

Bone Mineral Density and Importance of a Gluten-Free Diet in Patients With Celiac Disease in Childhood

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ABSTRACT. *Objectives.* Celiac disease (CD), a common cause of malabsorption, is known to be associated with disorders of the skeleton, but there are conflicting data about the effect of diet on bone metabolism. The aims of this study were to investigate the prevalence of osteopenia; to identify the relationship between bone mineral density (BMD), serum calcium, and parathyroid hormone levels; and to determine the effect of gluten-free diet on BMD in children with celiac disease.

Design. The study included 32 patients with CD (group 1) and 82 healthy controls (group 2). The patients with CD were evaluated under 2 subgroups, ie, 16 patients with recent diagnosis (group 1a) and 16 patients who follow their diet strictly (group 1b). BMD values and concentrations of calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone were determined on entry to the study and at 12 months in celiac patients. These values were compared with those of healthy control participants.

Results. BMD and bone mineral content values in patients with recent diagnosis were found to be significantly lower than the control group. The BMD values in patients with recent diagnosis were significantly increased after a gluten-free diet for 1 year. Osteopenia was found more commonly in patients with recent diagnosis than patients in whom a gluten-free diet had been instituted. At 1-year follow-up, osteopenia was not resolved with the gluten-free diet, and this was especially true in patients without gastrointestinal manifestation. In patients with recent diagnosis (group 1a), the mean calcium level was found to be lower than the patients who follow their diet strictly (group 1b). There was a positive correlation between calcium level and BMD and bone mineral content.

Conclusions. BMD is almost invariably low in newly diagnosed celiac patients in childhood. We therefore recommend that BMD should be evaluated in patients with CD. Strict gluten avoidance promoted a significant increase in BMD. However, values still remained markedly low after 1 year of follow-up in some patients. These patients should be followed for longer periods of time with yearly BMD evaluation, as 1 year of diet therapy was found to be insufficient for osteopenia to be resolved. *Pediatrics* 2001;108(5). URL: <http://www.pediatrics.org/cgi/content/full/108/5/e89>; *bone mineral*

density, celiac disease, gluten-free diet, osteopenia, osteoporosis, childhood.

ABBREVIATIONS. CD, celiac disease; GFD, gluten-free diet; BMD, bone mineral density; iPTH, intact parathyroid hormone; BMC, bone mineral content; SD, standard deviation.

Celiac disease (CD) is one of the common causes of malabsorption during infancy and childhood. The lesions of the small intestinal mucosa are secondary to a permanent intolerance to gluten. Osteoporosis, rickets, and osteomalacia can occur as a result of defective calcium absorption through the flattened mucosa sometimes associated with secondary lactose malabsorption, increased endogenous calcium use, fecal loss, and impaired vitamin D absorption. Adherence to a gluten-free diet (GFD) reverses the histologic changes in the intestine and also the biochemical evidence of calcium malabsorption. It has long been recognized that CD may be associated with disorders of the skeleton. Low bone mineral density (BMD) of all sites of skeleton has been shown to be a common complication of untreated CD.¹⁻³ GFD does not always lead to improvements in BMD,^{4,5} and some authors have reported that ~40% of treated patients with GFD have BMD below the normal mean.⁶ It has been reported, furthermore, that adolescent patients treated from early childhood have BMD that resembles that of the control group.⁷ A more recent study showed that a GFD promotes a rapid increase of BMD that leads to a complete recovery of bone mineralization in children and adolescents with CD.⁸ However, no data on the prevalence of osteopenia in patients with CD in children are currently available. Our aims in the present study were to determine the prevalence of osteopenia and to evaluate the effect of GFD on BMD in patients with CD in childhood.

PARTICIPANTS AND METHODS

Patients (Group 1)

The study included 32 patients with CD in childhood (group 1). In each child, the diagnosis of CD was made according to the criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition,^{9,10} by intestinal biopsy (demonstration of villus atrophy in the duodenal or jejunal mucosa). All patients had antiendomysium antibodies. Exclusion criteria were the presence of other disease(s) known to affect the BMD. None of the patients received hormone or dietary supplements, except for iron and zinc. After withdrawal of gluten from the diet, a full clinical remission was observed. Compliance with the diet was ascer-

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tained by measuring serum antiendomysium antibodies during the follow-up period.

