Bone mineral density status in patients with recent-onset rheumatoid arthritis

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Abstract

Background Osteoporosis is a sizable comorbidity complication in Rheumatoid Arthritis (RA) sufferers. In the current study, the prevalence of osteopenia and osteoporosis in active RA sufferers and the association of disease-related factors of osteoporosis and reduced bone mineral density (BMD) have been examined.

Methods In this cross-sectional study, 300 new-onset symptoms (less than one year) RA patients without a history of gluco-corticoids or DMARDs were selected. Biochemical blood measurements and BMD status were performed with dual-energy X-ray absorptiometry. According to the T-scores of the patients, they were divided into three groups: osteoporosis<-2.5, -2.5 < osteopenia <-1, and − 1 < normal. Also, the MDHAQ questionnaire, DAS-28, and FRAX criteria were calculated for all patients. Multivariate logistic regression was used to determine the associated factors of osteoporosis and osteopenia.

Results The Prevalence of osteoporosis and osteopenia was 27% (95%CI:22–32) and 45% (95%CI:39–51), respectively. The multivariate regression analysis showed that age could play a role as an associated factor for spine/hip Osteoporosis and Osteopenia. The female gender is also a predictor of Spine osteopenia Patients with Total hip Osteoporosis were more likely to have higher DAS-28 (OR 1.86, CI 1.16–3.14) and positive CRP (OR 11.42, CI 2.65–63.26).

Conclusion recent-onset RA patients are at risk for osteoporosis and its complications, regardless of using glucocorticoids or DMARDs. Demographic factors (e.g. age and female gender), patients' MDHAQ scores, and disease-related factors(e.g., DAS-28, positive CRP were associated with reduced BMD levels. Therefore, it is recommended that clinicians investigate early BMD measurements to have a reasonable judgment for further interventions.

Keywords Osteoporosis · Bone Mineral Density · Osteopenia · Rheumatoid arthritis · Cross-sectional study

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Introduction

Rheumatoid arthritis (RA) is a long-term systemic inflammatory ailment and, like an autoimmune disorder, motives symmetrical polyarthritis in large and small joints [1–3]. Epidemiological studies, i.e., in Europe and North America, have estimated that the 0.5–1.5% of the entire population has suffered from RA disease [3–10].

Despite many advances in the diagnosis and management of this disease, RA is one of the few illnesses in that patient and health practitioner subjective measures are the first-rate predictors of therapy response and future health consequences. Accordingly, more than a few questionnaires have been developed for RA severity determination. One of the most valid of these questionnaires is the health assessment questionnaire (HAQ).

HAQ can be used widely for patients from different age groups with various rheumatologic conditions, including RA. However, its length and the complex scoring system have decreased its clinical application [11].

Due to the limitations of HAQ, MDHAQ, a new version of this questionnaire, has been used in this study. The MDHAQ was initially developed as a functional status assessment in patients with rheumatoid conditions. Compared to the HAQ, its shorter substitute decreases patient and provider time commitment. Also, studies have shown that this test has better sensitivity in detecting changes in the performance of lower-end-of-the-scale patients than HAQ [12].

RA patients' symptoms are not always constant, and, in most patients, there are periods of flair and remission of the disease. One of the main tools in diagnosing the remission of the disease is the disease activity score (DAS). DAS is a continuous measure including the Ritchie articular index (RAI), a 28 swollen joint count, ESR or CRP, and general health. According to the mentioned criteria, the disease activity scores from 0 to 10. DAS ≤ 3.2 represents remission, values between 3.2 and 5.1 were defined as low activity, and more values than 5.1 represent high disease activity [13].

Osteoporosis is the most significant skeletal disorder, characterized by a decrease in Bone Mineral Density(BMD) and bone tissue destruction; it eventually causes bone narrowing and increases fracture risk [14, 15]. Furthermore, osteoporosis is critical comorbidity of RA, in which different pathophysiological procedures are involved in its pathogenesis [16].

Different methods have been suggested for bone quality measurements, such as MRI, quantitative computed tomography, and nuclear magnetic resonance [17]. Currently, Due to the cost-effectiveness and availability of BMD, this test is widely measured in the clinic. For this reason, almost all diagnostic criteria for osteoporosis and osteopenia are based on BMD [18]. Drug registration agencies in the United States and Europe have Recommended this test as a criterion for starting drug treatment, dose adjustments, and patient follow-up [19, 20].

Reduced BMD in RA patients may be caused by autoantibodies, systemic inflammation, and cytokine secretion such as interleukin 1, 6, 15, TNF-α, and activated T cell RANKL expression have harmful effects on bone density [21, 22]. Moreover, using glucocorticoid drugs as an effective treatment procedure plays an impairing role in Osteoporosis development in RA patients [23, 24]. Recent studies on RA patients have shown a BMD reduction in affected patients' hip and lumbar Spine bones.

