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Risk Factors for Decreased Bone Density in Adults ith 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 ith 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 ne ly diagnosed CD cases and to evaluate the effect of different independent variables on the development of osteopenia/osteoporosis in these patients.

Methods: Adult patients ith CD ho ere referred to a celiac clinic ere 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 as used to assess the odds ratio (OR) of different independent variables for osteopenia/osteoporosis.

Results: A total of 302 patients enrolled in this study, ith 64.2% being female and 35.8% male. The mean ± SD age as 29.73 ± 12.39. Overall, 71.2% of patients had osteopenia or osteoporosis. The odds of developing osteopenia/osteoporosis ere significantly higher in participants older than 30 years (OR: 2.19; 95% CI: 1.22 - 3.92; P = 0.008), under eight patients (OR: 2.38; 95% CI: 1.30 - 4.34; P = 0.005), and those ith histologically severe atrophy (OR: 2.22; 95% CI: 1.14 - 4.32; P = 0.019). The mean ± SD serum levels of 25-hydroxy vitamin D in CD patients ithout and ith osteopenia/osteoporosis ere 34.0 ± 17.1 ng/mL and 25.8 ± 14.2 ng/mL, respectively. Participants ith normal levels of 25-hydroxy vitamin D had a significantly lo er OR of developing osteopenia/osteoporosis than patients ith 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 sho ed that increasing age, eight loss, severe villous atrophy, and lo 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 ith various signs and symptoms, including extra-intestinal symptoms such as osteopenia and osteoporosis (1).

Osteoporosis is a systemic skeletal disease characterized by lo bone mass and subsequent increases in bone fragility and fracture susceptibility. Among bone metabolic diseases, osteoporosis is a common global public health problem ith 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 ith CD, and the nutritional, metabolic, and endocrine status of patients should also be considered. A areness of the bone conditions associated ith CD should be present. Therefore, there is an increasing trend for studies investigating the link bet een 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 sho n that lo 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 hether every ne 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 ne ly 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 as 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 ritten consent as obtained from all patients for the revie of their medical records.

3.2. Population

This cross-sectional analytical study took place from October 2017 to July 2022. The primary objective as to assess the frequency of osteopenia and osteoporosis and explore the odds of various factors on the likelihood of these bone disorders in patients ith 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, ere considered for inclusion based on specific criteria. A checklist encompassing age, sex, height, eight, physical examination, personal and family medical history, histological reports, anti-tissue transglutaminase (anti-tTG) levels, vitamin D levels, and other laboratory data as completed. The level of 25-hydroxy vitamin D as measured in included CD patients using the Radio-Immuno-Assay method. Dual-energy X-ray absorptiometry as employed to determine BMD in patients meeting inclusion criteria based on specified characteristics. Subsequently, demographic, clinical, and para-clinical findings of patients ith and ithout osteopenia/osteoporosis ere compared.

Body Mass Index (BMI) as categorized according to the World Health Organization (WHO) classification (13), ith four groups: (1) less than 18.5 kg/m^2 as under eight, (2) 18.5 to < 25 kg/m^2 as normal eight, (3) 25.0 to < 30 kg/m^2 as over eight, and (4) 30.0 kg/m^2 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) ere measured in all enrolled patients by the ELISA method, and a titer of 18 IU/mL or higher as considered positive.

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

3.4. Inclusion and Exclusion Criteria

All adult participants meeting the defined criteria for CD ere included in the study. Exclusion criteria encompassed individuals under 18 years old, those ho ere lactating or pregnant, those ith a history of alcohol consumption (more than 10 g/day), those using any medication that affects BMD or vitamin D levels ithin the past 6 months (e.g., calcium and vitamin D supplements), and those ith co-morbid disorders (including malignancy, kidney, liver, lung, heart diseases, etc.). Additional exclusions included individuals ith 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 under ent 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 (g/cm^2) as measured in three areas: The lumbar spine, hip, and femoral neck, using the Hologic Discovery DXA system (MA, Bedford, USA). Osteoporosis (T-score ≤ -2.5) and osteopenia (T-score bet een -1.0 and -2.5) ere defined using the WHO classification (16). Coefficients of variation based on preliminary measurements in 10 participants using this system ere 0.51% for the lumbar spine and 2.4% for the femoral neck.

3.6. Statistical Analysis

Data ere collected using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Continuous variables ere presented as means ± standard deviations, hile categorical variables ere 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 as applied hen the Kolmogorov-Smirnov test indicated significance for nonparametric continuous variables. A P-value < 0.05 as considered statistically significant. Logistic regression analysis, estimating odds ratios (ORs) and confidence intervals (CIs), as 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 as used for inclusion in multiple analyses.

4. Results

A total of 302 patients satisfied the inclusion criteria. The participants had a mean ± SD age of 29.73 ± 12.39, ranging from 18 to 70 years. Among them, 194 (64.2%) ere female, and 108 (35.8%) ere male. The mean ± SD BMI of the participants as 21.19 ± 5.05, ranging from 14.68 to 38.77 kg/m^2. The mean ± SD serum levels of anti-tTG and 25-hydroxy vitamin D ere 220.29 ± 208.98 IU/mL and 28.15 ± 15.50 ng/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 sho n 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 bet een patients ith and ithout osteopenia/osteoporosis is presented in Table 3.

