THE VALUES OF BONE MINERAL DENSITY IN PATIENTS WITH RHEUMATOID ARTHRITIS AND DEPRESSION SYNDROME

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Summary. Aim of the study was to evaluate the occurrence of depression syndrome (DS) and osteopenia in patients suffering from rheumatoid arthritis (RA) with respect to the physical, mental and iatrogenic factors. The impact of duration, severity and type of treatment of RA on these conditions were also examined.

Methods: A total of 40 RA adult female patients were studied using ARA criteria. For the estimation of depression, psychiatric interviews, psycho-tests, and rating on depression scale (Hamilton) were used. A specific attention was paid to the pre-morbid profile of the patients as related to previous emotional conflicts, and distressing life events. Bone mineral density (BMD) of the lumbar vertebras (L2-L4) was measured using Lunar DEXA densitometer.

Results: Twenty eight patients were found to have some degree of DS. The occurrence and intensity of DS were positively correlated with duration, and severity of RA, and negatively correlated with patients' occupational activities. DS was more frequent in patients treated with disease modifying drugs (DMD) and glucocorticosteroids (GCS). The mean values for BMD were somewhat lower in patients in whom DS was present, but the difference was not statistically significant. The values were also lower in patients who have been treated with DMD and GCS.

Conclusion: DS was more frequent in patients suffering from severe RA and was positively correlated with the duration of the disease and treatment with DMD and GCS. Osteopenia seems to be more pronounced in patients with DS and in those treated with DMD and GCS. Decreased life dynamism and reduced dietary intake of calcium, exercise and exposure to sunlight, all associated with DS could be, at least partially, responsible for the development of osteopenia. These results indicate to the necessity of careful psychiatric evaluation of RA patients in order to adapt anti-rheumatic therapy by decreasing DMD and GCS and eventually using antidepressants.

Key words: Rheumatoid arthritis, depression syndrome, bone mineral density, osteopenia, antidepressants

Introduction

As early as 1961, Kielholc pointed out the importance of DS in RA. A chronic and disabling pain and decreased physical and mental activity develop the fear and uncertainty for the future. This will trigger and aggravate depression and in its turn depression will have negative impact on the disease and well-being of the patient and some kind of *circulus vitiosus* will be established. Kielholc understands DS in RA as a reactive symptomatic condition due to the underlying disease and highlights the importance of the administration of GCS in its development (1, 2).

Hart claims, on the basis of personal research, that DS in RA patients may develop as a distinct clinical picture which may aggravate pain and other symptoms of RA (3).

Rimon examined ambulatory and in hospital conditions 100 RA female patients and found depression in 29% cases, of which over a half showed symptoms of depression prior to RA development (4).

Moldofski and Rotman claimed that patents treated with GCS are "less persistent, quiet, sad, and discontent", but could not specify whether this was due to the drugs or rheumatic disease itself (5).

As a chronic inflammatory disease, RA is characterized by persisting pain and reduced professional and everyday activities, negatively affecting patient's emotional life and social status, so favoring development of DS.

More serious and disabling RA, more aggressive therapies, and higher dosages, including GCS, DMD and other non-steroidal antirheumatics (NSAID), are necessary to control inflammation and this may significantly contribute to a development of DS.

It has been claimed that administration of antidepressants to RA patients has decreased pain and improved significantly functional status of these patients which suggests that DS may aggravate symptoms in RA (6).

It has been known for some time that prolonged and more aggressive GCS therapy, reduced exercise and intake of calcium favor a loss of mineral in bones (osteopenia) in RA patients. Numerous studies have reported a negative effect of GCS on bone mineral density (BMD). The effect of DS on BMD in RA is still debatable (2, 7).

The aim of our study was to explore the effect of DS on osteopenia in RA patients, as related to the severity of a disease and type of therapy administered to the patients. In addition, we wanted to see if patients suffering RA and DS differ from those without DS, and whether and what kind of anti-rheumatic therapy had an impact on the development of DS and osteopenia.

Method and patients

By the method of random choice, we analysed 40 RA female patients using ARA criteria. The patients were evaluated by certified rheumatologists from Niska Banja and were treated ambulatory and in hospital environment. Psychiatric and psychological evaluation of the patients were performed at the Psychiatry Clinic and the Institute for Mental Health, Clinical Center of Nis.

