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Factors Affecting Bone Mineral Density in Inflammatory Bowel Disease

İnflamatuvar Bağırsak Hastalığında Kemik Mineral Yoğunluğuna Etki Eden Faktörler

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ABSTRACT

Objectives: Inflammatory bowel disease (IBD) is a chronic disease, in which autoimmunity has been thought to involve the mucosal barrier, leading to a chronic inflammation and affecting different regions and layers of the gastrointestinal tract. The main types of IBD include ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis which often cannot be distinguished from the other ones. The prevalence of reduced bone mineral density (BMD) is higher in patients with IBD than healthy individuals. In this study, we aimed to evaluate the BMD in patients with UC, CD, and in healthy individuals.

Methods: A total of 71 IBD patients (21 CD, 50 UC) and 30 age- and sex-matched healthy individuals were included in this prospective study. Dual-energy X-ray absorptiometry was performed to measure BMD of the vertebra and femoral neck.

Results: There was no significant difference in the age, sex, and body mass index between the study and control groups ($p<0.05$). The BMD values were significantly lower in 16 of 21 CD patients (76.2%). A total of 27 patients (54%) with UC had pathological T-scores, indicating borderline significance ($p=0.058$). The reduction in BMD was not significant between the IBD patients treated with >5 g/day corticosteroids and those treated with ≤5 g/day or treatment-naive patients ($p>0.05$).

Conclusion: Our study results suggest that BMD is significantly lower in IBD patients, particularly in CD patients.

Keywords: Crohn's disease; dual-energy X-ray absorptiometry; osteopenia; osteoporosis; ulcerative colitis.

ÖZET

Amaç: İnflamatuvar bağırsak hastalığı, otoimmünitenin mukozal bariyeri kapsadığı, kronik bir inflamasyona yol açtığı ve gastrointestinal sistemin farklı bölgelerini ve katmanlarını etkilediği düşünülen kronik bir hastalıktır. Başlıca inflamatuvar bağırsak hastalığı tipleri, genellikle diğerlerinden ayırt edilemeyen ülseratif kolit, Crohn hastalığı ve belirsiz koliti içerir. Düşük kemik mineral yoğunluğunun prevalansı, sağlıklı bireylere göre inflamatuvar bağırsak hastalığı olan hastalarda daha yüksektir. Bu çalışmada, ülseratif kolit, Crohn hastalığı olan hastalarda ve sağlıklı bireylerde kemik mineral yoğunluğunun değerlendirilmesi amaçlandı.

Yöntem: Bu prospektif çalışmaya toplam 71 inflamatuvar bağırsak hastalığı olan hasta (21 Crohn hastalığı, 50 ülseratif kolit) ve 30 yaş ve cinsiyet uyumlu sağlıklı birey dahil edildi. Lomber omurga ve femur boynunun kemik mineral yoğunluğunu ölçmek için dual enerjili X-ışını absorpsiyometrisi yapıldı.

Bulgular: Çalışma ve kontrol grupları arasında yaş, cinsiyet ve beden kitle indeksi açısından anlamlı fark yoktu ($p<0,05$). Kemik mineral yoğunluğu değerleri 21 Crohn hastasının 16'sında (%76,2) anlamlı olarak daha düşüktü. Ülseratif kolitli toplam 27 hastanın (%54) patolojik T-skorları vardı, bu da sınırda anlamlılığa işaret ediyordu ($p=0,058$). > 5 g/gün kortikosteroidle tedavi edilen inflamatuvar bağırsak hastalığı olan hastalar ile ≤ 5 g/gün veya daha önce tedavi görmemiş hastalarla tedavi edilen inflamatuvar bağırsak hastalığı olan hastalar arasında beden kitle indeksindeki azalma anlamlı değildi ($p>0,05$).

Sonuç: Çalışmanın sonuçları inflamatuvar bağırsak hastalığı olan hastalarda, özellikle Crohn hastalarında kemik mineral yoğunluğunun anlamlı olarak daha düşük olduğunu göstermektedir.

