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Skeletal health assessment in Brazilian men with celiac disease at diagnosis: how important is it?

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HIGHLIGHTS

- Assessing BMD in CD patients is uncertain and studies in Brazil show lower BMD, especially in women, with limited data on men.
- Our results indicate a high prevalence of low BMD in males with CD, irrespective of their age, with older celiac men being particularly affected.
- CD patients benefit from BMD assessment at diagnosis for proper treatment and quality of life improvement.

ABSTRACT – Background – Low bone mass density (BMD) is an extraintestinal finding in celiac disease (CD). This may result in bone fractures leading to loss in quality of life. **Objective –** To assess BMD in male CD patients at diagnosis according to the patient's age. **Methods –** Descriptive retrospective carried out during the period between 2013 and 2023 in a single office that studied dual-energy X-ray absorptiometry (DXA) results in 28 male patients with a recent diagnosis of CD, divided into three groups: group 1 (age up to 18 years); group 2 (from 19 to 49 years of age) and group 3 (over 50 years of age). Were studied demographic and anthropometric parameters, time delay between symptoms onset and CD diagnosis and fracture occurrence. **Results** – Celiac patients studied had median age 36.0 years (IQR=16.5–50.7). Among them, 39.3% had osteopenia and 14.3% had osteoporosis. Only 36% of the sample had normal DXA values (group 1 with 37.5%; group 2 with 46% and group 3 with 14.2%). No pathological fracture was observed in this sample. CD diagnosis delay observed had median 1.0 year (IQR=1.0–4.7). When the number of individuals with normal and abnormal DXA results were compared, there was no difference in body mass index, time of diagnosis delay or Marsh classification (P=0.18). **Conclusion** – Male patients at the time of CD diagnosis showed a high prevalence of low BMD, which was particularly evident in individuals over 50 years of age.

Keywords – Celiac disease; bone; males.

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INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disease that occurs in genetically susceptible individuals as a result of an immune response to the ingestion of gluten. Its incidence appears to be increasing over time and it is estimated to have a worldwide seroprevalence of 1.45% and 0.7% of biopsy-proven CD[1]. Females are more affected than males; the pooled incidence rate in women is 17.4 per 100.000 persons-years, whereas in men it is 7.8 per 100.000 persons-years[2]. While gastrointestinal symptoms such as flatulence, abdominal pain, diarrhea and abdominal distention are the most recognized signs and symptoms, a significant proportion of individuals may present with extraintestinal signs and symptoms such as anemia, fatigue, infertility and low bone mass density (BMD)[2]. Surprisingly, the proportion of individuals with gastrointestinal symptoms has decreased over time while the number of individuals with extraintestinal phenotype has been observed[2].

The occurrence of metabolic bone disease in CD has long been recognized, manifesting mainly as osteopenia, osteoporosis and bone fracture[3]. The appearance of bone injury in this context is multifactorial[4], and the treatment with a strict gluten-free diet results in a rapid increase of BMD[5].

Although BMD is a well-recognized condition, easily screened by DXA (dual-energy X-ray absorptiometry), the question of who and when to assess BMD in patients with CD remains unanswered. In the Brazilian population, the majority of published studies have shown lower BMD in adults with CD of both sexes, but mainly in women[5-7]; however studies assessing bone health exclusively in men, at all ages at diagnosis, are scarce in the literature[8-10].

Therefore, we aimed to report DXA findings in a case series of Brazilian males at diagnosis of CD, examining bone health at various ages.

METHODS

Design and ethical issues: this was a retrospective descriptive study approved by the local Research Ethics Committee under protocol 39920920.2.0000.0103. The study was conducted according to the Good Clinical Practice Guidelines and the Declaration of Helsinki. The study was conducted by reviewing patients' clinical charts and carried out during the period between March 2013 and October 2023. All patients were treated by the same physician in a Gastroenterology reference medical office, in Curitiba, Paraná, Brazil. Informed consents for children/adolescents were obtained from their legal guardians.

Inclusion and exclusion criteria: to be included, male patients must have a clinical diagnosis of CD based on signs and symptoms, as well as positive serological findings of autoantibodies anti-endomysial-IgA and/or anti-transglutaminase antibodies-IgA, following determination of serum levels IgA[11]. All diagnoses were confirmed by histopathological findings in duodenal biopsies, according to the Marsh classification[12,13]. Female patients and those with incomplete records were excluded from the study.