In previous longitudinal studies, the annual hip T-score has changed from − 0.1% to -4.3% and − 0.3% to -2.4% in patients' lumbar spine bone [25]. Another statical study indicates that the relative risk of vertebral and pelvic fractures in RA patients is more than two-fold compared with normal individuals [26]. A recent study reveals that the frequency of osteoporosis may progress by almost 30% in RA patients [27]. In postmenopausal RA-affected women, the prevalence of osteoporosis varies from one-third to approximately 50% of patients based on extensive cohort studies [28, 29]. Previous studies on RA patients stated that senility, low Body Mass Index (BMI), female gender, high disease intensity, long disease duration, low functional capacity, and high accumulated dose of prescribed glucocorticoid are the risk factors for BMD reduction [30–32].

Even though various methods have been suggested for the probability of hip and major osteoporotic fracture, FRAX® has shown the most promising results. WHO and the Centre for Metabolic Bone Diseases developed FRAX as a PC-based algorithm to enable its application for physicians(http://www.shef.ac.UK/FRAX). FRAX processes the clinical risk factors, including sex, country, age, and BMI, and calculates the probability of hip and other major osteoporotic fracture (e.g., humerus, clinical spine, or wrist fracture) 10 years [33].

So far, the effect of disease-related factors on BMD and the extent of osteoporosis in newly onset RA patients are not entirely examined [34], and only a few papers have focused on the relationship between BMD and early-diagnosed RA. However, the interval between the diagnosis and BMD occurrence may be delayed up to five years in some cases [26]. Thus, more information is required to reveal the connection between RA and osteoporosis.

The present study was designed to determine the prevalence of osteopenic and osteoporotic patients based on their BMD, and other related factors in newly RA-diagnosed patients with no history of glucocorticoids or DMARDs.

Method and materials

In the present cross-sectional study, from November 2016 to December 2020, 342 patients suspected of RA from the Rheumatology clinic of Rajaei's hospital in Karaj-Iran were evaluated using the convenience sampling method. The onset of symptoms was in less than one year in all patients, and none have been treated with glucocorticoids or DMARDs. Inclusion criteria included new-onset RA patients (less than one year [35, 36]) who had 6 out of 10 criteria of the American Rheumatology Association in 2010. Patients younger than 18 years old, with previous treatment with Glucocorticoids and DMARDs medicines, Hormone replacement therapy (HRT), Bisphosphonate usage, history of malignancy in the last five years, concurrency of other autoimmune diseases, bone marrow hypoplasia, abnormal liver function tests, Chronic Kidney Disease, Diabetes Mellitus, hypo and hyperparathyroidism, and pregnancy were excluded.

Eventually, written informed consent was obtained from all 300 patients before enrolling in the study.

Trained nurses collected and recorded sociodemographic and clinical information, including gender, age, height (by reading the number on the height gauge), weight (by reading the number on the weight scale), BMI (weight in kilograms divided by height in meters squared), underlying diseases, menopausal condition, and the age at menopause (if exist) by interview. Patients have been classified according to their BMI to obese ≥ 30, $30 >$ overweight ≥ 25, and normal < 25. Then patients were asked to fill out the MDHAQ. The MDHAQ includes eight groups of questions, including dressing and grooming, grip, arising, hygiene, eating, activities, reach, and walking [37].

Then all patients were examined by a rheumatologist, and diseases related variables, including DAS28, were measured by the following formula:

DAS28 = 0.56*√(tender joint count) + 0.28*√(swollen joint count) + 0.014*GH + 0.36*ln (CRP + 1) + 0.96;

Then routine blood tests (using 5 cc blood sampling), including serum Ca level(measuring by CALCIUM ARZ Elisa Kit), 25-OH Vit D(measuring by PISHTAZTEB Elisa Kit), RF (rheumatoid factor, (measuring by titration technique), ESR(using capillary tube and a capillary blood sample (micro ESR)), CRP(performed on a Behring Nephelometer), and anti-CCP(Aeskulisa RA-CCP-Detect Elisa Kit), were collected and recorded. We considered the normal reference range for blood calcium in adults between 8.8 and 10.2 mg/Dl, Vit D levels between 30 and 50 ng/mL, and ESR between 0 and 22 and 0 to 29 mm/hr in men and women, respectively. According to regional cut-off points, RF, anti-CCP, and CRP were considered negative or positive.

At the first visit and before any treatment, dual-energy X-ray absorptiometry was used for hip and lumbar spine (Anteroposterior view of L2–L4) BMD measurement. The BMD quantities were executed using a densitometer (Hologic Horizon Wi DXA System, USA). According to the T-score, patients were divided as Osteoporotic (equal to or greater than -2.5), Osteopenic (-1 and -2.5), or Normal [15, 38].

With the help of the information obtained from questionnaires, interviews, and the FRAX tool, the 10-year probability of hip and major osteoporotic fractures was calculated. High-risk patients for osteoporotic fracture were defined as having more than 3% and 20% probability of hip or major osteoporotic fractures in 10 years. The Iranian model of FRAX was calculated with and without BMD settings, using https://www.sheffield.ac.uk/FRAX/tool.aspx?country=68.

