Osteopenia and osteoporosis in patients with dermatitis herpetiformis. Effect of gluten-free diet

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Abstract

Introduction: Dermatitis herpetiformis (DH) is a rare blistering disease which is accompanied by gluten-sensitive enteropathy. Intolerance of gluten is the most important feature of both diseases. In 70% of the cases, lesions in the small intestines of DH patients are histologically identical with those observed with celiac disease. However, those observed with celiac disease can be less intensive. Even though intestinal villous atrophy is observed in a majority of patients, clinical symptoms of malabsorption, especially diarrhea, are evident in only a portion of the cases. Demonstration of significantly lower bone mineralization in some patients using dual-energy X-ray absorptiometry (DXA) suggested the possibility of malabsorption complication in the form of osteoporosis in DH patients. The aim of the study was to evaluate the incidence of skeletal mineralization disturbances in patients with DH and to determine whether adherence to gluten-free diet can prevent these patients from the development of osteoporosis.
Material and methods: DXA examination of the lumbar spine and concentration of bone rebuilding markers in blood serum were carried out in 37 patients diagnosed with DH and in 27 healthy controls.
Results: Osteopenia and osteoporosis was found in more than half of the examined patients with DH. Postmenopausal women with a long history of the disease are at a higher risk. There is, however, increased rate of accelerated loss of bone mass in men and premenopausal women under the age of 65.
Conclusions: The obtained results allowed us to draw the following conclusion: DH is a pathological condition which is burdened with complication in the form of osteoporosis.

Key words: dermatitis herpetiformis, celiac disease, osteoporosis, diet therapy.

Introduction

In contrast to the physiological loss of bone density, in the course of some pathological conditions defects in skeletal mineralization occurred, which is called secondary osteoporosis. Bone mass defect may also accompany gluten-sensitive enteropathy (GSE), i.e., celiac disease (CD). This process is associated with decreased absorption of dietary factors that are necessary for maintaining adequate bone mass from abnormal intestines. Among the extra intestinal symptoms, loss of bone mass and bone metabolism disturbances are frequently present and can be the only signs of an otherwise silent celiac disease [1].

It has been demonstrated that gluten intolerance is a feature of dermatitis herpetiformis (DH) [2]. Common aetiology of both diseases is assumed, with

the most important role attributed to gluten intolerance [3-5].

DH is a bullous skin disease with polymorphic lesions: papules, erythemas, vesicles [6]. The most common sites of involvement are the sacral region, buttocks, scapulae, nape, elbows, knees, face and scalp. The lesions are accompanied by a very intensive itching which results in forming erosions and crusts [7]. DH is diagnosed based on a typical clinical picture as well as histological and immunopathological examination of the skin (DIF). Granular deposits of IgA in dermal papillae are pathognomonic for the disease [8-11]. The presence of IgA class antibodies directed against smooth muscle endomysium (IgAEmA) in patient's serum is also very important. These antibodies are viewed as a specific and sensitive marker of GSE, although they cannot be determined in about 30% of DH cases (latent enteropathy) and are revealed only after provocation with gluten [12-17].

New studies on the autoimmune pathogenesis of DH demonstrated that the key role in this process is the deamination reaction of a gluten metabolism product, which is carried out by tissue transglutaminase (tTG) [18, 19]. IgA EmA antibodies react with tTG, which acts as an autoantigen for those antibodies [20, 21]. Pathological changes in the small intestine, in the form of villous atrophy, are histologically identical with the ones observed in celiac disease, although they can be less pronounced [22, 23]. Both diseases affect the mucosa of small intestine. It results in development of a "flat mucosa" and subsequent disorders in intestinal absorption [24, 25].

Gluten-free diet (GFD) is essential in the treatment and has beneficial effects on both skin lesions and intestinal changes [26-29]. Malabsorption results in the deficiency of trace elements and insufficient absorption of calcium, magnesium, iron, folic acid and vitamin B complex. As a result deficiency anaemia and avitaminoses occur, especially concerning the fat-soluble vitamins such as vitamin D, with subsequent calcium deficiency [29-31]. Bone alternations were once thought to derive from calcium and vitamin D deficiency secondary to simple intestinal malabsorption [32].

