ORIGINAL PAPERS

Does dermatitis herpetiformis result in bone loss as coeliac disease does? A cross sectional study

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ABSTRACT

Introduction and objectives: coeliac disease (CD) and its cutaneous manifestation, dermatitis herpetiformis are both (DH) gluten-sensitive diseases. Metabolic bone disease is common among patients with CD, even in asymptomatic forms. Data are scarce about bone density in patients with dermatitis herpetiformis. The aim of our study was to compare bone mineral density (BMD) of celiac and dermatitis herpetiformis patients.

Methods: 34 coeliac patients, 53 with dermatitis herpetiformis and 42 healthy controls were studied. The mean age was 38.0 ± 12.1, 32.18 ± 14.95, 35.33 ± 10.41 years in CD, dermatitis herpetiformis, and healthy controls, respectively. Bone mineral density of the lumbar spine, the left femoral neck and radius were measured by dual-energy X-ray absorptiometry. Low bone density, osteopenia and osteoporosis were defined as a body mass density (BMD) T-score between 0 and -1, between -1 and -2.5, and under -2.5, respectively.

Results: at lumbar region, consisting of dominantly trabecular compartment, a decreased BMD was detected in 49 % (n = 26) patients with dermatitis herpetiformis, 62 % (n = 21) of CD patients, and 29 % (n = 12) of healthy controls, respectively. Lower BMD were measured at the lumbar region in dermatitis herpetiformis and CD compared to healthy subjects (0.993 ± 0.136 g/cm^2 and 0.880 ± 0.155 g/cm^2 *vs.* 1.056 ± 0.126 g/cm^2; p < 0.01). Density of bones consisting of dominantly cortical compartment (femoral neck) did not differ in dermatitis herpetiformis and healthy subjects.

Conclusions: our results show that a low bone mass is also frequent among patients with dermatitis herpetiformis. Bone mineral content in these patients is significantly lower in those parts of the skeleton which contain more trabecular than cortical bone.

Key words: Dermatitis herpetiformis. Coeliac disease. Osteoporosis. Bone mineral density.

INTRODUCTION

Dermatitis herpetiformis (DH), or Duhring's disease is a chronic blistering skin condition, characterised by vesicles filled with a watery fluid on the extensor surfaces of the elbows, buttocks and knees (1). The name *herpetiformis* derives from the fact that the vesicles manifest as small dense clusters similar to those seen in herpes simplex. Dermatitis herpetiformis is linked to gluten sensitivity and has a clear relationship to coeliac disease (CD), but enteropathy is usually less severe than that found in patients with CD (2).

The most common age at onset of the DH symptoms is between the 3rd and 4th decades. Interestingly, males have a higher prevalence of DH (1.5-2:1) unlike CD (1:2-4) (3). Both diseases show strong genetic predisposition: the incidence of DH and CD among first-degree relatives is about 15 times higher than in the general population (4), and a close association between DH and human leukocyte antigen-DQ2 or DQ8 (5,6) has been reported, such as in CD (7).

Transglutaminase (TG) plays a central role in gluten intolerance. Tissue TG is the major autoantigen for CD, which is a ubiquitous molecule in many tissues (8,9). In patients with DH, epidermal TG also appears to be the dominant autoantigen. It is homologous to tissue TG within the enzymatically active domains and its main function in the epidermis to save the integrity of the skin. The expression of epidermal TG is primarily seen in the epidermis and small intestine (10,11).

Gluten-free diet (GFD) is the basis of the therapy in both DH and CD. A gluten challenge causes flares of the cutaneous symptoms. Adherence to GFD not only reduces skin symptoms, malabsorption and villous atrophy, but also decrease the risk of small bowel lymphoma.

