Journal of Gastrointestinal & Digestive System

Salazar et al., J Gastrointest Dig Syst 2018, 8:1
DOI: 10.4172/2161-069X.1000550

Research Article Open Access

Relationship between the Diet and the Bone Mineral Density in Children with Celiac Disease

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Received date: January 05, 2018; **Accepted date:** January 27, 2018; **Published date:** February 02, 2018

Abstract

Objective: To analyze whether there were any deficiencies in the celiac diet that could affect dual X-ray absorptiometry (DXA), comparing a diet with gluten to one without gluten.

Methods: Forty-three children aged 1-13 years diagnosed with celiac disease (CD) were studied. Bone mineral density (BMD) was measured using DXA. A food questionnaire was completed before the start of the gluten-free diet (GFD) and again one year after diagnosis, when the patient was on a strict GFD.

Results: Lumbar spine BMD (g/cm^2) increased over the one-year follow-up (P<0.001). We did not find significant differences in the percentages of energy intake and nutrients: carbohydrates (47.94% *vs.* 47.02%), lipids (34.73% *vs.* 36.24%) and proteins (17.65% *vs.* 16.60%). We found deficient vitamin D intake in both the gluten-containing and the GFDs. In observing the relationships between dietary intake and Z-score BMD, we found a significant correlation with the vitamin D intake at diagnosis.

Conclusion: The GFD is a healthy diet, similar in both macronutrients and micronutrients to a diet with gluten. The principal factor for BMD improvement is adequate proper compliance with the GFD.

Keywords: Celiac disease; Dual X-ray absorptiometry; Gluten free diet; Vitamin; Protein; Vitamin D; Bone mineral density

Introduction

Celiac disease (CD) is a systemic immune disease caused by gluten and related prolamines in genetically susceptible individuals, and characterized by the presence of a variable combination of clinical manifestations that depend on gluten intake, specific antibodies, the HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy [1]. The treatment of celiac disease requires a life-long diet with the exclusion of all foods containing gluten or related prolamines. The gluten-free diet (GFD) has traditionally been declared healthy, but there are studies that suggest that it may be associated with some nutritional deficiencies due to the exclusion of gluten-containing cereals, which are rich in iron, fiber, and B vitamins [2,3]. Thus, the literature includes reports of decreased intakes of B vitamins, calcium, vitamin D, magnesium, iron, folic acid, and fiber, which could have an impact on blood levels (with decreased concentrations of vitamin B6, vitamin B12, and vitamin D) and in the development of anemia and osteopenia. This deficient intake is partly due to the lower fiber, iron, folate, thiamine, riboflavin, and niacin content of gluten-free foods [3-5]. When it comes to macronutrients, the literature has descriptions of higher intakes of lipids and lower intakes of carbohydrates, which may be attributable to processed gluten-free foods usually being rich in fats and sugars with a high glycemic index [3,5].

On the other hand, celiac disease has 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. 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 [1,6,7]. The availability of dual X-ray absorptiometry (DXA) has contributed significantly to the monitoring of the 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 [8]. However, these measures do not reflect the dynamic nature of bone tissue. In contrast, biochemical markers of bone metabolism provide a more dynamic picture of the change during both bone growth and modelling, and their measurement may be useful in the assessment of metabolic bone diseases and growth disorders in children. Bone formation markers are formed during different phases of osteoblast development and reflect osteoblast function and bone formation. These markers include bone alkaline phosphatase (BAP), osteocalcin, and procollagen 1 peptides. The resorption markers are products of bone type 1 collagen degradation, mainly peptides and small molecules. Hydroxyproline, pyridinoline, and deoxypyridinoline are degradation products found in the urine, while N-terminal and C-terminal cross-linked peptides can be found in both serum and urine [9,10].

The aim of our study was to analyze whether there were any deficiencies in the intake of calories, essential nutrients, vitamins, dietary elements (i.e., iron, calcium, zinc, and phosphorus), and fiber in the diet of children diagnosed with celiac disease that could affect

the DXA. Our secondary goal was to assess whether there are changes in the bone markers when a patient begins a GFD and, if there are, whether those changes have some relationship with changes in the DXA.

