Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2026.76069
Turk J Osteoporos

The Relationship Between Rheumatoid Arthritis and Osteoporosis and Factors Contributing to This Connection

Romatoid Artrit ile Osteoporoz Arasındaki İlişki ve Bu Bağlantıya Katkıda Bulunan Faktörler

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Abstract

Objective: Rheumatoid arthritis (RA) is a chronic autoimmune condition marked by ongoing synovial inflammation and associated with multiple extra-articular manifestations, including osteoporosis (OP). Loss of bone mineral density (BMD) in RA arises from ongoing inflammation, glucocorticoid therapy, reduced mobility, and several metabolic influences. This study sought to ascertain the prevalence and pattern of OP among RA patients and to identify clinical, biochemical, and disease-related factors linked to reduced BMD.

Materials and Methods: This prospective cross-sectional research (January 2024-January 2025) included 120 adults diagnosed with RA. Clinical evaluation comprised the disease activity score-28 (DAS-28) in addition to the health assessment questionnaire disability index. Laboratory investigations involved measuring vitamin D, calcium, parathyroid hormone, thyroid function, and inflammatory indicators. Dual-energy X-ray absorptiometry was employed for estimating BMD and it was categorized in accordance with World Health Organization standards.

Results: Of the 120 participants (mean age 41.5 years; 90% women), 33.3% exhibited reduced BMD, with 29.1% meeting criteria for OP. Individuals with decreased BMD tended to be older, had lower body mass index, longer RA duration, elevated thyroid-stimulating hormone, more frequent subclinical hypothyroidism (25% vs. 10%), and reduced vitamin D. They also showed higher disease activity (DAS-28: 4.9 vs. 2.6, $p<0.001$). Independent predictors of decreased BMD were advanced age, female sex, prolonged disease duration, subclinical hypothyroidism, vitamin D deficiency, and elevated DAS-28.

Conclusion: OP is prevalent and multifactorial in RA. Routine evaluation of thyroid function, vitamin D status, and strict disease activity control are vital to mitigate bone loss.

Keywords: Osteoporosis, rheumatoid arthritis, bone mineral density, vitamin D

Öz

Amaç: Romatoid artrit (RA), eklem iltihabı ve yıkımının yanı sıra osteoporoz (OP) gibi belirgin ekstra-artiküler komplikasyonlarla seyreden kronik sistemik otoimmün bir hastalıktır. RA'da kemik mineral yoğunluğu (KMY) kaybı, kronik enflamasyon, glukokortikoid kullanımı, immobilite ve metabolik faktörlerin birleşik etkisiyle gelişir. Bu çalışma, RA hastalarında OP prevalansını belirlemeyi ve düşük KMY ile ilişkili klinik, biyokimyasal ve hastalıkla ilişkili belirteçleri tanımlamayı amaçladı.

Gereç ve Yöntem: Ocak 2024-Ocak 2025 tarihleri arasında yapılan bu prospektif kesitsel çalışmaya 120 erişkin RA hastası dahil edildi. Klinik değerlendirmede sağlık değerlendirme anketi engellilik indeksi ve hastalık aktivite skoru-28 (DAS-28) kullanıldı. Laboratuvar incelemelerinde tiroid fonksiyon testleri, D vitamini, kalsiyum, paratiroid hormonu ve enflamatuvar belirteçler değerlendirildi. KMY, çift enerjili X-ışını absorbsiyometri yöntemiyle ölçülerek Dünya Sağlık Örgütü kriterlerine göre sınıflandırıldı.

