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Effects of Low-Dose Corticosteroids on Clinical Outcomes and Bone Mineral Density Parameters in Rheumatoid Arthritis Patients

Romatoid Artritli Hastalarda Düşük Doz Kortikosteroidin Klinik Bulgular ve Kemik Mineral Yoğunluğu Üzerine Etkileri

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Abstract

Objective: Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints and frequently leads to bone loss. Glucocorticoids (GCs), widely prescribed for their anti-inflammatory properties in RA, have a controversial impact on bone health when used in low doses. This study evaluates the effect of low-dose GC use on bone mineral density (BMD) and the risk of osteoporosis (OP) in RA patients.
Materials and Methods: This study was conducted at the Rheumatology Outpatient Clinic of Erciyes University Faculty of Medicine. A total of 74 RA patients and 39 healthy controls (≥18 years) were included. Demographic data [age, gender, body mass index (BMI)] and clinical assessments (disease activity score-28), RA quality of life questionnaire was recorded using a standardized form.
Results: RA patients had significantly lower BMD and T-scores at the lumbar spine and femur compared to healthy controls (p<0.001). Among RA patients, those taking corticosteroids had lower BMI (p=0.012) and femur T-scores (p=0.011); however, no significant differences were observed in other clinical or laboratory parameters. Logistic regression analysis determined that age is an independent risk factor for OP [odds ratio (OR)=1.13, 95% confidence interval (CI): 1.04-1.24, p=0.005] and the use of low-dose GC was negatively associated with the risk of OP (OR=0.36, 95% CI: 0.11-0.99, p=0.048).
Conclusion: This study hypothesizes that low-dose GC therapy does not increase OP risk in RA patients and may even reduce it in some cases, with age being a key predictor, highlighting the importance of personalized treatment strategies for bone health.
Keywords: Rheumatoid arthritis, glucocorticoids, low-dose corticosteroids, bone mineral density, osteoporosis

Öz

Amaç: Romatoid artrit (RA), öncelikli olarak eklemleri etkileyen kronik bir otoimmün hastalık olup sıklıkla kemik kaybına yol açar. RA tedavisinde antienflamatuvar özellikleri nedeniyle yaygın olarak reçete edilen glukokortikoidlerin (GK), düşük dozda kullanıldıklarında kemik sağlığı üzerindeki etkileri tartışmalıdır. Bu çalışma, RA hastalarında düşük doz GK kullanımının kemik mineral yoğunluğu (KMY) ve osteoporoz (OP) riski üzerindeki etkilerini değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: Bu çalışma, Erciyes Üniversitesi Tıp Fakültesi Romatoloji Polikliniği'nde yürütüldü. Çalışmaya 74 RA hastası ve 39 sağlıklı kontrol bireyi (≥18 yaş) dahil edildi. Katılımcıların demografik verileri [yaş, cinsiyet, vücut kitle indeksi (VKİ)] ve klinik değerlendirmeleri (hastalık aktivite skoru, RA yaşam kalitesi ölçeği) standart bir form aracılığıyla kaydedildi.
Bulgular: RA hastalarının, sağlıklı kontrollere kıyasla lomber omurga ve femur bölgelerinde anlamlı derecede daha düşük KMY ve T-skorlarına sahip olduğu saptandı (p<0,001). RA hastaları arasında kortikosteroid kullananlarda VKİ (p=0,012) ve femur T-skorları (p=0,011) daha düşük bulunurken, diğer klinik veya laboratuvar parametrelerde anlamlı bir fark gözlenmedi. Lojistik regresyon analizine göre yaş, OP için bağımsız bir risk faktörü olarak belirlendi [risk oranı (RO)=1,13, %95 güven aralığı (GA): 1,04-1,24, p=0,005] ve düşük doz GK kullanımı OP riskiyle negatif yönde ilişkili bulundu (RO=0,36, %95 GA: 0,11-0,99, p=0,048).
Sonuç: Bu çalışma, düşük doz GK tedavisinin RA hastalarında OP riskini artırmadığı ve bazı durumlarda bu riski azaltabileceğini göstermektedir. Yaş, OP açısından temel belirleyicilerden biri olarak öne çıkmakta ve kemik sağlığını korumada kişiselleştirilmiş tedavi stratejilerinin önemini vurgulamaktadır.
Anahtar Kelimeler: Romatoid artrit, glukokortikoidler, düşük doz kortikosteroidler, kemik mineral yoğunluğu, osteoporoz

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that predominantly targets the joints. It is characterized by a progressive symmetric inflammation of affected joints causing cartilage destruction, bone erosion, and disability (1). The worldwide prevalence of RA is estimated to be between 0.4% and 1.3%, depending on demographic and regional factors such as sex and age. The occurrence of RA is significantly higher in women, approximately two to three times that in men, and peaks during the sixth decade of life (2).

