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Bone mass density in patients with rheumatoid qrthritis: Influence of disease activity

Mohammadreza Shafiepour[1], Tahereh Kahnooji[2], Zahra Kamiab[3], Mahmood Kahnooji[1], Mitra Abbasifard[1*]

[1] Department of Internal Medicine, Ali-Ibn Abi-Talib Hospital, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [2] Clinical Research Development Unit, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [3] Department of Community Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Rheumatoid arthritis (RA) can affect bone density. Given the significant risk of low bone mass density (BMD) in RA patients, the present study aims to investigate the BMD in these patients. The present cross-sectional study included 415 RA patients from the Rafsanjan Rheumatology Clinic. The patients were included in the study by census based on the inclusion criteria, which included a physician's diagnosis of RA according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, at least three months of disease history, and age between of 35 and 70 years. The BMD was measured using the dual-energy x-ray absorptiometry method in both the hip and the spine, and the RA severity was determined using the disease activity score-28 (DAS-28) index. The mean age of RA patients was 56.49 ± 11.73 years, with females accounting for 86.7% (300 people). The frequency of osteoporosis was 7.5% (26 people), and osteopenia was 43.6% (151 people) based on hip bone density, and 33% (137 people) and 38.1% (158 people) based on spine density, respectively. Age, fracture history, and DAS-28 score increased the probability of developing osteopenia or osteoporosis based on hip and spine bone density. According to the findings of a study in RA patients, increasing age, history of bone fracture, and DAS-28 score increase the probability of osteopenia or osteoporosis. Therefore, it is advised to pay close attention to the mentioned factors to prevent complications in these patients.

Keywords: Dual-Energy X-ray Absorptiometry; Bone density; Osteopenia; Osteoporosis; Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a common inflammatory, chronic, and systemic disease that causes joint problems. Arthritis may be temporary, but it usually progresses to chronicity and joint destruction within a few months to a few years [1]. The disease is typically characterized by symmetric polyarthritis, with progressive destruction of joints and surrounding tissues evident over time [1, 2]. The disease is three times more common in women and has a higher incidence in the third to fifth decade of life [3]. A meta-analysis published in 2021 found that the global prevalence of RA was 0.46%, and the point prevalence of the disease was 0.45% during 1986-2014 [4].

The prevalence of RA was 1.2% in a study conducted in Yazd and roughly 0.37% in a national study based on the Community Oriented Program for the Control of Rheumatic Diseases

*Corresponding author: Mitra abbasifard; Assistant Professor of Rheumatlogy, Department of Internal Medicine, AliIbn Abi-Talib Hospital, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
Tel: +989133905950 .Phone: +983434280185.Email: dr.mabbasifard@gmail.com

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(COPCORD) questionnaire [5].

Most cases of RA have a hidden and gradual onset, accompanied by fatigue, anorexia, general weakness, muscle and bone pain, and, in some cases, fever without a diagnosed infectious cause [6]. Patients with RA become unable to perform activities within a few years of the disease's onset, and disability is one of the disease's most common complications [7]. The involvement of the small peripheral joints of the hands results in cartilage destruction, bone erosion, and joint deformation [8]. The disease progresses differently in different people, so some patients have only one oligoarthritis with a brief period of illness and joint damage. In contrast, others have progressive polyarthritis with various complications. The musculoskeletal, cardio-pulmonary, renal, and skin systems are involved in this disease, and different manifestations appear depending on the type of involvement. Although the pathogenesis of the disease is still unknown, clinical, laboratory, and radiological imaging findings are used to make a diagnosis [1].

RA patients have lower bone mass density (BMD). In RA patients, disease duration, inflammation intensity, gender, age, meno-pause status, low body mass index (BMI), reduced physical activity, and steroid treatments are risk factors for osteoporosis [9, 10]. Secondary osteoporosis is common during the disease due to glucocorticosteroid drugs [11]. Vitamin D deficiency contributes significantly to osteopenia and increases the risk of spontaneous fractures in RA patients worldwide. In contrast, Vitamin D also plays a vital role in reducing inflammation [1]. The increased risk of osteoporosis in RA patients is significant; however, there is little information available about it, as well as the occurrence of osteoporotic fractures in these patients and their risks about age groups, gender, anatomical position and glucocorticoid use [12].

