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Bone mineral density and growth in children with coeliac disease on a gluten free-diet

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Background/aim: To evaluate changes in growth and bone metabolism during consumption of a gluten-free diet (GFD) in children with coeliac disease (CD).

Materials and methods: Thirty-seven children with CD (mean age of 8.8 ± 4.6 years, 21 girls) were enrolled. Anthropometric measurements, bone mineral density (BMD) in lumbar 2–4 vertebrae, and serum alkaline phosphatase, calcium, and phosphorus levels at diagnosis and at follow-up were recorded.

Results: The mean follow-up period was 3.5 ± 2.3 years. The BMD of patients was significantly lower than that of control subjects at the time of diagnosis but not after 1 year of the GFD. Incidence of low BMD with respect to z-scores for chronological age (CA) was significantly higher than z-scores for height age (HA) (P = 0.006). At the first year of GFD, BMD, BMD z-score, height-for-age z-scores, and weight-for-age z-scores were significantly increased compared with the baseline, but not after 1 year of the GFD.

Conclusion: In CD, the first year of GFD is important in weight gain, linear growth, and improvement of BMD. A considerable relation of low BMD in children with CD, with respect to z-scores for CA, may be a result of misinterpretation of low BMD due to short stature.

Key words: Bone mineral density, children, coeliac disease, gluten-free diet

1. Introduction

Coeliac disease (CD) is a common inflammatory enteropathy causing certain lifelong complications, including osteoporosis (1–3). Bone mineral density (BMD) is frequently low in newly diagnosed CD cases. A gluten-free diet (GFD) reverses the changes in bone metabolism associated with CD. An increase in, or stabilization of, BMD is particularly evident during the first year on such a diet (1,2,4–10). Recovery of bone abnormality is correlated with the duration of the GFD, but such a restricted diet may cause bone mineralization to be inadequate (11). In addition, BMD interpretation in children of short stature may lead to misdiagnosis of low bone BMD, because of the small bone size of such children (12,13).

In this retrospective study, we evaluated trends in height, weight, and BMD in children with CD on a long-term GFD and determined the effect of height on BMD z-score calculations.

2. Materials and methods

The medical files of 109 patients diagnosed with CD between 1 June 2004 and 1 June 2007 at the Pediatric Gastroenterology Department of Ankara University School of Medicine were retrospectively reviewed using the revised criteria from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (14).

The study excluded patients with any other chronic illness, those that had been prescribed any drug that affected bone metabolism, those were followed up for less than 1 year after diagnosis, and those who refused to adhere to the GFD.

A total of 37 patient charts meeting the inclusion criteria were formally reviewed. Age, sex, height, weight, and BMD levels at the lumbar 2–4 vertebrae (L2–L4), as well as serum levels of total protein, albumin, total calcium (Ca), inorganic phosphorous, and total alkaline phosphatase (ALP) at diagnosis and at follow-up, were recorded. Compliance with the GFD was also noted.

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Based on patients' self-reports or low titer levels of tissue transglutaminase antibody, occasional gluten intake was noted. Patients strictly adherent to the GFD were compared to those who occasionally consumed gluten.

Patients with gastrointestinal symptoms, including chronic diarrhea and malabsorption, were considered to have classical CD; those with unusual intestinal complaints, including constipation, or extraintestinal symptoms such as anemia and/or short stature were classified as having atypical CD. Patients with elevated antibody levels characteristic of CD and who exhibited loss of villi of the small intestine but who had no signs or symptoms of CD were considered to have silent CD (14).

BMD was measured using a Hologic Discovery A instrument employing dual-energy X-ray absorptiometry (DEXA). BMD z-scores were determined for both chronological age and height for every patient, and were compared to the mean L2–L4 BMDs of 143 healthy age- and sex-matched Turkish children (77 girls, mean age of 10.8 ± 3.3 years). Z-scores were calculated in terms of both chronological age and height using the following formula:

z-score = (patient BMD) – (mean BMD of healthy age- and sex-matched children)

Standard deviation of healthy age- and sex-matched children

Osteoporosis was considered present when a z-score was less than −2, and osteopenia was present when a z-score ranged from −1 to −2 (15). The weight-for-age z-scores (WAZs) and height-for-age z-scores (HAZs) were calculated by comparing patient data with the growth charts of healthy age- and sex-matched Turkish children (16,17).

The study protocol was approved by the Ethics Committee of the Ankara University School of Medicine. Informed consent was obtained from each patient's parents.