Osteoporosis (OP) is considered a significant extra-articular complication of RA, contributing to increased morbidity and fracture risk. OP is characterized as a progressive metabolic bone disease, leading to diminished bone mass and compromised microarchitecture of bone tissue. This results in elevated bone fragility and an increased fracture propensity (3). OP is more prevalent in RA patients than in the general population, contributing to increased morbidity and fracture risk (4,5). Bone loss due to RA is associated with some factors. Firstly, it has been demonstrated that this is associated with OP mechanisms. Secondly, it has been shown that the disease is associated with additional disease-specific factors. These additional factors include systemic inflammation, reduced physical activity, and inadequacies in disease management (6). Furthermore, the risk of fracture is higher in patients suffering from RA than in the general population, even in cases where bone density is preserved. The following general risk factors for OP have been identified: advanced age, low body mass index (BMI), female gender, previous history of fracture, menopause, hypogonadism or low vitamin D level, smoking, and alcohol use (7). However, in RA patients, factors such as chronic inflammation due to disease activity, long disease duration, presence of erosive disease, anti-citrullinated protein antibody (ACPA) positivity and physical activity limitation stemming from joint damage further accelerate bone loss (8).

Disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids (GCs) utilized in the management of the disease also exert direct or indirect effects on bone metabolism. GCs are widely used in the management of RA and provide rapid symptomatic relief through their anti-inflammatory effects. GCs are utilized as bridge therapy in RA treatment or until the effect of DMARDs occurs, and they are effective in slowing disease progression and increasing the number of patients reaching remission. They are included in guidelines for the management of RA. Long-term or high-dose use of GCs has been associated with osteoporotic bone loss (9,10). However, the use of low-dose GCs may suppress osteoclast activity by controlling inflammation and thus partially offset bone loss (11). The stabilizing effect of GCs has been shown to depend on factors such as disease activity, dose of GCs administered, and duration of treatment. In addition, increasing the cumulative dose of GCs may double the risk of OP. Continuous oral GC use has been linked to dose-dependent bone loss and a higher risk of fractures, particularly within the first 3-6 months of treatment (12). Consequently, it is recommended that GCs be tapered as soon as clinically feasible (13).

The findings on the effects of low-dose GC use on bone health in RA patients have been inconclusive. Some studies have found a direct association between low-dose GC use and low bone mass (14-16). While others have not found this link (17,18). The observed variations may be attributed to factors such as the study population, the duration of GC use, dosage discrepancies, and additional variables impacting bone health. The present study was undertaken to conduct a comprehensive evaluation of bone health among individuals with RA receiving low-dose GC treatment. In this regard, the study's primary aim was to enhance the existing body of knowledge concerning the impact of these pharmaceutical agents on bone health. This objective was pursued through a meticulous analysis of bone density, the risk of OP, and the interplay of associated clinical factors.

Materials and Methods

Study Participants and Design

This prospective observational study was conducted in the Rheumatology Outpatient Clinic of Erciyes University Faculty of Medicine, Department of Physical Medicine and Rehabilitation.

Participants aged 18 years or older who met the RA classification criteria proposed by American College of Rheumatology/ European League Against Rheumatism (EULAR) in 2010 (19), and who agreed to participate in the study were included in the study after written informed consent was obtained. The clinical and demographic data of the patients were analyzed prospectively, while the results of the blood and imaging studies were evaluated retrospectively. In this study, a certain threshold was set for the evaluation of patients using GCs. Patients using 5 mg prednisolone or an equivalent dose of GCs for at least three months were classified as the low-dose corticosteroid group (20). Also demographic characteristics such as gender, age, and BMI, clinical data such as disease duration, comorbidities (diabetes, hypertension, cardiovascular diseases), smoking, drugs used in RA treatment, GC use and fracture history were evaluated with a standardized form.

Assessment of disease activity was performed using the disease activity score-28 (DAS-28), which is a tool designed to assess disease activity in RA across 28 joints. The DAS-28 score is calculated based on the count of tender and swollen joints, levels of erythrocyte sedimentation rate or C-reactive protein value, and the patient's global visual analog scale (VAS) assessment (21). The assessment of fatigue levels was conducted utilizing a VAS, wherein participants were invited to indicate their level of fatigue on a scale ranging from 0-10, with 0 representing no fatigue and 10 representing unbearable fatigue. The evaluation of quality of life was facilitated by the rheumatoid arthritis quality of life scale (RAQoL). The RAQoL has been meticulously developed to assess how RA influences daily life activities, individual skills, coping mechanisms and social relationships. The total score obtained from the scale ranges from 0-30, with higher scores indicating deterioration in quality of life (22). There is a Turkish validity and reliability study of the RAQoL scale (23).

