

Relationship Between Physical Disability, Disease Activity and Osteoporosis in Patients With Rheumatoid Arthritis

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Objectives: This study aims to assess the relationship between the physical disability, degree of disease activity, and bone mineral density in menopause patients diagnosed with rheumatoid arthritis (RA).

Patients and methods: The study included 130 females (mean age 62.77±7.51 years; range 57 to 69 years) who reached menopause, and were diagnosed with RA. Bone mineral density was measured at the lumbar spine level and femur (femur head, entire femur) through osteodensitometry with dual X-ray absorptiometry. Age, weight, height, body mass index, environment (urban, rural), age of the menarche and the onset of menopause, duration of menopause, smoker/non-smoker status, RA stage, RA onset age, duration of RA, extra-articular manifestations, the presence of rheumatoid factor, erythrocyte sedimentation rate, C reactive protein, disease activity score 28, and physical disability quantified by modified health assessment questionnaire were used for evaluating the RA activity.

Results: The mean body mass index was 27.74±4.37 kg/m², the mean duration of menopause was 16.42±8.15 years. About 44.62% of the patients had osteoporosis. Osteoporosis frequency increased with RA stage: 23.81% in stage II, 55.0% in stage III, and 77.78% in stage IV. About 58% of the patients received prednisone treatment. Independent risk factors for osteoporosis were: age, environment, body mass index, duration of menopause, rheumatoid factor presence and extra-articular manifestations, duration of RA, modified health assessment questionnaire, erythrocyte sedimentation rate and C reactive protein.

Conclusion: Physical disability and disease activity contribute to the occurrence of osteoporosis in patients diagnosed with RA.

Key words: Disease activity score; menopause; osteoporosis; rheumatoid arthritis.

Rheumatoid arthritis (RA) is a disease characterized by a systemic chronic inflammation which mainly affects the joints through cytokines, chemokines and metalloproteinases. Osteoporosis (OP) is considered to be an extra-articular manifestation of RA,¹ with the prevalence of OP being higher in RA patients than in the general population.²

Potential etiological factors include glucocorticoid treatment, decreased physical activity with progressive disease, and a direct effect of inflammatory mediators on bone turn-

over. Current controversies include how these factors could influence the RA patients. The influence of these factors is likely to be more clearly defined nearly in the disease process, when bone mass is highest and change is more easily quantified since there is less influence of previous treatment or the manifestation of the menopause period.³

This study aims to assess the relationship between physical disability, disease activity, and bone mineral density (BMD) in postmenopausal patients with RA.

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PATIENTS AND METHODS

The study included 130 women (mean age 62.77 ± 7.51 years; range 57 to 69 years) followed by the Rheumatology Clinic in the Clinical Emergency Hospital of Constanta and Clinical Railway Hospital Constanta between January 2008 and January 2010. The women reached menopause at ages between 49 and 75 years. Inclusion criteria were as follows: postmenopausal women meeting American College of Rheumatology 1987 revised criteria for RA, with disease duration of more than two years.⁴ Exclusion criteria were as follows: having secondary OP related with an etiology other than RA, and taking corticosteroid treatment for diseases such as hyperparathyroidism, thyroid disease, and diabetes mellitus, having no BMD measurement.

Demographic variables related to RA and therapeutic variables of the patients were obtained through patient interviews. The following variables were collected: age, weight, height, body mass index (BMI), environment (urban, rural), age at menarche and the onset of menopause, duration of menopause, smoker/non-smoker status, BMD, RA stage, age at onset of RA, duration of RA, extra-articular manifestations (represented by simple chronic anemia, pulmonary fibrosis and rheumatoid nodules), the presence of rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score 28 (DAS28), and physical disability quantified by modified health assessment questionnaire (mHAQ). Treatment included disease modifying anti-rheumatic drugs and corticosteroids.

