







# Risk Factors for Decreased Bone Density in Adults with Celiac Disease

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## Abstract

**Background:** Celiac disease (CD) is an autoimmune disease characterized by inflammation in the intestine, causing atrophy of the mucosal villi of the small intestine. Celiac disease can manifest with various signs and symptoms, including extra-intestinal symptoms such as osteopenia and osteoporosis.

**Objectives:** Our study aimed to determine the frequency of osteopenia/osteoporosis in newly diagnosed CD cases and to evaluate the effect of different independent variables on the development of osteopenia/osteoporosis in these patients.

**Methods:** Adult patients with CD who were referred to a celiac clinic were evaluated for osteopenia/osteoporosis using dual-energy X-ray absorptiometry. This cross-sectional analytical study took place from October 2017 to July 2022. Logistic regression analysis was used to assess the odds ratio (OR) of different independent variables for osteopenia/osteoporosis.

**Results:** A total of 302 patients enrolled in this study, with 64.2% being female and 35.8% male. The mean  $\pm$  SD age was  $29.73 \pm 12.39$ . Overall, 71.2% of patients had osteopenia or osteoporosis. The odds of developing osteopenia/osteoporosis were significantly higher in participants older than 30 years (OR: 2.19; 95% CI: 1.22 - 3.92;  $P = 0.008$ ), underweight patients (OR: 2.38; 95% CI: 1.30 - 4.34;  $P = 0.005$ ), and those with histologically severe atrophy (OR: 2.22; 95% CI: 1.14 - 4.32;  $P = 0.019$ ). The mean  $\pm$  SD serum levels of 25-hydroxy vitamin D in CD patients without and with osteopenia/osteoporosis were  $34.0 \pm 17.1$  ng/mL and  $25.8 \pm 14.2$  ng/mL, respectively. Participants with normal levels of 25-hydroxy vitamin D had a significantly lower OR of developing osteopenia/osteoporosis than patients with vitamin D deficiency (OR: 0.37; 95% CI: 0.21 - 0.62;  $P < 0.001$ ). Other variables, including gender, anti-tTG levels, and GI manifestations, did not significantly increase the OR of developing osteopenia/osteoporosis.

**Conclusions:** The present study showed that increasing age, weight loss, severe villous atrophy, and low levels of vitamin D can significantly increase the OR of developing osteopenia/osteoporosis in CD patients. Until further studies are conducted, bone mineral density (BMD) evaluation is especially recommended in these high-risk subgroups of CD patients.

**Keywords:** Celiac Disease, Osteoporosis, Osteopenia, Bone Density, Histology

## 1. Background

Celiac disease (CD) is an autoimmune disease characterized by inflammation in the intestine, causing atrophy of the mucosal villi of the small intestine (1). In the general population, the prevalence of CD is about 1% (2). Celiac disease can manifest with various signs and symptoms, including extra-intestinal symptoms such as osteopenia and osteoporosis (1).

Osteoporosis is a systemic skeletal disease characterized by low bone mass and subsequent increases in bone fragility and fracture susceptibility. Among bone metabolic diseases, osteoporosis is a common global public health problem with high morbidity. Many factors contribute to the development of osteoporosis, including genetic, environmental, and endocrine factors (3). Therefore, it is recommended that local healthcare programs be designed to reduce the

prevalence of avoidable risk factors for osteoporosis and related fractures (4).

Osteopenia/osteoporosis are often associated with CD, and the nutritional, metabolic, and endocrine status of patients should also be considered. Awareness of the bone conditions associated with CD should be present. Therefore, there is an increasing trend for studies investigating the link between osteopenia/osteoporosis and CD (5). Dual-energy X-ray absorptiometry (DEXA) is a non-invasive method for assessing bone mineral density (BMD). Decreased BMD in CD may be due to compromised absorption of calcium and vitamin D (6). Several studies have shown that low BMD is a common complication of CD and recommend screening for osteoporosis at the time of diagnosis (7). On the other hand, it is unclear whether every new case of CD should undergo DEXA (8-10). Furthermore, evidence supporting the effect of independent variables on osteopenia/osteoporosis in CD is limited (11, 12).