Demographic and disease-related variables are significantly associated with BMD in RA patients; however, the risk factors for decreased BMD in RA patients must be investigated [13]. The current study investigated BMD using dual-energy x-ray absorptiometry (DXA) in RA patients referred to the Rafsanjan rheumatology clinic.

Materials and Methods

Study Design

This cross-sectional study included 415 RA patients referred to the Rheumatology Clinic in Rafsanjan (a city in southern Iran) from 2020 to 2021.

Sampling technique

The participants were selected by census sampling.

Sample size determination

All RA patients referring to the Rafsanjan rheumatology clinic in 2020-2021 were assessed (n = 415).

Patient Identification

The inclusion criteria included a rheumatologist's diagnosis of RA based on American College of Rheumatology (ACR) criteria [14], at least three months of disease history, and age between 35 and 70 years. Exclusion criteria included factors affecting bone metabolism, including underlying diseases (hyperparathyroidism, cancer, kidney failure, etc.), medications use (anticonvulsant drugs, warfarin, etc.), pregnancy, and a weight of more than 100 kg. All participants provided informed consent. A researcher-made checklist was used as the data collection tool, which included variables of age, gender, education, marital status, place of residence, weight, height, BMI, occupation, physical activity (Metabolic equilibrium of task (MET)), history of fracture and its location, menopause, Menopause duration, disease duration, disease activity score-28 (DAS-28), history of smoking, consuming alcohol and opium, and exposure to cigarette smoke (passive smoker).

Data Collection

The Dual-Energy X-ray absorptiometry (DXA) method measured BMD in the hip and

spine (L1-L4) for all participants (Stratos, MEDIX 90, France). The test results were recorded as Femoral Neck T-Score and Lumbar spine L1-L4 T-Score. The diagnosis of osteoporosis and osteopenia was defined according to the classification of the World Health Organization (WHO) as follows: osteoporosis: T score ≤ -2.5, osteopenia: T score -1 to -2.5 [15]. The DAS-28 index was used to determine the activity of RA. The DAS-28 was calculated based on the number of joints with swelling, the number of joints with tenderness, erythrocyte sedimantation rate (ESR), and the patient's global estimate of status. DAS-28 ≤ 2.6 indicates remission. 2.6 < DAS-28 ≤ 3.2 indicates mild disease activity. 3.2 < DAS-28 ≤ 5.1 indictes moderate disease activity and DAS-28 > 5.1 indictaes high disease activity [16]. Participants were classified into three groups based on their score in the International Physical Activity Questionnaire (IPAQ). To calculate MET in this study. In terms of total walking MET-min/wk, the groups included low activity (<600 MET-minutes/week), moderate activity (≥600 MET-min/wk), and high activity (≥3000 MET-min/wk) [17].

Ethical Considerations

All study participants provided written consent, which was accepted and approved by the Rafsanjan University of Medical Sciences in Rafsanjan, Iran. This study was conducted per the Declaration of Helsinki. Ethical approval for this study was obtained from the ethical committee before the study with Ref. No IR.RUMS.REC.1400.245.

Statistical Analysis

The collected data were analyzed by SPSS 24 (IBM SPSS Inc., Chicago, IL, USA) and SAS.9/2 (SAS Institute Inc., Cary, NC, USA) software. The results were reported as mean ± standard deviation for quantitative data with normal distribution, as median (3rd quartile-1st quartile) for non-normal quantitative data, and as number (percentage) for qualitative data. One-way ANOVA was used to compare the mean score of quantitative variables with normal distribution, and, if significant, Tukey's multiple comparisons test was used to compare the mean score of paired groups in the three investigated groups (normal, osteopenia, osteoporosis). The non-parametric Kruskal-Wallis H test and Mann-Whitney U test were used to compare the median of the paired groups in the three investigated groups to compare the median score of the quantitative variables with non-normal distribution. The Chi-square test and Chi-square test for trend (for two-state variables) or Fisher's exact test were used to compare the frequency distribution of qualitative variables in the three studied groups.

