Bone Health in Children With Celiac Disease Assessed By Dual X-ray Absorptiometry: Effect of Gluten-free Diet and Predictive Value of Serum Biochemical Indices

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ABSTRACT

Objectives: In the present study, we aimed to assess bone status and the effect of gluten-free diet (GFD) in children with celiac disease (CD), and to evaluate the predictive value of standard serum biochemical indices in the diagnosis of bone mineral density (BMD) disturbances.

Methods: Forty-five children at the time of diagnosis of CD (group A, 77.8% girls) and 36 children receiving GFD for >2 years (group B, 75% girls) were included. Sixteen children in group A were reexamined 12 months after initiation of GFD. Serum measurements of biochemical bone health indices and BMD, assessed by dual x-ray absorptiometry, were obtained.

Results: Patients after 1 year of receiving GFD had higher BMD z scores compared with baseline (-1.45 ± 0.28 vs -0.61 ± 0.25, respectively, $P = 0.004$). BMD z scores were significantly lower than expected for the normal population, after 1 ($P = 0.03$) or at least 2 ($P < 0.001$) years of receiving GFD. In group B, BMD z score was positively correlated with 25-hydroxy vitamin D levels ($P = 0.009$). In the repeated measurements group, 25-hydroxy vitamin D differed between pre- and post-GFD ($P = 0.018$). No biochemical index was capable of predicting an abnormal BMD z score (receiver operating characteristic curve analysis, all of the areas under the curve <0.66).

Conclusions: GFD has a beneficial effect on bone health. Two years receiving diet do not ensure normalization. Biochemical markers are not indicative of BMD disturbances. Dual x-ray absorptiometry should be included in the standard management of children with CD.

Key Words: bone indices, bone mineral density, celiac disease, dual x-ray absorptiometry, gluten-free diet

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Celiac disease (CD) is an immune-mediated intestinal disorder, characterized by inflammation and flattening of the small bowel villi as a result of a permanent intolerance to gluten, which is present mainly in wheat, barley, and rye (1). It includes a wide spectrum of clinical manifestations ranging from the classical severe symptoms of diarrhea and failure to thrive, shortly after the introduction of gluten, to the subclinical or even silent form of the disease diagnosed later in life (2,3). One of the consequences, in both forms, is metabolic bone disease, which has a multifactorial etiology, including impaired absorption and fecal loss of calcium and vitamin D, as well as disturbance of the normal bone turnover resulting from the effect of inflammatory mediators on osteoclasts and osteoblasts (4,5).

The availability of dual x-ray absorptiometry (DXA) during the last 20 years has contributed significantly to the monitoring of bone status in patients with CD. DXA is a simple, low-cost method that has been widely used for the assessment of bone health in these patients; however, DXA measurements are determined by geometric parameters of the skeleton, and occasionally in patients with growth retardation, adjustment according to age and sex may be inadequate (6,7).

Calcium and vitamin D disturbances and their effect on the growing skeletons of children with CD, as evaluated by DXA, have been studied extensively during the last 2 decades (8–11). The majority of these studies have demonstrated reduced bone mineral density (BMD) in untreated patients with CD, which may be reversed with GFD (8,11–15); however, several key issues remain unanswered. The minimum period of GFD after which an improvement in BMD should be expected has not been determined (8,11–13). Furthermore, it is questionable whether the age of diagnosis affects the degree of improvement because older children may present slower rates of recovery (10,16,17).

In the present study, we sought to assess the status of standard bone health, biochemical indices, and DXA measurements in patients with newly diagnosed CD. We also evaluated the effect of a strict GFD on the evolution of these parameters. Finally, we analyzed whether an abnormally low BMD z score could be predicted by the indices of bone metabolism that are used in everyday clinical practice.

METHODS

The present study comprised children with CD diagnosed and followed in the gastroenterology unit of the First Department of Pediatrics of the University of Athens in Aghia Sophia Children's Hospital, Athens, Greece. Informed consent was obtained from the parents of all of the children, and the study was approved by the local ethics committee. The diagnosis was made according to the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (18).

The cross-sectional component of the analysis included 45 children newly diagnosed as having CD (group A) and 36 children

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receiving GFD for >2 years (group B). Sixteen children among those in group A formed the prospective component, had all of the tests repeated after 12 months receiving GFD, and were not included in group B. Any patient receiving calcium or vitamin D supplementation or other medication was excluded from the study. Autoimmune disease (diabetes or thyroiditis) was not present in our study groups at the time of the evaluation. Demographic data (sex, date of birth) and disease characteristics (age at diagnosis, disease duration, GFD duration) were recorded for every participant.