Results are presented as means ± SDs with descriptive statistics. Student's unpaired t-test and Friedman's test were used as appropriate. When the variances were unequal or the distributions were not normal, the Mann–Whitney U test was performed. The bivariate two-tailed correlation test was run, and Spearman's correlation coefficients calculated when correlations were sought. The significance level was set at $P < 0.05$. Bonferroni correction ($P < 0.008$) was used when adherence to the GFD was compared among patients. Statistical analyses were performed using SPSS, version 11.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 37 patients, 56.8% were female. The median age at diagnosis was 8.8 ± 4.6 years (range 1.25–16 years). In total, 27 (72.9%) patients were prepubertal at presentation, 20 (54.1%) patients had classical disease, 13 (35.1%) patients had atypical disease, and 4 (10.8%) patients had silent CD. The mean follow-up period was 3.5 ± 2.3 years (1–8 years).

The WAZs, HAZs, weights, and heights at the baseline and at follow-up are shown in Table 1. At diagnosis, the heights and weights of 17 (45.9%) patients were within normal ranges. In 14 and 11 children, respectively, the HAZs and WAZs were <−2. At follow-up, significant increases in heights, weights, HAZs, and WAZs were evident after the first year of the GFD compared to the baseline. Despite there being no difference in HAZs and WAZs over the 3 consecutive years of the GFD, a significant increase was observed in weight over the first 2 years and in height over all 3 years (Table 1).

All of the patients with low WAZs at the baseline exhibited significant weight gain and their WAZs were within the normal range after 3 years on the GFD. However, at that time, the HAZs remained at <−2 in 3 of 14 children with low HAZs at the baseline.

On diagnosis, the mean BMD was significantly lower in children with CD (0.507 ± 0.1 g/cm^2) than in controls (0.5913 g/cm^2) ($P = 0.005$); however, this difference was eliminated after 1 year of the GFD. Significant improvements in BMD and BMD z-scores for both height

Table 1. Mean height-for-age z-scores (HAZs), weight-for-age z-scores (WAZs), lumber spine bone mineral density (BMD), and BMD z-scores for chronological age (CA) and height age (HA) (±SD) of coeliac patients at diagnosis and upon follow-up.

	Diagnosis	1 year	2 year	3 year	4 year	P values*
N	37	26	20	17	14	
HAZs	−1.6 ± 1.6	-1.3 ± 1.6	−1 ± 1.1	– 0.7 ± 1.2	−1.1 ± 1	0–1 year = 0.02
WAZs	−1.4 ± 1.1	−0.8 ± 1	−0.6 ± 0.6	−0.9 ± 0.8	−1 ± 0.7	0–1 year = 0.02
BMD L2–4 (g/cm^2)	0.507 ± 0.1	0.550 ± 0.1	0.634 ± 0.2	0.614 ± 0.1	0.679 ± 0.6	0–1 year = 0.001
BMD z-scores for CA	−0.9 ± 1.1	−0.4 ± 0.9	−0.1 ± 0.1	−0.7 ± 0.9	−0.8 ± 0.9	0–1 year = 0.001
BMD z-scores for HA	−0.2 ± 1.1	0.1 ± 0.8	0.3 ± 1.5	−0.1 ± 0.7	0.1 ± 1.3	0–1 year = 0.01

*P values in 1–2 years, 2–3 years, and 3–4 years > 0.05 for HAZs, WAZs, BMD, and BMD z-scores for CA and HA.

age (HA) and chronological age (CA) were evident after 1 year of the GFD compared to the baseline (P = 0.001, P = 0.01, and P = 0.001, respectively), with a BMD increment of 0.043 ± 0.14 g/cm^2; however, no change was evident in later years (Table 1). At presentation, we found no correlation between BMD z-scores calculated with HA and CA (P > 0.05).

The incidence of osteopenia and osteoporosis at the time of diagnosis is shown in Table 2. Incidence of low bone density was significantly higher when calculated for CA (P = 0.006).

Serum Ca and ALP levels significantly increased after the first year of the GFD, compared to the baseline (P = 0.02 and P = 0.03, respectively), but no later changes were evident (Table 3). We found no difference in levels of total protein, albumin, or phosphorus between diagnosis and in later years (all P values > 0.05).

