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# Factors Associated with Low Bone Mineral Density at the Time of Diagnosis in Children with Celiac Disease

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**What is already known on this topic?**

It has been reported in many studies that some children diagnosed with Celiac disease (CD) have low bone mineral density (BMD). However, which subgroup of children with CD is at risk for low BMD is still controversial.

**What this study adds?**

This study showed that in children newly diagnosed with CD, age at diagnosis, gender, body size, Celiac symptoms, biochemical parameters, tissue transglutaminase antibody-IgA level, human leukocyte antigen type and histopathological stage have no predictive values for low BMD.

## Abstract

**Objective:** It has been reported that bone mineral density (BMD) is decreased in children with Celiac disease (CD) compared to their healthy peers. The aim of this study was to reveal possible risk factors for low BMD in Turkish children newly diagnosed with CD.

**Methods:** Eighty-six patients (2-18 years old) with CD were included in this retrospective study. The relationship between their lumbar BMD z-scores calculated according to their chronological age (CA) and height age (HA) and their clinical, laboratory [biochemical parameters, tissue transglutaminase antibody-IgA (TTGA) levels, human leukocyte antigen (HLA) types] and histopathological parameters were evaluated.

**Results:** The mean age of the patients at diagnosis was 8.06 ± 4.08 years. The BMD z-score CA was ≤-2 standard deviation (SD) in 26.7% of the patients. The BMD z-score HA was ≤-2 SD in 12.8% of the patients. The BMD z-score HA only correlated with their age at diagnosis of CD ($r_s$ value 0.269). However, there was no statistically difference between the BMD z-score HA >-2 SD and ≤-2 SD subgroups regarding their clinical, laboratory and histopathological parameters.

**Conclusion:** Low BMD is common in children with newly diagnosed CD. Age at diagnosis, gender, body size, Celiac symptoms, biochemical parameters, TTGA level, HLA type, and histopathological stage had no predictive values in terms of low BMD in this patient group.

**Keywords:** Low bone mineral density, Celiac disease, children, risk factors

## Introduction

Celiac disease (CD) is a chronic disease characterized by inflammation of the proximal small intestine triggered by gluten in wheat, barley and rye in genetically predisposed individuals (1,2). Patients may present with typical findings such as abdominal distension, inability to gain weight, loss of appetite, vomiting, and diarrhea, or with atypical findings such as short stature, treatment-resistant iron deficiency anemia, and/or delayed puberty (3). One of the most common complications of CD is metabolic bone disease (4). It has been reported in many studies that some of the children diagnosed with CD have low bone mineral density (BMD) (5,6,7). However, the necessity of screening

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for low BMD with dual energy X-ray absorptiometry (DEXA) method at diagnosis or during follow-up in pediatric CD is still controversial. In order to decide who should be screened in a cost-effective way, we aimed to investigate which subgroups of children with CD are at risk of low BMD. In the literature, several factors including hypocalcemia due to malabsorption, vitamin D deficiency, secondary hyperparathyroidism, low physical activity due to fatigue, autoimmune factors, and inflammation have been suggested to be associated with low BMD. However, in most of these studies, the number of cases was limited and results were varied (4,8,9,10,11,12). In a recent retrospective cohort study, the only difference between the group with the BMD z-score of <-2 standard deviation (SD) and the rest of the cases was the low (<-0.4) standard deviation of the body mass index (BMI) (13).

In this study, it was aimed to determine the frequency of low BMD at the time of diagnosis and to investigate those parameters which can predict low BMD in Turkish children diagnosed with CD.

## Methods

In this retrospective study, a total of 99 patients, aged 2-18 years, who were diagnosed with CD histopathologically and whose BMD was measured at admission to İnönü University Pediatric Gastroenterology, Hepatology and Nutrition Clinic, between 2010 and 2019, were determined. Following this, a total of 13 patients with an additional diagnosis of type 1 diabetes mellitus, hypothyroidism, hyperthyroidism, Turner syndrome and/or precocious puberty (which could affect BMD) were excluded from this study in order to avoid interpretation difficulties. For the remaining 86 patients, the demographic and clinical features of the patients at diagnosis (age, gender, complaints at presentation, height, weight and BMI), laboratory data [serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), 25-OH vitamin D, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin, vitamin B12, folate, zinc, tissue transglutaminase antibody-IgA (TTGA), human leukocyte antigen (HLA)-DQ2, and HLA-DQ8], histopathological results of endoscopic biopsies, and lumbal (L1-L4) BMD levels measured by the DEXA method were examined from the hospital information system, retrospectively.