Assessment of Bone Mineral Density

An investigation into body composition and bone mineral density (BMD) assessment was conducted, with BMD measurements being evaluated in the lumbar spine (L1-L4) and femur using dual-energy X-ray absorptiometry (DEXA). The DEXA measurements were performed at Erciyes University Faculty of Medicine, Department of Nuclear Medicine, with the data obtained using the Hologic QDR series X-ray bone densitometer (USA) being analyzed from the system. The diagnosis of OP was made according to the World Health Organization criteria, with a T-score ≤-2.5 being indicative of the condition (24).

The Erciyes University Faculty of Medicine Clinical Research Ethics Committee reviewed and approved the study protocol (approval no: 2021/613, date: 22.09.2021). The study was conducted following the tenets of the Declaration of Helsinki.

Statistical Analyses

IBM SPSS 23.0 software was used for data analysis. The Shapiro-Wilk test was employed to assess the normal distribution of data. To assess differences in categorical variables across groups, chi-square and Fisher's exact tests were applied. Normally distributed variables were compared using the independent samples t-test, whereas the Mann-Whitney U test was applied for data that did not follow a normal distribution. Logistic regression analysis (univariate and multiple models) was performed to identify independent predictors of OP in RA patients. Of the 74 patients included in the study, 39 who were diagnosed with OP were included in the regression analysis. Potential and statistically significant predictor variables in simple comparison or univariate analysis were included in the model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each. Statistical significance was set at $p<0.05$ unless otherwise stated.

Results

The present study comprised a total of 74 patients and 39 healthy control subjects. The mean age of the patients was 56.81±7 years and 54.07±7.44 years in the control group. There was no statistically significant difference in age between the two groups (p=0.070). The study found that 97.3% (n=72) of the patients and 94.9% (n=37) of the control group were female, and no significant difference was found between the groups in terms of gender distribution (p=0.607). Similarly, no significant difference was found between the two groups in terms of BMI (p=0.146). The mean disease duration in the patient group was 14.02±6.20 years, with rheumatoid factor (RF) positivity detected in 74.3% and ACPA positivity in 81.7% of the patients. The prevalence of comorbidities among the patient population was found to be 66.7%, with the most prevalent being hypertension (34.6%) and neuropathic pain (21.0%). Regarding treatment modalities, 44.4% of patients were administered GCs, while 43.2% were undergoing biological DMARD therapy. Furthermore, 48.8% of the patient group were undergoing treatment for OP. The mean vitamin D levels were 22.95 ng/mL (17.55-32) in the patient group and 24.2 ng/mL (15.50-31.3) in the control group, and no significant difference was observed between the two groups (p=0.914).

Concerning BMD, the patient group exhibited statistically significantly lower T-scores. Notably, the T-scores in the L1-L4 vertebrae and femur regions demonstrated a marked decrease compared to the control group ($p<0.001$). Comprehensive data are delineated in Table 1.

Table 1. Demographic, clinical, and bone mineral density characteristics of patients with rheumatoid arthritis and healthy controls

	Patients (n=74)	Controls (n=39)	p
Age, year	56.81±7	54.07±7.44	0.070[β]
Female gender, n (%)	72 (97.3)	37 (94.9)	0.607
BMI (kg/m²)	31.8±5.6	33.4±5.3	0.146*
Disease duration, years	14.02±6.20		
RF positivity, n (%)	55 (74.3)		
RF titer	31.75 (12.88-77.40)		
ACPA positivity, n (%)	60 (81.7)		
ACPA titer	241.5 (33.12-500)		
Comorbidities			
Yes, n %	54 (66.7)		
Cardiac disease, n (%)	13 (16)		
Pulmonary disease, n (%)	16 (19.8)		
Hypertension (HT), n (%)	28 (34.6)		
Neuropathy, n (%)	17 (21.0)		
Diabetes mellitus (DM), n (%)	9 (11.1)		
Hypothyroidism, n (%)	9 (11.1)		
Current steroid dose (mg)	0 (0-5)		