Bulgular: Ortalama yaşı 41,5 olan 120 hastanın (%90'ı kadın) %33,3'ünde anormal KMY, %29,1'inde ise OP saptandı. Anormal KMY'ye sahip hastalar daha ileri yaşta, daha düşük beden kütle indeksine sahip, daha uzun hastalık süresine, yüksek tiroid uyarıcı hormon düzeylerine,

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Received/Geliş Tarihi: 28.11.2025 **Accepted/Kabul Tarihi:** 23.04.2026 **Epub:** 05.05.2026

Cite this article as/Atıf: Ibrahem EM, Haridi MAMA, Ebrahim FTS. The relationship between rheumatoid arthritis and osteoporosis and factors contributing to this connection. Turk J Osteoporos. [Epub Ahead of Print]

daha sık subklinik hipotiroidiye (%25'e karşı %10) ve daha düşük D vitamini düzeylerine sahipti. Ayrıca bu hastalarda hastalık aktivitesi daha yüksekti (DAS-28: 4,9'a karşı 2,6; p<0,001). Düşük KMY'nin bağımsız belirteçleri ileri yaş, kadın cinsiyet, uzun RA süresi, subklinik hipotiroidi, D vitamini yetersizliği ve yüksek DAS-28 olarak belirlendi.

Sonuç: OP, RA hastalarında yaygın ve çok faktörlü bir komplikasyondur. Tiroid fonksiyonlarının ve D vitamini düzeylerinin rutin değerlendirilmesi ile hastalık aktivitesinin etkin kontrolü, kemik kaybını önlemede kritik öneme sahiptir. Elde edilen bulguların desteklenmesi amacıyla ek araştırmalar yapılması gerekmektedir.

Anahtar kelimeler: Osteoporoz, romatoid artrit, kemik mineral yoğunluğu, D vitamini

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder marked by constant synovial inflammation, cumulative joint damage, and a spectrum of extra-articular manifestations. In addition to its prominent effects on the musculoskeletal system, RA is now recognized as a multisystem disorder linked to several systemic complications, including cardiovascular morbidity, hematologic abnormalities, and importantly, osteoporosis (1,2).

Osteoporosis—defined by diminished bone mineral density (BMD) and degradation of bone microarchitecture—represents an integral source of patient morbidity in RA because it markedly heightens the risk of fragility fractures (3,4). Chronic inflammation, long-standing corticosteroid use, immobility, and nutritional deficiencies collectively contribute to accelerated bone loss in this population (5).

Chronic inflammatory conditions such as RA promote excessive release of pro-inflammatory cytokines, which disturb the normal equilibrium between bone formation and resorption. This cytokine-driven imbalance alters bone composition and plays a leading role in the evolution of osteoporosis among individuals with RA (6).

In the current study our objective was to explore the association between RA and osteoporosis and focusing on the key factors that may cause or affect osteoporosis progress in patients with RA.

Materials and Methods

Study Setting and Design

The present study was structured as a hospital-based cross-sectional prospective study and implemented in outpatient clinics and rheumatology unit in the department of internal medicine. It was performed in the period between January 2024 and January 2025. The present study was registered at clinicaltrials.gov with NCT06038292.

Selection Criteria

Adults with a confirmed diagnosis of RA, verified according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (7), aged at least 18 years or older were included in the study.

Participants were ruled out if they had any condition that could independently affect bone metabolism, including pregnancy, lactation, hyperthyroidism, primary hyperparathyroidism, Cushing's syndrome, prolonged immobility, osteomalacia, malabsorption disorders, malignancy, or if they were receiving antiresorptive or anabolic therapy for osteoporosis.

Sample Size Calculation

The sample size was anticipated via G*Power version 3.1.9.4, with parameters set at a 5% alpha level, 80% statistical power, and a 95% confidence interval. Considering that the prevalence of osteoporosis among individuals with RA is approximately 20% (up to 50% in postmenopausal women) and nearly double that of the general population (8), the calculated sample size was 106 participants. To compensate for potential attrition, 120 patients were ultimately enrolled.

Ethical Approval

The research was carried out in full adherence to the ethical rules of the Declaration of Helsinki. Approval was acquired from the Assiut Faculty of Medicine's Ethics Committee (IRB: 04-2024-200741, date: 04.03.2024). Each participant was thoroughly informed about the study objectives and procedures. Prior to enrollment, signed informed consent was acquired.

Data Collection

History taking and clinical evaluation

All participants were evaluated through a thorough medical history review, accompanied by complete general and musculoskeletal examinations. A focused rheumatologic assessment was carried out for each patient, which included clinical evaluation of functional status using the Health Assessment Questionnaire Disability Index (9). Disease activity was estimated using the disease activity score-28 (DAS-28) (10).

