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ORIGINAL ARTICLE

Bone mineral density directly correlates with duodenal Marsh stage in newly diagnosed adult celiac patients

ÁLVARO GARCÍA-MANZANARES[1], JOSÉ M TENIAS[2] & ALFREDO J LUCENDO[3]

[1]*Department of Endocrinology and Nutrition, Complejo Hospitalario Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain,* [2]*Research Support Unit, Complejo Hospitalario Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain, and* [3]*Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Ciudad Real, Spain*

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Abstract

Objectives. To estimate the prevalence of low bone mineral density (BMD) in a prospective series of adult celiac patients and to identify nutritional and metabolic factors associated with osteoporosis and osteopenia. ***Methods.*** Patients over 18 years of age who were consecutively and newly diagnosed with celiac disease (CD) were recruited. A bone density scan with dual-energy X-ray absorptiometry was carried out on the left hip and lumbar spine; nutritional parameters were analyzed and a hormone study conducted in order to exclude secondary low BMD. ***Results.*** 40 patients (36 females/4 males) between the ages of 18 and 68 (mean 44.25 years) were recruited. Overall, at the moment of diagnosis 45% of patients exhibited low BMD at both demarcations. Risk of hip fracture was generally low, but ascended to mild in patients with villous atrophy ($p = 0.011$). Differences in major fracture risk were also observed depending on Marsh stage ($p = 0.015$). Significant differences were observed in nutritional status between patients with and without duodenal villous atrophy, with body mass index and blood levels of prealbumin, iron, vitamin D and folic acid significantly lower in Marsh III stage patients. No differences were found in blood hormone levels between Marsh stages or BMDs. The degree of bone mass loss in the lumbar spine directly correlated to Marsh stage. In the hip, a parallel association between BMD and Marsh stage was also observed, but did not reach statistical significance. ***Conclusion.*** Duodenal villous atrophy, through malabsorption, was the main determinant factor for low BMD in adult-onset CD patients.

Key Words: *bone density scan, bone mineral density, celiac disease, gluten enteropathy, osteopenia, osteoporosis*

Introduction

Celiac disease (CD), an autoimmune disorder triggered and maintained by the ingestion of food containing gluten, manifests in genetically susceptible individuals. CD affects between 1% and 3% of the European and US population at some stage in life [1], leading to a chronic inflammatory process that affects the small bowel mucosa and submucosa, thus impairing the absorption of macro- and micronutrients. Pathogenesis of CD includes cytotoxic T-lymphocyte activation in the intestinal lamina propria [2] and production of antibodies with autoimmune characteristics, resulting in a wide range of local and systemic clinical manifestations [3].

Up until 20 years ago, CD was considered to be present predominantly in children. In recent years, however, several epidemiological studies have shown that the incidence rates of adult-onset CD have increased continuously over time [3–9]. In general, CD in adults presents with mild and non-specific clinical symptoms, with digestive complaints being either absent or of secondary importance [10,11]. It is thus common for adult patients to go undiagnosed for many years, with the average diagnostic delay estimated to be up to 17 years [5].

Correspondence: Alfredo J Lucendo, MD PhD, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, 13700 Tomelloso, Spain. Tel: +34 926525927. Fax: +34 926525870. E-mail: alucendo@vodafone.es

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Osteoporosis is a systemic disease characterized by low bone mineral density (BMD), associated with impairment of bone microarchitecture and a consequently higher fracture risk [12]. Together with its clinical expression in terms of bone fractures, it constitutes a serious public health problem, with annual spending three to six times higher than that for stroke or breast cancer [13]. Despite the perception that it is a problem primarily in the elderly, osteoporosis is a very common disease; however, because it can be asymptomatic for many years, its prevalence among young people is not well known.

The association of CD with osteoporosis was first described in the 1930s. It is estimated that at the moment of diagnosis, one-third of pediatric-onset CD patients have osteoporosis, one-third osteopenia and only the remaining one-third retain a normal BMD [12,14]. Indeed, CD patients exhibit a prevalence for osteoporosis two times higher than that of the non-affected population in the same age group, being low body mass index (BMI) and advanced histological villous atrophy predictors of a low BMD [14]. Decreased BMD associated with pediatric CD responds to a gluten-free diet (GFD), with gradual restoration to normal levels within 2 years [15]. The earlier in life the treatment is started, the better the response [16], making osteoporosis a reversible problem in celiac children.