The patients with CD were divided into 2 groups: 16 patients with recent diagnosis (group 1a) and 16 patients who follow their diet strictly (group 1b). Group 1a included 16 newly diagnosed patients with CD. Of these patients, 7 were females. The age range was 3.5 to 17 years with a mean of 10.6 years; the median duration of symptoms before diagnosis was 3.2 years (range: 1.5–6 years). Seven patients had persistent diarrhea and short stature, 4 had short stature and iron deficiency anemia, 2 had short stature and pubertal delay, 1 had persistent diarrhea and selective immunoglobulin A deficiency, 1 had growth retardation and type I diabetes mellitus, and 1 had alopecia areata.

Group 1b included 16 celiacs treated with GFD for a mean time of 40.4 months (range: 19–84 months). They were 12 males and 4 females. The mean age was 11.5 years with a range of 5 to 18 years. At the diagnosis, 7 patients had persistent diarrhea, 5 had persistent diarrhea and short stature, 3 had short stature, and 1 had iron deficiency anemia. All of these patients in this group were asymptomatic at the beginning of this study.

Controls (Group 2)

The control group consisted of 82 children (31 girls, 51 boys, mean age: 9.8 ± 2.3 years) randomly selected from patients with upper respiratory infection. Their weights and heights were within the third and 97th percentiles for age. The participants were excluded if they had a history of chronic illness, and if they had taken any vitamin preparation, hormone, or calcium supplement regularly. For each patient, we selected at least 3 controls, matched for sex and age, for measurements of z score. For those patients who are in the same age and sex, z score was calculated by using the values of the same age-matched participants in the control group.

Measurements

Biochemical Measurements

Biochemical parameters were obtained at baseline and at 12 months. In serum samples, we determined serum total calcium, phosphate, total alkaline phosphatase, and intact parathyroid hormone (iPTH). Concentrations of calcium, phosphorus, and alkaline phosphatase (Roche Diagnostics GmbH, Mannheim, Germany) were determined with Hitachi 717 autoanalyzer (Tokyo, Japan) and calcium values were corrected for albumin where appropriate. Serum calcium and phosphate concentrations (mg/dL) were measured by a timed-endpoint biuret method and total alkaline phosphatase (U/L) by enzymatic rate method. The iPTH (Diagnostic Products Corporation, Los Angeles, CA) was measured by chemiluminescent enzyme assay with the IMMULITE 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA).¹¹

Densitometry

BMD and bone mineral content (BMC) were measured on entry to the study and at 12 months, at the lumbar spine (L1–4) using dual energy radiograph bone densitometer (Norland XR-36; Norland Co, Madison, WI). In the control group, BMD and BMC were measured on entry to the study. The precision of the densitometer is determined from measurements made on a patient repeatedly within a short time (weekly) and coefficient variant is calculated 0.5%.

BMD and BMC were expressed in absolute terms (g/cm² and g/cm, respectively) and the absolute BMD for each patient

was then expressed as a z score (see equation in right column) when compared with the mean BMD of an age- and sex-matched healthy control group.¹²

The z score was used in this study for the purpose of analysis of risk factors for reduced bone mass, as the z score eliminates the effects of age and sex by considering each patient's BMD in relation to the age- and sex-matched normal population. Osteopenia was defined as a z score lower than -1.0 .¹²

z score =

$$\frac{\text{patient BMD} - \text{mean BMD of age- and sex-matched normals}}{\text{standard deviation (SD) of BMD of age- and sex-matched normals}}$$

Statistics

The results of biochemical parameters and the BMD were expressed as mean values \pm SD. The mean BMD values of the patients groups and control participants were compared with each other. In addition, BMD values were expressed as z score, defined as the deviation of the individual value from the mean value of each reference group expressed in units of the standard deviation. In newly diagnosed celiac patients, the z score values of the patients with and without gastrointestinal symptoms were compared with each other. The Wilcoxon signed rank test and the Mann-Whitney U test were used when comparing paired and unpaired data respectively. Correlation was evaluated by the Spearman rank test. Differences were regarded as significant at $P < .05$. All data were analyzed with a computer program for statistical analysis SPSS version 5.0 (Microsoft Corporation, Chicago, IL).

Ethics

Informed consent was obtained from all the parents of the patients and volunteers; the study was approved by the Ethical Committee of the Medical Faculty, University of Ankara.

