Original Article

Frequency of Low Bone Mineral Density in Saudi Patients with Inflammatory Bowel Disease

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ABSTRACT

Background/Aims: Metabolic bone disease is common in patients with inflammatory bowel disease (IBD). Our aim was to determine the frequency of bone loss among Saudi patients with IBD and possible contributing risk factors. **Settings and Design:** We retrospectively reviewed Saudi patients with IBD, between 18 and 70 years of age, who had bone mass density (BMD) determined by dual-energy X-ray absorptiometry scanning at one of three hospitals in the Kingdom of Saudi Arabia from 2001 to 2008. **Patients and Methods:** Case notes and BMDs results were carefully reviewed for demographic and clinical data. Low bone mass, osteopenia, and osteoporosis were defined according to the WHO guidelines. **Statistical Analysis Used:** Predictive factors for BMD were analyzed using group comparisons and stepwise regression analyses. **Results:** Ninety-five patients were included; 46% had Crohn's disease (CD) and 54% had ulcerative colitis (UC). The average age was 30.9±11.6 years. Using T-scores, the frequency of osteopenia was 44.2%, and the frequency of osteoporosis was 30.5% at both lumbar spine and proximal femur. Only 25.3% of patients exhibited a BMD within the normal range. Our results revealed a positive correlation between the Z-score in both the lumbar spine and the proximal femur and body mass index (BMI) (P=0.042 and P=0.018, respectively). On regression analysis BMI, age, and calcium supplementation were found to be the most important independent predictors of BMD. **Conclusions:** Saudi patients with IBD are at an increased risk of low BMD and the frequency of decreased BMD in Saudi patients with CD and UC were similar. BMI and age were the most important independent predictors of low BMD.

Key Words: Bone mineral density, inflammatory bowel disease, osteopenia, osteoporosis, Saudi

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Metabolic bone disease, including osteomalacia, osteopenia, and osteoporosis, is common in patients with inflammatory bowel disease (IBD) and has been considered to be an extraintestinal manifestation.[1] With the advent of dual-energy X-ray absorptiometry (DXA) scanning, it has become possible to quantify bone mineral density (BMD) easily and noninvasively. BMD is measured as the number of grams of bone mineral per square centimeter (g/cm^2) and is usually expressed as the number of standard deviations (SD) above or below the mean of the adult population at the age of peak bone mass (the T-score) or the mean of age- and sex-matched healthy controls (the Z-score).[2,3] BMD is considered a major determinant of bone strength and is the strongest predictor of fracture risk.[4,5] Patients with IBD have a high prevalence of decreased bone mass and an increased frequency of osteoporotic fractures compared to healthy subjects.[6,7] The estimated prevalence of low BMD among patients with IBD varies greatly between studies, depending on the population studied, the study design, the measurement site, and the definition used. In uncontrolled clinical studies, osteopenia has been documented in up to 77% of IBD patients, and osteoporosis has been reported in as many as 48% of patients with IBD.[8,9] Some studies have indicated that Crohn's disease (CD) and ulcerative colitis (UC) carry similar risks for osteoporosis and fragility fractures.[8,10]

The exact pathogenesis underlying this effect is not clearly understood, but it is likely to be multifactorial and includes general risk factors for osteoporosis. In addition, disease-

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specific risk factors related to cumulative corticosteroid therapy[11] and disturbances of calcium homeostasis, including malabsorption and vitamin D deficiency, are thought to contribute to altered bone mass.[12,13] Age, gender, smoking, reduced body weight or low body mass index (BMI),[14,15] ileal resection and disease duration[16] are also considered potential contributory factors. Moreover, the inflammatory process may also negatively influence bone metabolic activity by releasing cytokines that interact with bone metabolism.[17,18]

The prevalence of IBD in Saudi Arabia has increased over the past few decades.[19,20] Thus, there is a growing need to increase awareness of IBD-associated osteopenia and osteoporosis among physicians, particularly gastroenterologists. To our knowledge, no studies have been conducted to assess the frequency of low bone mass in Saudi patients with IBD. The aim of this cross-sectional study was to determine the frequency of low BMD in adult Saudi patients with IBD and to assess possible contributing factors to bone loss.

PATIENTS AND METHODS

Study design and patients

We retrospectively reviewed Saudi patients with IBD, between 18 and 70 years of age, who had BMD measured at one of three hospitals in the Kingdom of Saudi Arabia from 2001 to 2008. The three hospitals that participated in this study were King Fahd Hospital of the University in Al Khobar, King Fahd Specialist Hospital in Dammam and King Khalid University Hospital in Riyadh.

