

Evaluation of Bone Densitometry in Rheumatoid Arthritis Case Control Study

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Abstract

Background: Rheumatoid arthritis is a systemic autoimmune inflammatory disease that causes joint deformity, including erosion of bone, and narrowing of the joint space. Osteoporosis is more prevalent among rheumatoid arthritis patients than in the general population.

Objective: To determine changes in the bone mineral density in rheumatoid arthritis patients and to evaluate factors were associated with bone mineral density.

Patients and Methods: In this study, 70 cases with rheumatoid arthritis were included and 70 healthy subjects on the other hand as a control group. The data were collected including socio-demographic information of all patients' age, gender, medical histories included systemic diseases, types of biological agents, use of supplements, duration of the disease, smoking, and regular exercise. Bone mineral density was evaluated by using bone densitometry in two areas including Lumber 1 to lumber 4 and neck of the left femur. Statistical analyses were performed by using Statistical Package for Social Sciences (SPSS) version 22; Fisher's exact test and Chi-square test Student's t-test of two independent samples was used to comparing two means. A p-value of ≤ 0.05 was considered statistically significant.

Results: In the rheumatoid arthritis group according to T-spine scores the prevalence of osteoporosis was 22.9%, osteopenia was 42.9% and normal bone mineral density was 34.4% compared with the control group 4.3%,42.9%,52.9% successively which were statistically significant difference between the two groups ($p = 0.003$). According to femur neck T-scores in the rheumatoid arthritis group, 17.1% had osteoporosis, 34.3% had osteopenia and 48.6% had normal bone mineral density compared with the control group 2.9%,24.3%,72.9 respectively which were statistically significant difference between the two groups ($p = 0.003$). lumber spine was the commonest site affected by osteoporosis (16 cases,22.9 %)and the second most common site was the femur neck (12 cases ,6.6%). The cases of 50 years and older were most commonly affected by osteoporosis (p -value = 0.0001). No significant association was detected

between bone mineral density (as assessed with spine T-scores and femur T-scores) with gender, duration of the disease, BMI, exercise, supplement, systemic disease, and diabetes.

Conclusion: Osteoporosis and osteopenia were considered as common complications in rheumatoid arthritis, the age of the patient also considered as a risk factor for reduced bone mineral density.

Keywords: Rheumatoid Arthritis; Bone Mineral Density; Osteoporosis; Osteopenia

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disease that causes chronic inflammation of the synovial membrane, with consequent destruction and deformity. The etiology of rheumatoid arthritis it is unclear but genetic and environmental factors have a role in developing RA [1]. The manifestations of rheumatoid arthritis are not only limited to the joints, but also have extra-articular manifestations like rheumatoid nodules, vasculitis, episcleritis, pulmonary fibrosis, pericarditis, anemia, and osteoporosis [2,3]. The prevalence of RA approximately is 1.0% in the general population, and affects women more than men. RA patients experience pain, stiffness, tenderness, and articular damage of the joints leading to functional disability, which reduces the quality of life [4-6].

Rheumatoid arthritis is chronic inflammatory arthritis associated with changes in biochemical properties of the bone and leads to the alteration in the bone components through the increased production of the pro-inflammatory cytokines or through the effect of hormone-mediated mechanisms [7-9]. In addition to the risk factors of osteoporosis, other factors may play important role in the development of osteoporosis including physical disability, inadequate treatment, and disease activity [10-12]. Osteoporosis is more common in

patients with rheumatoid arthritis than in the general population. The prevalence of concurrent osteoporosis is 50%. Osteoporosis causes pain and increase the risk of fracture after falling [13]. The chronic synovial inflammation in rheumatoid arthritis promote osteoclastogenesis, which leads directly to both focal and generalized bone loss and increased risk of fracture, also there are many indirect factors that associate inflammatory arthritis contribute to the risk of osteoporosis, as weight loss, immobility, and chronic use of medicines, such as glucocorticoids [14].

Osteoclast play important role in bone resorption in rheumatoid arthritis patient, orchestrated by T-lymphocytes, monocytes, and fibroblasts in the synovium of inflammatory joints that involved in the disease processes, which produce osteoclast differentiation-inducing factors. Osteoclast differentiation is mainly promoted by the receptor activator of nuclear factor-kappa B ligand (RANKL), which is up-regulated by a large number of the inflammatory cytokines involved in the pathogenesis of rheumatoid arthritis [15]. A better understanding of the pathogenesis of RA has improved treatment of the disease, particularly using biological agents and JAK-inhibitors.

