

Bone Density and Bone Metabolism in Patients with Inflammatory Bowel Disease

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ABSTRACT

Background/Aims: Patients with inflammatory bowel disease (IBD) are at high risk for low bone mineral density (BMD). This study aimed to evaluate BMD in IBD patients and its relationship with bone metabolism in a group of Iranian patients. **Patients and Methods:** A cross-sectional study was conducted on patients with IBD to assess BMD status and serum biochemical factors. After getting the demographic data from 200 patients, they were screened using dual-energy X-ray absorptiometry of the lumbar spine (L2-L4) and femoral neck for BMD status. Serum levels of calcium, phosphate, alkaline phosphatase (ALP), and 25-hydroxyvitamin D (25-OH vitamin D) were measured to assess the bone metabolism status. **Results:** Two hundred patients with IBD were enrolled in the study. One hundred and eighty three (91.5%) patients were identified as having ulcerative colitis (UC) and 17 (8.5%) as having Crohn's disease (CD). Based on the lumbar and femoral neck bone mass densitometry, 148 (74.4%) patients had low BMD at either lumbar spine or femoral neck. Of these, 100 patients (50.3%) were osteopenic and 48 patients (24.1%) were osteoporotic. A 58.6% and 61% of patients with UC had low BMD in the lumbar and femoral neck, respectively. These results for those with CD were 76.5% and 70.6%, respectively. The mean of femoral neck and lumbar T-scores in patients with UC were -1.14 and -1.38, and in patients with CD were -1.24 and -1.47, respectively ($P > 0.05$). The mean (\pm SD) levels for calcium (Ca) in UC and CD were in the normal range. The mean (\pm SD) levels of ALP and 25-OH vitamin D in both the groups were in the normal range, and in comparison between groups (UC and CD), no significant differences were observed ($P = 0.20$ for ALP and $P = 0.44$ for 25-OH vitamin D). In the assessment of correlation between biochemical markers and BMD, an inverse correlation between lumbar T-score and ALP or 25-OH vitamin D only in patients with UC was observed. **Conclusions:** The high prevalence of low BMD in the Iranian population with IBD needs attention. The subclinical vitamin D deficiency may contribute to bone loss in IBD patients, which is more pronounced in patients with UC in this study because of the small population of patients with CD.

Key Words: Inflammatory bowel disease, osteopenia, osteoporosis

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There is a growing body of evidence that patients with inflammatory bowel disease (IBD) are at increased risk for osteopenia and osteoporosis. The prevalence of osteoporosis is changeable depending on the studied population and the technique of bone density measurement used.^[1] The reason for this is not clearly understood but certain factors

are related to the disease itself (intestinal inflammation, extent of lesions, disease duration), whereas others depend on the patient (nutritional status, hormonal status) or the treatment (corticosteroids or surgical resection).^[2]

Several studies have demonstrated a decrease in bone mineral density (BMD) in patients with Crohn's disease (CD), and to a lesser extent in ulcerative colitis (UC). The higher prevalence of bone disease in CD patients is thought to be related to ileal and small intestine involvement of disease causing vitamin D and calcium malabsorption, estrogen deficiency, malnutrition, and so on.^[2,3] But most recent studies found no significant differences in the prevalence of osteoporosis between patients with UC and those with CD.^[4-7]

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We have conducted a cross-sectional population-based study to assess the BMD in a group of Iranian patients with IBD in North-West region of the country, in addition to studying the possible risk factors, such as the general characteristics and serum biochemical markers to predict the low BMD.

PATIENTS AND METHODS

A cross-sectional study was conducted on 200 patients with IBD in a group of Iranian patients in East Azerbaijan province located in North-West of Iran. This region is mountainous and about 6 months of the year is cold with frequent rain and snow.

Two internal medicine residents, using a designed questionnaire from specialty and subspecialty university hospitals, outpatient clinics, and private offices, gathered the initial data retrospectively. After obtaining the basic data, the patients were called over telephone and were invited for a face-to-face interview about the current disease and the history of probable risk factors. The patients were examined. The activity and severity of diseases were evaluated based on the Truelove–Witts severity index for UC and the Harvey–Bradshaw severity index for CD to quantify disease activity.^[8,9] Some important data, such as endoscopy and biopsy results, were extracted from their documents and finally bone mineral densitometry and serum biochemical markers, such as calcium (Ca), phosphorus, alkaline phosphatase (ALP), and 25-hydroxyvitamin D (25-OH vitamin D), were checked.

