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Decreased vitamin D levels in children and adolescents with Celiac disease: A nationwide cross-sectional study

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ABSTRACT

Aims: Vitamin D deficiency results from malabsorption in Celiac disease (CD), and it may also be involved in the pathogenesis of CD. There is no clarity regarding vitamin D deficiency in CD. We investigated the frequency of vitamin D deficiency in children with CD compared with controls.

Methods: The database of the Turkish Ministry of Health was used for the cross-sectional descriptive study. Children with CD whose serum tissue transglutaminase (tTG) and serum 25-hydroxyvitamin D [25(OH)D] levels were available in the registry were included. The CD group was further subdivided into tTG (IgG and/or IgA) antibody-negative and positive subgroups. Individuals with CD were classified as compatible and non-compatible with a gluten-free diet (GFD) (GFD-compatible and GFD-non-compatible groups), respectively. Children who had no known malabsorption syndrome formed the control group.

Results: The median serum 25(OH)D level was 18.5 ng/mL in children with CD (n=6717) and 30.7 ng/mL in the control group (n=6717) ($p<0.001$). The vitamin D levels of the GFD-compatible (n=1102) and GFD-non-compatible groups (n=5615) were 19.36 ng/mL and 18.30 ng/mL, respectively ($p<0.001$). The rate of vitamin D deficiency was 56% in the CD group and 12% in the control group ($p<0.001$).

Conclusions: This study found significantly lower serum vitamin D levels in children and adolescents with CD. The results suggest children with CD should be evaluated for vitamin D levels and followed periodically.

Introduction

Celiac disease (CD) is an immune-mediated systemic disease triggered by the intake of gluten in genetically susceptible individuals. The prevalence of CD in the general population is estimated to be 1% in the world (1). Malabsorption caused by villous damage in CD may result in several nutritional deficiencies, including vitamin D (2). Exist different approaches to the routine evaluation of vitamin D levels and treatment of vitamin D deficiency in patients with CD (2).

Vitamin D is a micronutrient that plays an important role in calcium and bone metabolism (3,4). Vitamin D deficiency in the early stages of life may be associated with autoimmune diseases, including CD. Vitamin D might also be a potential protective factor for CD due to its role in immune system regulation (3-5). The variation in the frequency of CD according to the season of birth is partly explained by the seasonal fluctuation in vitamin D levels (6-11). Similarly, a higher frequency of CD in societies living in northern latitudes is partially associated with lower sun exposure (12). Apart from the role of vitamin D in the pathogenesis of CD, vitamin D deficiency observed in patients with CD has been associated with intestinal malabsorption caused (2). A low vitamin D level causes changes in bone metabolism decreasing bone mineral density and an increase in fracture risk (13).

The literature is inconsistent about the frequency of vitamin D deficiency in children with CD. There is also no consensus on the evaluation of vitamin D levels in CD. It has been emphasized that larger studies are required (2). This study evaluated the vitamin D levels in a large series consisting of children and adolescents diagnosed with CD. We investigated the frequency of vitamin D deficiency in children with CD compared with the controls.

Methods

This nationwide study was conducted using the ICD10 registry of the Turkish Ministry of Health National Electronic Database, which covers the public health insurance of more than 95% of the Turkish population, under the supervision of the Ministry of Health. We included child and adolescent (age ≤18 years) patients with CD (ICD: K90.0) who had a serum 25-hydroxyvitamin D [25(OH)D] measurement in the registry and was prescribed gluten-free nutrients provided by the Social Security Institution, between 2014 and 2021. The cases were identified using the ICD10 codes. We excluded patients without a tissue transglutaminase antibody (tTG, IgG and IgA) result. We also excluded patients who were diagnosed with other forms of malabsorption (ICD: K90.1-9). Demographic characteristics (e.g., sex, age), standardized 25(OH)D (ng/mL), and the date of the measurements (for seasonality purposes) were recorded. The CD group was further divided into tTG (IgG and/or IgA) antibody-positive and negative subgroups. Antibody-negative patients were considered compatible with a gluten-free diet (GFD) (GDF-compatible group), and positive patients as GFD-non-compatible (GFD-non-compatible group) (14).