Although villous atrophy is present in 70% of patients with DH, yet diarrhoeas, which are typical for celiac disease are observed only in some cases [29, 33]. However, there is no evidence as yet to suggest that symptom-free celiac disease or DH patients run an increased risk of osteoporosis or malignant intestinal lymphoma, the prevention of osteoporosis seems to be the strongest indicator for widespread screening today [34, 35].

It has been demonstrated that CD, including its latent form, may be accompanied by osteopenia and osteoporosis [36-38]. Literature data confirm significantly lower bone mineralization in patients with CD, evaluated in densitometry [39-42].

It is controversial whether gluten-free diet is sufficient enough to prevent the development of this complication [36, 37, 43]. According to some authors, gluten-free diet observed for some time contributes to the reconstruction of intestinal mucosa and restoration of crypts. Some investigators report that gluten-free diet can ameliorate, but not normalize the process of skeletal mineralization [44]. Others confirm the protective role of restrictive gluten-free diet in the development of reported complications [37, 45, 46]. Failure to achieve an optimal bone mass in childhood and adolescence as well as other risk factors, probably play a role in further changes [47-49].

Material and methods

The aim of the study was to determine whether bone mineralization defects, such as osteopenia and osteoporosis, are present in patients with DH. In addition, in this study we evaluate their frequencies in patients with and without gluten-free diet.

The examined group consisted of 37 patients who were treated in the Department of Dermatology and Venerology of Medical University of Lodz. These patients were previously diagnosed with DH based on the clinical picture and immunopathological examinations. The group was comprised of 18 women (13 before and 5 after menopause) and 19 men. Mean age of patients was approximately 45 years (range between 17 and 80 years); mean duration of the disease was 9.3 years.

The control group consisted of 27 subjects without any skin disease, age and sex matched. The control group comprised 17 women (10 before and 7 after menopause) and 10 men; mean age was 51 years (range between 23 and 80 years).

Dual-energy x-ray absorptiometry (DXA) of lumbar spine and determination of markers of bone reconstruction were performed in all patients from the examined and the control groups. We compared T-values (DXA) for the same bone in both groups.

In order to exclude impact of factors other than malabsorption on skeletal mineralization, evaluation of physical activity, calcium intake, cigarette smoking, and use of medications and coexistence of chronic disease influencing the condition of the skeleton was performed in both groups. The groups did not differ statistically with respect to physical activity, dietary calcium intake or value of the Body Mass Index. The incidence of cigarette smoking in the control group was significantly higher compared to the study group. No chronic diseases or use of medications was observed in both groups. Occasionally, our patients with DH were treated with topical steroids. We always use the first choice drug for DH – sulfone (Disulone/Dapson).

The studied group was divided according to GFD based on the established criteria [13]. Mean duration of gluten-free diet was 6.66 years (SEM=1.35):

- group I – 15 patients on GFD (excluding gluten form the diet or gluten intake lower than 10 g daily for at least 6 months);
- group II – 22 patients without any diet applied (gluten intake higher than 10 g daily).

In both groups the following factors were determined in the peripheral blood serum: Ca^{2+}, K^{+}, Na^{+}, Mg^{2+}, Cl^{-} as well as the ionogram, blood cell count, sedimentation rate, levels of glucose, hepatic transaminases, urea and creatinine. General urine test and results of all laboratory tests were within the normal range. Daily calcium intake in the diet of patients with DH (mean =1104.05 mg/24 hours) and in control group (mean =972.5 mg/24 hours), as well as BMI, were not statistically different.

Densitometric examinations of L1-L4 spine section were made with dual photon X-ray absorptiometry using DPX instrument (Lunar, Madison, USA). The BMD (bone mineral density) value was expressed as g/cm^2 and interpreted against the T-score scale.

