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Alimentary Tract

Bone mass in women with celiac disease: Role of exercise and gluten-free diet

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ABSTRACT

Background and aim: Celiac patients report fatigue and reduced social activities, which may decrease physical activity. This study investigated the physical activity, fatigue and bone mineral density in celiac women at diagnosis and during diet.
Materials and methods: The first group ($n = 48$) had the bone mineral density measured at diagnosis and after 2 years of a gluten-free diet; in the second group ($n = 47$) bone mineral density was measured at diagnosis and after 5 years of a gluten-free diet. Both groups completed a physical activity questionnaire and visual analogue scale for the perception of fatigue at diagnosis and follow-up. Data about smoking habits, alcohol use, presence of gastrointestinal symptoms, drug therapy and body mass index were also collected.
Results: At diagnosis, the two groups were similar for all considered variables. At follow-up, the mean body mass index and physical activity questionnaire's score were similar to baseline. The bone density increased in both groups, whilst the physical activity questionnaire and visual analogue scale remained unchanged.
Conclusion: The improvement in bone density following a gluten-free diet was significant after 2 years; physical activity is frequently low and plays a minor role in determining the changes in bone mineral density.

1. Introduction

Celiac disease is frequently associated with known risk factors for a reduced bone mass [1–3], including a low body mass index (BMI) [4], early menopause [5], fatigue limiting exercise [6] and reduced social and physical activities [7,8]. Celiac disease is also associated with a reduced bone mineral density (BMD) [9] and osteoporosis [10]. Consequently, a significant association between bone fractures and celiac disease has been described [9–11]. In celiac disease, the BMD is not simply related to nutrient malabsorption and the presence of gastrointestinal symptoms; a low BMD is also common in patients without gastrointestinal symptoms [12] as well as in asymptomatic individuals [13] and persons with dermatitis herpetiformis [14] in whom minimal intestinal damage occurs [15]. The presence of villous atrophy and nutrient malabsorption, altered immunity in the mucosa and circulating antibodies may all play a role in the low BMD observed in patients with celiac disease [16]. Physical exercise is a source of bone turnover and is recommended for preventing osteoporosis and bone metabolism problems [17,18]. No data are currently available on the role of physical activity in celiac disease patients in relation to BMD, at diagnosis through follow-up, and diet.

The present study has been designed to evaluate the relationships amongst physical activity, fatigue and BMD in women with celiac disease following a gluten free diet (GFD). Moreover, the study aimed to assess the optimal timing of BMD measurements in adult celiac patients after the beginning of a GFD.

2. Methods

2.1. Participants

Patients with celiac disease were recruited from an outpatient clinic devoted to celiac disease at the Federico II University of Naples.

Based on previous data on BMD in celiac disease [19] the proposed sample of 45 subjects for each group would have a power of 95.9% to yield a statistically significant result.

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From 2003 to 2005, we enrolled newly diagnosed women with celiac disease meeting the inclusion/exclusion criteria. Women met inclusion criteria if they were of age 20–60 years, and were diagnosed with celiac disease exhibiting positive anti-transglutaminase antibodies, anti-endomysium antibodies (EMA), and pathological intestinal biopsy (evaluated using the Oberhuber-modified Marsh classification) [20,21].

Exclusion criteria were the use of oral contraceptives, oral corticosteroid treatment, hormone replacement therapy or hysterectomy, Cushing's syndrome, physical impairment limiting physical activity, nervous system disease, major psychiatric disorder and drug/alcohol abuse. All patients gave informed consent and the study protocol was approved by the Ethics Committee of the University Federico II of Naples (*Diagnosis and Follow-up of Celiac Disease in Adults*).

We enrolled one hundred and ten consecutive CD patients at diagnosis randomly allocated in two groups of 55. In the first group, we evaluated the BMD at diagnosis and again after 2 years on a GFD (*2-year FU*); in the second group, the BMD was assessed at diagnosis and again after 5 years on a GFD (*5-year FU*). In all cases, BMD was measured at the right femur and lumbar spine using dual-energy X-ray absorptiometry (DEXA). During the follow-up period, seven patients were excluded as they refused to repeat the second BMD evaluation and two patients because they were not strictly compliant with the GFD (evaluated by anti-transglutaminase levels). Six additional patients ultimately dropped out as they did not return for follow-up visits. In sum, 48 women of 2-year FU group and 47 women of 5-year FU group were followed until completion of the study and through to data analysis.