The normality of the frequency distribution of the quantitative variables was evaluated using the non-parametric Kolmogorov-Smirnov test and calculating the skewness and kurtosis indices. Levene's test also evaluated the homogeneity of the variance of the studied groups, and no violation of this assumption was observed (P < 0.05). The regression model of the proportional odds model for ordinal responses was used to determine the predictive factors of Femur BMD, Femur total T-Score and Femur neck T-score. The variables were added to the regression model in steps. The predictive variables entered in the regression model included age, gender (premenopausal women, postmenopausal women, and male), body mass index (BMI), education level, physical activity, bone fracture history, disease course, and DAS-28. The odds ratio with a 95% confidence interval for the relationship between the predictive and response variables was reported. The significance level was considered 0.05 in the tests.

Patient and public involvement

Our research was not designed, conducted, reported on, or disseminated with the participation of patients or the general public.

Results

The current study included 415 RA patients with a mean age of 56.49 ± 11.73 years. Three hundered participants were female (86.7%). Information on spine bone mass was available for all 415 patients, while informtion

on hip bone mass was available only for 346 patients (10 participants were excluded due to a history of orthopedic surgery in the hip area, and 59 participants due to technical difficulties in performing densitometry). Based on hip BMD, 26 patients (7.5%) had osteoporosis, and 151 patients (43.6%) had osteopenia. While, based on spine BMD, osteoporosis and osteopenia was obseryed in 137 (33%) patients and 158 (38.1%) patients, respectively. Given the great importance of gender and menopause in women, the gender variable was classified once as male or female and once as premenopausal women, postmenopausal women, and male. According to hip BMD, the patients were divided into three groups: normal, osteopenia, and osteoporosis. The results indicated that the frequency of post-menopausal women was higher in the three groups ($P < 0.001$). The three groups differed significantly in terms of mean age, weight, height, BMI, marital status, education level, and

Table1: Frequency distribution of demographic and clinical characteristic variables in patients with RA based on hip BMD

Variable	Total (N=346)	Normal (n=169)	Osteopenia (n=151)	Osteoporosis (n=26)	Test statistic df	P-value
Gender_1					$\chi^2 = 0.258$	0.612*
Male (%)	46 (13.3)	21 (12.4)	21 (13.9)	4 (15.4)	df = 1	
Female (%)	300 (86.7)	148 (87.6)	130 (86.1)	22 (84.6)		
Gender_2					$\chi^2 = 20.456$	< 0.001‡
Premenopausal women (%)	81 (23.4)	57 (33.7)	22 (14.6)	2 (7.7)	df = 4	
Postmenopausal women (%)	219 (63.3)	91 (53.8)	108 (71.5)	20 (76.9)		
Male (%)	46 (13.3)	21 (12.4)	21 (13.9)	4 (15.4)		
Age (year)	56.49 ± 11.73	52.38 ± 11.18[a]	59.20 ± 10.66[b]	67.38 ± 9.82[c]	F = 29.856 df = 2, 343	< 0.001†
Weight (kg)	71.74 ± 12.78	75.38 ± 12.83[a]	69.31 ± 11.07[b]	62.15 ± 13.85[c]	F = 18.610 df = 2, 343	< 0.001†
Height (cm)	156.36 ± 7.66	157.51 ± 7.31[a]	155.78 ± 7.27[ab]	152.15± 10.21[b]	F = 6.470 df = 2, 343	0.002†
BMI (kg/m^2)	29.38 ± 5.07	30.44 ± 5.17[a]	28.64 ± 4.61[b]	26.82 ± 5.40[b]	F = 9.060 df = 2, 343	< 0.001†
Marital status					$\chi^2 = 10.516$	0.001*
Single# (%)	31 (9.0)	8 (4.7)	17 (11.3)	6 (23.1)	df = 1	
Married (%)	315 (91.0)	161 (95.3)	134 (88.7)	20 (76.9)		
Occupation					F = 2.999	0.543**
Unemployed/retired	290 (83.8)	136 (80.5)	130 (86.1)	24 (92.3)	df = -	
Non-government employee	36 (10.4)	22 (13.0)	13 (8.6)	1 (3.8)		
Government employee	20 (5.8)	11 (6.5)	8 (5.3)	1 (3.8)		
Place of residence					$\chi^2 = 1.269$	0.260*
Urban (%)	252 (72.8)	127 (75.1)	108 (71.5)	17 (65.4)	df = 1	
Rural (%)	94 (27.2)	42 (24.9)	43 (28.5)	9 (34.6)		
Education level					$\chi^2 = 26.770$	< 0.001‡
Illiterate (%)	79 (22.8)	26 (15.4)	38 (25.2)	15 (57.7)	df = 4	
Diploma and lower (%)	236 (68.2)	122 (72.2)	103 (68.2)	11 (42.3)		
University (%)	31 (9.0)	21 (12.4)	10 (6.6)	0		
Physical activity					$\chi^2 = 22.047$	< 0.001‡
Low (%)	135 (39.0)	46 (27.2)	75 (49.7)	14 (53.8)	df = 4	
Moderat (%)e	188 (54.3)	106 (62.7)	71 (47.0)	11 (42.3)		
High (%)	23 (6.6)	17 (10.1)	5 (3.3)	1 (3.8)		