The control group included persons who had none of the above-mentioned malabsorption syndromes, including CD, and who had a 25(OH)D measurement in the registry. Before the analyses, there were 8.317 patients and 47,072 control subjects aged 1-18 years. Since only the subjects with a vitamin D level between 1 and 50 ng/mL were included in the analysis, the sample size was reduced to 8127 in the study and 44,786 in the control group. The propensity score matching was used with the nearest neighbor method and 1:1 allocation ratio yielding 6.717 subjects in each group. Sex, age, and seasonality were considered in the propensity score matching analysis. We excluded patients and controls who were prescribed vitamin D supplements during the previous year. Figure 1 shows a flowchart of the study design.

Serum 25(OH)D levels were analyzed with the immunoassay method or high-pressure liquid chromatography in Turkey. Vitamin D deficiency was defined as <20 ng/mL (50 nmol/L), and vitamin D insufficiency was defined as 20 to 29.9 ng/mL (50-74.9 nmol/L) (15,16). 25(OH)D levels higher than 30 ng/mL were considered normal; vitamin D deficiency was defined as a serum 25(OH)D level less than 20 ng/mL, and insufficiency between 20 and 30 ng/mL.

Statistical Analysis

Statistical analyses were conducted using R software (R Core Team, 2020). The normality of data distribution was investigated using the Kolmogorov-Smirnov test. Continuous variables are presented as medians (quartile deviation). The Mann-Whitney U or Kruskal-Wallis H tests were used to test between-group differences. To prevent any p-hacking problems when studying a large sample, the r effect size was given for Mann-Whitney U tests, and the eta-squared effect size was given for the Kruskal-Wallis H tests. To determine the correlations between age and vitamin Ds, Spearman's correlation coefficients were calculated. Differences in different vitamin D-level categories were compared using Pearson's chi-square test. Dunn-Bonferroni post hoc test was conducted for pairwise comparisons. Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off value for vitamin D in the patient and control groups using the Youden J index. Two-sided $p<0.05$ was considered statistically significant.

Results

The median age of the CD group (n=6717) and control group (n=6717) was 10 years (4 quartile deviation). The proportion of male sex in the CD group and control group was 60%. The median vitamin D levels in the CD group and the control group

were 18.49 ng/mL and 30.70 ng/mL, respectively, and the difference was statistically significant (p<0.001) (Table 1).

The median vitamin D levels in the GFD-compatible (n=1102) and GFD-non-compatible (n=5615) groups were 19.36 ng/mL and 18.30 ng/mL, respectively, and the difference was statistically significant. In a post hoc analysis, vitamin D levels were significantly different (p<0.001) in all pairwise comparisons (Table 2).

Vitamin D deficiency was detected in 56% of the CD group and 12% of the control group. The percentage of patients with vitamin D insufficiency was 30% in the CD group and 35% in the control group. Vitamin D level was normal at 14% in the CD group and 53% in the control group (p<0.001) (Table 3).

There was an inverse correlation between age and vitamin D levels in the CD and control groups (r=-0.268 and r=-0.473, respectively; p<0.001).

