Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

ORIGINAL ARTICLE

Bone mineral density in Iranian children with celiac disease

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ABSTRACT

Aim: The current study aims to evaluate bone mineral density (BMD) in patients with celiac disease who were referred to the celiac clinic of Shahid Rahimi Hospital in Khorramabad, Iran, in 2020.

Background: Extraintestinal presentations of celiac disease are widespread and, if neglected, can be devastating. Osteoporosis, one of the extraintestinal manifestations of celiac disease, often remains undiagnosed until advanced stages and can impose a significant burden on patients with celiac and health systems. Nonetheless, the prevalence and characteristics of osteoporosis in celiac disease are unknown in Iran.

Methods: This was a cross-sectional study at the celiac clinic of Shahid Rahimi Hospital in Khorramabad, Iran. Participants were 48 patients under 18 years diagnosed with Marsh II and Marsh III stages of celiac disease (who need to be on a gluten-free diet) at the pediatrics celiac clinic in 2020. All patients were recruited, completed a questionnaire, and had their blood biochemical parameters analyzed. Then their bone mineral density (BMD) was measured through dual-energy x-ray absorptiometry at the Asia Imaging Center in Khorramabad under the supervision of a radiologist and pediatric rheumatologist.

Results: The mean age of the children was 9.96±3.17 years. The minimum and maximum ages of the participants were 4 and 17 years, respectively. Of all 48 children who were included (48), 34 (70.8%) were female, and 14 (29.2%) were male. In the femoral region bone densitometry, 35.4% were normal, 41.7% had lower limit normal, and 22.9% had low bone density. In the lumbar region, 39.6% were normal, 25% were Lower limit normal, and 35.4% had low bone density. No significant correlation was found between age, sex, place of residence, Marsh stage, gluten-free diet, and bone densitometry in both lumbar and femoral regions. Nonetheless, we detected a statistically significant relationship between bone density in the lumbar region and two HLA types, namely HLA DQ8 and HLA DQ2/8 (P=0.016).

Conclusion: The results of the current study provided further evidence that all children with advanced celiac disease should be screened for metabolic bone diseases. Besides those in Marsh II and Marsh III, patients in Marsh I stage should also be investigated for low bone mineral density.

Keywords: Celiac disease, Bone mineral density, Osteoporosis.

(Please cite as: **Ahmadipour S, Rostami Nejad M, Faraji Goodarzi M, Heidarifard S, Sedaghat B, Anbari K. Bone mineral density in Iranian children with celiac disease. Gastroenterol Hepatol Bed Bench 2023;16(2):167-172. https://doi.org/10.22037/ghfbb.v16i2.2638).**

Introduction

Celiac disease (CD) is a common adverse health condition with different intestinal and extraintestinal involvements (1). This autoimmune disease, which can inflict both sexes from all age groups, has a strong genetic basis and is closely linked to HLAs DQ2 and DQ8 (2). In predisposed individuals, celiac disease is

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precipitated by environmental exposure to gluten, a prolamin protein found in different grains such as wheat, rye, and barley (3, 4). Classic presentations of the disease are failure to thrive, chronic diarrhea, weight loss, iron deficiency, and celiac, more commonly present with fatigue, bloating, constipation, abdominal pain, and osteoporosis (2). Although there are vast differences in the prevalence of celiac disease in different regions of the world (which cannot be exclusively explained by genetic and environmental factors), globally, approximately 1% of the population is affected (5).

Osteoporosis is a celiac disease presentation in children and adults and is associated with a high risk of osteoporotic fractures (6, 7). Although the precise underlying mechanisms of osteoporosis in celiac disease remain to be elucidated, several factors such as autoimmunity, inflammatory cytokines in the circulation, and malabsorption of vitamin D, calcium, and magnesium are proposed to be involved (7). Therefore, as soon as the diagnosis of celiac disease is made, an assessment of bone mineral density should be considered (8). Conversely, considering the close interrelation between celiac and osteoporosis, patients with idiopathic osteoporosis must be serologically tested for celiac disease (9).

Osteoporosis, which can be detected by low bone mineral density (BMD), is prevalent in patients with celiac disease (regardless of symptoms) and affects up to 70% of celiac patients (10, 11). Therefore, timely diagnosis and intervention through consumption of a gluten-free diet and calcium and vitamin D supplementation can minimize the risk of fractures in celiac patients. Nonetheless, to the authors' knowledge, the rate and characteristics of osteoporosis due to celiac disease has not been identified and reported neither in Iran nor elsewhere in the region. The current study investigates the rate and characteristics of celiac-related osteoporosis in a cohort of Iranian children from Khorramabad.