Materials and Methods

We conducted an observational, descriptive, and prospective study in which we collected data for patients diagnosed with celiac disease in the pediatric digestive diseases unit over 4 years, from April 1, 2012 to March 31, 2016. For each patient, we collected data corresponding to 1 year. A food questionnaire was completed on three alternating days (one of them on a holiday or weekend) before the start of the GFD and again one year after diagnosis, when the patient was on a strict GFD. We directed the parents or guardians of the children to document with the utmost possible accuracy the amounts of food ingested, how the foods were prepared, and the brands of the products consumed.

We evaluated the following: caloric intake and the percentage of calories consumed relative to the patient's energy requirements calculated by means of the Schofield equation for weight, height, and level of activity (the level of activity was estimated based on the information gathered from the parents in the clinical interview at the time of diagnosis); the percentage of carbohydrates, proteins, lipids, and fatty acids (FAs) composition of the total consumed; the percentage of vitamins and dietary elements consumed in relation to the dietary reference intakes (DRIs) of the National Academy of Sciences of the United States [11-14]; and the daily amount of fiber consumed. We calculated these values using the software application Dietsource Junior®. In addition to the dietary assessment, we collected anthropometric data (weight, height, body mass index [BMI], brachial perimeter, triceps fold, Waterlow weight-for-height classification) at the beginning of the study and a year later.

The data for these variables were collected by a nurse before the visit, using the same scale (accurate to 0.1 kg) and stadiometer (accurate to 0.1 cm). The weight, height, and BMI values were expressed as standard deviations using the tables of Fernández et al. as a reference [15]. We also collected data from blood tests performed at diagnosis before starting the GFD and a year after, concurrent with the administration of the food questionnaire. We assessed the following parameters: hemoglobin, hematocrit, serum iron, transferring saturation index (TSI), IgA, IgA anti-tissue transglutaminase and antigliadin, IgA or IgG anti-endomysium (if required), HLA (only at diagnosis), folic acid, vitamin B6, vitamin B12, homocysteine, calcium, phosphorus, parathyroid hormone (PTH), vitamin D, type I procollagen N-terminal peptide (TPINP), and C-telopeptide (CTx). We also tested for parasites in three samples taken on alternating days to rule out parasitic disease at diagnosis.

Bone mineral density (BMD) and bone mineral content (BMC) were measured, on entry to the study and at 12 months, at the lumbar spine (L1-4) using DXA. BMC was expressed in absolute terms (g/cm). BMD was expressed in g/cm^2 and as a Z-score (i.e., the deviation of the patient's value from the mean divided by the standard deviation of values obtained in a population of children of the same age and gender) [16].

The study was approved by the Committee on Ethics and Clinical Research at our hospital. We established the following inclusion criteria: 0-13 years of age; diagnosed with celiac disease, based on the criteria of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, during the period under study; and receiving follow-up care at the pediatric digestive diseases unit.

The exclusion criteria were the following: children 14 years of age or older; diagnosed with celiac disease at a time outside the period under study; children with celiac disease already undergoing treatment for this condition; presence of a chronic underlying condition other than celiac disease; undergoing chronic treatment (more than 1 month of duration) with some type of drug, hormone, calcium, iron, or vitamin D supplement; persistence of positive celiac disease markers a year after initiation of the GFD; lack of a signed informed consent; following some type of exclusion diet in addition to the GFD for more than one month; having a metal implant; and permanent paralysis.

Data are expressed as mean ± standard deviation (SD). To test the changes between parametric data, a paired 2-tailed t-test was used, assessing changes in mean values with the Wilcoxon test. Univariate and multivariate analyses of BMD and BMC were performed to assess relationships between potential risk factors. Variables shown to be associated with a low BMD were assessed using multivariate logistic regression models to determine risk for development of poor bone health. Non-parametric tests were utilized for variables demonstrating skewed distributions. Analysis of covariance (ANCOVA) was performed to adjust for any variables influencing primary outcome variables. Data analysis was completed using the IBM SPSS 19.01 statistical software. A value of $P<0.05$ was considered significant.