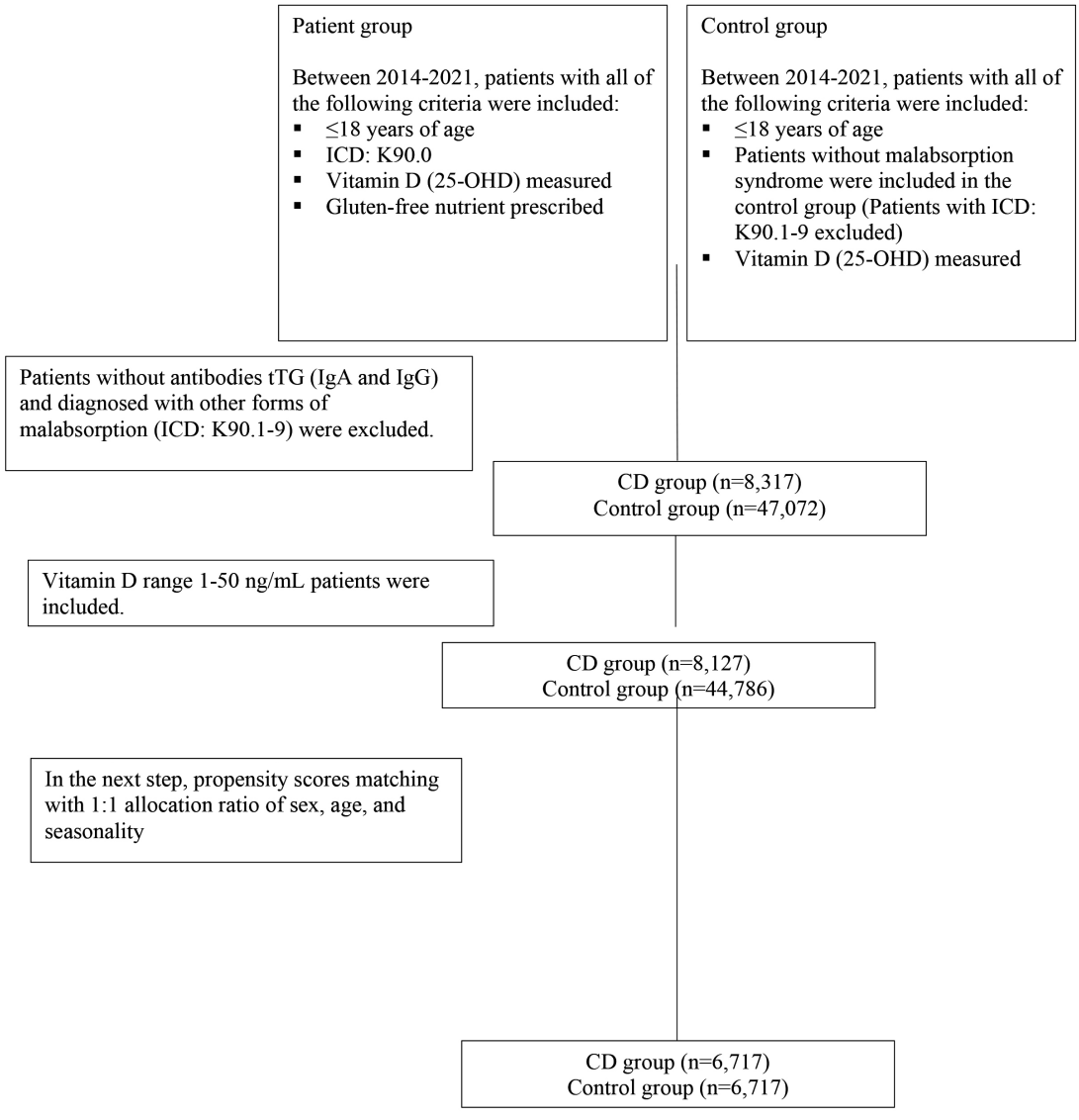

Figure 1. Flow chart of the study population
tTG: Tissue transglutaminase antibody, CD: Celiac disease

Table 1. Serum 25(OH)D levels in the CD group and control group

	Overall (n=13,434)	CD group (n=6,717)	Control group (n=6,717)	p value
Vitamin D, ng/mL, median (quartile deviation)	24.78 (8.18)	18.49 (6.39)	30.70 (7.19)	**<0.001***

*Mann-Whitney U test; means statistically significant. 25(OH)D: 25-hydroxyvitamin D, CD: Celiac disease

Table 2. Serum 25(OH)D levels in the CD group and control group according to gluten-free diet compatibility

