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Investigation of the Factors Affecting Bone Mineral Density in Children with Celiac Disease

Seyed Mohsen Dehghani,[1] **Homa Ilkhanipour**,[2] **Leila Samipour**,[2] **Ramin Niknam**,[3] **Iraj Shahramian**,[4] **Fateme Parooie**,[4] **Morteza Salarzaei**,[4] **and Masoud Tahani** [4]

[1]Shiraz Transplant Research Center, Shiraz University of Medical Science, Shiraz, Iran
[2]Department of Pediatric, Shiraz University of Medical Science, Shiraz, Iran
[3]Gastroenterohepatology Research Center, Shiraz University of Medical Science, Shiraz, Iran
[4]Pediatric Gastroenterology and Hepatology Research Center, Zabol University of Medical Sciences, Zabol, Iran

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Correspondence to
Iraj Shahramian
Pediatric Gastroenterology and Hepatology Research Center, Zabol University of Medical Sciences, Zabol 9861615881, Iran.
Email: ir_buper@yahoo.com

ORCID iDs
Seyed Mohsen Dehghani
https://orcid.org/0000-0001-5930-0110
Homa Ilkhanipour
https://orcid.org/0000-0002-8087-8432
Leila Samipour
https://orcid.org/0000-0002-1491-9742
Ramin Niknam
https://orcid.org/0000-0002-2608-8018
Iraj Shahramian
https://orcid.org/0000-0002-4134-1405
Fateme Parooie
https://orcid.org/0000-0002-2367-3780
Morteza Salarzaei
https://orcid.org/0000-0001-5508-8669

ABSTRACT

Purpose: Children with celiac disease (CD) are at an increased risk of low bone mineral density (BMD) owing to malabsorption of fat-soluble vitamins, inflammation, and malnutrition. This study aimed to determine the prevalence and risk factors for low BMD in Iranian children with CD.
Methods: This prospective cohort study examined 149 Iranian children with CD between 2011 and 2018 at Zabol University of Medical Sciences. BMD was measured using dual-energy X-ray absorptiometry. Demographic, clinical, and laboratory data were collected from patients' medical records. Logistic regression analysis was performed to identify the factors associated with low areal BMD (BMD-Z <−2) in the lumbar spine and femoral neck. Descriptive data were analyzed using the mean, standard deviation, and relative frequency. Data were analyzed using the chi-square test, *t*-test, and analysis of variance.
Results: Of the 149 children with CD, 27.5% had osteoporosis. The mean body mass index (BMI) Z score was −1.28±1.2. Lower BMI was associated with a higher likelihood of BMD-Z (odds ratio 2.17; $p \leq 0.05$).
Conclusion: Overall, the findings of this study showed that there was no correlation among Marsh classification, presence of specific human leukocyte antigens, and low BMD in Iranian children with CD. BMI can be a predictor of bone density in children with CD and may be applied clinically in early screenings to evaluate the bone health status in these children.

Keywords: Celiac disease; Bone density; Glutens; Body mass index

INTRODUCTION

Celiac disease (CD) is a multifactorial immune-mediated disorder triggered by the ingestion of gluten and other gluten-related proteins in genetically predisposed patients. Human leukocyte antigen (HLA) DQ alleles, coding α and β chains of MHC-DQ2 and MHC-DQ8 heterodimers, have been shown to be necessary, but not sufficient, for the development of CD. Moreover, gluten is the required environmental exposure for the development of CD in genetically predisposed individuals, likely in addition to other constitutional and/or acquired factors [1]. CD is a common chronic disease that affects 0.5–1% of the world's population.

Masoud Tahani
https://orcid.org/0000-0002-0213-9087

Conflict of Interest
The authors have no financial conflicts of interest.