Table 1. Continued

	Patients (n=74)	Controls (n=39)	p
Total steroid duration (months)	12 (3.75-30)		
Tender joint count	4.10±4.32		
Swollen joint count	0.45±1.02		
Patient global score	5.04±1.90		
Physician global score	4.36±1.86		
CRP (mg/L)	3.67 (1.5-7.71)		
ESR (mm/h)	23 (15-32.5)		
DAS28-ESR	3.43±1.04		
DAS28-CRP	3.02 (2-3.61)		
VAS Fatigue	5 (4-7)		
RAQoL	15.36±7		
Treatments			
Steroid use, n (%)	36 (44.4)		
MTX use, n (%)	61 (75.3)		
HCQ use, n (%)	57 (77)		
SSZ use, n (%)	34 (45.9)		
LEF use, n (%)	31 (41.9)		
bDMARD use, n (%)	32 (43.2)		
Anti-TNF use, n (%)	14 (18.9)		
JAK inhibitors use, n (%)	5 (6.8)		
Abatacept use, n (%)	3 (4.1)		
IL-6 inhibitor use, n (%)	4 (5.4)		
OP treatment, n (%)	39 (48.8)		
OP diagnosis duration (months)	18.5 (0-89)		
OP medications used			
Bisphosphonates use, n (%)	24 (29.6)		
Denosumab use, n (%)	16 (19.8)		
Vitamin D (ng/mL)	22.95 (17.55-32)	24.2 (15.50-31.3)	0.914
L1 BMD (g/cm²)	0.860±0.15	0.96±0.12	0.000*
L2 BMD (g/cm²)	0.90±0.16	1.01±0.12	0.000$^{\beta}$
L3 BMD (g/cm²)	1.22±2.33	1.02±0.21	0.005$^{\beta}$
L4 BMD (g/cm²)	0.92±0.14	1.0±0.21	0.001$^{\beta}$
L1-L4 BMD (g/cm²)	0.89±0.15	1.01±0.12	0.000$^{\beta}$
L1 T-score	-1.34±1.31	-0.27±1.02	0.000*
L2 T-score	-1.18±1.43	-0.21±1.11	0.000$^{\beta}$
L3 T-score	-1.3±1.19	-0.35±1.28	0.000
L4 T-score	-1.4±-1.28	-0.20±1.12	0.000$^{\beta}$
L1-L4 T-score	-1.3±1.20	-0.31±1.11	0.000$^{\beta}$
Femoral neck BMD (g/cm²)	0.73±0.11	0.80±0.27	0.000$^{\beta}$
Total femur BMD (g/cm²)	0.84±0.168	0.95±0.17	0.000$^{\beta}$
Femoral neck T-score	-0.99±1.06	-0.22±1.05	0.000
Total femur T-score	-0.79±0.98	0.26±0.96	0.000*

n: Number of patients, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, DAS28: Disease activity score in 28 joints, VAS: Visual analog scale, RAQoL: Rheumatoid arthritis quality of life, MTX: Methotrexate, HCQ: Hydroxychloroquine, SSZ: Sulfasalazine, LEF: Leflunomide, bDMARD: Biologic disease-modifying antirheumatic drug, TNF: Tumor necrosis factor, JAK: Janus kinase, IL-6: Interleukin-6, BMD: Bone mineral density, T-score: Standard deviation score used to assess bone density, OP: Osteoporosis, *: Independent Samples t-test, $^{\beta}$: Mann-Whitney U test

A comparison was made between individuals who used corticosteroids (n=36) and those who did not use corticosteroids (n=38). The results revealed that BMI (p=0.012) and total femur T-score (p=0.011) were significantly lower in the corticosteroid group. However, no significant differences were observed between the two groups for other demographic, clinical and laboratory parameters. A comprehensive overview of the findings is provided in Table 2.

In the present study, a comparison was made between RA patients diagnosed with OP who used corticosteroids (n=24) and those who did not use corticosteroids (n=15). No significant difference was found in terms of demographic, clinical and laboratory characteristics, and DEXA results (Table 3).

Logistic regression analysis was performed to evaluate the factors affecting the presence of OP in both univariate and multivariate models. Univariate analysis revealed a significant

Table 2. Comparison of bone mineral density and t-scores in rheumatoid arthritis patients with and without corticosteroid use