The problem is more complex in adult-onset CD, since the bone mass peak, or maximum amount of calcium that can be accumulated in the bones, is reached at the beginning of adulthood (20 and 30 years). After this period, BMD suffers a steady decline [17]. There is thus a certain amount of agreement with regard to the need to investigate the bone mineral status of celiac patients in order to plan therapeutic interventions [18], even though recent studies indicate only scant benefits for this strategy [19]. As for the inverse association, several studies have shown that the frequency of subclinical CD in patients diagnosed with osteoporosis is 10 times that of patients without osteoporosis [20].

Despite this clear association, after nearly a century of study, we still do not know the pathogenic mechanism and determining factors of low BMD in CD, its true incidence in adult-onset CD and more importantly, the best treatment for these patients in addition to GFD, since studies have produced mostly discordant data to date. Determining the main risk factors associated with osteoporosis in this group of patients would thus allow us to rationalize the use of diagnostic testing in order to increase its cost-effectiveness.

The aim of this study is to estimate the prevalence of low BMD in a series of adult patients newly diagnosed with CD and to identify the nutritional and/or metabolic factors associated with osteoporosis and osteopenia.

Patients and methods

Study design and participants

For this cross-sectional study, the authors prospectively recruited patients over 18 years of age who had been newly diagnosed with CD and attended in the Department of Gastroenterology at the Hospital General de Tomelloso (Spain), with a coverage reference population of roughly 67,360 inhabitants (based on data from the year 2009).

Adult-onset CD was defined based on the following five basic diagnostic criteria: i) presence of a concordant gluten enteropathy in duodenal biopsies ranging from stage I (increased density of intraepithelial lymphocytes >25%) to stage III (villous atrophy), classified in accordance with the system proposed by Michael Marsh in 1992 [21]. A minimum of six samples were taken from the second and/or third duodenal portions with the aid of endoscopic jumbo forceps. The samples were then analyzed by board-certified pathologists from Hospital General de Tomelloso. Duodenal biopsies were repeated in all patients exhibiting a Marsh I stage 6 months after setting up a strict GFD in order to confirm the resolution of lymphocytic infiltrate. When necessary, CD3 immunostaining was carried out to better assess Marsh I and II stages; ii) existence of compatible clinical symptoms, including digestive and extragastrointestinal symptoms; iii) positive immunoglobulin (IgA) anti-tissue transglutaminase antibody (tTGA) titers. The positivity threshold was established at 2 U/ml. In cases of IgA deficiency, IgG tTGA was determined; iv) presence of an HLA-DQA1*05-DQB1*02 (DQ2) or HLA-DQA1*03-DQB1*0302 (DQ8) haplotype, which confers risk for CD. Gene analyses were made with the polymerase chain reaction (PCR)-based typing techniques from ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood and v) clinical, histopathological and biochemical recovery after the initiation of a GFD. Those patients who only exhibited improvement of symptoms after GFD without evidence of histological and analytical recovery were given the diagnosis of gluten sensitivity and were not included in this study.

Since no single test can detect the early stages of celiac disease without atrophy, a combination of clinical history, positive serology, HLA-DQ compatibility and gluten dependence of symptoms and histological lesions was used to make the CD diagnosis.

Exclusion criteria included pregnancy, a previous diagnosis or a diagnosis established during the study

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of a known cause for low BMD (e.g. drugs and toxins, hematological causes and hormonal and metabolic disorders).

Analytical study

After the diagnosis of CD and before setting up a GFD, blood and urine samples were obtained to analyze several nutritional, hormonal and metabolic parameters.

Basic studies. Complete blood count, hemostasis and blood biochemistry including glucose, creatinine, calcium, phosphorus, sodium, potassium, aspartate aminotransferase (AST), alanine aminotranferease (ALT), gamma-glutamyltranspeptidase (γ-GT), total alkaline phophatase, cholesterol, triglycerides, immunoglobulin serum levels, C-reactive protein.

Markers of malabsorption. Albumin, prealbumin, vitamins A, B12 and D3, folic acid, magnesium, copper, iron, ferritin, transferrin and the transferrin saturation index.

Hormonal study to exclude secondary low BMD. Thyrotropin-stimulating hormone (TSH), dehydroepiandrosterone sulfate (S-DHEA), parathormone (PTH), prolactin and insulin-like growth factor-1 (IGF-1) were determined in all patients. Furthermore, when there was a morphotype or additional data concordant with Cushing syndrome, a determination of blood cortisol levels after administration of 1 mg of dexamethasone (Nugent's test) was used as a screening method. Although no erectile dysfunction or hypoandrogenization was observed in the men included in the study, the authors also analyzed luteinizing hormone (LH), follicle-stimulating hormone (FSH) and total free testosterone in male subjects and progesterone and stradiol in female subjects in order to exclude hypogonadism as a cause for low BMD.