It is recommended by the International Society for Clinical Densitometry (ISCD) and National Osteoporosis Foundation (NOF)

that Dual –Energy X-ray Absorptiometry (DEXA) testing should be done for all adults rheumatoid arthritis patients, as well as women over 65years old, those who suffer a fragility fracture, patients on chronic glucocorticoids therapy and anyone at the high risk of fracture.

To evaluate bone mineral density (BMD) in patients with rheumatoid arthritis, and to establish which factors were associated with low BMD.

Patients and Methods

This prospective cross-sectional case-control study was conducted in Hawler Teaching Hospital Department of Rheumatology. This study was approved by the Ethical Committee at the college of Medicine in the Hawler Medical University. All the patients were signed informed consent forms before being included in the study. No therapeutic intervention was made and the patients' data were kept confidential. The study was composed of 70 patients with RA and 70 controls healthy, socioeconomic matched controls patients were taken.

Inclusion criteria: According to the American College of Rheumatology/European League Against Rheumatism ACR/EULAR 2010 criteria for rheumatoid arthritis all patients with RA are included in the study [19].

Exclusion criteria: Patients with psoriasis, inflammatory bowel disease, dementia, pregnancy, thyroid diseases secondary cases of osteoporosis, were excluded from our study.

According Declaration of Helsinki Physical examination and questionnaires the consent was obtained. The data were collected including sociodemographic variables of all

patients; age, gender, medical history included, systemic disease type of biology treatment, using supplements, duration of RA, regular exercise, and smoking.

The height and weight were measured and respondents were dressed in light clothes and did not wear shoes. Body mass index (BMI) was calculated from the height and weight recorded while performing a DEXA scan. The BMI was calculated based on the formula $\text{weight (kg)/height (m)}^2$. The standard categorization of BMI by The Centers for Disease Control and Prevention (CDC) [20], indicates less than 18.5 as underweight, 18.5–24.9 as normal, 25.0–29.9 as overweight, and 30.0 and above as obese.

Bone mineral density of the lumbar spine in the anterior- posterior view (AP) (vertebrae L1 to L4), and the left femoral neck) was measured using a DXA scanner. Following World Health Organization (WHO) definitions of osteopenia and osteoporosis were used: osteopenia, T-score < -1 to > -2.5 SD (compared to the young normal mean), and osteoporosis, T-score ≤ -2.5 SD. The lowest value of BMD measured in the lumbar spine, the femoral neck was used [21]. For patients under the age of 50, a Z-score ≤ -2.0 SD (compared to the age-matched mean) was considered to be below the expected range for age [22]. For calculation of T- and Z-scores the BMD values of the patients were compared with reference values provided by the DXA scanner.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 25). Chi-square test of association was used

to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was less than 5. Student's t-test of two independent samples was used to compare two means. A p-value of ≤ 0.05 was considered statistically significant.

Results

Seventy patients with rheumatoid arthritis had been included in the study and considered as cases, on the other hand, 70 persons with no RA were included which considered as a control group. The mean age \pm SD of the cases was 47.03 ± 11.53 years, and that of the control was 46.54 ± 12.66 years ($p = 0.813$). No significant differences were detected in the age distribution of cases

and controls ($p = 0.479$) as presented in Table (1). The majority (87.1%) of the whole sample were females, but there was no significant difference in the gender distribution of the two groups ($p = 0.130$). Around half (50.7%) of the patients were obese, and 31.4% were overweight. Again no significant difference was detected between the two groups ($p = 0.685$). More than one-third (37.1%) of the control group were practicing exercise, this proportion was significantly ($p = 0.025$) higher than the proportion among the cases (20%). The table also shows that 10% of the whole sample were smokers, but the differences between the two groups were not significant ($p = 0.260$).

Table (1): Basic characteristics of the study groups

	Case		Control		Total		P-value
	No.	(%)	No.	(%)	No.	(%)	
Age (years)							
20-29	4	(5.7)	9	(12.9)	13	(9.3)	
30-39	14	(20.0)	12	(17.1)	26	(18.6)	
40-49	25	(35.7)	18	(25.7)	43	(30.7)	
50-59	14	(20.0)	16	(22.9)	30	(21.4)	
60-69	13	(18.6)	15	(21.4)	28	(20.0)	0.479
Mean(\pm SD)	47.03	(± 11.53)	46.54	(± 12.66)			0.813†
Gender							
Female	58	(82.9)	64	(91.4)	122	(87.1)	
Male	12	(17.1)	6	(8.6)	18	(12.9)	0.130
BMI (Kg/m ²)							
< 25	12	(17.1)	13	(18.6)	25	(17.9)	
25-29	20	(28.6)	24	(34.3)	44	(31.4)	
≥ 30	38	(54.3)	33	(47.1)	71	(50.7)	0.685
Mean(\pm SD)	31.55	(± 6.94)	30.08	(± 5.67)			0.172†
Exercise							
Yes	14	(20.0)	26	(37.1)	40	(28.6)	
No	56	(80.0)	44	(62.9)	100	(71.4)	0.025
Smoking							
Yes	9	(12.9)	5	(7.1)	14	(10.0)	
No	61	(87.1)	65	(92.9)	126	(90.0)	0.260
Total	70	(100.0)	70	(100.0)	140	(100.0)	