Global assessment of disease activity was performed by measurement on a visual analog scale from 0 to 100 mm. Disease activity score 28 was calculated by assessing the 28 tender joint count and 28 swollen joint count,⁵ and ESR was calculated by the Westergren method.⁶ Physical disability was assessed by the mHAQ.⁷ C-reactive protein was estimated by the NycoCard Reader.⁸ Bone mineral density was measured at the lumbar spine (L₂-L₄) and femur and femoral neck by dual energy X-ray absorptiometry using an Alpha DPX-type (GE Lunar Corp., Madison, WI). Bone mass was assessed by means of BMD (g/cm²), using the T-score and Z-score. Osteoporosis was defined on the basis of dual energy X-ray

absorptiometry, according to the World Health Organization, when the T-score was at least 2.5 standard deviations (SD) below the average young adult value, a value of ± 1 SD was defined as normal, and between -1.0 and -2.5 SD was defined as osteopenia.⁹

Vertebral fractures (T₄-L₅) were diagnosed with X-rays of the dorsolumbar spine, and fracture evaluations were made by an experienced radiologist using Genant's semi-quantitative method.¹⁰

Fractures other than spinal fractures such as femur, humerus, or forearm fractures were diagnosed through questioning the subjects. Fractures which occurred as a result of minor trauma such as falling from standing height were considered to be osteoporotic fractures.

Statistical analysis

Bivariate analysis was used to compare demographic variables as well as variables related to RA in patients with and without treatment with corticosteroids. Student's t-test was used for comparing variables with continuous normal distribution, the Mann-Whitney U test was used for comparing variables with continuous non-normal distribution, and the Chi-square test was used for dichotomous variables. We performed a multivariate analysis for the variables which are significantly associated with OP. We used other models of logistic regression where OP represented the dependent variable, and the independent variables were those which were statistically associated with OP in the bivariate analysis. The variables were included in the regression equation through the stepwise method. *P* was considered statistically significant at a value of less than 0.05. Statistical analysis was performed using a computer program (MedCalc for Windows, v10, Mariakerke, Belgium).

RESULTS

Demographic characteristics of the group are given in Table 1. The mean age of the patients was 62.77 years, and the distribution by age showed that only 2.3% were under the age of 50, 36.9% were aged between 50 and 59 years, 46.9% were aged between 60-70 years, and 13.8% were aged over 70 years. The majority of

the participants (78.46%) came from urban areas, the medium BMI was 27.74 kg/m², the median age of menopause was 46.35 years, the median duration of menopause was 16.42 years, and the median age of menarche was 14.02 years. The majority of the patients were non-smokers (82.3%).

A measurement of BMD revealed that 44.62% of the patients had OP, 30.0% had osteopenia, and only 25.39% had BMD within the normal range (Table 1). Approximately 37.69% of the patients had spinal, and 35.38% had femoral OP.

The mean value of BMD was 0.94 g/cm² at the level of the lumbar spine (L₂-L₄), 0.81 g/cm² at the right femoral neck, 0.80 g/cm² at the left femoral, 0.83 g/cm² at the total right hip, and 0.81 g/cm² at the total left hip.

The dependent variables of RA are presented in Table 1. None of the patients had RA in stage I. The mean mHAQ score was 1.61±0.50, the mean value of DAS28 was 4.77, the mean ESR was 48.62 mm/h, and the mean CRP was 8.62 mg/dl.

The majority of the patients were in stage II (48.5%), 30.8% were in stage III, and 20.8% were in stage IV RA.

