# Correlation Between Low Bone Density and Disease Activity in Patients with Ulcerative Colitis

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## ABSTRACT

### BACKGROUND

Different clinical and epidemiological studies using dual-energy X-ray absorptiometry have shown an increased prevalence of low bone mineral density in patients with inflammatory bowel diseases. The aim of this study was to assess the correlation between bone density and the disease activity in patients with ulcerative colitis.

### METHODS

In this cross-sectional study, 52 patients with ulcerative colitis (duration of the disease less than 5 years) were invited to our research center, Golestan province, northeast of Iran, during February 2012 up to August 2012. A demographic checklist and Simple Clinical Colitis Activity Index was completed for each patients and 5 cc of blood sample was taken after obtaining the informed consent. We used colorimetry method for measuring serum calcium, UV method for serum phosphorus and ELISA for serum vitamin D. Dual-energy X-ray absorptiometry was done to evaluate the bone density. Data analysis was done using SPSS software version 16. Normality of data was assessed using Kolmogorov–Smirnov test. T and ANOVA tests were used if data had normal distribution. Mann-Whitney U or Kruskal-Wallis tests were used for the remaining data. Correlation between qualitative variables was evaluated by Chi-square test.

### RESULTS

The mean (±SD) age and disease activity of the patients were 37.72 (±12.18) years and 4.78 (±1.98), respectively. There were no correlation between disease activity and mean age. Low bone density was seen in 30.8%, 11.5%, and 15.4% in spine, femur neck, and hip, respectively. There was no relationship between Z-score of total hip, spine, and femur neck with disease activity, age, and duration of disease ($p$>0.05).

### CONCLUSION

Our results showed an acceptable rate of low bone density in patients with ulcerative colitis without any correlation with the disease activity index.

KEYWORDS
Ulcerative colitis; Z-score; Bone densitometry; Low bone density

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## INTRODUCTION

Inflammatory bowel disease (IBD) is an immune based disorder that is more prevalent in Caucasians. Its incidence is increasing in these populations,[1] which could have several complications. Osteoporosis (low bone density) is one of the most common and important consequences of inflammation in the bowel mucosa.[2]

Different clinical and epidemiological studies using dual-energy X-ray absorptiometry(DXA) have shown an increased prevalence of low bone mineral density (BMD) in patients with IBD.[3] Risk of pathologic fractures among patients with IBD is reported to be higher than general population.[4]

Some investigators reported that low BMD was more common in Crohn's disease (CD) than ulcerative colitis (UC); although other studies indicated that both diseases had the same degrees of bone loss.[5] Using the World Health Organization (WHO) criteria, studies have shown a prevalence of 40-50% for osteopenia and 10-25% for osteoporosis in patients with IBD, which are together defined as low bone density.[6]

Several factors can play role in the pathogenesis of low BMD (osteoporosis) in IBD such as corticosteroid therapy, malnutrition, small bowel resection, vitamin D (25-hydroxyvitamin D [25- OHD]) and calcium deficiency, hypogonadism, disease activity and duration, sex hormones deficiency, smoking, proinflammatory cytokines, and genetic.[2-4] Among these factors, it has been proven that age and corticosteroid use have a more important role in lower bone density.[7] So, normal bone modeling and remodeling can be affected by IBDs by various factors, resulting in decreased bone formation and/or increased bone resorption.[6] Moreover, vitamin D deficiency may induce rising in PTH levels and 1, 25$(OH)_2$ D via causing hypocalcaemia. This form of vitamin D [1, 25$(OH)_2$D] activates osteoclastic function and leads to mobilization of skeletal calcium stores. Also vitamin D deficiency can affect calcium metabolism, matrix ossification, the rate of bone turnover, and bone mineral density.[6,8] In patients with IBD, calcium intake does not show predictor effect on bone mineral density while decreased intake causes lower bone mineral density.[8]

Non-invasive method of DXA made it is easy to measure BMD. There are two different score for showing BMD results as the number of standard deviations (SD) above or below the mean for a young adult population (T-score) or an age-matched population (Z-score).[7]

There are controversies regarding the magnitude of low bone density in patients with IBDs and the suitable therapeutic approach.[7] This study was designed in a population of ulcerative colitis cases in Northeast of Iran to measure the bone density and evaluate the relationship of the colitis activity and the bone density in these patients.

## MATERIALS AND METHODS

This cross-sectional study was conducted in 2012 in Golestan province (northeast of Iran). All patients with a definite diagnosis of ulcerative colitis (based on colonoscopy and histopathological confirmation) during the previous 5 years were enrolled. The protocol of this project was confirmed in the local Ethics Committee of Golestan University of Medical Sciences and informed consent was taken from all the patients.

Inclusion criteria were: Duration of diagnosis not more than 5 years (to decrease the probability of the disease complications), no history of smoking, not being in acute phase of the disease, and no need to hospital admission at the time of study.