*By Fisher's exact test. †By t-test for two independent samples. The others by Chi-square test

It is evident in Table (2) that 74.3% of the controls were taking supplements, compared with 47.1% of the cases ($p = 0.001$). The prevalence of diseases in the whole sample was as follows: systemic diseases (24.3%), diabetes (5%). All the differences between

the two groups regarding the prevalence of diseases were not significant. The table shows that 24.3% of the cases were on Infliximab, 61.4% on etanercept, 7.1% on adalimumab and 7.1% were on rituximab.

Table (2): Drug intake and clinical characteristics of the two study groups

	Case		Control		Total		P-value
	No.	(%)	No.	(%)	No.	(%)	
Supplements							
Yes	33	(47.1)	52	(74.3)	85	(60.7)	
No	37	(52.9)	18	(25.7)	55	(39.3)	0.001
Systemic diseases							
Yes	19	(27.1)	15	(21.4)	34	(24.3)	
No	51	(72.9)	55	(78.6)	106	(75.7)	0.430
Diabetes							
Yes	6	(8.6)	1	(1.4)	7	(5.0)	
No	64	(91.4)	69	(98.6)	133	(95.0)	0.116*
Infliximab							
Yes	17	(24.3)	0	(0.0)	17	(12.1)	
No	53	(75.7)	70	(100.0)	123	(87.9)	< 0.001
Etanercept							
Yes	43	(61.4)	0	(0.0)	43	(30.7)	
No	27	(38.6)	70	(100.0)	97	(69.3)	< 0.001
Adalimumab							
Yes	5	(7.1)	0	(0.0)	5	(3.6)	
No	65	(92.9)	70	(100.0)	135	(96.4)	0.058*
Rituximab							
Yes	5	(7.1)	0	(0.0)	5	(3.6)	
No	65	(92.9)	70	(100.0)	135	(96.4)	0.058*
Total	70	(100.0)	70	(100.0)	140	(100.0)	

*By Fisher's exact test. The others by the Chi-square test

It is evident in Table (3) that the means of all the indicators of BMD were significantly less than those of the control group.

Table (3): Means of the bone mineral density indicators of the cases and controls

Indicators	Case		Control		P-value*
	Mean	(±SD)	Mean	(±SD)	
T-spine	-1.54	(±1.51)	-0.96	(±1.09)	0.010
T-femur	-1.24	(±1.22)	-0.67	(±0.87)	0.002
Z-spine	-0.92	(±1.48)	-0.47	(±1.13)	0.048
Z-femur	-0.88	(±1.22)	-0.41	(±0.94)	0.012

*By t-test of two independent sample

Table (4) shows that the prevalence of osteoporosis (according to the T-spine scores) among cases was 22.9%, compared with 4.3% of the control group ($p = 0.003$).

The prevalence of osteoporosis (according to T-femur scores) was 17.1% among cases and 2.9% among the controls ($p = 0.003$).

Table (4): Bone mineral density as assessed by T-spine and T-femur scores among cases and controls

Scores	Case		Control		Total		P-value
	No.	(%)	No.	(%)	No.	(%)	
T-spine							
Osteoporosis	16	(22.9)	3	(4.3)	19	(13.6)	
Osteopenia	30	(42.9)	30	(42.9)	60	(42.9)	
Normal	24	(34.3)	37	(52.9)	61	(43.6)	0.003
T-femur							
Osteoporosis	12	(17.1)	2	(2.9)	14	(10.0)	
Osteopenia	24	(34.3)	17	(24.3)	41	(29.3)	
Normal	34	(48.6)	51	(72.9)	85	(60.7)	0.003
Total	70	(100.0)	70	(100.0)	140	(100.0)	

Table (5) considered the cases only. It is evident that the highest prevalence of osteoporosis and osteopenia was among patients aged 50 years or older ($p = 0.001$). No significant association was detected between bone mineral density (as assessed

with T-femur scores) with gender ($p = 0.210$), duration of the disease ($p = 0.560$), BMI ($p = 0.054$), exercise ($p = 0.095$), supplement ($p = 0.558$), systemic disease ($p = 0.862$), and diabetes ($p = 0.139$).

