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Low bone mineral density in Greek patients with inflammatory bowel disease: prevalence and risk factors

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Abstract

Background A high prevalence of osteopenia and osteoporosis is observed in patients with inflammatory bowel disease (IBD). Various risk factors of bone loss have been suggested in IBD. The aim of the present study was to investigate the prevalence of low bone mineral density (BMD) and to identify related risk factors in Greek patients with IBD.

Methods One hundred and eighteen consecutive IBD patients were included. All patients underwent bone densitometry by dual energy X-ray absorptiometry at the femoral neck and lumbar spine levels. Serum levels of 25 hydroxyvitamin D (25 OH D), 1.25 dihydroxyvitamin D (1.25 OH 2D), osteocalcin, calcitonin and homocysteine were measured in all participants.

Results Forty (33.9%) patients were normal, 55 (46.6%) were osteopenic, and 23 (19.5%) were osteoporotic. No significant differences between IBD patients with osteopenia or osteoporosis and those with normal BMD concerning the use of steroids and the examined biochemical markers were found. Statistically significant differences among the three groups were found for body mass index (BMI), age and disease duration (P=0.002, P<0.0001 and P=0.03 respectively). Multivariate analysis revealed that the most significant factors associated with BMD were age and BMI (P<0.0001). A weak but statistically significant correlation was also found for disease duration (P=0.04).

Conclusions There is a high prevalence of osteopenia and osteoporosis in Greek patients with IBD. Low BMI, age and disease duration are the most important independent risk factors for osteoporosis in Greek IBD patients.

Key words bone mineral density, Crohn's disease, osteocalcin, vitamin D, ulcerative colitis

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Introduction

Low bone mineral density (BMD), defined as osteopenia or osteoporosis, is a common consequence of inflammatory bowel disease (IBD). Epidemiological studies using the World Health Organization (WHO) diagnostic criteria [1] have shown a prevalence of 40-50% for osteopenia and 10-25% for osteoporosis in IBD [2,3].

It has been suggested that the pathogenesis of bone loss in IBD patients is multifactorial. Although the underlying mechanisms are not completely understood, the suggested most important risk factors include disease activity and duration, malnutrition, steroid therapy, calcium and vitamin D deficiency, sex hormone deficiency and smoking [4]. The results of the existing studies are not consistent. For example, several studies have shown a direct correlation between corticosteroids and a decrease in BMD in patients with IBD [5,6]. However, some studies have demonstrated no relationship between corticosteroid use and low BMD in IBD [7,8].

The decreased BMD in IBD patients with active disease might result from the effects of certain proinflammatory cytokines, recognized to be effective in bone remodeling [9].

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It has been suggested that IBD affects normal bone modelling and remodeling, resulting in decreased bone formation and/or increased bone resorption [4].

Various biochemical markers of bone turnover including markers of bone resorption (deoxypyridinoline and cross-linked N-telopeptides of type 1 collagen) (Ntx) and markers of bone formation (osteocalcin and bone specific alkaline phosphatase) have been used in several studies examining the possible mechanisms of bone loss in patients with IBD. Consistent findings are raised levels of markers of bone resorption and reduced levels of markers of bone formation [10]. Moreover, vitamin D insufficiency has been shown to influence calcium metabolism, matrix ossification, the rate of bone turnover and bone mineral density [11]. Hyperhomocysteinemia has been found strongly associated with low-bone mineralization and osteoporosis in Crohn's disease (CD) patients [12].

The aim of the present study was to assess the prevalence of osteopenia and osteoporosis in a Greek population of adult patients with IBD and to determine what patient characteristics and serum biochemical factors might be used to predict bone loss.

Patients - Methods

Patients

This is a single-centre prospective clinical study, conducted between January 2007 and December 2008. One hundred and eighteen consecutive IBD patients followed up at the Department of Gastroenterology of the University Hospital of Heraklion, Crete, were included in this study. The diagnosis of ulcerative colitis (UC) and CD was based on standard criteria [13,14] and the Montreal classification was used for disease phenotyping [15,16]. All participants, patients and controls, were of Greek origin. The disease activity was evaluated at the time of serum collection using the CD activity index (CDAI) score [17] for CD and the simple clinical colitis activity index (SCCAI) [18] for UC patients. Baseline patients' demographic characteristics are shown in Table 1. The exclusion criteria of the study included diseases known to affect bone metabolism such as malignant diseases, celiac disease, short bowel disease, kidney failure, liver disease, thyroid disease, diabetes mellitus and the use of medications such as bisphosphonates, sodium fluoride and calcitonin.