This study was approved by the Ethics Committee for Medical Research of the Alborz University of Medical Sciences (ABZUMS) (Ethical code: **IR.ABZUMS. REC.1399.217**).

Statistical analysis

The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous and categorical variables were presented as mean $\pm$ standard deviation (SD) and number (%), respectively. Prevalence of osteoporosis and osteopenia was reported with a 95% confidence interval (95% CI). One-way analysis of variance was used to investigate the relationship between continuous variables with BMD categories. The Chi-square test was also used to assess the relationship between categorical variables with BMD categories. Logistic regression with Wald stepwise method determined the most critical spine and hip osteoporosis and osteopenia factors. Initially, in the univariate model, variables with a $p < 0.2$ entered the final model. All tests were two-tailed, and $p \leq 0.05$ was considered statistically significant. All statistical analysis was performed in SPSS software (version 20).

Results

Patient characteristics

Patient characteristics and BMD measurements are shown in Table 1. Accordingly, 84% (252 patients) were female, the patient's mean age was 57.14 ± 12.46 years old, and their minimum and maximum ranges were 20 and 87 years old, respectively. The frequencies of the postmenopausal and premenopausal women were 75% (189 women) and 25% (63 individuals), respectively. The incidence of the normal

Table 1 Demographic, laboratory and clinical characteristics of the 300 Patients who examined with BMD measurement

Sociodemographic variables	
Mean ± SD age, years (n = 300)	57.14 ± 12.46
Women, n (%)	252 (84)
Postmenopausal, n (%)	189 (75)
Mean ± SD age at menopause, years	48 ± 3.5
Men, n (%)	48 (16)
Mean ± SD Height, cm	165.41 ± 7.75
Mean ± SD Weight, kg	70.47 ± 9.36
Mean ± SD BMI, kg/m2	25.79 ± 3.29
Normal, n (%)	141 (47)
Overweight, n (%)	126 (42)
Obese, n (%)	33 (11)
Disease-related variables	
Median (IQR) symptom duration, weeks	21 (16–26)
Mean ± SD DAS28	4.06 + 1.94
Mean ± SD MDHAQ score, 0–3 scale	0.6 + 0.58
Mean ± SD ESR	30.01 + 24.4
Mean ± SD Ca Level, mg/dL	9.11 + 0.55
Mean ± SD vit D Level, ng/mL	18.44 + 10.31
Positive RF, n (%)	246 (82)
Positive CRP, n (%)	153 (51)
Positive Anti-CCP, n (%)	240 (80)
Mean ± SD BMD, T score; Spine L2-4	-1.26 + 1.19
Total hip	-0.95 + 1.08
Normal BMD Spine L2-4, n (%)	126 (42)
Total hip, n (%)	150 (50)
Either spine and hip, n (%)	84 (28)
Osteopenia Spine L2-4, n (%)	108 (36)
Total hip, n (%)	120 (40)
Either spine and hip, n (%)	135 (45)
Osteoporosis Spine L2-4, n (%)	66 (22)
Total hip, n (%)	30 (10)
Either spine and hip, n (%)	81 (27)

BMI: Body Mass Index, BMD: Bone Mineral Density, RF: Rheumatoid Factor

BMI, overweight, and obese was 47% (141 patients), 42% (126 patients), and 11% (33 patients), respectively.

The median symptom duration was 21 weeks with an interquartile range of 16 to 26 weeks.

Due to demographic variables, average height, weight, and BMI were 165 ± 7.71 cm, 70.47 ± 9.36 kg, and 25.79 ± 3.29 kg/m², respectively. The Mean ± SD was 4.06 ± 1.94 for DAS28 and 0.6 ± 0.58 for MDHAQ.

Laboratory studies show that the Calcium, Vitamin D, and ESR were 9.11 ± 0.55 mg/dL, 18.44 ± 10.31 ng/mL, and 30.01 ± 24.4 mm/hr, respectively. On the other hand, positive RF, Positive CRP, and Positive Anti-CCP were seen in 82%, 51%, and 80% of patients.

Furthermore, the spinal and hip T-score averages were − 1.26 ± 1.19 and − 0.95 ± 1.08, respectively.

Prevalence of osteoporosis/osteopenia

According to Table 1, the prevalence of osteoporosis and osteopenia was 27% (95%CI:22–32) and 45% (95%CI:39–51), respectively. The frequency of spinal osteopenia and osteoporosis was 36% (95%CI:31–42) and 22% (95%CI:17–22) compared to 42% (95%CI:36–49) in the normal group. Moreover, the Prevalence of hip bone osteopenia and osteoporosis were equal to 40% (95%CI:34–46) and 10% (95%CI:7–14) in comparison with 50% (95%CI:44–56) of normal samples. Therefore, based on BMD, the prevalence of spinal osteoporosis is higher than hip bone in affected RA patients. Also, the frequency of simultaneous complications with spinal and hip osteopenia is higher than with spine or hip osteoporosis alone.