## 2. Objectives

Our study aimed to determine the frequency of osteopenia/osteoporosis in newly diagnosed CD cases and to evaluate the effect of various independent variables on the development of osteopenia/osteoporosis in these patients.

## 3. Material and Methods

### 3.1. Ethical Approval/Statement

Approval of this study was obtained from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.412), and the research adhered to the ethics declaration of Helsinki for medical research. Informed written consent was obtained from all patients for the review of their medical records.

### 3.2. Population

This cross-sectional analytical study took place from October 2017 to July 2022. The primary objective was to assess the frequency of osteopenia and osteoporosis and explore the odds of various factors on the likelihood of these bone disorders in patients with CD.

All adult participants undergoing CD evaluation at the Celiac Clinic (Fars Celiac Registry, Approval ID: IR.SUMS.REC.1399.525), a referral center in southern Iran, were considered for inclusion based on specific criteria. A checklist encompassing age, sex, height, weight, physical examination, personal and family medical history, histological reports, anti-tissue

transglutaminase (anti-tTG) levels, vitamin D levels, and other laboratory data was completed. The level of 25-hydroxy vitamin D was measured in included CD patients using the Radio-Immuno-Assay method. Dual-energy X-ray absorptiometry was employed to determine BMD in patients meeting inclusion criteria based on specified characteristics. Subsequently, demographic, clinical, and para-clinical findings of patients with and without osteopenia/osteoporosis were compared.

Body Mass Index (BMI) was categorized according to the World Health Organization (WHO) classification (13), with four groups: (1) less than 18.5 kg/m<sup>2</sup> as underweight, (2) 18.5 to < 25 kg/m<sup>2</sup> as normal weight, (3) 25.0 to < 30 kg/m<sup>2</sup> as overweight, and (4) 30.0 kg/m<sup>2</sup> or higher as obese.

### 3.3. Celiac Disease Definition

Celiac disease diagnosis relied on a duodenal biopsy and a positive anti-tTG (14). Serum levels of anti-tTG (IgA) were measured in all enrolled patients by the ELISA method, and a titer of 18 IU/mL or higher was considered positive.

Upper gastrointestinal (GI) endoscopy and duodenal biopsies were conducted in participants with positive anti-tTG. Specimens were stained with hematoxylin/eosin and histologically classified according to the Oberhuber-modified Marsh classification (15). In this study, CD was defined as an anti-tTG  $\geq$ 18 IU/mL and Marsh type 2 or higher in histology. All patients had an ordinary diet and consumed gluten, and the interval between duodenal biopsy and anti-tTG testing was less than one month.

### 3.4. Inclusion and Exclusion Criteria

All adult participants meeting the defined criteria for CD were included in the study. Exclusion criteria encompassed individuals under 18 years old, those who were lactating or pregnant, those with a history of alcohol consumption (more than 10 g/day), those using any medication that affects BMD or vitamin D levels within the past 6 months (e.g., calcium and vitamin D supplements), and those with co-morbid disorders (including malignancy, kidney, liver, lung, heart diseases, etc.). Additional exclusions included individuals with immunoglobulin A deficiency, Marsh type 0 or 1 in histology, other causes of villi atrophy, patients on a gluten-free diet, and non-cooperative patients. Celiac disease patients exhibiting abnormal BMD underwent evaluation by an endocrinologist to

exclude secondary causes of decreased BMD (including thyroid, parathyroid, diabetes mellitus, etc.) as potential confounders.

### 3.5. Dual-Energy X-ray Absorptiometry

Under the supervision of an endocrinologist, BMD ( $\text{g}/\text{cm}^2$ ) was measured in three areas: The lumbar spine, hip, and femoral neck, using the Hologic Discovery DXA system (MA, Bedford, USA). Osteoporosis (T-score  $\leq -2.5$ ) and osteopenia (T-score between  $-1.0$  and  $-2.5$ ) were defined using the WHO classification (16). Coefficients of variation based on preliminary measurements in 10 participants using this system were 0.51% for the lumbar spine and 2.4% for the femoral neck.