Data are expressed as mean ± standard deviation (SD), or n (%).

BMI: Body Mass Index, df: Degree of Freedom

Included single, divorced, and widowed

* P-value derived from Chi-square test for trend

† P-value derived from one-way ANOVA, groups with different English letters are significantly different ($P < 0.05$) according to the Tukey's multiple comparisons test

** P-value derived from Fisher's exact test

‡ P-value derived from Chi-square test

physical activity (P < 0.05). Table1 displays the variable's results separately. The risk factors' investigation for osteoporosis in RA patients based on hip BMD shows that the frequency distribution of passive smoking in patients with osteoporosis was 26.9% (P = 0.034), and illegal drugs use was 11.5% (P = 0.025). The frequency of bone fractures was higher (P < 0.001) in patients with osteopenia and osteoporosis, with the majority of fractures occurring in the hand and elbow. Women with osteoporosis had a 4.5-year earlier menopause than other women (P < 0.001). DAS-28 index was higher in osteoporotic women than other women (P = 0.001) (Table 2).

Table 2: Frequency distribution of osteoporosis risk factors in RA patients based on hip BMD

Variable	Total (N=346)	Normal (n=169)	Osteopenia (n=151)	Osteoporosis (n=26)	Test Statistic df	P-value
Smoker (%)	29 (8.4)	12 (7.1)	14 (9.3)	3 (11.5)	$\chi^2 = 0.852$ df = 1	0.356*
Passive smoker (%)	101 (29.2)	60 (35.5)	34 (22.5)	7 (26.9)	$\chi^2 = 4.498$ df = 1	0.034*
Alcohol use (%)	1 (0.3)	1 (0.6)	0	0	-	-
Opium drug (%)	23 (6.6)	6 (3.6)	14 (9.3)	3 (11.5)	$\chi^2 = 5.004$ df = 1	0.025*
Bone fracture history	46 (13.3)	10 (5.9)	29 (19.2)	7 (26.9)	$\chi^2 = 16.318$ df = 1	< 0.001*
Bone fracture location					-	-
No fracture (%)	310 (89.6)	161 (95.3)	129 (85.4)	20 (76.9)		
Spine (%)	3 (0.9)	0	3 (2.0)	0		
Hip (%)	1 (0.3)	0	0	1 (3.8)		
Wrist and hand (%)	8 (2.3)	3 (1.8)	5 (3.3)	0		
Ankle (%)	13 (3.8)	2 (1.2)	8 (5.3)	3 (11.5)		
Knee and leg (%)	8 (2.3)	2 (1.2)	4 (2.6)	2 (7.7)		
Elbow (%)	3 (0.9)	1 (0.6)	2 (1.3)	0		
Menopause (%)	219 (73.0) (N=300)	91 (61.5) (n=148)	108 (83.1) (n=130)	20 (90.9) (n=22)	$\chi^2 = 19.010$ df = 1	< 0.001*
Menopause duration (year)	13.0 (8.0-19.0) (N=219)	13.0 (7.0-17.0)[a] (n=91)	13.0 (8.0-19.75)[ab] (n=108)	17.50 (12.25-26.00)[b] (n=20)	$\chi^2 = 7.219$ df = 2	0.027†
Disease duration (year)	6.0 (4.0-10.0)	6.0 (3.0-8.5)[a]	6.0 (4.0-11.0)[b]	6.0 (4.0-18.0)[ab]	$\chi^2 = 7.596$ df = 2	0.022†
DAS-28	4.0 (2.0-7.0)	4.0 (2.0-6.0)[a]	5.0 (2.0-7.0)[b]	6.50 (3.75-9.00)[c]	$\chi^2 = 14.011$ df = 2	0.001†