This disorder affects people of all ages and sexes. Clinical symptoms differ from those of asymptomatic patients with severe malnutrition. The initial diagnosis is usually determined by celiac serology, and its confirmation often requires intestinal biopsy. There have been substantial increases in the prevalence and incidence over the last two decades for reasons that are certainly environmental [2]. Two of the complications of CD are bone problems and decreased bone mineral density (BMD) [3]. This arthropathy is a result of malabsorption of calcium and vitamin D, secondary to hyperparathyroidism and metabolic bone diseases in patients with CD [4]. Skeletal diseases related to CD have been reported as non-intestinal symptoms. In addition to osteoporosis and osteopenia in patients with atypical CD, lower back pain, musculoskeletal pain, and weak proximal muscles are possible clinical symptoms of this disease [5]. Based on studies by Tau et al. [6], Mora et al. [7], and Fedewa et al. [8], BMD is significantly lower in children with untreated CD compared to treated cases of CD.

Recent studies on young children with CD have examined BMD and even severe osteoporosis at the time of diagnosis [9]. Other studies have evaluated bone status in children with CD and showed that BMD at least 2 years after the diagnosis of gluten free diet is significantly lower than expected [10,11]. There have not been enough studies in this field in Iran. The high prevalence of metabolic bone disease in children with CD highlights the importance of identifying factors that affect low BMD and finding appropriate solutions to this problem [3]. Regarding the importance of recognizing the factors affecting bone density and clinical bone health preservation in patients with CD, this study aimed to investigate the factors affecting BMD in Iranian children with CD.

MATERIALS AND METHODS

Subjects

This prospective cohort study examined 148 children aged 2–18 years with CD who underwent dual-energy X-ray absorptiometry (DEXA) after the diagnosis of CD at Zabol University of Medical Sciences between 2011 and 2018. The sample size was estimated according to the following formula:

$$N = \frac{z^2 \mathrm{p}(1 - \mathrm{p})}{d^2}$$

(N=population size, Z=critical value of the normal distribution at the required confidence level, p=sample proportion, d=margin of error)

Inclusion and exclusion criteria

Children were included in the study under the following conditions: CD confirmed by clinical symptoms, serological tests, and intestinal biopsy; age between 2 and 18 years; and consent from the parents. The exclusion criteria were as follows: not meeting the above criteria or having a low BMD due to hematological, hormonal, or metabolic disorders.

Ethical considerations

The Ethics Unit of Zabol University of Medical Sciences reviewed and confirmed this study. The corresponding ethical codes are IR.sums.med.rec.1397.156.

Measurement

1. Demographic information

Information on height, weight, time of diagnosis, first symptoms, drug or supplement consumption, history of bone fracture, and other related complications was collected.

2. BMD measurement

BMD was measured in the lumbar and femoral areas using DEXA, without special injections and prepared according to standard steps using a Hologic device (Horizon® DXA System; Breast & Skeletal Health U.S. Product, New York, NY, USA). The BMD was expressed as absolute (g/cm^2), and the absolute BMD for each patient was expressed as the Z-score after comparing the mean BMD in healthy children. The patients and healthy controls were adjusted regarding the age. Osteoporosis was defined as a Z-score <−2, and if the Z-score was between −1 and −2, osteopenia was diagnosed [12].

Statistical analysis

After data collection, the BMD status of all cases was analyzed using the Student *t*-test, Fisher exact test, chi-square test, and SPSS software version 23 (IBM Co., Armonk, NY, USA). Unpaired Student *t*-test was used for normally distributed variables, and the Mann–Whitney test was used for anomalously distributed variables. For qualitative variables (name and rank), both Fisher exact test and chi-square test were used in the crosstab. The low BMD odds ratio (OR) due to a specific variable was used as a relevance criterion, and multivariate logistic regression analysis was conducted to determine the effect of confounding variables. The significance level was set at a *p*-value <0.05.

RESULTS

Demographic characteristics

A total of 149 patients diagnosed with CD between 2011 and 2018 based on clinical suspicion, serology, and intestinal biopsy was included in this study, and BMD was performed using the DEXA method. There was no significant difference between age and sex distribution and baseline body mass index Z score (BMI-Z score) in patients who did not undergo DEXA scans compared to other patients (mean age, 8.7 vs. 8.5 years; sex, 58.4% female vs. 61.4% female; BMI-Z score, −1.06 vs. −1.28, respectively; $p>0.05$ for each comparison). The mean age at diagnosis of CD was 8.7 years. As **Table 1** shows, 94 (63%) of the 149 children in the study were female and 55 (37%) were male. The difference between sexes was statistically significant ($p<0.05$). The average time between diagnosis and the first DEXA scan was 6 months. The mean BMI-Z score was −1.28±1.2. The family history was positive in 17 patients (11.1%).