For all participants at the time of the first and second BMD evaluation, we collected data on their weight, height, BMI, age at menarche and age at menopause if applicable. The presence of fatigue and its intensity was evaluated using a visual analogue scale (VAS) in which the patients were asked to answer the following question: 'How did you feel in the last week?' marking a scale consisting of a 10-cm line with the sentence 'I never feel tired' at the extreme left and 'I always feel tired' at the opposite extreme. The possible score ranged from 0 to 10. The nutritional status of each patient was defined at diagnosis and follow-up by measuring laboratory indices: the serum iron concentration, haemoglobin, albumin and plasma cholesterol.

We also investigated smoking habits and alcohol habitual intake, the presence of gastrointestinal symptoms (*i.e.*, diarrhoea, abdominal discomfort/pain) and any drug therapy.

Anti-transglutaminase antibodies were measured in the blood of all patients again at time of the second BMD evaluation. The serum level of plasma vitamin D [1,25(OH)D3] was measured at diagnosis and follow-up (ng/ml) [19]. A VAS scale was used to evaluate the reported compliance with the GFD [23] and an expert dietician evaluated the accuracy of the compliance and the average calcium consumption per day (low, <0.5 g; moderate, 0.5–1 g; high, ≥1 g) [22,23].

2.2. Questionnaire

All participants completed the short version of the International Physical Activity Questionnaire (IPAQ) at diagnosis and again after 2 and 5 years on the GFD, as appropriate.

The IPAQ estimates the extent to which a person has performed health-enhancing physical activity over the previous 7 days and covers four domains of physical activity: at home, during transport, occupational and leisure time physical activity. The participants calculated how many days (frequency) they were physically active, and on such days, how much time (duration) they spent physically active. According to the score achieved in the IPAQ questionnaire, we categorised the physical activity of the participants as *low* for walking, *moderate* for moderate physical activity and *high* for vigorous physical activity [24].

Table 1
Background characteristics (age, body mass index (BMI), frequency of gastrointestinal symptoms and selected laboratory tests evaluating the nutritional status) of the 2-year follow-up (2-year FU) and 5-year follow-up (5-year FU) women; the seric concentration of anti-transglutaminase antibodies is also reported (normal values < 7 U/ml). Data are expressed as means ± standard deviation (SD) or percentages.

	2-Year FU	5-Year FU	*p*
Age (years)	35.1 ± 11.3	35.1 ± 8.7	0.99
BMI (kg/m^2)	22.3 ± 4.3	22.3 ± 4.3	0.80
Gastrointestinal symptoms (% of women reporting GI symptoms)	63.6	56.4	0.43
Haemoglobin (g/dl)	12.1 ± 2.0	12.1 ± 2.3	0.92
Serum iron (μg/dl)	47.7 ± 27.0	53.8 ± 31.7	0.37
Cholesterol (mg/dl)	156.8 ± 36.4	152.1 ± 32.2	0.60
Albumin (g/dl)	4.1 ± 0.5	4.3 ± 0.4	0.17
Anti-transglutaminase antibodies (U/ml)	80.3 ± 91.1	83.9 ± 87.0	0.85

2.3. Measuring BMD

DEXA was used to measure the BMD at two sites: the right proximal femur (neck and Ward's triangle) and the lumbar spine (level L4) using a Hologic QDR-4500A (S/N 45622). The BMD was expressed as g/cm^2. According to the World Health Organisation, we defined osteopaenia as a BMD between −1.0 and −2.5 SD below the norm for young healthy adults of the same sex (*T*-score <−1.0 and >−2.5) and osteoporosis as a BMD of −2.5 SD or below (*T*-score ≤−2.5) [25].

2.4. Statistical analysis

The data are expressed as means ± standard deviation (SD) and percentage.