The diagnosis of CD was made according to the revised criteria of the European Committee of Pediatric Gastroenterology, Hepatology and Nutrition (14). TTGA titer was considered positive if it was increased three times or more above the laboratory upper limit of 18 AU/mL. The modified Marsh-Oberhuber classification was used for histopathological staging (15) and patients with stage ≥2 were diagnosed with CD. Type of admission was classified as typical in patients presenting with classical gastrointestinal symptoms such as chronic diarrhea and it was classified as atypical in those who presented with other symptoms, such as short stature or anemia (14). The SD scores of the weight, height, and BMI values of the patients [weight SD (WSD), height SD (HSD), BMI SD] and height age (HA) were calculated according to the Turkish percentile charts (16,17). BMD measurements were performed using a Hologic 4500w (Bedford, MA, USA) bone densitometer device. BMD z-scores were calculated according to chronological age (CA) and HA using lumbar 1-4 BMD (g/cm$^2$) values. BMD z-scores were calculated by reference to the BMD data of healthy Turkish children in the study of Goksen et al. (17,18). Since the z-score under the age of two could not be calculated by these data, only those cases whose CA and/or HA were equal to or above two years of age were included in this study. The correlations between the BMD z-scores and the clinical, laboratory, and histopathological parameters according to CA and HA were examined. A BMD z-score ≤-2 SD was considered as low BMD (19). The patients were divided into two groups; namely, those with a BMD z-score >-2 SD and ≤-2 SD according to CA and HA, and the groups were compared in terms of their clinical, laboratory and histopathological parameters.

Ethical approval for the study was obtained from İnönü University Scientific Research Ethics Committee (decision no: 2021/1536, date: 01.06.2021). The study was carried out in accordance with the principles of the Declaration of Helsinki.

Since this study was retrospective, informed consent was not obtained from the patients.

### Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 20.0 software. Normality of distribution for the data was tested using visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses are presented as percentile, mean and standard deviation. Correlation analysis was performed to determine whether there was a relationship between two numerical variables, and if so, the direction and severity of this relationship. Spearman rank correlation was preferred for correlation analysis as some numerical data were not normally distributed. Spearman rank difference correlation coefficient was expressed as $r_s$. Normally distributed numerical data were compared using the independent samples t-test and non-normally distributed numerical data were compared using the Mann-Whitney U test. Pearson's chi-squared test was used to compare the frequency rates

of categorical variables. A value of $p < 0.05$ was considered statistically significant. Logistic regression analysis was performed to evaluate whether weight and height z-scores pose a risk for low BMD.

## Results

The mean age at diagnosis of the patients (67 girls, 19 boys) was 8.06 ± 4.08 (2.25-17.71) years. The mean WSD was -1.59 ± 1.20 SD, mean HSD was -1.66 ± 1.29 SD, and HSD was < -2 SD in 33.7% of the patients at the time of diagnosis.

BMD z-score according to CA was found to be ≤-2 SD in 26.7% of the patients. BMD z-score according to HA was found to be ≤-2 SD in 12.8%.

When the correlations between BMD z-scores (according to CA and HA) and the clinical and laboratory parameters were examined, a positive correlation was found between the BMD z-score CA and WSD and HSD ($r_s$: 0.373 and 0.380 respectively), a negative correlation was found between the BMD z-score CA and serum ALT and AST levels ($r_s$: -0.246 and -0.296 respectively). In addition, a positive correlation was found between the BMD z-score HA and age at diagnosis ($r_s$: 0.269) (Table 1).