Those patients who had a history of corticosteroids consumption in the previous six months were excluded from the study. Fifty two patients who met the inclusion criteria were referred to Golestan Research Center of Gastroenterology and Hepatology (GRCGH). A checklist including demographic information (age and sex) and data about the duration of disease, any complication related to the intestinal disease and history of treatment was completed for each patient. Simple clinical colitis activity index (SCCAI) was used to evaluate the disease activity. This index, which was defined firstly by Walmsley in 1998, consisted of scores for five clinical criteria

and showed a highly significant correlation with existing more complex scoring systems and therefore could be useful in the initial assessment of patients with ulcerative colitis.[9]

SCCAI is a 5-item questionnaire that assesses the severity of bowel disease using clinical symptoms including number of defecations in a day, during the night, emergency feeling for defecation, seeing blood in the stool, general feeling of well-being, and extra-intestinal manifestations. Persian version of this questionnaire is not validated in our country. So for using in this study we translated it to Persian and culturally adapted following the standard forward- backward translation method. Then it was explained for 10 patients with ulcerative colitis to see if there is any problem in understanding the questions as a pilot study. Results showed that all patients fulfilled the questionnaire completely. So, during the study a medical doctor performed the interview trying to help the patients understand the items well.

The patients were referred to 5th Azar hospital (the academic hospital affiliated to the University) for measuring BMD by DXA (Lexxos-DMS, France). Z-Score less than -2 was considered as low bone density based on the latest recommendations of International Society for Clinical Densitometry (ISCD).[10]

Fasting blood sample was taken to detect serum levels of calcium (Ca), phosphorous (P), and vitamin $D_3$. Our measuring methods were colorimetry for Ca (Pars Azmoon, Iran), UV method for P (Pars Azmoon, Iran), and ELISA for vitamin D (Euroimmune, Germany).

Data analysis was done using SPSS software version 16. Normality of data was assessed using Kolmogorov–Smirnov test. T and ANOVA tests were used if the data had normal distribution. Mann-Whitney U or Kruskal-Wallis tests were used for the remaining data. Correlation between qualitative variables was evaluated by Chi-square test.

## RESULTS

Of the patients, 61.5% were women and the remaining were men (38.5%). Mean (±SD) patients' age was 37.72(±12.18) years. There was no significant difference in age between men and women ($p$=0.40).

Simple clinical colitis activity index varied from 3 to 13. There was no significant difference in disease activity index between men (4.52±2.31) and women (4.47 ±1.44) ($p$=0.29).

No significant correlation was seen between activity index or disease duration and BMD ($p$>0.05).

The result of bone densitometry showed no low mineral density in total hip and femoral neck of the patients but 36.6% of them had low bone density in lumbar vertebra (table 1).

There was no significant difference between BMD of total hip ($p$=0.94), femoral neck ($p$=0.13), and lumbar vertebra ($p$=0.38) in men and women. Also no correlation was found between mean age of patients with low mineral density and normal group ($p$>0.05,table 2).

As shown in table 3, serum levels of calcium, phosphorus, and vitamin D were normal in our patients (table 3).

## DISCUSSION

Results of this study on patients with ulcerative colitis showed a prevalence of about 30.8%, 11.5%, and 15.4% low bone density (Z-score<-2) in spine, femur neck, and hip area. No correlation between disease activity index and bone density was found. And none of our patients had abnormal amounts of calcium, phosphorus, and vitamin D (as shown in table 3). We had no control group in our research (one of our limitations) and some comparisons could not be done exactly.

Clinical data from different studies showed a variety of low bone density prevalence in various populations. Although there has been a discordance between the results depending on using Z-score or T-score,[2] either of them could be used in evaluation of bone density of patients. In this study we used Z-score based on the newest definition by ISCD.[10]

Khadgawat and colleagues had shown that spine and hip BMD in patients with IBD in India was sig-

**Table 1:** Bone density classification of hip, femoral neck, and lumbar vertebra in patients with ulcerative colitis

| Region of Interest (ROI) | Low Bone Density N (%) | Normal N (%) |
|---|---|---|
| Total hip(Z-Score) | 8 (15.4) | 44 (84.6) |
| Femoral neck (Z-Score) | 6 (11.5) | 46 (88.5) |
| Lumbar vertebra (Z-Score) | 19 (36.6) | 33 (63.5) |

**Table 2:** Mean (±SD) age of patients with ulcerative colitis and bone mineral density

| Region of Interest (ROI) | Mean (± SD) age | | *p*-value |
|---|---|---|---|
| | normal | Low bone density | |
| Total hip(Z-Score) | 38.82(±12.77) | 32.37(±7.08) | 0.059 |
| Femoral neck (Z-Score) | 38.71(±12.3) | 29.4(±7.76) | 0.134 |

