Incidence of low bone mineral density and contributing factors in inflammatory bowel disease

İnflamatuvar barsak hastalığında düşük kemik mineral dansitesi sıklığı ve etkileyen faktörler

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Background and Aims: *Inflammatory bowel disease is a chronic, non-infectious disease of gastrointestinal tract that chracterized by remissions and exacerbations under the name of ulcerative colitis and Crohn's disease. Decreased bone mineral density is identified in inflammatory bowel disease. The mechanism of this decrease is not exactly understood but it is reported as multifactorial. The aim of our study is to compare ulcerative colitis and Crohn's disease, in terms of bone mineral density by evaluating the factors of the decrease in bone mineral density in inflammatory bowel disease.* ***Materials and Methods:*** *102 ulcerative colitis and 39 Crohn's disease patients between the ages of 18 and 70 who are followed in Antalya Eğitim ve Araştırma Hastanesi Internal medicine and Gastroenterology clinical department included in the study. The patients bone mineral density in the lumber vertebrae and femoral neck regions were measured by dual energy x-ray absorptiometry method.* ***Results:*** *Spine and femur T scores were similar in the two groups (spine: Crohn's disease= -1,5±1,4; ulcerative colitis= -1,5±1,3; femur: Crohn's disease= -1,1±1,1; ulcerative colitis= -0,9±1,0). In Crohn's disease group, osteoporosis was present in %38 of the patients and osteopenia was present in %35 of the patients. In ulcerative colitis group, osteoporosis was present in %21 of the patients and osteopenia was present in %46 of the patients.* ***Conclusion:*** *As a result of the study, we determine that there is an association between inflammatory bowel disease and the use of steroid, disease duration, disease activity, age and body mass index. A comparison of patients' disease activities and bone mineral density demonstrated significantly lower femur neck Z/T scores for patients with SEO activity levels >150 compared to those with SEO activity levels <150 in the ulcerative colitis group (p=0,005, p=0,020). There was a positive correlation between body mass index and lumbar vertebra T score, femur neck Z/T (p=0,031, p=0,000, p=0,000). Among steroid users, femur neck Z score was significantly lower compared to non-steroid users (p=0,027). There was a negative correlation between disease duration and femur neck T score, i.e., bone mineral density decreased with increasing disease duration (p=0,023). There was a negative correlation between age and femur neck T score (p=0,014).*

Key words: *Ulserative colitis, Crohn disease, bone mineral density*

Giriş ve Amaç: *İnflamatuvar barsak hastalığı ülseratif kolit ve Crohn hastalığı adı altında temelde 2 formu kapsayan remisyon ve alevlenmelerle seyreden gastrointestinal sistemin kronik enfeksiyöz olmayan inflamatuvar hastalığıdır. İnflamatuvar barsak hastalarında kemik mineral yoğunluğunun azaldığı tespit edilmiştir. Bu azalmanın mekanizması tam anlaşılmamış olmakla birlikte multifaktöriyel olduğu belirtilmektedir. Çalışmamızın amacı inflamatuvar barsak hastalarında kemik mineral yoğunluğundaki azalmayı etkileyen faktörleri değerlendirilerek ülseratif kolit ve Crohn hastalığı'nı kemik mineral yoğunluğu açısından karşılaştırmaktır.* ***Gereç ve Yöntem:*** *Çalışmaya 18-70 yaş arası Antalya Eğitim ve Araştırma Hastanesi Dahiliye ve Gastroenteroloji kliniğinden takipli 102 ülseratif kolit ve 39 Crohn hastalığı dahil edildi. Hastaların kemik mineral yoğunluğu ölçümleri dual enerji x-ray absorbsiyometre yöntemiyle lomber vertebra ve femur boynunda yapıldı.* ***Bulgular:*** *Her iki hastalık grubunda lomber vertebra ve femur boynu T skorları benzerdi (lomber vertebra: Crohn hastalığı= -1,5±1,4; ülseratif kolit= -1,5±1,3; femur boynu: Crohn hastalığı= -1,1±1,1; ülseratif kolit = -0,9±1,0). Crohn hastalığı grubunda (n=39) %38 oranında osteoporoz, %35 oranında osteopeni tespit edildi. Ülseratif kolit grubunda (n=102) %21 oranında osteoporoz, %46 oranında osteopeni tespit edildi.* ***Sonuç:*** *Çalışmanın sonucunda inflamatuvar barsak hastalarında steroid kullanımı, vücut kitle indeksi, hastalık süresi, hastalık aktivitesi ve yaş ile kemik mineral yoğunluğunun ilişkili olduğunu belirledik. Ülseratif kolit grubunda SEO aktivite düzeyi >150 olan hastaların femur boynu Z/T skorları, SEO aktivite düzeyi <150 olan hastalara göre anlamlı olarak daha düşük bulundu (p=0.005, p= 0.02). Vücut kitle indeksi ile lomber vertebra T skoru, femur boynu Z/T skoru rasında pozitif korelasyon vardı (p=0.031, p=0.000, p=0.000). Ülseratif kolit hastalarında, steroid kullanan grupta femur boynu Z skoru (Ort.±S.S -0.62±0.74), steroid kullanmayan gruptan (Ort.±S.S -0.18±0.98) anlamlı olarak daha düşüktü (p=0.027). Hastalık süresi ile femur boynu T skoru arasında negative korelasyon vardı, yani hastalık süresi arttıkça kemik mineral yoğunluğunda azalma tespit edildi (p=0.023). Yaş ile femur boynu Z/T skorları arasında negative korelasyon vardı (p=0.014).*

