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Original Article

A Case-Control Study on Risk Factors of Osteoporosis in Patients with Crohn's Disease

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Background: Osteoporosis has been frequently reported in patients with inflammatory bowel diseases, especially Crohn's disease.

Methods: All consecutive Crohn's disease patients who attended the GI Clinics at Shariati Hospital, Tehran, Iran, from 2004 to 2007 were evaluated. A BMD-DEXA assessment was performed for all patients. Among those patients diagnosed with osteoporosis (T score ≤ -2.5 SD), 30 patients were chosen as study cases. Of those who were not diagnosed with osteoporosis, 85 were chosen as the control group. A thorough patient history including: age, sex, body mass index, cumulative corticosteroid dose, previous fracture, history of bowel resection, site and duration of disease, smoking and consumption of calcium and vitamin D, was taken from all patients through a face-to-face interview. Independent sample Student's *t*-test, Chi-square, and logistic regression analyses were used for data analysis.

Results: In this study, a multivariable modeling technique revealed a higher osteoporosis risk in those who had a lower body mass index, previous fractures and longer disease duration. A cumulative corticosteroid dose of 10 – 35 g provided the highest osteoporosis risk. Age, sex, bowel resection, site of disease, smoking and consumption of calcium and vitamin D did not show any relationship with osteoporosis.

Conclusion: The highest osteoporosis risk was seen in patients with a cumulative 10 – 35 g corticosteroid dose and could be due to both steroid inefficiency in reducing Crohn's disease inflammation as well as the cumulative drug dose and it's adverse effect on patients.

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Introduction

Patients with inflammatory bowel disease (IBD), especially Crohn`s disease (CD), are at increased risk of developing osteoporosis which is reported in 30 – 40% of CD patients.[1,2] Depending on the population studied the prevalence of osteoporosis has been reported to range from 12% to 42% in patients with IBD.[3]

It has been suggested that the pathogenesis of osteoporosis in patients with CD is multifactorial. Disease activity and duration[2,4,5] low body weight or body mass index (BMI)[5,6] calcium and vitamin D deficiency[5] small bowel involvement or resection,[6] gender, increasing age[7] immobilization and life style risk factors (e.g. smoking, excessive alcohol intake, physical inactivity)[8] as well as genetic factors[2] have been implicated.

Several studies have shown a direct correlation between corticosteroids and a decrease in bone mineral density (BMD) in patients with IBD.[6–11]

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However, not all studies have demonstrated a relationship between corticosteroid use and low BMD in IBD patients.[1,12]

Corticosteroid therapy may be an independent risk factor for the development of osteoporosis in patients with CD. In one BMD study performed on CD patients; it was shown that both groups who had a low life-time corticosteroid dose therapy with or without dietary manipulation, had a similar BMD to that of age-matched normal controls. Whereas, BMD was significantly reduced in those treated predominately by corticosteroids.[13] However, it is difficult to separate the effects of corticosteroids from those of disease activity.[14] Although corticosteroids may be mechanistically responsible for bone loss, their use may also serve as a marker for more severe disease activity that is responsible for bone loss. Decreased bone mass in patients with high disease-activity IBD might result from the effects of certain inflammatory cytokines such as tumor necrosis factor, interferon and interleukin (IL-6), which are recognized to be effective in bone remodeling.[2]

In patients with CD and reduced BMD the prevalence of vertebral fractures (i.e. manifest osteoporosis) was strikingly high at 22%, even in those aged less than 30 years.[15] Previous fragility fracture is also mentioned as a risk factor for osteoporosis.[7]

Data on calcium intake as a predictor of BMD are conflicting. Although there are data suggesting that a one-time survey to determine the current calcium intake will not help to predict BMD in IBD, persistently reduced calcium intake does appear to lead to lower BMD. Although vitamin D is undoubtedly important in bone health, vitamin D intake and serum vitamin D levels do not correlate well with BMD.[16]

The multifactorial pathogenesis of bone loss in IBD makes it difficult to assess the importance of each single contributing factor. It is generally agreed that there is a need to increase awareness for IBD-associated osteoporosis. However, the best ways in which to identify at-risk patients remain to be established. The aim of this study is therefore, to determine the prevalence of osteoporosis in patients with CD and possible risk factors.