Bone metabolism. Serum bone alkaline phosphatase was tested as a marker of bone formation, N-urinary terminal telopeptide of collagen type I (NTx) as a resorption marker and 24-h urinary calcium excretion as a marker of calcium intake.

Bone mineral densitometry

Before beginning the GFD, bone density scans with dual-energy X-ray absorptiometry (DEXA) were carried out on the left hip and lumbar spine (L2–L4) with the aid of a Norland XR-46 Quick Scan equipped with pencil beam technology (Norland Medical systems Inc., White Plains, NY, USA). The results were reported in two terms: measured areal density in g/cm^2 and T-score (the number of standard deviations (SD) above or below the mean for healthy young adults of the same sex and ethnicity as the patient). T-score calculations were derived from values for a standardized reference population provided by the DEXA manufacturer.

The WHO cut-off point was used to define osteoporosis (T-score less than or equal to –2.5 SD), osteopenia (T-score greater than –2.5 SD and less than –1 SD) and normal bone density (T-score greater than or equal to –1 SD) [22].

Fracture risk estimated with the aid of FRAX®

The authors used the WHO fracture risk assessment tool FRAX, which separately estimates the probability of 10–year risk for hip fractures and major osteoporotic bone fractures, including clinical lumbar spine, femur neck, forearm (ulna/radius) and shoulder fractures [22]. The clinical risk factors included in the FRAX model are information on race, age, sex, weight, height, femoral neck BMD, a history of previous fracture, parental history of hip fracture, current smoking, use of oral glucocorticoids for more than 3 months, rheumatoid arthritis, other secondary causes of osteoporosis and alcohol intake of three or more units per day [23]. The FRAX tool allowed us to classify patients into different fracture risk levels according to thresholds for absolute fracture risk published by the National Osteoporosis Guidelines Group (NOGG) [24]. The average risk in the 50- to 54-year-old age group according to FRAX varies between 0.5% and 1.2% for hip fracture and between 5.7% and 9% for major fractures.

Fracture-risk was assessed by using the online calculation tool in the FRAX official web page (www.shef.ac.uk/FRAX), including bone density scan data in g/cm^2, in order to minimize the age effect of the T-score in younger patients who had not yet reached their bone mass peak. Two researchers made the estimation separately in order to guarantee results; discordances were solved by agreement.

Statistical analysis

Categorical variables were expressed as counts and percentages, whereas continuous variables were expressed as means with SD or as medians with interquartile range after checking normal distribution by Shapiro–Wilk test. The independent Mann–Whitney and Kruskal–Wallis tests were used for continuous variables while the χ^2 test was used for categorical variables in comparisons. Correlation between Marsh stage and tTGA titers was estimated by Spearman's correlation (Rho) test.

A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using

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Table I. Demographic data of the series of patients diagnosed with adult-onset CD.

Patient characteristics	
Female/Male (%)	36/4 (90/10)
Mean age (range) (years)	44.25 (18–67)
Mean diagnostic delay ± SD (months)	127.53 (155.11)
Family history (%)	6 (15%)
Associated autoimmune diseases (%)	14 (35%)
Positive tTGA (%)	13 (32.5%)
Primary symptoms (%)	
Diarrhea	6 (15%)
Anemia	12 (30%)
Abdominal pain	4 (10%)
Dyspepsia	15 (37.5%)
Weight loss	5 (12.5%)
Dysphagia	3 (7.5%)
Hypertransaminasemia	8 (20%)
Hypocalcemia	1 (2.5%)
Dermatitis	1 (2.5%
Family screening in type 1 DM	3 (7.5)
Duodenal lesion stage	
Marsh I	23 (57.5%)
Marsh II	4 (10%)
Marsh III (a, b, c)	13 (32.5%)
HLA haplotype	
DQ2	35 (87.5%)
DQ8	5 (12.5%)
BMD	
Normal at all levels	22 (55%)
Osteopenia at either demarcation	12 (30%)
Osteoporosis at either demarcation	6 (15%)

Abbreviations: BMD = bone mineral density; CD = celiac disease; DM = diabetes mellitus; SD = standard deviation; tTGA = transglutaminase antibody.

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the SPSS software for Windows, version 15.1 (SPSS Inc., Chicago, IL, USA).

Ethics

All patients provided informed written consent. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Complejo Hospitalario Mancha Centro.