Methods

Study design

All patients who were diagnosed with celiac disease between 20 March 2020 and 21 March 2021 at the Khorramabad hospital who were younger than 18 and met the inclusion criteria were recruited. The included children were either diagnosed with celiac (Marsh II and III) or those for whom the diagnosis of celiac had been made previously. Our exclusion criteria were: history of taking any drug affecting bone metabolism such as corticosteroids, antiepileptics, heparin, cyclosporin, statins, beta-blockers, calcium, Vitamin D, bisphosphonates, proton pump inhibitors. A checklist was used to collect the information from the files, which included: age, gender, height, weight, age at celiac diagnosis, initial symptoms, consumption of gluten-free diet, lactose intolerance, thyroid disorders, osteoporosis risk factors, medications, and supplements (particularly calcium, and vitamin D), dairy products consumption, and information about BMD measurement.

Relevant biochemical parameters were measured, and blood levels of calcium, phosphorous, thyroid hormones, alkaline phosphatase, and vitamin D were determined. If laboratory results were normal, bone densitometry was performed in the femoral neck, lumbar, and spinal regions under the direct supervision of a radiologist. Bone densitometry was carried out in all patients who needed a gluten-free diet, namely those in Marsh II and Marsh III stages, and patients with Marsh I were excluded. In children younger than 3, only lumbar densitometry was carried out; in patients between 3 and 13, the lumbar region and whole body (except the head) were scanned, and those older than 13 had their lumbar, neck, and femoral areas bone densitometry performed.

Statistical analyses

After compilation of the information, all data was recorded in the SPSS software version 22 and was analyzed by a medical statistician. Descriptive analyses, standard central tendency, and dispersion measures were used for continuous variables. Independent T-test, Pearson Correlation Coefficient, and one-way Analysis of Variance were used to evaluate the differences between different groups of patients after controlling for confounding variables.

Ethical considerations

Informed consent was obtained from all participants (or their guardians), and the authors sought medical ethics committee appropriate local ethical approval (Ethical No: IR.LUMS.REC.1399.227). All stages of the study were in complete accordance with the Helsinki declaration.

Table 1. Distribution of bone mineral density measurements of the lumbar spine and femoral neck in children with celiac disease

Investigated Area	Normal (-1< Z score < 1)	Lower Limit Normal (-2 < Z score < -1)	Low Bone Density (-2 < Z score < -1)	Osteoporosis (Z score < -2)	Total
Femoral	17 (35.4)*	20 (41.7)	8 (16.7)	3 (6.3)	48 (100)
Lumbar	19 (39.6)	12 (25)	14 (29.2)	3 (6.3)	48 (100)

* Number of patients (percent)

Table 2. Distribution of bone mineral density measurements in femoral region by Gender

Variable	Distribution of bone mineral density measurements in femoral region				X^2	P value
Gender	Normal (-1< Z score < 1)	Lower Limit Normal (-2< Z score < -1)	Low Bone Density (Z score < -2)	Total	2.226	0.328
Female	12 (35.3)*	16 (47.1)	6 (17.6)	34 (100)		
Male	5 (35.7)	4 (28.6)	5 (35.7)	14 (100)		

* Number of patients (percent)

Table 3 Distribution of bone mineral density measurements in lumbar region by Gender

Variable	Distribution of bone mineral density measurements in femoral region				X^2	P value
Gender	Normal (-1< Z score < 1)	Lower Limit Normal (-2< Z score < -1)	Low Bone Density (Z score < -2)	Total	0.155	0.925
Female	13 (38.2)*	9 (26.5)	12 (35.3)	34 (100)		
Male	6(42.9)	3 (21.4)	5 (35.7)	14 (100)		

* Number of patients (percent)

Table 4. Distribution of bone mineral density measurements of the lumbar spine in children with celiac disease who followed and those who did not follow gluten-free diet

Variable	Distribution of bone mineral density measurements in lumbar region				X^2	P value
Consumption of Gluten-free diet	Normal (-1< Z score < 1)	Lower Limit Normal (-2 < Z score < -1)	Low Bone Density Z score < -2	Total	3.664	0.16
Yes	19 (44.2)*	10 (23.3)	14 (32.6)	43 (100)		
No	-	2 (40)	3 (60)	5(100)		

