Bone mineral density and vitamin K status in children with celiac disease: Is there a relation?

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ABSTRACT

Background/Aims: To investigate bone mineral density (BMD) in children with celiac disease (CD) and to evaluate the association between vitamin K levels and osteoporosis.

Materials and Methods: Children with CD and age- and sex-matched healthy control subjects were prospectively included in the study. BMD was measured, and serum anti-tissue transglutaminase IgA, ferritin, folate, vitamin B12, 25-hydroxy vitamin D and K2, calcium, phosphate, alkaline phosphatase, and parathormone were assayed in all subjects.

Results: Overall, 72 patients (mean age 11.69±3 years, 59.7% female) and 30 healthy subjects (mean age 12.27±2.12 years, 63.3% female) were enrolled. The mean BMD Z score of the celiac group was significantly lower than that of the control group (−1.23±1.07 vs. −0.35±1.04, p=0.001). Vitamin D and K2 values did not differ significantly between the two groups (p>0.05). BMD was positively correlated with vitamin D (r=0.198, p=0.001) and negatively with PTH (r=−0.397, p=0.002).

Conclusion: The BMD of celiac patients was lower than that of the control subjects. There was no difference in terms of vitamin D and K2 levels between the two groups. Further studies investigating the level and effect of vitamin K on bone in CD are needed.

Keywords: Celiac disease, bone density, vitamin K

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder characterized by an immune response to ingested gluten peptides in genetically susceptible individuals. The estimated prevalence of CD is between 0.5% and 1.26% in America and Europe, respectively (1). Dalgic et al. (2) recently reported the prevalence of CD in Turkey at 0.47%. CD is characterized by classical gastrointestinal (GI) symptoms, such as diarrhea, malabsorption, weight loss, vomiting, abdominal discomfort, and distension in infants and small children. However, extraintestinal disorders (including anemia, osteoporosis, dermatitis herpetiformis, neurological problems, and infertility) may also be symptoms of the disease, even in the absence of GI symptoms, especially in later ages and in adults (1,3).

Low bone mineral density (BMD) has been reported in many patients with CD, both treated and untreated (3). Bone mineralization depends on metabolic, nutritional, endocrine, and genetic factors. The exact mechanism involved in osteopenia in children with CD remains unclear. Micronutrient malabsorption, inflammatory cytokines, and autoimmunity may impact bone metabolism in CD. Impaired absorption of necessary nutrients for bone mineralization such as calcium and vitamins D and K may represent the principal cause of low BMD (4). Previous studies of adults have proposed that vitamin K exhibits a beneficial role in bone mineral metabolism by acting as a cofactor in the post-translational carboxylation of several bone proteins (5). This study was intended to investigate BMD in children with CD and to assess the relationship between low BMD and vitamin K levels.

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MATERIALS AND METHODS

Patients and controls

From December 1st, 2015 to February 28th, 2016, children between the age of 8-14 years residing in Erzurum, Turkey (the latitude of the city is 41:17E) were prospectively recruited for the study. The patient group was formed from 26 newly diagnosed (ND) patients with CD and 46 patients undergoing follow-up for CD (mean follow-up time 2.4 years). The diagnosis of CD was based on the criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (villous atrophy in duodenal mucosa, positive serological markers of disease, and clinical improvement after gluten-free diet (GFD)) (6). Patients were categorized into three groups: newly diagnosed (ND), good GFD compatible, and non-GFD compatible, based on anti-tissue transglutaminase (anti-tTG) IgA levels. Normal tTG IgA levels (0-20 U/ml) were defined as good GFD adherence, and high tTG IgA levels (>20 U/ml) were defined as poor GFD adherence. Patients receiving treatment that might affect bone metabolism (including vitamin D, corticosteroids, vitamin K, calcium supplement, or anticonvulsants) and patients with type 1 diabetes, Down syndrome, hypothyroidism, or systemic disease were excluded, because these would compromise the BDM results. Overall, 30 age- and sex-matched healthy children with negative serologic tests for CD were enrolled as a control group. No history of chronic illness, congenital or acquired bone disease, competitive sporting activities, or use of medication involving hormones, vitamin, or calcium supplements was present in any of the healthy subjects. Informed consent was obtained from the parents of all enrolled participants. The study was approved by the local ethics committee.

