The ratios of patients with low hemoglobin were 19 (24.3%) and 9 (11.5%) before and after receiving GFD ( $P=0.006$ ). Likewise, lower than the normal serum iron was observed in 14 (17.9%) patients before treatment while no patients had below a normal range of serum iron after treatment ( $P=0.006$ ). Using serological tests and the biopsy examination of the small intestine, the CD was diagnosed in 1.8 to 14.6% of patients with iron deficiency anemia.<sup>10,11</sup> In another study by Baghbanian et al on 402 patients with iron deficiency anemia, 10.4% of them were diagnosed with CD as well.<sup>12</sup> Similarly, Rajalahti et al showed that 82 (18%) patients from 455 children with CD suffered from anemia.<sup>13</sup> Based on the findings of Poggi et al, the prevalence of anemia was reported as 34% in patients with CD.<sup>14</sup> In other studies, the prevalence of anemia in patients with CD was reported as 53%<sup>15</sup> and 20%.<sup>16,17</sup> Anemia can present in CD even in the absence of classic abdominal symptoms secondary to the loss of iron in the intestinal enterocytes, the reduced daily absorption of iron, and rarely due to gastrointestinal bleeding which all can lead to iron deficiency anemia in CD.

In the present study, 5 (6.4%) patients showed lower than a normal level serum calcium before treatment while all patients represented a normal calcium level after the treatment although this change was not statistically significant. Below a normal range serum phosphorus was noted in 24 (30.7%) and 5 (6.4%) patients before and after the treatment, respectively ( $P=0.001$ ). Further, vitamin deficiency was observed in 66 (84.6%) and 15 (19.2%) patients before and the treatment, respectively ( $P=0.001$ ). In various studies on patients with CD, the prevalence of low bone density presenting as osteoporosis or osteopenia was reported between 9 and 72%.<sup>18,19</sup> This wide range may partially reflect differences in patients' demographic features, as well as diagnostic and therapeutic methods. The impaired absorption of calcium and vitamin D is well known in patients with CD.<sup>20</sup> In addition, the role of inflammatory cytokines has been found as a contributing factor.<sup>20</sup> In a study in Saudi Arabia on 90 children with CD, 8%, 76%, and 21% of patients had deficiencies in calcium, vitamin D, and phosphorus, respectively. Furthermore, all patients had low bone density.<sup>21</sup> The serum levels of vitamin D, calcium, and phosphorus affect each other and are also regulated by hormones such as the parathyroid hormone. Nevertheless, the nutritional absorption of calcium and vitamin D represents the most important factor affecting their serum levels. Blazina et al concluded that patients with CD, who have been under a long-term strict GFD, were at the risk of low bone density due to the inadequate nutritional absorption of calcium and vitamin D.<sup>22</sup> The results of our study showed that treatment with GFD improved the serum levels of vitamin D, calcium, and phosphorus. Although this study did not evaluate the nutritional absorption of these nutrients, it seems that sticking to GFD in a short period can improve the

**Table 1.** Basic Laboratory Tests in Patients With Celiac Disease at Diagnosis and 6 Months After Treatment

Parameters		Minimum	Maximum	Mean	SD	P value
Weight (kg)	At diagnosis	7.3	58.5	27.61	10.70	<0.001
	6 months after treatment	9.50	69	29.7	11.77	
Body mass index	At diagnosis	5.81	31.93	16.33	3.6	0.006
	6 months after treatment	12.07	36.63	16.20	3.65	
Fast blood glucose (mg/dL)	At diagnosis	68	550	116	92	0.003
	6 months after treatment	75	210	95	20	
Gamma glutamyl transferase (IU/L)	At diagnosis	9	48	16.5	7.2	<0.001
	6 months after treatment	1	65	11	7.7	
Aspartate amino transferase (IU/L)	At diagnosis	7	82	28.6	11.2	<0.001
	6 months after treatment	10	40	24.9	7.1	
Alanine amino transferase (IU/L)	At diagnosis	9	65	21.5	11.5	0.37
	6 months after treatment	10	41	19.7	5.8	
Alkaline phosphatase (IU/L)	At diagnosis	5.9	1182	565	240	0.923
	6 months after treatment	65	540	572	579	
Hemoglobin (g/dL)	At diagnosis	8	15.2	12.5	1.64	<0.001
	6 months after treatment	10	15	12.8	1.09	
Iron ( $\mu$ g/dL)	At diagnosis	7.7	136	69.8	22.3	<0.001
	6 months after treatment	50	140	77.8	15.8	
Total iron binding capacity ( $\mu$ g/dL)	At diagnosis	31	545	338	62	<0.001
	6 months after treatment	70	560	347	78.5	
Ferritin (ng/mL)	At diagnosis	3.68	224	41.7	35.7	<0.001
	6 months after treatment	11	270	64.4	47.2	