Data collection

a. Demographic and anthropometric parameters, such as weight, height and bone mass index (BMI);
b. Time delay between symptoms onset and CD diagnosis;
c. Fractures occurrence;
d. DXA values assessed at the lateral distal femur and anterior posterior spine. This assessment should be performed during the first patient assessment following CD diagnosis. BMD *z*-score was used for interpretation, adjusted for age, sex, weight and height[14].

The WHO classification was used in males aged 50 years and older. In young adult males (less than 50 years of age), the *z*-scores were used, and a clinical diagnosis of osteoporosis was made if the *z*-score ≤-2.0 in addition to a history of fragility fracture[15].

In children and adolescents, the diagnosis of osteoporosis was made when one or more vertebral fractures were present, in the absence of local disease or high-energy trauma or, when the *z* -score ≤-2.0 in the presence of a clinically significant fracture (two or more long bone fractures by age 10 years; or three or more long bone fractures at any age up to the age of 19 years)[16].

Data analysis

Data was collected in frequency tables. Nominal data were expressed in percentages. The central tendency of numerical data was expressed as means and standard deviation (SD) if the distribution was normal and as median and interquartile range (IQR) if the distribution was nonparametric. Comparisons of BMI, age, and diagnostic delay between individuals with normal and abnormal DXAs were performed using the unpaired *t*-test and Mann Whitney test and the Marsh classification by using the chi-squared test. The adopted significance was 5%.

RESULTS

Twenty-eight male patients, all Caucasians were included in the study. Demographic and anthropometric data, as well as data on CD are shown in TABLE 1.

TABLE 1. Characteristics of the studied sample: 28 male patients with celiac disease.

Age- years (IQR)	8–69.0- median 36.0 (16.5–50.7)
Age (categorical) – years	
8–18	8/28 (28.6%)
19–50	12/28 (42.8%)
51–69	8/28 (28.6%)
Diagnosis delay – years (IQR)	1 to 15 years; median 1.0 (1.0–4.7)
Body mass index- kg/m^2	mean 22.3±5.22 (13.1–33.4)
Duodenal biopsy (n)	
Marsh I	4/28 (14.2%)
Marsh II	5/28 (17.8%)
Marsh III	19/28 (67.8%)
Fractures (n)	3/28 – 10.7% Sites: clavicle, foot, and hand, all of them in group 1

N: number; IQR: interquartile range.

TABLE 2 shows data on age at diagnosis, delay in diagnosis, BMI, histological data and DXA findings in the femur and spine for all studied patients.

a. DXA values in celiac males in group 1 – up to the age of 18 years (n=8)

Three fractures were observed in this group, but none of them was considered clinically significant for osteoporosis diagnosis. In this group 3/8 (37.5%) had normal DXA; 2/8 (25%) had *z* score ≤2 in the femur; 1/8 (12.5%) had *z* score ≤2 in the spine and 2/8 (25%) had *z* score ≤2 in both spine and femur.

b. DXA values in celiac males in group 2 – 19 to 49 years of age (n=12)

The values of DXA in this age group showed that 6/12 (50.0%) had normal DXA; 2/12 (16.7%) had *z* score ≤2 in the spine; and 4/12 (33.3%) had *z* score ≤2 in both the femur and spine. None had isolated alteration in the femur.

c. DXA values in group 3 or celiac males – over 50 years of age (n=8)

The DXA value in this age group showed that 1/8 (12.5%) had normal DXA values; 3/8 (37.5%) had osteopenia in both sites; 2/8 (25.0%) had osteoporosis in both sites, 1/8 (12.5%) had osteopenia in the femur and osteoporosis in spine, and 1/8 (12.5%) had osteopenia only in the spine.

TABLE 3 shows that 39.3% of the studied celiac patients had osteopenia and 14.3% had osteoporosis, compared to findings of other countries.

Considering the entire sample, 36% had normal DXA values and 64% had abnormal values (7% had low BMD in the femur; 14% had low DMD in the spine and 43% had low BMD in both sites).

FIGURE 1 shows the comparison of BMD in the three age groups.