It is well known that both diseases have associations with other extraintestinal diseases, mainly of autoimmune type. Moreover, CD associates with metabolic bone disease. The frequency of low bone mineral density (BMD) among coeliac patients varies widely between different studies due to differences in diagnostic criteria, geographical distribution and patient selection (12-14). The presence of significant malabsorption leads to a more severe bone loss in CD (15), although BMD is lower in asymptomatic patients compared to healthy subjects, as well (16).

The fracture rate was observed to be high in CD patients compared to controls in a recent meta-analysis including data of more than 20,000 subjects (8.7 *vs.* 6.1 %; pooled odds ratio: 1.43; 95 % confidence interval 1.15-1.78) (17).

There are only a few small studies in the literature considering bone metabolism in DH patients. Moreover, these observations have provided conflicting data regarding BMD in DH, so the need for further studies to determine the fracture risk in DH is clear. This study aims to compare the bone density of DH patients to CD and healthy controls.

METHODS

Fifty-three DH and 34 CD patients were enrolled from the outpatient gastroenterology clinic of the 2nd Department of Medicine, Semmelweis University, and 42 healthy control (HC) subjects from the clinical staff taking into consideration the matching of gender and age. As an inclusion criterion, all patients and controls were adults. All coeliac patients reported themselves as being on a gluten free diet (GFD) since their diagnosis. There were 2 newly diagnosed CD and 2 DH patients. Their diagnosis was confirmed 6 months before and they also were on GFD. 11.8 % of CD patients had mild gastrointestinal symptoms (bloating or loose stool), but there were no diarrhoea present among them. A third of the DH patients (33 %) were not on strict GFD. Similar ratio of DH patients (15.1 %) had abdominal complaints, but none of them had have skin symptoms from the 6 months previous to be recruited for this study. The study protocol was approved by the local Ethic Committee and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki. Following written informed consent patients underwent osteodensitometry, upper panendoscopy and blood tests.

Patients suffering thyroid or primary parathyroid dysfunction or other chronic diseases were excluded from this study. Those patients who were treated with steroids were also excluded. Previously known metabolic diseases affecting the bone metabolism was also considered as an exclusion criterion. Diagnosis of DH was established in all patients by the presence of typical clinical features and by demonstrating granular IgA deposits in the dermal papillae of uninvolved perilesional skin on direct immunofluorescence. Diagnosis of CD was established in all patients by the presence of clinical features, anti-endomysium antibody (EMA) serology and small intestinal histology.

Serum levels of calcium (Ca), phosphorous and albumin were measured in every study subject. EMAs were assessed by indirect immunofluorescence on monkey oesophageal sections by using fluorescein isothiocyanate and antihuman IgA as secondary antibody.

Small bowel biopsies were also performed in the DH group at the moment of diagnosis; specimens were stained with hematoxylin-eosin and investigated via light microscopy. The grading system based on Marsh-Oberhuber classification of small intestinal enteropathy in CD was used to assess the histological abnormalities: stage 0 –normal mucosa; stage 1 –increased intraepithelial lymphocyte count; stage 2 –cryptal hyperplasia and increased intraepithelial lymphocyte count; and stage 3a-3c –mild/moderate/severe villous atrophy with increased intraepithelial lymphocyte (18).

BMD measurements were performed by dual-energy X-ray absorptiometry of the lumbar spine, the left femoral neck and the non-dominant radius using a Hologic QDR 4500C instrument (Hologic©, Waltham, MA). For analysis, software v. 9.03D was used. Z-scores (the number of standard deviations from age- and sex-matched healthy controls) and T-scores (number of standard deviations from peak bone mass, i.e. the maximum BMD value reached by an adult) were calculated according to the manufacturer's reference curves. The third National Health and Nutrition Examination Surveys normative data were used as a reference database for femoral bone density measurements. World Health Organization criteria for low BMD were applied for this analysis (19): osteopenia were defined as a BMD T-score below -1 and -2.5, and osteoporosis were defined as a BMD T-score were under -2,5. Quality control was maintained by daily scanning of an anthropometric spine phantom. The coefficient for the variation of BMD measurements on the spine phantom over a period of 4 years was 0.35 % in our laboratory.