Our study selected patients with IBD in whom BMD was determined by DXA scanning. The diagnosis of IBD (either CD or UC) was confirmed based on clinical, endoscopic, radiologic, and/or histopathologic biopsy.[21] Their demographic and clinical data were obtained by careful review of their hospital charts and electronic records. Each patient's age, gender, menopausal status, smoking history, disease duration, prior surgery, past history and duration of corticosteroid use, use of other medications, calcium and vitamin D supplementation, and past history of bone fractures were documented on a data extraction sheet. Height and weight were measured, and BMI was calculated as weight/height^2 (kg/m^2). The serum levels of calcium, phosphorus, and hemoglobin were also documented. Patients with malignancy and renal or hepatic failure and patients known to have other secondary causes of osteoporosis were excluded.

Bone mineral density measurement

The BMD (g/cm^2) of the anterior–posterior lumbar L2–L4 vertebrae and the proximal femur was determined using a standard DXA analysis (DXA, Hologic QDR 4500, Waltham, MA) at the radiology department of each hospital and were reviewed by a single radiologist (F.M.) who was blind to the patients' diagnosis and clinical data. Bone mass was determined according to the WHO guidelines. Osteopenia was defined as a T-score between -1 and -2.5 SD below the mean value for the young adult population, and osteoporosis was defined as a T-score greater than 2.5 SD below the population mean.[4] Because the majority of our patients were young and because we included male subjects, we also used Z-scores in our analysis. Normal bone mass was defined as a Z-score greater than -2 SD below the mean, and low bone mass was defined as a Z-score less than -2 SD below the mean at the lumbar spine or femoral neck.[22] Both lumbar and proximal femur T-scores and Z-scores were calculated using validated manufacturers' reference ranges.

Ethical considerations

This study was approved by the research and ethics committee at the University of Dammam and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Statistical analysis

The results are presented as the mean±SD. Student's unpaired *t* tests were used when appropriate. When variances were unequal or the distribution was not normal, the Mann–Whitney *U* test was performed. Frequencies were compared using the Chi-squared test or Fisher's exact test. Pearson's correlation coefficients were calculated for continuous variables. Stepwise regression analysis was performed to determine the independent risk factors for low BMD. Two-tailed values for significance were used in all statistical tests, and significance was defined as $P<0.05$. Statistical analyses were performed using SPSS statistical package, versions 16 (SPSS Inc., Chicago, IL).

RESULTS

Baseline clinical and laboratory characteristics

A total of 95 Saudi patients with IBD (44 with CD and 51 with UC) were identified, and the mean age was 30.9±11.6 years. The sample consisted of 39 males and 56 females. The baseline clinical characteristics and laboratory data are shown in Table 1. Compared to patients with CD, patients with UC were significantly older ($P=0.001$), exhibited longer disease duration ($P=0.008$) and had significantly higher BMI values ($P=0.048$). There were no significant differences in gender distribution between the two diseases. Three women in the UC group and none of the women in the CD group were postmenopausal. A majority of our CD patients had Ileocolonic disease (43%) and the remaining had ileal or colonic diseases (32% and 25%, respectively). Patients with UC had Pancolitis, left-sided disease, or Proctitis in 53%, 35%, and 15% respectively. Smokers represented 7.8% of the UC patients ($n=4$) and 11.4% of the patients with

Table 1: Baseline characteristics of patients with inflammatory bowel disease

Variable	CD (*n*=44)	UC (*n*=51)	IBD (*n*=95)
Age (years)	26.0±7.8	35.2±12.7	30.9±11.6
Gender (m/f)	16/28	23/28	39/56
Height (cm)	160.0±7.7	160.7±9.2	160.4±8.5
Weight (kg)	55.9±17.2	63.9±19.4	60.2±18.8
BMI (kg/m^2)	21.8±6.4	24.6±7.1	23.3±6.9
Duration of disease (years)	4.6±3.0	7.1±5.1	5.9±4.4
History of fracture (y/n)	0/44	3/48	3/92
Steroid use for >3 months (y/n)	42/2	48/3	90/5
History of bowel resection (y/n)	9/35	1/50	10/85
Smoking (y/n)	5/38	4/47	9/85
Arthritis (y/n)	4/40	3/48	7/88
Vitamin D supplementation (y/n)	33/9	43/4	76/13*
Calcium supplementation (y/n)	36/7	44/3	80/10**
Azathioprine (y/n)	29/14	22/25	51/39**
5 ASA (y/n)	5/38	9/38	14/76**
Biologic therapy (y/n)	14/29	6/41	20/70**
Bisphosphonates use (y/n)	5/38	9/38	14/76**
Calcium (NL 8.5–10.5 mg/dL)	8.5±0.5	8.8±0.4	8.7±0.5
Phosphorous (NL 2.5–4.9 mg/dL)	3.4±0.9	3.4±0.7	3.4±0.8