Table (5): Bone mineral density of cases as assessed by T-femur scores by the studied factors

	T-femur scores categories						P-value
	Osteoporosis		Osteopenia		Normal		
	No.	(%)	No.	(%)	No.	(%)	
Age(years)							
20-29	0	(0.0)	0	(0.0)	4	(100.0)	
30-39	3	(21.4)	5	(35.7)	6	(42.9)	
40-49	1	(4.0)	10	(40.0)	14	(56.0)	
50-59	0	(0.0)	6	(42.9)	8	(57.1)	
60-69	8	(61.5)	3	(23.1)	2	(15.4)	0.001*
Gender							
Female	11	(19.0)	17	(29.3)	30	(51.7)	
Male	1	(8.3)	7	(58.3)	4	(33.3)	0.210*
Duration of the disease (years)							
< 5	1	(9.1)	2	(18.2)	8	(72.7)	
5-9	2	(10.5)	8	(42.1)	9	(47.4)	
10-14	4	(18.2)	9	(40.9)	9	(40.9)	
≥ 15	5	(27.8)	5	(27.8)	8	(44.4)	0.560*
BMI (Kg/m ²)							
< 25	5	(41.7)	4	(33.3)	3	(25.0)	
25-29	2	(10.0)	10	(50.0)	8	(40.0)	
≥ 30	5	(13.2)	10	(26.3)	23	(60.5)	0.054*
Exercise							
Yes	0	(0.0)	7	(50.0)	7	(50.0)	
No	12	(21.4)	17	(30.4)	27	(48.2)	0.095*
Supplement							

Yes	7	(21.2)	12	(36.4)	14	(42.4)	
No	5	(13.5)	12	(32.4)	20	(54.1)	0.558
Systemic diseases							
Yes	4	(21.1)	6	(31.6)	9	(47.4)	
No	8	(15.7)	18	(35.3)	25	(49.0)	0.862
Diabetes							
Yes	1	(16.7)	0	(0.0)	5	(83.3)	
No	11	(17.2)	24	(37.5)	29	(45.3)	0.139*
Total	12	(17.1)	24	(34.3)	34	(48.6)	

*By Fisher's exact test. Others by the Chi-square test

In Table (6) the cases only are included but the BMD was assessed by the T-spine scores. Osteoporosis and osteopenia are mainly prevalent among the cases aged 50 years and above ($p < 0.001$). No significant association was detected between BMD with gender ($p = 0.557$), duration of the disease (0.917), BMI

($p = 0.205$), exercise ($p = 0.296$), tea ($p = 0.306$), supplement ($p = 0.803$), and systemic disease ($p = 0.429$). The majority (83.3%) of the diabetic had neither osteoporosis nor osteopenia, compared with 29.7% of those who don't have diabetes ($p = 0.016$).

Table (6): Bone mineral density of cases as assessed by T-spine scores by the studied factors

	T-spine scores categories						P-value
	Osteoporosis		Osteopenia		Normal		
	No.	(%)	No.	(%)	No.	(%)	
Age (year)							
20-29	0	(0.0)	0	(0.0)	4	(100.0)	
30-39	1	(7.1)	8	(57.1)	5	(35.7)	
40-49	4	(16.0)	11	(44.0)	10	(40.0)	
50-59	1	(7.1)	9	(64.3)	4	(28.6)	
60-69	10	(76.9)	2	(15.4)	1	(7.7)	< 0.001*
Gender							
Female	14	(24.1)	23	(39.7)	21	(36.2)	
Male	2	(16.7)	7	(58.3)	3	(25.0)	0.557*
Duration of the disease							
< 5	1	(9.1)	6	(54.5)	4	(36.4)	
5-9	5	(26.3)	8	(42.1)	6	(31.6)	
10-14	5	(22.7)	10	(45.5)	7	(31.8)	
≥ 15	5	(27.8)	6	(33.3)	7	(38.9)	0.917*
BMI (Kg/m ²)							
< 25	5	(41.7)	3	(25.0)	4	(33.3)	
25-29	6	(30.0)	7	(35.0)	7	(35.0)	
≥ 30	5	(13.2)	20	(52.6)	13	(34.2)	0.205*
Exercise							
Yes	1	(7.1)	7	(50.0)	6	(42.9)	
No	15	(26.8)	23	(41.1)	18	(32.1)	0.296*
Supplement							
Yes	8	(24.2)	15	(45.5)	10	(30.3)	
No	8	(21.6)	15	(40.5)	14	(37.8)	0.803
Systemic diseases							
Yes	6	(31.6)	6	(31.6)	7	(36.8)	