Calculations were performed using SPSS statistics 15.0 software. Paired and independent sample Student's t-tests, Pearson correlations were applied. The results were presented as mean ± standard deviation. Results were considered significant when p < 0.05.

RESULTS

Thirty-four coeliac patients and 53 with DH were enrolled from the outpatient clinic of our department. Their data were compared to 42 healthy controls in this cross sectional study. The mean age was 38.0 ± 12.1 in CD, 32.18 ± 14.95 in DH patients, and 35.33 ± 10.41 in healthy controls (p = NS). 8.8 % of CD, 7.4 % of DH patients and 7.1 % of HC were postmenopausal women (p = NS). Main demographical and clinical parameters of all groups are shown in table I.

Table I. Main demographical and clinical parameters of patients with coeliac disease (CD), dermatitis herpetiformis (DH) and healthy control (HC), expressed as mean ± standard deviations

	HC (n = 42)	Differences HC vs. DH	DH (n = 53)	Differences DH vs. CD	CD (n = 34)	Differences HC vs. CD
Age (years)	35.33 ± 10.41	NS	32.18 ± 14.95	NS	38.0 ± 12.1	NS
Body mass index (kg/m²)	24.25 ± 4.08	NS	23.25 ± 5.07	p < 0.01	20.82 ± 2.78	p < 0.01
Postmenopausal (%)	7.1	NS	7.4	NS	8.8	NS
Duration of disease (years)	-		10.96 ± 6.53	NS	10.58 ± 8.69	
Serum calcium levels (mg/dl)	9.48 ± 0.52	NS	9.64 ± 0.36	p < 0.01	9.34 ± 0.44	NS
Albumin (g/dl)	-		4.58 ± 0.33	p < 0.05	4.46 ± 0.52	

NS: Non significant differences.

A lower BMD was documented at lumbar spine in both groups of patients (DH and CD) compared to HC. Lumbar BMD was significantly lower in CD compared to DH patients. Femoral and radius BMD did not differ in DH compared to HC subjects. However a lower BMD was observed at both sites in CD patients compared to HC subjects. Data of the two groups of patients and HC were compared. Statistically significant differences were obtained from all three measurement sites between CD and HC. Main results are presented in figures 1-3.

A low BMD was observed at the lumbar spine (n = 26, 49 %) and the radius (n = 31, 58 %) of DH patients; in contrast, a decreased mineral density at the femoral neck was found in a lower proportion of DH patients (n = 11, 21 %). 62 % (n = 21) and 71 % (n = 24) of celiac patients also had a low BMD at the lumbar spine and non-dominant radius, respectively. The proportion of low bone mass at the femoral neck was higher (n = 17, 50 %) among CD patients. The minority of subjects in HC group exhibited a low bone mass (n = 2, 5 %), independently from the site of the measurement. Data and significance values are detailed in table II.

Regarding to the T-score at lumbar axis, it value was -0.855 ± 1.227 g/cm² in patients with DH, and -1.848 ± 1.398 g/cm² in those with CD (p < 0.001). At left femoral neck,
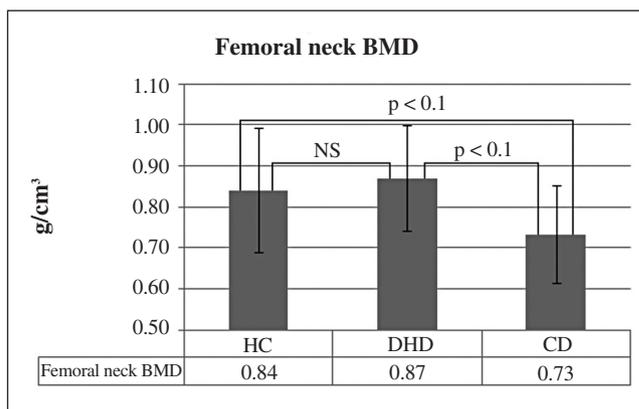

Fig. 2. Bone mineral density of patients with coeliac disease (CD), dermatitis herpetiformis (DHD) and healthy controls (HC) at the femoral neck, represented as mean and standard deviations (NS: non-significant differences).