Results

We recruited a total of 43 patients with celiac disease. The mean time for diagnosis of celiac disease was 4.8 years (± 3.64 years). Ninety-three percent of patients presented with symptoms (the majority being gastrointestinal) and 7% were asymptomatic at diagnosis. The patient population was within the normal range expected for nutritional indices with a mean weight-for-age Z-score of -0.62 (± 0.98) and a height-for-age Z-score of -0.95 (± 1.27). These parameters increased significantly after a year. Table 1 shows age at diagnosis, height-for-age Z-score, weight-for-age Z-score, BMI Z-score, triceps fold, brachial perimeter, BMD, and BMC at diagnosis and one year later. Lumbar spine BMD (g/cm^2) and BMC (g/cm) increased over the one-year follow-up ($P<0.001$), with a Z-score<-2 in 35.5% of the patients at diagnosis and in 18.2% of the patients one year later.

	Mean ± SD at diagnosis	Mean ± SD at 1 year	Significance
Time (years)	4.8 (3.64)		
Sex (M/F)	39%/61%		
SD weight	-0.62 (0.98)	-0.02 (1.03)	P<0.001
SD height	-0.95 (1.27)	-0.12 (1.08)	P<0.001

Waterlow Index	95.73 (10.03)	98.40 (11.07)	P=0.072
BMI	-0.21 (0.99)	-0.12 (1.06)	P=0.46
SD triceps fold	-0.12 (0.99)	0.01 (1.14)	P=0.49
DS brachial perimeter	0.09 (1.27)	0.30 (1.43)	P=0.37
BMD (g/cm^2)	0.47 (0.13)	0.52 (0.13)	P<0.001
Z-score BMD	-1.41 (1.19)	-1.07 (1.12)	P<0.001

Table 1: Demographic, anthropometric, and densitometric characteristics in patients at diagnosis (group A) and in patients receiving gluten-free diet for 1 year (group B); [M: Male; F: Female; BMI: Body Mass Index; BMD: Body Mass Density; SD: Standard Deviation].

Our analysis of energy and macronutrient distributions did not reveal significant differences in the percentages of caloric intake relative to the estimated energy requirements for age, sex, and daily physical activity (112% *vs.* 106%). We also found no differences in the intake of the different essential nutrients: carbohydrates (47.94% *vs.* 47.02%), lipids (34.73% *vs.* 36.24%), and proteins (17.65% *vs.* 16.60%). An analysis of the intake of different types of FAs revealed significant differences, with an increase in the intake of monounsaturated FAs in the GFD (44.01% *vs.* 47.84%; P=0.015) and a decrease in saturated FAs (41.63% *vs.* 36.35%; P=0.01). Regarding vitamins, we found deficient vitamin D intake both in the gluten-containing and the GFDs, and no significant differences in its intake depending on the type of diet (25.35% *vs.* 34.46%; P=0.32). As for dietary elements, we found deficient zinc and fiber intake in both diets. We only found significant differences in the intake of phosphorus (246% *vs.* 276% of the adequate intake; P=0.029), with normal intakes and no differences between both diets for sodium; calcium; iron; zinc; folic acid; fiber; and vitamins B6, B12, A, and E (Table 2).

At the beginning of the study, laboratory tests revealed low hemoglobin and ferritin values, which subsequently showed significant improvement. Vitamin B12, folic acid, homocysteine, calcium, and phosphorus levels were within normal ranges and showed no changes in the control performed at one year. Vitamin D and PTH levels were within the normal range at the beginning and at one year, although they changed in a statistically significant way (with the levels of vitamin D increasing and those of PTH decreasing) (Table 3).

As in normal children, there was a significant correlation between Z-score BMD and weight (r=0.552, P<0.001), height (r=0.471, P<0.001), BMI (body mass index) (r=0.391, P=0.002), and brachial perimeter (r=0.298, P=0.022) at diagnosis. These significant correlations were also there at one year between BMD and weight (r=0.348, P=0.024) and height (r=0.426, P=0.005).

Examining the relationships between dietary intake and Z-score BMD, we only observed a significant correlation with the vitamin D intake at diagnosis. No other relationships were observed with other dietary or biochemical parameters and Z-score BMD at diagnosis or at one year (Table 4).