	Patients without corticosteroid (n=38)	Patients with low-dose corticosteroid (n=36)	p
Age (years)	55.7±7.4	57.9±6.4	0.197$^{\beta}$
Female gender, n (%)	37 (97.4)	35 (97.2)	0.969
BMI (kg/m²)	33.35±5.20	30.13±5.52	**0.012***
Disease duration (years)	14.23±6	13.4±6.60	0.564*
CRP (mg/L)	5.16±7.17	7.48±8.08	0.241$^{\beta}$
ESR (mm/h)	26.27±12.9	23.9±15	0.390$^{\beta}$
DAS28-ESR	3.39±1.02	3.5±1.08	0.567*
DAS28-CRP	2.89±1.22	2.98±1	0.364$^{\beta}$
VAS fatigue	5.35±2	5.5±1.72	0.542*
RAQOL	14.21±6.46	16.57±7.40	0.132*
Vitamin D level (ng/mL)	24.83±9.38	24.7±11.05	0.491*
Fracture presence, n (%)	3 (8.3)	4 (12.1)	0.603
Hip fracture presence, n (%)	0 (0)	1 (3)	0.293
Smoking status			
Never	28 (77.8)	24 (72.7)	0.874
Former smoker	5 (13.9)	6 (18.2)	
Current smoker	3 (8.3)	3 (9.1)	
Exercise frequency			
None	14 (38.9)	20 (60.06)	0.107
1-5 days per week	20(55.6)	10 (30.3)	
≥5 days per week	2 (5.6)	3 (9.1)	
L1 BMD (g/cm²)	0.86±0.14	0.85±0.16	0.777*
L2 BMD (g/cm²)	0.91±0.16	0.90±0.16	0.461*
L3 BMD (g/cm²)	0.95±0.13	0.98±0.23	0.737$^{\beta}$
L4 BMD (g/cm²)	0.93±0.15	0.90±0.14	0.363*
L1-L4 BMD (g/cm²)	0.90±0.16	0.90±0.14	0.830*
L1 T-score	-1.25±1.25	-1.43±1.4	0.478*
L2 T-score	-1.05±1.5	-1.31±1.41	0.392*
L3 T-score	-1.23±1.19	-1.33±1.21	0.651*
L4 T-score	-1.20±1.31	-1.4±1.25	0.388*
L1-L4 T-score	-1.21±1.21	-1.40±1.22	0.429*
Femoral neck BMD (g/cm²)	0.75±0.115	0.70±0.09	0.33*
Total femur BMD (g/cm²)	0.87±0.12	0.79±0.19	0.069$^{\beta}$
Femoral neck T-score	0.88±0.13	0.81±0.12	0.13*
Total femur T-score	-0.5±0.94	-1.09±0.94	**0.011***

n: Number of patients, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, DAS28: Disease activity score in 28 joints, VAS: Visual analog scale, RAQoL: Rheumatoid arthritis quality of life, BMD: Bone mineral density, *: Independent samples t-test, $^{\beta}$: Mann-Whitney U test

association between the risk of OP and age and corticosteroid treatment. The risk of OP increased significantly with increasing age (OR=1.15, 95% CI: 1.06-1.25, p=0.001). Conversely, patients receiving corticosteroid therapy exhibited a significantly lower risk of OP (OR=0.34, 95% CI: 0.13-0.88, p=0.027). The analysis revealed that factors such as gender, BMI, disease duration, vitamin D levels, and fracture history did not attain statistical significance in their association with OP (p>0.05). However, no significant association between ACPA and RF and BMD was found in our study (data not shown).

Multivariate analysis indicated that age and corticosteroid treatment were independent risk factors for OP. The risk of OP increased with age (OR=1.13, 95% CI: 1.04-1.24, p=0.005), while the risk remained significantly lower in patients receiving corticosteroid therapy (OR=0.36, 95% CI: 0.11-0.99, p=0.048). The remaining variables exhibited no statistically significant impact on OP (Table 4).

Discussion

The present study evaluated the effects of low-dose corticosteroid use on BMD, OP risk, and clinical parameters in patients with RA. A comparison was made between the BMD values measured by DEXA in RA patients and those in a healthy control group. It was found that BMD values were significantly lower and T-scores decreased in the L1-L4 vertebrae and femur regions in RA patients. Furthermore, in the RA patient group, BMI and total femur T-score were lower in patients using corticosteroids. However, no significant differences were observed between the two groups concerning other demographic, clinical, and laboratory variables. Logistic regression analysis revealed that age emerged as an independent risk factor for OP, while corticosteroid use was not found to increase the risk of OP, but was inversely associated with the likelihood of its development.

The risk of OP is elevated in patients suffering from RA in comparison to the general population, and this increase can

Table 3. Comparison of clinical and bone mineral density parameters between rheumatoid arthritis patients with osteoporosis using and not using corticosteroids