When the number of individuals with normal and abnormal DXA results were compared, there was no difference in BMI (P=0.20), time of diagnosis delay (P=0.51) and Marsh classification (P=0.18).

DISCUSSION

Our findings show that low BMD is frequent in males with CD, regardless of age. Additionally, celiac men over the age of 50 were the most affected. According to Larussa et al.[4] the presence of low BMD at diagnosis ranged from 38 to 72% and a meta-analysis by Heikkila et al.[22] showed that, in these individuals, the fracture risk increased by 30%. In the present study, low BMD affected 64% of the sample, particularly affecting 62.5% of those with less than 20 years.

TABLE 2. Comparative data from several countries on osteopenia and osteoporosis among male patients.

country	Year	Author	N	Osteopenia (%)	Osteoporosis (%)
USA	2001	Meyer et al.[17]	23	80.0	45.0
Poland	2012	Szymczak et al.[18]	35	59.5	23.0
India	2012	Chakravarthi et al.[19]	24	43.0	18.0
Hungary	2013	Kocsis et al.[20]	113	36.0	18.0
United Kingdom	2015	Pritchard et al.[21]	85	28.0	5.0
Italy	2018	Galli et al.[22]	61	42.5	17.8
Brazil	2023	Kotze et al.	28	39.3	14.3

TABLE 3. Data on age at diagnosis, diagnosis delay, body mass index and results of dxa in the studied patients (n=28).

Age at Diagnosis (y)	Diagnosis delay (y)	BMI (kg/m²)	Biopsy (Marsh)	Femur (DXA)	Spine (DXA)
8	1	18.8	M-III	Osteopenia	Normal
9	4	16.7	M-III	Normal	Normal
12	1	13.1	M-III	Normal	Normal
12	11	14.3	M-III	Osteopenia	Osteopenia
13	8	28.2	M-II	Osteopenia	Normal
14	5	16.1	M-II	Osteopenia	Osteopenia
16	11	30.4	M-III	Normal	Normal
18	2	26.1	M-I	Normal	Normal
22	15	20.1	M-III	Normal	Normal
23	5	17.7	M-III	Osteopenia	Osteopenia
24	6	18.4	M-III	Osteopenia	Osteopenia
27	1	17.5	M-III	Normal	Osteopenia
32	2	20.7	M-II	Osteopenia	Osteopenia
36	1	23.9	M-III	Normal	Normal
36	2	26.2	M-I	Normal	Normal
39	1	24.8	M-III	Normal	Osteoporosis
44	1	32.7	M-I	Normal	Normal
47	1	24.9	M-III	Osteoporosis	Osteoporosis
49	1	33.4	M-III	Normal	Normal
49	1	23.1	M-II	Normal	Normal
50	1	27.3	M-I	Osteopenia	Osteoporosis
51	2	22.3	M-II	Osteopenia	Osteopenia
52	1	22.2	M-III	Osteoporosis	Osteoporosis
59	1	17.5	M-III	Normal	Osteopenia
61	2	21.3	M-III	Osteopenia	Osteopenia
64	3	20.2	M-III	Osteoporosis	Osteoporosis
67	1	25.3	M-III	Normal	Normal
69	1	23.1	M-III	Osteopenia	Osteopenia

Y: years; dxa: dual-energy x-ray absorptiometry.