Laboratory data

Laboratory investigations included:

- Complete blood count: Determined using an automated hematology analyzer (e.g., Sysmex XN-Series).
- Liver function tests: Involved serum alanine aminotransferase, aspartate aminotransferase, serum albumin, and alkaline phosphatase all measured using enzymatic colorimetric methods on an automated chemistry analyzer (Cobas Integra 400 Plus, Roche Diagnostics, Germany) with commercially available reagent kits supplied by the manufacturer.
- Kidney function tests: Included serum urea and creatinine, analyzed by enzymatic and ion-selective electrode methods using the same automated analyzer (Cobas Integra 400 Plus, Roche Diagnostics) and reagent kits from Roche Diagnostics.

- Erythrocyte sedimentation rate (ESR): Specified by the Westergren method.
- C-reactive protein (CRP): Measured by immunoturbidimetric assay (Roche Diagnostics).
- Serum uric acid, lipid profile (total cholesterol, high density lipoproteins, low density lipoproteins, and triglycerides), random blood glucose, and hemoglobin A1c were also analyzed with Roche reagent kits on the same platform.
- Rheumatoid factor plus anti-cyclic citrullinated peptide antibodies: Identified by indirect immunofluorescence using the Kallestad kit (Bio-Rad Laboratories, USA), as directed by the manufacturer.
- Serum calcium was done by HumaStar 200 automated analyzer (Human Diagnostics Worldwide, Wiesbaden, Germany) utilizing an enzymatic colorimetric method.
- Thyroid function assessment: A chemiluminescence-based analyzer (Dimension VISTA, Siemens Healthcare Diagnostics, Deerfield, IL, USA) was used to detect serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) in order to evaluate thyroid function. The reference values adopted were TSH (0.49-3.29 mU/L), FT4 (9.8-18.8 pmol/L), and FT3 (3.3-6.1 pmol/L), according to the manufacturer's directions.
- Serum parathyroid hormone (PTH) concentrations: Quantified via a chemiluminescent immunoassay using the Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA).
- Vitamin D assessment: Measured using vitamin D ELISA Kit (catalogue no: 201-12-8108, China). vitamin D level was recognized as sufficient [25(OH)D ≥75 nmol/L], insufficient [25(OH)D 50-74 nmol/L], and deficient [25(OH)D <50 nmol/L] according to the Endocrine Society guidelines (11).

Bone mineral densitometry (BMD)

Dual-energy X-ray absorptiometry (DEXA) was used to estimate BMD, performed with a GE Lunar densitometer (Madison, WI 53717-1915, USA). Scans were conducted at the lumbar spine (L2-L4), femoral neck, and distal radius in accordance with standardized operating procedures, with values adjusted for age, sex, body weight, and ethnicity.

Based on the World Health Organization criteria, DEXA-derived T-scores were interpreted as follows: normal BMD (≥-1.0), osteopenia (between -1.0 and -2.5), osteoporosis (≤-2.5), and severe or established osteoporosis (≤-2.5 accompanied by one or more fragility fractures) (12).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 24.0 (IBM Corp., Chicago, IL, USA). Continuous variables were pointed out as mean ± standard deviation or as median (range), while categorical variables were displayed as frequencies and percentages. Comparisons between groups were performed using the chi-square test and independent t-tests. Associations between continuous variables were examined with Pearson's correlation, whereas multivariate regression modeling was utilized to determine independent predictors of reduced (BMD in RA patients. Statistical significance was set at $p<0.05$.

Results

Baseline clinical and demographic data of enrolled patients (Table 1)

The study population had a mean age of 41.54 years, and women constituted the majority of participants (90%). Most individuals were from rural areas (66.7%). The average duration of RA was 6.18 years. Regarding disease activity, 18 patients (15%) were in remission, whereas 39 patients (32.5%) each had mild and moderate activity, and 24 patients (20%) exhibited high activity. Full descriptive characteristics are presented in Table 1.