ASA: Aminosalicylic acid, CD: Crohn's disease, IBD: Inflammatory bowel disease, UC: Ulcerative colitis, *Data available for 89 patients only, **Data available for 90 patients only

CD (*n*=5). The frequency of bowel resection was found to be higher among patients with CD than among UC patients (11.8% and 2%, respectively). However, among CD and UC patients who had used corticosteroids for at least 3 months were quite similar (95.5% and 94.1%, respectively). None of the patients with CD had a previous history of bone fracture, but 3 of the 51 patients with UC had previously broken a bone. The mean serum levels of calcium and phosphorus were within the normal range for both disease groups.

Bone mineral density measurement

The frequency of low bone mass (defined as a Z-score less than -2 SD) was 39.4% for all IBD patients (37.2% for CD patients and 41.2% for UC patients), and no significant differences were observed between the two groups (*P*=0.695). Low bone mass was more prevalent in the lumbar spine than in the proximal femur [36.5% vs 19.4%, Table 2].

Table 2: Frequency of low bone mineral in patients with inflammatory bowel disease

Site	Prevalence of low bone mineral density (%) (95% CI)			*P* value*
	CD	UC	IBD	
Z-score				
L1-L4	35.7 (20.6–50.1)	37.3 (23.5–50.1)	36.5 (26.6–46.5)	0.878
Proximal femur	21.2 (06.5–35.9)	17.9 (05.3–30.6)	19.4 (10.1–28.8)	0.727
Combined¥	37.2 (22.1–52.3)	41.2 (27.2–55.2)	39.4 (29.3–49.4)	0.695

¥Presence of low bone mass density in either site, **P* value denotes differences between patients with Crohn's disease and ulcerative colitis

Table 3: Frequency of osteopenia and osteoporosis at different sites, based on T-scores (%) (95% CI)

Site	CD	UC	IBD	*P* value*
Prevalence of osteopenia				
L1–L4	41.9 (26.5–57.2)	41.2 (27.2–55.2)	41.5 (31.3–51.6)	0.947
Proximal femur	48.6 (31.2–66.0)	55.8 (40.4–71.3)	52.6 (41.2–63.9)	0.524
Prevalence of osteoporosis				
L1–L4	32.6 (18.0–47.2)	27.5 (14.8–40.0)	29.8 (20.4–39.2)	0.590
Proximal femur	14.3 (02.1–26.5)	11.6 (01.7–21.6)	12.8 (05.2–20.4)	0.746

CD: Crohn's disease, IBD: Inflammatory bowel disease, UC: Ulcerative colitis, **P* value denotes differences between patients with Crohn's disease and ulcerative colitis (Chi-squared or Fisher's exact test was used)

Based on the WHO definition and T-scores, the frequency of osteopenia among the IBD patients was 41.5% at the level of the lumbar spine and 52.6% at the level of the proximal femur, with no significant difference between CD and UC patients [Table 3]. Additionally, the frequency of osteoporosis did not differ between patients with CD and patients with UC, but it was higher at the level of lumbar spine than the proximal femur (29.8% vs 12.8%). The frequencies of osteopenia and osteoporosis of both the lumbar spine and the proximal femur among all IBD patients were 44.2% and 30.5%, respectively. Only 25.3% of patients exhibited a BMD within the normal range. The two disease groups (CD and UC) did not differ significantly in terms of the mean Z- and T-scores obtained from various measurement sites at the level of the lumbar spine and proximal femur [Table 4].

Correlation and predictive factors for low bone mineral density

Pearson correlation coefficient between BMD and age, BMI, duration of disease, calcium and phosphorus level

were determined to identify predictive factors of low BMD. Results are summarized in Table 5. BMI correlated positively with both the Z-score and the T-score at both skeletal sites examined; however, the most significant correlation between BMI and T-scores was observed at the proximal femur. Although we did not observe a significant correlation between serum levels of calcium and Z- or T-scores, serum levels of phosphorus were shown to correlate positively with T-scores for the lumbar spine. Age and duration of disease did not reach statistical significance when correlated with BMD. The same happened for gender, steroid use, history of prior surgery, history of fracture, or the use of other medications. On the other hand, supplementation with both calcium and vitamin D was shown to exhibit significant negative correlation with Z- and T-scores at the lumbar spine and the proximal femur. The correlations between patients' baseline characteristics and their corresponding Z-scores or T-scores are shown in Table 6.