	GC users (n=24)	Non-GC users (n=15)	p
Age (years)	59±6.46	60±3.83	0.618$^{\beta}$
Female gender, n (%)	23 (95.8)	15 (100)	0.423
BMI (kg/m^2)	30.6±5.5	33.6±5.6	0.064*
Disease duration (years)	14.14±6.48	15.06±5.20	0.857*
RF positivity, n (%)	16 (66.7)	10 (66.7)	1
ACPA positivity, n (%)	20 (83.3)	10 (66.7)	0.229
Vitamin D level (ng/mL)	27.39±11.15	24.86±9.80	0.467$^{\beta}$
Fracture presence, n (%)	3 (13.6)	1 (6.7)	0.503
Hip fracture presence, n (%)	1 (4.5)	0 (0)	0.403
L1 BMD (g/cm^2)	0.76±0.10	0.73±0.09	0.282*
L2 BMD (g/cm^2)	0.805±0.105	0.781±0.104	0.377*
L3 BMD (g/cm^2)	1.814±4.32	0.828±0.089	0.172$^{\beta}$
L4 BMD (g/cm^2)	0.856±0.109	0.819±0.109	0.336*
L1-L4 BMD (g/cm^2)	0.822±0.81	0.794±0.085	0.248*
L1 T-score	-2. 17±0.91	-2.3±0.88	0.540*
L2 T-score	-2. 05±1.01	-2.25±0.97	0.424*
L3 T-score	-2.02±0.78	-2.32±0.80	0.206*
L4 T-score	-1.86±1	-2.2±0.99	0.330*
L1-L4 T-score	-2.05±0.76	-2.3±0.77	0.280*
Femoral neck BMD (g/cm^2)	0.67±0.07	0.71±0.11	0.279*
Total femur BMD (g/cm^2)	0.77±0.11	0.82±0.09	0.156*
Femoral neck T-score	-1.38±1.13	-0.95±1.17	0.133$^{\beta}$
Total femur T-score	-1.4±0.92	-0.1±0.75	0.165*

n: Number of patients, BMI: Body mass index, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, BMD: Bone mineral density, GC: Glucocorticoid, *: Independent samples t-test, : Mann-Whitney U test

Table 4. Univariate and multivariate logistic regression analysis of factors associated with osteoporosis

	Osteoporosis			
	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.15 (1.06-1.25)	0.001	1.13 (1.04-1.24)	0.005
Gender (female)	1.15 (0.07-19)	0.922		
BMI (kg/m²)	0.97 (0.89-1.06)	0.574		
Disease duration (years)	1.03 (0.97-1.10)	0.252	1.04 (0.95-1.13)	0.393
Vitamin D level (ng/mL)	1.03 (0.98-1.08)	0.208	1.03 (0.97-1.09)	0.294
Fracture presence, n (%)	0.85 (0.17-4.13)	0.844		
Steroid use, n (%)	0.34 (0.13-0.88)	0.027	0.36 (0.11-0.99)	0.048

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

be attributed to several interconnected mechanisms. Immune-mediated processes and inflammatory cytokines contribute to the development of OP by directly affecting bone metabolism. Chronic inflammation in RA causes bone loss by increasing osteoclast activity driven by synovial fibroblasts, macrophages, and Th17 cells. This process promotes osteoclastogenesis through increased expression of RANKL and suppression of OPG. Furthermore, the Wnt pathway, which is critical for osteoblast activity, is inhibited by increased DKK-1 and sclerostin levels (25). This results in a reduction in the activity of osteoblasts, leading to insufficient bone formation.

Pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha, interleukin-6, and interleukin-1) play a key role in RA-related bone loss. These cytokines enhance osteoclast activity through increased RANKL expression while concurrently suppressing osteoblast function by inhibiting the Wnt signaling pathway. This imbalance causes reduced bone formation and increased bone resorption, contributing to OP in RA patients (26). A Mendelian randomization study has indicated that the association between RA and OP/BMD may be predominantly attributable to secondary factors. These factors encompass the utilization of antirheumatic therapy and diminished physical activity. It is conceivable that prior observational studies may have been influenced by these variables (27).

GCs cause bone loss by promoting osteoblast and osteocyte apoptosis, inhibiting osteoblast formation, and increasing osteoclast activity. GCs impair osteoblast function and negatively affect bone turnover by suppressing the WNT and RANK-RANKL-osteoprotegerin pathways. Increased levels of RANKL lead to bone destruction by increasing osteoclast activity, while inhibition of the WNT pathway reduces osteoblast activity (26,28). GCs inhibit osteoblast function by suppressing IGF-1 transcription. They also affect bone mineralization by reducing intestinal calcium absorption and causing loss of muscle mass. These mechanisms play a central role in the development of GC-induced OP (29,30). The impact of low-dose corticosteroids on bone health remains controversial, with conflicting evidence in the literature (31). While some studies suggest that corticosteroids may increase bone loss, other studies show that this effect is not evident with low-dose and short-term use (32). In addition, corticosteroid use is generally associated with a more severe disease course and poorer functional status, suggesting an association between the degree of systemic inflammation and fracture risk. Some recent studies have suggested that low-dose, short-term systemic GC use may stabilize bone metabolism by controlling inflammation rather than increasing the risk of bone loss (5).