No	10	(19.6)	24	(47.1)	17	(33.3)	0.429
Diabetes							
Yes	1	(16.7)	0	(0.0)	5	(83.3)	
No	15	(23.4)	30	(46.9)	19	(29.7)	0.016*
Total	16	(22.9)	30	(42.9)	24	(34.3)	

*By Chi-square test and Fisher's exact test

Discussion

Osteoporosis and fractures are two common complications in patients with RA and that affect quality of life [23]. This study was done to evaluate bone mineral density in patients with rheumatoid arthritis and compare it with bone mineral density in healthy control.

Our results support the prevalence of osteoporosis (according to the T-spine scores) among cases was 22.9%, compared with 4.3% of the control group, and the prevalence of osteoporosis (according to T-femur scores) was 17.1% among cases and 2.9% among the controls. These results are similar to those of Brand *et al* [24] they found that low BMD higher in RA patients than normal age and gender-matched populations. The status of bone mass in RA has been investigated in some case-control and longitudinal studies [25-29]. Bone mass in RA was shown to be lower compared with non-RA controls. This study also found that 34.3% of rheumatoid arthritis patients had normal BMD at the spine, 42.9% had osteopenia, compared with the control group 52.9% had normal BMD, 43.6% had osteopenia which was in agreement with the cohort study, 43.3% had normal BMD, and 43.3% had osteopenia, at the lumbar spine [30], regarding femur 48.6% of RA patients had normal BMD and 34.3% had osteopenia compare with control group were 72.9%, 24.3%. Zhang *et al* [31] found that rheumatoid arthritis had either osteoporosis

or osteopenia in the lumbar spine, and 44.9% had either osteoporosis and osteopenia in the femoral neck.

In the current study lumbar spine was the most common site for RA patients 22.9%, followed by the femur neck 17.1%, these findings are in agreement with the study done by Eman *et al* [30] they reported that lumbar spine was the most common site for osteoporosis in RA patients followed by the femur.

In this study, female more commonly affected by in rheumatoid arthritis females (24.1%) than in men with RA (16.7%) which is in agreement with the research done by Yoon *et al* [32] found that patient with rheumatoid arthritis were arranged by gender the prevalence of osteoporosis in the female are more common than in the male.

In the present study, it is evident that the patients with age 50 years or older had more chance for developing osteoporosis and osteoporosis at the femur ($P = 0.001$), also patients with age 50 years or above were more prevalent for osteoporosis and osteopenia at the spine ($P < 0.001$), which were significant. It is known that low bone mineral density (BMI) and age are associated factors of osteoporosis in patients with RA as well as non-rheumatoid arthritis population, osteoporosis and osteopenia in both spine and femur more common in the thinner patients but this was not significant which was in agreement with the study done by Mobini *et*

al. [33] this study reported that age and BMI were associated factors of decreased BMD and osteoporosis in RA.

Our rheumatoid arthritis patients with osteoporosis who had long RA duration than those had no osteoporosis, but this difference not significant ($P= 0.56$), this result in agreement with those done by Eman et al [30]. And Sinigaglia *et al* [34] they also found that rheumatoid arthritis patients with spine or femoral osteoporosis had longer disease duration, these results are consistent with those Güler-Yüksel *et al* [35] they reported that decreased BMD and aggressive joint disease found in RA patients with early, active, erosive diseases and a positive rheumatoid. The other factors including disease duration, exercise, taking the supplement and systemic disease in the development of osteoporosis was not significant.

Conclusions

In conclusion the reduction of BMD was more common in patients with rheumatoid arthritis than in the control group. Decrease BMD is not necessarily correlated with disease duration, BMI, systemic diseases supplement or regular exercise. DEXA scanning is the most accurate diagnostic method for evaluating osteoporosis in patients with RA. Our study has some limitations.

Recommendations

BMD was detected once in each patient, so we recommend doing another study and measuring BMD more than one time and comparing it with different therapy taken by the patient.

Source of funding: Nill

Ethical clearance: This study was approved by the Ethical Committee at the college of Medicine in the Hawler Medical University.

Conflict of interest: This research done by one researcher.

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