EXTRA-ARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS - PREDICTORS OF OSTEOPOROSIS

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Abstract: *In rheumatoid arthritis the extra-articular manifestations present a marker of disease severity and are accompanied by increased morbidity and mortality The aim of this paper is to study the relationship between extra-articular manifestations and osteoporosis in patients with rheumatoid arthritis. The study included 130 menopausal women diagnosed with rheumatoid arthritis. Bone mineral density was measured at lumbar spine and femoral by means of dual X-ray osteodensitometry. The obtained variables were analysed by bivariate analysis and logistic regression. The mean age was 62.77±7.51 years old. The medium duration of rheumatoid arthritis was 7.91±7.85 years, the frequency of extra-articular manifestations was 25.38%. The frequency of osteoporosis was 44.62%. The frequency of osteoporosis is statistically significantly higher in patients with rheumatoid arthritis who have extra-articular manifestations. The presence of extra-articular manifestations in patients with rheumatoid arthritis should draw attention to the need to determine bone mineral density.*

INTRODUCTION

Rheumatoid arthritis (RA) is a disease characterized by chronic systemic inflammation that especially affects the joints through cytokines, chemokines and metalloproteinases. Approximately 40% of patients with RA present extra-articular manifestations (EAMs) (1,2) such as pleuropulmonary, cutaneous, cardiovascular, hematological bone (ex: osteoporosis), manifestations. They are found especially in patients with severe forms of the disease, with the presence of high titres anti-cyclic citrullinated protein antibodies (anti-CCP) and rheumatoid factor (FR). EAMs occur mainly due to the systemic inflammatory process, being pathogenically mediated by the action of the same cytokines that determine the articular manifestations.(3,4) EAMs present a marker of disease severity and are accompanied by increased morbidity and mortality.(5)

AIM

The aim of this paper is to study the relationship between extra-articular manifestations and osteoporosis in patients with rheumatoid arthritis.

MATERIALS AND METHODS

One hundred and thirty women, consecutively admitted in the Rheumatology Clinical, were included in the study. They are menopausal and are between 49 and 82 years old. All the patients fulfilled ACR 1987 revised for RA criteria.(6)

The patients are living in the Constanţa district and have a disease duration of at least 2 years (patients with early RA were excluded).

Demographic variables, variables related to RA and therapeutic variables were obtained by interview (table no. 1). The following parameters were collected: age, body mass index, living environment (rural or urban), duration of menopause, time since menopause was installed, smoker or not, bone mineral density, osteoporotic fractures, stage of RA, age of RA onset, duration of RA, the presence of EAMs (represented by anaemia of chronic disease, pulmonary fibrosis and rheumatoid nodules), presence of RF, erythrocyte sedimentation rate (ESR) level, C reactive protein (CRP) level, the score of disease activity measured by DAS 28 (Disease Activity Score 28), physical disability quantified by MHAQ score (modified Health Assessment Questionnaire), treatment of RA (disease modifying antirheumatic drugs, DMARD), corticoid treatment.

Global assessment of disease activity was realized by measuring it on a visual analogue scale – VAS from 0 to 100 mm. Joint evaluation consisted in counting the painful joints (28 joints) and swollen joints (28 joints). Disease activity score (DAS 28) was calculated using the 28 joints, VAS and ESR.(7)

Physical disability was assessed by the modified Health Assessment Questionnaire, (M-HAQ).(8)

Bone mineral density was measured at lumbar level (L2-L4) and femur level (femoral neck, entire femoral bone) by Dual Energy X-Ray Absorbtiometry (DXA) by means of a DPX-Aplha (Lunar – General Electric) machine.

Bone mass was assessed by means of BMD (mg/cm^2), T score and Z score. Osteoporosis was defined, based on WHO proposal, when T score was with at least 2.5 SD under the medium of a young adult, a value of ± 1 SD was considered normal while a value between -1 and -2.5 was considered osteopenia.(9)

Diagnosis of vertebral fracture (T4-L5) was made by means of dorso-lumbar spine X-ray – which was performed in each patient by the same experienced radiologist. A semi-quantitative method was used (type Genant).(10)

Fractures other than spinal fractures such as femur,

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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.

Bivariate analysis was used to compare demographic variables as well as variables related to RA in patients with and without EAMs. For continuous variables with normal distribution comparison "t student" test was used while for the ones with non-normal distribution Mann-Whitney U test was used. For dichotomous variables was used χ^2 test. P value was considered statistically significant when less than 0.05. Logistic regression was used to verify if EAMs can be considered independent risk factors for osteoporosis.

Statistical analysis was performed using a computer program MedCalc for Windows, 10th version).