Results

Participants, demographics and symptoms

Between January 2008 and March 2011, 40 adult patients were consecutively diagnosed with CD (36 females/4 males). All of them gave their informed consent to participate in the current study. The mean age was 44.25 years (range: 18–67) while the mean BMI was 25.3 ± 5.2 kg/m^2 (range: 15.2–38.5). Table I shows the demographic and clinical characteristics of the participants.

No patients presented clinical or analytical alterations suspicious of kidney or liver disease. Five patients (12.5%) suffered from diabetes mellitus (DM, type 1 in one patient and type 2 in the remaining four). Five out of the 40 patients (12.5%) had a previous diagnosis of autoimmune thyroiditis and were on treatment with thyroxine to maintain normal hormone levels. Normal parameters of thyroid function had been present for at least the last 4 years before the onset of CD. No patients received supplementation with vitamins, calcium or iron, nor were any subjects taking medication with the ability to act on bone metabolism, except for proton pump inhibitors in 12 out of the 40 cases (30%), mainly because of dyspeptic or gastroesophageal reflux-related symptoms. One patient received intermittent treatment with inhaled corticosteroids because of bronchial asthma, but had never been treated with systemic steroids.

Personal histories of intestinal resections or previously detected small bowel diseases conditioning malabsorption were absent. No patients showed previously detected osteoporosis or bone fractures.

Only six patients (15%) presented diarrhea at the moment of diagnosis, with the most frequent symptoms being dyspepsia (37.5%), anemia (30%), hypertransaminasemia (20%) and weight loss (12.5%) (Table I).

Histopathological Marsh stages in duodenal biopsies

Twenty-three patients (57.5%) presented with a lymphocytic duodenitis or Marsh I stage, 4 patients (10%) presented with a Marsh II stage and the remaining 13 patients (32.5%) had the villous atrophy typical of a Marsh III stage. Of this last group, Marsh IIIa was identified in six patients, IIIb in four and IIIc in the remaining 3 patients. A positive and significant correlation between Marsh stage and tTGA titers was observed (Spearman's Rho 0.69; $p < 0.001$) in parallel with previously reported information indicating that tTGAs show higher sensitivity and specificity for CD diagnosis in patients with villous atrophy [12,25,26].

Analytical parameters

At the moment of diagnosis, most of the nutritional serum levels analyzed were normal except for 25-hydroxy (OH) vitamin D serum levels, which were below normal in 87.5% of the series. Important differences were noted after separately analyzing patients without duodenal villous atrophy (Marsh I and II) and those with villous atrophy (Mash III): BMI and serum levels of prealbumin, iron, 1,25-OH vitamin D and folic acid all resulted significantly lower in Marsh III patients (analytical data are shown

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Table II. Nutritional parameters in adult celiac patients at the moment of diagnosis, related with Marsh stages for duodenal mucosal damage.

	Global (n = 40)	Marsh I & II (n = 27)	Marsh III (n = 13)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-Value
BMI (kg/m^2)	25.3 ± 5.2	26.4 ± 5.5	22.9 ± 3.8	0.027
Hemoglobin (g/dl)	13.2 ± 1.5	13.3 ± 1.5	13.0 ± 1.5	0.58
Calcium (mg/dl)	8.8 ± 0.5	8.7 ± 0.6	8.9 ± 0.4	0.36
Phosphorus (mg/dl)	3.4 ± 0.4	3.4 ± 0.4	3.4 ± 0.5	0.60
Magnesium (mg/dl)	2.1 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	0.45
Albumin (g/dl)	4.4 ± 0.6	4.5 ± 0.5	4.2 ± 0.8	0.19
Prealbumin (mg/dl)	24.4 ± 5.6	26.1 ± 5.4	20.7 ± 4.4	0.002
Copper (μg/dl)	114.6 ± 22.7	116.9 ± 20.0	109.8 ± 27.5	0.32
Iron (μg/dl)	73.3 ± 30.0	80.1 ± 29.5	59.3 ± 26.8	0.055
Ferritin (ng/ml)	55.5 ± 71.8	64.2 ± 82.1	37.3 ± 40.4	0.067
Triglycerides (mg/dl)	137.1 ± 209.9	166.7 ± 250.4	75.7 ± 35.8	0.01
Cholesterol (mg/dl)	188.5 ± 41.6	203.1 ± 41.0	158.2 ± 22.6	<0.001
Transferrin (mg/dl)	290.5 ± 51.9	293.9 ± 52.5	283.3 ± 52.0	0.40
1,25-OH vitamin D (pg/ml)	37.7 ± 18.4	32.0 ± 14.8	50.1 ± 19.8	0.006
25-OH vitamin D (ng/ml)	16.8 ± 8.2	16.8 ± 8.1	16.8 ± 8.7	0.80
Vitamin A (μg/dl)	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.56
Vitamin B12 (pg/ml)	490.0 ± 240.2	513.3 ± 237.7	437.5 ± 248.1	0.27
Folic acid (ng/ml)	9.6 ± 4.5	10.6 ± 4.0	7.3 ± 5.0	0.018

Abbreviations: BMI = body mass index; SD = standard deviation.