The recorded parameters for each patient during the first visit included: age, gender, menopausal status, smoking status, body mass index (BMI), location, extent and duration of the disease, disease activity indices and ongoing treatments and previous use of corticosteroids. Laboratory parameters such as red and white blood cell count, hemoglobin, hematocrit, platelet count, glucose, total protein, albumin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were determined in all patients.

Informed consent was obtained from all patients and the Ethics Committee of the Medical Faculty of University Crete approved the protocol of this study.

Bone mineral density measurements

BMD was evaluated at the lumbar spine (L1 to L4) and the femoral neck using the Lunar Prodigy dual-energy X-ray absorptiometry (DXA) system (Lunar Prodigy, GE, USA). BMD results were expressed as T-scores which is the number of standard deviations (SD) of the patients BMD from the mean peak value for a reference population with the same sex and race. Patients were classified according to WHO's criteria as normal (T-score > -1 SD at both lumbar spine and hip), osteopenic (T-score from -1.0 SD to -2.5 SD at either lumbar spine or hip or both) and osteoporotic (T-score ≤ -2.5 at either lumbar spine or hip or both).

Laboratory tests

Blood samples were collected from all IBD patients in the morning after an overnight fast. After centrifugation (3500g for 15 min) serum samples were stored at -80^{0}C until assayed. Radioimmunological assays supplied by Biosource Europe S.A. (Nivelles, Belgium) were used to measure 25 hydroxyvitamin D (25 OH D), 1.25 dihydroxyvitamin D (1.25 OH 2D), osteocalcin and calcitonin. The measurements were performed according to the manufacturer's instructions. Serum concentrations of homocysteine were measured by *a* high performance liquid chromatography method and on an *IMx* analyzer (Abbott Labs, Chicago, IL, USA).

Statistical analysis

Box and Whisker plots were used to summarize and display data concerning T-scores. Comparisons between two groups were made by the Student's t-test or Mann-Whitney U test. Comparisons between the three patient groups with normal, osteopenic or osteoporotic BMD levels were made by the Kruskal-Wallis test (non parametric ANOVA). A multiple regression analysis (stepwise method using covariates with significance <0.1) was used to adjust for confounders. A level of $p<0.05$ was considered statistically significant. All analyses were two-tailed and processed using the MedCalc software package (MedCalc software, Belgium).

Results

The distribution of T-scores at lumbar spine and femoral neck of UC and CD patients is presented in Figure 1. Using the WHO's diagnostic criteria 40 (33.9%) IBD patients were classified as normal, 55 (46.6%) were osteopenic and 23 (19.5%) were classified as osteoporotic. Fifteen out of the 23 osteopenic patients (65.2 %) had also Z score <-2 SD. Among CD patients osteopenia was found in 31 (48.4%) and osteoporosis in 15 (23.5%) cases. In UC patients 23 (42.6%) had osteopenia and 8 (14.8%) osteoporosis. No significant difference between UC

Table 1 Patients' demographic and clinical parameters

	UC	*CD*	*Total*
Number	54	64	118
Mean age (yrs)	42	36	39
Male	24	28	52
Female	30	36	66
Active	16	21	37
Inactive	38	43	81
Mean disease duration (yrs)	8.3	9.8	9.1
Current smokers	17	39	56
Non-smokers	27	21	48
Ex-smokers	10	4	14
Disease location			
Proctitis(UC)/ileum(CD)	3	19	
Left sided colitis (UC)/colonic (CD)	31	18	
Extensive colitis (UC)/ileum+colon (CD)	20	27	
Disease behavior (CD)			
Stenosing		20	
Fistulizing			19
Inflammatory			25
Current treatment*			
Steroids	12	18	30
Azathioprine	3	28	31
Infliximab	3	19	22
Adalimumab	0	4	4
Salazopyrine or 5-aminosalcylic acid	49	36	85