Previous studies have reported that the use of corticosteroids causes a loss of BMD, particularly in the hip. A meta-analysis showed that RA patients treated with GC had decreased BMD at the femoral neck and spine and higher fracture rates compared with non-GC or healthy controls (33). Hall et al. (34) observed a decrease in BMD at the spine and hip in RA patients using steroids, but this decrease was more pronounced in the hip region. Martin et al. (14) demonstrated a decrease in appendicular (hip region) bone mass in RA patients receiving low-dose corticosteroids. In addition, another study suggested that the most adverse effect of corticosteroids was seen in the hip rather than the spine, and that the reliability of spinal BMD measurements may be reduced by comorbidities such as osteoarthritis (35). Our study also supports these findings because the total femur T-score was significantly lower in patients using GCs compared to the RA group. This suggests that GCs may increase bone loss, particularly in the hip, and bone health in the femur may be more at risk. However, it should be noted that in the multivariate regression analysis of our study, the use of GCs was found to be a protective factor against OP. This finding suggests that the anti-inflammatory effects of GCs may have a potential protective role against bone loss. Chronic inflammation itself is an important factor that can cause bone loss in RA, and GCs may indirectly limit bone loss by suppressing this inflammation. In addition, patients on corticosteroids are more frequently screened for OP and may be more likely to receive OP treatment, which may also explain the protective effect.

One study showed that RA patients had lower BMD compared with an age-matched non-RA control group. BMD values in the RA control group were found to be higher than those in the RA group on steroids, despite longer disease duration. In

particular, it has been reported that the synergistic effect of methotrexate and low-dose GCs may contribute to bone loss, but GCs combined with DMARDs may have beneficial effects in terms of preserving bone mass (36). Significant BMD loss at the femoral neck and lumbar spine was found in RA patients with and without low-dose prednisolone in a study of 84 RA patients (33). Another study found no significant difference in BMD loss between the two groups during a mean follow-up of 89.6 months and concluded that low-dose oral GCs do not increase the overall risk of OP in RA patients (17). Similarly, another study found that low-dose GCs were not directly associated with BMD (37) but cumulative prednisone levels were higher in osteopenic women (38).

However, a study using the Clinical Practice Research Datalink found no difference in the risk of osteoporotic fractures between current low-dose oral GC use (≤7.5 mg PED/day) and past GC use in RA patients. However, low-dose GC use was associated with an increased risk of clinical vertebral fracture (39). In another study, no increased risk of OP fracture was found in RA patients with an average daily dose ≤5.0 mg. However, an increased risk of OP fracture was reported for doses >5.0 mg (40). In addition, a review conducted by the EULAR showed that reviews of the harms of long-term GC therapy (including OP and OP fractures) in RA patients could not reach a definitive conclusion for the dose range of 5-10 mg PED daily (41). These conflicting results suggest that the effects of GCs on bone health should be assessed not only by BMD measurements, but also by fracture risk and bone turnover markers. Findings suggest that osteoporotic fractures may occur early in women with RA, independent of GC use (42). A previous study reported that the risk of osteoporotic fracture was higher in patients using GCs, even in the presence of osteopenia, compared with the control group. It was emphasized that this increased risk was also seen in patients using low doses of GCs and that the adverse effects of GCs on bone were not only due to high-dose use (20). There are studies suggesting that bone quality, which cannot be assessed with current techniques, may be more affected by GCs than BMD. Van Everdingen et al. (43) reported an increased rate of vertebral fractures despite no significant difference in BMD. Various methods such as magnetic resonance imaging, quantitative computed tomography, and nuclear magnetic resonance have been proposed to measure bone quality (44). However, because BMD measurement is inexpensive and widely available, it is the most commonly used method in clinical practice. Therefore, almost all diagnostic criteria for OP and osteopenia are based on BMD (24). This suggests that although BMD is an important indirect measure of fracture risk, the risk of fracture from corticosteroid use may be high, especially in postmenopausal patients. Therefore, a more comprehensive assessment of the effects of GCs on bone must take into account the incidence of fractures and structural changes in bone microstructure. It has been suggested that patients on GCs have a higher risk of osteoporotic fractures than controls, despite having higher BMD (45). A meta-analysis of observational studies showed that the incidence of hip and vertebral fractures after GC use was higher than estimates based on BMD reduction alone (46). The fact that GCs induces micro-architectural changes in certain active bone zones may explain this (47). However, these changes are not directly reflected by a decrease in BMD. In our study, although we evaluated the incidence of fractures, we did not find a significant difference between the groups in terms of hip fractures. However, the limited number of participants makes it difficult to make a definitive judgment on this issue. Larger studies with longer follow-ups are needed to better understand the changes in bone microstructure, especially in patients using GCs. In the future, analyses based not only on BMD measurements but also on advanced techniques to assess bone microarchitecture may help to predict fracture risk more accurately.