When stepwise logistic regression analysis was performed, BMI and calcium supplementation were found to be independent predictors of the lumbar spine (L1–L4) Z-score (P=0.042 and P=0.001, respectively, r^2=0.186) and T-score (P=0.014 and P<0.001, respectively, r^2=0.201). BMI alone was also found to be predictive at the proximal femur (P=0.018, r^2=0.087). Finally, both BMI and age were revealed to be independent predictors of the T-score at the proximal femur (P=0.007 and P<0.001, respectively, r^2=0.223).

Table 4: Bone mineral density measurement (mean±SD) in patients with inflammatory bowel disease

Site	CD	UC	IBD	*P* value*
Z-score				
L1–L4	–1.48±1.67	–1.31±1.76	–1.38±1.71	0.717
Proximal femur	–1.06±1.33	–0.84±1.36	–0.94±1.34	0.556
T-Score				
L1–L4	–1.74±1.68	–1.53±1.92	–1.63±1.81	0.685
Proximal femur	–1.31±1.26	–1.24±1.39	–1.27±1.33	0.864

**P* value denotes differences between patients with CD and UC, CD, Crohn's disease, IBD: Inflammatory bowel disease, UC: Ulcerative colitis

Table 5: Pearson's correlation coefficient for IBD patients, comparing clinical characteristics and biochemical markers with baseline Z-scores and T-scores of the lumbar spine and proximal femur

Characteristics	Z-score		T-score	
	L1–L4	Proximal femur	L1–L4	Proximal femur
Age (years)	0.122	-0.078	0.088	-0.122
BMI (kg/m^2)	0.221*	0.274*	0.263*	0.363**
Duration of diagnosis (years)	-0.024	-0.092	-0.029	-0.079
Calcium (mg/dL)	0.146	-0.035	0.100	-0.080
Phosphorous (mg/dL)	-0.193	-0.136	-0.227*	-0.209

*Correlation was significant at the 0.05 levels (two-tailed), **Correlation was significant at the 0.01 levels (two-tailed), BMI: Body mass index, IBD: Inflammatory bowel disease

DISCUSSION

Altered BMD is a common problem for individuals with gastrointestinal diseases, such as chronic liver disease, pancreatic diseases, celiac disease, and inflammatory bowel disease.[23] Our study confirmed an overall high frequency of reduced BMD among Saudi patients with IBD and based on T-scores, only one quarter of our patients had normal BMD. Unfortunately, we could not find similar local studies with which to compare our results. The frequency of low bone mass and osteoporosis in this study was much higher than the prevalence reported in a systematic review of the literature on osteoporosis in gastrointestinal diseases conducted by the American Gastroenterological Association using pooled data of patients with CD and UC. The systematic review found a low bone mass prevalence of 6% in the lumbar spine and 13% in the hip, as well as an osteoporosis prevalence of 14% in the lumbar spine and 16% in the hip.[24] The frequency reported in the current study was also higher than the recently reported prevalence in comparably aged Asian patients.[25,26] However, our results are similar to recent reports regarding the prevalence of BMD in IBD patients in Egypt and the United States.[27,28]

In contrast to several studies,[8,9] we found a higher frequency of low bone mass in the lumbar spine than in the femoral region. However, our data are in agreement with other reports that have also demonstrated a higher prevalence of decreased BMD in the lumbar spine.[25,27,28] This pattern of increased loss of trabecular bone compared with cortical bone was also seen in postmenopausal and steroid-induced bone disease.[29,30] Most of the patients in our study were young (a mean age of 30.9±11.6 years), and only 3 of the 56 female patients were postmenopausal. However, 95.5% of the CD patients and 94.1% of the UC patients had used glucocorticoids for more than 3 months, a fact that may have contributed to the bone loss patterns observed in our patients.

Several studies have reported a trend toward lower BMD in patients with CD when compared with UC patients in both the hip and the lumbar spine,[26,31-34] the hip region alone[24] or the lumbar spine alone.[8] The higher prevalence of bone disease in CD is thought to result from ileal and small intestinal involvement, ileal resection, hepatobiliary complications, and the use of cholestyramine, which can lead to vitamin D deficiency, calcium malabsorption, or malnutrition.[35] Our study, similar to others,[8,10,36] failed to demonstrate a difference in the frequency of bone loss between the CD and UC patients.