Note. SD: Standard deviation.

**Table 2.** The Levels of Vitamins and Minerals in Patients With Celiac Disease at Diagnosis and 6 Months After Treatment With a Gluten-Free Diet

Parameters		Minimum	Maximum	Mean	SD	P Value
Calcium (mg/dL)	At diagnosis	0.7	11	9.16	1.50	0.773
	6 months after treatment	9	11	9.44	0.408	
Phosphorus (mg/dL)	At diagnosis	3.7	6.9	4.82	0.66	0.54
	6 months after treatment	4	5.8	4.97	0.39	
Zinc ( $\mu$ g/dL)	At diagnosis	10	110	73.3	25.1	<0.001
	6 months after treatment	1.1	110	81.6	28.9	
Magnesium (mg/dL)	At diagnosis	1.5	2.6	2.17	0.25	<0.001
	6 months after treatment	1.5	24	2.79	2.45	
Folic Acid (nmol/mL)	At diagnosis	4.7	55.4	16.5	9.1	<0.001
	6 months after treatment	3	100	22.39	14.7	
Vitamin B12 (pg/mL)	At diagnosis	30	2111	405	294	0.324
	6 months after treatment	4.1	900	433	174.5	
Vitamin D (pmol/L)	At diagnosis	2.3	90	25.3	18.5	<0.001
	6 months after treatment	4.1	90	43.2	17	

Note. CD: celiac disease; SD: standard deviation.

**Table 3.** Micronutrient Reference Ranges

Micronutrients	Reference Range
Vitamin B12	1500-180 µg/mL
Calcium	10.2-8.5 mg/dL
Vitamin D	95-36 pmol/L
Folic acid	47.6-11.3 nmol/mL
Hb	1-5 years: 10.9-15 g/dL 5-18 years: 11.9-17.7 g/dL
Serum iron	50-120 µg/dL
Magnesium	2.1-1.7 mg/dL
Phosphorous	5.5-4.5 mg/dL
Total iron binding capacity	240-450 µg/dL
Zinc	1 to 10 years: 80-110 µg/dL 10 to 18 years: 90-120 µg/dL

Note. Hb: hemoglobin.

nutritional absorption of calcium and vitamin D in patients with CD.

In our study, the mean level of serum folic acid increased from 16.5 to 22.39 after 6 months of treatment with GFD ( $P=0.001$ ). Contrarily, the level of folic acid was lower than normal in 25 (32%) and 10 (12.8%) patients before and after treatment, respectively ( $P=0.001$ ). Folate deficiency was reported in 8 to 85% of adults and 10 to 40% of children with CD.<sup>23</sup> In another study, one-third of teenagers with CD showed folate deficiency at diagnosis.<sup>24</sup> In a prospective study on patients with gluten-sensitive enteropathies (42 with CD and 8 with dermatitis herpetiformis), 17 (42.5%) patients showed folate deficiency which was significantly higher compared to the controls (10 out of 120, 8.3%). On the other hand, no significant difference was observed between patients and controls regarding vitamin B12 (7 of 40, 17.5% against 11 of 120, 9.2%).<sup>24,25</sup> In patients with untreated CD, the level of serum folate was less correlated with intestinal atrophy.<sup>25</sup> Vilpolla et al described that 13 out of 35 (37%) patients with untreated CD had lower than normal erythrocyte folic acid concentration.<sup>26</sup> Similarly, Macfarlan et al found that 55 patients (45 women and 10 men) with CD under GFD had normal erythrocyte folate concentration.<sup>27</sup> In a somewhat contradictory scenario, Hallert et al asserted that patients with CD under GFD for at least 10 years and no histological evidence of intestinal damage had plausible folate status.<sup>28</sup> In another study, folate deficiency was reported in 20% of patients with CD.<sup>29</sup> Overall, folate deficiency in CD patients may reflect nutritional inadequacy in GFD which has been proven to have various nutritional deficiencies.<sup>29</sup> In fact, the low consumption of daily folate in treated CD patients was reported in comparison with the control.<sup>29</sup> In this regard, receiving the supplements of folic acid and vitamin B12 for a 6-month period can be beneficial in patients with CD under long-term GFD.<sup>29</sup>