Data are expressed as n (%), or median (1st quartile – 3rd quartile).
df: Degree of Freedom
* P-value derived from Chi-square test for trend
† P-value derived from non-parametric Kruskal-Wallis H test, groups with different English letters are statistically significantly different (P < 0.05) according to the non-parametric Mann-Whitney U test
RA, rheumatoid arthritis
BMD, bone mineral density

BMD investigation results in RA patients, according to spine BMD and dividing patients into three groups of normal, osteopenia, and osteoporosis, are shown separately in Table 3. The results of evaluating osteoporosis risk factors in RA patients based on spine BMD are shown in Table 4. The results show that increasing age, increases the chance of osteopenia and

Table 3: Frequency distribution of demographic and clinical characteristic variables in RA patients based on spine BMD

Variable	Total (N=415)	Normal (n=120)	Osteopenia (n=158)	Osteoporosis (n=137)	Test Statistic df	P-value
Gender_1					$\chi^2 = 3.459$	0.177*
Male (%)	53 (12.8)	10 (8.3)	25 (15.8)	18 (13.1)	df = 2	
Female (%)	362 (87.2)	110 (91.7.4)	133 (84.2)	119 (86.9)		
Gender_2					$\chi^2 = 3.977$	0.409*
Premenopausal women (%)	124 (29.9)	40 (33.3)	46 (29.1)	38 (27.7)	df = 4	
Postmenopausal women (%)	238 (57.3)	70 (58.3)	87 (55.1)	81 (59.1)		
Male (%)	53 (12.8)	10 (8.4)	25 (15.8)	18 (13.1)		
Age (year)	55.17 ± 12.31	54.78 ± 12.96	55.56 ± 12.44	55.06 ± 11.65	F = 0.142 df = 2, 244	0.868†
Weight (kg)	71.36 ± 13.31	71.80 ± 12.91	71.95 ± 13.98	70.29 ± 12.88	F = 0.666 df = 2, 244	0.514†
Height (cm)	156.96 ± 7.69	156.67 ± 7.25	157.47 ± 8.02	156.73 ± 7.71	F = 0.488 df = 2, 244	0.614†
BMI (kg/m2)	28.99 ± 5.25	29.24 ± 4.80	29.05 ± 5.48	28.72 ± 5.39	F = 0.331 df = 2, 244	0.718†
Marital status					$\chi^2 = 0.344$	0.842*
Single#	36 (8.7)	9 (7.5)	15 (9.5	12 (8.8)	df = 2	
Married	379 (91.3)	111 (92.5)	143 (90.5)	125 (91.2)		
Occupation					$\chi^2 = 0.577$	0.968*
Non-employed/ Retired (%)	341 (82.2)	97 (80.8)	130 (82.3)	114 (83.2)	df = 4	
Non-government job (%)	45 (10.8)	1147 (11.7)	18 (11.4)	13 (9.5)		
Government job (%)	29 (7.0)	9 (7.5)	10 (6.3)	10 (7.3)		
Place of residence					$\chi^2 = 1.166$	0.558*
Urban (%)	309 (74.5)	85 (70.8)	120 (75.9)	104 (75.9)	df = 2	
Rural (%)	106 (25.5)	35 (29.2)	38 (24.1)	33 (24.1)		
Education level					$\chi^2 = 7.901$	0.095*
Illiterate (%)	85 (20.5)	33 (27.5)	31 (19.6)	21 (15.3)	df = 4	
Diploma and lower (%)	289 (69.6)	73 (60.8	111 (70.3)	105 (76.6)		
University (%)	41 (9.9)	14 (11.7)	16 (10.1)	11 (8.0)		
Physical activity					$\chi^2 = 7.209$	0.125*
Low (%)	147 (35.4)	34 (28.3)	60 (38.0)	53 (38.7)	df = 4	
Moderate (%)	152 (58.8)	80 (66.7)	85 (53.8)	79 (57.7)		
High (%)	24 (5.8)	6 (5.0)	13 (8.2)	5 (3.6)		