Anthropometric measurements and bone mineral density

Anthropometric parameters, including height and weight, were assessed in all participants. Weight and height were determined using a portable digital standard stadiometer (Charder®, MS4900, Taichung City, Taiwan). Z scores for weight, height, and body mass index (BMI) for age were calculated based on the data from the general Turkish pediatric population (7). The lumbar spine BMD is the most representative indicator of total body less head BMD. Hip, femur, and neck BMD is not recommended because of variabilities in the skeletal development of the growing organism (8). Dual energy X-ray absorptiometry (g/cm^2) was employed to determine bone mass and density. Z scores according to age, height, pubertal stage, and bone age were calculated (9). For pediatric individuals, the definition of low bone mass is defined as BMD Z score is less than or equal to −2.0 adjusted for age, sex, and body size, the definition of osteoporosis requires the presence of BMD Z score of ≤-2.0 and a clinically significant fracture history, namely, vertebra compression fracture or long-bone fracture of the lower extremities or two or more long-bone fractures of the upper extremities (10).

Biochemical measurements

Human anti-tTG IgA was measured at the time of diagnosis and during follow-up visits using an immunoenzymatic assay. Laboratory parameters including complete blood count, 25-hydroxy vitamin D3, calcium, phosphate, magnesium, alkaline phosphatase (ALP), and parathormone (PTH) were assayed. Serum vitamin K2 concentrations were measured using a human-specific sandwich enzyme-linked immunosorbent assay (Human Vitamin K2 ELISA immunoassay kit; Cat. No. MBS9302591, Mybiosource, USA).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM Inc.; SPSS Statistics for Windows, Version 18.0. Chicago, IL, USA). The variables were investigated using Kolmogrov Simirnov/Shapiro-Wilk test and visual methods (histograms and probability plots) to determine normal distribution. Descriptive analyses were presented using means and standard deviations for normally distributed variables, and median and minimum-maximum for the non-normally distributed and ordinal variables. The differences in parametric data between CD and healthy participants were calculated using Student's t distribution. The differences between continuous variables were evaluated using the non-parametric Mann-Whitney U test. The non-parametric Kruskal-Wallis test was used for statistical analysis of the celiac groups. The correlation coefficients and their significance were calculated using the Pearson/Spearman test. A p-value <0.05 was considered to be statistically significant.

RESULTS

The anthropometric measurements of patients with CD and the control group are shown in Table 1. The mean Z scores of height for age, weight for age, BMI, and BMI in celiac patients were significantly lower compared with the control group ($p<0.05$). The patient and control groups had no clinically fracture history. When the serum levels of bone mineral metabolism parameters were eval-

Table 1. Anthropometric data of patients with celiac disease and those in the control group

	Patients (n=72)*					Controls* (n=30)	p#
	New diagnosed (n=26)	Good GFD (n=21)	Poor GFD (n=25)	p	Total Patients (n=72)		
Mean age (years)	10.9±3.4	11.6±2.8	12.4±2.7	0.2	11.69±3.04	12.27±2.12	0.490
Weight Z score	−2.55±1.22	−1.6±1.57	−1.65±1.41	0.01	−1.96±1.45	−0.55±1.05	0.001
Height Z score	−2.34±1.15	−1.34±1.61	−1.49±1.32	0.02	−1.75±1.41	−0.56±1.24	0.001
BMI Z score	−1.53±0.89	−1.15±1.31	−0.98±0.99	0.113	3.5 (1-16)**	7.5 (4-13)**	0.001

BMI: body mass index; GFD: gluten-free diet
*: values are mean±SD
**: values are median (min-max)
#: comparison of the total patients and controls

Table 2. Serum levels of bone mineral metabolism parameters and vitamins in patients with celiac disease and those in the control group