Table 1. General features of study group (n=130)

Demographic features	n	%	Mean±SD
Age (years)			62.77±7.51
Environment			
Urban	102	78.46	
Rural	28	21.54	
Weight (kg)			67.43±11.33
Height (cm)			1.56±0.06
Body mass index (kg/m ²)			27.74±4.37
Menarche (years)			14.02±2.02
Menopause (years)			46.35±4.82
Duration of menopause (years)			16.42±8.15
Smoker	23	17.69	
Former smoker	18	13.85	
Bone mineral density-T-score			
Osteoporosis	58	44.62	
Osteoporosis lumbar spine	49	37.69	
Osteoporosis femoral neck	46	35.38	
Osteopenia	39	30.00	
Normal body mass index	33	25.39	
Bone mineral density (g/cm ²)			
Lumbar spine (L ₂ -L ₄)			0.94±0.17
Right femoral neck			0.81±0.14
Left femoral neck			0.80±0.15
Total right hip			0.83±0.18
Total left hip			0.81±0.21
Rheumatoid arthritis dependent variables			
Rheumatoid arthritis stage			
I	0	0	
II	63	48.5	
III	40	30.8	
IV	27	20.8	
Rheumatoid factor	97	74.6	
Extra-articular manifestations	33	25.4	
Age of rheumatoid arthritis onset (years)			54.86±9.79
Rheumatoid arthritis duration (years)			7.91±7.85
Modified health assessment questionnaire			1.61±0.50
Disease activity score 28			4.77±1.2
Erythrocyte sedimentation rate (mm/h)			48.62±29.45
C-reactive protein (mg/dL)			8.62±18.49
Extra-articular manifestations			
Simple chronic anemia	27	19.23	
Rheumatoid nodules	10	7.69	
Pulmonary fibrosis	3	2.3	

SD: Standard deviation.

Extra-articular manifestations were present in 25.4% of the patients, among which 27 patients (19.23%) presented chronic anemia, 10 patients (7.69%) presented rheumatoid nodules, and three patients (2.3%) had pulmonary fibrosis (Table 1).

Rheumatoid arthritis was seropositive in 74.6% of the patients. An assessment of DAS28 showed that 11.5% (n=15) of the patients had reduced disease severity (DAS28 \leq 3.2), 43.8% (n=57) had moderate activity (DAS28 between 3.2 and 5.1), and 44.6% (n=58) had significantly high activity (DAS28 $>$ 5.1). C-reactive protein level was higher than 20 mg/dl in 16 patients (12.31%), and ESR was higher than 20 mm/h in 97 patients (74.62%).

Fifty-eight percent of the patients used 7.5-10 mg/day prednisone equivalent of corticosteroids. Patients on corticosteroid treatment received corticosteroids for more than

one year. Regarding other treatments, the majority of the patients received leflunomide (49%), followed by those who received methotrexate (44%), combinations of disease modifying anti-rheumatic drugs (21%), and hydroxychloroquine (16%), sulfasalazine (14%), and biological therapy (9%). No patient received anti-osteoporotic medication.

Table 2 shows the bivariate analysis of the demographic and RA related variables in patients with and without OP. Osteoporosis was significantly associated with old age, urban environment, lower body weight, lower BMI, late menarche, longer duration of menopause, stage IV RA, the presence of extra-articular manifestations and RF, higher duration of RA, higher ESR, higher CRP, higher mHAQ score, and higher DAS28. Therefore, rural environment