**Some patients received more than one drug.*
UC, Ulcerative Colitis; CD, Crohn's Disease

and CD patients concerning the prevalence of osteopenia or osteoporosis was found. Among all female patients with IBD, 9 (7 UC and 2 CD) were postmenopausal. Comparison of the epidemiologic parameters showed no significant difference between CD and UC, except for age (p=0.001). Eight CD patients had a history of bowel resection. Among them one had normal BMD, 5 were osteopenic and 2 osteoporotic. Concerning the use of corticosteroids, 30 IBD patients were under current use, and another 21 patients had used steroids in the past. Among the 11 newly diagnosed cases, 6 of the 9 (66.6%) CD patients were found to have low BMD (3 osteopenic and 3 osteoporotic), whereas the only 2 newly-diagnosed UC patients had normal T-scores.

Table 2 shows the clinical and laboratory data of IBD patients with osteopenia or osteoporosis compared with those with normal BMD. No significant differences between UC and CD patients concerning the examined serum markers were found. BMI, age and disease duration were significantly different among the three examined groups (normal BMD, osteopenia and osteoporosis). BMI was significantly lower in IBD patients with osteoporosis compared with those with osteopenia and normal BMD. Disease duration was significantly shorter in IBD patients with normal BMD compared with those with osteopenia and osteoporosis. The percentage of IBD patients who had received corticosteroids was numerically higher in the osteopenic or osteoporotic group

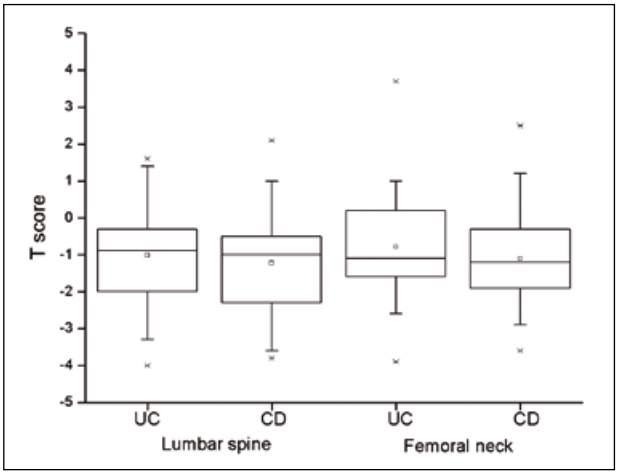

Figure 1 Distribution of T-scores in IBD patients. The boxes indicate the interquartile range with median value. Bars show the 5th and 95th percentiles and data points representing the 1st percentile and the 99th percentile are shown as x

compared with the normal BMD group but the difference was not statistically significant. Mean osteocalcin levels were higher and mean calcitonin levels were lower in IBD patients with osteoporosis compared with the other two groups but the differences did not reach statistical significance (p=0.07 and p=0.09 respectively). Mean serum levels of CRP, 25 OH D, 1.25 OH 2D were not significantly different in IBD patients with osteoporosis compared with the other two groups (p>0.05). Moreover, no significant differences were found in subgroup analysis concerning sex, disease localization, disease type, disease activity, bowel surgery, smoking status and medications used.

Table 3 shows the factors associated with BMD in the multivariate analysis. After adjustment with other covariates, the parameters associated with BMD both of femoral neck and lumbar spine were age, BMI and duration of the disease. No significant association of BMD with serum levels of osteocalcin or calcitonin was found.

Discussion

In this study we found that about two thirds of Greek patients with IBD have low BMD. The prevalence of osteopenia and osteoporosis was 46.6% and 19.5% respectively. No significant difference between CD and UC was found. No association between BMD and the examined biochemical markers was found. Moreover use of steroids, smoking, disease activity, disease localization, bowel surgery and gender had no influence on BMD. On the other hand, age, BMI and duration of the disease were the main determinants for BMD in the multivariate model, independent of other confounding factors.

The prevalence of osteoporosis (19.5%) in our cohort of Greek IBD patients is comparable with that reported from other European countries (10-25%) [8,19,20]. Moreover the proportion of IBD patients with osteopenia was 46.6% which is comparable with the corresponding value reported in other studies 40-50% [8,19,20]. These findings underline the importance of carefully assessing all IBD patients for BMD and initiating appropriate treatment in those with a pathological BMD.