Markers of bone rebuilding, i.e., osteocalcine (ELISA-Osteo Kit CIS, Bio International, France) and β cross laps (CTX, cross laps, Osteometer AIS, Denmark) were determined in blood serum by immunoelectrochemiluminescence (ECLIA) with ELECSYS 1010 instrument (Roche) using sandwich-type method. Bone isoenzyme of alkaline phosphatase (Alkaphase B kit, Metra Biosystems, Mountain View, CA) was determined by ELISA method with Quidel Metra BAP assay.

Statistical analysis

The collected data were analyzed with the program Statgraphic version 6.0. The mean, standard deviation and the median were calculated for all the variables.

Obtained results as a number of observations were statistically analysed with χ^2 independence test for four- and two-field table. A value of $p<0.05$ was taken as the level of significance.

Results

Results of bone mineral density examination

In the examined group, mean BMD value was 1.04 g/cm^2. Mean BMD value in the control group was 1.20 g/cm^2. Mean BMD values were higher in the control group than in the examined group, however the differences were not statistically significant ($p>0.05$).

In the group of patients with DH, osteopenia was diagnosed based on BMD examination with the T-score scale (1.0SD>x<2.5SD) in 11 patients (fraction =0.3), while osteoporosis (>2.5SD) in 12 patients (f=0.32).

In the control group, values of the BMD index against the T-score scale were within the normal range in 25 subjects (f=0.92). Two, however, were women above 55 years of age who had values that were typical for osteoporosis (f=0.07). A statistically significant difference was observed for the BMD values on the T-score scale between the study and control groups ($p<0.001$) (Table I).

In the group of men with DH (mean age =42.47 years), osteopenia and osteoporosis were diagnosed in 12 out of 19 patients (f=0.63). There were no bone mineralization defects in any of the men from the control group. A statistically significant difference between those values in the sub-groups of men from the examined and control groups was revealed ($p<0.00$).

In the group of women with DH (mean age =47.22 years), disturbances in skeletal mineralization constituted a fraction of 0.61, 7 out of 13 premenopausal women (f=0.54) and 4 out of 5 postmenopausal women. No statistically significant differences were observed for BMD in g/cm^2 between the sub-groups of women and men. Osteopenia and osteoporosis were not diagnosed in women before the age of 55 from the control group.

In the sub-group of women over the age of 55, osteopenia and osteoporosis were diagnosed in 2 cases (f=0.28). In the age group of patients younger than 35, osteopenia and osteoporosis was observed in 3 out of 12 cases (f=0.25) of patients with DH. Bone mineralization disturbances were not observed in subjects younger than 35 years of age.

In the groups divided according to application of the gluten-free diet, no statistically significant differences in the BMD values on the T-score were found (Table II).

Results of determination of bone rebuilding markers

Osteocalcine-normal ranges:

men	11-43 ng/ml
women premenopausal	12-41 ng/ml
women postmenopausal	20-48 ng/ml

Table I. BMD (T-score) in the studied (I) and control groups (II)

Fraction	men		p	women >55 y		p	women <55 y		p
	I	II		I	II		I	II	
norm	0.37	1	p<0.001	0.46	1	p<0.01	0.2	0.74	p<0.05
osteopenia/ osteoporosis	0.63	0		0.54	0		0.8	0.26	

Table II. The studied group: correlations between BMD (T-score) and gluten-free diet application

	normal		osteopenia		osteoporosis	
	[n]	[fraction]	[n]	[fraction]	[n]	[fraction]
Group – without diet n=22	8	0.36	5	0.23	9	0.41
Group – gluten free diet n=15	6	0.40	6	0.40	3	0.20
Comparison between groups	NS					

In the examined group, mean osteocalcine value was 30.91 ng/ml. It was below normal in 2 patients (f=0.05), within normal range in 28 patients (f=0.76) and above normal in 7 patients (f=0.19). The value of this marker in the control group of healthy subjects was similar (mean 31.71 ng/ml); all values in this group were within normal range.