Materials and Methods

Patients

From June 2004 to March 2007, we enrolled all consecutive CD patients aged 20 – 80 years who attended one of three outpatient gastroenterology (GI) clinics at Shariati Hospital in Tehran, Iran and consented to be enrolled in the study. A BMD assessment was performed for all patients. According to their BMD-DEXA results, 30 patients amongst those with osteoporosis (T score ≤ -2.5 SD) were chosen as cases. For the control group we chose 85 patients who were not diagnosed with osteoporosis.

The diagnosis of CD was verified based on well-established clinical, endoscopic, radiological, histological and surgical criteria as described by Lennard-Jones. CD was defined as the existence of perianal disease (skin tags, abscess, and fistula), skip lesions at endoscopy, cobblestone appearance, mucosal ulceration on colonoscopy, aphtous ulceration, deep inflammation or chronic terminal ileal inflammation with or without radiological evidence of skip lesions, structuring disease, fistulizing disease, or small intestinal involvement and noncaseating granuloma.[17]

One of the criteria for excluding patients from the study was the presence of another chronic illness known to affect bone mineral status. Patients undergoing hormone replacement therapy (HRT) or any exogenous sex-hormones were also excluded.

Measurement of bone mineral density

Total BMD of the left femur (neck, inter-trochanteric area, shaft and Ward's triangle) were assessed by DXA (LUNAR Corp., Madison, WI, USA). Results were expressed in absolute values (g/cm^2) and as the number of standard deviations above or below the age- and sex-adjusted reference values of young healthy adults (T score).

According to the World Health Organization criteria, osteoporosis was defined as a T score ≤ -2.5 SD and osteopenia as a T score between -2.5 and -1 SD).[18]

All scans were performed by the same operator. The device was calibrated daily and the technical error was estimated to be less than 1%.

Clinical assessment

The following data were obtained for each patient from his/her medical records and a questionnaire: date of disease onset, duration of disease (years), site of disease (small bowel only, small bowel and colon, colon only), history of bowel resection, history of previous fractures, smoking (more than one pack/year during entire life was defined as a positive answer) and

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consumption of calcium and vitamin D. Weight and height were measured without shoes and with light indoor clothing. The BMI was calculated as weight/height^2 (kg/m^2).

All measurements were performed by a single investigator on the same scale and stadiometer. Cumulative dose of corticosteroids was obtained by multiplying all doses of corticosteroids prescribed either orally or parenterally by the total duration of disease and relative potency to hydrocortisone (CCD=Potency*Dose*Duration).[19,20]

Statistical analysis

Independent sample Student's *t*-test was used to assess statistical differences between the mean ages at the time of diagnosis in participants of the two groups. Categorical variables included age (>40, <40 years), BMI (>25, <25 kg/m^2), total duration of disease (>5, <5 years), smoking, CCD (<10, 10 – 35, >35 g), history of bowel resection, previous fracture, calcium and vitamin D supplementation, and site of disease were compared with χ^2 test between cases and controls. To determine factors predictive for osteoporosis in Crohn's patients, stepwise logistic regression analysis was performed for variables that had a *P* value of <0.2 in χ^2 test which included age, BMI, duration of disease, CCD, previous fracture history, calcium and vitamin D supplementation and performance of bowel resection as independent variables. Statistical significance was defined as a *P* value <0.05. Ninety-five percent confidence intervals (CIs) were estimated using the exact binomial distribution. Quantitative variables were presented as mean±SD. The SPSS version 13.0 (SPSS Corp., Chicago, Ill.) was used for data analysis.

Ethical considerations

All subjects gave informed consent prior to entering the study. The study protocol was approved by the Institutional Review Board, Digestive Disease Research Center, and Tehran University of Medical Sciences.

Results

A total of 115 patients with CD (60 men and 55 women) were enrolled in the study: 30 as cases (T score< -2.5 SD) and 85 as controls (T score≥ -2.5 SD). The male to female ratio was 1.3:1 in cases and 1:1 in the control group (*P*=NS). Mean±SD age at first diagnosis was 31.9±14.9 and 29.7±10.8 years in cases and controls, respectively (*P*=NS). CD was restricted to the small bowel in 11 (37%) and 21 (25%) patients in the case and control groups respectively, whereas 10 (33%) cases and 30 (35%) controls had involvement of both small bowel and colon. Nine (30%) cases and 34 (40%) controls had involvement of the colon only (*P*= NS).