BMD was assessed in all patients at the lumbar spine (L2–L4) and hip (femoral neck) using dual-energy X-ray absorptiometry with the same instrument (LUNAR DPC apparatus Madison, WI, USA) and by the same operator. In bone mineral densitometry, normal BMD is defined as T-score ≥ -1 , osteopenia is defined as T-score < -1 and > -2.5 , and osteoporosis as T-score ≤ -2.5 .^[10]

The data were analyzed using the SPSS 14 software. The quantitative data were given as mean \pm SD. The mean differences of qualitative variables and quantitative variables were evaluated using the Chi-square test and independent sample *t* test, respectively. For detection of correlation, Spearman coefficients were used. The logistic regression was used for evaluating the independent risk factors. The results were considered significant at the levels of $P \leq 0.05$.

RESULTS

Of the 200 IBD patients identified, 183 (91.5%) were identified as UC and 17 (8.5%) as CD. The mean age of the patients, in UC group was 37.16 ± 14.86 (range 13–76 years) and in CD was 34.58 ± 12.72 (range 17–69 years). In

patients with UC male to female ratio was 1.07 and in CD patients was 1.83. The other characteristics are summarized in Table 1. None of the patients reported a history or symptoms suggestive of bone fracture at baseline or during the follow-up period.

A strong and statistically significant correlation was found between T-scores for femoral neck and lumbar spine ($r = 0.62$, $P < 0.0001$). The mean \pm SD of femoral neck and lumbar spine T-scores in patients with UC were -1.14 ± 1.03 and -1.38 ± 1.29 , and in patients with CD were -1.24 ± 1.04 and -1.47 ± 1.34 , respectively ($P > 0.05$). Among these patients, 148 (74.4%) patients had low BMD at either lumbar spine or femoral neck. Of these, 100 (50.3%) had osteopenia, however, 48 (24.1%) patients were osteoporotic. BMD in the UC group compared with that of the CD

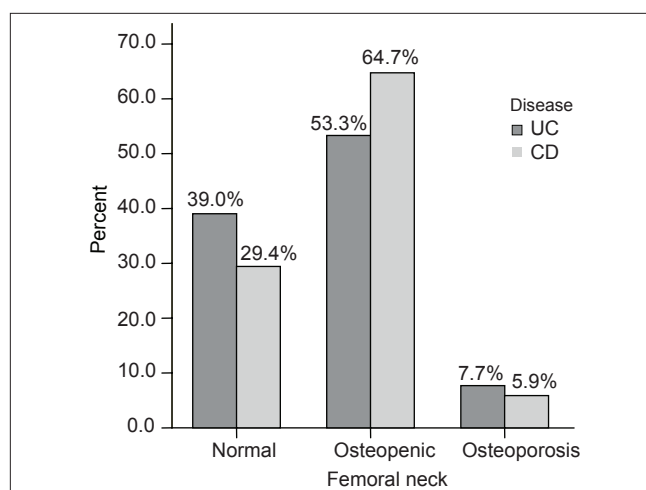


Figure 1: The comparison of bone mineral density in UC and CD based on femoral neck densitometry. Abbreviations: UC, ulcerative colitis; CD, Crohn's disease

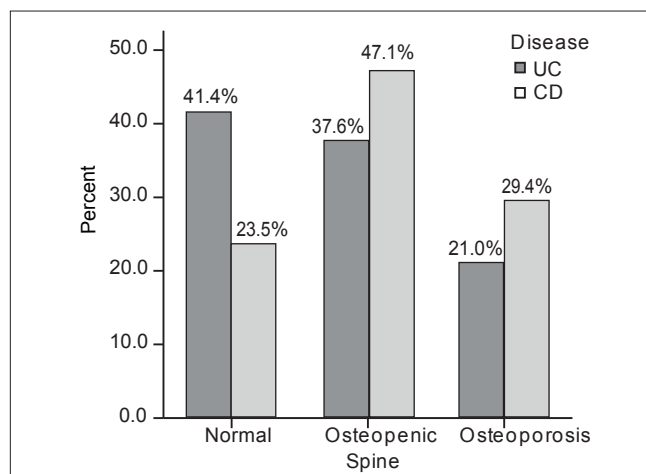


Figure 2: The comparison of bone mineral density in UC and CD based on lumbar densitometry. Abbreviations: UC, ulcerative colitis; CD, Crohn's disease