**Comparison between the BMD z-score CA groups:** When the BMD z-score CA groups (> -2 SD and ≤-2 SD groups) were compared in terms of their clinical features; it was found that the mean WSD and HSD values were different between the groups (Table 2) and it was significantly lower in the group with BMD z-score CA ≤-2 SD. Logistic regression revealed that WSD between -2 SD and -3 SD had 10.5 Odds ratio (OR) [1.12-97.91, 95% confidence interval (CI)], WSD < -3 SD had 36.75 OR (3.50-386.30, 95% CI), and HSD < -2 SD had 4.62 OR (1.65-12.93, 95% CI) for BMD z-scores CA ≤-2 SD.

There were no differences between the groups in terms of age at diagnosis, gender, BMI SD, and type of admission (Table 2).

When the BMD z-score CA groups were compared in terms of their laboratory findings; the AST level was significantly higher, and the vitamin B12 and P levels were significantly lower in the BMD z-score CA ≤-2 SD group than the > -2 SD group. There was no difference between the groups in terms of the other biochemical parameters, HLA DQ2 or DQ8 positivity rates, and the distribution of histopathological stages.

**Comparison between the BMD z-score HA groups:** There were no differences between the groups in terms of their clinical parameters, laboratory parameters, genotype characteristics or the distribution of their histopathological stages (Table 3).

**Table 1. The relationship of BMD z-score with clinical and laboratory parameters at the time of diagnosis**

| | BMD z-score CA | | BMD z-score HA | |
|---|---|---|---|---|
| | p | $r_s$ | p | $r_s$ |
| **Age at diagnosis** | 0.529 | -0.069 | **0.015** | **0.269** |
| **Weight SDS** | **0.000** | **0.373** | 0.959 | 0.006 |
| **Height SDS** | **0.000** | **0.380** | 0.404 | -0.094 |
| **BMI SD** | 0.393 | 0.094 | 0.337 | 0.108 |
| **Serum calcium mg/dL** | 0.345 | 0.104 | 0.179 | -0.153 |
| **Serum phosphorus mg/dL** | 0.131 | 0.168 | 0.876 | -0.018 |
| **Serum alkaline phosphatase U/L** | 0.192 | 0.156 | 0.506 | 0.081 |
| **Serum 25-OH vitamin D ng/mL** | 0.262 | -0.128 | 0.872 | -0.019 |
| **Serum albumin g/dL** | 0.162 | 0.157 | 0.387 | 0.100 |
| **Serum alanine aminotransferase U/L** | **0.025** | **-0.246** | 0.616 | -0.057 |
| **Serum aspartate aminotransferase U/L** | **0.007** | **-0.296** | 0.130 | -0.172 |
| **Serum ferritin ng/mL** | 0.989 | -0.003 | 0.871 | -0.031 |
| **Serum vitamin B12 pg/mL** | 0.403 | 0.102 | 0.563 | 0.073 |
| **Serum folate ng/mL** | 0.275 | 0.154 | 0.401 | 0.121 |
| **Serum zinc mg/dL** | 0.974 | 0.004 | 0.232 | -0.142 |
| **TTGA AU/mL** | 0.817 | -0.025 | 0.344 | 0.106 |

Spearman rank correlation test. $P < 0.05$ is significant. $r_s$: Spearman rank difference correlation coefficient.
SDS: standard deviation score, BMI SD: body mass index standard deviation, HA: height age, BMD: bone mineral density, CA: chronological age, TTGA: tissue transglutaminase antibody

**Table 2. Comparison of BMD z-score CA subgroups according to clinical, laboratory and histopathological features at diagnosis**

