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Impact of a gluten-free diet on bone mineral density in celiac patients

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ABSTRACT

Background: Osteoporosis (OP) is a metabolic bone illness that may complicate celiac disease (CD). It can lead to devastating consequences because of low bone mass and fragility fractures.

Purpose: To study the OP prevalence in a group of Brazilian patients with CD and the value of a gluten free diet (GFD).

Methods: Retrospective study of celiac female patients from a single University Center followed with bone densitometries. Results from densitometry made at first visit were compared with a second study after a median time of 5 years. During this period, patients were submitted to a GFD according to orientations from special program training. Calcium and vitamin D were prescribed to those patients who did not reach the minimal daily requirement through diet.

Results: Forty-one celiac female patients, mean age 46.1 ± 14.8 years, were included. The prevalence of osteopenia at first visit was 56.1% and that of osteoporosis 29.2%. Osteoporosis was associated with longer disease duration (p = 0.01). The second densitometry was performed in a median time of 5 years (range 1 to 13 years) and disclosed 58.9% osteopenia and 28.2% osteoporosis. The GFD improved bone mass, mainly at (of) spine (comparison of T score with p = 0.03 and of bone mass in g/cm^2 with p = 0.02), but it was not sufficient to reduce the number of osteopenic (p = 0.9) and osteoporotic patients (p = 0.4). During the follow up period 25% of osteoporotic patients developed low impact fractures.

Conclusion: Bone health is notably impaired at baseline in CD patients, especially in those with a diagnostic delay. A GFD modestly improved bone mass density with low impact fractures occurring in one third of patients during the follow up period.

Key words: Celiac disease. Osteoporosis. Bone densitometry. Gluten-free diet.

INTRODUCTION

Celiac disease (CD) is a chronic enteropathy caused by gluten intolerance in genetically predisposed individuals (1). It causes intestinal villous atrophy, crypt hyperplasia and lymphocytic inflammatory infiltration in the proximal part of small intestinal mucosa (1). The prevalence of osteoporosis (OP) in CD patients is considered to be higher than in normal population (3.4% *vs.* 0.2%) (1). A meta-analysis by Olmos et al. (2) confirmed a positive association between bone fractures and CD in adult patients.

The appearance of OP in CD seems to be multifactorial: malabsorption of nutrients that are essential for bone mineralization (3), direct action of pro inflammatory cytokines misbalancing bone formation and reabsorption (4), secondary hyperparathyroidism (5) and hypogonadism (4) are some of proposed explanations.

There is a debate in the literature about whether the gluten-free diet (GFD) may help in the restoration of bone mass; while some authors have found benefit (6-8), others deny it (9,10). A third group found out that bone mineral density values normalize only in children that follow a strict GFD (11). Newnham et al. (12) studying bone mass for 5 years in a group of 99 celiac patients found that GFD increased bone mass only in those with osteopenia or OP, mostly in the first year.

OP is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture (2). The compromised bone mass predisposes to low impact fractures mainly at vertebrae, hip and distal forearm, causing important functional loss and increasing patients' mortality. It has been shown that in one year after hip fracture, 20% of patients will have died and another 20% will have lost their autonomy (12). Although very important, long term strategy for diagnosis and treatment in CD patients with low bone mass remains to be established.

OP diagnosis is done by densitometry by DXA (dual energy X-ray absorptiometry) that is a method based on the

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principle of photon absorption, which allows the quantification of calcium in the tissues (13). The values obtained by DXA are compared with those from a healthy young person and from this comparison the T-score is calculated. A T-score from 0 to -1 is considered to be normal; from -1 to -2.5 it is considered as osteopenia and bellow -2.5, OP. The Z score is the same comparison, but now relative to healthy individuals of the same age as the studied patient, and should be used for evaluation of pre-menopausal women and men < 50 years (13).

Bone mass suffers influence from lifestyle and race among other variables, having a pattern that varies according to the studied population. In the present study we aimed to analyze the bone mass of a group of Brazilian adult celiac patients to verify the prevalence of low bone mineral density as well as the effect of GFD.