	Patients (n=72)*					Controls* (n=30)	p#
	New diagnosed (n=26)	Good GFD (n=21)	Poor GFD (n=25)	p	Total Patients (n=72)		
Calcium (mg/dL)	9.6±0.5	10.1±0.9	9.8±0.3	0.013	9.9±0.63	9.5±1.4	0.260
Phosphate (mg/dL)	4.9±0.6	4.6±0.7	4.6±0.7	0.25	4.7 ±0.72	3.9±0.64	0.001
Magnesium (mg/dL)	1.9±0.08	1.9±0.1	1.8±0.1	0.26	1.9±0.1	2.05±0.2	0.001
ALP (U/L)	235±68	250±115	216±72	0.64	216 (84-593)**	149 (63-367)**	0.002
PTH (pg/mL)	85.4±70.6	62.7±33.6	82±68.4	0.2	65 (22-395)**	45 (16-81)**	0.001
Ferritin (ng/mL)	7 (3-139)**	26.2 (11-93)**	21.2 (1-96)**	0.001	25.2±24.8	39.6±38.4	0.018
Folate (ng/mL)	3.5 (1-16)**	7.5 (4-13)**	5.6 (2-52)**	0.01	7.7±8	8.17±6.2	0.25
Vitamin B12 (pg/mL)	254 (156-692)**	414 (60-845)**	389 (199-804)**	0.001	384±172	393±228	0.74
Vitamin D (ng/mL)	17.88±9.19	19.76±10.67	19.86±8.8	0.7	17.2(1-46.4)**	15.8(4.3-46.6)**	0.340
Vitamin K (nmol/L)	2.21±1.57	2.67±2.31	3.07±2.46	0.6	2.64±2.1	3.05±2.3	0.420
BMD Z score	−0.93±1.48	−0.96±1.25	−0.77±0.89	0.8	−1.23±1.07	−0.35±1.04	0.001

BMI: body mass index; GFD: gluten-free diet
*: values are mean±SD
**: values are median (min-max)
#: comparison of the total patients and controls

uated, no hypocalcemia was detected in patients with CD, and serum calcium levels did not differ significantly from those in the control group (p>0.05). Serum phosphate, magnesium, ALP, and PTH values differed significantly between the two groups (p<0.05). On comparing the CD and control groups, it was observed that Vitamin D and K_2 values did not differ (p=0.34 and p=0.42, respectively). Likewise, when the patient and control group were categorized according to their BMD values (low BMD and osteoporosis), vitamin D and K_2 values did not differ significantly. The lumbar spine BMD Z score in CD was significantly lower compared with that in the control

group (−1.23±1.07 vs. −0.35±1.04, p=0.001) (Table 2). Patients with CD were divided into three groups based on diet adherence. The good GFD compatible group had been treated with GFD for 2.7 years (range, 0.5-10.5 years) and the non-GFD compatible group for 3.3 years (range, 0.5-13.6 years). Patients in the ND group had lower height Z scores, weight Z scores, and BMI than those in the poor GFD adherence and good GFD adherence groups (p=0.02, p=0.01, p=0.008, respectively) (Table 1). Serum calcium levels were lower in ND patients, whereas no significant difference was observed in serum phosphate, magnesium, ALP, PTH, vitamin D, and vitamin K levels, or BMD Z scores among the three groups (Table 2).

Bone mineral density was correlated positively with vitamin D (r=0.198, p=0.001) and negatively with PTH (r=−0.397, p=0.002), whereas no correlation was found between BMD and BMI Z score or vitamin K. PTH was positively correlated with TTG (r=0.270, p=0.02).

DISCUSSION

This study investigated the prevalence of metabolic bone disease and the association between vitamin K levels and low BMD in children with CD. Our results revealed lower BMD in patients with CD compared with healthy participants, but unexpectedly, there was no difference in vitamin D or K_2 levels between the two groups.

Numerous studies have assessed BMD in CD. Children with CD have a lower bone mass at diagnosis compared with healthy controls and have revealed complete recovery or significant improvement of BMD following diet therapy (11-14). In this study, we also observed a lower BMD in celiac patients compared with the healthy subjects. However, we observed no differences between ND, good GFD adherence, and poor GFD adherence patients with CD. This may be due to a lack of strict, long-term compliance with GFD in patients with CD and good GFD adherence. Patients with CD should continue a GFD to significantly increase bone mass during early childhood and puberty, which is a period of rapid growth and development. Furthermore, in addition to adhering to a GFD, patients with CD must also receive adequate calcium and vitamin D support (15,16).