### 3.6. Statistical Analysis

Data were collected using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means  $\pm$  standard deviations, while categorical variables were expressed as frequency/percentages. Group comparisons involved the independent *t*-test for continuous variables and the chi-square test for categorical variables. The Mann-Whitney U test was applied when the Kolmogorov-Smirnov test indicated significance for nonparametric continuous variables. A P-value  $< 0.05$  was considered statistically significant. Logistic regression analysis, estimating odds ratios (ORs) and confidence intervals (CIs), was employed to assess the odds of various independent variables on osteopenia/osteoporosis. For regression analysis, a cut-off P-value of less than 0.3 in univariate analysis was used for inclusion in multiple analyses.

## 4. Results

A total of 302 patients satisfied the inclusion criteria. The participants had a mean  $\pm$  SD age of  $29.73 \pm 12.39$ , ranging from 18 to 70 years. Among them, 194 (64.2%) were female, and 108 (35.8%) were male. The mean  $\pm$  SD BMI of the participants was  $21.19 \pm 5.05$ , ranging from 14.68 to  $38.77 \text{ kg}/\text{m}^2$ . The mean  $\pm$  SD serum levels of anti-tTG and 25-hydroxy vitamin D were  $220.29 \pm 208.98 \text{ IU}/\text{mL}$  and  $28.15 \pm 15.50 \text{ ng}/\text{mL}$ , respectively. The demographic, clinical, and para-clinical features of the participants are summarized in Table 1.

The frequency of osteopenia and osteoporosis in the three regions of the lumbar spine, hip, and femoral neck is shown in Table 2. Overall, 215 (71.2%) patients had osteopenia or osteoporosis in at least one of these regions.

A comparison of demographic, clinical, and para-clinical findings between patients with and without osteopenia/osteoporosis is presented in Table 3.

The mean age of patients with osteopenia/osteoporosis ( $30.68 \pm 13.12$  years) was significantly higher than that of the normal group ( $27.37 \pm 10.03$  years). Although the frequency of osteopenia/osteoporosis was higher in women (74.2%) compared to men (65.7%), the gender difference did not reach statistical significance ( $P = 0.12$ ). Despite a slightly elevated mean anti-tTG level in participants with osteopenia/osteoporosis ( $228.69 \pm 217.32 \text{ IU}/\text{mL}$ ) compared to the normal group ( $199.53 \pm 186.33 \text{ IU}/\text{mL}$ ), this difference was not statistically significant ( $P = 0.41$ ). Notably, the mean 25-hydroxy vitamin D level in participants with osteopenia/osteoporosis was significantly lower than in the normal group ( $P < 0.001$ ).

A logistic regression analysis was conducted to assess the odds of different independent variables on osteopenia/osteoporosis, as detailed in Table 4. Participants aged over 30 exhibited a significantly higher likelihood of developing osteopenia/osteoporosis compared to those under 30 years old (OR: 2.19; 95% CI: 1.22 - 3.92;  $P = 0.008$ ). The odds of developing osteopenia/osteoporosis were significantly elevated in underweight individuals (BMI  $< 18.5 \text{ kg}/\text{m}^2$ , OR: 2.38; 95% CI: 1.30 - 4.34;  $P = 0.005$ ) and participants with histologically severe atrophy (Marsh 3c, OR: 2.22; 95% CI: 1.14 - 4.32;  $P = 0.019$ ) when compared to the normal group. Additionally, participants with normal vitamin D levels (25-hydroxy vitamin D level  $\geq 30 \text{ ng}/\text{mL}$ ) had a significantly lower likelihood of developing osteopenia/osteoporosis than those with vitamin D deficiency (OR: 0.37; 95% CI: 0.21 - 0.62;  $P < 0.001$ ). Notably, other variables such as gender, anti-tTG levels, GI manifestation, and ethnicity did not significantly augment the OR of developing osteopenia/osteoporosis.