RESULTS

BMD and BMC were significantly lower in newly diagnosed patients with CD (group 1a) than in control group ($P < .05$; Table 1). Age adjusted BMD z score was significantly different between subgroups: group 1a, -1.55 ± 1.36 ; group 1b, -0.67 ± 0.85 ($P < .05$).

Osteopenia (z score lower than -1.0) was found in 50% of patients with CD (group 1a = 62.5%; group 1b = 37.5%). In 25% of patients, z score was found lower than -2.5 , and all of these patients were newly diagnosed patients (group 1a = 50%).

Age-adjusted BMD increased during the first year of dietary recommendation (Table 1). After 1 year of GFD, the percentage of patients who had osteopenia had decreased considerable. In the groups 1a and 1b, 50% and 33.3% of patients who had osteopenia at the beginning of the study showed normal z score after treatment for 1 year with GFD, respectively. Although bone mineral measurements were significantly increased after treatment for 1 year, some of the patients with osteopenia still had BMD values 1

TABLE 1. BMD Before and After 12 Months of Treatment (Mean \pm SD)

		Baseline	1 Year	Significance P Value
Group 1a	BMD (g/cm ²)	0.51 ± 0.11	0.56 ± 0.09	.041
	BMC (g/cm)	13.66 ± 6.39	15.57 ± 4.82	.006
	z score	-1.55 ± 1.36	-0.38 ± 1.19	.028
Group 1b	BMD (g/cm ²)	0.58 ± 0.16	0.64 ± 0.22	.005
	BMC (g/cm)	18.29 ± 8.72	22.59 ± 12.77	.008
	z score	-0.67 ± 0.85	-0.37 ± 0.98	.011

SD below the normal range (5 of 10 patients in group 1a; 4 of 6 patients in group 1b).

Among the newly diagnosed patients (group 1a), 8 patients without gastrointestinal symptoms (chronic diarrhea, abdominal distension, abdominal pain and vomiting) had significantly reduced age adjusted BMD, which was as low as in the other 8 patients with these symptoms (Table 2). Of the patients with gastrointestinal symptoms, 5 patients had a z score lower than -1.0 (3 of 5 had <2.5) and 3 had higher than -1.0 (normal z score). Among the patients without gastrointestinal symptoms, 5 had a z score lower than -2.5 and 3 had higher than -1.0 (normal z score). After 1 year of GFD, although all of the patients with gastrointestinal symptoms had normal z scores, 5 patients in the group without gastrointestinal symptoms still had BMD values 1 SD below the normal range (2 of 5 had <2.5).

The mean serum concentrations of calcium, phosphate, total alkaline phosphatase, and *i*PTH were within the normal range (Table 1); however, 2 patients had a minor reduction of calcium (8.3 and 8.5 mg/dL) and increase in *i*PTH (235 and 101 pg/mL) in the newly diagnosed group (group 1a). Also osteopenia was present in 2 patients (z score: -2.75 and -3.56). Although serum calcium and *i*PTH values were normal after treatment for 1 year, 1 of the patients still had BMD values 1 SD below normal range (z score: 0.25 and -2.87 respectively). The mean calcium concentration of the newly diagnosed patients (group 1a) was significantly lower than of the treated group (group 1b) and control group ($P < .05$), whereas no significant difference was found between the groups with respect to serum phosphate, alkaline phosphatase, and *i*PTH levels ($P > .05$; Table 3). Although the mean serum calcium concentration increased after 1 year of GFD, this change was not significant.

In the newly diagnosed patients (group 1a), a positive correlation was found for BMD versus serum calcium levels ($r = 0.37$, $P < .05$), whereas there was no correlation between BMD and other bone metabolism indices (phosphate, alkaline phosphatase, and *i*PTH). Significant positive correlations were found for BMD versus age in all groups ($r = 0.78$ in group 1a, $r = 0.67$ in group 1b, and $r = 0.59$ in control group; $P < .05$). In the newly diagnosed celiac group, no correlation was observed between BMD and each of the following variables: the length of clinical history and severity of symptoms or other biochemical abnormalities, such as hemoglobin concentration, serum iron level, and serum albumin level. In the treated group, there was no correlation between the duration of GFD and BMD.