Body composition and age are closely related to BMD. Previous studies have shown that lean body mass and fat mass have beneficial effects on bone mass. In particular, it has been reported that lean body mass may support bone mass through mechanical loading forces on bone, whereas fat mass may influence osteoblast/osteoclast function by increasing BMD through hormonal metabolism of adipocytes (37). In the present study, there was no significant difference in BMI between the healthy control group and the RA patients, while it was observed that the BMI of RA patients using GCs was lower. Previous studies have shown that fat and lean body mass are significantly lower in osteoporotic women (37). The metabolic effects of GC use and loss of lean mass through increased muscle protein breakdown may be one of the mechanisms that explain the lower BMI. In addition, the low levels of physical activity commonly observed in RA patients may contribute to both bone loss and loss of lean mass.

The relationship between age and the loss of bone mass in people with RA has been shown in previous studies (31). This association is expected because older people have a longer exposure to risk factors that can lead to bone loss. These factors include GC use, low estrogen levels, prolonged immobility, and increased inflammation. Similarly, in our study, we used logistic regression analysis to show that older age is an independent risk factor for OP. This finding highlights the determinant effect of age on bone health and supports the importance of early OP screening in RA patients.

Previous studies have suggested that RF may exert a titration-dependent effect on BMD, and that the effect may be more pronounced in combination with ACPA by creating a subclinical inflammatory environment due to increased immune complex activity. Furthermore, low BMD, particularly in the femoral neck, has been reported to be associated with the presence of ACPA and RF. Therefore, careful monitoring of OP in seropositive RA patients is recommended (48). However, no significant association between ACPA and RF and BMD was found in our study.

A multifaceted approach, including lifestyle changes, optimal nutrition, and structured exercise programs, is essential to

reduce the risk of OP and fractures in people with RA. Studies have shown that regular weight-bearing and resistance exercise improves bone and muscle health and reduces the risk of fractures. These non-pharmacological strategies, when combined with appropriate medical treatment, can help people with RA maintain bone strength and overall musculoskeletal health (49). However, our study observed that approximately half of the RA patients did not engage in regular exercise. This finding highlights that physical inactivity remains a significant issue among RA patients and represents a contributing factor to the increased risk of OP. Lack of exercise can lead to a reduction in lean body mass, decreased muscle strength, and accelerated bone loss, thereby increasing the risk of falls and fractures through a critical pathophysiological mechanism. Therefore, strategies for OP management in RA patients should not be limited to pharmacological treatment alone but should also incorporate structured exercise programs and lifestyle modifications.

The study used a prospective design and analyzed the patients' clinical and laboratory data in detail. Factors that may influence the risk of OP, such as vitamin D levels, smoking, and exercise frequency, were recorded, and the groups were directly compared with regard to GC use. In addition, OP risk factors were evaluated using both univariate and multivariate models, and new data were presented that may contribute to studies in this area, which have so far produced conflicting results.

Study Limitations

Our study has some limitations. The relatively small number of patients may limit the generalizability of the results, so studies with larger cohorts are needed. In addition, as this is an observational study, it is not possible to establish a causal relationship with certainty. The long-term effects of the duration and dose of corticosteroid use could not be fully assessed in this study, so this effect should be investigated in more detail in future long-term follow-up studies. In addition, dietary intake and dietary characteristics were not assessed, so these factors should be investigated in future studies for their possible effects on OP risk.

Conclusion

Our findings suggest that low-dose GC use does not elevate OP risk in RA patients and may, in some cases, be linked to a lower risk. However, further large-scale longitudinal studies are needed to confirm this association. Age stands out as one of the strongest predictors of OP. Adopting individualized treatment approaches to effectively manage OP in RA patients is considered an important strategy for maintaining bone health.

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Ethics

Ethics Committee Approval: The Erciyes University Faculty of Medicine Clinical Research Ethics Committee reviewed and approved the study protocol (approval no: 2021/613, date: 22.09.2021).

Informed Consent: Who agreed to participate in the study were included in the study after written informed consent was obtained.

Footnotes

Authorship Contributions

Concept: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C., Design: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C., Data Collection or Processing: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C., Analysis or Interpretation: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C., Literature Search: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C., Writing: S.K.B., H.K., T.F.Ç., G.C., S.S., İ.C.

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