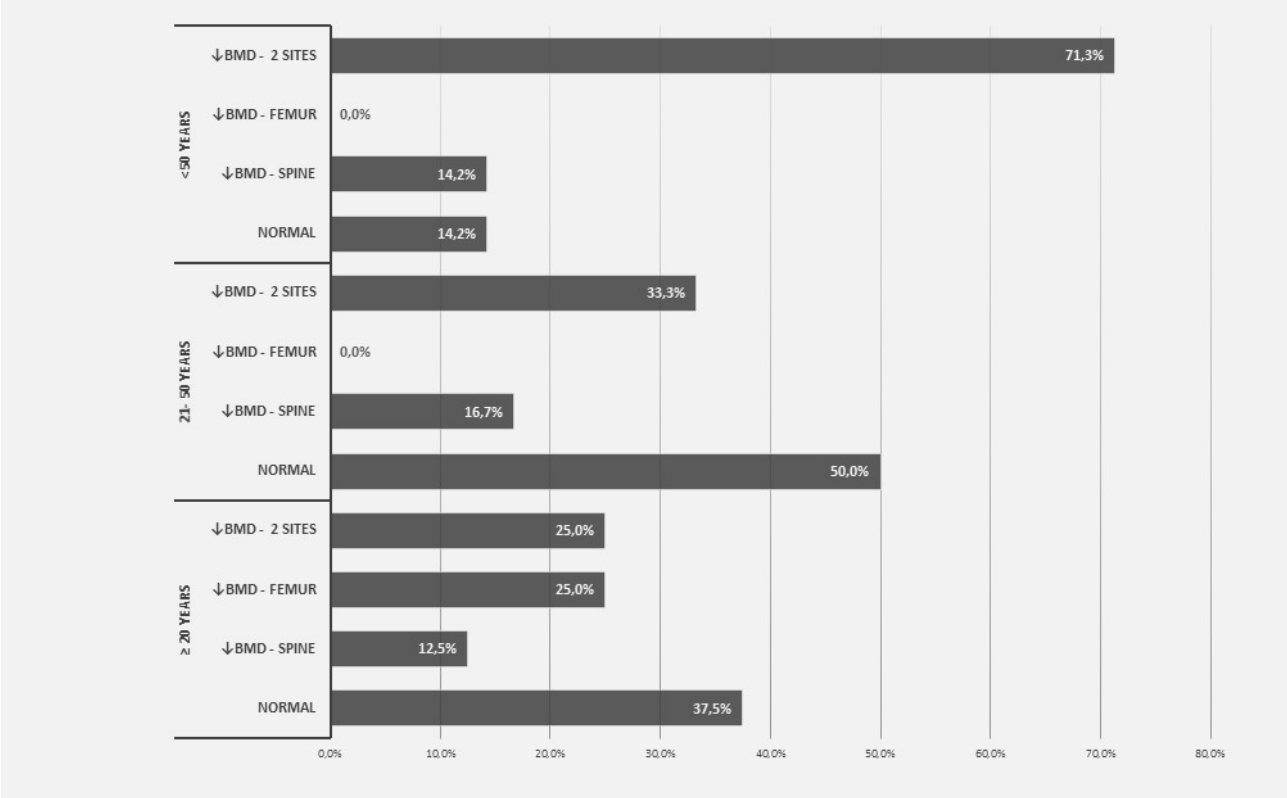

FIGURE 1. Comparison between DXA values by age groups in 28 male patients with celiac disease.
BMD: bone mass density.

Villous atrophy and small bowel changes caused by CD can reduce calcium and vitamin D absorption, leading to increased PTH levels (secondary hyperparathyroidism) which induce osteoclast activity with bone absorption, resulting in bone loss, general malnutrition and weight loss[4]. Persistent hypocalcemia with reduced bone mineralization may also cause osteomalacia or rickets in children[3]. Associated hypogonadism also affects bone quality increasing the risk of fractures in later years. Chronic inflammation with increased levels of anti TNF-α, IL-6, and IL-1 promotes elevated RANKL levels and osteoclast activation, contributing to bone reabsorption[3].

Ethnic variations in bone accrual have been reported by several multiethnic studies in countries with different cultures and alimentary habits[1]. Our results are consistent with existing findings showing that low BMD is common in Brazilian patients[5]. Therefore, reaction to gluten may be the main responsible for the skeletal damage. Despite the worldwide recognition, low BMD in CD is frequently underdiagnosed and undertreated[2].

Regarding delay in the diagnosis of CD, several authors have raised this issue in several countries[2,6]. Sayar et al., in Turkey, reported that the mean duration of symptoms before diagnosis was 14.2±15.7 months, which was similar to ours[23]. This might be attributed to a lack of disease awareness[2,24].

Despite the small number of cases, we detected low BMD in celiac children and adolescents. Bone accrual in childhood determines bone health later in life. Loss of bone strength during childhood can lead to increased morbidity, reducing quality of life in childhood and adolescence. In this age group, reduced BMD may be evident at CD diagnosis[25]. DXA can aid in the diagnosis and management of bone fragility disorders in all age groups[26].