## 5. Discussion

This study assessed bone mineral density in adult patients with CD. More than two-thirds of our patients had osteopenia or osteoporosis in at least one of their regions. In examining various variables within the subgroup analysis, older participants and underweight patients had a higher likelihood (OR) of developing osteopenia/osteoporosis. Additionally, we observed a high probability of osteopenia/osteoporosis in participants with severe histologic atrophy (Marsh 3C) compared to other histologic groups. Furthermore, patients with normal vitamin D levels were less likely

**Table 1.** Characteristics of the Patients with Celiac Disease (N = 302)<sup>a</sup>

Variables	Values
<b>Age (y)</b>	
Mean ± SD	29.73 ± 12.39
Minimum-maximum	18 - 70
<b>Gender</b>	
Male	108 (35.8)
Female	194 (64.2)
<b>BMI (kg/m<sup>2</sup>)</b>	
Mean ± SD	21.19 ± 5.05
Minimum-maximum	14.68 - 38.77
<b>Ethnicity</b>	
Fars	232 (76.8)
Others	70 (23.2)
<b>Education</b>	
Diploma or less	208 (68.9)
More than diploma	94 (31.1)
<b>Anti-tissue transglutaminase (IU/mL)</b>	
Mean ± SD	220.29 ± 208.98
Median	132.85
<b>GI manifestations</b>	
	206 (68.2)
<b>Breast-feeding Milk type</b>	
	212 (70.2)
<b>Marsh classification</b>	
Marsh 2	14 (4.6)
Marsh 3a	97 (32.1)
Marsh 3b	115 (38.1)
Marsh 3c	76 (25.2)
<b>25-hydroxy vitamin D (ng/mL)</b>	
Mean ± SD	28.15 ± 15.50
Median	25.25
Minimum-maximum	3.50 - 104.00
<b>Celiac disease in the family</b>	
	19 (6.3)
<b>Familial marriage in the parents<sup>2</sup></b>	
	32 (10.6)

Abbreviations: BMI, Body Mass Index; GI, gastrointestinal.

<sup>a</sup>Values are expressed as No (%) or mean ± SD.

**Table 2.** Frequency of Osteopenia/Osteoporosis in Celiac Disease Patients (N = 302)

Variables	No. (%)
<b>Lumbar spine osteopenia</b>	127 (42.1)
<b>Lumbar spine osteoporosis</b>	46 (15.2)
<b>Femoral neck osteopenia</b>	130 (43.0)
<b>Femoral neck osteoporosis</b>	48 (15.9)
<b>Hip osteopenia</b>	120 (39.7)
<b>Hip osteoporosis</b>	39 (12.9)

(OR) to develop osteopenia/osteoporosis than those with vitamin D deficiency.

The frequency of metabolic bone disease in patients with CD is increased due to several mechanisms (17, 18). One of the possible mechanism of osteoporosis in CD is

calcium malabsorption leading to secondary hyperparathyroidism, which contributes to cortical bone loss. Several studies have demonstrated low BMD in CD, attributed to high levels of serum cytokines that trigger osteoclasts (IL-2, IL-6, and TNF-alpha) and low

**Table 3.** Demographic, Clinical, and Paraclinical Findings in Celiac Disease Patients with (N = 215) and Without (N = 87) Osteopenia/Osteoporosis <sup>a</sup>