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in Table II). Regarding blood hormone levels, no differences were found among patients from different Marsh stages (Table III). C-reactive protein (as a marker of inflammation) and international normalized ratio (INR, as a marker of vitamin K deficiency) were similar for all patients, regardless of Marsh stage and BMD.

Bone mineral densitometry

At the moment of CD diagnosis, hip density scans estimated a mean ± SD T-score of 0.93 ± 1.67, with a femoral neck bone mass of 0.86 ± 0.15 g/cm^2. The T-score in the lumbar spine was –0.23 ± 1.99 with an L2–L4 overall bone mass of 1.01 ± 0.22 g/cm^2. Three patients were under the age of 21, which could result in lower T-scores as they had not yet reached their bone mass peak.

Nevertheless, BMD at the moment of CD diagnosis was not associated with patient age.

A low hip BMD (defined as T-scores less than –1 SD) was observed in 20% of patients (2.5% osteoporosis and 17.5% osteopenia). In the lumbar spine, the prevalence of low BMD reached 42.5% (12.5% osteoporosis and 30% osteopenia). Overall, 45% of celiac patients exhibited low BMD at either or both demarcations at the moment of diagnosis.

Risk of bone fractures in adult celiac patients

In our adult patients newly diagnosed with CD, the overall risk for hip fracture was 0.3 ± 0.5%, but significant differences were observed after stratifying patients according to Marsh stage: In Marsh I and II patients (non-villous atrophy), the risk was low (0.3 ± 0.2%), ascending to mild (0.7 ± 0.8%) in patients with the villous atrophy characteristic of Marsh III (p = 0.011) (Table IV). This represents a risk 3.5 times greater than that of the first group.

Table III. Hormonal parameters in adult celiac patients at the moment of diagnosis related with Marsh stages for duodenal mucosal damage.

	Global (n = 40)	Marsh I & II (n = 27)	Marsh III (n = 13)	
	Mean ± SD	Media ± SD	Mean ± SD	p-Value
TSH (μg/ml)	2.9 ± 1.5	2.8 ± 1.3	3.1 ± 2.0	0.15
T4 (ng/dl)	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	0.50
S-DHEA (μg/dl)	136.6 ± 61.5	133.8 ± 57.8	141.4 ± 69.8	0.60
PTH (pg/ml)	49.0 ± 20.6	52.3 ± 23.1	43.4 ± 14.8	0.48
IGF-1 (ng/ml)	153.6 ± 75.4	156.5 ± 79.7	149.3 ± 71.5	0.96

Abbreviations: TSH = thyrotropin-stimulating hormone; T4 = thyroxine; S-DHEA = dehydroepiandrosterone sulfate; PTH = parathyroid hormone; IGF-1 = insulin-like growth factor 1; SD = standard deviation.

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Table IV. Bone densitometry parameters and bone remodeling serum markers in adult celiac patients at the moment of diagnosis related with Marsh stage for duodenal mucosal damage.

	Global (n = 40)	Marsh I & II (n = 27)	Marsh III (n = 13)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-Value
Hip T-score	0.2 ± 1.7	0.6 ±1.4	-0.6 ± 1.9	0.06
Lumbar axis T-score	-0.2 ± 1.9	0.2 ± 1.7	-1.3 ± 1.9	0.012
L2–L4 BMD (g/cm^2)	1.0 ± 0.2	1.1 ± 0.2	0.9 ± 0.2	0.007
Hip fracture risk (%)	0.3 ± 0.5	0.2 ± 0.3	0.7 ± 0.8	0.011
Major fracture risk* (%)	2.3 ± 1.4	2.0 ± 0.9	3.1 ± 2.0	0.015
Femoral neck BMD (g/cm^2)	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.078
Bone alkaline phosphatase (ng/ml)	12.9 ± 5.1	11.8 ± 4.6	15.2 ± 5.5	0.055
NTx urinary levels (nmol bone collagen equivalents/mmol creatinine)	47.4 ± 45.6	43.1 ± 51.3	56.6 ± 29.2	0.046
Urinary calcium excretion (mg/24 h)	153.8 ± 119.6	175.9 ± 129.6	104.3 ± 76.3	0.08

Abbreviations: L2–L4 = lumbar vertebrae 2 to 4; BMD = bone mineral density; NTx = N-urinary terminal telopeptide of collagen type I; SD = standard deviation.
*Estimated with the combined WHO fracture risk assessment tool FRAX® for lumbar spine, femur neck, forearm and shoulder osteoporotic fractures.