Skeletal DXA measurements were obtained by a Lunar Prodigy Pro densitometer (GE Healthcare Technologies, Waukesha, WI). We recorded BMD (grams per square centimeter) of the lumbar spine (vertebras O_1-O_4) and respective z scores adjusted for age and sex (as provided for pediatric populations by the densitometer), according to the 2007 guidelines of the International Society for Clinical Densitometry (ISCD) (19). As suggested by the ISCD guidelines, the patients, depending on their BMD z scores, were characterized as "low BMD for chronologic age," if BMD z score <-2.0, and "BMD within the normal range for chronologic age," if BMD z score >-2.0.

Laboratory investigation in serum included calcium (normal range 8.2–110 mg/dL), phosphorus (normal range 4–6 mg/dL), alkaline phosphatase (ALP; different age-adjusted ranges as provided in reference (19)), 25-hydroxy vitamin D (25-(OH)-D) (normal range 20–60 ng/mL), and parathormone (PTH; normal range 15–60 pg/mL). With the exception of vitamin D (20) and ALP (21), all of the reference ranges were provided by the hospital's laboratories where the analyses were done. According to these cutoffs, every patient was characterized as normal or abnormal for each parameter (Ca <8.2 mg/dL, P <4 mg/dL, 25-(OH)-D <20 ng/mL, and PTH >60 pg/mL).

All of the patients had serum antibodies against endomysium and tissue transglutaminase (t-TG) measured and were classified as serology positive if they had at least 1 positive (t-TG >20 IU or EMA ≥1:20 titer) or serology negative if both indices were negative (t-TG ≤20 IU and EMA <1:20 titer).

Statistical Analysis

Two types of analyses were performed: First, in the independent, cross-sectional component, patients were divided into 2 groups: the baseline (group A) and the receiving-GFD (group B). Patients with repeated measurements were included only in the baseline group to preserve independence. In the prospective analysis, at baseline and after 1 year of receiving GFD, only patients with repeated measurements were included (group C). Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as absolute (n) and relative (%) frequencies. Comparisons of categorical variables were made by Fisher exact test. Student t test was used for the comparison of means, whereas repeated measurements were compared by Wilcoxon matched-pairs signed rank test because of the small sample size. Correlations between continuous variables were assessed by Pearson r. To assess the ability of various biochemical indices to distinguish patients having "low BMD for chronologic age" from those with "BMD within the normal range for chronologic age," nonparametric receiver operating characteristic curve (ROC) analysis was applied. Areas under the curve (AUCs) with corresponding 95% confidence intervals are reported. Using this approach, we can evaluate the ability of a new method to identify individuals, who are already characterized as abnormal by the reference criterion standard method (in this case, those with "low BMD for chronologic age" as defined by DXA). Values of AUC may range from 1 (perfect discrimination) to 0.5 (absence of ability to identify abnormal individuals). $P \leq 0.05$ was considered statistically significant for all types of comparisons. Data were analyzed using the Stata 11.0 statistical software (StataCorp, College Station, TX).

TABLE 1. Demographic data and disease characteristics in patients at diagnosis (group A) and in patients receiving gluten-free diet for at least 2 years (group B)

Variable	
Group A (n = 45)	
Age, y	9.0 ± 3.6
Age at diagnosis, y	9.0 ± 3.6
Disease duration at diagnosis, y	2.9 ± 3.1
GFD duration, mo	n.a.[§]
Sex, female, n (%)	35 (77.8)
Group B (n = 36)	
Age, y	10.1 ± 4.4
Age at diagnosis, y	3.7 ± 3.4
Disease duration at diagnosis, y	1.2 ± 1.9
GFD duration, mo	77.7 ± 54.3
Sex, female, n (%)	27 (75.0)

GFD = gluten-free diet; n.a. = not applicable.

RESULTS

Demographic Data and Disease Characteristics

Demographic data and disease characteristics for all of the patients are shown in Table 1. The workup of 16 children (62.5% girls), among those in group A, with a mean age at diagnosis of 8.9 ± 3.5 years and mean disease duration of 3.3 ± 3.4 years, was repeated after 12 months of GFD.