Table 6: Comparison of Z-scores and T-scores at the spine (L1–L4) and proximal femur, based on various factors

Characteristics	Z-score		T-score	
	L1–L4	Proximal femur	L1–L4	Proximal femur
Gender				
Male	–1.44±1.98	–0.85±1.26	–1.69±2.09	–1.23±1.27
Female[1]	–1.34±1.52	–1.00±1.40	–1.58±1.60	–1.31±1.38
History of fracture				
Present	–2.60±1.51	–1.40±0.92	–3.67±1.75	–2.47±1.70
Absent[1]	–1.34±1.71	–0.92±1.36	–1.56±1.78	–1.23±1.30
Steroid use				
Present	–1.37±1.73	–0.89±1.35	–1.62±1.83	–1.24±1.35
Absent[1]	–1.58±1.44	–2.07±0.46	–1.76±1.47	–1.97±0.46
Vitamin D supplementation				
Present	–1.59±1.54*	–1.04±1.32	–1.85±1.66*	–1.39±1.29
Absent[1]	–0.22±2.40	–0.75±1.43	–0.38±2.41	–1.02±1.44
Calcium supplementation				
Present	–1.62±1.53*	–1.10±1.30*	–1.88±1.64*	–1.43±1.27*
Absent[1]	0.43±2.28	0.06±1.15	0.27±2.28	–0.24±1.19
Azathioprine use				
Present	–1.13±2.02	–0.97±1.40	–1.42±2.12	–1.35±1.30
Absent[1]	–1.71±1.27	–1.07±1.25	–1.92±1.38	–1.34±1.30
History of prior surgery				
Present	–1.55±1.71	–1.45±1.73	–1.73±1.80	–1.71±1.49
Absent[1]	–1.36±1.72	–0.89±1.31	–1.62±1.82	–1.23±1.31
5-ASA				
Present	–1.6±1.39	–0.93±0.98	–1.91±1.55	–1.36±1.15
Absent[1]	–1.35±1.8	–1.04±1.39	–1.59±1.89	–1.35±1.33

[1]Reference category, *Significant at the 0.05 levels (two-tailed)

The clinical importance of altered BMD relates mainly to fragility fractures and subsequent morbidity and mortality. Several population-based studies have reported increased osteoporotic fractures in patients with IBD.[37,38] Only 3 of our patients (3.2%, all from the UC group) reported a fracture in their medical history. This result may be partially explained by the fact that this retrospective study used hospital notes that typically only report major fractures, such as hip and symptomatic spinal fractures. The low BMD and increased risk of bone fracture in patients with IBD likely result from a combination of multiple pathogenic factors. The most widely reported correlation was corticosteroids therapy in patients with IBD.[39] Our study failed to demonstrate the role of steroids in bone loss, probably due to insufficient statistical power. It is noteworthy however that, other studies have noted the absence of this association.[8,40-42] The high percentage of steroid use among our patients may have reflected high disease activity, but we were unable to conclusively establish the activity index because of the retrospective nature of this study.

Similar to other studies, regression analyses of our data revealed BMI as an important risk factor affecting BMD changes in both CD and UC groups. Noble *et al*.[43] found BMI to be the strongest independent risk factor associated with osteoporosis. Calcium and phosphorus levels were within the normal range for most of our patients; however, we were not able to evaluate vitamin D status and parathyroid hormone (PTH) levels because these tests are not typically performed on IBD patients at our hospitals. Our study revealed a significant, negative correlation between both calcium and vitamin D supplementation and Z- and T-scores in the lumbar spine and proximal femur. In addition, calcium and vitamin D supplementation was revealed to be an independent predictor of T-scores and Z-scores in the lumbar spine. Malabsorption of calcium and vitamin D, which can be accompanied by a compensatory increase in PTH levels, can lead to reduced bone formation, which has been suggested to be an important determinant of BMD among patients with IBD.[44] Because osteoporosis and osteomalacia are indistinguishable using BMD measurements, the lack of information regarding vitamin D status is one of the limitations of our study. Other limitations include the retrospective, cross-sectional nature of the study and the examination of patients from specialty gastroenterology clinics, which may have led to selection bias and a consequent overestimation of the frequency of bone loss. Also, the timing of DXA scanning

in relation to the time of diagnosis was not known. Despite these limitations, to our knowledge, this is the first study assessing the frequency and risk factors of altered BMD among Saudi patients with IBD.

In conclusion, Saudi patients with IBD demonstrated a high risk of low BMD and this risk was related to BMI and age but was independent of steroid use and type of IBD. It is necessary to take into account the risk of decreased BMD in all patients with IBD but because of our small sample size, a well-controlled large nationwide study is needed to confirm our findings.

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