Regarding the overall risk of major fracture, it was low (2.3 ± 1.4%), but significantly higher in Marsh III (3.1 ± 2.0%) than in Marsh I and II patients (2.0 ± 0.9%) (p = 0.014) (Table IV).

Relationships between duodenal mucosal lesion, BMD and metabolic parameters

The degree of bone mass loss in the lumbar spine directly correlated to Marsh stage in duodenal biopsies (p = 0.033); thus, the T-score for Marsh I patients was 0.38 ± 1.84, for Marsh II it was –0.65 ± 0.50, and for Marsh III it was –1.30 ± 1.89. A parallel association between BMD and Marsh stage was also observed in hip T-scores, but it did not reach statistical significance (p = 0.18) (Figure 1).

Overall, only 18.8% of patients exhibiting a non-atrophic villous mucosa (Marsh stages I and II) presented some degree of low BMD at either demarcation, compared with 70% of patients with atrophic mucosal Marsh stages (IIIa, b and c) (p = 0.009).

Moreover, Marsh III patients also presented a lower BMI (p = 0.022) and lower serum levels of prealbumin (p = 0.03), cholesterol (p < 0.001), triglycerides (p = 0.006), iron (p = 0.013) and folic acid (p = 0.025), all of which are indicative of malnutrition/malabsorption. Additionally, significantly lower NTx urinary levels (p = 0.026) were observed in Marsh I and II stages compared with Marsh III stage (Tables II and III).

Comparing the patients with osteoporosis, osteopenia or normal BMD at any level, significant differences were observed regarding several analytical parameters; thus, hemoglobin, cholesterol, prealbumin, folic acid and iron serum levels were significantly lower in patients with lower BMD (Table V).

Discussion

This single-center prospective study analyzes the prevalence of low BMD and its related nutritional, metabolic and histopathological risk factors in a cohort of adult patients newly diagnosed with CD. The authors found that the stage of duodenal mucosal injury (following Marsh's classification) was the most important factor in determining low BMD. The prevalence of low BMD in newly diagnosed adult CD patients (45%) parallels that previously reported in other studies [20,27–33].

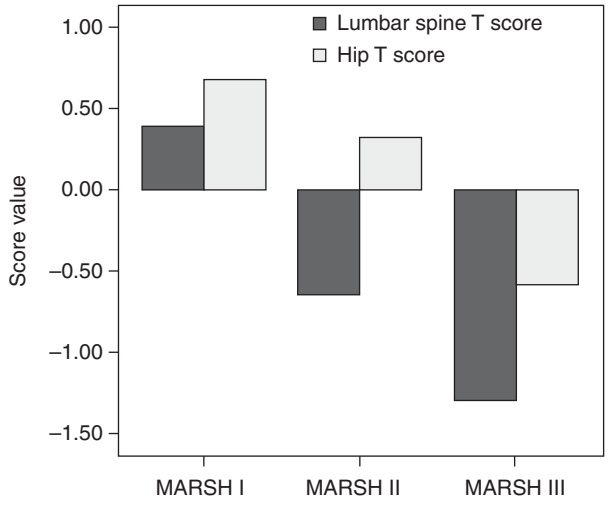

Figure 1. Graphic representation of average bone mineral density (BMD) related with Marsh stage in a cohort of adult patients newly diagnosed with celiac disease. BMI is expressed as T-score and determined by dual-energy X-ray absorptiometry of the hip and lumbar spine. Marsh stage of duodenal damage directly associated with impaired BMD, which reached statistical significance at the level of the lumbar spine.

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Table V. Nutritional parameters in adult celiac patients at the moment of diagnosis, related with BMD.