Laboratory Investigations

Table 2 shows the results on biochemical markers in groups A and B. In group B, no relation among the biochemical indices and the duration of GFD, the age at diagnosis, and the disease duration at diagnosis was found. In the 16 patients of group A with repeated measurements, mean values of Ca (pre vs post: 9.3 ± 0.4 vs 9.8 ± 0.3 mg/dL, $P = 0.001$), PTH (pre vs post: 45.9 ± 31.6 vs 28.9 ± 14.7 pg/mL, $P = 0.011$), and 25-(OH)-D (pre vs post: 25.7 ± 12.8 vs 32.1 ± 12.6 ng/mL, $P = 0.022$) differed significantly between the 2 assessments, whereas P (pre vs post: 4.7 ± 0.5 vs 4.7 ± 0.5 mg/dL, $P = 0.83$) and ALP (pre vs post: 284.9 ± 66.6 vs 293.2 ± 111.0 IU/L, $P = 0.75$) were comparable. When we evaluated the proportion of patients falling out of the normal ranges, however, only 25-(OH)-D status differed after 12 months of receiving GFD (pre vs post: 37.5% vs 0% abnormal, $P = 0.018$).

DXA Measurements

Absolute values of BMD (grams per square centimeter) and z scores for groups A and B are presented in Table 3. In group A, 28.8% of patients had z scores <-1.96, meaning that almost 30% were below the 2.5th percentile of the normal population. Although in children receiving GFD this proportion improved, 8.3% of those

TABLE 2. Bone health indices in patients at diagnosis (group A) and in patients receiving gluten-free diet for at least 2 years (group B)

Variable	Mean ± SD (% abnormal*)
Group A (n = 45)	
Calcium, mg/dL	9.5 ± 0.5 (2.2)
Phospshorus, mg/dL	4.9 ± 0.5 (2.2)
Alkaline phosphatase, IU/L	280.8 ± 86.6 (6.7)
Parathormone, pg/mL	49.8 ± 29.5 (21.4)
25-(OH)-D, ng/mL	24.8 ± 10.5 (35.7)
Group B (n = 36)	
Calcium, mg/dL	9.7 ± 0.3 (0)
Phospshorus, mg/dL	4.8 ± 0.5 (2.8)
Alkaline phosphatase, IU/L	247.4 ± 87.8 (0)
Parathormone, pg/mL	33.2 ± 15.6 (5.7)
25-(OH)-D, ng/mL	29.3 ± 17.3 (34.3)

25-(OH)-vitamin D = 25-hydroxy vitamin D; SD = standard deviation.
* % Abnormal: The percentage of individuals below the lower normal limit for calcium, phosphorus, and 25-(OH)-vitamin D, or the percentage of individuals above the lower normal limit for parathormone and alkaline phosphatase.

patients were still below the 2.5th percentile of the normal population. Both groups had z scores significantly lower than the expected mean in normal children (expected z score = 0, standard deviation = 1, both $P < 0.001$). When we excluded 4 children who were serology positive from group B, the BMD z score improved to -0.54 ± 0.79, but it was still significantly lower than that expected in normal children ($P < 0.001$). When we assessed whether the duration of GFD, the age at diagnosis, and the disease duration at diagnosis affected the BMD z score, we found that there was no correlation in group B (Pearson $r = -0.08$ $P = 0.6$, $r = 0.17$ $P = 0.3$, and $r = -0.04$ $P = 0.78$, respectively). The age at diagnosis and the disease duration at diagnosis did not affect the BMD z score in group A either (Pearson $r = 0.15$ $P = 0.3$ and $r = 0.06$ $P = 0.66$, respectively).

In the repeated measurements group (group C), BMD improved from 0.59 ± 0.19 at baseline to 0.75 ± 0.21 after 12 months of receiving GFD ($P < 0.001$). Similarly, BMD z scores increased from -1.45 ± 0.28 to -0.61 ± 0.25 ($P = 0.004$). At both instances (baseline and receiving GFD for 12 months), z scores were significantly lower than that expected in the normal population ($P < 0.001$ and $P = 0.03$, respectively).

TABLE 3. Lumbar spine bone mineral density in untreated children (group A) and in individuals receiving gluten-free diet for at least 2 years (group B)

Variable	Mean ± SD
Group A (n = 45)	
BMD, g/cm^2	0.63 ± 0.20
BMD z score	−1.12 ± 1.54
Group B (n = 36)	
BMD, g/cm^2	0.67 ± 0.17
BMD z score	−0.58 ± 0.80

BMD = bone mineral density; SD = standard deviation.