Table 1. Demographic characteristics of children participating in the determination study of bone density in the understudy group

Variable	Female (63%, n=94)	Male (37%, n=55)	Total (n=149)
Age (y)	8.7±3.6	8.6±3.6	8.7±3.6
Diagnosis time (mo)	6.3±2.6	6.3±2.4	6.3±2.6
Weight for age Z score	−1.05±1.6	−1.15±1.2	−1.07±1.5
BMI-Z score	−1.27±1.2	−1.3±1.4	−1.28±1.2
Family history (%)	12.7	9.3	11.1

Values are presented as mean±standard deviation.
BMI-Z score: body mass index Z score.

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Histopathologic findings

According to our histopathological examination, most of the patients were classified as Marsh IIIb (37.58%), followed by IIIa (32.89%), IIIc (24.16%), and IIb (5.37%). No type IV cases were observed (**Fig. 1**).

HLA typing

The results of HLA typing showed that most patients (62 cases, 50.82%) were HLA DQ2 positive. HLA DQ7, HLA DQ6, HLA DQ5, and HLA DQ8 were present in 7 (5.74%), 10 (8.20%), 19 (15.57%), and 24 (19.67%) cases, respectively (**Fig. 2**).

Factors affecting low areal bone mineral density

In the univariate logistic regression for low bone mineral density Z score (BMD-Z score) at scan, only the BMI-Z score (OR, 0.42%; confidence interval, 0.35–0.60) was significantly associated with BMD-Z. Age, sex, HLA, and Marsh classification were not significantly correlated with low BMD-Z (p>0.05). Multivariate logistic regression was not performed because the only significant risk factor in the non-variable analysis was the BMI-Z score. Low BMD was more likely to occur in patients with a high level of total tissue transglutaminase (tTG) antibody. However, this association was not statistically significant. In contrast, tTG IgA antibody levels were not significantly associated with the risk of low BMD (**Table 2**).

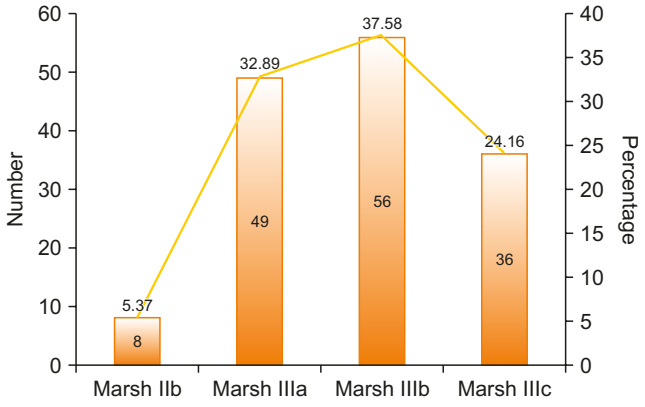

Fig. 1. Histopathological findings in children with celiac disease.

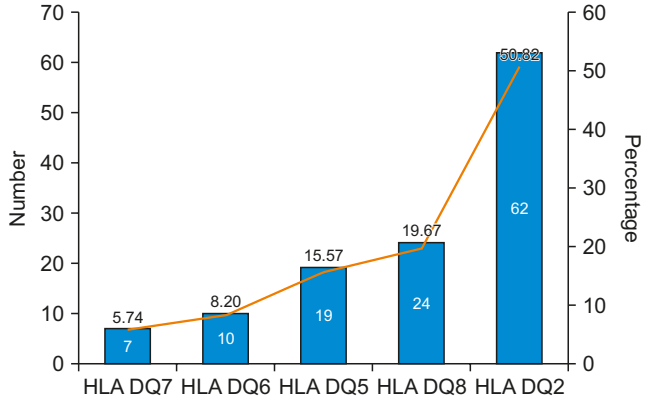

Fig. 2. Frequency of human leukocyte antigens (HLA) in children with celiac disease.