Variables	Osteopenia/Osteoporosis	Normal	P-Value <sup>b</sup>
Age (y) <sup>c</sup>	30.68 ± 13.12	27.37 ± 10.03	0.019
<b>Gender <sup>d</sup></b>			0.119
Male	71 (65.7)	37 (34.3)	
Female	144 (74.2)	50 (25.8)	
<b>BMI (kg/m<sup>2</sup>) <sup>d</sup></b>			0.054
Under weight	82 (79.6)	21 (20.4)	
Normal weight	101 (67.3)	49 (32.7)	
Overweight	18 (58.1)	13 (41.9)	
Obese	14 (77.8)	4 (22.2)	
<b>Ethnicity <sup>d</sup></b>			0.340
Fars	162 (69.8)	70 (30.2)	
Non-fars	53 (75.7)	17 (24.3)	
<b>Education <sup>d</sup></b>			0.598
Diploma or less	150 (72.1)	58 (27.9)	
More than diploma	65 (69.1)	29 (30.9)	
<b>GI manifestations <sup>d</sup></b>	145 (70.4)	61 (29.6)	0.651
<b>Celiac disease in the family <sup>d</sup></b>	10 (52.6)	9 (47.4)	0.065
<b>Familial marriage in the parents <sup>d</sup></b>	21 (65.6)	11 (34.4)	0.462
<b>Marsh classification <sup>d</sup></b>			0.234
Marsh 2	10 (71.4)	4 (28.6)	
Marsh 3a	67 (69.1)	30 (30.9)	
Marsh 3b	77 (67.0)	38 (33.0)	
Marsh 3c	61 (80.3)	15 (19.7)	
<b>Anti-tissue transglutaminase (IU/mL); mean ± SD - Median <sup>e</sup></b>	228.69 ± 217.32 - 142.40	199.53 ± 186.33 - 119.26	0.408
<b>25-hydroxy vitamin D (ng/mL); mean ± SD - Median <sup>e</sup></b>	25.81 ± 14.19 - 23.50	33.96 ± 17.08 - 32.00	< 0.001

Abbreviations: BMI, Body Mass Index; GI, gastrointestinal.

<sup>a</sup>Values are expressed as No. (%) or mean ± SD.

<sup>b</sup>P < 0.05 was considered statistically significant.

<sup>c</sup>Independent Samples *t*-test.

<sup>d</sup>Chi-squared test.

<sup>e</sup>Mann-Whitney U-test.

levels of cytokines that play an inhibitory role (IL-18, IL-12) (19, 20).

In our study, despite the higher frequency of osteopenia/osteoporosis in women, there were no statistically significant differences between the genders. This finding supports previous data indicating that the frequency of osteopenia and osteoporosis in CD does not significantly differ between genders (21, 22).

In the present study, participants over 30 had higher odds of developing osteopenia/osteoporosis. This observation corroborates findings from other studies (23, 24) that suggest aging increases the incidence of low BMD in patients with CD. A study by Marcella D.

Walker et al. found a high prevalence of osteoporosis among people over 50 years of age (7).

In our research, similar to some reports (25, 26), severe histological atrophy (Marsh 3c) increased the odds of osteoporosis in patients with CD. Walker et al. showed that the increase in the severity of intestinal villus atrophy was associated with the male gender and lower T-score in the 1/3 radius (7). These data support the hypothesis about the impact of intestinal damage on BMD. In CD, atrophy of the intestinal epithelium leads to a decreased surface area for calcium and vitamin D absorption. Hypocalcemia and low levels of vitamin D contribute to secondary hyperparathyroidism. Consequently, there is high bone turnover and bone loss due to increased levels of serum PTH (27, 28).

**Table 4.** The Odds of Different Independent Variables on Developing Osteopenia/Osteoporosis in Patients with Celiac Disease Using Logistic Regression Analysis