The patient were women aged 35-65 years. Mean age is 50.1 ± 11.29 . Patients' professional occupations were: 14 housewives, 4 workers, 6 administrative employees with high school education, 1 nurse, 9 with university-level education (1 doctor, 2 economists, 2 lawyers, 1 engineer and 3 professors in intermediate school) and 6 pensioners (2 workers and 4 administrative employees with intermediate school).

The psychiatric examination was performed by two independent psychiatrists and included repeated interviews, psycho-tests and rating on depression scale according to Hamilton (8).

The DS was ascertained when the score obtained on the depression scale was higher than 20. Reliability of rating between two independent assessments was within high correlation range. Deviation higher than 10 of the total score was considered as strong correlation, but in the case of greater deviation, patients were excluded from the experiment.

Particular attention was paid to the most frequent depression symptoms. The pre-morbid profile of DS was determined, and the presence of previous emotional conflicts and the effects of life distressing events were registered.

DS was analyzed also in relation to the severity of RA, and therapy (DMD, GCS, NSAID, duration, posology) that was administered to the patient.

The diagnosis of RA rests on the presence of a constellation of clinical and laboratory features, as examplified by the 1987 American College of Rheumathology (ACR) revised criteria. Four of the following seven criteria must be met, and criteria 1-4 have been present for at least 6 weeks: 1. Morning stiffness in and around joints lasting 1 hour or ore before maximal improvement

2. Soft tissue swelling (arthritis) of three or more joint areas

3. Swelling (arthritis) of the proximal interphalangeal, metacarpo-phalangeal or wrist joints

4. Symmetrical arthritis

5. Subcutaneous nodules

6. Positive test for rheumatoid factor

7. Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints

In our practice these criteria are known as ARA criteria (9).

The severity of RA was determined radiologically by Steinbrocker's degrees (10).

Our patients are allocated to specific "functional classes" (American College of Rheumatology functional classification of rheumatoid arthritis) (11):

Class I: Completely able to perform usual activities of daily living (self-care, vocational, and avocational)

Class II: Abele to perform usual self-care and vocational activities, but limited in avocational activities

Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities

Class IV: Limited in ability to perform usual selfcare, vocational and avocational activities.

The activity of disease was evaluated by American College of Rheumatology criteria for clinical remission of rheumatoid arthritis. A minimum of five of the following for at least 2 consecutive months:

1. Morning stiffness not to exceed 15 minutes

2. No fatigue

3. No joint pain

4. No joint tenderness or pain on motion

5. No soft-tissue swelling in joints or tendon sheaths

6. Erythrocyte sedimentation rate (Westerngren's method) less than 30 mm/hour (females) or 20 mm/hour (males) (12).

Clinical remission cannot be diagnosed in the presence of manifestations of active vasculitis, pericarditis, pleuritis, myositis, and/or unexplained recent weight loss or fever.

The estimation of bone mineral density was done in all patients at the Institute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases in Niska Banja using Lunar Densitometer based on dual photon absorptiometry of X-rays (Dual Energy X-ray Absorptiometer - Dexa apparatus). A constant source of radiation was used (X-rays at 78 keV and "Kedge" with cerium filter). This provides continual dualenergy radiation at 40 keV and 70 keV. The accuracy and reproducibility of this device is \pm 1%. Patients underwent anterior-posterior scan of lumbar (L1-L4) vertebras. The results were computed and processed with Lunar software. Absolute values of BMD for each lumbar vertebra were expressed in grams per cm^2 (g/cm²). Mean values for L2-L4 MBD density were also calculated in g/cm² and expressed as percentages of the normal values adjusted for patient's age. Osteopenia was ascertained when the values were lower than mean -1 standard deviation obtained in the control group of healthy, age-adjusted individuals. Therefore osteopenia represents more than 12% mineral loss compared the control group.

Results

Based on the psychiatric evaluation 28 out of the total 40 patients were registered with DS. Table 1 reports the distribution of depressed patients as a function of age. As could be seen patient's age appeared to be a risk factor for the development of DS particularly above the age of 40 years.