| | | BMD z-score by chronological age | | |
|---|---|---|---|---|
| **Variable** | **All patients n = 86** | **> -2 SD n = 63** | **≤-2 SD n = 23** | **p** |
| **Age at diagnosis** | 8.06 ± 4.08 | 7.79 ± 3.90 | 8.80 ± 4.58 | NS* |
| **Female**<br>**Male** | 67 (77.9%)<br>19 (22.1%) | 47 (74.6%)<br>16 (25.4%) | 20 (87%)<br>3 (13%) | NS** |
| **Typical presentation** | 25 (29.1%) | 18 (28.6%) | 7 (30.4%) | NS** |
| **Weight SDS** | -1.59 ± 1.20 | -1.27 ± 1.05 | -2.46 ± 1.18 | **< 0.001*** |
| **Height SDS** | -1.66 ± 1.29 | -1.32 ± 1.16 | -2.64 ± 1.16 | **< 0.001*** |
| **BMI SD** | -0.84 ± 1.09 | -0.73 ± 0.98 | -1.16 ± 1.32 | NS* |
| **Serum calcium mg/dL** | 9.41 ± 0.50 | 9.46 ± 4.22 | 9.30 ± 0.67 | NS* |
| **Serum phosphorus mg/dL** | 4.89 ± 0.70 | 4.99 ± 0.65 | 4.62 ± 0.75 | **0.032*** |
| **Serum alkaline phosphatase U/L** | 208.13 ± 69.60 | 209.19 ± 67.53 | 205.16 ± 76.93 | NS* |
| **Serum 25-OH vitamin D ng/mL** | 21.56 ± 13.40 | 20.40 ± 11.33 | 24.74 ± 17.90 | NS* |
| **Serum albumin g/dL** | 3.89 ± 0.40 | 3.93 ± 0.34 | 3.76 ± 0.55 | NS* |
| **Serum alanine aminotransferase U/L** | 20.61 ± 10.38 | 19.65 ± 9.83 | 23.27 ± 11.61 | NS* |
| **Serum aspartate aminotransferase U/L** | 31.48 ± 10.35 | 29.60 ± 8.45 | 36.68 ± 13.26 | **0.027*** |
| **Serum ferritin ng/mL** | 13.27 ± 13.38 | 14.07 ± 14.62 | 10.40 ± 7.52 | NS* |
| **Serum vitamin B12 pg/mL** | 349.65 ± 181.95 | 378.64 ± 193.44 | 253.62 ± 86.88 | **0.001*** |
| **Serum folate ng/mL** | 8.89 ± 4.25 | 9.35 ± 3.97 | 7.36 ± 4.94 | NS* |
| **Serum zinc mg/dL** | 64.71 ± 13.39 | 64.48 ± 13.15 | 65.33 ± 14.35 | NS* |
| **TTGA AU/mL** | 118.73 ± 55.86 | 116.36 ± 51.75 | 125.20 ± 66.71 | NS* |
| **HLA DQ2 positive** | 66 (76.7%) | 47 (74.6%) | 19 (82.6%) | NS** |
| **HLA DQ8 positive** | 12 (14.0%) | 10 (15.9%) | 2 (8.2%) | NS** |
| **Histopathological stages**<br>**2**<br>**3A**<br>**3B**<br>**3C** | <br>6 (7.0%)<br>21 (24.4%)<br>38 (44.2%)<br>21 (24.4%) | <br>5 (7.9%)<br>19 (30.2%)<br>26 (41.3%)<br>13 (20.6%) | <br>1 (4.3%)<br>2 (8.7%)<br>12 (52.2%)<br>8 (34.8%) | NS** |

P < 0.05 is significant. P > 0.05 is not significant (NS). *Independent Student's t-test. **Crosstab, chi-squared tests.
SDS: standard deviation score, SD: body mass index standard deviation score, TTGA: tissue transglutaminase antibody-IgA, HLA: human leukocyte antigen, CA: chronological age, BMD: bone mineral density

## Discussion

In the literature, it has been reported that BMD was found to be lower in those children with CD compared to healthy children (5,6,7,12).

In various studies, it has been reported that the rate of children with a BMD z-score CA <-2 SD was 10.8-16% at the time of diagnosis (11,12). Kalayci et al. (4), in an earlier study on 16 pediatric patients diagnosed with CD, reported this rate to be much higher (50%). However, in a recent large-series study conducted in the USA, the rate of cases with a BMD z-score <-2 SD was reported to be lower than in other studies (6.8%) (13). As can be seen, varying rates of low BMD in children with CD have been reported in different societies or at different centers or different times even in the same society. In our study, BMD z-scores CA were found to be ≤-2 SD in 26.7% of the children with CD at the time of diagnosis.