Table 2. Comparison between patients with and without osteoporosis

	T-score ($>$ -2.5) (n=72)			T-score ($<$ -2.5) (n=58)			p
	n	%	Mean \pm SD	n	%	Mean \pm SD	
Demographic variables							
Age (years)			58.75 \pm 5.37			67.76 \pm 6.79	<0.0001
Weight (kg)			70.58 \pm 11.87			63.52 \pm 9.34	0.0003
Height (cm)			1.56 \pm 0.07			1.56 \pm 0.07	0.673
Body mass index (kg/m ²)			28.97 \pm 4.66			26.22 \pm 3.47	0.0003
Menarche (years)			13.54 \pm 1.45			14.60 \pm 2.44	0.002
Menopause (years)			46.58 \pm 4.46			46.05 \pm 5.28	0.534
Duration of menopause (years)			12.17 \pm 6.87			21.71 \pm 6.35	<0.0001
Smoker	9	12.50		14	24.14		0.134
Former-smoker	12	16.67		6	10.34		0.434
Rheumatoid arthritis							
Rheumatoid arthritis stage							
II	48	66.67		15	25.86		<0.0001
III	18	25.00		22	37.93		0.162
IV	6	8.33		21	36.21		0.0002
Rheumatoid factor,	42	58.33		55	95.83		<0.0001
Extra-articular manifestations	6	8.33		27	46.55		<0.0001
Age at rheumatoid arthritis onset (years)			54.17 \pm 5.64			55.72 \pm 13.25	0.369
Duration of rheumatoid arthritis (years)			4.58 \pm 3.16			12.03 \pm 9.78	<0.0001
Modified Health Assessment Questionnaire			1.52 \pm 0.52			1.73 \pm 0.45	0.021
Disease Activity Score			4.39 \pm 1.23			5.24 \pm 0.98	<0.0001
Erythrocyte sedimentation rate (mm/h)			35.21 \pm 20.13			65.26 \pm 30.80	<0.0001
C-reactive protein (mg/dL)			3.14 \pm 4.44			15.41 \pm 25.78	<0.0001
Rheumatoid arthritis treatment							
Corticosteroids	36	50.00		40	68.97		0.045
Medications							
Methotrexate	21	29.17		37	63.79		0.0002
Sulfasalazine	9	12.5		9	15.52		0.810
Leflunomide	36	50.00		27	46.55		0.830
Hydroxychloroquine	15	20.83		6	10.34		0.169
DMARDs combinations	9	12.50		18	31.03		0.017
Biological therapy	9	12.50		3	5.17		0.258

SD: Standard deviation; DMARD: Disease Modifying Antirheumatic Drug.

Difference between patients with and without osteoporosis was analyzed by applying the Student's t-test (continuous data with normal distribution), Mann-Whitney U test (continuous data with non-normal distribution), and Chi-square test (dichotomous variables); p was considered statistically significant at a value of less than 0.05.

Table 3. Logistic regression usage for evaluating the implication of demographic variables (independent variables) in the occurrence of osteoporosis (dependent variables)

Variable	Coefficient	SD	<i>p</i>	Odds ratio	95% CI
Age	0.51	0.14	0.0004	1.67	1.26 to 2.22
Body mass index	-0.73	0.20	0.0003	0.47	0.32 to 0.71
Duration of menopause	0.19	0.08	0.0228	1.20	1.02 to 1.41

SD: Standard deviation; CI: Confidence interval.
Logistic regression shows that age, BMI and duration of menopause may be independent risk factors for osteoporosis.

Table 4. Logistic regression usage for identifying rheumatoid arthritis variables (independent variables) which may be risk factors for osteoporosis

Variable	Coefficient	SD	<i>p</i>	Odds ratio	95% CI
Rheumatoid factor	2.25	0.85	0.0052	9.5	1.96 to 46.12
Extra-articular manifestations	2.51	0.90	0.0051	12.32	2.12 to 71.52
Rheumatoid arthritis duration	0.31	0.09	0.0003	1.36	1.16 to 1.61
mHAQ	2.94	0.98	0.0027	0.05	0.01 to 0.36
DAS28	0.61	0.31	0.0492	1.83	1.00 to 3.35
C-reactive protein	0.15	0.05	0.0026	1.15	1.05 to 1.27

SD: Standard deviation; CI: Confidence interval; mHAQ: Modified health assessment questionnaire; DAS28: Disease Activity Score 28.
Logistic regression shows that rheumatoid factor, extra-articular manifestations, rheumatoid arthritis duration, mHAQ score, DAS28, erythrocyte sedimentation rate and C-reactive protein may be risk factors for osteoporosis.

and stage II RA seemed to be protective factors for OP. From the background drugs, only methotrexate and DMARs combinations were significantly associated with OP. The use of corticosteroids was statistically significantly associated with osteoporosis.

Logistic regression was used to measure the independent contribution of each factor to OP, including any factor that has been identified in the bivariate analysis and was statistically associated with OP. We explored several logistic regression models as presented in Tables 3 and 4. We showed that the mHAQ score and DAS28 do not independently contribute to the occurrence of OP (Table 5).