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Table 2. Factors affecting low areal bone mineral density

Variable	Unadjusted OR (95% CI)	*p*-value
Sex (reference:female)	0.90 (0.48–1.69)	0.75
Age (y)	1.02 (0.94–1.10)	0.67
BMI-Z	0.42 (0.35–0.60)	<0.001
Diagnosis time	1.00 (0.99–1.00)	0.10
tTG (U/mL)	1.01 (1.00–1.02)	0.06
tTG IgA (U/mL)	0.98 (0.96–1.00)	0.10
HLA	1.05 (0.98–1.11)	0.53
Marsh classification	0.44 (0.16–1.22)	0.11

OR: odds ratio, CI: confidence interval, BMI-Z: body mass index Z, tTG: tissue transglutaminase antibody, tTG IgA: tissue transglutaminase IgA antibody, HLA: human leukocyte antigen.

Table 3. The distribution of different mean bone density measures

Bone mineral density	Z-score≥–1 (%)	–2≤Z-score≤–1 (%)	Z-score≤–2 (%)	Mean±Standard deviation
Lumbar 1 spine	41.9	34.7	23.4	–1.10±1.15
Lumbar 2 spine	31.9	45.8	22.3	–1.30±1.20
Lumbar 3 spine	28.4	41.6	30.0	–1.30±1.16
Lumbar 4 spine	30.6	40.3	29.1	–1.45±1.24
Total lumbar spine	35.9	40.0	24.1	–1.16±1.13
Neck of left femur	21.5	38.2	40.3	–1.67±0.93
Trochanter of left femur Z score	40.9	40.8	18.3	–0.84±0.81
Intertrochanter of left femur	49.9	28.4	21.7	–0.90±0.95
Total left femur	34.1	34.2	31.7	–1.43±1.20
Total	40.3	32.2	27.5	–1.16±1.11

The distribution of different mean bone density measures

The most frequent Z-score was ≥–1, which was present in 40.3% of patients. However, –2≤Z-score≤–1, which indicates osteopenia, was reported in 32.2% of patients and was mostly present in the second, third, or fourth lumbar spine (45.8%, 41.6%, and 40.3%, respectively). Osteoporosis (Z-score ≤–2) was observed in 27.5% of the patients, mostly involving the neck of the left femur (40.3%; **Table 3**).

DISCUSSION

In this study, which examined the factors affecting BMD in patients with CD, the number of female was higher than that of male (63% vs. 37%, respectively). A systematic review suggested that the prevalence of CD among female is nearly twice of that among male, which is consistent with our study [8]. In this study, the mean age at time of CD diagnosis was 8.7 years. We found no significant relationship between BMD and Marsh classification. Pantaleoni et al. [13] reported no relationship between BMD and Marsh III in patients with CD [13]. Trovato et al. [14] evaluated the association of BMD with symptoms and Marsh classification in 99 children with CD aged 4 to 15 years with the tTG2 antibody, positive test results for the anti-tTG2 antibody, and histologic class-based damage. There was no relationship between BMD and anti-tTG2 titer, histology, and symptoms [14]. However, a study by Choudhary et al. [15] on BMD in CD patients showed that most patients with Marsh III CD had low BMD. García-Manzanares et al. [16] found that the Marsh classification is the most important determinant of low BMD at diagnosis. A meta-analysis by Fedewa et al. [8] reported malabsorption and inflammation as the cause of BMD reduction in patients with CD. Mucosal lesions can lead to malabsorption and decreased serum calcium and vitamin D levels in secondary hyperparathyroidism and metabolic bone diseases [8]. One cause of osteoporosis is vitamin D deficiency due to malabsorption [4,17]. In this study, bone density reduction was found to be

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independent of mucosal injury. This may be due to the chronic secretion of pro-inflammatory cytokines by gastrointestinal mucosal immune cells, which stimulates bone resorption by osteoclasts. In fact, low BMD in children is not clinically predictable [10]. In this study, there was no correlation between BMD and HLA. However, in a study by López et al. [18], HLA B8 was identified as the most common antigen in atypical CD patients referred to the hospital with extra-intestinal manifestations, and HLA variants were identified as important in the incidence of symptoms. Their results were not in line with this study.