METHODS

This is a retrospective study approved by the local Committee of Ethics in Research, which followed 41 women with CD diagnosed according to World Gastroenterology Organization (14) from a single gastroenterology center in a university hospital. The inclusion period went from January 2002 to June 2015. Demographic profile, gynecological and obstetric antecedents, disease duration at first densitometry, as well as results of bone densitometry by DXA, were obtained through chart review. OP diagnosis was done when the patients had at least -2.5 standard deviations (SD) below the young-adult mean bone mass density (BMD) or T-score in lumbar spine and/or femoral neck (13). Patients with OP at first densitometry were compared with those without it for demographic and gynecological/obstetrical data. GFD was orientated in a special training program supported by the local Gastroenterology Clinic and adherence to diet was checked through direct questioning during follow up visits by the attending doctor and by serological tests (negative antiendomysium antibody after one year of GFD). Calcium and vitamin D supplementation were offered to all of them with intake less than the minimal daily requirement (1.5 g of calcium and 600 UI vitamin D3/daily). All patients were also referred to a local association of celiac patients for guidance on aspects of the disease, mainly about GFD.

Patients that did not receive drug treatment for OP had their densitometries done at first visit compared with the last one obtained to study the value of the GFD. It was also calculated and compared the Fracture Risk Assessment Tool (FRAX) values at the moment of first and second densitometries. FRAX is an instrument that estimates the fracture risk in the next 5 years, taking into account not only DXA values but also genetic and environmental factors (14).

Data was analyzed by frequency and contingency tables. Central tendency was expressed in mean ± SD for parametric data and median and interquartile range (IQR) for non-parametric data. Association studies were done with chi-squared test and Fisher test for nominal data. Association studies of numerical data such as comparison of first and last densitometry were done by paired t test or Wilcoxon matched pairs signed rank test according to data distribution. Comparison of patients with or without OP at first densitometry was done by and Mann Whitney and unpaired t-test. Significance adopted was of 5%. The software Graph Pad Prism version 5.0 was used for calculations.

RESULTS

All 41 patients were female aged from 13 to 76 years (mean 46.1 ± 14.8); 3/41 (7.3%) were smokers; 22/41 (53.6%) had had menopause. The age of menarche ranged from 10-17 years (median 13.0; IQR = 12.0-15.0) and of menopause, from 40-57 years (median 49.5; IQR = 47.7-52.2). These women had had 0-5 pregnancies (mean 1.0; IQR = 0-2.7).

In this sample 14.6% had normal bone mass, 56.1% had osteopenia and 29.2% had OP at first densitometry.

Comparing data of patients with OP at first densitometry with those without it, results of table I were found and they show that only disease duration was associated with OP.

These patients were followed for a median time of 5 years (range 1 to 13 years; IQR = 2.0-10.0) until the second densitometry. During this period, 5/41 (12.1%) entered menopause and 30% of osteoporotic patients (4/12) developed low impact fracture. The verified fractures were on the hip, rib, wrist and ankle.

At the second densitometry evaluation 12.8% of patients had normal bone mass; 58.9% had osteopenia (p = 0.9 in

Table I. Comparison of celiac patients with and without osteoporosis at first densitometry

	With osteoporosis n = 12	*Without osteoporosis n = 29*	*p*
Age-years (mean ± SD)	22.6 (45.6 ± 12.5)	13.0-76.0 (46.7 ± 16.2)	0.87*
Disease duration-years median (IQR)	2.0-29.0 8.0 (4.2-18.5)	1.0-28.0 3.0 (2.0-6.0)	0.01**
Number of pregnancies median (IQR)	1.0-4.0 1.0 (1.0-2.0)	0-5.0 1.5 (0-3)	0.39**
Menarche age- median (IQR)	11-15 12.0 (12.0-15.0)	10.0-17.0 13.0 (12.0-14.0)	0.93**
Menopause‡	5/11-45.4%	10/26-38.4%	0.69§
Tobbaco exposure‡‡	2/12-16.6%	0/27	0.08§§

*Unpaired T-test. **Man Whitney. §Chi-squared test; §§Fisher test; ‡Missing data in 4 patients; ‡‡Missing data in 2 patients; SD: Standard deviation; IQR: Interquartile rate.