RESULTS

The characteristics of the studied group are presented in table no.1. EAMs were present in 33 patients: 27 patients had anaemia of chronic disease, 10 patients with rheumatoid nodules, and 3 patients pulmonary fibrosis.

Table no. 1. General features of study group (n=130)

DEMOGRAPHIC VARIABLES	
Age (years)	62.77±7.51
Urban environment, (%)	102(78..46)
Rural environment, (%)	28(21.54)
BMI (kg/m^2)	27.62±4.43
Menopause (years)	46.35±4.83
Duration of menopause (years)	16.42±8.15
Smoker (%)	23(17.69%)
Former smoker (%)	18(13.85%)
BONE MINERAL DENSITY	
Osteoporosis, (%)	58(44.62%)
Osteopenia, (%)	39(30%)
BMD normal, (%)	33(25.38%)
RHEUMATOID ARTHRITIS VARIABLES	
RA stage	
II, (%)	63(48.46%)
III, (%)	40(30.77%)
IV, (%)	27(20.77%)
Rheumatoid factor, (%)	97(74.62%)
Extra-articular manifestations (%)	33(25.38%)
Age of RA onset (years)	54.86±9.89
Duration of RA (years)	7.91±7.85
MHAQ	1.61±0.50
DAS 28	4.77±1.2
ESR (mm/h)	48.62±29.45
CRP (mg/dL)	8.62±18.49
THERAPY VARIABLES	
Glucocorticoids	
Current user, (%)	49(37.69)
Ever user, (%)	76(58.46)
DMARDs	
Methotrexate, (%)	58(44.62)
Salazopirine, (%)	18(13.85)
Leflunomide, (%)	63(48.46)
Hydroxychloroquine, (%)	21(16.15)
Combinations of DMARD, (%)	27(20.77)
Biological, (%)	12(9.23)

BMI – body mass index; MHAQ – modified Health Assessment Questionnaire; DAS 28 – disease activity score; ESR – erythrocytes sedimentation rate; PCR – C reactive protein; DMARD - disease modifying antirheumatic drugs

We compared patients with RA who have EAMs with those who do not have EAMs. Table no. 2 presents the bivariate analysis of patients with RA depending on the presence of EAMs.

The demographic variables by which patients with EAMs differ statistically significantly from those without EAMs

are: older age, the environment of origin, longer menopause and former smoker status.

Table no 2. Comparison between patients with and without extra-articular manifestations

	without EMAs n=108	with EMAs n=22	P
DEMOGRAPHIC VARIABLES			
Age (years)	61.42±6.94	66.73±7.83	0.0004
Urban environment, (%)	69(71.13)	33(100)	0.001
Rural environment, (%)	28(28.87)	0(0)	0.001
BMI (kg/m^2)	27.64±4.04	28.06±5.30	0.630
Duration of menopause (years)	14.71±7.34	21.45±8.46	<0.0001
Smoker (%)	14(14.43)	9(27.27)	0.159
Former smoker (%)	18(15.86)	0(0)	0.017
BONE MINERAL DENSITY			
Osteoporosis, (%)	31(31.96)	27(81.82)	<0.0001
Osteopenia, (%)	36(37.11)	3(9.09)	0.004
BMD normal, (%)	30(30.93)	3(9.09)	0.023
RHEUMATOID ARTHRITIS VARIABLES			
RA stage			
II, (%)	54(55.67)	9(27.27)	0.008
III, (%)	25(25.77)	15(45.45)	0.057
IV, (%)	18(18.56)	9(27.27)	0.413
Rheumatoid factor, (%)	70(72.16)	27(81.82)	0.384
Age of RA onset (years)	54.13±9.52	57.00±10.37	0.146
Duration of RA (years)	7.29±8.08	9.73±6.90	0.123
MHAQ	1.53±0.48	1.85±0.48	0.003
DAS 28	4.43±1.15	5.79±0.66	<0.0001
ESR (mm/h)	37.54±21.49	81.18±25.39	<0.0001
CRP (mg/dL)	4.23±6.19	21.51±32.16	<0.0001
THERAPY VARIABLES			
Glucocorticoids			
Current user, (%)	31(31.96)	18(54.55)	0.035
Ever user, (%)	55(56.70)	21(63.64)	0.621
DMARDs			
Methotrexate, (%)	34(34.05)	27(72.73)	0.0004
Salazopirine, (%)	9(9.28)	9(27.27)	0.021
Leflunomide, (%)	45(46.39)	18(54.55)	0.543
HQ, (%)	15(15.46)	6(18.18)	0.092
Combinations of DMARD, (%)	9(9.28)	18(54.55)	<0.0001
Biological, (%)	12(12.37)	0(0)	0.076

EAMs - extra-articular manifestations; BMI – body mass index; MHAQ – modified Health Assessment Questionnaire; DAS 28 – disease activity score; ESR – erythrocytes sedimentation rate; PCR – C reactive protein; DMARD - disease modifying antirheumatic drugs; HQ - Hydroxychloroquine

The frequency of osteoporosis is statistically significantly higher in patients with RA who have EAMs compared to those without EAMs (81.82% vs 31.96%). In contrast, the frequency of osteopenia and normal BMD is statistically significantly higher among patients who do not have EAMs.