	CD group (n=6,717)		Control group (n=6,717)	p value
	Non-compatible group (n=5,615)	Compatible group (n=1,102)		
Vitamin D, ng/mL, median (quartile deviation)	18.30 (6.36)	19.37 (6.50)	30.70 (7.19)	<0.001*

Post-hoc analysis for *Kruskal-Wallis H test; differences in the level of vitamin D significant in all pairwise comparisons (p<0.001). CD: Celiac disease, 25(OH)D: 25-hydroxyvitamin D

Table 3. Comparison of the rates of vitamin D deficiency, insufficiency, and normal vitamin D levels between the CD group control group

	Vitamin D deficiency (vitamin D <20 ng/mL)	Vitamin D insufficiency (vitamin D 20-29.9 ng/mL)	Normal vitamin D (vitamin D >30 ng/mL)	p value
CD group n, (%)	3,774 (56)	1,997 (30)	938 (14)	<0.001*
Control group n, (%)	820 (12)	2,349 (35)	3,528 (53)	

*Pearson chi-square test, CD: Celiac disease

Figure 2 shows the results of the area under the ROC curve analysis. According to Youden's index, the cut-off value of ≤23.195 ng/mL for vitamin D had 68% sensitivity and 80% specificity to predict the classification of an individual as CD.

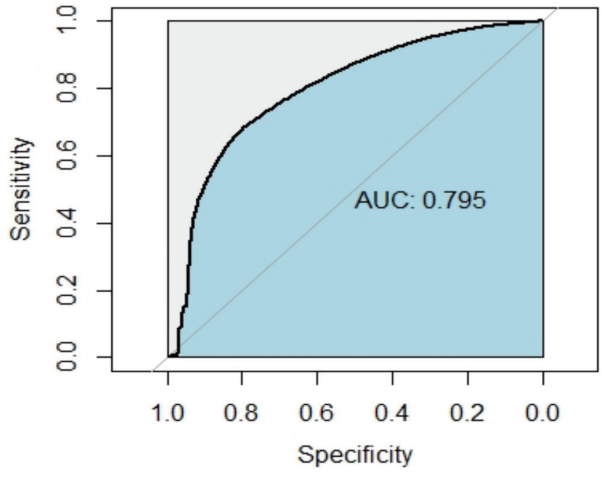

Figure 2. The cut-off value of vitamin D for predicting the CD group vs. control group. For vitamin D AUC=0.795, p<0.001, cut-off value 23.195 ng/mL, 68% sensitivity, 80% specificity
AUC: Area under the curve, CD: Celiac disease

Discussion

This study found lower vitamin D levels among patients with CD than the controls. The proportion of patients with normal vitamin D levels was 12% in the CD group and 56% in the control group. However, in patients with CD, vitamin D levels in patients with good adherence to a GFD were higher than in patients with poor GFD adherence, suggesting still lower vitamin D levels among CD patients with worse GFD compliance.

Several studies have concluded controversial results on serum 25(OH)D levels at the time of CD diagnosis, and while receiving GFD therapy in patients followed up with CD (17,18). Recently, Ahlawat et al. (19) reported that there was no difference between 25(OH)D levels in patients with newly diagnosed CD and controls. Similarly, Villanueva et al. (20) reported that vitamin D levels in patients with CD were not different from the controls. Lerner et al. (21) compared the vitamin D levels in patients with newly diagnosed CD and children with non-specific abdominal pain and observed no difference. In contrast, in the study by Lionetti et al. (2), vitamin D levels in children and adolescents with CD were found to be lower at the time of diagnosis compared with the control group. In this study, the frequency of vitamin D deficiency in patients with CD was 31%, whereas this rate was 12% in the control group. In previous retrospective studies conducted with a limited number of cases, the frequency of vitamin D deficiency in patients with CD ranged from 27% to 70% (22-24).