Data are expressed as mean ± standard deviation (SD), or n (%).
BMI: Body Mass Index, df: Degree of Freedom
Included single, divorced, and widowed
* P-value derived from Chi-square test for trend
† P-value derived from one-way ANOVA

Table 4: Frequency distribution of osteoporosis risk factors in RA patients based on spine BMD

Variable	Total (N = 415)	Normal (n = 120)	Osteopenia (n = 158)	Osteoporosis (n = 137)	Test statistic df	P-value
Smoker (%)	28 (6.7)	6 (5.0)	13 (8.2)	9 (6.6)	$\chi^2 = 1.140$ df = 2	0.566*
Passive smoker (%)	129 (31.3)	38 (31.7)	47 (29.7)	44 (32.1)	$\chi^2 = 0.219$ df = 2	0.896*
Alcohol use (%)	0				-	-
Opium use (%)	20 (4.8)	7 (5.8)	5 (3.2)	8 (5.8)	$\chi^2 = 1.523$ df = 2	0.468*
Bone fracture history	40 (9.6)	13 (10.8)	16 (10.1)	11 (8.0)	$\chi^2 = 12.377$ df = 2	0.959*
Bone fracture location					-	-
No fracture (%)	375 (90.4)	107 (89.2)	142 (89.9)	126 (92.0)		
Spine (%)	5 (1.3)	1 (0.8)	0	4 (2.9)		
Hip (%)	1 (0.2)	1 (0.8)	0	0		
Wrist and hand (%)	6 (1.4)	2 (1.7)	3 (1.9)	1 (0.7)		
Ankle (%)	18 (4.3)	6 (5.0)	7 (4.4)	5 (3.7)		
Knee and leg (%)	8 (1.9)	3 (2.5)	4 (2.5)	1 (0.7)		
Elbow (%)	2 (0.5)	0	2 (1.3)	0		
Menopause (%)	248 (68.5) (N=362)	80 (67.2) (n=119)	87 (65.4) (n=133)	81 (73.6) (n=110)	$\chi^2 = 0.509$ df = 1	0.775*
Menopause duration (year), median (IQR)	14.09 (8.0-20.0)	13.84 (9.5-17.0) (n=119)	13.30 (9.0-19.0) (n=133)	15.15 (11.50-21.75) (n=110)	$\chi^2 = 2.85$ df = 2	0.240†
Disease duration (year), median (IQR)	7.76 (4.0-11.0)	8.14 (5.0-11.0)	7.98 (4.75-11.25)	7.1 (2.5-17.0)	$\chi^2 = 2.4$ df = 2	0.300†
DAS-28, median (IQR)	4.91 (2.0-7.0)	5.24 (4.0-8.0)	4.5 (2.0-7.0)	5.0 (3.5-8.5)	$\chi^2 = 1.69$ df = 2	0.424†

Data are expressed as n (%) or median (1st quartile – 3rd quartile).

df: Degree of Freedom

* P-value derived from Chi-square test for trend

† P-value derived from non-parametric Kruskal-Wallis H test, groups with different English letters are statistically significantly different (P < 0.05) according to the non-parametric Mann-Whitney U test