The deficiency of vitamin B12 in CD seems to be negligible as the absorption of this vitamin mainly occurs at the end of the ileum.<sup>30</sup> However, assessing the status of vitamin B12 in CD showed low circulating levels in 5 to 41% of untreated patients.<sup>17,31,32</sup> The serum vitamin B12 level has been independent of the clinical presentation of CD,<sup>33,34</sup> the degree of villous atrophy, and gender.<sup>34</sup> Vitamin B12 deficiency in CD is often mild and limited to conditions with the involvement of ileum,<sup>31</sup> and is corrected by GFD,<sup>27</sup> unless in patients with concurrent pancreatic insufficiency or pernicious anemia.<sup>35</sup> Hallert et al showed that vitamin B12 level was well preserved in 30 CD patients under long-term therapy with GFD.<sup>28</sup> In a double-blinded clinical trial on 65 patients with CD under GFD, the daily administration of 0.8 mg folic acid, 0.5 mg cyanocobalamin, and 3 mg pyridoxine for 6 months increased the mean serum level of vitamin B12 from 405 to 433, but this change was not statistically significant. Similarly, below normal level of vitamin B12 was noted in 13 (13.6%) and 7 (9%) patients before and after the treatment which was not statistically significant.<sup>29</sup>

In our study, the mean level of serum zinc in patients with CD increased from 73.3 to 81 after 6 months of treatment with GFD ( $P=0.001$ ). Furthermore, the serum level of magnesium was lower than normal in 3 (3.8%) patients and 1 (1.28%) patient before and after 6-month of treatment with GFD, respectively, but this change was not statistically significant. Zinc deficiency was described in more than 50% of patients with untreated CD.<sup>36</sup> This may be due to disordered absorption secondary to villous atrophy. Other factors such as chelation by fatty acids, excessive protein loss enteropathy, or increased enterocyte turnover may also lead to zinc deficiency in CD.<sup>37</sup> Furthermore, zinc deficiency may lead to abnormal sexual maturity, growth retardation, and impaired wound healing, and a reduced sense of taste.<sup>38</sup> Therefore, it is plausible to attribute some CD-associated signs/symptoms (e.g., growth retardation and anorexia) to zinc deficiency. Moreover, magnesium deficiency was reported in about 20% of patients with untreated CD.<sup>39</sup> In addition, it was comparable in healthy individuals and patients with untreated, treated, or subclinical CD.<sup>39</sup> Nevertheless, persistent magnesium deficiency in treated CD patients probably indicates the low level of magnesium in GFD.<sup>40</sup> Therefore, patients with CD ought to be encouraged to consume magnesium-rich foods.

## Conclusion

In general, the reduced levels of serum iron, folate, vitamin B12, vitamin D, zinc, and magnesium were documented in patients with CD. In most patients, these nutritional shortages were resolved following management with a GFD. However, the nutritional deficiencies of folate, vitamin B12, and vitamin D may persist in some patients with treated CD leading to clinical demonstrations such as anemia, neurological complications, osteoporosis, and

osteopenia. Annual screening is recommended since there is no consensus or guideline on screening the nutritional status of vitamins and minerals in CD patients.

### Ethical Approval

The study was approved by the Ethics Committee of the Research for Shiraz University of Medical Sciences (Ir.sums.med.rec.1396.27).

### Conflict of Interest Disclosure

None.

### Informed Consent

Informed consent was acquired from the parents.

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### Authors' Contributions

SMD: Supervision, concept, and design; AA: Clinical studies and data gathering; IS: Drafting and critically revising the manuscript; NR, FF, and SH: Data collection and analysis.

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