The majority of the studies have shown a negative correlation between BMD and use of steroids in IBD patients [5,6,20,21]. However, this was not confirmed by some other reports [7,8], including our study. Recent studies in pediatric IBD patients have shown that osteoporosis is already present before steroid treatment [22,23]. Moreover, treatments for IBD

Table 2 Clinical and laboratory data of inflammatory bowel disease (IBD) patients with osteoporosis compared with those with osteopenia and normal bone mineral density (BMD)

Parameter	Normal BMD	Osteopenia	Osteoporosis	p value
Age, yrs	40.4±12.9	49.2±14.4	57.0±16.8	<0.0001
Body mass index, kg/m^2	25.7±4.8	25.6±4.7	21.9±2.5	0.002
Duration of disease, yrs	8.0±7.3	10.7±7.5	11.8±11.1	0.03
Use of steroids (%)	39.0	43.7	47.5	0.56
C-reactive protein, mg/L	2.4±2.1	2.7±2.3	3.2±2.8	0.86
Homocysteine, μmol/L	13.1±4.1	13.7±4.5	15.4±4.8	0.30
25 OH D, ng/mL	41.3±19.7	36.5±30.0	34.2±29.2	0.19
1.25 OH D2, pg/mL	15.7±13.4	12.8±8.3	13.1±6.7	0.58
Osteocalcin, ng/mL	4.8±2.5	5.4±2.9	7.8±5.2	0.07
Calcitonin, pg/mL	5.9±2.7	5.0±1.3	4.8±1.6	0.09

Table 3 Results of the adjusted analysis concerning determinants of bone mineral density (BMD) in inflammatory bowel disease (IBD) patients

Variable	Femoral Neck			Lumbar Spine		
	Coefficient	r	p	Coefficient	r	p
Age, yrs	-0.041	-0.471	<0.0001	-0.044	-0.414	<0.0001
Body mass index, kg/m^2	0.093	0.271	<0.0001	0.110	0.281	<0.0001
Duration of disease, yrs	-0.024	-0.316	0.042	-0.029	-0.190	0.044
Serum osteocalcin, ng/mL	-0.0002	-0.214	0.173	-0.0012	-.0168	0.191
Serum calcitonin, pg/mL	0.0005	0.109	0.169	0.0004	0.123	0.145

that minimize steroid doses have been found to be associated with a reduced risk of osteoporosis [24]. The short-term use of steroids supported with the recent use of steroid sparing agents (immunosupressants, anti-TNF) could explain our finding of absence of association between steroid use and BMD. A weakness of our study was the absence of data concerning the total dose of steroids used by the patients.

Vitamin D status has also been suggested as an important risk factor for the development of osteoporosis in IBD [11,25]. However, in our cohort no association between the measured serum levels of 25 OH D or 1.25 OH 2D and BMD was found. The influence of sunshine in Crete probably plays a significant role in the vitamin D status of IBD patients. A recent Greek study showed also normal vitamin status in IBD patients with osteoporosis [26].

Hyperhomocysteinemia has been suggested to play a role in the development of osteoporosis in Crohn's disease patients [12]. However, the results of the present study do not indicate a significant correlation between circulating homocysteine concentrations and low BMD. Previous studies including ours have shown mild hyperhomocysteinemia is common in IBD patients mainly associated with the thrombotic risk of these patients [27].

Calcitonin and osteocalcin are calciotropic hormones, often employed as biomarkers of bone formation status [10]. In the present study, although there was a trend of increased serum osteocalcin and decreased serum calcitonin levels in IBD patients with osteoporosis, no significant association between these hormones and BMD was found.

There is evidence that both body mass and composition, affect bone density in IBD. Several cross-sectional studies have shown that BMI is correlated with BMD [28,29] and the results of the present study confirm this association. Although the mechanisms behind this correlation are unknown, a role of fat mass and adipokines has been suggested [30,31].

The cross-sectional design of our study is an important limitation since we are unable to determine whether the examined parameters influence future changes in BMD (positively or negatively). Therefore, follow-up studies are needed in order to evaluate these parameters in relation to the changes in BMD and if they confer a risk for fractures in IBD patients.

In conclusion, our study showed that the prevalence of osteopenia and osteoporosis is high in a Greek cohort of IBD patients. Major risk factors for low BMD values were low BMI, age and disease duration.

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