The chi-square test and analysis of variance (ANOVA) were used to compare categorical and continuous data, respectively.The two-sample and pairwise *t*-test (confidence intervals set to 95%) was used to compare the mean BMD values of each group at the first and second evaluations.

The statistical programme used was the Statistical Package for the Social Sciences (SPSS) for Windows, version 12.0.

Statistical significance was accepted as $p < 0.05$. Multiple tests were corrected for type 1 error using Tukey's method.

3. Results

3.1. Baseline characteristics

At diagnosis, age, BMI, frequency of gastrointestinal symptoms and nutritional status evaluated using selected laboratory tests were similar in both groups (Table 1). Histology revealed from Marsh 1 (11% of cases) to Marsh 3c lesions (45% of cases).

Smoking habits and alcohol intake were similar in the two groups (data not shown).

The mean ages at menarche and menopause were similar in both groups (age of menarche, 12.30 ± 1.21 years for 2-year FU and 12.52 ± 1.71 years for 5-year FU; age at menopause, 48.71 ± 1.75 years for 2-year FU and 49.33 ± 1.53 years for 5-year FU). Ten women (9%) were in menopause (six in 2-year FU and four in 5-year FU).

At baseline, the mean BMD at the right proximal femur (neck and Ward's triangle) and the lumbar spine (level L4) were not significantly different in both two groups ($p > 0.05$). About the 52% of patients of 2-year FU and 5-year FU had a pathological BMD at

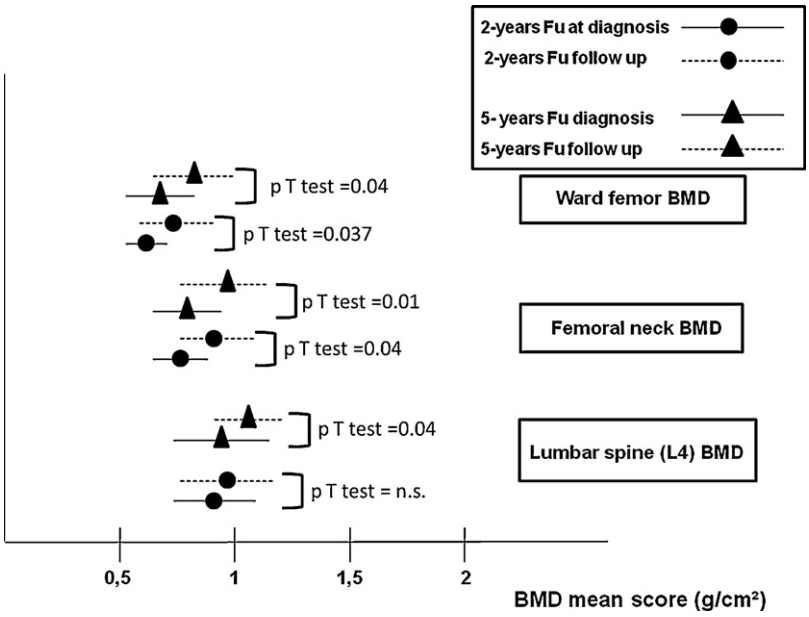

Fig. 1. Lumbar and femur bone mineral density (BMD) values at diagnosis and at follow-up in the 2-year follow-up (2-year FU) and 5-year follow-up (5-year FU) women. Data are expressed as mean ± standard deviation (SD).

diagnosis. According to our protocol, no therapy for osteoporosis was prescribed to participants with low BMD at diagnosis.

At diagnosis, no correlation between BMD values and severity of histological lesion was found (data not shown).

Frequency of a pathological BMD in relation to the presence of gastrointestinal symptoms or the nutritional status was similar in the two groups: the prevalence of hypochromic anaemia, hypoalbuminemia, plasma cholesterol levels (below 150 mg/die) was not significantly different between both groups ($p > 0.05$).

About 58% of the 2-year FU and 56% of the 5-year FU reported a low calcium intake (less than 500 mg/die); the 1,25(OH)D3 levels were within the normal range both in the 2-year FU and 5-year FU group (19.90 ± 11.90 ng/ml vs. 20.30 ± 12.20 ng/ml, respectively; $p > 0.05$).

