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Bone Loss Correlated with Parathyroid Hormone Levels in Adult Celiac Patients

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ABSTRACT

BACKGROUND:
Celiac disease (CD) is a gluten-sensitive enteropathy with intestinal and extra-intestinal presentations in genetically predisposed cases. Musculoskeletal problems are one of the most common extra-intestinal manifestations in adult patients with CD. In the present study, we evaluated parathyroid hormone (PTH) levels in men and premenopausal women with CD who had osteoporosis and osteopenia.

METHODS:
This was a cross-sectional study of 387adult patients with CD who were referred to the Mashhad Celiac Disease Center between 2014 and 2019. We excluded bone loss confounding factors, including cases with endocrine disorders, corticosteroid consumption, smoking, and age of more than 55 years. Factors such as intestinal pathology, bone mineral density (BMD), serum level of anti-tTG, serum vitamin D, and PTH levels were also assessed at the time of diagnosis.

RESULTS:
Femoral osteopenia was found in 140 (36.2%) patients, and osteoporosis was observed in 55 (14%) patients. Spinal osteopenia and osteoporosis were observed in 127 (33%) and 63 (16.4%) patients, respectively. High levels of PTH were detected in 72/193 (27.2%) of the patients with CD. There was a significant difference between PTH levels in patients with osteopenia, osteoporosis, and normal BMD ($P=0.0001$).

CONCLUSION:
This study showed a correlation between low BMD and PTH levels in patients with CD, which suggests autoimmune endocrine disorder as a cause of osteopenia and osteoporosis.

KEYWORDS:
Celiac disease; Bone mineral density; Osteopenia; Osteoporosis; Parathyroid hormone

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INTRODUCTION

Celiac disease (CD) is a chronic, immune-based enteropathy in genetically-predisposed individuals, which is observed due to gluten exposure. CD has a wide range of intestinal and extra-intestinal manifestations. These manifestations include typical presentations such as malabsorption, weight loss, steatorrhea, dyspepsia, and atypical presentations including anemia, musculoskeletal and growth problems, and infertility. Musculoskeletal problems and low bone mineral density (BMD) are common extra-intestinal manifestations of CD.[1,2] Although various studies have been reported the low BMD in CD, a wide variation of bone loss prevalence (28-70%) has been reported,[3] and most studies in this area are cross-sectional and have not excluded menopause as a confounding factor.[4] We have recently shown that bone loss was more prevalent in CD with excluding the most important confounding factors, including menopause in women.[5] Patients with impaired bone mass have an increased risk of fractures, which has a negative effect on the quality of life and is an economic burden for both patients and health systems.[6] There are many theories about the pathophysiology of bone loss in CD, ranging from malnutrition and malabsorption of vitamins and hyperparathyroidism [7] to the increase in inflammatory cytokines.[8] Although the possibility of effective gluten free diet (GFD) on bone loss has been examined in previous studies, in some studies, there was not any effect for GFD, and also there was not any effect for usual medical treatment of osteoporosis in some other studies.[9] Therefore, the pathophysiology and treatment of bone loss in CD are still unknown. It has been reported that patients with CD had 40% higher risk of fracture compared with the aged match control group.[10] The endocrine disorder is one of the manifestations of CD, including type 1 diabetes and thyroid disorders, but little is known regarding its association with hyperparathyroidism or parathyroid hormone (PTH) level. PTH receptors are expressed on osteoblasts and increase the receptor activator of nuclear factor KB ligand (RANKL) expression, bone resorption, and osteoclastogenesis.[11] In this study, PTH levels were assessed in patients with CD with and without loss of BMD before a gluten-free diet. BMD is measured by dual-energy X-ray absorptiometry (DXA) and has been determined as the gold standard method for the diagnosis of osteoporosis. DXA is one of the parameters of the fracture risk assessment tool (FRAX).[12] In the present study, we evaluated the probable correlations between, serum PTH level, anti tTG, Ca, vitamin D, and intestinal pathology, with BMD.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted on patients who were referred to the Celiac Disease Center in Mashhad (Iran) during 2014 -2019. Informed consent in writing was obtained from each patient, and the study protocol was confirmed by the Ethics Committee of Mashhad University of Medical Sciences (Ethics number: IR.MUMS.fm.REC.1395.59).

BMD was measured using DXA in the femur and spine. According to the World Health Organization (WHO) criteria, bone mass with T scores above -1.0 are defined as normal, between -1.0 and -2.4 are defined as osteopenia or low bone mass, and equal or below -2.5 are defined as osteoporosis mostly based on the lumbar spine and femoral neck.