There were no statistically significant differences in the examined group between mean values of osteocalcine in women and men (25.15 and 36.36 ng/ml) and between women before and after the age of 55 (24.50 and 26.85). In the groups divided according to gluten-free diet, fractions of patients with normal osteocalcine values were not significantly different.

β-cross laps-normal ranges:

men	0.01-0.30 ng/ml
women premenopausal	0.01-0.28 ng/ml
women postmenopausal	0.01-0.32 ng/ml

Marker of resorption, i.e., β-cross laps in the examined group was within the range from 0 to 1.46 ng/ml (mean 0.5 ng/ml). The β-cross laps below normal range were found in 1 patient (f=0.027), above normal in 22 patients (f=0.59) and normal in 14 cases (f=0.38).

In the control group, mean value of the bone resorption marker was 0.233 ng/ml, with the minimum at 0.114 and maximum at 0.414 ng/ml. Three subjects (f=0.11) had results above the normal range, while the remaining 24 persons (f=0.88) were within normal range. These results are mostly normal in contrast to the examined group and statistically significant difference was obtained for the distribution of this feature between the groups ($p<0.05$) (Table III). There was no statistically significant difference found in the level of this marker between women and men from the examined group (0.42 and 0.58 ng/ml).

A difference was observed for the value of β-cross laps between the group without the GFD and the group with gluten excluded form of diet. In the first group, increased values of β-cross laps concentrations were obtained in 15 out of 22 patients (f=0.68), while in patients on GFD such results were found in 7 out of 15 patients (f=0.47), with no statistically significant difference found ($p>0.05$) (Table III).

Both in the examined group and in the control group there were no deviations from the normal in the values of bone isoenzyme of alkaline phosphatase.

Discussion

Morphologic changes in the intestine that develop in CD and DH on the base of immunological processes lead in consequence to disturbances in intestinal absorption that may lead to secondary osteoporosis [16, 44]. Majority of studies reveal the presence of osteoporosis in approximately 50% of patients with CD even in latent form [37, 39]. However, little information is available on the biochemical bone turnover markers in patients treated with GFD [50]. So far, similar studies have not been performed in a group of patients with DH [51]. In contrast to postmenopausal osteoporosis, interventional studies in secondary osteoporosis are often limited by a small study population and data about the efficacy of any treatment in prevention of

Table III. The studied and control groups – comparison of β-cross laps

	< normal		normal		> normal	
	[n]	[fraction]	[n]	[fraction]	[n]	[fraction]
The study group n=37	1	0.027	14	0.38	22	0.59
The control group n=27	0	0	24	0.88	3	0.11
Comparison between groups	p<0.05					

fractures are therefore lacking [52]. Our paper shows the study of bone changes in DH patients. According to other authors, a short systemic therapy with steroids and rare topical treatment with steroids seems to be of no significance [36, 37].

In DH, as compared with CD, the extent of morphological changes in the bowel is smaller [52]. Thus, one could expect a low degree of disturbed absorption or even absence. However, patients with DH periodically present with stomachaches, anaemia and/or diarrheas. Experimental studies confirm disturbed absorption of calcium, Vitamin D and trace elements.

Starting from middle age, both in men and in women gradual loss of bone mass occurs [53]. This process is quickened in women in early years after the menopause and after the age of 65 in men [54, 55]. In case of secondary disorders decrease in bone mass may occur in younger patients [49].

In the presented study, BMD measurements by densitometry of lumbar spine revealed reduced values, indicating loss of bone mass and osteoporosis in a significant percentage of patients with DH. It should be noted that in the T-score of DXA examination, the majority of women after menopause from the examined group had established osteopenia or osteoporosis. Results obtained in premenopausal women are also characteristic. Disturbances in skeletal mineralization on the DXA examination were found in more than half of these women and one of them had also a history of pathological fracture. Such results in patients with DH suggest a similar risk of osteoporosis in premenopausal as in postmenopausal women.