Laboratory data in enrolled patients (Table 2)

A total of 18 patients (15%) demonstrated thyroid function results compatible with subclinical hypothyroidism. The mean vitamin D level was 62.82 nmol/L, with 90 patients (75%) having sufficient levels and 30 patients (25%) exhibiting vitamin D insufficiency. The average serum calcium concentration was

Table 1. Initial data of the study participants

	n=120
Age (years)	41.54±11.27
Sex	
Male Female	12 (10%) 108 (90%)
Body mass index (kg/m^2)	27.87±3.77
Smoking	15 (12.5%)
Diabetes mellitus	35 (29.2%)
Hypertension	19 (15.8%)
Family history of rheumatoid arthritis	25 (20.8%)
Duration of the disease (years)	6.18±2.19
Lines of therapy	
Corticosteroids Duration (years) Doses (mg)	40 (33.3%) 1.07±0.50 7.50±2.45
Hydroxychloroquine Methotrexate Leflunomide Sulphasalazine Biological agents	102 (85%) 69 (57.5%) 56 (46.7%) 11 (9.2%) 7 (5.8%)
HAQ-DI	1.02±0.06
DAS-28 score	4.78±1.65
Classes of disease activity	
Remission Mild Moderate High	18 (15%) 39 (32.5%) 39 (32.5%) 24 (20%)

Data expressed as mean (standard deviation), frequency (percentage).
HAQ-DI: Health assessment questionnaire-disability index, DAS-28: Disease activity score-28

8.04 g/dL, and the mean PTH level was 36.27 ng/mL. These findings are summarized in Table 2.

DEXA scan and its category among the studied patients (n=120)

Mean BMD was -0.63 (gm/cm^2). Category of patients based on BMD was normal (66.7%), osteopenia (4.2%) and osteoporosis (29.1%). A total of 12 (10%) patients had severe osteoporosis.

Baseline data of studied patients based on DEXA scan (Table 3)

Patients with abnormal BMD were older, had a lower body mass index, and exhibited a significantly longer duration of RA (8.56±3.01 vs. 2.18±0.76 years; p<0.001). This group also demonstrated markedly higher disease activity, as reflected by elevated DAS-28 scores (4.90±1.23 vs. 2.60±1.11; p<0.001). All individuals with reduced BMD had either moderate (40%) or high (60%) disease activity, with none achieving remission or displaying mild activity. Additional details are provided in Table 3.

Table 2. Baseline laboratory data in enrolled patients

	n=120
Hemoglobin (g/dL)	11.52±2.82
Platelets (10^3/uL)	292.37±114.01
Leucocytes (10^3/uL)	7.10±1.67
Urea (mg/dL)	6.25±2.67
Creatinine (mg/dL)	1.08±0.17
Albumin (g/dL)	37.14±5.62
AST (u/L)	29.40±7.34
ALT (u/L)	23.91±8.50
RBG (mg/dL)	135.96±21.89
HbA1C	5.61±0.46
CRP (mg/dL)	11.21±4.44
ESR (mm/hr)	25.67±7.87
LDL (mg/dL)	126.82±39.33
HDL (mg/dL)	42.05±8.63
Triglycerides (TGs) (mg/dL)	157.11±50.80
Cholesterol (mg/dL)	213.19±48
TSH (mu/L)	3.05±1.12
SCH	18 (15%)
Vitamin D (nmol/L)	62.82±18.78
Class of vit. D	
Sufficient Insufficient	90 (75%) 30 (25%)
Calcium (mg/dL)	8.04±2.22
Parathyroid hormone (PTH) (ng/mL)	36.27±13.14

Data represented as frequency (percentage), mean (standard deviation).
AST: Aspartate transaminase, ALT: Alanine transaminase, RBG: Random blood glucose, HbA1C: Glycosylated haemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, SCH: Subclinical hypothyroidism

Laboratory data of patients based on DEXA scan (Table 4)

Patients with low BMD exhibited significantly higher TSH levels (4.05±1.29 vs. 2.05±1.10 µU/L; p<0.001) and a greater prevalence of subclinical hypothyroidism (SCH) compared to those with normal BMD (25% vs. 10%; p=0.03). Additionally, vitamin D levels were notably lower in patients with abnormal BMD (55.03±23.92 vs. 66.71±14.24 nmol/L; p=0.001). Table 4 summarizes the laboratory results comparing the two groups.