	Normal (n = 22)	Osteopenia (n = 12)	Osteoporosis (n = 6)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-Value
Age (years)	38.6 ± 11.2	46.7 ± 10.9	45.0 ± 21.1	0.31
Females, n(%)	21 (95.5%)	9 (81.8%)	6 (100%)	0.29
BMI (kg/m^2)	25.4 ± 5.6	26.1 ± 5.1	23.5 ± 4.6	0.6
Hemoglobin (g/dl)	13.1 ± 1.5	13.8 ± 1.1	12.1 ± 1.5	0.07
Calcium (mg/dl)	8.6 ± 0.6	9.0 ± 0.4	9.0 ± 0.5	0.14
Phosphorus (mg/dl)	3.5 ± 0.4	3.2 ± 0.3	3.3 ± 0.6	0.12
Magnesium (mg/dl)	2.1 ± 0.2	2.1 ± 0.1	1.9 ± 0.3	0.24
Albumin (g/dl)	4.5 ± 0.5	4.5 ± 0.4	4.0 ± 1.1	0.63
Prealbumin (mg/dl)	25.4 ± 6.0	25.2 ± 4.2	19.5 ± 4.6	0.04
Copper (μg/dl)	118.4 ± 20.7	105.2 ± 23.6	118.0 ± 28.5	0.27
Iron (μg/dl)	73.6 ± 29.4	83.7 ± 28.4	47.2 ± 21.3	0.05
Ferritin (ng/ml)	59.7 ± 88.5	56.7 ± 42.3	21.5 ± 20.7	0.11
Triglycerides (mg/dl)	173.0 ± 278.4	100.9 ± 46.4	74.6 ± 20.6	0.40
Cholesterol (mg/dl)	193.4 ± 48.3	192.9 ± 34.0	162.2 ± 18.9	0.13
Transferrin (mg/dl)	290.1 ± 59.1	297.7 ± 47.5	284.0 ± 38.2	0.92
25-OH vitamin D (ng/ml)	16.7 ± 8.0	17.1 ± 6.3	16.8 ± 12.6	0.52
Vitamin A (μg/dl)	0.6 ± 0.2	0.5 ± 0.2	0.4 ± 0.1	0.37
Vitamin B12 (pg/ml)	492.6 ± 251.7	520.7 ± 259.8	423.8 ± 173.9	0.80
Folic acid (ng/ml)	10.7 ± 3.8	8.6 ± 3.9	7.0 ± 7.3	0.05

Abbreviations: BMD = bone mineral density; BMI: body mass index; SD = standard deviation.

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It is interesting to note that in past few years the number of celiac patients diagnosed in adulthood has increased significantly [3,4,9], which could be due either to an increase in the incidence of the disease or to increased clinical awareness and improved diagnostic techniques of a disease with a long, fluctuating and often subclinical course [34,35]. With the advent of genetic analyses for screening patients suspected of having CD with negative serology [36], an increase in the number of patients with atypical symptoms has been observed [37]; in fact, classic malabsorptive symptoms were not predominant in the celiac adult series, which is in agreement with previously published studies [3,4,38]. It was also noted that symptoms were not helpful in estimating either the degree of damage to the small bowel mucosa or the degree of BMD loss. This is also in concordance with previously reported results in which low BMD was described in CD patients presenting classic symptoms [18], subclinical manifestations [39] and even asymptomatic disease [34].

Two different theories have been proposed to explain the etiopathogenesis of low BMD in CD. The first to be presented entails the malabsorption associated with intestinal mucosal damage; in fact, osteomalacia was present from the first descriptions of the disease [40]. The second, more recently proposed theory invokes the chronic inflammation that characterizes CD as the origin of low BMD [41]. It must be noted, however, that C-reactive protein resulted normal, with similar values in different patients regardless of Marsh stage and BMD. It is likely that a combination of both factors contributes to low bone mass in CD. Vitamin D deficiency is common in CD patients and present in 87.5% of our series; however, celiac patients do not present alterations in the expression of vitamin D receptors [42], nor is there an increased number of genetic mutations in the receptor which could interfere with vitamin D metabolism [43]. Lactose intolerance is present in 10% of celiac patients, but increases to 50% in the presence of evident symptoms of secondary malabsorption [10], leading to dietary restrictions. However, it should be remembered that dietary intake of vitamin D only represents 5–10% of the daily requirements [44]; the remaining part comes from solar exposition. No differences were observed in serum levels of calcium, phosphorus, magnesium or 25-OH vitamin D between patients with or without low BMD and villous atrophy. However, several serum markers of nutritional status and BMI were significantly lower in those adult patients with low BMD and exhibiting a Marsh III stage, in parallel to reported results from children [14], which indicates that malnutrition/malabsorption conditioned by villous atrophy is an important factor in determining osteoporosis and osteopenia.