Relation of DXA Measurements to Bone Health Biochemical Indices

In group A, no relation was found between DXA measurements and bone health biochemical indices. In particular, BMD z scores were not affected by PTH status in either group ($P = 0.65$). In group B, BMD z scores were significantly higher in those patients with normal 25-(OH)-D status compared with those with abnormal status (-0.42 ± 0.75 vs -1.0 ± 0.68, $P = 0.009$). In the repeated measurements component, baseline 25-(OH)-D status was not related to baseline z scores ($P = 0.99$) or to the increase of z score after 12 months of receiving GFD ($P = 0.15$).

Predictive Value of Bone Indices in Identifying Individuals With Abnormal DXA Measurements

Table 4 presents the results of ROC analysis for Ca, P, ALP, PTH, and 25-(OH)-D. In the entire population, none of the indices performed adequately in distinguishing patients with ''low BMD for chronologic age.'' All of the AUCs were between 0.51 and 0.66, with Ca achieving the best result (0.66). In this case, if we want to obtain a sensitivity of at least 80%, a cutoff $\leq$9.9 mg/dL is required, resulting in a specificity of only 18.5%. Applying Ca as a classification index and $\leq$9.9 mg/dL as the optimal cutoff would result in correctly identifying 81% of patients with ''low BMD for chronologic age,'' but simultaneously misclassifying 82% of individuals with ''BMD within the normal range for chronologic age'' as abnormal. At diagnosis, the results were similar. Calcium achieved, again, the best results (AUC 0.71), however, with only marginally improved sensitivity/specificity (a cutoff $\leq$9.8 mg/dL results in sensitivity of 84.6% and specificity of 24.6%). P had the best predictive value in children receiving GDF for at least 2 years. The estimated AUC was 0.84, and a cutoff $\geq$5.1 mg/dL provides sensitivity of 100% and specificity of 72.7%.

DISCUSSION

In the present study, children with untreated CD had significantly lower BMD z scores compared with children receiving GFD. GFD had a beneficial effect, resulting in a significant increase in bone density. These findings are in concordance with previous studies, which also concluded that adherence to strict GFD alone is capable of increasing the bone mass values. These outcomes were observed both in children with CD (8,12,16) and adults (22) with repeated measurements, as well as in studies including independent samples (11,14); however, several issues remain controversial. The dispute concerns the possibility of full recovery of the genetically predisposed peak bone mass, as well as the minimum period receiving GFD, required for the normalization of BMD. Some studies have shown that 1 year is sufficient for increasing the bone mass values to levels that are comparable to those found in the general normal population (11,12). In contrast, others have demonstrated that despite the remarkable increase within 1 year, normal standards were not achieved (8). Our study is in agreement with the latter, because 1 year receiving GFD, in the repeated measurements group, resulted in significantly improved BMD, without reaching normal values. Furthermore, our results indicate that impaired bone health may not be fully reversed after 2 years of receiving GFD because z scores were still below the expected values for the normal population.

The relation between the age of intervention and the observed improvements is an issue addressed frequently in the literature. The results are conflicting because some studies support a favorable trend toward children starting GFD at a younger age

TABLE 4. Receiver operating characteristic curve analysis of Ca, P, ALP, PTH, and 25-(OH)-D in distinguishing between individuals having ''low bone mineral density for chronologic age'' from those with ''bone mineral density within the normal range for chronologic age'' as defined by dual x-ray absorptiometry

	AUC overall (95% CI)	At diagnosis (95% CI)	Receiving GFD for ≥2 y (95% CI)
Ca	0.66 (0.49–0.84)	0.71 (0.53–0.90)	0.58 (0.15–0.99)
P	0.51 (0.34–0.69)	0.60 (0.40–0.80)	0.84 (0.69–0.98)
ALP	0.54 (0.40–0.69)	0.65 (0.48–0.82)	0.61 (0.27–0.94)
PTH	0.57 (0.40–0.75)	0.51 (0.29–0.73)	0.68 (0.37–0.99)
25-(OH)-D	0.51 (0.30–0.69)	0.50 (0.27–0.73)	0.54 (0.02–0.99)

ALP = alkaline phosphatase; AUC = area under the curve; Ca = calcium; CI = confidence interval; GFD = gluten-free diet; 25-(OH)-D = 25-hydroxy vitamin D; PTH = parathormone.