Correlation between BMD with other variables (Table 5)

There are negative significant correlations between BMD with age, duration of disease, ESR, CRP and TSH and DAS-28. Meanwhile, there are significant positive correlations between BMD with vitamin D and serum calcium. These results are demonstrated in Table 5.

Table 3. Baseline data of studied patients according to DEXA scan

	Abnormal BMD* (n=40)	Normal BMD (n=80)	p-value
Age (years)	49.20 ± 13.23	40.21±9.99	**<0.001**
Sex			
Male Female	5 (12.5%) 35 (87.5%)	7 (8.8%) 73 (91.3%)	0.36
BMI (kg/m^2)	23.90±3.97	28.09±2.14	**0.01**
Smoking	10 (25%)	5 (6.3%)	0.005
Diabetes mellitus	11 (27.5%)	24 (56%)	0.47
Hypertension	6 (15%)	13 (16.3%)	0.54
Family history of RA	8 (20%)	17 (21.3%)	0.53
Duration (years)	8.56±3.01	2.18±0.76	**<0.001**
Lines of therapy			
Steroid Duration (years) Doses (mg)	10 (25%) 1.06±0.50 7.56±1.98	30 (37.5%) 1.08±0.45 6.89±2.71	0.90 0.56 0.87
Hydroxychloroquine Methotrexate Leflunomide Sulphasalazine Biological agents	37 (92.5%) 22 (55%) 18 (45%) 3 (7.5%) 4 (10%)	65 (81.3%) 47 (58.8%) 38 (47.5%) 8 (10%) 3 (3.8%)	0.08 0.42 0.47 0.48 0.16
HAQ-DI	1.03±0.04	1.01±0.05	0.55
DAS-28 score	4.90±2.60	2.60±1.11	**<0.001**
Classes of activity			
Remission Mild Moderate High	0 0 16 (40%) 24 (60%)	18 (22.5%) 39 (48.8%) 23 (28.7%) 0	**<0.001**

Data provided as mean (standard deviation), frequency (percentage).
BMD: Bone mineral density, BMI: Body mass index, RA: Rheumatoid arthritis, HAQ-DI; Health assessment questionnaire-disability index, DAS: Disease activity score, DEXA: Dual-energy X-ray absorptiometry

Predictors of abnormal BMD in RA (Table 6)

To find independent determinants of low BMD in RA patients, a multivariate logistic regression analysis was carried out. Results were demonstrated as odds ratios with 95% confidence intervals and corresponding p-values. The analysis demonstrated that older age, female sex, longer disease duration, SCH, vitamin D insufficiency, and higher DAS-28 scores were all significant independent predictors of abnormal BMD in RA patients ($p<0.001$ for each). Detailed results are provided in Table 6.

Discussion

Despite significant progress in elucidating the pathogenic mechanisms of RA and the availability of effective pharmacologic therapies, RA-related complications remain a major clinical concern. Osteoporosis is among the most common and debilitating extra-articular manifestations, which leads to increased morbidity and reduced life quality. The chronic inflammatory environment in RA, characterized by heightened levels of cytokines like tumor necrosis factor-α, interleukin-1, and interleukin-6, promotes osteoclast-mediated bone resorption while inhibiting osteoblast function, resulting in progressive and generalized bone loss (1,2).

Therefore, implementing systematic screening for osteoporosis and promptly identifying patients at high risk is crucial. Early detection enables timely preventive and therapeutic strategies, which can reduce fracture incidence and enhance overall musculoskeletal health in subjects with RA.

In this study, 120 patients with confirmed RA were evaluated to determine the prevalence of osteoporosis. Reduced BMD was observed in 40 patients (33.3%), aligning with prior studies that reported similar rates of osteoporosis among RA populations, such as a previous report indicating a prevalence of 27.6% (5), whereas an Egyptian study conducted by Hassan et al. (13) observed that 34% of RA patients had osteoporosis, with 4% experiencing severe forms complicated by fractures.