Classically used areal BMD measurements are closely related to age and height. Since BMD increases with age in childhood, it is evaluated by calculating the z-score according to age and gender. Since the BMD z-score calculated according to CA is found to be misleadingly lower in children with short-stature, it is recommended to correct the BMD z-score according to the height or HA in these children (20). Short stature is common in children diagnosed with CD at the time of admission. In our study, short stature was found in 33.7% of the cases in our study, and therefore, the BMD z-scores were calculated according to both CA and HA. In most of the studies evaluating BMD in children with CD, the BMD z-score was calculated according to CA (4,11,13). Tuna Kırsaçlıoğlu et al. (12), found short stature in 37.8% of 37 pediatric patients diagnosed with CD, and when they calculated the BMD z-score according to HA at the time of diagnosis, they found <-2 SD in 2.7%. In our study, BMD z-score HA was found to be ≤-2 SD in 12.8% of the cases.

**Table 3. Comparison of BMD z-score HA subgroups according to clinical, laboratory and histopathological features at diagnosis**

| | | BMD z-score by height age | | |
|---|---|---|---|---|
| **Variable** | **All patients n = 81** | **> -2 SD n = 70** | **≤-2 SD n = 11** | **p** |
| **Age at diagnosis** | 8.40 ± 3.98 | 8.56 ± 4.02 | 7.35 ± 3.68 | NS* |
| **Female** | 62 (76.5%) | 54 (77.1%) | 8 (72.7%) | NS** |
| **Male** | 19 (23.5%) | 16 (22.9%) | 3 (27.3%) | |
| **Typical presentation** | 23 (28.4%) | 19 (27.1%) | 4 (36.4%) | NS** |
| **Weight SDS** | -1.59 ± 1.22 | -1.55 ± 1.28 | -1.81 ± 0.83 | NS* |
| **Height SDS** | -1.64 ± 1.31 | -1.64 ± 1.36 | -1.61 ± 1.03 | NS* |
| **BMI SD** | -0.86 ± 1.10 | -0.79 ± 1.07 | -1.32 ± 1.18 | NS* |
| **Serum calcium mg/dL** | 9.42 ± 0.48 | 9.39 ± 0.43 | 9.56 ± 0.74 | NS* |
| **Serum phosphorus mg/dL** | 4.87 ± 0.68 | 4.87 ± 0.66 | 4.85 ± 0.85 | NS* |
| **Serum alkaline phosphatase U/L** | 210.39 ± 70.01 | 212.64 ± 70.66 | 197.10 ± 68.04 | NS* |
| **Serum 25-OH vitamin D ng/mL** | 21.70 ± 13.38 | 21.80 ± 13.97 | 21.11 ± 9.72 | NS* |
| **Serum albumin g/dL** | 3.89 ± 0.39 | 3.89 ± 0.39 | 3.90 ± 0.43 | NS* |
| **Serum alanine aminotransferase U/L** | 20.49 ± 10.61 | 19.69 ± 10.00 | 26.00 ± 13.45 | NS* |
| **Serum aspartate aminotransferase U/L** | 30.73 ± 9.63 | 30.03 ± 9.55 | 35.60 ± 9.19 | NS* |
| **Serum ferritin ng/mL** | 13.49 ± 13.69 | 13.49 ± 13.69 | - | NS* |
| **Serum vitamin B12 pg/mL** | 351.37 ± 181.30 | 347.83 ± 186.30 | 380.71 ± 140.47 | NS* |
| **Serum folate ng/mL** | 8.69 ± 4.18 | 8.70 ± 3.88 | 8.57 ± 6.97 | NS* |
| **Serum zinc mg/dL** | 65.21 ± 13.17 | 64.69 ± 12.93 | 68.09 ± 14.75 | NS* |
| **TTGA AU/mL** | 120.34 ± 56.73 | 122.63 ± 59.47 | 105.77 ± 32.68 | NS* |
| **HLA DQ2 positive** | 62 (76.5%) | 52 (74.3%) | 10 (90.9%) | NS** |
| **HLA DQ8 positive** | 10 (12.3%) | 10 (14.3%) | 0 (0%) | NS** |
| **Histopathological stages** | | | | |
| **2** | 6 (7.4%) | 5 (7.1%) | 1 (9.1%) | |
| **3A** | 19 (23.5%) | 17 (24.3%) | 2 (18.2%) | NS** |
| **3B** | 36 (44.4%) | 31 (44.3%) | 5 (45.5%) | |
| **3C** | 20 (24.7%) | 17 (24.3%) | 3 (27.3%) | |