The mean age of patients ith osteopenia/osteoporosis (30.68 ± 13.12 years) as significantly higher than that of the normal group (27.37 ± 10.03 years). Although the frequency of osteopenia/osteoporosis as higher in omen (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 ith osteopenia/osteoporosis (228.69 ± 217.32 IU/mL) compared to the normal group (199.53 ± 186.33 IU/mL), this difference as not statistically significant (P = 0.41). Notably, the mean 25-hydroxy vitamin D level in participants ith osteopenia/osteoporosis as significantly lo er than in the normal group (P < 0.001).

A logistic regression analysis as 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 ere significantly elevated in under eight individuals (BMI <18.5 kg/m^2, OR: 2.38; 95% CI: 1.30 - 4.34; P = 0.005) and participants ith histologically severe atrophy (Marsh 3c, OR: 2.22; 95% CI: 1.14 - 4.32; P = 0.019) hen compared to the normal group. Additionally, participants ith normal vitamin D levels (25-hydroxy vitamin D level ≥ 30 ng/mL) had a significantly lo er likelihood of developing osteopenia/osteoporosis than those ith 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 ith CD. More than t o-thirds of our patients had osteopenia or osteoporosis in at least one of their regions. In examining various variables ithin the subgroup analysis, older participants and under eight patients had a higher likelihood (OR) of developing osteopenia/osteoporosis. Additionally, e observed a high probability of osteopenia/osteoporosis in participants ith severe histologic atrophy (Marsh 3C) compared to other histologic groups. Furthermore, patients ith normal vitamin D levels ere less likely

Table 1. Characteristics of the Patients ith Celiac Disease (N = 302) [a]

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

Abbreviations: BMI, Body Mass Index; GI, gastrointestinal.
[a]Values are expressed as No (%) or mean ± SD.

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

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

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

The frequency of metabolic bone disease in patients ith 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, hich contributes to cortical bone loss. Several studies have demonstrated lo BMD in CD, attributed to high levels of serum cytokines that trigger osteoclasts (IL-2, IL-6, and TNF-alpha) and lo

Table 3. Demographic, Clinical, and Paraclinical Findings in Celiac Disease Patients ith (N = 215) and Without (N = 87) Osteopenia/Osteoporosis [a]

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

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

[a] Values are expressed as No. (%) or mean ± SD.

[b] $P < 0.05$ as considered statistically significant.

[c] Independent Samples *t*-test.

[d] Chi-squared test.

[e] 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 omen, there ere no statistically significant differences bet een the genders. This finding supports previous data indicating that the frequency of osteopenia and osteoporosis in CD does not significantly differ bet een 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 lo BMD in patients ith 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 ith CD. Walker et al. sho ed that the increase in the severity of intestinal villus atrophy as associated ith the male gender and lo er 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 lo 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 ith Celiac Disease Using Logistic Regression Analysis

Variables	Univariate Analysis		Multiple Analysis	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age (y)		0.015		0.008
≥ 30	1.963 (1.142 - 3.377)		2.187 (1.221 - 3.916)	
< 30	1.0		1.0	
BMI		0.021		0.005
< 18.5 (under eight)	1.938 (1.104 - 3.402)		2.376 (1.301 - 4.342)	
≥ 18.5 (others)	1.0		1.0	
Gender		0.120		0.075
Male	1.501 (0.900 - 2.503)		1.656(0.951 - 2.884)	
Female	1.0		1.0	
Celiac disease in the family		0.072		0.065
Yes	2.365 (0.926 - 6.040)		2.571 (0.941 - 7.024)1.0	
No	1.0			
Familial marriage in the parents		0.463		0.415
Yes	1.337 (0.615 - 2.906)		1.439 (0.600 - 3.452)	
No	1.0		1.0	
Ethnicity		0.342		0.134
Fars	1.347 (0.729 - 2.489)		1.670 (0.854 - 3.264)	
Others	1.0		1.0	
Education		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	
Milk type		0.984		0.607
Breastfeeding	0.994 (0.577 - 1.714)		1.173 (0.639 - 2.153)	
Others	1.0		1.0	
GI manifestations		0.652		0.244
Yes	1.133 (0.660 - 1.944)		1.426 (0.785 - 2.590)	
No	1.0		1.0	
Anti-tissue transglutaminase level	0.999 (0.998 - 1.001)	0.274	0.999 (0.998 - 1.000)	0.179
Histological findings		0.046		0.019
Marsh 3c	1.901 (1.012 - 3.571)		2.217 (1.139 - 4.316)	
Others	1.0		1.0	
25-hydroxy vitamin D level		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) sho ed that under eight patients had a higher risk of osteoporosis compared to normal-eight CD patients. This finding is consistent ith the results of our study, hich sho ed an increased OR of osteopenia at a BMI of less than 18.5 kg/m^2. 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 t o-thirds of patients ith CD had lo 25-hydroxy vitamin D concentrations (31). In their studies, vitamin D deficiency as one of the main variables associated ith lo BMD in CD, hich 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, hich induces cortical bone loss (32).

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

that gender, GI manifestations, and ethnicity ere not associated ith osteopenia/osteoporosis in CD, hich is consistent ith our results (33).

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

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

5.1. Conclusions

The present study sho ed that advancing age, lo BMI, severe villous atrophy, and lo 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 as approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.525) and as conducted based on ethics Declaration of Helsinki for medical research.

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Informed Consent: Written informed consent has been obtained from all patients to revie their medical records.

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