T-scores were 0.182 ± 1.183 g/cm² in DH patients, and -1.165 ± 1.295 g/cm² in CD patients, respectively (p < 0.001). There were no significant differences between the T-score values obtained from above the distal third of the radius between this two groups of patients (-1.342 ± 1.378 g/cm² and -1.551 ± 1.329, p = NS; respectively).
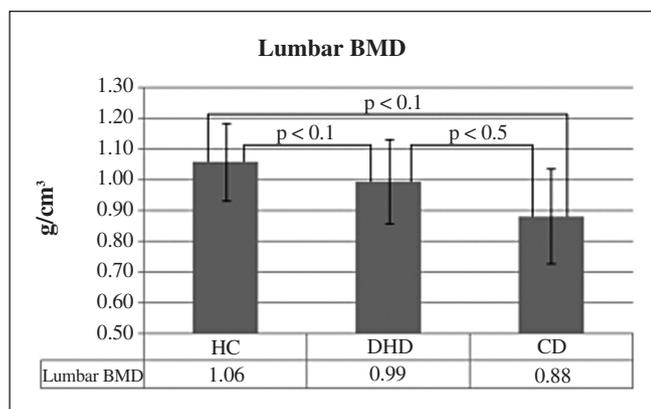

Fig. 1. Bone mineral density of patients with coeliac disease (CD), dermatitis herpetiformis (DHD) and healthy controls (HC) at lumbar spine, represented as mean and standard deviations.
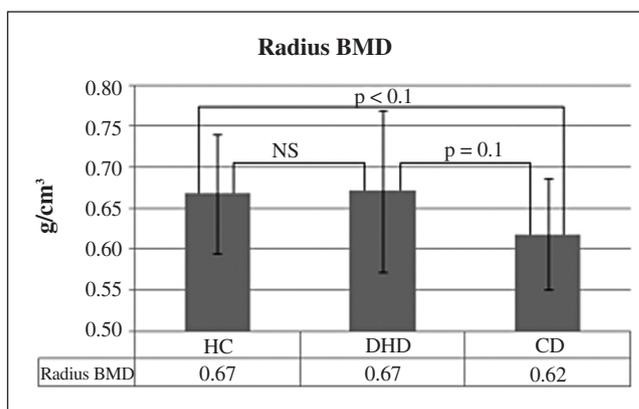

Fig. 3. Bone mineral density of patients with coeliac disease (CD), dermatitis herpetiformis (DHD) and healthy control (HC) at the radius (p: significance; NS: non-significant differences).

Table II. Osteodensitometric parameters of the subjects with coeliac disease (CD), dermatitis herpetiformis (DH) and healthy control (HC), expressed as mean ± standard deviation

	Bone mineral density (g/cm^2)	T-score	Z-score
Lumbar region			
CD	0.880 ± 0.155	-1.848 ± 1.398	-1.490 ± 1.263
	p < 0.01	p < 0.01	p < 0.01
DH	0.993 ± 0.136	-0.855 ± 1.227	-0.509 ± 1.216
	p < 0.05	p < 0.05	NS
HC	1.056 ± 0.126	-0.269 ± 1.151	-0.060 ± 1.173
Left femoral neck			
CD	0.733 ± 0.151	-1.165 ± 1.295	-0.784 ± 1.131
	p < 0.01	p < 0.01	p < 0.01
DH	0.870 ± 0.128	-0.182 ± 1.183	0.224 ± 0.890
	NS	NS	NS
HC	0.841 ± 0.119	-0.211 ± 1.053	0.009 ± 0.984
Non-dominant radius			
CD	0.618 ± 0.068	-1.551 ± 1.329	-1.226 ± 1.358
	p = 0.01	NS	NS
DH	0.670 ± 0.098	-1.342 ± 1.378	-0.751 ± 1.114
	NS	p < 0.01	NS
HC	0.667 ± 0.072	-0.822 ± 1.106	-0.478 ± 1.122

NS: Non significant differences.