The variables dependent on RA in which patients with EAMs differ statistically significantly from those without EAMs are represented by: higher MHAQ, higher DAS 28, higher ESR and higher PCR.

In stage II of RA, the percentage of patients with EAMs is statistically significantly lower than those who do not have EAMs (27.27% vs 55.67%)

The current use of CS is statistically significantly higher in the group of patients with EAMs compared to those without EAMs (54.55% vs 31.96%).

Methotrexate, sulfasalazine and combinations of DMARDs are the background drugs by which patients with EMAs differ statistically significantly from those without EAMs.

We used logistic regression and found that EAMs are an important risk factor for osteoporosis (tables no 3, 4, 5).

CLINICAL ASPECTS

DISCUSSIONS

Demographic and dependent variables of RA identified in our study as risk factors for osteoporosis in menopausal RA patients are represented by: age, urban environment, body mass index, duration of menopause, the presence of RF, duration of RA, DAS 28 and ESR. Stage II of RA appears to be a protective factor for osteoporosis.(11)

The presence of EAMs is statistically significantly associated with osteoporosis, but on the other hand patients with EAMs are older, longer menopause - demographic variables that represent risk factors for osteoporosis (table no 2). However, following the logistic regression, we found that EAMs are risk factors for osteoporosis regardless of age and duration of menopause (table no. 3) - so after adjusting for age and duration of menopause, a patient's risk of osteoporosis is 8.58 times higher compared to patients who do not have EAMs.

Table no. 3. Logistic regression usage for identifying rheumatoid arthritis variables which may be risk factors for osteoporosis

Variable	Coefficient	SD	P	Odds ratio	95% CI
EAMs	2.14	0.63	0.0008	8.58	2.45 - 29.98
Age	0.11	0.052	0.0259	1.12	1.01 - 1.24
Duration of menopause	0.19	0.061	0.0018	1.21	1.07 - 1.36

SD: standard deviation; CI: confident interval; EAMs: Extra-articular manifestations;

EAMs are also a risk factor for osteoporosis independent of RA-dependent variables (table no. 4). Thus, the risk of a patient having osteoporosis is 12.32 times higher for patients with EAMs compared to those who have no EAMs, after adjusting for RF, duration of RA, MHAQ, DAS 28 and PCR (table no. 4).

Table no. 4. Logistic regression usage for identifying rheumatoid arthritis variables which may be risk factors for osteoporosis

Variable	Coefficient	SD	P	Odds ratio	95% CI
RF	2.25	0.80	0.005	9.50	1.96 - 46.11
EAMs	2.51	0.89	0.005	12.32	2.12 - 71.52
Duration of RA	0.31	0.085	0.0003	1.36	1.15 - 1.61
MHAQ	-2.94	0.98	0.002	0.05	0.007 - 0.35
DAS 28	0.60	0.30	0.04	1.83	1.00 - 3.35
CRP	0.14	0.04	0.002	1.15	1.05 - 1.27

SD: standard deviation; CI: confident interval; EAMs: Extra-articular manifestations; RA – rheumatoid arthritis; MHAQ – modified Health Assessment Questionnaire; DAS 28 – disease activity score; PCR – C reactive protein; RF - Rheumatoid factor

EAMs are risk factors for osteoporosis and independent of the corticosteroids ever user (table no. 5).

Table no. 5. Logistic regression usage for identifying rheumatoid arthritis variables which may be risk factors for osteoporosis

Variable	Coefficient	SD	P	Odds ratio	95% CI
EAMs	2.28	0.51	<0.0001	9.85	3.61 - 26.86
CS ever user	0.85	0.41	0.0394	2.34	1.04 - 5.27

SD: standard deviation; CI: confident interval; EAMs: Extra-articular manifestations; CS: corticosteroids

In the literature we have not found studies to evaluate the relationship of EAMs with osteoporosis, only one study investigates the possible involvement of EAMs in the occurrence of osteoporotic fractures.(12)

EAMs are more likely to be a surrogate marker of the severity of rheumatoid arthritis than a factor that acts per se in the production of osteoporosis.

CONCLUSION

The presence of EAMs in patients with RA should draw attention to the need to determine bone mineral density.

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