These findings underscore that individuals with RA face a substantially higher risk of developing osteoporosis in

Table 4. Laboratory data of patients given the DEXA scan

	Abnormal BMD* (n=40)	Normal BMD (n=80)	p-value
Hemoglobin (g/dL)	11.08±2.45	11.98±2.44	0.43
Platelets (10^3/uL)	299±56.87	289.37±108.77	0.08
Leucocytes (10^3/uL)	7.22±1.51	7.09±1.33	0.17
Urea (mg/dL)	6.70±2.09	6.05±2.01	0.29
Creatinine (mg/dL)	1.09±0.23	1.08±0.11	0.11
Albumin (g/dL)	38.14±3.44	37.14±5.06	0.07
AST (u/L)	30±7.21	29.20±7.21	0.22
ALT (u/L)	24.44±8.11	23.01±8.76	0.32
RBS (mg/dL)	136.78±21.21	135.16±21.44	0.48
HbA1C	5.62±0.49	5.59±0.89	0.07
CRP (mg/dL)	18±4.10	5.81±2.01	**0.03**
ESR (mm/hr)	29.89±7.17	11.67±2.34	**0.01**
LDL (mg/dL)	127.91±39.98	123.80±30.11	0.11
HDL (mg/dL)	44.57±8.20	41.15±8.20	0.67
TGs (mg/dL)	160±50.80	156.21±50.77	0.15
Cholesterol (mg/dL)	217.17±34.91	212.89±56.09	0.78
Calcium (mg/dL)	8.02±2.98	8.37±3.09	0.18
PTH (ng/mL)	37.89±13.12	35.67±12.54	0.11
TSH (mu/L)	4.05±1.29	2.05±1.10	**<0.001**
SCH	10 (25%)	8 (10%)	**0.10**
Vitamin D (nmol/L)	55.03±23.92	66.71±14.24	**0.001**
Class of vit. D			**0.002**
Sufficient Insufficient	23 (57.5%) 17 (42.5%)	67 (83.3%) 13 (16.3%)	

Data stated as frequency (percentage), mean (standard deviation).
AST: Aspartate transaminase, ALT: Alanine transaminase, RBS: Random blood sugar, HbA1C: Glycosylated haemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDL: Low density lipoprotein, HDL: High density lipoprotein, TGs: Triglycerides, TSH: Thyroid stimulating hormone, SCH: Subclinical hypothyroidism, BMD: Bone mineral density, *: This included those with osteoporosis and osteopenia, DEXA: Dual-energy X-ray absorptiometry, PTH: Parathormone

Table 5. Correlation between bone mineral density with other variables

	r value (p-value)
Age (years)	**-0.36 (0.03)**
Body mass index (kg/m^2)	0.12 (0.18)
Duration (years)	**-0.41 (0.02)**
Laboratory data	
Hemoglobin (g/dL)	-0.21 (0.06)
Platelets (10^3/uL)	-0.06 (0.91)
Leucocytes (10^3/uL)	-0.10 (0.11)
Urea (mg/dL)	0.11 (0.21)
Creatinine (mg/dL)	0.12 (0.58)
Albumin (g/dL)	0.08 (0.07)
AST (u/L)	0.18 (0.21)
ALT (u/L)	-0.10 (0.21)
RBG (mg/dL)	0.04 (0.41)
HbA1C	0.19 (0.08)
CRP (mg/dL)	**-0.50 (0.001)**
ESR (mm/hr)	**-0.53 (0.001)**
LDL (mg/dL)	0.10 (0.08)
Cholesterol (mg/dL)	0.10 (0.18)
HDL (mg/dL)	0.11 (0.40)
TGs (mg/dL)	0.19 (0.39)
TSH (mu/L)	**-0.55 (0.001)**
Vitamin D (nmol/L)	**0.76 (0.001)**
Calcium (mg/dL)	**0.20 (0.04)**
PTH (ng/mL)	0.10 (0.31)
HAQ-DI	0.18 (0.87)
DAS-28 score	**-0.60 (<0.001)**