Determinants of osteoporosis/osteopenia

According to our results in Table 2, the sexual distribution of patients was assessed based on spinal and hip BMD. The prevalence of spinal osteopenia in women was more than two-fold compared to men (39.3% vs. 18.75%) (p = 0.020). On the other hand, the incidence of hip osteoporosis in men was more than two-fold that in women (18.75% vs. 8.3%) (p = 0.007). In addition, we observed a greater frequency of spine bone osteoporotic state in men (31.25%). Nevertheless, in women, the prevalence of spine osteopenia was more significant than their hip BMD results, in which men were superior. As well as gender, our result has also shown a significantly higher incidence of spine and hip osteoporosis in postmenopausal women with RA.

As demonstrated in Table 1, our participants' mean ± SD age is 57.14 ± 12.46. Also, the average age of patients with spinal and hip osteoporosis was higher than the osteopenia and normal unaffected groups (p < 0.001). In addition, the mean age of patients with spinal and hip Osteopenia was considered higher than the normal group (p < 0.001). By aging, as claimed by spinal and hip BMD results, the rate of osteoporosis increases noticeably, showing the coincidence between osteoporosis progression and aging

A comparison of the height and weight of patients in mentioned groups showed that the mean height and weight of affected patients with spinal osteoporosis were lower than in osteopenia and normal groups (p < 0.001 and p = 0.012), however, there was no significant difference between osteopenia and normal groups regarding their weights (p > 0.05). In the case of the hip bone, osteoporosis patients were shorter than the Osteopenia and normal groups (p < 0.001), while

Table 2 Association of diseases related variable and demographic characteristics based on spinal and hip bone mass density

	Normal			Osteopenia			Osteoporosis			p-Value		
	Spine, n=126	Total hip, n=150	Either, n=84	Spine, n=108	Total hip, n=120	Either, n=135	Spine n=66	Total hip, n=30	Either n=81	Spine	Total hip	Either
All (n=300)	126 (42)	150 (50)	84 (28)	108 (36)	120 (40)	135 (45)	66 (22)	30 (10)	81 (27)	-	-	-
Men, (n=48)	24 (50)	15 (31.25)	12 (25)	9 (18.75)	24 (50)	15 (31.25)	15 (31.25)	9 (18.75)	21 (43.75)	0.020	0.007	0.014
Women, (n=252)	102 (40.5)	135 (53.6)	72 (28.6)	99 (39.3)	96 (38.1)	120 (47.6)	51 (20.2)	21 (8.3)	60 (23.8)	<0.001	<0.001	<0.001
Postmenopausal (n=189)	54 (28.6)	84 (44.4)	30 (15.9)	84 (44.4)	84 (44.4)	99 (52.4)	51 (27)	21 (11.1)	60 (31.7)	<0.001	<0.001	<0.001
Premenopausal (n=63)	48 (76.2)	51 (81)	42 (66.7)	15 (23.8)	12 (19)	21 (33.3)	0	0	0			
Age <50 y (n=84)	63 (75)	69 (82.1)	57 (67.9)	18 (21.4)	15 (17.9)	24 (28.6)	3 (3.6)	0	3 (3.6)	<0.001	<0.001	<0.001
50y-60y (n=129)	45 (34.9)	60 (46.5)	24 (18.6)	63 (48.9)	66 (51.2)	81 (62.8)	21 (16.3)	3 (2.3)	24 (18.6)			
>60 y (n=87)	18 (20.7)	21 (24.1)	3 (3.4)	27 (31)	39 (44.8)	30 (34.5)	42 (48.3)	27 (31)	54 (62.1)			
Height, cm	167.50±7.11	165.84±6.19	167.04±6.33	165.53±6.56	166.78±8.42	167.04±7.01	161.23±8.89	157.80±7.51	161.0±8.45	<0.001	<0.001	<0.001
Weight, kg	71.60±9.51	71.50±8.79	70.04±8.70	70.97±8.52	69.93±7.91	71.98±9.26	67.50±9.89	67.50±10.21	68.41±9.84	0.012	0.072	0.022
BMI, kg/m2	25.51±2.93	26.03±3.22	25.11±2.84	26.02±3.69	25.20±3.45	25.87±3.53	25.96±3.27	26.98±2.55	26.38±3.24	0.449	0.013	0.044
Body type (according to BMI) Normal (n=141)	63 (44.7)	63 (44.7)	45 (31.9)	45 (31.9)	75 (53.2)	63 (44.7)	33 (23.4)	3 (2.1)	33 (23.4)	0.085	<0.001	0.043
Overweight (n=126)	54 (42.9)	72 (57.1)	36 (28.6)	51 (40.5)	30 (23.8)	57 (45.2)	21 (16.7)	24 (19)	33 (26.2)			
Obese (n=33)	9 (27.3)	15 (45.5)	3 (9.1)	12 (36.4)	15 (45.5)	15 (45.5)	12 (36.4)	3 (9.1)	15 (45.5)			
Calcium, mg/dl	9.10±0.56	9.08±0.46	9.05±0.536	9.05±0.453	9.00±0.576	9.03±0.465	9.22±0.66	9.65±0.523	9.30±0.645	0.151	<0.001	<0.001
Vitamin D, mg/dl	19.26±10.57	19.33±10.14	21.33±10.36	17.92±10.38	16.52±9.27	17.07±9.65	17.72±0.9.70	21.63±13.58	17.73±10.83	0.498	0.016	0.009
ESR	24.66±23.85	23.92±20.83	18.17±15.58	32.47±24.38	37.72±27.02	38.52±26.16	35.86±24.33	28.9±23.05	36.14±23.14	0.025	0.043	0.032
Positive CRP	63 (50)	60 (40)	36 (42.8)	51 (47.2)	69 (57.5)	33 (63.4)	39 (59.1)	24 (80)	18 (85)	0.123	0.160	0.017
Positive Anti-CCP	102 (81)	117 (78)	18 (21.4)	78 (72.2)	99 (82.5)	39 (75)	60 (90.9)	24 (80)	21 (100)	0.732	0.932	0.009
RF Positive (n=246)	102 (41.5)	117 (47.6)	63 (25.6)	87 (35.4)	102 (41.5)	111 (45.1)	57 (23.2)	27 (11)	72 (29.3)	0.578	0.161	0.067
Negative (n=54)	24 (44.4)	33 (61.1)	21 (38.9)	21 (38.9)	18 (33.3)	24 (44.4)	9 (16.7)	3 (5.6)	9 (16.7)			
DAS28 high disease activity (>5.1) (n=12)	3 (25)	3 (25)	6 (50)	6 (50)	8 (66.7)	6 (50)	3 (25)	1 (8.3)	0	0.449	0.065	0.054
low disease activity (<3.2) (n=18)	6 (33.3)	3 (16.7)	9 (50)	5 (27.7)	12 (66.7)	15 (83.3)	7 (38.8)	3 (16.7)	3 (16.7)			
remission (<2.6) (n=270)	117 (43.3)	144 (53.3)	69 (25.5)	97 (35.9)	100 (37)	114 (42.2)	56 (20.7)	26 (9.6)	78 (28.9)			