	At diagnosis (SD)	**1 year later (SD)**	**Significance (P)**
%Energy (Kcal/day) (1)	112.60 (48.74)	106.92 (22.59)	0.92
%CH	47.94 (5.25)	47.02 (5.88)	0.43
%Lipids	34.73 (6.64)	36.34 (5.23)	0.35
%Protein	17.65 (4.68)	16.60 (2.91)	0.33
%MIFA/%TL	15.25 (2.01)/44.01(5.81)	17.38 (2.36)/47.84 (6.52)	0.015
%PIFA/%TL	5.05 (2.44)/14.54 (7.03)	5.74 (1.81)/15.80 (4.99)	0.46
%SFA/%TL	14.45 (2.85)/41.63 (8.23)	13.20 (1.96)/36.35 (5.42)	0.01
Vitamin D (2)	25.35 (29.51)	34.46 (31.45)	0.32
Folic acid (2)	230.03 (156.08)	188.07 (83.76)	0.362
Vitamin A (2)	152.60 (126.85)	146.03 (129.70)	0.9
Vitamin B6 (2)	232.96 (232.69)	181.53 (170.48)	0.316
Vitamin B12 (2)	423.00 (265.72)	462.14 (250.85)	0.97
Vitamin C (2)	133.35 (114.92)	100.89 (69.24)	0.12

Vitamin E (2)	81.35 (39.29)	96.28 (43.28)	0.1
Sodium (2)	155 (81.33)	138 (65.46)	0.58
Calcium (2)	108.25(42.00)	103.50(30.32)	0.53
Phosphorus (3)	248.4 (65.2)	278.3 (58.7)	0.002
Magnesium (2)	153.17 (89.35)	128.96 (52.75)	0.2
Iron (2)	174.92 (90.81)	144.82 (48.42)	0.13
Zinc (2)	70.03 (39.51)	61.07 (18.28)	0.87
Fiber (g/day)/%	14.16 (7.66)/	12.84 (5.52)/	0.374
RDI	56.64 (30.64)	51.36 (22.08)	

Table 2: Dietary intake in children with celiac disease at time of diagnosis and after 1 year on a gluten-free diet; [SD: Standard Deviation; MIFA: Monounsaturated Fatty Acids; PIFA: Polyunsaturated Fatty Acids; SFL: Saturated Fatty Acids; % TL: Percentage of Total Lipids; RDI: Reference Daily Intake; (1) %Energy: Refers to the percentage of caloric intake ingested, as a function of estimated caloric intake for weight, age, and sex with mild physical activity according to Schofield's formula for weight and height; (2) Percentage of intake according to the RDI; (3) percentage of intake according to AI (adequate intake)].

	At diagnosis (SD)	**1 year later (SD)**	**Significance (P)**
IgA ATG (UI/ml)	96.55 (37.73)	7.58 (12.83)	<0.001
Ferritin (mcg/l)	17.12 (14.53)	40.75 (32.32)	<0.001
Hemoglobin (mg/dl)	12.02 (1.29)	12.93 (0.88)	<0.001
Vitamin B12 (pg/ml)	632.25 (231.44)	725.91(340.99)	0.084
Vitamin D (nmol/l)	76.81 (20.23)	87.06 (26.36)	0.039
PTH (pg/ml)	35.71 (14.74)	27.79 (13.30)	0.004
Magnesium (mg/dl)	2.08 (0.17)	2.01 (0.31)	0.487
Products of bone type 1 collagen degradation (pg/ml)	1128.68 (475.06)	1152.09 (441.43)	0.76
Type I procollagen N-terminal peptide (TPINP) (ng/ml)	600.46 (169.43)	643.53 (190.66)	0.44
Bone alkaline Phosphatase (U/l)	122.22 (20.06)	117.26 (30.35)	0.421
Folic acid (ng/ml)	10.66 (5.90)	14.24 (4.59)	0.004
Homocysteine (mcmol/l)	8.34 (3.54)	7.49 (2.78)	0.198
Calcium (mg/dl)	9.77 (0.47)	9.97 (0.20)	0.142
Phosphorus (mg/dl)	5.17 (0.50)	5.08 (0.60)	0.472

Table 3: Hematologic and biochemical parameters; [ATG: Anti-antitransglutaminase Antibodies; SD: Standard Deviation].