RA, rheumatoid arthritis; BMD, bone mineral density; IQR, interquartile range; DAS-28, disease activity score 28

or osteoporosis in the adapted model (P < 0.0001) while increasing BMI decreases the chance of osteopenia or osteoporosis (P < 0.0001). The risk of osteopenia or osteoporosis was higher in patients with a history of bone fracture (P < 0.0001) and lower in patients with moderate or high physical activity compared to patients with low physical activity (P < 0.0001). The chance of osteopenia or osteoporosis increased with increasing DAS-28 score (P = 0.0002). The results of the model based on spine BMD show that the variables of age, BMI, history of bone fractures, and DAS-28 index had a significant effect so that in the adapted model, increasing age and BMI increased and decreased the chance of osteopenia or osteoporosis (P < 0.0001). Patients with a history of bone fracture had a higher risk of osteopenia or osteoporosis, and increasing the DAS-28 index increased the risk of osteopenia or osteoporosis Table 5.

Table 5: Factors predicting hip and spine T-Score using stepwise Proportional Odds Model for ordinal responses (Normal, osteopenia, and osteoporosis)

Variable	Femur Total T-Score				Spine L1-4 T-Score			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (year)	1.07 (1.05 – 1.09)	< 0.0001	1.07 (1.05 – 1.09)	< 0.0001	1.099 (1.069 - 1.129)	< 0.0001	1.104 (1.072 – 1.136)	< 0.0001
BMI (kg/m^2)	0.91 (0.87 - 0.95)	< 0.0001	0.91 (0.87 - 0.95)	< 0.0001	0.895 (0.849 - 0.944)	< 0.0001	0.874(0.821 – 0.930)	< 0.0001
Bone fracture history	3.49 (1.87 – 6.51)	< 0.0001	3.49 (1.87 – 6.51)	< 0.0001	3.528 (1.651 - 7.538)	0.0011	2.817(1.252 – 6.338)	0.0123
DAS-28	1.12 (1.05 – 1.19)	0.0002	1.12 (1.05 – 1.19)	0.0002	1.120 (1.045 - 1.201)	0.0014	1.112(1.029 – 1.202)	0.0075
Physical activity		< 0.0001		< 0.0001	---	---	----	---
Low	1.000		1.000					
Moderate	0.420 (0.27 – 0.65)		0.42 (0.27 – 0.65)					
High	0.194 (0.07 – 0.51)		0.19 (0.07 – 0.51)					

OR: Odds Ratio, CI: Confidence Interval

* Variables entered into the multivariable model including Age, gender (premenopausal women, postmenopausal women, male), BMI (body mass index), education level, physical activity, bone fracture history, disease course, DAS-28

Discussion

RA has several risk factors, including race, genetic predisposition, female gender, old age, bone density, obesity, sex hormones, endocrine disorders, repetitive injuries, occupational activities, nutritional factors, and lifestyle [18-20]. This disease has different systemic manifestations, and its main feature is continuous inflammatory synovitis, which usually involves the peripheral small and large joints and causes cartilage destruction, bone erosion, and joint deformation. BMD is affected in RA patients due to the severity of inflammation, immobility, and use of steroids. The prevalence of osteoporosis is higher due to various causes, including genetic and environmental factors, and is particularly prevalent in affected women [21]. According to the findings of the current study, 33% and 7.5% of RA patients had osteoporosis, and 38% and 43.1% had osteopenia based on hip and spine BMD. In a study in Iran, the prevalence of osteopenia and osteoporosis in postmenopausal women and men in the age of 50 was reported as 78.2% and 77.3%, respectively [22]. The results of the study by Lee et al. showed that the prevalence of osteoporosis in the studied women was 46.8%, with an overall prevalence of osteoporosis and osteopenia of 90.8%. It was also discovered that RA patients had significantly lower bone density than healthy people[13]. In another study [23], this rate was reported to be 13.3% in women with RA. In RA patients, the frequency of osteoporosis ranges from 12.3% to 38.9% in the lumbar spine and from 6.3% to 36.3% in the hip [24, 25]. There is a more than twofold increase in the risk of vertebral fractures in RA patients and a sixfold increase in patients with chronic disease [25]. Vertebrae fractures can also be observed during the first year of the disease, and one of every three women with RA reported the fracture within five years of follow-up [26].

The current study's findings in examining the factors affecting bone mass in RA revealed that the probability of osteopenia or osteoporosis increases with age. Aghaei et al. reported that increasing age and disease duration decreases bone mineral density and improves the overall prevalence of osteoporosis in RA patients [27].