Regarding mucosal damage, Walter et al. in the United States, reported partial villous atrophy in 58.2% and 41.8% of total atrophy in celiac patients[21]. In addition, Garcia-Manzanares et al., in Spain, found that BMD directly correlated with duodenal Marsh stage in newly diagnosed adult celiac patients[27]. Although our study did not find a significant association between low BMI, degree of mucosal atrophy or diagnostic delay, some of the patients studied had

such characteristics and had low BMD. Galli et al., in Italy, found that age ≥45 years, underweight and having significant histological damage were risk factors associated with low BMD in adults with CD[20].

This study is limited by the small sample size and its retrospective nature. Furthermore, we did not include data on lifestyle habits such as diet, physical activity and smoking, nor laboratory data (calcium, PTH or vitamin D level). However, biochemical markers were not indicative of BMD disturbances and no biochemical indexes was capable of predicting an abnormal BMD *z* score[10].

Regardless of age, our study clearly shows the need to focus on BMD assessment in CD male individuals. Mosca et al., from Denmark, in a systemic review of the literature, concluded that it might be critical to assess BMD at the time of CD diagnosis[24]. Fouda et al., in Canada, reported that, at diagnosis, approximately one-third of adult patients with CD have normal BMD, one-third have osteopenia and one-third have osteoporosis[28]. In the present study, the authors require DXA in all patients at the diagnosis of CD, independently of age or sex, as well as preconized by the American College of Gastroenterology[29].

The current findings corroborate that all patients with CD having BMD assessed at diagnosis may receive adequate treatment orientation to improve their quality of life and to avoid complications, such as fractures. Given the high prevalence of low BMD in patients with CD, it is surprising that there are scarce publications on dietary and non-dietary guidelines for the management of osteoporosis in CD, despite the fact that dietary and/or pharmaceutical interventions can potentially improve bone health[5,24,30].

In summary, should patients with CD be screened for osteoporosis? Yes, regardless of age, sex, or geographic location.

CONCLUSION

Male patients at the time of CD diagnosis showed a high prevalence of low BMD, which was particularly evident in individuals over 50 years of age.

Authors' contribution

All authors contributed to the study conception and design. Data collections were performed by Kotze LMS and Kotze LR. Kotze LMS, Skare TL, Kotze LR and Nisihara R commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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RESUMO – Contexto – A baixa densidade de massa óssea (DMO) é um achado extraintestinal na doença celíaca (DC). Isso pode resultar em fraturas ósseas levando à perda de qualidade de vida. **Objetivo –** Avaliar a DMO em pacientes masculinos com DC no momento do diagnóstico de acordo com a idade do paciente. **Métodos –** Estudo retrospectivo descritivo realizado no período entre 2013 e 2023 em um único consultório que estudou resultados de "*dual-energy X-ray absorptiometry*" (DEXA) em 28 pacientes do sexo masculino com diagnóstico recente de DC, divididos em três grupos: grupo 1 (idade até 18 anos); grupo 2 (de 19 a 49 anos) e grupo 3 (acima de 50 anos). Foram estudados parâmetros demográficos e antropométricos, tempo decorrido entre o início dos sintomas e o diagnóstico da DC e ocorrência de fraturas. **Resultados –** Os pacientes celíacos estudados tinham mediana de idade de 36,0 anos (IIQ=16,5–50,7). Dentre eles, 39,3% apresentavam osteopenia e 14,3% apresentavam osteoporose. Apenas 36% da amostra apresentou valores normais de DEXA (grupo 1 com 37,5%; grupo 2 com 46% e grupo 3 com 14,2%). Nenhuma fratura patológica foi observada nesta amostra. O atraso no diagnóstico da DC observado teve mediana de 1,0 ano (IQR=1,0–4,7). Quando comparado o número de indivíduos com resultados de DEXA normais e alterados, não houve diferença no índice de massa corporal, tempo de atraso no diagnóstico ou classificação de Marsh (P=0,18). **Conclusão –** Pacientes do sexo masculino no momento do diagnóstico da DC apresentaram alta prevalência de baixa DMO, o que foi particularmente evidente em indivíduos com mais de 50 anos de idade.

Palavras-chave – Doença celíaca, osso, sexo masculino.

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