Table 1. Age distribution of depressed patients

Age of RA patients	Number of	Number of patients
(years)	RA patients	with DS
30-39	10	3 (30%)
40-49	10	9 (90%)
50-59	10	8 (80%)
60-69	10	8 (80%)
Total	40	28 (70%)

Table 2 reports the occurrence of DS as a function of disease duration. Patients that suffered from RA for more than 5 years were more prone to develop DS than those with more recent onset of the disease.

Table 2. Relation of disease duration and DS

RA	Number of	Number of patients
(duration in years)	RA patients	with DS
0-5	8	3 (37.5 %)
6-10	14	10 (71.4 %)
11-15	11	9 (81.8 %)
over 15	7	6 (85.7 %)
Total	40	28 (70.0 %)

Table 3 reports the occurrence of DS as a function of radiological classification of joint damage. Strong correlation was observed between severity of RA and development of DS in patients that suffered from end stage of the disease, only. However small number of RA patients in this group (2) does not allow any definitive conclusion.

Table 3. Relation of joint damage and DS

RA stage	Number of	Number of patients
	RA patients	with DS
Ι	10	7 (70.0 %)
II	22	15 (68.2 %)
III	6	4 (66.6%)
IV	2	2 (100.0 %)
Total	40	28 (70.0 %)

Tables 4 and 5 report the incidence of the DS as a function of disease activity. The incidence was somewhat higher in patients with highly active, inflammatory RA and in patients that had important joint destructions (functional class III) as compared to the classes I and II (Tables 4 and 5).

Table 4. Relation of RA disease activity with DS

RA activity	Number of RA patients	Number of patients with DS	
Remission	21	13 (61.9 %)	
High activity	19	15 (78.9 %)	
Total	40	28 (70.0 %)	

Table 5. Relation of RA functional class with DS

RA functional class	Number of RA patients	Number of patients with DS	
Ι	10	6 (60 %)	
II	6	4 (66.6 %)	
III	24	18 (75 %)	
IV	_	_	
Total	40	28 (70 %)	

Table 6 reports the occurrence of DS as a function of ongoing antirheumatic therapy. It is apparent that patients that are receiving DMD or GCS were more prone to develop DS than those that have only NSAIDs.

Table 6. Effects of antirheumatic therapy on DS occurence

RA treatment	Number of	Number of
KA treatment	RA patients	patients with DS
DMD	14	10 (71.4 %)
DMD+CS	22	16 (72.7 %)
NSAID	4	2 (50.0 %)
Total	40	28 (70.0 %)

Table 7 shows the values for bone mineral density (BMD) obtained in RA patients with and without DS. BMD values are somewhat lower in RA patients with DS, but this is not statistically significant.

Table 7. BMD (L_2 - L_4 in g/cm²) in RA patients with DS

Patients' age (years)	RA	DS	Р
30-39	1.184 ± 0.08	1.172 ± 0.04	_
40-49	1.146 ± 0.05	1.138 ± 0.05	n.s.
50-59	1.042 ± 0.08	1.022 ± 0.08	n.s.
60-69	1.008 ± 0.11	0.966 ± 0.07	n.s.

Table 8 shows the values for bone mineral density (BMD) as a function of ongoing anti-rheumatic therapy. BMD values are somewhat lower in RA patients with DS, that are receiving DMD or DMD with GCS, but the difference in both groups is not statistically significant.

Table 8. Effect of antitheumatic therapy on BMD (L_2 - L_4 in g/cm²)

RA treatment	RA	DS	Р
DMD	1.096 ± 0.095	1.092 ± 0.10	n.s.
DMD+CS	1.077 ± 0.116	1.030 ± 0.10	n.s.
NSAID	1.187 ± 0.070	1.235	-

The pre-morbid profile of patients with DS most commonly comprises the features of a cyclothymic personality or reveals hypersensitive subjects who are less socially adaptable and prone to seek support from friends or relatives. They are basically distrustful, rather rigid in social communication, and commonly suppressing aggression. Such persons are frequently awkward while communicating their problems, and display poor verbalization (alexitymia). They are scrupulous (with the sense of responsibility) and commonly originate from several-member rural families. The early emotional conflicts (loss of mother or of close person, childhood disease, deranged family relations, early separation) are frequently present. In a number of them (3), distressing events occurred shortly (up to one year) before RA started and these events were frequently found in depressed patients. The most common events were the loss of spouse, divorce, loss of job.