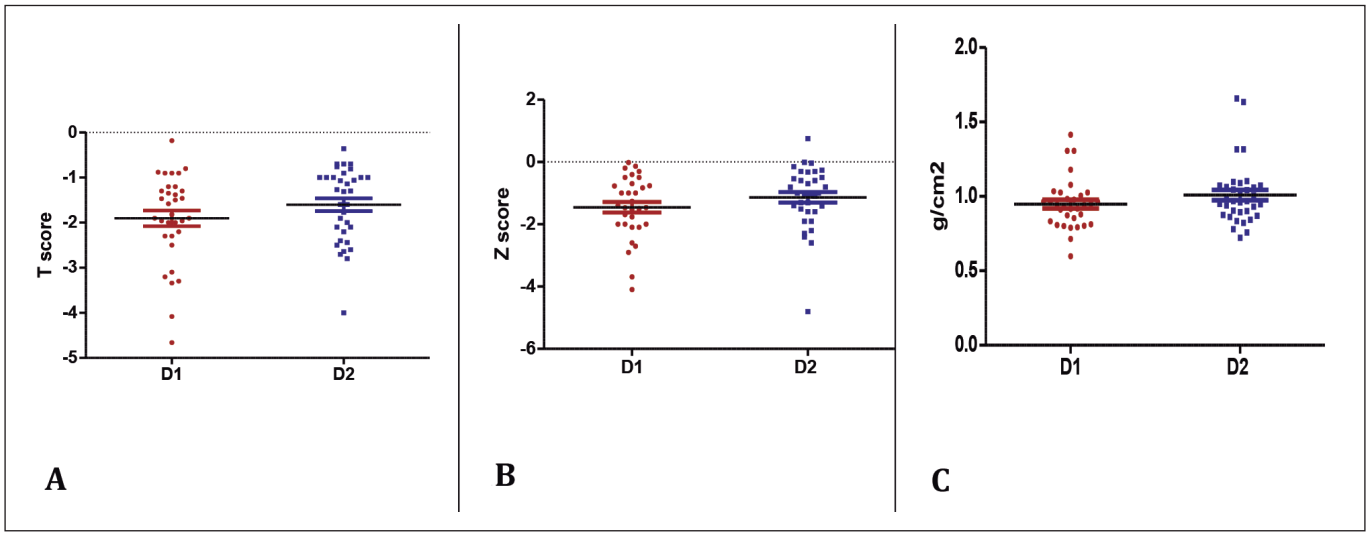

Fig. 1. A. Values of T-score in the first densitometry (D1: mean value of -1.45 ± 0.88) and last densitometry (D2: mean value of -1.21 ± 0.75); p = 0.03*. B. Values of Z-score in the first densitometry (D1: mean value of -1.46 ± 0.98) and last densitometry (D2: mean value of -1.13 ± 1.00); p = 0.15*. C. Values of bone density in g/cm2 in the first densitometry (D1: median value of 0.943; IQR = 0.822 to 1.016) and last densitometry (D2: median value = 0.968; IQR = 0.875 to 1.072); p = 0.02**.

relation to first densitometry) and 28.2% had OP (p = 0.2 in relation to first densitometry). The comparison of T, Z-score and bone mass in g/cm^2 in the femur is on table II, showing no differences in either of studied parameters.

All patients on treatment for OP with drugs (bisphosphonates) were excluded from this comparative analysis.

The 5 year risk of fracture calculated according to FRAX Brazil (14) showed that at the time of the first densitometry there was a fracture risk from 17.5 to 31.2% (median 23.8%; IQR = 20.2-28.4%) and in the second densitometry, from 16.5 to 33.8% (median 22.1%; IQR = 20.1-28.0%), with p = 0.84 (Mann Whitney test).

DISCUSSION

The analysis of bone densitometry of this sample has highlighted some important facts. The first one is that the great majority of celiac patients from our sample had low bone mass either because of OP or osteopenia. The mean age of studied patients at first visit in our clinic was relatively high (46 years of age) and this may have contributed to such high prevalence. Nevertheless, CD can be quite silent or may present with atypical features (16); so a late diagnosis is not surprising in this context. The classic mode of presentation with diarrhea or a malabsorption syndrome as the mode of presentation is seen in fewer than 50% of individuals (16). When patients with OP of our sample were compared with those without it, the disease duration but not the patients' age was associated with OP, showing that the importance of disease mechanisms involved in OP may overcome those related to age. Such finding emphasizes the need for an active search of OP in CD patients and early institution of its treatment.