A higher ratio of patients had severe villous atrophy within the CD group compared to DH patients, according to Marsh-Oberhuber grading system (in CD group 3 % of patients presented stage 0, 9 % stage 1-2, 26 % stage 3a, 15 % stage 3b, and 47 % stage 3c; in DH group, 8 % of patients exhibited a stage 0, 24 % had stage 1-2, 38 % stage 3a, 13 % stage 3b, and stage 3c was present in 17 % of patients).

Table III. Distribution of bone mineral density of patients with coeliac disease (CD), dermatitis herpetiformis (DH) and healthy controls (HC) enrolled in our study

	Skeletal region	Osteoporosis n (%)	Osteopenia n (%)	Normal bone density n (%)
CD	L2-4	11 (32)	10 (30)	13 (38)
	FN	9 (26)	8 (24)	17 (50)
	R	9 (26)	15 (44)	10 (30)
DH	L2-4	4 (8)	22 (41)	27 (51)
	FN	2 (4)	9 (17)	42 (79)
	R	7 (13)	24 (45)	22 (42)
HC	L2-4	2 (5)	10 (24)	30 (71)
	FN	2 (5)	10 (24)	30 (71)
	R	0 (0)	11 (26)	31 (74)

L2-4: lumbar axis 2-4; FN: left femoral neck; R: non-dominant radius.

There was a tendency, but no significant difference, to present a higher BMD in DH patients with normal villous structure (Marsh-Oberhuber grade 0-2) compared to patients with villous atrophy (grade 3a-c), being at lumbar axis 0.985 ± 0,092 *vs.* 0.997 ± 0,145 g/cm^2 (p = NS), at femoral neck 0.912 ± 0,034 *vs.* 0.890 ± 0,123 g/cm^2 (p = NS); and at radius 0.757 ± 0,062 *vs.* 0.686 ± 0,079 g/cm^2 (p = NS).

Sixty-two percent of DH patients presented EMA positive. BMD did not differ in EMA positive compared to EMA negative DH patients (lumbar axis: 0.795 ± 0.344 *vs.* 0.885 ± 0.320 g/cm^2 [p = NS]; femoral neck: 0.553 ± 0.395 *vs.* 0.698 ± 0.229 g/cm^2 [p = NS]; and radius: 0.551 ± 0.272 *vs.* 0.608 ± 0.204 g/cm^2 [p = NS], respectively).

Correlations between BMD, EMA status and Marsh stage for enteropathy were not observed.

Serum calcium levels (Ca) were corrected with serum albumin in every group of subjects. Corrected Ca values were not significantly different between the DH and CD groups (10.33 ± 0.48 *vs.* 9.89 ± 0.71 mg/dl; p = NS). There was a higher albumin serum concentration in DH compared to CD patients (4.58 ± 0.33 *vs.* 4.46 ± 0.52 g/dl, respectively; p < 0.05), however serum calcium levels differed significantly (Table I). A higher phosphorous serum concentration was also observed in DH compared to CD patients (1.16 ± 0.16 *vs.* 1.14 ± 0.12 mg/dl; p < 0.01). Patients with CD presented a lower body mass index (BMI) than that with DH and HC (p < 0.01). Further parameters regarding the possible malabsorption status of patients are presented in table I.