Different characteristics of the variables are presented in Table 1.

Bone mineral density evaluation

BMD of the left femur was estimated. BMD (expressed as mean±SD T score) was -2.7±0.6 in cases and -0.7±0.9 in controls (*P*=0.0001). In the control group 42 (49%) patients had osteopenia (-2.5 SD ≤T score≤ -1 SD), and 43 (51%) had a normal BMD (T score> -1 SD).

Multivariate regression analysis

All independent variables with a *P* value<0.2 in the χ^2 test that included age, BMI, duration of disease, CCD, previous fracture history, calcium and vitamin D supplementation and evidence of bowel resection were tested in the model. After stepwise backward exclusion of variables with a threshold of *P*=0.05, BMI, previous fracture, duration of disease and cumulative dose of corticosteroids eventually remained in the model as significant predictors for osteoporosis (Table 2). It was shown that 10 – 35 g and >35 g CCD was associated with the highest and lowest risk of osteoporosis, respectively. None of the other variables were significant independent predictors for BMD and were therefore excluded from the model.

Discussion

Bone loss is a common problem for individuals with CD.[4,21] What is less clear, however, are the factors that result in its development. In this study multivariate modeling revealed a higher osteoporosis risk in those having lower BMI, previous fractures and longer duration of the disease. CCD of 10 – 35 g provided the highest osteoporosis risk. Age, sex, bowel resection, site of disease, smoking and consumption of calcium and vitamin D did not show any relationship with the risk of osteoporosis. However, it should be mentioned that the relationship between CD and the role of these factors are controversial.

In this study, a BMI <25 kg/m^2 was reported in

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Table 1. Summary of demographic and clinical characteristics of study patients

Variable	Case group (*n*=30)	Control group (*n*=85)
Gender (M/F)	17/13	43/42
Age [years, *n* (%)] **		
<40	15 (50)	57 (67)
≥40	15 (50)	28 (33)
BMI* [kg/m^2, *n* (%)] **		
<25	26 (87%)	60 (71%)
≥25	4 (13%)	25 (29%)
Smoking, *n* (%)	2 (7%)	9 (11)
CCD*** [g, *n* (%)] **		
<10	10 (33%)	24 (28)
10 – 35	8 (27%)	42 (49)
>35	12 (40%)	19 (22)
Bowel resection, *n* (%) **	12 (40%)	14 (17)
Previous fractures, *n* (%) **	5 (17%)	5 (6)
Intake of Ca-vitamin D, *n* (%) **	23 (77%)	46 (54)
Duration of disease [years, *n* (%)] **		
<5	11 (37%)	47 (57)
≥5	19 (63%)	35 (43)

* Body mass index;**P <0.2 for comparison of cases and controls (χ^2); ***Corticosteroid cumulative dose

86.7% of CD patients with osteoporosis, which is in agreement with previous reports, both in healthy subjects[22] and in patients with IBD.[4, 23–25]

In IBD, most studies demonstrate a negative correlation between BMD and glucocorticoid use[12,26] but not all authors agree on the relationship between long-term glucocorticoid use and continuing bone loss.[1,3,27] Whereas prospective studies do suggest sustained bone loss at both trabecular and cortical sites in long-term glucocorticoid users with IBD, a decrease in bone mass is also observed in patients with active CD who do not use glucocorticoids.[3] However, accurately predicting which corticosteroid dose will cause more clinically significant bone loss is still a question. It has been suggested that patients whose lifetime corticosteroid dose (prednisone/prednisolone) was more than 10 g had especially low bone mineral density.[11] In the present study, we have categorized CCD in three levels to define which dose would provide less clinically significant bone loss.