BMI: Body Mass Index, RF: Rheumatoid Factor, DAS28: Disease Activity Score

Table 3 Comparison of the frequencies for the high-risk of osteoporotic fractures according to FRAX criteria

	FRAX Criteria with BMD (%, p-Value)	FRAX Criteria without BMD (%, p-Value)
Female	78.88%, 0.032	80%, 0.09
Menopause	59.15%, < 0.0001	89.16%, < 0.0001
BMI < 25 kg/m2	53.33%, 0.059	65.33%, 0.005
ESR elevation	34.44%, 0.09	38%, 0.105

BMI: Body Mass Index, BMD: Bone Mineral Density, FRAX: Fracture Risk Assessment Tool, ESR: Erythrocyte Sedimentation Rate

Table 4 Multivariable logistic regression analyses for high-risk of fracture of FRAX criteria

	FRAX with BMD Criteria		FRAX without BMD Criteria	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age (year)	1.07 (1.03 to 1.11)	< 0.001	1.11 (1.08 to 1.14)	< 0.001
Female	4.27 (1.85 to 9.95)	< 0.001	6.23 (2.21 to 10.25)	< 0.001
BMI (kg/m2)	0.95 (0.85 to 1.05)	0.04	0.64 (0.5 to 0.78)	< 0.001
Disease duration (week)	1. 01(1 to 1.02)	0.188	1.02 (1 to 1.04)	0.130

BMI: Body Mass Index, BMD: Bone Mineral Density, FRAX: Fracture Risk Assessment Tool

there was no statistically significant difference between Osteopenia and normal groups (p = 0.296).

The Chi-square test results in Table 2 show statistically significant BMI and BMD alteration between hip osteoporosis-affected patients and the normal group (p = 0.013). After sorting patients based on their BMI levels into normal, overweight, and obese groups, it was apparent that with increasing BMI, the occurrence of hip osteoporosis and osteopenia augmented significantly (p < 0.001).

In hip osteoporosis patients, Ca and Vit D levels were higher than in the two groups of normal and osteopenia in a statistically significant manner (p < 0.001 and p = 0.016).

A comparison of serum levels of RF in different groups did not show a significant difference (p > 0.05). Similarly, measured DAS28 in new-onset RA patients showed no significant difference between disease activity level and spine and hip osteoporosis (p < 0.001).

The prevalence of spinal osteoporosis directly was related to the female gender, postmenopausal condition, aging, shorter height, and lower weight. Also, hip osteoporosis is affected by postmenopausal condition, aging, shorter height, higher BMI, and higher Ca and Vit D levels.

Table 3 shows related dichotomous factors to the FRAX score. In FRAX with BMD setting, high-risk patients were more likely to be female (p-Value: 0.032), especially

postmenopausal women (p < 0.001). Similar data has been seen in FRAX without BMD.