Anahtar kelimeler: *Ülseratif kolit, Crohn hastalığı, kemik mineral yoğunluğu*

INTRODUCTION

Inflammatory bowel disease is a chronic, non-infectious, inflammatory disease resulting from an exaggerated immune response to several antigens or environmental factors in genetically susceptible individuals, and the exact cause is currently unknown. There are essentially two forms of the disease: ulcerative colitis (UC) and Crohn's disease (CD).

Bone mineral density (BMD) is one of the most relevant assessment parameters in the diagnosis and follows up of systemic diseases such as osteoporosis. In patients

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with inflammatory bowel disease (IBD), BMD was lower than in healthy controls, and reduced BMD was identified in 30%–75% of patients with IBD (1,2). Low BMD etiology in patients with inflammatory bowel disease has been associated to some extent with corticosteroid (CS) use. Several other factors, including calcium imbalances, vitamin D deficiency with malabsorption, sex hormone deficiency, inflammatory cytokines, and low body mass index, may also contribute to this multifactorial process (3).

This study aims to identify the relationships between osteoporosis and disease age, disease activity, site of involvement, BMI, sex, age, history of surgery, smoking, steroid or immunosuppressant use, extraintestinal findings, and complications in patients with IBD and to compare patients with ulcerative colitis and Crohn's disease in terms of BMD.

MATERIALS and METHODS

A total of 141 patients with inflammatory bowel disease, 102 with ulcerative colitis, and 39 with Crohn's disease, aged 18-70 years, being monitored by the Internal Diseases and Gastroenterology departments of Antalya Training and Research Hospital between January 2010 and June 2012 were included in this study.

In this retrospective, cross-sectional study, the IBD diagnosis of each patient was established based on endoscopic, histopathologic (endoscopic biopsy, surgical material), and radiologic data. Clinical data, diagnosis, site of involvement, disease activity, BMI, smoking history, and steroid use were assessed for UC and CD. Patients who had had a bone mineral densitometry measurement with Lunar DEXA over the past one year were included. Patients' BMIs were calculated. Their disease activity at the time their BMDs were measured with DEXA was evaluated. All patients were contacted to obtain a detailed history, and information was gathered with respect to their sex, smoking, BMI, contraception use (in females), appendectomy history, disease age, and site of involvement, intestinal resection history, steroid use, extraintestinal manifestations, and complications. The association of BMD with these parameters was investigated. BMD measurements of UC and CD patients were compared.

RESULTS

A total of 141 patients with inflammatory bowel disease, 102 with ulcerative colitis (57 males, 45 females), and 39 with Crohn's disease (15 males, 24 females) were included in the study. In the CD group (n=39), 15 patients (38%) had osteoporosis and 14 (35%) had osteopenia, whereas in the UC group (n=102), 22 patients (21%) had osteoporosis and 47 (46%) had osteopenia.