The mechanism of CD-associated osteopenia is multifactorial. A chronic malabsorption of nutrients affects bone formation (vitamins D and K, and calcium), whereas chronic intestinal inflammation (increased production of cytokines and autoimmune alterations) and trace element and magnesium deficiencies may be factors involved in low BMD in patients with CD (4,17). Several adult studies have reported that vitamin K plays an important role in optimizing bone health (18-20), and an increased fracture risk has been reported in individuals with low vitamin K intake (21). Previous studies have suggested that vitamin K promotes bone mineralization by increasing the carboxylation of osteocalcin, a protein synthesized by osteoblasts, and by affecting calcium balance, a key mineral in bone metabolism. Vitamin K deficiency has been shown to result in the increased synthesis of undercarboxylated osteocalcin (ucOC). The amount of ucOC is thought to be a sensitive indicator of vitamin K status (22).

One previous study shows that the individuals who have lower serum level of vitamin K or higher ucOC have a higher risk of having low BMD and developing osteoporotic fractures (23). Van Summeren et al. (24) reported higher circulating ucOC values in healthy children compared with adults. Clinical trials with vitamin K supplements in both healthy children and children with cystic fibrosis have shown a decreased level of circulating ucOC and thus improved vitamin K levels (25,26). Data concerning the role of vitamin K and bone health in CD are limited. Mager et al. (27) examined the vitamin K status (serum levels of protein induced in vitamin K absence-II whose abnormal values are indicative for vitamin K deficiency) in ND children with CD and reported that 25% had suboptimal levels at the time of diagnosis.

Both vitamin K1 (phylloquinone) and vitamin K2 (menaquinone) promote bone mineralization. However, menaquinone has been shown to be more potent. Vitamin K_2 is found in fermented dairy and soy products, fish, meat, liver, and eggs and is also produced by intestinal bacteria (23). In this study, we observed no difference in levels of vitamin K_2 between patients with CD and healthy participants. Similarly, ND disease, good GFD adherence, and poor GFD adherence patients with CD had comparable vitamin K_2 levels. Vitamin D levels did not differ between patients with CD and healthy participants. This may be attributed to a generally low intake of vitamin D in healthy children and adolescents in Eastern Anatolia (28). Adequate vitamin D and calcium intake plays an important role in the prevention and treatment of osteoporosis.

Poor calcium and vitamin D nutrition and lower concentrations of circulating ionized calcium result in PTH se-

cretion and increased PTH levels (secondary hyperparathyroidism). We observed higher phosphate, ALP, and PTH levels in patients with CD compared with the control group. We also detected minor hypocalcemia in ND patients with CD. This may be related to chronic calcium malabsorption. However, there were no differences in serum phosphate, ALP, and PTH levels between ND, good GFD adherence, and poor GFD adherence patients with CD. Although not statistically significant, PTH levels were higher in ND and poor GFD adherence patients with CD than in patients with CD and good GFD adherence. Selby et al. (29) observed reduced BMD related to secondary hyperparathyroidism without vitamin D deficiency in patients with CD. Valdimarsson et al. (30) reported that patients with CD who were maintaining a GFD have secondary hyperparathyroidism and low BMD.

In this study, a higher level of anti-tTG IgA in patients with CD was correlated with higher PTH levels (r=0.270, p=0.02). Tissue transglutaminase is a cross-linking enzyme that partly functions by stabilizing the tissue matrix. It is found in various cells and tissues, including bone and cartilage matrix proteins, and osteoblasts. It has been implicated in various diverse biological roles and regulates cell-matrix interactions by binding and cross-linking extracellular matrix proteins. Impairment of bone mineral metabolism in CD has been attributed to several factors other than calcium and vitamin D malabsorption. Secondary hyperparathyroidism has been reported in CD (29). Anti-tTG antibodies that form in CD may affect activity by binding to tTG in bone tissue. This may result in the elevation of PTH levels because of bone mineralization impairment.

The limitation of the present study is that the levels of calcium, phosphorus, and vitamin K in participants' diets were unknown because dietary anamnesis was not obtained from all the participants. We cannot know the extent of their dietary compliance prior to participation because this is a cross-sectional study, and patients with longstanding diagnosis participating in our study did not attend regular checkups.

Bone mineral density was lower in patients with CD than in the healthy participants, whereas no difference was found in levels of vitamin D and K_2 between the groups. In addition, no correlation was observed between vitamin K levels and osteopenia. Further studies investigating the level and effect of vitamin K on bone in CD are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from The Ethics Committee of Erzurum Regional Training and Research Hospital (Decision Date: May 28, 2015; Decision No: 37732058-53/2862).

Informed Consent: Informed consent was obtained from patients who participated in this study.

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