Anahtar sözcükler: Crohn hastalığı; ülseratif kolit; dual-enerjili X-ışını absorpsiyometrisi; osteopenia; osteoporoz.

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Inflammatory bowel disease (IBD) is a group of inflammatory diseases of the colon and small intestine, leading to life-threatening complications. Crohn's disease (CD) and ulcerative colitis (UC) are both forms of IBD, which are characterized by recurrent or permanent gastrointestinal inflammation; however, there is no medical or surgical cure.[1-3] In general, IBD is diagnosed in adolescents and adults.[4,5] It has minimal effects on survival and most of the patients with IBD reach advanced age.[6,7] About 15–20% of IBD patients are diagnosed at the age of ≥50 years.[8,9] Therefore, it is of utmost importance to evaluate the effects of IBD on other concurrent diseases in elderly patients.

As IBD is associated with bone loss, osteoporosis is one of the complications of the disease, posing a higher risk for elderly patients.[10] Osteoporosis is characterized by low bone mineral density (BMD) and bone mass along with micro-architectural bone tissue deterioration, resulting in an increased risk for micro- and macro-fractures.[11] Dual-energy X-ray absorptiometry (DXA), an enhanced form of X-ray technology, is used in the diagnosis of osteoporosis.[12] According to the World Health Organization (WHO), osteoporosis in postmenopausal women and elderly males is defined as a bone density T-score of 2.5 standard deviation (SD) or more below the average value for young adults.[13] The National Health and Nutrition Examination Survey (NHANES III) declares the recommended reference ranges of the femoral neck measurements in white women.[14]

Methods

Study Design and Study Population

This single-center and prospective study included a total of 71 IBD patients (21 CD, 50 UC) and 30 age- and sex-matched healthy individuals. Patients with chronic obstructive pulmonary disease, diabetes mellitus, primary bone diseases or as a result of, for example, chronic kidney disease, liver diseases, lupus erythematosus, malignancy, thyroid/parathyroid disease, and pregnant women as well as postmenopausal women under estrogen replacement therapy were excluded from the study.

The diagnosis of CD and UC was made on clinical, endoscopic, radiological, and histological findings. Data including demographic and clinical characteristics of the patients, biochemical parameters, affected areas, body mass index (BMI), and steroid use were recorded. The control group included individuals without chronic diarrhea and those without first-degree relatives having IBD. The Harvey-Bradshaw Index (HBI) was used to assess the disease activity in the patients with CD. The SEO-Index was used to evaluate the severity of UC.

Measurement of BMD

The BMD of the femoral neck and lumbar spine was measured using the DXA (Hologic QDR1000™ densitometer, GE Medical Systems, Wisconsin, USA). The results were recorded in g/cm^2 and presented either as Z-score or as T-score.

According to the WHO guidelines, low BMD was expressed by T-score, while T-scores within –1 SD were considered normal, T-scores from –1 SD to –2.5 SD were considered osteopenia, and values <–2.5 were considered osteoporosis.[15]

Statistical Analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed in mean±SD or median (min-max), while categorical variables were expressed in number and frequency. The Chi-square test was used to compare categorical variables between the groups. An independent samples t-test and Mann–Whitney U-test were used to compare normally distributed categorical variables between the groups. The univariate analysis and Kruskal–Wallis test were carried out to compare continuous variables for multiple groups, if normal distribution was met. Significant p-values for pairwise comparisons were corrected using the Bonferroni test. $p<0.05$ as considered statistically significant.

Ethical Consideration

The study protocol was approved by the Institutional Ethics Committee of the Cukurova University, Medical Faculty. The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from each participant.