* Number of patients (percent)

Table 5. Distribution of bone mineral density measurements of the femoral in children with celiac disease who followed and those who did not follow gluten-free diet

Variable	Distribution of bone mineral density measurements in femoral region				X^2	P value
Consumption of Gluten-free diet	Normal (-1< Z score < 1)	Lower Limit Normal (-2 < Z score < -1)	Low Bone Density Z score < -2	Total	0.058	0.972
Yes	15 (39.4)	18 (41.9)	10 (23.3)	43(100))		
No	2 (40)	2 (40)	1 (20)	5(100)		

* Number of patients (percent)

Results

Forty-eight children with celiac disease were included in this study, and their BMD was measured. The mean age of the children was 9.96±3.17. The youngest child was aged 4, and the oldest was 17. 54.2% of children were younger than 10, and 45.8% were ten years or older. Of the children who were included, 34 (70.8%) were female, and 14 were male (29.2%). 16.7 % of the participants lived in rural areas, and 83.3 % resided in cities. 89.6% of the children with celiac disease followed a gluten-free diet, but 15.4 had not followed it carefully.

Five children had skeletal pain and were referred to a pediatric rheumatologist for further assessment and treatment (all received alendronate). Based on the Marsh staging system, 11 children (22.9%) fell into the Marsh II category, and 37 (77.1%) were classified as Marsh III.

Table 1 demonstrates bone mineral density in femoral and lumbar regions. In the femoral area, the bone density of 35.4% of children was normal, 41.7% were in lower limit, 16.7% had a low bone density, and 6.3% had osteoporosis. In the lumbar region, 39.6% were normal, 25% were in lower normal limit, 29.2 had a low bone density, and 6.3% were osteoporotic. In this

study, 6.3% of children were osteoporotic, but the celiac disease was not suspected, and no investigation or treatment was initiated.

In chi-square analysis, the difference in distribution of bone density in the lumbar region of children with celiac disease with regard to age was not statistically significant (P=0.247). In the femoral region, low bone density and lower limit normal in children younger than 10 were 19.2% and 34.6% respectively. In children 10 years and older, these figures were 27.3% and 50% respectively, which was not significant (P=0.239).

As tabulated in Tables 2 and 3, there was no difference in distribution of bone mineral density in the lumbar and femoral regions (P=0.925 and P=0.328) between boys and girls with celiac disease. Moreover, as can be seen in table 8-4, there was no difference in distribution of BMD in the lumbar and femoral regions between children with celiac disease who were residing in rural areas and those who lived in cities (P=0.646 and P=0.462).

In the femoral region in children in Marsh II stage, 36.4% had low bone mineral density, and 54.5 were in lower limit normal. In patients in Marsh III, 18.9% had low bone density, and 37.8% were in lower BMD limit in the femoral region. Nonetheless, in chi-square analysis, this difference was not statistically significant (P=0.106). In the lumbar region, similarly, there was no statistically difference in distribution of bone mineral density amongst children with celiac disease in different Marsh stages (P=0.965).

In the lumbar region, most children with lower normal limit BMD had HLA DQ 8 and the majority of those with osteoporosis had HLA DQ2/8. In chi square analysis, this difference was statistically significant (P=0.016), nonetheless, in the femoral region, the difference was not statistically significant (P=0.122). When compared by one way ANOVA, there were no differences in the means of initial TGG in children with celiac disease with regard to bone mineral density.

As tabulated in Tables 4 and 5 there was no difference in distribution of bone mineral density in the lumbar (p=0.16) and femoral (p=0.972) regions of children who followed and those who did not follow gluten-free diet.

Discussion

It is clear from our results that there was evidence of an ongoing financial cost for the Luton and Dunstable hospital to care for our coeliac patient cohort during this 12 year period. These results add further weight to the previous studies that have suggested that coeliac disease is not optimally managed within the community.

Celiac disease has recently been identified as one of the main causes of bone mineral density loss (also known as metabolic osteopathy) which can even present in asymptomatic patients and increase the risk of fracture (12). It should be mentioned, however, that genetic factors play the major role in decreased bone density and osteoporosis, and almost 80% of the osteoporosis risk is genetic. Nonetheless, environmental factors such as nutrition, exercise, and metabolic diseases such as celiac disease are also influential in the development of osteoporosis (13).