The etiology of OP in CD is multifactorial. The first one is malabsorption of micronutrients due to villous atrophy (17). A negative calcium balance is partially due to this mechanism (17); another cause is the reduction of calcium intake due to secondary lactose intolerance (18). Also unabsorbed fatty acids bind calcium reducing its intestinal absorption (18). Low calcium levels trigger a compensatory increase in parathyroid hormone (PTH) responsible for

Table II. Comparison of hip values between the two densitometries

	First densitometry	*Last densitometry*	*p*
T-score (mean ± SD)	-3.960 to -0.100 (-1.45 ± 0.88)	-3.400 to -0.010 (-1.21 ± 0.75)	0.19*
Z-score median (IQR)	-3.600 to -0.070 -0.700 (-1.860 to -0.300)	-3.000 to -0.100 -0.700 (-1.110 to -0.330)	0.24**
g/cm^2 (mean ± SD)	0.500 to 1.165 (0.805 ± 0.131)	0.588 to 1.385 (0.844 ± 0.158)	0.30*

*Paired t-test; **Wilcoxon matched pairs signed rank test. SD: Standard deviation; IQR: Interquartile rate. T-score refers to the number of standard deviations away from the average value of the young people. Z-score refers to number of standard deviations away from the average value of the people of the same age and gender.

bone reabsorption resulting in OP (18,19). Intestinal malabsorption could also lead to some deficits of other minerals (such as zinc, copper, etc.) and vitamins that affect normal bone metabolism (18). A decrease of IGF-I (insulin growth factor I) is observed in osteoporotic patients. Untreated celiac patients may have low IGF-I levels and the zinc deficiency has been suggested as its cause (18).

Vitamin D is also deficient among CD patients despite the fact that diet only provides 5-10% of required vitamin D (20,21), with the rest being achieved from sunlight exposure. No changes in the expression of vitamin D receptors have been detected in this population (22).

Systemic inflammation with increased levels in both mucosal and serum pro-inflammatory cytokines (mainly IL [interleukin]-6, TNF [tumor necrosis factor]-α and IL-1) stimulate osteoclastogenesis and bone reabsorption (18,22). It has been shown that serum levels of IL-6 inversely correlate with BMD (23). Autoantibodies against osteoprotegerin, an osteoclastogenesis inhibitory factor, have been described by some authors (24) but not confirmed by others (25).

Hypogonadism is also a contributor to OP in CD (18). Amenorrhea and early menopause have been described in women and credited to malnutrition and hormone imbalance (18). Androgen resistance and hyperprolactinemia are considered to be a possible adjunctive factor risk for male OP (18).

In our patients the GFD has helped to increase bone mass mainly in spine. Our results are according with those of Tau et al. (6), Pantaleoni et al. (7) and Di Stefano et al. (8). With the GFD, the levels of interleukin-6, but not of TNF-α, decrease (26). Results regarding parathyroid function in treated celiac patients show that they are similar to control group excluding a residual secondary hyperparathyroidism (27). Nevertheless, it is important to note that the achieved increase was modest as the number of osteoporotic and osteopenic patients remained almost the same. During the observation period, around 12% of the sample entered menopause and this could have some interference in bone mass. Despite this, the fracture risk calculated by the FRAX (14), an instrument that also takes into account this variable, did not change.

There are some limitations to the present study. The first is its retrospective nature and difficulties raised by this type of design; the second is that the sample was composed only by adult women, not allowing inferences in men or children. The third is that compliance to a GFD was checked, but this adherence is known to be associated with cognitive, emotional and socio-cultural influences (28). GFD may have barriers to its institution, including availability, cost, safety of gluten-free foods and gluten cross-contamination (29).

So, further studies with prospective design allowing a more strict control of all implicated variables and with higher number of patients are warranted.

To conclude, we can say that in Brazilian celiac women, bone health is notably impaired at baseline in these patients, especially in those with a diagnostic delay. A GFD modestly improved BMD with low impact fractures occurring in one third of patients during the follow up period.

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