Table 1: The general characteristics of patients with ulcerative colitis compared with Crohn's disease

General characteristics	Ulcerative colitis	Crohn's disease	P value
Age (mean±SD)	37.61±14.86	34.58±12.72	0.41
Sex (%)			
Male	51.9	64.7	0.31
Female	48.1	35.3	
Duration of disease (mean±SD) years	5.39±5.51	5.82±6.92	0.80
Smoking habit (%)			
Yes	14.8	5.9	0.22
Passive smoking	10.9	23.5	
No	74.3	70.6	
Milk abstinence since diagnosis (%)			
Yes	63.2	47.1	0.19
No	36.8	52.9	
Oral contraceptive using (%)			
Yes	13.2	41.7	
No	86.8	58.3	0.009
Corticosteroid using (%)			
Yes	33.9	23.5	
≤10 mg/day*	48.4	25	0.38
>10 mg/day	51.6	75	
No	66.1	76.5	
Corticosteroid ever used (%)			
Yes	69.4	52.9	0.16
No	30.6	47.1	
Calcium and vitamin D supplementation (%)			
Yes	15.5	18.8	0.73
No	84.5	81.3	
Menopausal females (%)	18.8	0	0.34
Site of the disease (%)	Proctitis	Ileal	—
	27.7	20	
	Left-sided	Ileocolonic	
	54.2	33.3	
	Extensive	Colonic	
	18.1	46.7	
		Isolated upper disease	
		0	
Activity of disease (%)			
Active	34.3	43.8	
Remission	65.7	56.2	—
Severity of disease (%) ^(11,12)			
Mild	7.4	37.5	—
Moderate	16	18.8	
Severe	76.6	43.8	
Calcium (mg/dL) (Normal range: 8.6–10.3 mg/dL)	10.02	9.67	0.83
Phosphorus (mg/dL) (Normal range: 2.6–4.5 mg/dL)	3.92	3.89	0.84
Alkaline phosphatase (Normal range: 64–306 IU/L)	246.88	185.99	0.20
25-OH vitamin D (Normal range: 9.2–52 ng/mL)	15.41	12.78	0.44

*Adjusted based on the prednisolone dose

group is shown in Figures 1 and 2 separately for femoral neck and lumbar spine. As shown in these figures, based on lumbar densitometry, the percentage of osteopenia and osteoporosis in CD was higher than UC but based on femoral neck, the rate of osteoporosis in patients with CD

was a little lower than that in patients with UC. However, there was no significant difference between the presence of low BMD and the type of disease separately in each level of densitometry ($P = 0.44$ for femoral neck and $P = 0.53$ for lumbar spine).

In UC patients, 76.9% with severe activity, 75% with moderate activity, and 73.7% with mild activity had a low BMD ($P = 0.96$). In CD patients, 85.7% with moderate-to-severe activity and 70% with mild activity had a low BMD ($P = 0.45$). Despite the high prevalence of low BMD in these patients, there was no significant difference between the severity of these diseases and BMD status.

In the primary evaluation we found no differences between the mean age of the males and females ($P = 0.88$) and the mean age of males was lower than females among osteoporotic patients [Table 2]. Considering these, we observed that most of the patients among low-BMD patients were male (53.5% male vs 46.5% female) and most of the normal BMD patients were female (39.5% male vs 60.5% female) ($P = 0.04$).

The prevalence of osteoporosis among menopausal females was 50% compared with 9.9% among nonmenopausal females, and normal BMD was seen among 11.1% of menopausal females versus 29.6% in nonmenopausal women ($P < 0.0001$).

A total of 75.2% of patients who used corticosteroids were either osteopenic or osteoporotic, similar to patients without a history of corticosteroid use (76.2%; $P = 0.87$).

In spite of the extended duration of disease in osteoporotic and osteopenic IBD patients in comparison with normal BMD patients (5.71 vs 4.94 years), it did not have any significant difference ($P = 0.36$). In UC patients, based on the location of involvement we found that in patients with low BMD, 24.6%, 56%, and 19.4% were with proctitis, left side colitis, and pancolitis respectively, compared with patients with normal BMD (37.2%, 48.8%, and 14.0%, respectively) without significant differences ($P = 0.25$). The above analysis was performed for CD patients as well. In low BMD patients, 53.8% of patients had ileal involvement (ileum and ileocolon) and 46.2% had only colon involvement.