In the UC group, the mean lumbar vertebra Z-score was –1.1±1.2, the mean T-score was –1.5±1.3, the mean femur neck Z-score was –0.3±0.9, and the mean T-score was –0.9±1.0. In the CD group, the mean lumbar vertebra Z-score was –1.0±1.3, the mean T-score was –1.5±1.4, the mean femur neck Z-score was –0.6±0.9, and the mean T-score was –1.1±1.1. UC and CD patients did not differ significantly in lumbar vertebra and femur neck Z/T-scores (p >0.05).

Disease duration was not significantly correlated with lumbar vertebra Z/T-score or femur neck Z-score (p >0.05).

Table 1. BMD and disease activity relationship

		UC activity (SEO)		
		<150	**>150**	
		Mean±SD	**Mean±SD**	**p**
Ulcerative colitis group	Lumbar vertebra Z-score	–0.95±1.30	–1.33±0.91	0.150
	Lumbar vertebra T-score	–1.39±1,42	–1.70±0.95	0.283
	Femur neck Z-score	–0.16±0.94	–0.72±0.76	**0.005**
	Femur neck T-score	–0.72±0.97	–1.20±0.86	**0.020**
Independent samples t-test				
		CD activity (HB)		
		<5	**>5**	
		Mean±SD	**Mean±SD**	**p**
Crohn's disease group	Lumbar vertebra Z-score	–1.28±1.11	–0.53±1.49	0.083
	Lumbar vertebra T-score	–1.76±1.38	–0.99±1.47	0.110
	Femur neck Z-score	–0.45±0.90	–0.86±0.83	0.169
	Femur neck T-score	–0.93±1.08	–1.44±0.98	0.152

Independent samples t-test

There was a negative correlation between disease duration and femur neck T-score, i.e., BMD decreased with increasing disease duration (r= –0.192 p=0.023).

BMI and lumbar vertebra T-score were not significantly correlated (p >0.05). There was a positive correlation between BMI and lumbar vertebra T-score, femur neck Z/T (p=0.031 p=0,000, p=0.000). No correlations between age and lumbar vertebra Z/T-score or femur neck Z-score were noted (p >0.05). There was a negative correlation between age and femur neck T-score (p=0.014).

No relationships were found between BMD and site of involvement, extraintestinal involvement, smoking history, surgery history, and BMD in either of the disease groups. A comparison of patients' disease activities and BMD demonstrated significantly lower femur neck Z/T-scores for patients with SEO activity levels >150 compared to those with SEO activity levels <150 in the UC group (p=0.005, p=0.020). Comparison of lumbar vertebra BMD ratios in UC patients did not yield a similar result (p >0.05). There was no relationship between the disease activity and BMD in CD (p >0.05) (Table 1).

Lumbar vertebra Z/T score or femur neck Z/T score did not differ significantly by sex in the UC or CD groups (p >0.05). In the UC group, there were no significant differences in BMD between premenopausal and postmenopausal women (p >0.05). In the CD group, postmenopausal women had decreased lumbar vertebra T-scores (p=0.025). In both disease groups, neither lumbar vertebra Z/T scores nor femur neck Z/T scores of smokers and non-smokers differed significantly (p >0.05).

In the UC group, a comparison of lumbar vertebra Z/T scores and femur neck Z/T scores of patients using and not using steroids did not demonstrate a significant difference (p >0.05). Among steroid users, the mean femur neck Z-score was significantly lower than that of non-steroid users (p=0.027). In the Crohn's disease group, no difference in lumbar vertebra Z/T scores or femur neck Z/T scores was identified between steroid users and non-steroid users (p >0.05). In the overall patient population, femur neck Z-score was reduced with steroid use (p=0.015) (Table 2).

Twenty-five (24.5%) patients in the UC patient group (n=102) and 13 patients (33.3%) in the CD group (24.5%) had a smoking history of at least 1 pack year. In both groups, neither lumbar vertebra Z/T scores nor femur neck Z/T scores differed significantly between smokers and non-smokers (p >0.05).

Extraintestinal findings were observed in 12 (11.8%) patients in the UC group (n=102) compared with 7 (17.9%) in the CD group (n=39). Arthralgia was the most common extraintestinal finding in both groups. Neither lumbar vertebra Z/T scores nor femur neck Z/T scores differed significantly between patients with or without extraintestinal findings in either group (p >0.05). In the UC group (n=102), 32 patients (31.4%) used steroids during the course of treatment, and the mean cumulative dose used was 3.2±1.1 g. In the CD group (n=39), 13 patients (33.3%) used steroids, and the mean cumulative dose used was 1.2±0.4 g. Lumbar vertebra Z/T scores or femur neck T-scores did not differ between patients who had and had not used steroids in the UC group (p >0.05).