Consistent with the literature, the frequency of vitamin D deficiency in the current study was 56% in patients with CD and 12% in the control group. Ciacci et al. (17) reported lower vitamin D levels in adult patients with newly diagnosed CD and in adult patients with good adherence to a GFD. In our study, we observed that the vitamin D levels in children and adolescents with CD were lower than in the controls. Similarly, vitamin D levels in children and adolescents with good adherence to GFD were higher than in patients with poor GFD adherence and lower than in the control group. Similar to our study, Lu et al. (25) reported that patients with CD had lower vitamin D levels. Additionally, they found that patients with CD receiving a GFD had vitamin D levels close to those of the control group. The author group hypothesized that vitamin D might play a potential role in the pathogenesis of CD (25). Deora et al. (22) reported that micronutrients other than vitamin D and iron returned to

normal in the 18th month in the follow-up of patients with CD who were started a GFD, but they remained at a suboptimal level even though there was an increase in vitamin D and iron levels. In our study, despite a slightly higher level of vitamin D with the GFD, it was still suboptimal.

There is no clear consensus on the routine evaluation of 25(OH)D level and vitamin D supplementation in patients with CD (2). In 2016, The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition recommended serum 25(OH)D measurement at the time of diagnosis and annual follow-up after celiac serology returns to normal in children with CD (26). The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition have not published any recommendations in this regard. The results obtained in our study with many patients suggest the necessity for evaluating vitamin D in CD. It is also recommended to ensure the maintenance of vitamin D levels at normal levels in all children and adolescents (2,3). Our analysis also showed that, although the vitamin D levels in patients with CD were higher with GFD, it was still suboptimal. This result points to the importance of vitamin D therapy in patients with CD.

The potential causes of lower levels vitamin D levels in patients with CD are controversial. Traditionally, it is thought to be due to the malabsorption of fat-soluble vitamins (2). Relatively improved vitamin D levels in patients CD with a GFD in our study supports this notion. However, another interesting hypothesis is that vitamin D deficiency observed in the early stages of life may play a role in the pathogenesis of CD rather than its outcome (25,27). Various conditions such as genomic polymorphism and variability in the gut microbiota observed in patients with CD contribute to the low vitamin D levels concerning low vitamin D synthesis (2).

The limitations of our study are that it was designed retrospectively, and the data were obtained through the ICD codes. Another limitation may be the potential differences in the measurement of vitamin D levels in different laboratories. The use of vitamin D supplements was retrieved from the prescription records, limiting the exact knowledge of their use by the patients. Data such as obesity, which may affect vitamin D levels, and geographical features of the region where the patients lived were also not evaluated. Among the strengths of the current study are its large sample size, representation of all regions across the country, and children of all ages and weights.

Conclusion

In conclusion, this study showed lower vitamin D levels in children with CD. Although some improvement was observed in vitamin D levels in patients who were GFD-compatible, it was still lower than in the control group. Due to the close relationship between bone and skeletal health and CD, we suggest that all children with CD be evaluated for vitamin D levels at diagnosis and periodically after that and that children with a deficiency should be managed properly.

Ethics

Ethics Committee Approval and Informed Consent: This nationwide study was conducted with the permission of the Ministry of Health. Ethics committee approval and informed consent were not required for national data studies.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Z.A., M.K., Ş.S.E., O.Ç., M.M.Ü., N.A., Ş.B., Design: Z.A., M.K., Ş.S.E., O.Ç., E.İ., M.Ç., N.A., Ş.B., Data Collection or Processing: Z.A., M.K., Ş.S.E., O.Ç., E.İ., M.M.Ü., N.A., Ş.B., Analysis or Interpretation: Z.A., M.K., Ş.S.E., N.B., E.İ., M.M.Ü., M.Ç., N.A., Ş.B., Literature Search: Z.A., M.K., Ş.S.E., N.B., M.Ç., N.A., Writing: Z.A., M.K., Ş.S.E., N.B., O.Ç., E.İ., M.M.Ü., M.Ç., N.A., Ş.B.

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