Calcium absorption disorder in people with gastrointestinal malabsorption increases fecal calcium, decreases urinary calcium, and causes a negative calcium balance. Under similar conditions, vitamin D absorption is inversely correlated with the amount of stearate. The increase in parathyroid hormone enhances the function of renal enzyme 1-α-hydroxylase and converts 25-hydroxyvitamin D to its active type to increase calcium absorption from the small intestine [19-21]. Deficiency of calcium-binding intracellular proteins in CD restricts the entry of calcium into the intestine. In addition, during steatosis, calcium binds to the fat in the intestinal lumen and is excreted into the stool. However, the amount of calcium is reduced owing to lactose intolerance [22]. Hypocalcemia increases the levels of parathyroid hormone, which is observed in newly diagnosed celiac patients; however, the levels decrease back to its normal range after a gluten-free diet. Owing to the correlation between bone formation and absorption, when bone change increases, both of these processes accelerates, and markers of both phases of bone change increases [23]. In this study, no relationship was found between low BMD and age at CD diagnosis. In another study, Zanchetta et al. [24] reported that children >4 years had a longer period between symptoms and diagnoses than younger infants. In this cross-sectional study, 27.5% of patients with CD had low BMD, which was almost 11 times lower than that expected in a healthy sample of children.

Regarding the possible causes of low BMD in pediatric patients with CD, we found no correlation between BMD and Marsh scoring levels. We also found no correlation between the presence of specific HLAs and BMD. The only significant correlation found was between BMD and the BMI-Z score, which is in line with the hypothesis that malnutrition plays a role in the development of low BMD. This finding indicated that the BMI-Z score could be an indicator of overall nutritional status. In addition, this suggests that the positive relationship between the BMI-Z score and BMD-Z is because of the skeletal reaction to weight gain. Several studies have reported low levels of calcium and vitamin D in patients with low BMD [25-27]. Some studies have suggested that a patient's self-restrictive diet is a main factor for malnutrition [28,29]. Tavakkoli et al. [28] indicated that 59% of dairy avoidance was among patients who self-diagnosed as "wheat-sensitive" [28]. In contrast, Carroccio et al. [29] reported significantly lower dietary calcium intake among patients with multiple food sensitivitiy. Patients exclude dairy products from their diet to prevent symptoms.

BMI is one of the easiest and most applicable indicators of body composition that is associated with the health of patients [30]. Bode et al. [31] reported that patients with CD who controlled their disease had better body composition than those without CD. Poor celiac treatment is associated with muscle atrophy. Conversely, for patients with controlled nutritional intake, lower levels of systemic inflammation can be effective in improving body composition [32]. Webster et al. [3] also reported that a higher BMI was associated with lower odds of a low BMD-Z score in the initial DEXA analysis. Factors associated with body composition include nutrition, physical activity level, and medications; analyses on these factors were not performed in the present study and was one of the limitations of the present

study. There are a limited number of studies on bone status among Iranian children with CD [33-35]. None of these studies reported a reference mean BMD for Iranian children, and none focused on the pediatric population. Ganji et al. [35] reported a 36% prevalence of osteoporosis and 55% prevalence of osteopenia in adult patients with CD. Another study by Sayar et al. [36] reported that among Turkish adult patients with CD, 15.2% had osteoporosis and 67.3% had osteopenia. Our results were not in line with these findings, as our patient population only included children. The osteoporosis and osteopenia rates in the current study were 27.5% and 32.2%, respectively. A number of studies have indicated that lifestyle modification, gluten-free diet, and regular exercise can improve the BMD of pediatric patients with CD [37,38].

Overall, the findings of the present study showed that there was no correlation between Marsh classification, presence of specific HLAs, and low BMD in Iranian children with CD. BMI can be a predictor of bone density in children with CD and may be applied clinically in early screenings to evaluate the bone health status in these children.

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