Regression analysis

The fracture risk for the FRAX criteria was identified by multivariable logistic regression analyses (Table 4). In BMD modified setting, age (OR: 1.07, CI: 1.03 to 1.11, p < 0.001), female sex (OR: 4.27, CI: 1.85 to 9.95, p < 0.001), and BMI (OR: 0.95, CI: 0.85 to 1.05, p = 0.04) and in non-BMD modified setting age (OR: 1.11, CI: 1.08 to 1.14, p < 0.001), female sex (OR: 6.23, CI: 2.21 to 10.25, p < 0.001), and BMI (OR: 0.64, CI: 0.5–0.78, p < 0.001) were independently associated with fracture risk.

The regression analysis results in Table 5 showed that age could predict spine/hip osteopenia and osteoporosis. The female gender was also a predictor of spine/hip osteopenia and hip osteoporosis. Based on our results, by increasing a year of patients' age, the odds of spine/hip osteopenia increased about 6–9%, and spine/hip osteoporosis increased about 16–27%. Moreover, the female gender can act as a protective factor for hip osteopenia and osteoporosis ($OR_{Female/Male}$: 0.30, CI: 0.13–0.65, P: 0.004 $OR_{Female/Male}$: 0.10, CI: 0.02–0.44, P: 0.002). Although being a woman was associated with spine osteopenia ($OR_{Female/Male}$: 2.39, CI:1.02–5.59, P: 0.043(.

After adjusting for potential confounders, data showed that higher scores in MDHAQ were associated with total hip osteopenia (OR: 2.68, CI: 1.33 to 5.53, p: 0.0063), spine osteoporosis (OR: 1.21, CI: 1 to 1.41, p: 0.0025), and total hip osteoporosis (OR: 1.81, CI: 1.51 to 2.11, p: 0.018). Also, patients with total hip osteoporosis were more likely to have higher disease activity scores (OR: 1.86, CI: 1.16 to 3.14, p: 0.0122) and positive CRP (OR: 11.42, CI: 2.65 to 63.26, p: 0.0023).

Discussion

Osteoporosis is a common middle to old-age disease associated with several risk factors. Apart from the exorbitant and debilitating cost, this disease leads to various complications and mortality. Fracture-related osteoporosis is the prime cause of disability and a significant cause of burden on the health economy in many world regions [39].

According to the WHO standard and our results, about 36% and 22% of the community suffer from spinal osteopenia and osteoporosis. In comparison, Hip bone osteopenia and osteoporosis prevalences were 40% and 10%, respectively. Studies have shown similar results; Mikuls et al. reported that in their study, 55% (n = 94) of African Americans with recently-onset RA were osteopenic or

Table 5 OR (95% CI) of determinants of Osteoporosis and Osteopenia in the Spine and the Hip according multivariate logistic regression analysis

	Osteopenia				Osteoporosis			
	Spine		Total hip		Spine		Total hip	
	OR (95% CI)	p- Value	OR (95% CI)	p- Value	OR (95% CI)	p- Value	OR (95% CI)	p- Value
Age (year)	1.06 (1.03 to 1.09)	0.0410	1.09 (1.06 to 1.12)	0.0110	1.16 (1.11 to 1.20)	< 0.0001	1.27 (1.18 to 1.38)	< 0.0001
Female gender	2.39 (1.02 to 5.59)	0.0368	0.63 (0.31 to 1.28)	0.2070	0.8723 (0.38 to 2.05)	0.7478	0.3147 (0.06 to 1.40)	0.1288
BMI (kg/m2)	1.02 (0.95 to 1.10)	0.5275	0.90 (0.77 to 1.03)	0.0608	1.02 (0.93 to 1.12)	0.5552	1.3 (1.07 to 1.53)	0.0085
Symptom Duration, weeks	1.01 (0.96 to 1.06)	0.5740	1 (0.95 to 1.05)	0.8484	1.02 (0.97 to 1.08)	0.3317	1.07 (0.95 to 1.18)	0.3065
MDHAQ	1.45 (0.72 to 2.94)	0.053	2.68 (1.33 to 5.53)	0.0063	1.21 (1.01 to 1.41)	0.0025	1.81 (1.51 to 2.11)	0.018
DAS28	0.93 (0.76 to 1.13)	0.4982	0.86 (0.70 to 1.05)	0.1529	0.98 (0.77 to 1.25)	0.8868	1.86 (1.16 to 3.14)	0.0122
Positive CRP	0.80 (0.46 to 1.37)	0.4240	0.67 (0.38 to 1.16)	0.1629	1.04 (0.54 to 2.01)	0.8900	11.42 (2.65 to 63.26)	0.0023
Positive RF	1.03 (0.54 to 1.99)	0.9256	0.80 (0.41 to 1.56)	0.5247	2.04 (0.81 to 5.93)	0.1520	3.47 (0.37 to 58.04)	0.3333
Positive Anti CCP	0.4780 (0.26 to 0.86)	0.0155	0.94 (0.51 to 1.74)	0.8440	2.4 (1.03 to 6.73)	0.0464	0.51 (0.11 to 2.60)	0.4055