In a study in Korea, the prevalence of osteoporosis increased from 46.3% in the 45-64 age group to 68.7% in the over 70 age group [28]. Larijani et al. also noted that after age 40, the spine and hip BMD significantly decreased for every ten years of age increase [29]. Maximum bone mass, one of the important determinants of osteoporosis, has been reported in the spine and hip area of women aged 29 to 36 and in men aged 20 to 24 years [30]. Aging is one of the most important factors affecting bone mass loss and increasing the prevalence of osteoporosis, which is one of the common problems among older people. The three main mechanisms of osteoporosis in women are failure to achieve optimal bone strength during growth and development, excessive bone absorption that causes a decrease in bone mass, and failure to replace lost bone due to defects in bone formation. Estrogen deficiency after menopause also contributes to its development. The process of bone mass loss accelerates with age, increasing the prevalence of osteoporosis increases in the elderly [31]. In RA patients, however, increasing prevalence will be influenced by risk factors and high-risk conditions [21].

The study's findings showed that lowering BMI increases the probability of osteopenia or osteoporosis. Body weight is one of the influencing factors in bone mineral density, and a decrease in body weight is associated with a reduction in bone mineral density [32]. Body weight imposes mechanical pressure on bone tissue, which increases osteogenic stimulation and, ultimately, bone mass [33]. Increased fat tissue can also cause bone tissue absorption by increasing inflammatory cytokines and tumor necrosis factors [34]. Adipose tissue cells are the primary source of estrogen sex hormone production in menopausal women. An increase in fat tissue, combined with an increase in estrogen production, decreases osteoclast function, increases osteoblast activity and bone synthesis, and reduces bone resorption [35]. The current study found that a history of bone fracture, low physical activity, and an increase in the DAS-28 score increase the probability of osteopenia or osteoporosis. A history of bone fracture, with an odds ratio of 3.498, was one of the most substantial risk factors for osteoporosis in the present study. Similarly, previous studies have considered the occurrence of prior fractures in people as a risk factor for future fractures, and the risk of fractures due to osteoporosis is higher immediately after the event. Treating osteoporosis in patients with previous fractures may potentially lead to a 50% reduction in the risk of future fractures. This could be due to a higher risk of osteoporosis in people with a previous fracture [36].

In people with osteoporosis, more fractures occur in bones with lower density and under more pressure than the rest of the body's skeletal system [37]. Reduced physical activity and insufficient movement throughout life cause a decrease in bone minerals, whereas exercise increases bone mineral density [38]. However, studies have shown that the effect of exercise on bone mineral density varies depending on the type of activity, duration, and intensity [39]. By the beginning of the middle age period, body mass decreases, and as a result, bone strength and density decrease, which increases the risk of fractures and osteoporosis[40].

The skeletal system adapts to increasing bone density in response to various types of stress by engaging in physical activity and strengthens itself against future injuries. Moreover, physical activity affects the amount of muscle and bone density. Hormonal changes and increased secretion of anabolic hormones, such as growth hormone and IGF-1, also play an essential role in bone protection, calcium release control, and muscle contraction by increasing muscle mass [41].

One of the current study's strengths is that it includes all patients with rheumatoid arthritis referred to Rafsanjan's only rheumatology clinic, which increases the generalizability of the results. The study has limitations because there is no

control group, and we cannot compare the results to the control group (normal population). It is suggested that future studies with longitudinal designs and a control group (normal age and sex match individual) investigate the factors causing osteoporosis in these patients. The generalizability of the results is limited due to the study's design and sample size.

Conclusion

Study findings suggest that increasing age, decreasing BMI, a history of bone fracture, low physical activity, and an increasing DAS-28 score increased the probability of osteopenia or osteoporosis in RA patients. The history of previous fractures was the most powerful factor influencing osteoporosis in these patients. Therefore, it is suggested to pay attention to the mentioned factors in RA patients and to avoid the adverse consequences of fractures caused by osteoporosis.

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Conflict of Interests

The authors declare no conflict of interest.

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