Rheumatoid Arthritis: Evidence for Bone Loss in Premenopausal Women

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ABSTRACT. ***Objective.*** To assess bone mineral density (BMD) status in patients with rheumatoid arthritis (RA).

Methods. Rheumatoid factor-positive premenopausal women with RA meeting the American College of Rheumatology criteria were enrolled. Exclusion criteria included diseases or drugs that affect BMD, except for glucocorticoids, and smoking. Evaluation consisted of a questionnaire, physical examination, and laboratory tests. Lumbar spine and right proximal femur BMD were measured with a DPX-Lunar DEXA scanner. Data were analyzed by Student t test, chi-square, and multivariate analysis.

Results. We studied 78 patients with RA and 39 controls; 82% were Caucasian, with mean age 35.5 ± 6.7 years, and mean disease duration 48 ± 51 months. Among patients, 74.4% had been treated with glucocorticoids, with a mean daily dose of 9.7 ± 5.9 mg. Mean lumbar spine BMD was 1.157 ± 0.124 g/cm^2 in the RA patients, and 1.223 ± 0.147 g/cm^2 in controls ($p < 0.01$). Mean right proximal femur BMD did not differ significantly. Lumbar spine osteopenia correlated with "no physical activity at work" status, low body weight, and duration of glucocorticoid therapy. Femoral neck osteopenia correlated with "no physical activity at work" status, Steinbrocker class III, erosions of the hands, and high erythrocyte sedimentation rate (ESR). Trochanteric osteopenia correlated with "no physical activity at work" status, erosions on hand radiographs, low body weight, high ESR, and anemia.

Conclusion. Patients with RA of relatively short disease duration already exhibited significantly lower lumbar spine BMD. The identification of prognostic markers for bone loss in patients with RA should not only prompt early therapeutic intervention, but also facilitate early preventive measures. (J Rheumatol 2005;32:1020–5)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOPOROSIS
BONE MASS DENSITOMETRY GLUCOCORTICOID

Rheumatoid arthritis (RA) afflicts about 1% of the general population. It preferentially affects women, with a higher incidence after the fifth decade of life[1]. Studies have been conducted in search of more effective and affordable therapies for RA with reduced toxicity in order to prevent deformities, disability, and other sequelae[2-10].

Patients with RA also have lower bone mass than healthy controls, and the most significant loss appears to occur early after disease onset[11]. Bone loss in RA has 3 different presentations: (1) affecting the subchondral bone, (2) osteopenia adjacent to the inflamed joint, and (3) generalized bone loss, involving the axial and appendicular skeleton[11]. While periarticular osteopenia may vary with disease severity, skeletal osteopenia may increase the risk of bone fractures and associated disability[12].

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Osteoporosis is a major public health problem affecting mostly women over 50 years of age[13]. Patients with RA are commonly peri- or postmenopausal, creating a major confounding factor in interpretation of the true effect of the disease on bone metabolism.

We evaluated bone mineral density (BMD) in a group of premenopausal patients with RA, compared to matched controls, in order to determine the RA-specific effect on bone mass reduction and the potential risk factors associated.

MATERIALS AND METHODS

Patients and controls. Female patients meeting the American College of Rheumatology (ACR) criteria[14] for the diagnosis of RA who were rheumatoid factor positive and premenopausal with regular menses were considered for enrollment. Patients were referred from divisions of rheumatology and internal medicine and/or private practices in the metropolitan area of Porto Alegre, Brazil.

To minimize confounding factors (genetic diversity, socioeconomic status, and ethnicity) that could influence variation in BMD, female controls were first- or second-degree relatives identified by patients with RA.

The exclusion criteria included diseases (e.g., diabetes mellitus, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hypogonadism, early menopause, malabsorption syndrome or chronic diarrhea, kidney failure) or chronic use of medicine (e.g., anticoagulants, anticonvulsants, bisphosphonates, calcitonin, vitamin D) known to affect bone mass[15]. This study was approved by the Research Committee of the Hospital de Clínicas de Porto Alegre.