(10,16,17); however, others have shown BMD z scores comparable with those of control subjects after 1 year receiving GFD even in older children (11,12). In a study including children and adolescents with CD, Mora et al (23) concluded that a prolonged diet normalizes BMD, independent of GFD starting before or during puberty. Additionally, Scotta et al (17) concluded that spine BMD is influenced significantly by both the age at diagnosis and the duration of GFD. Our study disagrees with these results because no relation among BMD z scores, duration of GFD, and age at diagnosis was documented.

The different ages at diagnosis between groups A and B reflect the changing pattern of CD, as described in a previous study from our unit (24). In particular, children receiving GFD were diagnosed relatively far in the past (>2 years), when the disease presented during the first years of life. In contrast, recently diagnosed children have mainly mild forms of CD manifesting later in childhood or even adolescence.

Several confounding factors influence the results in similar studies. The most important, probably, is the adherence to GFD, which is extremely difficult to evaluate because children may be involuntarily exposed to gluten (25). After excluding 4 children with positive serology from group B, BMD z scores remained significantly lower than the expected; however, this characterization, as compliant or not, is based on a single time point and may not accurately represent the entire period of receiving GFD (26,27).

In the repeated-measurements group, abnormal 25-(OH)-D status was found more frequently at baseline, compared with the values found after 1 year receiving GFD and it was normalized in all of the children. This finding cannot be explained, and no seasonal variation in the time of blood sampling was noticed. Furthermore, in Greece, the sufficiency of vitamin D depends mainly on sun exposure rather than on dietary intake. In the group of the 16 children with repeated measurements, Ca was significantly lower and PTH significantly higher at baseline than after 12 months receiving GFD, although the percentages outside the normal range were similar. Our results are in agreement with those reported by other researchers, which include disturbances in the biochemical level such as increased PTH (9,11,28) and abnormal levels of vitamin D (9), whereas ALP is rarely affected (9). No significant disturbances in bone biochemical indices have been reported in other studies (8,10).

Among patients receiving GFD for at least 2 years, those with abnormal vitamin D status had significantly lower z scores compared with those with normal vitamin D status. The observed rate of disturbed vitamin D status in group A was 34% and remained the same in group B. Although direct comparisons between groups A and B are not appropriate, we could argue, based on that observation, that a significant part of those patients in group B with low vitamin D could have been vitamin D deficient from the start and may have remained below the normal levels for long intervals or even throughout the GFD period. This prolonged effect of vitamin D deficiency could account for the impaired BMD.

A significant finding in our study is the poor performance of serum biochemical bone metabolism indices, which are being used in everyday clinical practice by physicians treating patients with CD, in predicting individuals with ''low BMD for chronologic age'' as defined by the ISCD. The only exception was P in children receiving GFD for at least 2 years, in which higher values of P (≥5.1 mg/dL) identified children with abnormal DXA z scores fairly well. This result should be interpreted with caution because only 3 of 36 children in this group had BMD z scores<−2.0. The overall results indicate that DXA cannot be replaced by serum biochemical indices and should be the method of choice for the evaluation of bone health.

The main drawback of our study was the relatively small number of patients, which may have reduced the power to detect significant correlations and the limited (1 year) time of follow-up in the repeated measurements component. A longer period of observation could answer crucial questions, such as the timing of normalization of BMD in patients receiving GFD. In addition, no data were available on the dietary habits of the individuals included in the analysis, especially the daily intake of calcium. The ROC analysis was based on classifying patients according to a predetermined cutoff. This approach does not mean that patients with BMD z scores >−2.0 are healthy. They may have impaired bone health because it is not possible to know what the DXA values would have been in the absence of CD. A second drawback is that we did not evaluate bone resorption markers such as osteocalcin or fragments of collagen (P1NP: N-terminal propeptide of type 1 procollagen, P1CP: C-terminal propeptide of type 1 procollagen), which may have performed better in identifying patients with reduced BMD. These tests are not widely available to most clinicians who are managing patients with CD, and therefore cannot be incorporated in the standard clinical practice.

CONCLUSIONS

Our study has demonstrated that bone derangement coexists with untreated CD and that a strict GFD can offer great improvement, although the minimum required period for normalization may be longer than 2 years. Biochemical markers are not indicative of BMD disturbances. Health specialists should include DXA in the standard workup in the diagnosis of CD.

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