DISCUSSION

Similarly to our study, an increased frequency of OP (44%) was also observed in the study of Nolla

et al.¹¹ Other studies showed a prevalence of OP between 7% to 26% at the femoral level, and 19% to 32% at the spinal level.^{12,13}

Old age and lower BMI seem to be among the independent risk factors for OP. Late menarche and longer duration of menopause are significantly associated with OP, a finding which is in accordance with other studies. Thus we showed that years since menopause may be more important than chronological age in postmenopausal OP.¹⁴

We further demonstrated that the environment may represent an independent risk factor for OP. Even after adjusting for disability (mHAQ), the risk of OP in people from urban areas is 3.5 times higher compared with rural areas.¹⁵ A reason for this may be that unlike patients in urban areas, patients in rural areas take more physical exercise. It is known that physical exercise represents a stimulus of the musculoskeletal system, and an

Table 5. Logistic regression usage for evaluating mHAQ score and DAS28 contribution (independent variables) to the occurrence of osteoporosis (dependent variables)

Variable	Coefficient	SD	<i>p</i>	Odds ratio	95% CI
mHAQ	0.37	0.42	0.3837	1.44	0.63 to 3.29
DAS28	0.60	0.18	0.0009	1.82	1.28 to 2.61

CI: Confidence interval; mHAQ: Modified Health Assessment Questionnaire; DAS28: Disease Activity Score 28.
Logistic regression shows that mHAQ score and DAS28 do not contribute independently to the occurrence of osteoporosis.

important factor in achieving and maintaining the body's bone capital.

Extra-articular manifestations are statistically associated with OP, but also with higher values of mHAQ, DAS28, ESR, and CRP.

Independent variables were required to achieve some criteria to be included in the stepwise regression. The most important criterion was for an independent variable to be statistically associated with OP in the bivariate analysis. Another criterion represented the possibility of independent variables to be confounders.

Extra-articular manifestations were statistically associated with OP and higher values of mHAQ, DAS28, ESR, and CRP. Therefore, the presence of RF was statistically associated with OP, but also with higher duration of PR, and higher values of mHAQ, ESR and CRP. To the best of our knowledge, other studies are in contradiction concerning indicating RF as a risk factor for OP.^{12,13} Moreover, only few studies have evaluated the relationship between extra-articular manifestations and OP. These variables were included in the regression logistic model, which showed that the duration of RA, mHAQ score, DAS28, ESR and CRP may be independent risk factors for OP.

In the bivariate analysis, mHAQ score and DAS28 were statistically associated with OP, and DAS28 and mHAQ score were not independent risk factors for OP as far as the relationship between mHAQ score and OP could be covered by DAS28.

The study has several limitations. First, it is a non-randomized study, and there are confounding factors. Confounding is a form of bias that can distort the measure of association between an exposure and disease, and must be eliminated. Logistic regression may be an efficient way to control the presence of any potential confounders at once, but the interpretation of the results may be limited due to the possible presence of other variables which may have been omitted. For example, age and the duration of menopause may be confounders, hence older age as well as longer duration of menopause were associated with OP. Furthermore, older women had longer durations of menopause. In the present study, age

and the duration of menopause were identified as independent risk factors for OP by using logistic regression. It is difficult to know whether the RA dependent variables, identified as risk factors for OP in the logistic regression, can be confounders (e.g. ESR and CPR can be confounders for DAS28).

Conclusion

Although OP may be common in patients with RA, it is difficult to estimate which particular targets and therapeutics may be the best approach in the future. The demographic variables measured in our study were shown to be involved in the occurrence of OP. Furthermore, the severity of RA was demonstrated to be a possible contributor in the occurrence of OP, without being an independent factor of physical disability. Therefore, we may conclude that OP may occur more frequently in patients with more severe forms of RA, and the duration of the disease tends to be longer in such cases.

Declaration of conflicting interests

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