Sample Size and Selection Criteria

We enrolled 387 adult patients with CD who were under 55 years old. BMD was evaluated in a single center using DXA for all of these patients. The modified Marsh classification was used in the classification of mucosal lesions.[13] An anti-tTG Kit (Euroimmun, Germany) was used to assess the levels of anti-tTG (Ig A). The cases with positive anti-tTG (Ig A) level and Modified Marsh Classification grade$\geq$2 were considered as having CD. Moreover, the patients who had a Marsh grade$<$2 but a high titer of anti-tTG,[14] positive DQ2-DQ8, and clinical symptoms were also considered as having CD. Postmenopausal women, pregnant women, drug use (steroids, anticonvulsants, anticoagulants, calcium supplements), patients with certain other diseases (chronic liver disease, chronic kidney disease, thyrotoxicosis, hypogonadism, and other malabsorptive disorders), smokers, and patients with alcohol abuse ($\geq$3 drinks/day) were excluded from the study due to the confounding factors. This study was performed on two groups of patients with CD: those with and those without bone loss. All patients signed informed consent forms, which were

approved by the Ethics Committee of Mashhad University of Medical Sciences.

Statistical analysis

Data were analyzed using SPSS software (version17.0.1, SPSS Inc., Chicago). The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. We compared the height, weight, BMI, vitamin D levels, BMD, and anemia in patients with normal bone density, osteopenia, and osteoporosis. The analysis of continuous variables was done using the t-test. The Pearson X^2-test was used for discrete variables ($P<0.05$ was considered significant). For detection of an association between variables with odds of occurrence of osteoporosis and osteopenia, we used multiple logistic regressions.

RESULTS

Our data included 387 adult patients with CD, 115 men (29.7%), and 272 women (70.3%), who were between 20 and 55 years old with a mean age of 32.98±13.43 years. Most of the patients with CD in our registry presented classic symptoms of the disease. The tTG titer was five times higher than the normal level in 80.9% of our patients. Most of our patients (92.5%) had a Marsh classification of 3 in the duodenal biopsy. All demographic features are presented in table 1.

The group of CD patients who had BMD in their record, had a mean age of 33.32±10.9 years. Normal femoral BMD was observed in 192 (49.6%), femoral osteopenia in 140 (36.2%), and osteoporosis in 55 (14%) patients. A normal spinal BMD was observed in 195 (50.6%) patients

Table 1: Demographic and characteristic data of patient

Variables	Number	Valid %	Variables	Number	Valid %
Sex			**25 OH D3**		
Male	115	29.7%	Normal	119	32.2%
Female	272	70.3%	Insuficiency	118	31.9%
Presentation			Low	133	35.9%
Classic	243	65%	**PTH**		
Non-classic	118	31%	Normal	193	73%
Screening	13	4%	High	72	27.1%
tTG (IgA)			**Femoral BMD**	387	
Low	15	4%	Normal	192	49.6%
<3 times ULN	26	6.8%	Osteopenia	140	36.2%
3-5times ULN	24	6.3%	Osteoprosis	55	14.2%
>5 times ULN	314	82.8%	**Lumbar BMD**	385	
Pathology			Normal	195	50.6%
Marsh 1,2	28	7.2%	Osteopenia	127	33%
Marsh 3	356	92.7%	Osteoprosis	63	16.4%

BMD: Bone mineral density; PTH:Parathyroid hormone; tTG:Tissue transglutaminase antibody

Table 2: The association of variables with odds of occurrence of bone loss in the femur according to multiple logistic regression

Variables	Osteoporosis			Osteopenia		
	OR adjusted	*P* value	CI 95%	OR adjusted	*P* value	CI 95%
Age	1.04	0.0001	1.02 – 1.07	0.90	0.18	0.90 – 1.00
Sex (male/female)	0.45	0.024	0.18 – 0.87	1.14	0.56	0.72 – 1.79
BMI	0.95	0.01	0.91 – 0.89	0.98	0.04	0.91 – 0.99
tTG>=200	1.12	0.87	0.24 – 5.19	1.29	0.64	0.43 – 3.89

Sex (Reference group=men)

with CD, while 127 (33%) patients had osteopenia, and 63 patients (16.4%) had osteoporosis. We measured the PTH levels in 193 of these CD cases. The PTH level was high in 72 (27.7%) patients. The D3 level was normal in 32.2%, low in 35.9%, and insufficient in 31.9% of the cases. There was a significant risk of femoral osteoporosis in men ($P=0.0001$, table 2).

Male patients have more risk of osteoporosis than women, but female patients are at more risk of osteopenia in the femur. Generally, there was no correlation between tTG levels, calcium, phosphor, and 25OH D_3 in patients with normal or low BMD, including those with osteopenia and osteoporosis. There was a significant correlation between pathology Marsh 3 with osteopenia and osteoporosis in the femoral neck ($P=0.014$), whereas there was no significant correlation for the lumbar area ($P=0.173$). The risk of osteopenia in the lumbar spine was increased by age, low BMI, and in male patients, but they were not risk factors for osteoporosis (table 3).

In the lumbar spine, there was also no correlation between bone loss with tTG level and pathology ($P=0.137$). There was a significant correlation between PTH level and osteoporosis in the femoral and spine ($P=0.00001$, table 4).