BMI: Body Mass Index, MDHAQ: Multidimensional Health Assessment Questionnaire, DAS28: Disease Activity Score, RF: Rheumatoid Factor, ANTI CCP: Anti-Cyclic Citrullinated Peptides, CRP: C-reactive protein

worse, and 16% (n = 27) were osteoporotic [40]. Also, in a meta-analysis study done by Bagheri et al., it was demonstrated that the lowest and highest calculated prevalence of femoral region osteoporosis was 1.5% and 43%. At the same time, the minimum and maximum spinal osteoporosis were 3.2% and 51.3% in all their examined population. Moreover, using a randomized model, this study estimated that 18.9% of Iranian women suffer from osteoporosis in the femoral [14]. In another case-control study by Heydari and Jalali, they reported a 45% incidence of hip osteoporosis in patients prescribed corticosteroid medicines. 30.4% of patients were categorized in normal control with no corticosteroid consumption. They also demonstrated that the corticosteroid-treated patients had a higher osteoporosis rate compared to non-corticosteroids treated patients (43.5% vs. 39%). In addition, they highlighted that a significant proportion of RA patients have current osteoporosis [41]. Furthermore, Lee and colleagues examined 1,322 postmenopausal females in Korea and reported that 46.8% of patients with RA also had osteoporosis [28]. In a recent study on non-pregnant women, Sai Ghara Naz et al. showed that the overall prevalence of osteoporosis was 42.2%, including 14.3% of women under the age of 45 and 50.7% over the age of 45 [42].

Although numerous studies have estimated the expected age of RA onset to be 30 to 60 years, the mean $\pm$ SD age of the participants in our study was 57.14 $\pm$ 12.46 years. Also, epidemiological studies on the Iranian population have reported the onset of RA at older ages. For example, Jamshidi et al. reported that the mean age ($\pm$SD) of new-onset RA patients in their study was 52.3 ($\pm$17.6) years [43]. Investigating the causes of this difference in the Iranian population requires further studies, but genetics, low public awareness of the disease, and late referrals may be among the causes.

In contrast, age has a pivotal role in the progression of osteoporosis and osteopenia disease. Our data showed that osteoporosis was higher than osteopenia in old ages in the normal group (p < 0.001). Similarly, the age of osteopenic patients was greater than normal individuals (p < 0.001). This result was supported by similar studies, which confirmed the relationship between the elderly and the rate of osteoporosis [28, 31, 42]. Similarly, in another case study, Soheili and colleagues observed that osteoporosis was associated with age over 50, joint pain, family history, physical activity, underlying disease, history of fractures, menopause condition, and dairy consumption [39]. Also, a study by Lee et al. showed that age above 70, higher prescribed doses of glucocorticoid medicine, more than ten years of struggle with RA, and high pain score on HAQ were the independent risk factors of osteoporosis [28].

Based on sex distribution, we observed that the prevalence of spinal osteopenia in women was more than twofold that in men (39.3% vs. 18.75%, p-value: 0.020). Our data demonstrated that high-risk patients are more likely to be women 78.88% and 80%, according to FRAX with and without BMD). Accordingly, multivariable logistic regression analyses on FRAX with and without BMD show an OR of 4.27 (CI: 1.85 to 9.95) and 6.23 (CI: 2.21 to 10.25). However, the female sex has always been considered an

osteoporotic fracture risk factor. For example, Johnell and Kanis reported that in comparison to men, women have a much greater risk of any osteoporotic fracture in their entire life (40–50% in women, and 13–22% in men) [44]. Our data demonstrated that female RA patients are at higher risk of osteoporotic fractures even in the early stages of the disease and before exposing to glucocorticoids.

One of the notable results of our study was the higher frequency of hip Osteopenia and osteoporosis in men with RA than in women. Our data demonstrated that this superiority in osteoporosis was more than two-fold compared to the female participants (18.75% vs. 8.3%). Although more studies are required to investigate this issue, late diagnosis of the disease in men is probably one of the causes. Studies have shown that male patients with rheumatological diseases tend to have delayed diagnoses; Because they may attribute pain and movement limitations to other activities and take longer to seek treatment [45]. As early diagnosis is important to slow the progression of the disease and limit joint damage, men with RA are more likely to develop complications such as osteopenia and osteoporosis.

We found that the prevalence of osteoporosis and osteopenia was significantly higher in postmenopausal individuals in comparison with premenopausal women (p-value < 0.001), to the extent that we could not observe any premenopausal women with osteoporosis in this study. Similarly, Guler et al. reported that only 1.3% of the premenopausal women were osteoporotic in their study [26]. In this regard, Guler's data is in line with our study and demonstrates the differences between premenopausal and postmenopausal women in the case of osteoporosis. Similar data were observed by FRAX so that 59.15% and 89.16% of high-risk patients were postmenopausal. Studies and sources have mentioned different pathophysiology for this topic. In general, with the onset of menopause, following a decrease in ovarian function and estrogen activity, osteoclast activity intensifies, as studies show that in the first 5 to 10 years, post-menopause women lose 30% and 15% of trabecular and cortical bones, respectively [46].