	At diagnosis	**1 year later**
Marsh	0.36	
Time to diagnosis	r=0.143; P=0.265	
Symptoms	0.483	
IgA ATG	r=-0.235; P=0.06	
PTH	r=0.129; P=0.35	r=0.032; P=0.84

Plasma vitamin D	r=0.249; P = 0.96	r=0.006; P=0.97
Bone alkaline phosphatase	r=0.140; P=0.39	r=-0.071; P=0.72
Type I procollagen N-terminal peptide (TPINP)	r=0.154; P=0.285	r=-0.062; P=0.727
Products of bone type 1 collagen degradation	r=0.154; P=0.285	r=0.081; P=0.632
Gender (M/F)	P=0.189	
Weight SD	r=0.552; P<0.001	r=0.348; P=0.024
Height SD	r=0.471; P<0.001	r=0.426; P=0.005
SD BMD	r=0.391; P=0.002	r=0.186; P=0.238
Brachial perimeter SD	r=0.298; P=0.022	r=0.303; P = 0.087
Triceps fold SD	r=0.214; P=0.104	r=0.127; P=0.481
%Energy intake	r=-0.275; P=0.07	r=-0.208; P=0.23
Protein intake	r=-0.057; P=0.169	r=-0.045; P=0.178
Calcium intake	r=-0.235; P=0.116	r=-0.187; P=0.289
Vitamin D intake	r=0.353; P=0.02	r=-0.230; P=0.19
Phosphorus intake	r=0.038; P=0.960	r=0.023; P=0.567

Table 4: Values of significance of the relations between Z-score BMD and different parameters; [ATG: Anti-antitransglutaminase Antibodies; SD: Standard Deviation; BMD: Bone Mineral Density].

Discussion

The present report is the first longitudinal study to evaluate bone mass and its relationship with dietary intakes, biochemical parameters, and different bone resorption and formation parameters. In our study, children with untreated CD had significantly lower BMD Z-scores at diagnosis than they did after one year of 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 a strict GFD alone is capable of increasing bone mass values [17-21]. The time period on the GFD needed for the total normalization of BMD is unknown. Different studies show that despite the remarkable increase within a year, normal standards were not achieved [21-23]. Our study coincides with these findings, because after 1 year of receiving a GFD, in the repeated measurements group, there was significantly improved BMD without reaching normal values. In children, it has been demonstrated that, if a GFD is not commenced before puberty, total recovery cannot be achieved [8,20,24,25].

The relationship between a delayed diagnosis and worse BMD has not been proved in different studies and has not been shown in our study either. Classically, this has been related with the existence of symptoms or lack of symptoms at diagnosis. We find that both symptomatic and asymptomatic children have reduced bone mass at diagnosis. Turner et al. had similar findings. Kalayci provides data that indicates that impaired bone heath is slower for patients without symptoms. This coincides with the theory that if there are no symptoms, the time to the diagnosis is longer, allowing for greater changes in BMD and promoting greater alterations [20,26,27]. These data make us think that osteopenia in patients with CD is independent of other symptoms, which supports the idea that the diagnosis of CD must be made as soon as possible.

In relation to diet, our study aimed to assess the quality of the GFD in the pediatric age group and its impact on DXA values. We found that the elimination of gluten from the diet did not lead to changes in calorie and essential nutrient intakes. Published case series that make overall assessments of the GFD found that the diet was normal (80-120% of the recommended caloric intake) or hypercaloric (>121% of the recommended intake), with a high calorie contribution from proteins and lipids [5,28-31]. In our study, we observed a normal calorie intake that was not above the past intake prior to the elimination of gluten from the diet, with a high percentage of proteins and lipids and a slightly lower carbohydrate intake. Traditionally, it has been argued that the introduction of a GFD entailed an increase in lipid consumption as a result of a reduction in the intake of carbohydrates from the elimination of gluten-containing cereals from the diet [28,29].

Our findings did not support this statement. In fact, we found an improvement in the FA profile intake with an increase in the intake of polyunsaturated fats and a decrease in the intake of saturated fats. One possible explanation is that more gluten-free products are now available for celiac patients, including bread and cereals. These products taste better and are more affordable, so patients do not change their habits and continue consuming cereals as they used to. Another factor that may be at play is the commitment of the parents of these patients to comply correctly with the diet, which motivates many of them to prepare meals at home using foods with adequate macronutrient, micronutrient, vitamin, and fiber contents, thus precluding the consumption of processed foods rich in lipids.