At diagnosis, the percentages of women performing low, moderate and high physical activity were similar in both the two groups; also the mean IPAQ score was comparable (1.65 ± 0.75 in 2-year FU women vs. 1.88 ± 0.80 in 5-year FU women; $p > 0.05$ in both cases).

No significant relationship was observed between the BMD for 2-year FU and 5-year FU and level of physical activity at diagnosis ($p > 0.05$ for the lumbar spine and for the proximal femur). The comparison of the perception of fatigue in the two groups at diagnosis showed no significant difference between the two groups ($p > 0.05$).

3.2. Follow up data

At follow-up, the anti-transglutaminase antibody and 1,25(OH)D3 levels were within the normal range in both groups ($p > 0.05$); the daily calcium intake did not change compared to that at diagnosis.

None of the CD women reported spontaneous fracture during the follow-up period, one reported a traumatic ankle fracture [26,27].

The 2-year FU women showed at follow up a mean BMI comparable to that at diagnosis ($p > 0.05$).

The mean BMD at femur was higher than that at diagnosis ($p = 0.04$ for the femoral neck and $p = 0.037$ for Ward's triangle), and no significant increase in the BMD was observed for the spine ($p > 0.05$).

For 5-year FU women the mean BMI at follow up was significantly higher compared to that at diagnosis (21.37 ± 2.98 kg/m^2 vs. 22.44 ± 3.44 kg/m^2, respectively; $p = 0.016$). The 5-year FU showed an increase of BMD at the femur and at the spine, for both being the BMD higher than at diagnosis ($p = 0.04$).

Fig. 1 summarises the BMD data for each group at diagnosis and follow-up.

3.3. BMD, physical activity and fatigue

The 2-year FU women reported 53.2% low physical activity and 10.6% high physical activity. The perception of fatigue was not decreased to the GFD at 2 years (2-year FU fatigue scores at diagnosis and follow-up, $p > 0.05$). The analysis of the fatigue scores compared to the levels of physical activity (low, moderate and high) showed that the women in 2-year FU reported a similar perception of fatigue at diagnosis and follow-up for each level assessed using the IPAQ questionnaire.

The 5-year FU women reported 46.3% low physical activity and 14.6% high physical activity. The perception of fatigue was increased to the GFD at 5 years (5-year FU fatigue scores at diagnosis and follow-up, $p > 0.05$). The patients in 5-year FU performing high physical activity (IPAQ score = 3) at the follow-up evaluation reported a greater perception of fatigue compared to the 5-year FU patients performing low physical activity ($p = 0.039$, *post hoc*).

The mean IPAQ score was not statistically distinct in 2-year FU and 5-year FU (1.60 ± 0.67 vs. 1.87 ± 0.88; $p > 0.05$). The comparison of the perception of fatigue in the two groups at follow-up showed no significant difference between the two groups ($p > 0.05$). The fatigue VAS mean score of the 5-year FU group performing high physical activity at follow-up was also significantly different compared to that of the women in 2-year FU who reported the same intensity of physical exercise at follow-up (4.50 ± 1.00 vs. 8.33 ± 0.58; $p = 0.002$). Table 2 reports the details of these findings.

No significant relationship was observed between the BMD for 2-year FU and 5-year FU and level of physical activity at the 2- and 5-year follow-ups ($p > 0.05$ at the lumbar spine and at the proximal femur in both groups).

Similar non significant differences were found in analysing the variation in physical activity reported at diagnosis and at

Table 2
Reported fatigue and correspondent International Physical Activity Questionnaire (IPAQ) scores (1 = low, 2 = moderate, 3 = high) in the 2-year follow-up and 5-year follow-up women both at diagnosis and follow up.