In normal BMD patients, ileal involvement and only colon involvement had a similar frequency (50%) ($P = 1.00$). In addition, the status of the BMD was not affected by the type of the disease-UC or CD ($P = 0.92$).

We measured some biochemical markers, such as calcium (Ca), phosphorus, alkaline phosphatase (ALP), and 25-hydroxyvitamin D (25-OH vitamin D), in both the groups of patients, and the mean levels are summarized in Table 1. In logistic regression analysis for evaluating the independent risk factors, we found that only age was most the predictive factor for low BMD ($P = 0.01$).

In the assessment of correlation between biochemical markers and BMD [Table 3], we found an inverse correlation between lumbar and femoral T-scores and ALP or 25-OH vitamin D only in patients with UC.

DISCUSSION

This study is one of the largest on a group of Iranian population with IBD who live in a mountainous region comprising mostly ethnic Azeri tribes. The prevalence of CD compared with UC is low in this region of Iran. We showed a high prevalence of low BMD in patients with IBD, independent of the type of disease (CD or UC). Generally (based on femoral neck and/or lumbar spine T-scores), we found a high prevalence of low BMD in our patients, which is one of the highest prevalence rates among previously published articles. The prevalence of low BMD has been reported in the range of 22–77% in some earlier studies.^[13-18]

Some other factors, such as sample size, using different techniques to measure BMD, and the use of Z-score instead of T-score contributed to these differences between previous studies. In a study from this country with 165 IBD patients performed in the capital city of Iran with different geography and ethnicity, the prevalence of osteopenia and osteoporosis was reported to be 26.7% and 5.4%, respectively, which is

Table 2: The age (mean±SD) and duration of disease in normal, osteopenic, and osteoporotic inflammatory bowel disease patients by gender

BMD status	All patients	Males	Females	P value (males and females)
Normal BMD				
Age (mean±SD)	33.55±9.74	34.64±9.92	32.84±9.75	0.56
Duration of disease (years)	4.97±5.24	3.47±3.12	5.96±6.12	0.13
Osteopenic BMD				
Age (mean±SD)	36.80±14.31	36.84±15.33	36.76±13.41	0.97
Duration of disease (years)	5.06±4.95	5.32±5.07	4.82±4.88	0.60
Osteoporotic BMD				
Age (mean±SD)	42.00±17.96	39.22±16.77	47.05±19.45	0.15
Duration of disease (years)	5.95±5.08	5.80±5.36	6.23±5.21	0.78

BMD: Bone mineral density

Table 3: The Spearman correlation coefficient and P value between biochemical markers and bone mineral density

Biochemical markers	Ulcerative colitis		Crohn's disease	
	Femoral T-score	Lumbar T-score	Femoral T-score	Lumbar T-score
Calcium	$r = 0.04$ $P = 0.55$	$r = 0.09$ $P = 0.20$	$r = -0.14$ $P = 0.58$	$r = 0.04$ $P = 0.85$
Phosphor	$r = -0.09$ $P = 0.19$	$r = -0.07$ $P = 0.32$	$r = 0.03$ $P = 0.88$	$r = 0.05$ $P = 0.83$
Alkaline phosphatase	$r = -0.18^*$ $P = 0.01$	$r = -0.14^{**}$ $P = 0.04$	$r = -0.10$ $P = 0.68$	$r = -0.19$ $P = 0.44$
25-OH vitamin D	$r = -0.18^*$ $P = 0.01$	$r = -0.20^{**}$ $P = 0.005$	$r = -0.13$ $P = 0.59$	$r = -0.31$ $P = 0.21$

*Correlation is significant at the 0.01 level (2-tailed). **Correlation is significant at the 0.05 level (2-tailed)

within the range of the western societies.^[19] Unpublished data from our region in healthy subjects of 20–69 years of age illustrated that 29.8% of all cases in lumbar spine and 28.4% in femoral neck had osteopenia and 13.1% in the lumbar spine and 6.81% in the neck of femur had osteoporosis. In a study by Larijani *et al.*, the corresponding percentages from the capital city of Iran for osteopenic healthy subjects was comparable to the results of this region to some extent, but the rate of osteoporosis in healthy subjects in our region was nearly 2–3 times higher than in Larijani *et al.*'s study population.^[20] This dissimilarity may suggest that the geographic and ethnic variation is likely to play an important role in the pathogenesis of low BMD in people in this area, especially in IBD patients who are susceptible to decrease in the BMD. On the other hand, metabolic bone disease is highly prevalent in the general population, especially in this area, and therefore to understand whether the IBD patients really are a risk group, a control group of healthy subjects from the same population should be included. Therefore, we recommend another comparative study between this population and healthy subjects with similar age and sex distribution.