Twenty-seven (72.9%) patients were prepubertal at presentation, but BMD z-scores did not differ from those of pubertal patients. Although prepubertal patients showed significant improvements in BMD and BMD z-scores for CA after the first year of the GFD (at the baseline, BMD 0.449 ± 0.1 g/cm^2, and z-score 1.2 ± 1; and after 1 year of the GFD, 0.518 ± 0.1 g/cm^2, and 0.56 ± 0.9; P < 0.001 and P < 0.001, respectively), we found no significant improvements in the BMD or BMD z-score of postpubertal patients.

We found no difference between patients with classical and atypical CD with respect to age, pubertal status, WAZs, HAZs, or serum levels of Ca, ALP, phosphorus, total protein, or albumin. The mean BMD was significantly lower at the baseline in patients with classical CD compared to those with atypical CD (P = 0.012), whereas the BMD z-scores for both CA and HA did not differ (Table 4). Low bone density was evident in 60% (12/20) of patients with classical CD, in 53.8% (7/13) of patients with atypical CD, and in 50% (2/4) of patients with silent CD.

In total, 21 patients strictly adhered to the GFD, but 16 patients exhibited occasional gluten intake. We found no difference in HAZs, WAZs, BMD increments, BMD z-scores, or Ca, ALP, phosphorous, total protein, or albumin levels of patients due to adherence to the GFD (P > 0.05). In later years, osteoporosis according to CA was only observed in two consecutive patients who initially had normal and osteopenic BMD and thereafter occasional gluten intake (Table 2).

4. Discussion

The relationship between low bone density and CD in children has been described in previous studies. Both cross-sectional and longitudinal studies have revealed variable but remarkable improvements in bone mass during consumption of a GFD (4–11,18,19). We showed that BMD was significantly lower in patients with CD, but significantly improved during the first year of a GFD. In contrast, Margoni et al. (19) reported that the BMD of children with CD (mean age of 9 years) remained lower than normal, even in the second year of a GFD. However, most pediatric studies have found significant increases in BMD during the first year of a GFD (4,5,7,9), but no difference thereafter (4,20,21). In the present study, we confirmed these results. Our longitudinal work showed that BMD did not significantly increase after 1 year of the GFD.

In several studies, BMD reduction by chronological age was found to be 16.5–65% (4–7, 9). In CD, the axial skeleton is the most affected region; thus, lumbar BMD measurements are preferred. Because BMD is closely associated with age, weight, and height, the smaller bone volumes of stunted patients may yield low BMD values (12). To cover this possibility, we calculated z-scores for both CA and HA, and low BMD was evident in 56.7% and 21.6% of patients, respectively (P = 0.006). A calculation of BMD z-scores for CA (only) in CD children of short stature may explain the high prevalence of low BMD in children with CD. We were unable to determine the bone age of all children because it was a retrospective study. Moreover, children would be exposed to radiation while determining bone age.

Turner et al. (6) found no difference in basal lumbar BMD z-scores between asymptomatic and symptomatic patients at presentation. In our study, patients with

Table 2. Frequency of low bone mineral density (BMD) in coeliac patients at diagnosis and follow-up.

		For chronological age N (%)	For height age N (%)	P value
At diagnosis	Osteopenia	17 (45.9)	7 (18.9)	
	Osteoporosis	4 (10.8)	1 (2.7)	
	Total low BMD	21 (56.7)	8 (21.6)	0.006
On follow-up	Osteopenia	6 (16.2)	2 (5.4)	
	Osteoporosis	2 (5.4)	0 (0)	
	Total low BMD	8 (21.6)	2 (5.4)	

Table 3. Bone health indices in coeliac patients at diagnosis and upon follow-up.

	Diagnosis	1 year	2 year	3 year	4 year	P values*
N	37	26	20	17	14	
Total calcium (mg/dL)	9.1 ± 0.6	9.5 ± 0.3	9.3 ± 0.5	9.6 ± 0.5	9.4 ± 0.6	0–1 year = 0.02
Total alkaline phosphatase (IU/L)	239.5 ± 101.5	276.5 ± 127.7	237.6 ± 92	250.7 ± 136.2	257.5 ± 153.1	0–1 year = 0.03
Phosphorous (mg/dL)	4.8 ± 0.9	7.5 ± 11.8	5 ± 0.7	4.8 ± 0.8	5.2 ± 0.8	0–1 year N.S.
Total protein (g/dL)	6.6 ± 1.2	7.1 ± 0.5	7.1 ± 0.6	7.2 ±0.6	7.2 ± 0.5	0–1 year N.S.
Albumin (g/dL)	4.1 ± 0.6	4.5 ± 0.4	4.3 ± 0.6	4.4 ± 0.3	4.4 ± 0.2	0–1 year N.S.