Regarding the decrease in prevalence of osteoporosis at a CCD> 35 g rather than the <10 g or 10 – 35 g groups, we suggest that the strong inhibitory effects of corticosteroids on inflammation may decrease the activity of the disease. The possibility that demineralization occurs in response to the intestinal inflammation itself is discussed in some studies.[1] It seems that more demineralization, which occurs in 10 – 35 g CCD, is not only due to the inefficiency of corticosteroids on reducing the inflammation of CD, but also is accompanied by the effects of

Table 2. Risk factors of osteoporosis in patients with Crohn's disease

Variables	Univariate OR (95%CI)	Multivariate OR* (95%CI)
BMI**(kg/m^2)		
≥25	1	1
<25	2.70 (0.85 – 8.56)	3.64 (1.04 – 12.75)
Previous fractures		
No	1	1
Yes	3.20 (0.85 – 11.96)	6.24 (1.31 – 29.70)
CCD*** (g)		
<10	1	1
10 – 35	1.52 (0.54 – 4.30)	1.46 (0.46 – 4.63)
>35	0.46 (0.16 – 1.31)	0.35 (0.11 – 1.10)
Duration of disease (years)		
<5	1	1
≥5	2.31(0.98 – 5.49)	2.71(1.02 – 7.19)

*Adjusted for all other variables in model (Age, CCD, duration of disease, BMI, previous fracture, Ca and vitamin D supplementation, bowel resection); **Body mass index; ***Corticosteroid cumulative dose

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accumulated corticosteroids which contribute to osteoporosis. The occurrence of osteoporosis in CCD<10 g mostly appears to be the result of uncontrolled inflammatory disease.

The other predictor for BMD in the present study was a history of previous fracture, which was in agreement with other reports that demonstrated the history of fracture in patients with IBD and their first degree relatives as one of the most important predisposing factors for osteoporosis and future fractures.[28] Here, we reported that 16.7% of cases and 5.9% of controls had a history of previous fracture. Klaus et al. reported 22% of CD patients with one or more vertebral fractures in which 35% were less than 35 years.[15]

The influence of duration of CD on BMD was determined in several longitudinal studies with conflicting results; one study showed no bone loss[12] and another reported a loss of up to 6.2%/years among steroid users.[29] In the present study, the duration of disease in 63.3% of patients with osteoporosis and 42.7% of non-osteoporotic patients was more than five years. In the study by Herzog et al.,[30] the duration of CD was an important risk factor for low BMD.

All other potential risk factors studied included age at onset of disease, sex, history of bowel resection, location of disease, non calcium-vitamin D supplementation and smoking which were non-predictive in the stepwise linear regression model.

In the studies by Silvennoinen et al.[31] and Zali et al.[24] smoking was found to be a risk factor for osteoporosis in women with IBD. In our study, no difference in BMD was found in patients who smoked and those who had never smoked. This finding was in accordance with reports by Gosh et al.[12]

A history of bowel resection, as an etiological factor in osteoporosis, was suggested by some previous reports.[7] However, our study, like some others, was unable to show any influence of bowel resection on BMD in patients with CD.[1,29]

Our study was most similar to the Siffledeen et al. study in 2004.[32] Location of disease, smoking, and age of onset were not predictive, whereas use of corticosteroids was an important risk factor.

Poor dietary intake and malabsorption of calcium and vitamin D may contribute to reduced BMD in some patients.[33] While calcium and vitamin D supplementation is recommended for the management of bone loss associated with IBD,[34] not all studies have identified vitamin D deficiency in these patients[35] or a benefit from vitamin D supplementation.[36] In our study, 76.7% of patients with osteoporosis had mentioned calcium-vitamin D supplementation. It was not determined that patients who had not received these supplements were at a higher risk for the development of osteoporosis. However, we cannot ignore the effect of a low sample size in our study on this finding.

Our study has some potential weaknesses and limitations. Our CD sample size was quite small, for which we had intended to select three matched controls. We had a lack of data for some effective factors such hormones' levels and precise information about supplementation therapy in our patients which should be considered in future studies.

In conclusion, patients with IBD are at risk for reduced BMD and the development of osteoporosis. A screening DXA to assess BMD is warranted for patients with CD and ulcerative colitis who are postmenopausal, have had vertebral fractures, or have been on prolonged corticosteroids. Further studies with larger sample sizes are required to determine predictive factors and the utility of prophylactically initiating medicines for all IBD patients who are starting corticosteroids for the first time.

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