Most frequent depression symptoms include: feelings of sadness, inclination to crying, insomnia (initial and at the end of sleep), feelings of inefficiency, loss of interest in work and other activities, anhedonia, mild retardation in speech and thought, mental and somatic anxiety, general somatic symptoms (heavy limbs, back and head, loss of energy, and feelings of tiredness), loss of libido, and occasional daily variations in symptoms, caused by the nature of the underlying disease.

Discussion

The results of this study suggest an inter-dependence between development of DS and osteopenia in RA patients. The following factors are found to be important for the development of DS in RA patients: age, severity and duration of RA, treatment with DMD or GCS and pre-morbid profile. This included early emotional conflicts and their reactivation through chronic and acute stress, continuing pain, fear of uncertainty, knowledge that the disease (RA) is uncurable, and reduced functional and professional capabilities.

In addition, lower values of BMD were noticed in patients with RA and DS but this was not statistically significant.

Our results concur with those from the relevant literature, and show interdependence of RA and DS. A London Guy Hospital study on a cohort of 50 hospitalized RA patients, found DS in 46% of patients using Beck depression inventory. The authors noticed that DS occurs earlier in males than in females. Hospitalization had a significant positive effect on depressive patients, irrespective of psychotropic drugs administration. Also, a significant correlation was observed between Beck scores and clinical evaluation on mental condition (13, 14).

Kuipers et al. showed that a six-week administration of Imipramine at a daily dose of 20-40 mg leads to clinical improvement in 60-70 % RA patients with extra-joint rheumatism (15).

Steiger performed a study with a 10-week administration of Imipramine (in addition to the basic antirheumatic therapy) to patients suffering RA and compared this group with other patients suffering various inflammatory and non-inflammatory diseases of musculoskeletal system. Of a total number of patients, 15 showed improvement after Imipramine (improvement in functional condition was registered in 7 patients, whilst hand pressure was improved in 7 patients). This was ascribed to the anti-depressive effect of the drug, since no antirheumatic effect of Imipramine was demonstrated (14).

Hart suggests that in addition to the basic antirheumatic therapy (DMD, GCS, NSAID), RA patients should be given also tricyclic antidepressants when sedative effect should be achieved (3). Glasgow study has demonstrated a significant improvement of RA in patients that have been administrated Tofranil (16).

Parker et al. examined the effectiveness of cognitive-behavioral and pharmacologic treatment of depression in rheumatoid arthritis (RA). Diagnoses of both major depression and RA were randomly assigned in 54 subjects. Analyses of parameters (measures of depression, psychosocial status, health status, pain, and disease activity) in persons with RA, indicated that cognitivebehavioral approaches to the management of depression were not found to be additive to antidepressant medication alone, but antidepressant intervention was superior to no treatment (17, 18).

Dickens et al. assessed the relative strength of the association of physical characteristics and social stresses with a diagnosis of depression in patients with rheumatoid arthritis. Depression and social difficulties were assessed in 74 patients with rheumatoid arthritis by using standardized research interviews. Rheumatoid arthritis activity, damage related to rheumatoid arthritis, and subjective functional disability were assessed with well-validated methods. Twenty-nine patients (39.2%) were depressed. Compared to nondepressed patients, depressed patients had more marked social difficulties related to rheumatoid arthritis (72.4% versus 46.7%, respectively) and more marked social difficulties independent of rheumatoid arthritis (55.2% versus 31.1%, respectively). With logistic regression, social difficulties, independent of rheumatoid arthritis, was the only variable significantly associated with depression. Demographic characteristics and rheumatoid arthritis were not associated with a diagnosis of depression. Recognition by clinicians of the importance of social stresses, independent of disease state, should lead to more appropriate and specific psychological and social treatment of depression in rheumatoid arthritis (19).