Thirty three percent of DH patients were not on a GFD. BMD parameters of non-adherent DH patients did not differ from those who followed a GFD (lumbar: 0.995 ± 0.152 vs. 1.025 ± 0.111 g/cm^2; p = NS; femoral neck: 0.833 ± 0.186 vs. 0.888 ± 0.155 g/cm^2; p = NS; and radius: 0.679 ± 0.146 vs. 0.670 ± 0.088 g/cm^2; p = NS). Mean parathyroid hormone serum concentrations were within normal ranges in all groups of subjects.

DISCUSSION

CD and one of its predominantly cutaneous manifestations, DH are both gluten-sensitive disorders. CD manifests with intestinal and extraintestinal symptoms with a same frequency (20,21). Both conditions are mediated by IgA-class autoantibodies, and an underlying genetic predisposition and environmental factors also play an important pathophysiological role.

The vast majority of DH patients do not have any abdominal complaint, even when more than 75-90 % of all cases present histological changes in their small bowel mucosa similar to those in CD patients: partial or total villous atrophy and lymphocytic infiltration of the bowel's mucous membrane (2,22).

Although osteopenia as a common complication of CD is well recognized, only a few data on BMD in DH were available; up to the present day, the association between DH and low BMD had been investigated only in three published studies (23-25).

Abuzakouk et al. (23) investigated the bone metabolism of 25 DH patients. The mean duration of the disease was 9 years. Neither BMD nor bone biomarkers were significantly different in patient and controls. One year long GFD prospectively controlled did not influence the BMD in a subgroup of patients. Di Stefano et al. (24) included 16 newly diagnosed DH and sufficient number of CD patients and healthy controls in their study. BMD was found to be lower in DH compared to HC, but it was higher than in CD patients. BMD correlated with BMI and nutritional status, but neither with age at diagnosis nor with age at onset of symptoms. BMD was significantly higher in DH patients exhibiting partial in contrast to those with subtotal villous atrophy. Lewis et al. identified 846 DH patients from the General Practice Research Database to evaluate the risk of bone fracture, malignancy and mortality among these patients: an increased risk of fracture at hip, forearm or any other bones were not found (25).

We have documented a higher frequency of low bone mass in patients with DH compared to healthy subjects; however it was observed to be lower than in CD. There is no definitive data in the literature regarding the origin of low BMD in DH. In contrast, the origin of a lowered bone mass in CD has been show to be multifactorial, being the most plausible explanations related to enteropathy and a concomitant malabsorption. In fact, the frequency of symptomatic enteropathy was reported to be lower in DH compared to CD patients (2).

Bone loss of patients suffering gluten sensitive diseases may depend of the grade of the enteropathy; we observed an association between the grade of villous atrophy and the BMD in DH patients, but not reaching statistical significance. Villous atrophy correlated to the degree of bone loss in this Hungarian cohort and also in a recently published Spanish research: Garcia-Manzanares et al. (26) documented that the degree of bone loss in the lumbar spine correlated to Marsh stage, moreover, significant differences in major fracture risk were observed depending on Marsh stage. However, in a recent study by Abuzakouk et al. (23) this association between BMD and the severity of enteropathy graded by the Marsh classification was not observed. Rodrigo-Sáez et al. have described that a severe villous atrophy was more frequent in coeliac patients with a younger age at diagnosis (27). In contrast, an opposite relationship was documented in a Hungarian cohort, in which the severity of histology at diagnosis was higher in adults than in children (Mars-Oberhuber 3 was presented in 92 % of adults and 57 % of children) (28). Based on these observations, one should remind that demographical and geographical characteristics of the studied populations should be considered while judging the relationship of enteropathy and its consequences.

Taking into consideration the previously mentioned conflicting results (23,24) additional multicentre studies enrolling many patients would be needed to clearly determine how relevant the grade of enteropathy is when assessing BMD in patients with DH.