In our spinal osteoporosis-affected cases, the average height and weight were lower than in the osteopenia and normal groups. This indicates that people with lower BMI are more susceptible to osteoporosis and osteopenia. The effect of BMI on BMD and fracture risk has been investigated in numerous studies. For example, a cohort study in 2013 showed that both men and women with RA, who were shorter than the studied population's median, exhibited more susceptibility to severe osteoporosis in the future [47]. Furthermore, osteoporosis progression coincident with height shortening may cause vertebral fractures in the following years [48]. In line with our findings and according to the regression model, Sai Qara Naz et al. have also claimed

that lower weight, older ages, and bone fracture history are significant osteoporosis risk factors [42].

In addition, we observed that BMI in Hip osteoporosis patients was higher than in osteopenia and Normal individuals, and this difference is considered significant. Despite increasing BMI, there was no significant difference between spinal osteoporosis and normal groups in the BMI. The incidence of osteoporosis has a decreasing trend in the overweight group, but with increasing BMI in the Obese group, the Prevalence of spinal osteoporosis has increased. On the other hand, with BMI increasing, the rate of hip osteopenia diminished in the overweight group while augmented in the obese group. Similar results have also been reported by Choi et al. and Saei Ghare Naz et al. [31, 42]. In this regard, Choi et al., by studying 353 postmenopausal women, demonstrated that higher BMI, Female gender, old age, longer disease duration, and higher prescribed glucocorticoid dose were independent risk factors for osteoporosis-related fractures. This group also revealed that osteoporosis-related fractures were present in 16.9% of women. Furthermore, they reported that 33.4–61% of patients with RA are considered at high-risk for osteoporotic-related fractures. Additionally, the percentages of patients with decreased BMD based on FRAX criteria with or without BMD score and WHO criteria (World Health Organization) stood at 47.2%, 61%, and 33.4%, respectively [31].

Measurement of different serum factors is one of the main bases for diagnosing and managing RA patients. In this study, 80% of patients were anti-CCP positive. Various studies have shown that anti-CCP-positive RA patients are more prone to severe and complicated cases of RA. Our analysis showed that a positive anti-CCP is significantly associated with spinal osteoporosis. Due to this, BMD should be assessed in the early stages in these patients. As shown in Table 5, CRP positivity is strongly associated with pelvic osteoporosis (OR: 11.42). CRP is one of the most widely used inflammatory factors in the clinic, and its increase can be a sign of various diseases. The CRP increment in these patients may be due to their osteoporosis condition and not RA. In other words, RA or another cause caused osteoporosis, and osteoporosis increased CRP. This is clearly stated in a study conducted by Ishii et al. [17].

This study showed that the minimum mean of Ca and Vit D levels belong to osteopenia patients, highlighting the importance of Ca and Vit D supplements in preventing nonvertebral and falls fractures in affected patients (50. We also illustrate that the Ca and Vit D levels are higher in hip osteoporosis patients. We guess that the increased level of minerals, Ca, and Vit D could result from taking extra supplements prescribed by various physicians, resulting from patients' old age and osteoporosis-related complaints.

We believe several further studies on rheumatoid arthritis disease timeline, glucocorticoid drugs dose in glucocorticoid therapy, and complete investigation of recent fractures, underlying disease, familial history, physical activity, menopause condition, and dairy consumption can further determine the effect of RA on osteopenia and osteoporosis.

While this study considers different parameters in the pathogenesis of osteoporosis in considerable sample size, there were some limitations. One of limitations in our study was the cross-sectional design, which although it can provide a reseonable population for studies, it can not establish a definite conlusion from the results. In addition, due to the lack of CRP history, the acuteness of CRP elevation was not clear. As a result, there is a possibility that some elevations are solely due to acute inflammations rather than chronic inflammation. Moreover, participants' lack of awareness in giving precise information and the long sampling duration may overshadow the results. Finally during 12 months of our study we had the COVID-19 pandemic occurance which was a challenge and limitation for gathering data from patients.

Conclusion

In conclusion, new-onset RA patients, who had never used glucocorticoids or DMARDs, are also at risk for osteoporosis and its complications. Our experiment suggests that old age, female gender, and low BMI, even in new-onset RA patients, are more likely to have a higher fracture risk (according to FRAX) and will probably benefit from early BMD measurements. According to our data, BMD status is mainly associated with demographic factors (e.g., age and female gender) and patients' MDHAQ scores, highlighting the importance of measuring BMD in women, the elderly, and patients with higher MDHAQ scores. In addition, positive anti-CCP appears to be associated with spinal osteoporosis. As a result, physicians should pay special attention to the bone health of this group of patients.

Therefore, it is recommended that clinicians investigate early BMD measurements to be aware of the BMD condition at the baseline and consider the associated factors in new-onset RA patients to have a reasonable judgment for further interventions.

Declarations

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