A study by Bernstein et al demonstrated that in children with celiac disease, metabolic bone disorders leading to osteopenia and osteoporosis are more common, and the authors proposed that this can be attributed to calcium and vitamin D malabsorption which is intensified by lactose intolerance (14). This theory has been approved by other studies which have demonstrated bone mineral density decreases in untreated patients with celiac disease which ultimately leads to pathologic fracture (15).

The results of bone densitometry in children with celiac in this study demonstrated that the prevalence of low bone mineral density in the lumbar and femoral regions were 35.4% and 22.9% respectively. This is in line with the findings of Meyer et al. who demonstrated that low bone density in lumbar and femoral regions were 34% and 27% respectively regardless of adherence to a gluten-free diet.

In the current study, low bone mineral density was generally more severe in boys, but there were no statistically significant differences in sex distribution of decreased bone density in femoral and lumbar regions. This is in agreement with the findings of Gangi et al. and in contrast with what Meyer et al. have reported. This discrepancy may be partly attributed to the differences in the study populations (16).

Five patients among those who were investigated in this study complained of skeletal and back pain and received alendronate under supervision of a pediatric rheumatologist. Three children (6.25%) had low bone density Z (Score < -2), and all had a history of low-trauma fracture. Therefore, it can be concluded that in this study, 6.25% of patients had osteoporosis, a finding in accordance with what reported by Ludvigsson et al. who asserted that the risk of low-trauma fracture is increased in patients with celiac diseases (17). This can be partly explained by the notion that in celiac disease, vitamin D and calcium malabsorption can lead to bone fragility with increased risk of low-trauma fracture. In this regard, our findings were consistent with those previously published in the literature.

In the current study, bone densitometry was carried out in the initial stages of the diagnosis, and in some patients, namely those in Marsh II and Marsh III stages who needed gluten-free diet, the imaging procedure was repeated after the initiation of the diet. Our findings demonstrated that there were no significant differences in lumbar and femoral bone density amongst children in different Marsh stages of celiac disease. (PV>0.05). Nonetheless, regardless of our results and their possible interpretations, it is imperative that all children in Marsh II and Marsh III stages of celiac disease should be screened and regularly monitored for low bone mineral density in the initial stages of the diagnosis.

Our results demonstrated that in the lumbar region, all children with lower-limit normal bone density had HLA DQ8 (100%), and the majority (57.1%) of those with low bone density had HLA DQ2/8 (P<0.05). Therefore, considering the significant differences in the prevalence of lumbar osteopenia amongst children with celiac disease with different HLA types, it is of vital importance that children with certain predisposing HLA types should undergo osteopenia diagnostic procedures and receive appropriate bone care. It should be mention, however, that our findings is in contrast with the outcomes of a study by Dehghani et al which did not demonstrate any relationship between HLA type, Marsh classification, and low bone mineral density in Iran (8).

Findings of the current study demonstrates that children with any history of low-trauma fracture should be further evaluated for possible diagnosis of celiac disease. This is in agreement with the findings of by Roshanzamir et al who contended that celiac disease may present with atypical presentation, particularly, low bone mineral density. Furthermore, it is highly recommended that in celiac and gastroenterology clinics where celiac disease is diagnosed and treated all across the country, bone densitometry should be carried out in the initial stages of the diagnosis, and repeated periodically later in the course of treatment.

In the end, it is recommended that with the view of controlling confounders, future similar studies in other provinces of Iran should be designed and carried out with larger cohorts, more variables, and longer follow up periods. Besides, it is advisable that for improving screening results, children with celiac disease who are not required to consume a gluten-free diet, namely those in Marsh I stage, should also undergo bone mineral density measurement. Considering grave consequences of osteoporosis in children with celiac disease, all diagnosed cases should be periodically screened for osteopenia and osteoporosis. In this regard, health policy-makers should implement effective nutrition strategies with calcium supplementation and physical activity promoting elements from the initial diagnosis stages and hold public education and awareness raising campaigns to promote parents' knowledge of the celiac disease to improve their children's nutrition and supplementation. The present study demonstrated that this can be of critical importance in remote and regional provinces (such as Lorestan) where osteoporosis in patients with celiac disease is woefully neglected, underreported, and understudied.

Conclusion

Findings of the current study demonstrated that bone mineral density studies should be seriously considered in children with celiac, particularly in those who are in Marsh II and Marsh III stages of the disease. However, it is advisable that children in the March I stage of the disease should also undergo regular bone mineral density evaluation as their celiac stage may progress.

Conflict of interests

The authors declare no conflict of interests.

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