AST: Aspartate transaminase, ALT: Alanine transaminase, RBG: Random blood glucose, HbA1C: Glycosylated haemoglobin, LDL: Low density lipoprotein, HDL: High density lipoprotein, TGs: Triglycerides, TSH: Thyroid stimulating hormone, PTH: Parathormone, HAQ-DI: Health assessment questionnaire-disability index, DAS: Disease activity score

comparison with the general population. The elevated risk is multifactorial, involving persistent systemic inflammation, long-term glucocorticoid use, decreased physical activity, hormonal changes, and the direct effects of proinflammatory cytokines on bone turnover (3,4).

In the present study, patients with reduced BMD were older and had lower body mass index compared to those with normal BMD. This aligns with earlier studies that have highlighted advanced age and lower BMI as significant risk factors for osteoporosis in individuals with RA (13-16).

Furthermore, our analysis demonstrated that patients with low BMD were more likely to be smokers. This result is consistent with prior research showing that smoking independently contributes to decreased bone density and an elevated risk of osteoporosis in individuals with RA (17,18).

Table 6. Predictors of abnormal BMD in patients with rheumatoid arthritis

Variables	Odds ratio	95% confidence interval	p-value
Age (years)	1.68	1.22-2.40	**<0.001**
Female sex	3.95	1.22-7.90	**<0.001**
Durtaion of disease (years)	2.09	1.41-5.18	**<0.001**
Smoking	0.89	0.23-1.90	0.19
Steroid therapy	1.32	0.55-2.12	0.57
Albumin (g/dL)	0.78	0.33-1.80	0.09
CRP (mg/dL)	1.24	0.44-2.17	0.21
ESR (mm/h)	1.20	0.78-2.67	0.08
SCH	5.09	3.58-14.78	**<0.001**
Insufficient vitamin D	3.45	2.19-8.10	**<0.001**
DAS-28 score	7.56	4.11-11.98	**<0.001**

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SCH: Subclinical hypothyrodism, DAS-28: Disease activity score-28, BMD: Bone mineral density

Another key observation from our study was that patients with abnormal BMD had a significantly longer duration of RA compared to those with normal BMD. This finding corroborates previous research highlighting that extended disease duration, which reflects the cumulative inflammatory burden, is a critical factor contributing to bone loss and the increased incidence of osteoporosis in RA patients (19,20).

In addition to demographic and lifestyle factors, disease-related variables significantly influence bone health in patients with RA. Our study demonstrated that patients with abnormal BMD had notably higher disease activity, as reflected by elevated DAS28 scores, compared to those with normal BMD. This finding aligns with prior evidence suggesting that increased disease activity exacerbates bone resorption and heightens the hazard of osteoporosis and structural joint damage (13,21).

Similarly, Ismail (22) reported that fracture risk was positively correlated with DAS28-ESR, further highlighting the detrimental impact of uncontrolled inflammation on bone metabolism in patients with RA.

Consistent with the role of inflammation in bone loss, our research spotted that patients with abnormal BMD had significantly greater levels of inflammatory markers, particularly CRP and erythrocyte ESR. Elevated CRP and ESR correlated with greater reductions in BMD, underscoring the detrimental effects of ongoing systemic inflammation on skeletal integrity. These results suggest that monitoring acute-phase reactants may help identify RA patients at heightened risk for osteoporosis.

In this study, glucocorticoid therapy, despite being a recognized risk factor for osteoporosis, revealed no discernible difference between patients with normal and abnormal BMD. Both groups received comparable mean doses and treatment durations. This lack of association may be attributable to the relatively low doses and short-term use of steroids among participants, or to the

influence of other confounding factors, including disease activity, vitamin D insufficiency, and coexisting thyroid dysfunction.

This finding may be explained by the modulatory role of low-dose glucocorticoids on bone metabolism. At low doses, glucocorticoids can mitigate inflammation-driven bone loss during active polyarthritis flares by suppressing pro-inflammatory cytokines, thereby reducing osteoclast activation and limiting bone resorption (23). This anti-inflammatory benefit may, to some extent, offset the direct deleterious effects of GCs on bone metabolism, potentially resulting in a neutral or even favorable net skeletal balance.