DISCUSSION

Several studies have reported the low BMD in patients with CD, and there are different theories about the pathophysiology of bone loss in such patients.[6-8] The low BMD was reported to be more prevalent among premenopausal women with CD compared with control patients.[15] Micronutrient deficiency in CD cases can

Table 3: The association of variables with odds of occurrence of bone loss in the lumbar spine according to multiple logistic regression

Variables	Osteoporosis			Osteopenia		
	OR adjusted	*P* value	CI 95%	OR adjusted	*P* value	CI 95%
Age	1.00	0.95	0.98 – 1.01	1.05	0.001	1.03 – 1.07
Sex (male/female)	0.73	0.18	0.46 – 1.15	2.66	0.001	1.28 – 5.56
BMI	0.97	0.15	0.94 – 1.00	0.96	0.08	0.92 – 1.00
TTG>=200	1.94	0.31	0.53 – 7.06	0.61	0.42	0.18 – 2.01

Sex (Reference group=male)

Table 4: The association of PTH with odds of occurrence of bone loss in patients with celiac disease

Variables	PTH		Odds ratio (OR)	*P* value
	Normal	High		
Osteoporosis(F)				
No	185(77.1%)	47(22.9%)	1	0.0001
Yes	15(45.5%)	18(54.5%)	4.03(1.88 – 8.61)	
Osteopenia(F)				
No	108(73.5%)	39(26.5%)	1	0.731
Yes	65(71.4%)	26(28.6%)	1.10(0.61 – 1.98)	
Osteoporosis(S)				
No	156(77.2%)	46(22.8%)	1	0.0001
Yes	17(47.2%)	19(52.8%)	3.79(1.82 – 7.88)	
Osteopenia(S)				
No	116(73.0%)	43(27.0%)	1	0.896
Yes	57(72.2%)	22(27.8%)	1.04(0.56 – 1.90)	

predispose patients to low BMD, and the possibility of low calcium and vitamin D. The kidneys, skeletal system, and intestines are involved in maintaining calcium hemostasis and bone density, and it is balanced by PTH and 1, 25-dihydroxyvitamin D (1, 25[OH] $_2$ D_3). The increased levels of serum PTH enhance the activity of renal 1-α-hydroxylase, which converts 25-vitamin D into 1, 25 vitamin D, in order to improve calcium absorption at the intestinal level. On the other hand, high levels of 1, 25 vitamin D might have a paradoxical effect on increasing bone resorption.[16] PTH and vitamin D are predictive factors of bone mineralization in patients with CD and promote cortical bone loss. However, in our study, patients with osteopenia and osteoporosis had significantly high PTH levels, without any significant correlation with vitamin 25 OH D_3 and calcium. There was a probable independent effect of PTH on bone mineralization in these patients. In other studies, hyperparathyroidism was common among adult patients who were newly diagnosed with CD (27 %) and also among children (12%–54%).[17,18] It has been shown that high PTH was correlated with low D3 and patients with high PTH had less response in bone recovery after GFD.[19] The effect of hyperparathyroidism on the acceleration of bone loss and bone fracture risk and as a prognostic factor was shown in CD cases.[20] Bone loss was also related to secondary hyperparathyroidism because of calcium malabsorption in patients with the CD even without vitamin D deficiency.[21-23] In our study, 35.9% of the patients had low 25 OH D_3, and 31.9% had insufficient 25 OH D_3 levels (67.8% total). There was no significant correlation between BMD with low and normal vitamin D levels. High PTH cannot be due to the low calcium and there is a possibility of an increase in pro-inflammatory cytokines, which are presented in high PTH or in those with the bone loss.[24] It has been reported that the high levels of circulating cytokines may have a role in bone homeostasis in CD cases.[25] It has also been reported that the patients with CD were at an increased risk of primary hyperparathyroidism (PHPT) (HR = 1.91; 95% CI: 1.44–2.52).[7] In our study, we did not have high Ca and Vit D, and we had no specific information on possible adenoma or hyperplasia of parathyroid and PHPT. Theoretically, long-standing undiagnosed CD could lead to parathyroid hyperplasia and ultimately to tertiary hyperparathyroidism.

We observed that there was a significant correlation between BMI and low BMD in the femoral neck. There was a correlation between low BMD in both the femoral neck and spine and PTH level. Like other studies, low BMD was common in all ages of premenopausal women and all ages of men in our study.[26] It has been shown that there was a correlation between high levels of anti-tTG and low BMD.[27] It is also possible that small intestinal inflammation with increased autoantibody levels triggers PTH. In our study, mucosal atrophy and autoantibody titer were not correlated with low BMD. It is better to screen BMD at the time of CD diagnosis, and more research is required on the pathophysiology of bone loss in these patients.

CONCLUSION

Patients with CD and low BMD had significantly high levels of PTH in comparison with the patients with normal bone density. High PTH had no correlation with 1,25[OH]$_2$ D_3 and Ca levels. Hyperparathyroidism or a high PTH level can be the cause of bone loss in patients with CD by autoimmune etiology. More research should also be done on the other causes of low BMD or high PTH, including different inflammatory cytokines in CD as possible factors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1395.59) and was a thesis of a medical student. All participants gave written informed consent to participate.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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None.

AUTHORS' CONTRIBUTIONS

NB, MM, and AB were involved in drafting and editing. YM was involved in experiments and data analysis. AG supervised the project. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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