Physical activity	Fatigue scores at diagnosis at follow up	*p* ANOVA	Fatigue scores	*p* ANOVA
2-Year follow-up				
IPAQ score 1	6.21 ± 1.93		5.78 ± 2.21	
IPAQ score 2	6.18 ± 2.44	0.64	6.00 ± 1.95	0.44
IPAQ score 3	5.33 ± 1.36		4.50 ± 1.00*	
5-Year follow-up				
IPAQ score 1	5.77 ± 1.78		5.11 ± 2.26□	
IPAQ score 2	5.89 ± 2.20	0.49	5.44 ± 1.24	0.034
IPAQ score 3	6.86 ± 2.11		8.33 ± 0.58*,□	

* 2-Year follow-up vs. 5-year follow-up International Physical Activity Questionnaire (IPAQ) at follow-up; *p* ANOVA = 0.002.
□ 5-Year follow-up with IPAQ score = 1 vs. 5-year follow-up with IPAQ score = 3; p = 0.039, post hoc.

follow-up (ΔIPAQ = IPAQ at follow-up − IPAQ at diagnosis) and BMD at the lumbar spine (lumbar spine ΔBMD = L4 BMD at follow-up − L4 BMD at diagnosis) and femur (femur ΔBMD = femoral neck BMD at follow-up − femoral neck BMD at diagnosis) ($p > 0.05$).

4. Discussion

A reduction in bone mass is common in celiac disease, as known risk factors for osteoporosis (heredity, gender, nutrition, endocrine factors and physical activity) are frequent in patients with the disease. Physical activity is a modifiable factor that can enhance bone accretion if the individual performs it regularly. To our knowledge, no data exist on the effect of physical exercise on BMD in celiac disease.

Our study confirms that in women with celiac disease, a low BMD appears to be not related to presence of overt malabsorption (gastrointestinal symptoms and low nutritional indices). Our data indicate that a low BMD is present in 55% of the patients not reporting gastrointestinal symptoms or alternative of nutritional indices [9,12], and, as expected, increases after a GFD [28,29]. In our study's population, the reported dietary calcium intake remained low after commencement of a GFD. However, the vitamin D levels in our patients were within the normal range both before and after the GFD, possibly due to the solar exposure of the study participants (all from Southern Italy), as already reported [19].

Our data confirm that during a GFD, an increase in BMD is possible in adult women with celiac disease and suggest that the BMD should be evaluated 2 years after beginning a GFD. The observed greater increase of BMD at the lumbar spine of the women at the 5-year follow-up compared to that of the 2-year FU group might have been related to the presence of lumbar disc degeneration (*i.e.*, osteophytes and end-plate sclerosis) [30] and not to a real increase in bone density, as a similar BMD increase was not found in the femur scansions.

More than half of women with celiac disease frequently report low physical activity both before and after a GFD. Physical activity tended to increase during a GFD and was higher in the group followed at 5 years than in that studied at 2 years, although the difference was not statistically significant. It should be noted that the BMD increased whilst on a GFD regardless of physical activity. Our study indicates that exercise indeed plays a minor role in the genesis of low BMD in women with celiac disease.

Chronic fatigue perception is frequent in women with celiac disease and it is not ameliorated by a GFD [6]. Our data indicate that fatigue perception increases over time as scores were higher in the 5-year FU women compared to 2-year FU women. A possible explanation is that depression has been found to increases in celiac patients over time and that depression and fatigue appear to be related to each other [6].

In conclusion, the findings indicate that physical activity is low in more than half of adult women with celiac disease whilst on a GFD, and is not related to the reported perception of fatigue. Exercise may play a minor role in determining the changes in BMD when compared to the sole effect of a GFD, which has the double effect of reducing inflammation and increasing calcium absorption. Our data suggest that at diagnosis, in celiac disease, inflammation, low calcium absorption/intake and low physical activity are factors determining reduced bone mass, as under most other clinical conditions. It may be possible that once bone mass peak has been reached, physical activity cannot exert the beneficial effect on bone accretion described during the adolescence and youth. However, one can hypothize that the BMD increase might be even greater than that described if health care givers reinforce in young adults calcium intake and physical activity during a GFD, as a fundamental part of celiac disease therapy. Further studies are needed to evaluate if, as for other clinical conditions, increased physical activity and calcium intake increase bone mass in treated adults with celiac disease.

Conflicts of interest
None declared.

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