In our study, we found that there was no significant difference between the presence of low BMD and type of disease separately in each level of densitometry, although the percentage of low BMD in patients with CD was higher than those with UC (75% vs 60%). The differences do not reach statistical significance probably due to small number of patients with CD in this region.

With regard to gender, BMD in healthy subjects, osteoporosis and osteoporosis-related fractures are usually considered for postmenopausal or elderly women,^[21,22] but these problems

also occur in men.

In this study, interestingly, we noticed the high prevalence of low BMD in male patients as compared with females despite the higher mean age of the women and long duration of disease in osteoporotic females rather than the same age males [Table 2]. In agreement with some studies by Jahnsen *et al.* and Robinson *et al.*, in the 2 patient groups studied (CD and UC), men had lower BMD than women.^[2,3] Ardizzone *et al.* found a significantly lower T-score in men than in women with UC but not in those with CD.^[16] Several risk factors for osteoporosis in men are the use of glucocorticoid for longer than 6 months, a history of nontraumatic fracture, hypogonadism, alcohol abuse, smoking, gastrointestinal disease, inactive lifestyle, and advancing age. In all societies, especially in our country, tobacco use is more prevalent in men than in women. Tobacco-related bone loss is linked to the duration of smoking and quantity. In addition, decreased body weight, low calcium absorption, decreased testosterone levels in combination with smoking cause males to be more osteoporotic than females.^[23,24] These results emphasize the importance of including men as well as women with IBD in screening programs for bone loss and in future pharmacologic trials for the prevention and treatment of osteoporosis.

In association with corticosteroid, the mechanism of bone loss is well known. It has been revealed that corticosteroid may suppress sex hormone secretion, and subsequently by the removal of the inhibitory effects of estrogen and testosterone on interleukin-6 (IL-6), which is known to stimulate osteoclast activity, has contributed to decreased BMD.^[25] Despite this, prior investigators have speculated controversies regarding the features of low BMD and corticosteroid use in IBD patients. In some of these studies, corticosteroid therapy appeared as the main osteopenic factor,^[16,19,26] whereas in others, such as in the present study, low BMD was found in the absence of past or present steroid treatment,^[27–29] although very low T-scores were most often observed in patients receiving high lifetime corticosteroid doses.^[23,30] Moreover, in another study by Jahnsen *et al.*, adverse but significant correlation was observed between corticosteroid and BMD only in patients with CD and this pattern was not found in patients with UC.^[3] This dissimilarity between different studies might be due to sample size, duration of the disease, or duration of corticosteroid therapy, and the accumulative doses of corticosteroid. Therefore, the resolution of existing controversies will require large follow-up studies.

On the basis of some studies,^[18,19,27] we found that the duration of the inflammatory process had no significant influence on BMD in all the patients. Despite this, Pollak *et al.* reported an inverse but significant correlation between the duration of disease and BMD.^[17] However, longer

disease duration may not necessarily reflect severe disease, as patients have variable disease activity and severity despite a long history of IBD. Habetzion *et al.* described that the difference in the literature may be related to the lack of age adjustment, since age is the single most important predictor of bone loss.^[27]

With regard to bone metabolism, it has been suggested that malabsorption and vitamin D deficiency, which accompanied by a high inflammatory activity induces bone degradation, and treatment with corticosteroids could be an important determinant of bone loss in IBD patients.^[11,15,16,19] This assumption was not supported by some other studies.^[12,18,21] In this study, we found that the 25-OH vitamin D levels in both the groups were in normal range but in lower limits. On the other hand, an inverse but significant correlation was found between serum levels of ALP and 25-OH vitamin D with femoral neck and lumbar BMD.

In conclusion, the subclinical vitamin D deficiency may contribute to bone loss in IBD patients, which is more pronounced for UC patients; this may be due to the small population of CD patients. Vitamin D deficiency is of real health concern in IBD patients. Screening of these patients regularly and supplementation with vitamin D and/or Ca could prevent osteoporotic process and its complications.

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