Table 2. Steroid use and BMD relationship

		Steroid		
		User	**Non-user**	
		Mean±SD	**Mean±SD**	**p**
All patients	Lumbar vertebra Z-score	–1.02±1.26	–1.09±1.16	0.766
	Lumbar vertebra T-score	–1.54±1.36	–1.35±1.31	0.441
	Femur neck Z-score	–0.27±0.97	–0.67±0.75	**0.015**
	Femur neck T-score	–0.84±1.04	–1.12±0.87	0.108
Ulcerative colitis group	Lumbar vertebra Z-score	–1.00±1.22	–1.17±1.19	0.520
	Lumbar vertebra T-score	–1.51±1.29	–1.40±1.36	0.684
	Femur neck Z-score	–0.18±0.98	–0.62±0.74	**0.027**
	Femur neck T-score	–0.76±1.01	–1.07±0.81	0.131
Crohn's disease group	Lumbar vertebra Z-score	–1.07±1.40	–0.88±1.08	0.680
	Lumbar vertebra T-score	–1.60±1.55	–1.23±1.20	0.453
	Femur neck Z-score	–0.49±0.93	–0.80±0.78	0.312
	Femur neck T-score	–1.04±1.09	–1.26±1.02	0.551

Independent samples t-test

Table 3. Immunosuppressant use and BMD relationship

		Immunosuppressive		
		User	Non-user	
		Mean±SD	Mean±SD	p
All patients	Lumbar vertebra Z-score	–0.98±1.28	–1.29±0.97	0.234
	Lumbar vertebra T-score	–1.44±1.35	–1.64±1.31	0.491
	Femur neck Z-score	–0.30±0.93	–0.79±0.79	**0.010**
	Femur neck T-score	–0.83±1.00	–1.34±0.87	**0.014**
Ulcerative colitis group	Lumbar vertebra Z-score	–0.95±1.26	–1.53±0.75	**0.013**
	Lumbar vertebra T-score	–1.41±1.30	–1.79±1.33	0.269
	Femur neck Z-score	–0.23±0.93	–0.74±0.77	**0.030**
	Femur neck T-score	–0.74±0.98	–1.38±0.61	**0.001**
Crohn's disease group	Lumbar vertebra Z-score	–1.06±1.34	–0.85±1.19	0.660
	Lumbar vertebra T-score	–1.52±1.51	–1.36±1.30	0.766
	Femur neck Z-score	–0.50±0.89	–0.88±0.86	0.242
	Femur neck T-score	–1.07±1.01	–1.26±1.26	0.624

Independent samples t-test

The mean femur neck Z-score in the group of patients with prior steroid use (mean±SD –0.62±0.74) was significantly lower than in the group of patients without prior steroid use (mean±SD –0.18±0.98) (p=0.027) (Table 20). In the CD group, lumbar vertebra Z/T scores or femur neck Z/T scores did not differ between patients with or without steroid use (p >0.05). When all patients were considered, femur neck Z-score decreased with steroid use (mean±SD –0.67±0.75 p=0.015) (Table 2).

In the UC group, comparison of lumbar vertebra T-scores among patients using and not using immunosuppressants yielded similar results (p >0.05). In the group of immunosuppressant users, lumbar vertebra Z-score and femur neck Z/T score were significantly lower than in non-users (p < 0.05). In the CD group, immunosuppressant users and non-users did not differ significantly in lumbar vertebra Z/T score or femur neck Z/T score (p >0.05) (Table 3).