P < 0.05 is significant. P > 0.05 is not significant (NS). *Independent Student's t-test. **Crosstab, chi-squared tests.
SDS: standard deviation score, BMI SD: body mass index standard deviation, TTGA: tissue transglutaminase antibody-IgA, HLA: human leukocyte antigen, BMD: bone mineral density, HA: height age

In the literature, there are varying results regarding the relationship between age at the time of CD diagnosis and BMD z-score CA. Turner et al. (11) found an inverse correlation between age at diagnosis and BMD z-score. In other studies, no relationship was found between the age at diagnosis and BMD z-score CA (9,10,13). In our study, no correlation was found between BMD z-score CA and age at diagnosis either. Although we detected a weak positive correlation between the age at diagnosis and BMD z-score HA, there was no statistically significant difference between the BMD z-score HA > -2 SD subgroup and the ≤-2 SD subgroup.

The studies evaluating the relationship between BMD z-score and gender or presenting features at the time of admission have failed to show the effect of these parameters on the BMD z-score (11,12,13). Similarly, in our study, no significant difference was found between the BMD z-score subgroups regarding these parameters. Puberty has positive effects on BMD in children, and delayed puberty is associated with low BMD. However, Tuna Kırsaçlıoğlu et al. (12) reported that 27 (72.9%) pediatric Celiac patients were prepubertal at presentation, but their BMD z-scores did not differ from those of pubertal patients. Since pubertal staging information could not be found in the medical records of most of our patients, the effect of puberty on BMD z-scores could not be interpreted in our study. Prospective studies which include pubertal evaluation are needed. There was a positive correlation between BMD z-score CA and WSD and HSD. It is known that the BMD z-score CA shows a decrease as body size decreases . When the BMD z-score was calculated according to HA, no difference was found between the groups in terms of WSD and HSD. In the study of Webster et al. (13), BMI SD was found to be significantly lower in cases with low BMD z-scores (< -2 SD). In our study, it was observed that the BMI SD values were lower in the BMD z-score ≤-2 SD groups for CA and HA. However, there was no statistically significant difference between the

groups in terms of BMI SD. The limited number of cases in our study may have affected this result.

In some studies, when evaluating the relationship between biochemical parameters and BMD at the time of diagnosis of CD, a negative correlation was found between PTH level and BMD and it was suggested that low BMD in CD was associated with vitamin D and/or Ca deficiency (4,8). However, in other studies, no correlation was found between the BMD z-scores at diagnosis and serum Ca, P, ALP, PTH, or vitamin D levels (9,10,13). Similarly, in our study, no correlation was found between BMD z-scores for either CA and HA and Ca, P, ALP, or vitamin D levels. There was no difference between the BMD z-score subgroups in terms of these parameters either. This indicates that there may be other factors affecting BMD in patients with CD, and that normal findings of Ca metabolism parameters do not exclude low BMD. Due to the retrospective design of our study, serum PTH could not evaluated since serum PTH levels had not been measured in most of our cases.

One of the extra intestinal findings which can be seen in the course of CD is liver involvement. While isolated elevation of transaminases is frequently observed, severe liver pathology or other accompanying chronic liver diseases (autoimmune, viral or metabolic) can be detected less frequently (21). In the literature, no study was found evaluating the relationship between BMD z-score and liver functions in patients with CD. In our study, the mean ALT levels were within normal ranges at the time of diagnosis, and there was no statistically significant difference between the BMD z-score subgroups for CA and HA. The mean AST level was found to be higher (slightly above the upper limit), in those patients with BMD z-score ≤-2 SD according to CA. Serum AST levels were not statistically different between the BMD z-scores for the HA subgroups. In our study, no correlation was found between BMD z-score and serum albumin, ferritin, vitamin B12, folic acid, zinc, or TTGA levels. Similarly, in the study of Webster et al. (13), no correlation was found between low BMD and serum albumin or TTGA levels.