Results

A total of 101 participants including 21 patients with CD (11 males and 10 females), 50 patients with UC (27 males and 23 females), and 30 healthy individuals (12 males and 18 females) were included in this study. The mean age was 44.29±13.47 (range: 18–63) years in the CD patients, 41.92±13.79 (range: 18–65) years in the UC patients, and 44.43±7.55 (range: 18–60) years in the control group. The mean BMI was 21.98±4.04 (range:16–30) kg/

m^2 in the CD patients, 25.80±4.68 (range:17–38) kg/m^2 in the UC patients, and 24.27±3.40 (range: 18–30) kg/m^2in the control group. Both groups did not differ significantly in relation to age, sex, and BMI-values (p>0.05) (Table 1).

Of the UC patients, six (12%) had extensive disease, 11 (22%) had pancolitis, 14 (28%) had left colonic disease, 12 (24%) had rectosigmoid disease, and seven (14%) had ulcerative proctitis. Among the patients with CD, 12 (57.1%) had ileocolonic CD, five (23.8%) had Crohn's colitis, and four (19%) had isolated ileal disease (Table 1).

Four patients with CD (19%) used >5 g/day steroid, while five patients with UC (10%) used >5 g/day steroid (Table 1). There was no relation between BMD values and use of corticosteroid >5 g/day (Table 1).

Among 21 CD patients, five (23.8%) had normal BMD values, 10 (47.6%) had osteopenia, and six (28.6%) had osteoporosis, indicating a statistically significant reduction in the BMD values, compared to the control group (p=0.002). Of 50 UC patients, 23 (46%) had normal BMD values, 20 (40%) osteopenia, and seven (14%) had osteoporosis, indicating a borderline statistical significance, compared to the control group (p=0.058). There was no significant difference in BMD between CD and UC (p=0.162) (Fig. 1).

Disease activity and BMD values in the patients with CD and UC are summarized in Table 2. Accordingly, four of 21 (19%) patients included in the study were in the active form of CD, whereas 12 of 50 (24%) UC patients had active disease. A coherence between the disease activity and BMD was not determined (p>0.005) (Table 2).

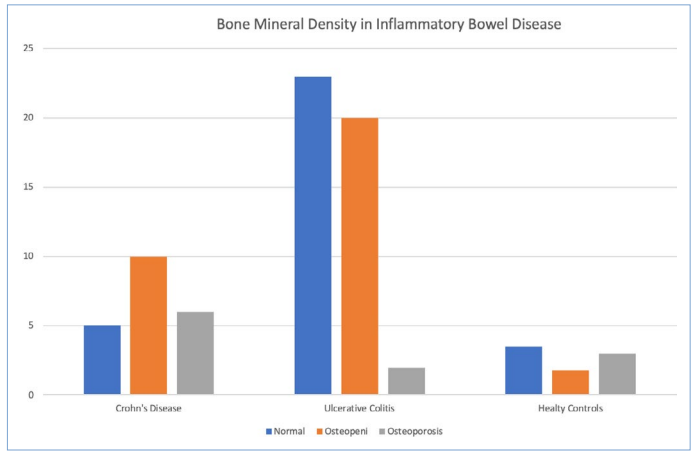

Figure 1. Bone mineral density in inflammatory bowel disease.

Table 1. Baseline demographic and clinical characteristics of the study population

	UC (n=50) Mean±SD (min-max) n (%)	CD (n=21) Mean±SD (min-max) n (%)	Control (n=30) Mean±SD (min-max) n (%)	p
Age, years[o]	41.92±13.79 (18–65)	44.29±13.47 (18–63)	44.43±7.55 (18–60)	>0.05
Sex[a]				>0.05
Male	27 (26.7)	11 (10.9)	12 (11.9)	
Female	23 (22.8)	10 (0.1)	18 (18.8)	
BMI[b], kg/m^2	25.80±4.68 (17–38)	21.98±4.04 (16–30)	24.27±3.40 (18–30)	>0.05
Steroid use (5<g/day)	5 (50)	4 (19)		>0.05
Affected region[a]				
Extensive colitis	6 (12)			
Pancolitis	11 (22)			
Left-sided colon	14 (28)			
Rectosigmoid	12 (24)			
Rectum	7 (14)			
Ileocolonic		12 (57.1)		
Colonic		5 (23.8)		
Ileal		4 (19)		

[a]Categorical data are given in number and frequency, unless otherwise stated. [b]Continuous data are given in mean±SD with min-max values, unless otherwise stated. SD: Standard deviation; UC: ulcerative colitis; CD: Crohn's disease; BMI: Body mass index.