In our study BMD in DH patients who were not on a GFD did not differ from those who were on it. Confusing results on the relationship between GFD and metabolism have been provided: most of studies demonstrated a lower prevalence of low BMD in coeliac patients who are on GDF (16,29), as well as GFD exert a beneficial effect on bone metabolism of coeliac patients (30-32). A similar prevalence of low BMD have been documented after one (33) and three years (34) on GFD, which shows that the main recovery in bone mass is reached in the first year of following the diet. Lewis et al. (35) observed that years of exposure to gluten before diagnosis of CD do not appear to influence BMD significantly. The relationship between GFD and bone restoration seems to be more pronounced in paediatric population (36,37): one year long GFD did not improve BMD in adult population according to the previously mentioned Irish study (23).

Calcium malabsorption has been suspected to be the most plausible cause of low BMD in CD (38). In our study corrected Ca serum levels were not significantly different between DH and the CD patients, but serum calcium levels differed significantly. There was a higher albumin serum concentration in DH patients compared to the CD group. Additionally, BMI was similar in HC and DH patients, while it was lower in the studied coeliac population.

Secondary hyperparathyroidism (39) and concomitant lactase deficiency (40) may also worsen Ca balance in CD. In fact, reduction of cortical bone mass is very common

in hyperparathyroidism, which should be tested in all patients with CD. Parathyroid hormone concentrations were within the normal range in our patients and bone loss was prominent in those bones containing mainly trabecular component.

An increased receptor-associated nuclear factor kappa ligand/osteoprotegerin ratio has been also detected in newly diagnosed patients with CD (41); this dissociation causing uncoupled bone remodelling have been also proved by the elevation of markers of increased bone turnover in CD (42,43). Local factors may affect the bone remodelling in CD as well. Several pro-inflammatory cytokines (interleukin (IL)-1, IL-6, and tumour necrosis factor alpha) are produced in the intestinal mucosa in CD and result in an increased osteoclast activity (44). Low levels of other cytokines, such as IL-12 and IL-18, result in osteoclastogenesis due to the lack of the inhibitory effects of these cytokines (45). Some data show increase serum pro-inflammatory cytokine concentrations (IL-8, tumour necrosis factor alpha) in DH patient (46). Milder degrees of bone loss in DH compared to CD were observed in our study. We are not able to explain this phenomenon based on our results. A more patchy distribution of villous atrophy or a marker cytokine alteration in CD compared to DH may be hypothesized in order to explain this phenomenon; however, these comparisons have been never performed until now.

A loss of bone density in the peripheral skeleton may persist despite normalization of lumbar and femoral bone density after patients are on a GFD. The importance of an early diagnosed of metabolic bone disease is clear in CD. The proper diagnostic workup and strict GFD is mandatory to prevent bone fractures, but timing of densitometry in the follow up has not been clarified, but to measure BMD after the first year on a GFD has been recommended proposed as useful.

Our results suggest the usefulness of measuring the bone density of DH patients, but doubts on the appropriate timing for the first bone density scan, the diagnostic workup and the most appropriate therapy for DH patients with a low BMD remain.

There are some limitations of our study. More complete and accurate information would have been achieved from in a greater number of patients, but we should remain that the incidence of DH has been estimated to be 8-16 times lower than that of CD (47,48). So, to the best of our knowledge, this study investigated BMD in the widest number of DH cases up to now. We did not examine more sophisticated laboratory parameters, as biomarkers related to bone formation and resorption, or cytokines. The exact role of these markers has not clarified in the diagnostic workup of gastrointestinal disorders involved with bone metabolism. Further investigation on this biomarkers will help to understand the pathogenesis of DH-associated bone loss.

As a conclusion, bone mineral content in patients with DH was significantly lower than in healthy controls, but higher than in CD. Bone mineral loss was more prominent in bones containing more trabecular than cortical compo-

nent. This phenomenon suggests a similar pathogenetic origin for DH and CD-associated osteopenia and osteoporosis, even when a relationship between the severity of villous atrophy and bone loss was not clearly shown. Further research will define a proper diagnostic and therapeutic algorithm for the management of DH.

ACKNOWLEDGEMENTS

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