*P values in 1–2 years, 2–3 years, and 3–4 years > 0.05 for total calcium, total alkaline phosphatase, phosphorous, total protein, and albumin levels.
N.S.: Nonsignificant

Table 4. Age, height, height-for-age z-scores (HAZs), lumber spine bone mineral density (BMD), and BMD z-scores for chronological age (CA) and height age (HA) of coeliac patients according to clinical type at diagnosis.

	Classical CD	Atypical CD	P value
Number of patients (%)	20 (54.1)	13 (35.1)	
Age (years)	7.3 ± 4.5	11 ± 4.1	N.S.
Height (cm)	109.6 ± 23.1	132.3 ± 17.6	P = 0.019
HAZs	–1.9 ± 1.3	–1.8 ± 1.5	N.S.
BMD L2–4 (g/cm^2)	0.445 ± 0.1	0.611 ± 0.1	P = 0.012
BMD z-scores for CA	–1.2 ± 1.1	–0.7 ± 1.1	N.S.
BMD z-scores for HA	–0.4 ± 1.1	0.01 ± 1.3	N.S.

N.S.: Nonsignificant

classical CD were shorter (due to their age) and had significantly lower BMDs than those with atypical CD. This difference in BMD is thought to be attributable to short stature, because the BMD z-scores for chronological age and height did not differ. Because BMD did not differ between groups, we concluded that clinical presentation did not influence BMD.

Prepubertal diagnosis is important in terms of bone restoration in CD patients. In previous studies, children diagnosed prepubertally exhibited significant BMD improvements (7,22). Similarly, we found that the BMD of prepubertal subjects increased significantly over the first year of treatment, thereby emphasizing the importance of bone restoration prior to puberty. Moreover, no significant improvements in the BMD or BMD z-score of postpubertal patients were determined.

Commencement of a GFD at younger ages normalizes BMD in CD children. Scotta et al. (23) revealed that initiation of a GFD prior to 2 years of age afforded a higher BMD. Tau et al. (5) reported that commencement of a GFD prior to 4 years of age resulted in BMD normalization approximately 1 year later. In this study, we found significant improvements in both BMD and BMD z-scores irrespective of age at presentation in the first year of the GFD.

The normal BMD increment of 10-year-old children is 0.02 g/cm^2 per year (5). Tau et al. (5) reported a BMD increment of 0.1 g/cm^2 over 14 months in children (4.9 ± 4.3 years old) with CD. Mora et al. (24) reported a BMD increment of 0.06 g/cm^2 over a 1.4-year period in patients with CD aged 2.5–20.5 years. In the present study, the BMD increment of children with CD (mean age 8.83 ± 4.6 years) was 0.043 ± 0.14 g/cm^2 during the first year of the GFD. In adults who were nonadherent to the GFD, BMD loss of up to 0.0057 g/cm^2 per year and a high prevalence of osteopenia and osteoporosis have been reported (8,25). Blazina et al. (25) found that even patients on a strict GFD were at risk of low BMD because of low intake of either Ca

or vitamin D. Occasional gluten ingestion, or a limited diet, may cause a reduction in BMD. Thus, two patients who had occasional gluten ingestion developed osteoporosis at follow-up despite having normal and osteopenic BMD at diagnosis. We were unable to definitively pinpoint minimal gluten exposure as the reason, because we could not investigate the effect of vitamin-D levels and other parameters that affect bone metabolism.

Children with CD placed on a strict GFD may exhibit late catch-up growth or may remain stunted (20,26,27). We found significant improvements in WAZs and HAZs at the end of the first year of a GFD. At follow-up, 21.4% of patients (3/14) remained short statured after the third year of the GFD, but all patients of low weight at presentation (11/11) were within normal weight ranges by the end of the second year of the GFD.

The principal limitation of our study was the relatively small number of patients and the lack of data on vitamin D and parathyroid hormone, as well as daily Ca intake.

In conclusion, the first year of a GFD is very important in terms of weight gain, linear growth, and improvement in BMD, especially in the prepubertal period. In short-statured children with CD, bone density may be compared with that in height-, age- and sex-matched controls to avoid misinterpretation of low bone density. In addition, no further follow-up BMD measurements may be required in children with CD on a GFD with normal-basal BMD.

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