DISCUSSION

Inflammatory bowel diseases (IBDs) are mostly diagnosed in young individuals but can flare up later in life and have high morbidity. Increased fragility fractures are one of the leading causes of morbidity. Both ulcerative colitis and Crohn's disease patients are known to have decreased BMD compared with the normal population (4). Most studies have demonstrated reduced BMD in patients with CD or UC compared with normal individuals, and no differences between the two diseases have been reported (4-5). Some studies have reported a higher incidence of osteoporosis in CD than in UC (4). Various mechanisms have been suggested to explain the higher prevalence of osteoporosis in CD compared with UC. Previous studies have noted that 30%–75% of patients with IBD had osteopenia and approximately 15% had osteoporosis (4-5). In our study, osteoporosis was more frequent among patients with CD, although the two groups did not differ significantly in terms of BMD. Osteoporosis was identified in 21% and 28% of patients in the UC and CD groups, respectively.

Early diagnosis and treatment of osteoporosis is critical in preventing complications in later life such as fractures and chronic pain. Low BMD is directly associated with fracture risk. This risk increases proportionally with age and low body mass index. The risk of fracture increases by 1% every year as the individual ages (4). Low BMI is an important risk factor in osteoporosis occurrence in patients with IBD. The Framingham osteoporosis study by Felson et al., demonstrated a negative correlation between osteoporosis and body weight, and BMI (6). This means that the risk of osteoporosis decreases as BMI increases (6). Jahnsen et. al reported that low BMD is correlated with low BMI in both groups of disease (7). In our study, there is a positive correlation between BMI and lumbar vertebra T-score and femur neck Z/T score in both disease groups (r=0.182 p=0.031, r=0.477 p=0.000, r=0.293 p=0.000). If patients have high BMI, their BMD increase. This supports the observation the IBD patients with high BMI have lower fracture risk. Consistently, osteoporosis was more common among patients with low BMI.

A review of the information in the literature underlines the significant role of cumulative steroid dose in bone loss in cross-sectional studies, although longitudinal

studies have identified no relationship between steroid use and BMD (7-9). Pollak et al. reported that, because patients with CD need higher doses of corticosteroids, a higher incidence of osteoporosis is seen in CD than in UC (10). Although we saw differences between the studies, it was shown that patients who use high cumulative doses of steroids have lower BMD. In our study, femur neck Z-score was significantly reduced in UC patients receiving a cumulative steroid dose of 2–5 g (p=0.027).

Studies have shown that disease localization did not have an effect on BMD. However, the incidence of osteoporosis was higher in CD patients who were operated on for ileal resection (11). In addition, there are some studies showing a correlation between ileal resection and low BMD, whereas some studies reported no relationship between them. Jahnsen et al. reported that disease localization had no effect on BMD (12). In our study, most of the patients who had been operated on were in the CD group. In the CD group, six patients had bowel resection history, whereas in the UC group, no patient had bowel resection. There was no relationship between having had an operation and BMD (p >0.05). We also observed no effect of disease localization on BMD (p >0.05).

A study by Reffitt et al. evaluating the relationship between disease activity and BMD determined that the femur neck and vertebra Z-scores of patients in the remission group were significantly higher than those of the group of patients with active disease. The same study also found that lumbar vertebra Z-scores were significantly higher in the group of patients who were in remission and taking azathioprine than in patients with active disease not receiving azathioprine (13). A study by Liu et al. concluded that BMD was not correlated with age, disease duration and activity, sites of involvement, steroid therapy, or immunosuppressive therapy (14). Disease activity in CD and BMD were not related in our study (p >0.05). However, femur neck Z- and T-scores were higher in remitting patients in the UC group (p < 0.05), supporting the hypothesis that pro-resorptive cytokines released in active disease might be responsible for decreased BMD. A relationship was not observed with BMD in patients receiving immunosuppressive therapy. However, a reduction in BMD of patients treated with an immunosuppressive agent was observed in the group of patients with UC. This was attributed to the fact that patients receiving immunosuppressive treatment in the UC patient group were of advanced ages (mean±SD 52.6±6.8) that their disease duration was longer (mean±SD 7.3±5.5 years) and that they had prior history of steroid use.

There was a negative correlation between femur neck T-score and disease duration and age in our patient group, (p=0.023 p=0.014) consistent with some previous reports (10-15).

In conclusion, as information in the literature also suggests, there are several factors affecting BMD in patients with IBD. One of the objectives of our study was to determine these risk factors for low BMD to enable implementation of the required measures and treatments. In our study, we found that steroid use, low BMI, disease duration, disease activity, and advanced age were associated with reduced BMD. Controlled and comprehensive prospective studies with large samples are needed to assess the factors affecting mineral density in IBDs.

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