Timonen et al. assessed the demographic and psychosocial profiles of patients with rheumatoid arthritis (RA) who committed suicide (20). Two control groups were used: osteoarthritis (OA) and suicide victims with neither RA nor OA. A study based on a prospective, 13yr follow-up database with linkage to national hospital discharge registers of all suicides (1296 males, 289 females) committed during the years 1988-2000 in the province of Oulu situated in northern Finland. Females were significantly over-represented among RA patients who committed suicide (52.6% RA women vs 17.3% women with neither RA nor OA). Comorbid depressive disorders preceded suicides in 90% of the female RA patients. Before their suicide, 50% of the female RA patients (vs 11% of the male RA patients) had experienced at least one suicide attempt. The method of suicide was violent in 90% of the RA females. RA males were less often depressive, but committed suicide after experiencing shorter periods of RA and fewer admissions than females. Attempted suicides and especially depression in female RA patients should be taken more seriously into account than previously in clinical work so that the most appropriate psychiatric treatment can be provided for such patients (20).

Our study was performed in the period of exceptional and difficult social and economic circumstances in Serbia, marked by a remarkable decline in the living standard of the population and a lack of a regular supply in drugs (particularly in DMD) used to treat RA. This contributed to a large extent to an aggravation of RA (disease activation and reduced remissions) and increased feelings of helplessness and hopelessness, and fear and uncertainty for the future. This certainly contributed to a development of DS. In our series of pa-

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tients GCS were often ascribed. Their pharmacological effect on DS has been known for a long time. Surprisingly, we found that DMDs (specify which ones) also increased the occurrence of DS (21, 22).

It is well known from the literature that GCS and reduced dietary intake of calcium, reduced exercise, and decreased exposure to the sunlight were the risk factors for the development of osteopenia. In our study the presence of DS also decreased BMD but this needs to be further investigated and confirmed (22-24).

In conclusion, we would like to stress that RA patients need psychiatric evaluation in order to adapt the treatment to its psychosomatic problems. Therefore, a close collaboration is necessary between the rheumatologist and psychiatrist. Taking into account the abovepresented results and as well as our own practice and others experiences, a significant role should be given to antidepressants, while treating RA patients.

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VREDNOSTI MINERALNE GUSTINE KOSTI KOD PACIJENATA SA REUMATOIDNIM ARTRITISON I DEPERESIVNIM SINDROMOM

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Kratak sadržaj: Predmet našeg rada je bila uzajamna povezanost reumatoidnog artritisa (RA) i depresivnog sindroma (DS) kod naših bolesnica, što je još jedan dokaz o neraskidivoj povezanosti some i psihe i bavljenje uticajem telesnih, psihičkih i medikamentnih faktora u lečenju RA u nastanku DS i osteopenije. Cilj rada je bio da ukažemo na korelaciju DS i osteopenije sa RA u zavisnosti od trajanja, stadijuma i aktivnosti bolesti, funkcionalnog stanja, kao i terapije RA. Metod rada. Ispitali smo 40 odraslih bolesnica sa RA (ARA kriterijumi). Za procenu depresivnosti koristili smo psihijatrijski intervju, psihotest i Rating scale za depresiju po Hamiltonu. Obratili smo posebnu pažnju na procenu premorbidne ličnosti pacijenta, postojanje ranog emocionalnog konflikta i uticaj životnih dogadjaja. BMD (Bone mineral density) – mineralna gustina kosti je merena na lumbalnoj kičmi (L2-L4) na DEXA denzitometru marke Lunar. Rezultati rada. Od ukupnog broja bolesnica (40), kod 28 je dokazano prisustvo DS. Pojava DS korelira sa dužinom trajanja RA, stadijumima RA, aktivnošću RA i funkcionalnim klasama. Depresivni sindrom se najčešće javljao u grupi bolesnica gde su u lečenju RA bili zastupljeni i kortikosteroidi. Vrednosti BMD su bile niže u grupi bolesnica gde je RA bio udružen sa DS, ali ova razlika nije bila statistički signifikantna. Zaključak. Za nastanak osteopenije odgovorni su glikokortikoidi u terapiji RA, kao i sniženje dijatelnog unosa kalcijuma, obima fizičke aktivnosti i umanjenje solarne ekspozicije, što je posledica DS i posledičnog pada životnih dinamizama. U terapiji RA neophodan je timski rad reumatologa i psihijatra. Pored antireumatske terapije, značajno mesto bi trebalo dati i antidepresivnim lekovima, pritom vodeći računa o terapiji osteopenije.

Ključne reči: Reumatski artritis, depresivni sindrom, mineralna gustina kosti, osteopenija, antidepresivi