HLA DQ2 alleles are detected in more than 90% of Celiac patients, and HLA DQ8 alleles are found in others (21). There was no difference between the BMD z-score CA and HA subgroups in terms of HLA DQ2 or DQ8 positivity rates. It was thought that this lack of difference was due to the high rates of these alleles in our cases. We could not find any other study evaluating this issue.

The relationship between BMD and histopathological staging at the time of diagnosis was evaluated in several studies and various results have been obtained. Lewis and Scott (22) did not report any relationship between BMD and the degree of villous atrophy (mild-severe) in 43 adults diagnosed with CD. In two different studies, it was shown that BMD is lower in those patients with histopathological stage Marsh 3 compared to those with Marsh 1-2 (23,24). In our study, no correlation was found between BMD z-scores (both CA and HA) and histopathological stage. In the studies which found a relationship between BMD and histopathological stage, BMD was reported to vary between the patient groups with Marsh stage 1-2 and Marsh stage 3. However, nowadays, the diagnosis of CD requires the presence of at least Marsh stage 2 histopathological findings. In our study, the cases with histopathological Marsh stage 2 or above were included, and Marsh stage 3 (a, b, c) was detected in more than 90% of the cases. Therefore, it was thought that we have a similar patient profile and similar results with the studies which evaluated the relationship between BMD z-scores and Marsh stage 3 subgroups (22). Based on these findings, we suggest that BMD is affected more negatively as histopathological findings become more severe, while the degree of low BMD does not differ between subgroups when the pathology is compatible with stage 3 disease.

### Study Limitations

The strengths of our study include that it was conducted on a higher number of patients compared to most studies in the literature (especially from our country) and the relationships of more parameters with BMD were evaluated in our study, compared to previous studies. In addition, the BMD z-scores were calculated according to both CA and to HA for all parameters. Also, patients with additional diseases which could have affected BMD were excluded from this study. The limitations include; firstly, the fact that some parameters (pubertal stage, PTH levels) could not be evaluated due to the retrospective nature of this study, and the second is that the patients were not homogeneously distributed in terms of histopathological stage.

## Conclusion

In conclusion, low BMD is common in children with CD at the time of diagnosis. When the BMD z-scores are calculated only according to CA, the frequency of low BMD seems misleadingly higher. However, when the BMD z-scores are corrected for HA, the frequency is slightly lower, though still high. Age at diagnosis, gender, body size, Celiac symptoms, biochemical parameters, TTGA level, HLA type and histopathological stage have no predictive value for low BMD. Further studies are needed to determine consistent parameters which predict low BMD in patients with CD. We recommend evaluating BMD at diagnosis in newly diagnosed pediatric Celiac patients until consistent factors

which can predict low BMD are identified. If these risk factors associated with low BMD can be found, switching to the assessment of only high risk groups will reduce costs.

### Ethics

**Ethics Committee Approval:** Ethical approval for the study was obtained from İnönü University Scientific Research Ethics Committee (decision no: 2021/1536, date: 01.06.2021).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Fatma İlknur Varol, Şükrü Güngör, Mukadder Ayşe Selimoğlu, Concept: Emine Çamtosun, Fatma İlknur Varol, Design: Emine Çamtosun, Data Collection or Processing: Emine Çamtosun, Fatma İlknur Varol, Şükrü Güngör, Mukadder Ayşe Selimoğlu, Analysis or Interpretation: Emine Çamtosun, Fatma İlknur Varol, Şükrü Güngör, Mukadder Ayşe Selimoğlu, Literature Search: Emine Çamtosun, Fatma İlknur Varol, Writing: Emine Çamtosun, Fatma İlknur Varol, Şükrü Güngör, Mukadder Ayşe Selimoğlu.

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