Table 2. Disease activity and bone mineral density in patients with ulcerative colitis and Crohn's disease

	n	T- score (L)	Z-score (L)	T-score (F)	Z-score (F)	p
Ulcerative colitis						
SEO activity <150	38	−0.94±1.13	−0.62±1.06	−0.67±0.92	−0.46±0.87	>0.05
SEO activity >150	12	−1.38±1.28	−1.01±1.23	−0.85±1.28	−1.29±1.36	>0.05
Crohn's disease						
HBI-activity <5	17	−1.38±1.37	−1.06±1.18	−1.37±0.91	−1.06±0.85	>0.05
HBI-activity >5	4	−1.37±1.85	−1.15±1.99	−0.97±1.20	−0.80±1.23	>0.05

HBI: Harvey-Bradshaw index.

Table 3. T- and Z-scores according to sex in patients with ulcerative colitis and Crohn's disease

	Ulcerative colitis			Crohn's disease		
	Female	Male	p	Female	Male	p
T-score L	−1.14±0.98	−0.96±1.32	0.594	−1.28±1.59	−1.48±1.32	0.755
Z-score L	−0.81±0.82	−0.64±1.31	0.584	−0.85±1.28	−1.29±1.36	0.457
T-score F	−0.94±0.90	−0.62±1.23	0.300	−1.69±0.96	0.93±0.83	0.070
Z-score F	−0.73±0.82	−0.26±1.02	0.083	−1.32±0.89	0.73±0.86	0.144

Data are given in mean±standard deviation, unless otherwise stated. L: Lumbar vertebra; F: Femoral neck.

The mean T- and Z-scores according to sex in patients with CD and UC are shown in Table 3 Accordingly, there was no statistically significant difference in the BMD values between female and male UC and CD patients (p>0.05) (Table 2).

Discussion

Low BMD in patients with IBD is a multi-factorial, well-known complication; however, the associated risk factors have not been fully elucidated, yet. In general, the BMD is reduced in patients with IBD, leading to osteoporosis and fractures, which can be deemed as an important health problem. According to the data related to bone diseases in patients with IBD, a decline in the BMD values has been reported in patients with IBD (CD, UC), compared to normal population. Age is a fundamental risk factor for decreased BMD values in IBD patients, while the type of disease (UC or CD) is not associated with osteoporosis.

Smoking, age, lack of exercise, and menopause are the established risk factors of osteoporosis in population, in particular, in IBD patients. Other IBD-specific features are osteoporosis and malnutrition, Vitamin D-deficiency, small bowel resection, and use of steroids which can increase the risk of fractures.[16] Time from the and a lower disease activity can be associated with the lower BMD values.[17]

Some of the agents in the treatment of IBD seem to affect BMD. Corticosteroids used in the treatment of IBD are the risk factors for osteoporosis, while azathioprine and treatment with anti-tumor necrosis-alpha factor increases the bone mass.[18,19]

Osteoporosis can be also diagnosed without any major trauma with a typical fracture, referring fragility fractures. Patients with IBD are exposed to a higher risk of developing osteoporosis and fragility fractures, although the underlying factors have not been fully understood, yet.[15,20] The risk of osteoporosis in IBD-patients is about 15% and is higher in older ages and those with low BMI. The annual risk of fracture is about 1% with the increased risk in advanced age. The risk of vertebral fractures is about 22% in patients with osteoporosis, whereas vertebral fractures are associated with diminished BMD.[21]