Osteopenia and osteoporosis were found in more than half of the examined patients with DH. It seems that such a large number of defects revealed in skeletal mineralization could be associated with GSE. Influence of other possible risk factors for osteoporosis was similar in both examined and control groups as well as in general Polish population [56].

In the group of patients with DH, serum concentrations of Ca^{2+} were within the normal range. Studies on CD undertaken by other authors revealed both normal and decreased levels of the examined element [57, 58]. Normal concentration of Ca^{2+} in blood serum of the examined patients seems to be caused by secondary hyperparathyroidism.

Bone mass acquired in the first years of life is probably the most important factor determining the condition of skeletal system for the whole life [59]. Patients with DH may achieve lower peak bone mass as a result of the pathological process in the small intestine which causes disturbances in absorption [54]. It is confirmed by results obtained in the examined group of patients with DH, who were characterized by a lower value of mean BMD as compared to the control group.

Persons who had not achieved the optimal bone mass in childhood and adolescence may develop osteoporosis without accelerated loss of bone mass [59]. Symptoms suggesting GSE should be quickly confirmed so that treatment could be introduced. Unfortunately, opposite to CD, whose symptoms appear in the first decade of life, first clinical symptoms of DH are present only in the older age, after the bone mass has been formed. In the examined group of patients, changes in concentration of osteocalcine, and mainly resorption marker – β-cross laps, were described. Elevated values of this marker, which were found in more than half of the patients, revealed increased resorption of the skeleton compared with the control group. This phenomenon was observed in a very small number of persons. This finding seems to confirm a special risk of osteoporosis in DH patients.

There are no homogenous data on the role of GFD in the development of osteoporosis in current literature. Some studies suggest that long-term (>5 years) of GFD is sufficient for maintaining adequate skeletal mineralization and its metabolism. It is confirmed by both results of densitometric studies and by determination of biochemical parameters in patients observing the GFD [37, 45]. Some authors report rebuilding of the bones even after first year of GFD on the base on increase in the parameter of BMD [37, 39].

Life-long GFD is established therapy for CD and DH it allows the intestinal mucosa to recover, improves nutrient malabsorption and osteoporosis [60, 61]. Gajewska et al. data show normal bone resorption and formation processes in most patients with celiac disease on gluten-free diet [62]. However, some cases had changes in the pattern of bone turnover markers. Similarly, no statistically significant effect of GFD on metabolic processes in the skeleton was demonstrated in the presented study.

In our densitometric examinations of patients not-observing the GFD osteoporosis was more frequent than in patients observing the diet, although the difference was not statistically significant. Corraza et al. [63] compared the BMD values in patients with gluten-sensitive enteropathy who were treated with GFD, not-observing the diet and healthy persons. These authors report higher values of BMD in diet-treated patients while the values are lower than in the group of healthy persons.

Effects of dietary improvement on bone metabolism in elderly underweight women with osteoporosis in a 12-month randomised controlled trial are as follows: reduction in bone resorption with a small beneficial effect on bone formation [64]. It's a good example for calcium and vitamin supplementation gluten-free diet in celiac disease and DH patients.

The results of the present study confirm the thesis that sole observation of GFD does not prevent from the development of defects in bone mineralization. High percentage of DH patients with diagnosed osteopenia and osteoporosis in spite of the gluten-excluding diet may result from lower peak bone mass obtained earlier as a result of a pathological process in the intestine.

The authors confirmed that the current advice concerning dietary adherence is necessary to avoid long-term complications, which are principally osteoporosis and small bowel lymphoma. However, risk of these complications diminishes very considerably in patients who are on GFD [65].

Conclusions

Osteopenia and osteoporosis are complications of DH and are encountered more frequently in patients with this disease than in healthy persons.

The fact that osteopenia and osteoporosis are observed in the course of DH even in young persons and in women before menopause reveals the necessity of routine bone mineral density measurements in all patients with DH.

The frequency of bone mineralization defects in patients observing and not-observing the GFD is similar, thus all patients with DH should receive supplementation of calcium and vitamin D.

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