DISCUSSION

The typical early presentation of CD occurs during the first 2 years of life, manifests as diarrhea and failure to thrive. The changes observed in the clinical features of CD during the past decades are remarkable. The findings of CD may be minor or atypical, and the disease can even be clinically silent.^{13,14} The atypical findings of CD include anemia, short stature, liver disease, and reduced bone mineralization. Low BMD of the total body skeleton has been shown to be a common complication of untreated CD.⁴⁻⁸ In newly diagnosed celiac adults, the prevalence of osteopenia and decreased BMD approaches 80% to 100%.² There are a few reports about the data on the effect of the disease on bone mineralization in children with CD. One previous study did not show decreased forearm BMC in children with CD diagnosed after the age of 3 years.¹⁵ The recent studies, however, showed that BMD of the forearm, lumbar spine, or entire skeleton was importantly reduced in children with CD.^{2,8,16} We found newly diagnosed CD to be strongly associated with low BMD. This is in agreement with the recent studies performed on patients with CD in childhood.^{2,7,8,16}

Determinants of BMD are age, sex, genetic-ethnic factors, hormonal status, calcium intake, physical activity, height, and weight. The major determinants of BMD are age, sex, and pubertal stage. Genetic factors are one of the predictors of peak bone density. The clinical measures of growth, height, and stage of pubertal development are primarily genetically determined. The dependence between BMD and growth parameters has been observed in several studies of normal healthy children,¹⁷⁻¹⁹ but the relevance of this relationship when assessing BMD in disorders in which growth may be affected has not been usually appreciated. Interpretation of BMD, for example, in children with chronic renal failure or CD will differ significantly if the values are corrected for height rather than age because of their marked short stature.^{12,20}

In adults, some reports found a low effect of the GFD for 1 year,^{3,4,21} whereas the others showed a remarkable improvement of bone mineralization for the same period.^{5,22-24} Ciacci²⁵ concluded that recovery of low BMD seemed probable only if GFD was started before the age of 25. In our study, the BMD values of the newly diagnosed patients improved remarkably after 1 year of GFD. In celiac patients, the mean annual increment of BMD after initiation of GFD was greater than that in normal growing children.² The spine BMD in children on a GFD <12 months was lower than in those on a diet for >24 months.²⁶ A more recent study showed that a GFD

TABLE 2. z Score at Baseline and 1 Year in Patients With or Without Gastrointestinal Symptoms (Chronic Diarrhea, Abdominal Distension, etc; Mean \pm SD)

z score	With Gastrointestinal Symptoms <i>n</i> :8	Without Gastrointestinal Symptoms <i>n</i> :8
Baseline*	-1.79 ± 1.07 ($-3.00/-0.63$)	-1.38 ± 1.60 ($-3.67/+0.25$)
1 y*	0.04 ± 0.56 ($-0.88/+0.60$)	-0.69 ± 1.75 ($-3.00/+1.13$)

* $P > .05$ (with gastrointestinal symptoms vs without).

TABLE 3. Serum Chemistry Values, BMD, and z Scores in Groups (Mean \pm SD)

	Group 1a (Newly Diagnosed)	Group 1b (Treated)	Group 2 (Healthy Controls)
Serum Ca (8.8–10.8 mg/dL)	9.4 \pm 0.6*	9.9 \pm 0.5	9.8 \pm 0.6
Serum PO ₄ (3.7–5.6 mg/dL)	4.8 \pm 0.6	5.1 \pm 0.6	5.0 \pm 0.5
Alkaline phosphatase (130–560 U/L)	254.5 \pm 132.6	279.5 \pm 144.3	226.3 \pm 129.6
iPTH (12–72 pg/mL)	57.3 \pm 62.2	39.9 \pm 24.6	29.7 \pm 23.7
BMD (g/cm ²)	0.51 \pm 0.11**	0.58 \pm 0.16	0.60 \pm 0.16
BMC (g/cm)	13.66 \pm 6.39**	18.29 \pm 8.72	18.80 \pm 9.09
z score	-1.55 \pm 1.36***	-0.67 \pm 0.85	-

* $P < .05$ versus group 1b and group 2; ** $P < .05$ versus group 2; *** $P < .05$ versus group 1b.

promotes a rapid increase of BMD that leads to a complete recovery of bone mineralization in children with CD.⁸ But, in these studies, z scores were not used to calculate the degree of osteopenia and annual increments of BMD. In our study, although BMD values of newly diagnosed patients were significantly increased after treatment for 1 year, 50% of the patients with osteopenia still had BMD values 1 SD below the normal range. In addition, in the treated patients who have been already on GFD for a mean period of 40.4 months (range: 19–84 months), osteopenia were found in 37.5% of the patients. These osteopenic patients have been on GFD for <4 years. When dietary treatment had been started in childhood, the BMD was found to be normal when investigated at least 10 years later.⁷ Patients who had adhered to a strict GFD for >4 years and normalized their small bowel mucosa had normal mean BMD.^{5,24} In the light of these data, we can conclude that although a significant increase in BMC may be detected after 1 year of a GFD, at least 4 years of GFD are required for a complete recovery of bone mineralization in some patients. To clarify whether the osteopenia in CD is completely reversible, the patients should be evaluated annually for bone mineralization.