According to the literature, hydrocortisone at a dose of ≥7.5 mg has been shown to cause relevant bone loss, which is higher in the 1st weeks of the treatment.[22] In their study, Bjarnson et al.[23] found no significant context between the vertebral and hip T-scores and the cumulative dosage of prednisolone. In another study, however, Silvennoinen et al.[24] examined the prevalence and risk factors of low BMD in patients with IBD. They showed that the patients with

a lifetime corticosteroid dose was >10 g, which had significantly lower BMD, compared to the groups without or <5 g of corticosteroid. In addition, the patients who never received per oral corticosteroids did not have decreased BMD. The authors concluded that there was no significant correlation between the cumulative dose of corticosteroids and BMD. Nevertheless, this can be attributed to the low number of patients receiving corticosteroids and low dose of cumulative corticosteroids used. The BMD values of the patients receiving >5 g steroids were lower, although it did not reach statistical significance, probably due to the small sample size in this dose group (p>0.05).

Furthermore, Reffitt et al.[25] analyzed the impact of active disease and remission on BMD in 137 patients with IBD (64 UC, 73 CD). The femoral and vertebral Z-scores of the patients with UC and CD who sustained in remission for longer than 3 years were significantly higher than the correlating Z-scores of the patients with active disease. The vertebral Z-scores were found to be significantly higher in patients who were in remission and receiving azathioprine, compared to the patients with active disease and not receiving azathioprine. On the other hand, in the literature, no significant coherence between the disease activity and reduced BMD has been described. In our study, four patients with CD and 12 patients with UC had active disease and we found no significant correlation between disease activity and low BMD, consistent with the literature (p>0.005).

In a prospective study investigating the prevalence and risk factors of osteoporosis in patients with CD, Hela et al.[26] performed femoral and vertebral BMD measurements using DXA. Osteoporosis and osteopenia were detected in 35.7% and 23.2% of the patients, respectively. Low BMD values were found to be correlated with the BMI, affected colon regions, and glucocorticoid therapy. Low BMI was found to be an independent risk factor for low BMD values. In another comparative study of patients with CD, UC, and healthy individuals, Jahnsen et al.[27] performed that femoral and vertebral BMD measurements using DXA, with the mean Z-scores of the patients with UC, were similar to the healthy individuals. However, the mean Z-scores were significantly lower in the CD patients. In our study, the decline in the BMD reached borderline statistical significance in patients with UC (p=0.058), while the CD patients had significantly lower BMD values (p=0.02), consistent with the literature.

In their study, Khadgawat et al.[28] evaluated BMD in 46 patients with IBD versus 46 age- and sex-matched healthy controls. The BMD measurement was performed using DXA. The mean duration of disease was 87.7 months. Compared to the healthy controls, there was a significant decline in the BMD in IBD patients. Compared to the control group, 29 patients had osteopenia and 21 patients had osteoporosis in the spine and hip region, respectively. Of these, four and seven patients had osteoporosis in the spine and hip region, respectively. The authors found no significant correlation between the BMD and age, duration of disease, and cumulative steroid dose. Similarly, in our study, there was no statistically significant difference in the BMD values between female and male UC and CD patients (p>0.05).

Nonetheless, this study has certain limitations. The sample size was relatively small and the number of patients who received steroids at a dose of >5 g in total was too low to draw a firm conclusion.

In conclusion, our study results showed a decline in the BMD in IBD patients, particularly in those having CD. Based on these findings, we can speculate that the BMD is significantly lower in IBD patients and regular follow-up is of utmost importance in these patients to prevent or manage osteoporosis. Further, large-scale, prospective, and randomized-controlled studies are needed to gain a better understanding of the role of BMD in the IBD.

Main Points

1. BMD is significantly lower in IBD patients, particularly in CD patients
2. Regular follow-up is of utmost importance in these patients to prevent or manage osteoporosis
3. Low BMD in IBD does not discriminate between men and women
4. Low BMD in IBD is independent of disease activity.

Disclosures

Ethics Committee Approval: This study was approved by the Cukurova University Medical Faculty, Ethics Committee with the Approval No 1/2 and Date: 06.01.2009.

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Conflict of Interest: None declared.

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