Variables	Univariate Analysis		Multiple Analysis	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
<b>Age (y)</b>		0.015		0.008
≥ 30	1.963 (1.142 - 3.377)		2.187 (1.221 - 3.916)	
< 30	1.0		1.0	
<b>BMI</b>		0.021		0.005
<18.5 (under weight)	1.938 (1.104 - 3.402)		2.376 (1.301 - 4.342)	
≥18.5 (others)	1.0		1.0	
<b>Gender</b>		0.120		0.075
Male	1.501 (0.900 - 2.503)		1.656 (0.951 - 2.884)	
Female	1.0		1.0	
<b>Celiac disease in the family</b>		0.072		0.065
Yes	2.365 (0.926 - 6.040)		2.571 (0.941 - 7.024)	
No	1.0		1.0	
<b>Familial marriage in the parents</b>		0.463		0.415
Yes	1.337 (0.615 - 2.906)		1.439 (0.600 - 3.452)	
No	1.0		1.0	
<b>Ethnicity</b>		0.342		0.134
Fars	1.347 (0.729 - 2.489)		1.670 (0.854 - 3.264)	
Others	1.0		1.0	
<b>Education</b>		0.598		0.197
Diploma or less	0.867 (0.509 - 1.476)		0.669 (0.363 - 1.233)	
More than diploma	1.0		1.0	
<b>Milk type</b>		0.984		0.607
Breastfeeding	0.994 (0.577 - 1.714)		1.173 (0.639 - 2.153)	
Others	1.0		1.0	
<b>GI manifestations</b>		0.652		0.244
Yes	1.133 (0.660 - 1.944)		1.426 (0.785 - 2.590)	
No	1.0		1.0	
<b>Anti-tissue transglutaminase level</b>		0.274		0.179
	0.999 (0.998 - 1.001)		0.999 (0.998 - 1.000)	
<b>Histological findings</b>		0.046		0.019
Marsh 3c	1.901 (1.012 - 3.571)		2.217 (1.139 - 4.316)	
Others	1.0		1.0	
<b>25-hydroxy vitamin D level</b>		0.001		< 0.001
Normal	0.409 (0.246 - 0.680)		0.365 (0.214 - 0.623)	
Deficiency	1.0		1.0	

Abbreviations: BMI, Body Mass Index; GI, gastrointestinal.

Galli et al. (29) showed that underweight patients had a higher risk of osteoporosis compared to normal-weight CD patients. This finding is consistent with the results of our study, which showed an increased OR of osteopenia at a BMI of less than 18.5 kg/m<sup>2</sup>. This may be due to malabsorption resulting in deficiencies in micronutrients such as calcium and vitamin D (1, 30).

Kemppainen et al. demonstrated that approximately two-thirds of patients with CD had low 25-hydroxy vitamin D concentrations (31). In their studies, vitamin D deficiency was one of the main variables associated with

low BMD in CD, which is similar to our findings. 25-hydroxy vitamin D is the principal form of vitamin D in circulation, and its level in the blood is thought to reflect nutritional status. Reduced calcium intake secondary to vitamin D deficiency results in increased PTH levels, which induces cortical bone loss (32).

There is no significant association between anti-tTG antibody levels and the odds of developing osteopenia/osteoporosis in our study. This observation is inconsistent with the report by Potter et al., who described an association between high levels of anti-tTG antibodies and low BMD. On the other hand, they found



that gender, GI manifestations, and ethnicity were not associated with osteopenia/osteoporosis in CD, which is consistent with our results (33).

The strengths of this study include a substantial sample size accompanied by strict diagnostic evaluations for all patients. Additionally, we had appropriate inclusion and exclusion criteria for participants, compared to similar studies.

We acknowledge several limitations to our study. This study was single-center and lacked a control group of the normal population. Except for vitamin D, other metabolic bone markers were not measured due to their high cost. We did not have enough data to analyze bone mineral content and Z-scores of our population, which is recommended for consideration in future studies, especially in individuals under 30 years old.

### 5.1. Conclusions

The present study showed that advancing age, low BMI, severe villous atrophy, and low levels of vitamin D can significantly increase the odds of developing osteopenia/osteoporosis in CD patients. Until further studies are conducted, BMD evaluation is especially recommended for these high-risk subgroups of CD patients.

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### Footnotes

**Authors' Contribution:** AZ and RN, study design, data collection and analysis, and manuscript drafting; LM and KN, concept and idea, study design, data analysis, interpretation, and manuscript revision; NM, FE, and SHS, study design, data interpretation, and manuscript revision. All authors contributed to the article and approved the submitted version.

**Conflict of Interests Statement:** All authors declare that they have no conflict of interest.

**Data Availability:** The dataset presented in the study is available on request from the corresponding author during submission or after publication.

**Ethical Approval:** This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.525 ) and was conducted

based on ethics Declaration of Helsinki for medical research.

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**Informed Consent:** Informed written consent has been obtained from all patients to review their medical records.

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