**Table 3:** Mean (±SD) serum level of calcium, phosphorus, and vitamin D in patients with ulcerative colitis

| Variable | Mean (±SD) | Normal Range |
|---|---|---|
| Phosphorus (mg/dL) | 8.89 (0.48) | 2.5-4.3 |
| Vitamin D(ng/mL) | 3.97 (4.24) | 2.5-32 |
| Calcium(mg/dL) | 72.04 (39.44) | 7.8-10.2 |

nificantly lower than the control group. No association was found between BMD and age, disease duration, and cumulative dose of corticosteroids. In this study, two-thirds of the patients had low BMD (according to WHO definition of osteoporosis and osteopenia) and daily calcium intake was inadequate in most patients.[11] Although the prevalence of low BMD was higher in Indian patients, the result of this study was similar to ours in regard to the low correlation between age and the disease duration with BMD. Although daily calcium intake of patients was not examined in our study, it seems there was no problem in terms of serum calcium of our patients. Since World Health Organization (WHO) has released a different definition for low bone density (bone densitometry as a T score -1 to -2.5),[12] there might be some differences between the results using T-score or Z-score in the analyses.

In the study by Tsironi and co-workers on 122 patients with IBD, age (older than 55 years) was identified as a risk factor for low femoral neck T-score. But the index of disease activity, disease duration, and sex did not have predictive value for bone density.[7] In our study, there was no relationship between disease duration and sex of patients with low bone density. In contrast to the mentioned study, no relationship was found between age and femoral neck T-score. It should be considered in mind that our patients were mostly younger than 50 years old (except for nine of them). So, there could be some correlation with age if there was a higher proportion of older patients in the study. This might be an issue of interest for further studies.

Similarly, there have been reported a much higher prevalence of low bone density in different studies from all over the world. In Austria, Kirchgatterer and colleagues reported low bone density in 27 patients with ulcerative colitis (71%), osteopenia in 20, and osteoporosis in 7 patients. Their findings can be due to the different definition used in their study.[13] In the present study, we just used the term "low bone density" which includes both osteoporosis and osteopenia, so about 37% of our patients had low bone density in lumbar vertebra that is so much better results compared with the above mentioned report.

Another example is the study by Ardizzo and colleagues in Italy on 51 patients with Crohn's disease and 40 patients with ulcerative colitis. They showed a similar T score in both groups, and only 8% of the patients with Crohn's disease, and 15% of the patients with ulcerative colitis had normal bone density. In the Regression models, the femur T score was significantly associated with duration of Crohn's disease. In patients with ulcerative colitis, spine T score was inversely associated with age and significantly correlated with sex of the individual (male). Femur T score was significantly associated with sex (men were more negative) and inversely related to the cumulative dose of prednisone.[14] We did not find a significant relationship between age, sex, and T-score. None of our patients were taking long-term corticosteroids. Also, we had no patient with Crohn's disease, and our analysis was mainly based on Z-score.

Some similar studies have been done in Iranian

patients with IBD. In Zali et al. study on 126 patients with ulcerative colitis and 39 patients with Crohn's disease in Tehran, 53 patients (1.32%) had decreased bone density of the lumbar spine or femoral neck. The density of the femoral neck was significantly reduced in patients with Crohn's disease. There were no differences between men and women in terms of bone mass. Most of the patients with Crohn's had hypocalcemia. Regression analysis showed that lumbar spine T-score was predictable with age, body mass index, and use of corticosteroids, whereas in the femoral neck, these factors were age, body mass index, smoking, and corticosteroid intake.[15] We did not enroll patients with Crohn's into the study, due to the low number of such patients in our region. Furthermore, in our study number of those with low bone density at the lumbar spine was lower than the mentioned study. The intake of calcium could be responsible for it, which was not measured in our study and it should be considered in next studies.

Shiraziand colleagues in a study on 200 patients with IBD in Tabriz reported that 74.4% of their patients had low bone density at the lumbar spine or femoral neck. Half of the patients were osteopenic and 24.1% were osteoporotic. The mean serum calcium was in the normal range. In Patients with ulcerative colitis inverse association between T score, alkaline phosphatase, and 25-hydroxyvitamin D was observed.[16] This report was similar to ours in regard to the normal range of calcium in patients with IBD, but there were more patients with low bone density than ours. There could be a difference because of the different duration of disease in their study.

Recently, a case-control study in Iran was performed by Mikaeli and co-workers, which showed no significant difference between patients with IBDs and controls in BMD of lumbar spine, femoral neck, and total hip or between men and women. They concluded that among different assumed risk factors, just aging and long-term use of corticosteroids really matter in decreased BMD in patients with ulcerative colitis.[2] In the present study, we did not include patients with long term usage of corticosteroids and also the mean age of our population was young. So these two important factors could not be implied in low bone densitometry in our study.

Our patients with ulcerative colitis had an acceptable bone density compared with other studies and low calcium and vitamin D level were not observed. Lack of dietary data and control group were our limitations. Daily calcium and vitamin D intake in patients with IBD could be a topic for future studies.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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