A low fiber intake is consistently found in the studies on the GFD [2,4,28,30,31] and is attributed to decreased consumption of gluten-containing cereals, which may contribute up to 35% of the daily fiber intake in children [31]. A possible solution to this problem could be to promote the consumption of pseudo-cereals, such as quinoa, amaranth, or buckwheat, which have higher fiber and polyunsaturated FA contents than cereals like rice. The intake of dietary elements and vitamins in both types of diet was normal except for vitamin D and zinc, in contrastwith other studies that show deficiencies in the intake of vitamin B6, iron, and calcium [3,29,30,32]. In regards to the insufficient intake of vitamin D both in the gluten-containing and in the GFD, it is worth noting, that while we did not find any 1,25-(OH) vitamin D serum levels in the severe deficiency (<25 nmol/l) range at any point, we observed a significant increase in its serum levels accompanied by a decline in PTH levels.

These two parameters are linked in our series at diagnosis, where an inverse correlation between both parameters (P=0.14) is proved. Hyperparathyroidism is common in patients newly diagnosed with CD. Different studies have found the rate of hyperparathyroidism in CD patients to be 54% [33]. Only 7% of the children in our study showed levels of PTH consistent with hyperparathyroidism. The drop in the PTH levels like those observed in our study have been documented in other studies [8,9]. A possible explanation for the absence of low serum vitamin D is that the population under study is from a geographical area (Seville) with high amounts of sunlight, which is an important source of this vitamin.

The increase in vitamin D levels and the decrease in PTH levels reveal an improvement in the homeostasis of vitamin D and calcium in patients that is not due to a greater consumption of them. In fact, our study revealed no relationship between calcium intake and DXA. This situation can explain the recuperation of the enteropathy, which allowed for increased absorption of vitamin D in the intestine and a better use of it for increasing the leveles of calbindin and calcium-binding protein, the vitamin D-regulated proteins that actively take up calcium from the intestinal lumen [18]. This improvement would cause a recuperation of the DXA parameters, as observed in our study, and explains the lack of relationship with the nutrient intake.

On other hand, the link between vitamin D intake and a better DXA at diagnosis described by other authors suggests supplementing vitamin D for celiac patients with osteopenia in order to stimulate their recovery [4,23]. Our data show the link between a large intake of vitamin D and better mineral health at diagnosis, although this relationship could not be shown in patients on a GFD. In fact, we know that although the principal factor for BMD improvement is adequate and proper compliance with the GFD, appropriate intake of vitamin D could stimulate a decrease in bone loss at diagnosis and so a vitamin D supplement should be recommended for those patients with vitamin D deficiency at diagnosis.

Other aims of ours were to analyze the possible change in the bone formation and resorption markers. In our study, with the exception of the improvement of the vitamin D and PTH parameters, all of the markers were within normal levels at diagnosis as at control one year later. We could not show any relationship between some of these markers and DXA either at diagnosis or at one year. There are a few studies on this topic which have shown results similar to ours [21,22,34,35]. Only Mager showed a decrease in the N-telopeptide-1-terminal at one year of the GFD [23]. The lack of a clear relationship in the literature leads us to believe that currently the real value of these markers is not known and that further investigation is necessary in order to know their real utility.

Conclusion

Children with CD have suboptimal bone health at the time of diagnosis. After one year of GFD, the DXA value improves but does not normalize. In these children, a good nutritional status is essential, so the better the nutritional and anthropometric parameters, the better bone health is. The GFD is an adequate and healthy diet, similar in both macronutrients and micronutrients to a diet with gluten; and, except for vitamin D intake, the GFD does not have any deficiencies. Therefore, the lack of total recuperation in the DXA value cannot be attributed to the GFD. Careful consideration should be given to routine supplementation of vitamin D at the time of diagnosis of CD in those patients with low vitamin D levels and elevated PTH levels. Finally, nowadays there are no bone turnover markers that can be used for the diagnosis and control of these patients, so much more research is needed in this field.

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