Vitamin D is crucial for bone metabolism, calcium homeostasis, and immune system regulation. In our study, patients with abnormal BMD exhibited significantly lesser levels of vitamin D and a greater frequency of vitamin D insufficiency. These results align with prior research demonstrating an inverted relation between status of vitamin D and bone loss in autoimmune conditions, including RA. Additionally, vitamin D deficiency may compromise immune regulation, thereby sustaining systemic inflammation and contributing to RA progression. Although some debate exists, the vast majority of evidence supports the link between lower vitamin D levels and more severe disease manifestations in RA (24,25).

Furthermore, reduced 25(OH)D levels have been linked with sarcopenia and diminished muscle strength, which can exacerbate skeletal fragility in patients with RA. Taken together, these findings highlight the multifaceted role of vitamin D deficiency, affecting both bone density and muscle function, and underscore its contribution to increased fracture risk and overall musculoskeletal vulnerability in RA (26).

Despite that serum calcium and PTH levels did not significantly differ between groups, patients with abnormal BMD exhibited calcium levels at the lower end of normal and a slight elevation in PTH. This pattern likely represents secondary hyperparathyroidism induced by chronic vitamin D deficiency, a recognized contributor to enhanced bone resorption and diminished bone density in RA.

In the present study, thyroid dysfunction, specifically SCH, was significantly more common in patients with low BMD, accompanied by elevated TSH levels. SCH was found to be an independent predictor of abnormal BMD, and the negative correlation between TSH and BMD reinforces this relationship. These results are clinically important, as thyroid hormones are critical regulators of bone turnover, and even mild thyroid dysfunction can favor bone resorption. Prior research has reported thyroid abnormalities in 6-34% of patients with RA (27-29) and suggested that subclinical thyroid abnormalities and variations in TSH levels are associated with altered BMD and a greater fracture risk (30-32).

The principal finding of this study was that multivariate logistic regression identified several independent predictors of abnormal BMD in RA patients: Older age, female sex, longer disease duration, subclinical hypothyroidism, vitamin D insufficiency, and higher DAS-28 scores. These results highlight the multifactorial etiology of bone loss in RA, demonstrating the interplay of inflammatory, endocrine, nutritional, and demographic factors in determining bone health.

Study Limitations

This study acknowledges some limitations. As this is a single-center study included a relatively small number of participants, the extent to which our findings can be applied to larger or more diverse populations may be limited. Longitudinal studies applying larger, more diverse cohorts are warranted to evaluate temporal changes in BMD and the long-term effects of therapeutic interventions.

Nonetheless, the prospective design and standardized data collection over a full year enhance the reliability and internal validity of the observed associations between RA-related variables and BMD.

Conclusion

Osteoporosis is a prevalent and clinically important comorbidity in patients with RA, driven by the combined effects of chronic inflammation, hormonal imbalances, nutritional deficiencies, and disease-specific factors. Key predictors identified in this study—including older age, female sex, longer disease duration, high disease activity, vitamin D insufficiency, and subclinical hypothyroidism—offer valuable guidance for risk stratification. These findings reinforce the importance of routine BMD assessment and metabolic evaluation in RA management. Early identification, effective disease control, correction of modifiable risk factors, and judicious use of bone-protective therapies are critical to reducing fracture risk and improving long-term outcomes in this patient population.

Ethics

Ethics Committee Approval: Approval was acquired from the Assiut Faculty of Medicine's Ethics Committee (IRB: 04-2024-200741, date: 04.03.2024).

Informed Consent: Prior to enrollment, signed informed consent was acquired.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M.I., M.A.M.A.H., F.T.S.E., Concept: E.M.I., M.A.M.A.H., Design: M.A.M.A.H., Data Collection or Processing: F.T.S.E., Analysis or Interpretation: F.T.S.E., Literature Search: E.M.I., F.T.S.E., Writing: E.M.I., F.T.S.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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