Clinical presentation of CD may be very subtle. We found that patients without gastrointestinal symptoms (chronic diarrhea, abdominal distention, etc) had osteopenia of the same degree as patients with these symptoms. Indeed, subclinical forms of CD are recently more frequently diagnosed,²⁷ and judging by the 8 patients included in this series, these patients seem to be susceptible to osteopenia at the least as much as patients with gastrointestinal symptoms. Molteni et al⁷ similarly found no correlation between osteopenia and severity of symptoms in adult patients. Furthermore, Corazza et al²⁸ found a reduced BMD in a group of 14 untreated patients with subclinical or silent presentation. Mazure et al²¹ found reduced BMD in asymptomatic relatives of patients with CD but not as much as in the symptomatic untreated patients. Finally, although lower in degree and frequency, osteopenia can also be observed among patients with subclinical or asymptomatic disease. Therefore, screening for osteopenia by measuring BMD in children with CD seems to be worthwhile. Indeed, patients with osteoporosis have been screened for CD and a tenfold increase in prevalence (3%) was found compared with the background population.²⁹ In our opinion, screening for

CD is indicated in all patients with osteoporosis or osteopenia.

A GFD results in rapid improvement of BMD, even in patients with minor symptoms and in older patients. Furthermore, untreated adult celiacs without symptoms of malabsorption (chronic diarrhea or weight loss) increased their low BMD during the first year on a GFD as much as did the group with such symptoms.²⁴ To our knowledge, there is no study that examined the annual BMD improvement in the patients with or without gastrointestinal symptoms in childhood. Of particular clinical interest is our finding that patients with gastrointestinal symptoms had a normal mineralization after 1 year of GFD, whereas, 5 out of 8 patients without these symptoms still had BMD values 1 SD below the normal range. We can not fully explain why the patients without gastrointestinal manifestations did not show satisfactory improvement in BMD after 1 year of GFD, whereas all of the patients with gastrointestinal manifestations showed improvement in BMD. This may be explained by the delayed diagnosis because of lack of gastrointestinal manifestations in this group, which could cause more extended disturbances in bone metabolism.

In CD, both in adults and in children, there are alterations in the bone mineral component that have been attributed to the abnormalities of the intestinal mucosa and to steatorrhea, which can cause malabsorption of calcium and of vitamin D, respectively.² The increased serum levels of parathyroid hormone and alkaline phosphatase and the decreased serum levels of calcium found in celiac patients are thought by some authors to be causes of enhanced bone catabolism.^{4,30,31} In the patients with CD who are on GFD, serum calcium levels were higher than the levels of the untreated patients and did not differ from those of healthy children. These findings agree with the previous studies^{32,33} and suggest that calcium absorption is normal in patients on GFD. However, in the present study, we observed increased serum levels of iPTH and decreased serum levels of calcium in only 2 of 16 patients with untreated celiacs and there were no other abnormal laboratory tests. One possible explanation for this apparent lack of evidence of abnormal mineral metabolism is that the disturbances in bone metabolism (increased catabolic process) in patients are so subtle that they are not detectable by routine studies. Furthermore, it seems reasonable to assume that subtle and prolonged metabolic disturbances might be related to the time

elapsed since such mucosal abnormalities had started.

CONCLUSION

Osteopenia is a frequent finding in untreated celiac children. Therefore, we recommend that BMD be evaluated in patients with CD. Although osteopenia complicates CD during childhood, strict gluten avoidance promotes a significant increase in bone mineralization. However, a complete restoration of osteopenia in each patient after 1 year of treatment was not obtained, especially in patients without gastrointestinal manifestation. Therefore, studies with considerable longer follow-up will be needed to determine whether remineralization continues and a complete restoration of bone mass can be achieved.

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