Studies developed in patients with inflammatory bowel disease likewise showed no association between vitamin D serum levels and bone disease [44]. Some less known functions of vitamin D include its role in activating T lymphocytes, which maintain the integrity of intestinal mucosa to prevent infections [45], and the regulation of protein binding to maintain the

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intestinal mucosa barrier [46]. This is why vitamin D deficiency has been proposed as a trigger for autoimmune disorders [47]. Deficiencies in other vitamins and minerals essential for normal bone metabolism have also been implicated in the origin of low BMD in CD [48]. However, the data from our patients showed no differences in these parameters (except for serum calcium and folic acid) between patients with normal or reduced BMD. Regarding hormonal factors, hyperparathyroidism has been proposed as a factor, since increased levels of PTH have been documented in celiac patients, even when vitamin D levels were normal [49]. Decreased IGF-1 serum levels have also been described in CD patients [50] as contributing to low BMD. However, in this study there were no differences with regard to this factor between patients with low or normal BMD.

The result of this study indicates that the presence of villous atrophy in duodenal mucosa constitutes the main risk factor significantly associated with low BMD in adult-onset CD. This is the first time that this association has been clearly established in the literature for adult patients, with several previous authors observing no differences [51]. Still, other studies examining dermatitis herpetiformis, a gluten-sensitive skin disease, described that subtotal villous atrophy was associated with more severe alterations in bone density scans [52] and a significantly lower BMI. This last result was also observed in this study.

The duodenal mucosal injury found in CD is caused by an autoimmune inflammatory response, and its intensity classified according to Marsh stages correlates directly and strongly to the degree of bone mass loss. In this context, studies developed on inflammatory bowel disease increasingly emphasize the role of the inflammatory response in decreasing BMD. Inflammatory activity, acting through the nuclear factor (NF)-kappa beta ligand (RANKL) system, is associated with elevated levels of osteoprotegerin [53,54]. Recent studies also support the hypothesis that the local humoral environment as determined by proinflammatory cytokines is a determinant for bone disease in celiac patients, in whom increased levels of interleukin (IL)-6 and RANKL/osteoprotegerin [55,56] would directly affect osteoclastogenesis and osteoblast activity. In a recent study, osteoprotegerin inactivating antibodies have also been implicated in the physiopathology of low BMD in CD [56]. Further molecular studies are needed to confirm these hypotheses.

The main consequence of osteoporosis is an increased fracture risk, which has been estimated to be 3.5–7 times higher in celiac patients than in the non-affected matched population [7]. Our study found that an increased hip fracture risk was only present in adult celiac patients with duodenal villous atrophy or Marsh III stage, which corresponded to those patients exhibiting analytical data characteristic of malnutrition/malabsorption. A previous paper also found that the increase in fracture events was confined to CD patients who exhibited 'classical malabsorption' [57].

Our findings confirm that, overall, adults diagnosed with CD have a small increased risk of fracture, which is in good agreement with data from other studies [31,58,59]. The risk of osteoporotic fracture (e.g. lumbar spine, femoral neck, ulna or radius) is higher than the overall risk, but is moderate at most.

The high heterogeneity in the ages of our patients could represent a limitation of our study and of others with discordant data [28]. Since some young adult patients had not yet reached their BMD peak at the moment of diagnosis, these patients were able to recover a normal BMD by avoiding the causative risk of malnutrition/malabsorption by following a GFD, which has proven to be a key factor in bone mineral recovery [60–63].

Our transversal and observational study design makes it difficult to establish a causal relationship between small bowel biopsy findings, nutritional status and BMD. New findings related to the follow-up of patients on a GFD may shed light on the relationship between gluten intolerance, digestive mucosal lesions and BMD.

Finally, the efficacy and cost-effectiveness of routine screening for osteoporosis in all adults newly diagnosed with CD has given rise to an important controversy in the literature, with some groups suggesting that it should be performed in all cases, either at the time of diagnosis or after 1 year of treatment with a GFD [64–66], while for other researchers, the modest increase in fracture risk does not justify the costs of such screening [33]. Our results indicate that a reasonable strategy may be to perform a bone density scan in those adult patients who present with small bowel villous atrophy or clinical and analytical data of malnutrition/malabsorption at the moment of diagnosis or when their age exceeds that at which bone mass peak is reached. In any case, a low BMD only explains 70% of bone fragility [67], with the remaining 30% depending on the quality of the bone microarchitecture and other less-known risk factors. The contribution of these factors, along with changes induced in them by a GFD, should be prospectively evaluated in further long-term studies.

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Castilla-La Mancha or FISCAM). AJ Lucendo: study conception and design, performance of endoscopic examinations and duodenal biopsies, data analysis and interpretation, drafting the manuscript, final approval of the manuscript. Á García-Manzanares: study conception and design, patient assistance, recording of data, data analysis and interpretation, drafting the manuscript, final approval of the manuscript. JM Tenias: study design, statistical analysis, data analysis and interpretation, final approval of the manuscript.

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