Clinical evaluation. Patients and controls were evaluated by a single exam-

iner unaware of their bone mineral status. Participants answered a comprehensive questionnaire about their general, gynecologic and obstetric health status, smoking, use of alcohol, daily intake of calcium, and life and family history of fractures[16-18]. Body weight and height were measured on the same day that bone densitometry was performed. Patterns of physical activity were defined according to Telama, *et al*[16] and Wilson, *et al*[17]. Briefly, physical activity at work and leisure time were assessed and defined as follows: (a) sedentary status: no physical activity at work and no physical leisure activities; (b) physical activity: number of days in the week and performance intensity of these activities, according to the following criteria: Mild: tasks that do not demand physical effort, causing no or minimal increase of respiratory rate or sweating; Moderate: tasks that demand physical effort, increasing respiratory rate and causing some sweating; Intense: tasks that demand physical effort, significantly increasing respiratory rate and intense sweating, leading to fatigue quickly[16,17].

Clinical assessment. (a) Disease severity: both clinical and radiographic disease characteristics were studied, including age at onset, disease duration, extraarticular manifestations, and Steinbrocker functional classification[19]. Hand and foot radiographs were used for disease staging according to Larsen score[20]. Radiographs were analyzed by radiologists unaware of the patients' BMD. (b) Disease activity: presence of fatigue, anorexia, unplanned weight loss, fever and span of morning stiffness, number of painful and swollen joints according to ACR 28-joint count[21,22]; patient's evaluation of pain and overall evaluation by patient and physician global assessment of RA disease activity was done with a visual analog scale from 0 to 10[22]. Anemia, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded[22]. Fractures were evaluated by history and vertebral radiograph in all patients[23].

RA treatment. Use and doses of glucocorticoid during the previous 6 months, and previous or current use of disease modifying antirheumatic drugs [chloroquine, methotrexate (MTX), gold salts, azathioprine, or sulfasalazine] was recorded.

Laboratory tests. Blood counts, ESR, CRP, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, osteocalcin, tartrate resistant acid phosphatase, and 24-hour calciuria[24] were recorded.

BMD evaluation. All bone densitometry scans were performed by the same person using a full-body bone densitometer (DPX-Alpha 8035 Lunar). Twice a week a calibration test was performed and the precision was evaluated through the use of a lumbar spine phantom. The phantom ranged from 1.250 to 1.292 g/cm^2, with an average of 1.2 ± 0.073 and variability index (VI) of 0.005. *In vivo* precision was evaluated in the short term (1 week) in 5 volunteers, with the following VI results: lumbar spine = 0.15; femoral neck = 2.78. All results were analyzed and interpreted by the same physician, using the World Health Organization criteria to classify BMD[25].

Statistical analysis. Intergroup differences were compared with Student's t test and a value of $p > 0.05$ was considered statistically significant. The differences of characteristics between RA patients and controls were compared by chi-square test, except for smoking score and family history of fractures, which were compared by Mann-Whitney test. Comparisons among controls and groups that used or did not use glucocorticoids and MTX were analyzed by 2-way ANOVA followed by the Student-Newman-Keuls test. Linear correlations between L2 and L4 and femoral neck, Ward's triangle, and trochanter BMD and their respective T-scores were evaluated by Pearson correlation analysis. Multivariate analysis of these variables was performed through logistic regression. All analyses were done with SPSS 8.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Seventy-eight women with RA and 39 controls were enrolled in the study. Table 1 shows anthropometric (weight and height) and gynecological data (regular menses, age of menarche, nulliparity, number of pregnancies, and use of oral contraceptives), race, family history of fractures, and smoking score (number of cigarette packs smoked per year). Daily calcium intake tended to be lower in patients with RA ($p = 0.080$).

Physical activity at work was significantly different between the groups: 21% of patients with RA versus 5% of controls ($p = 0.030$) had no physical activity. Both groups had no physical activities during leisure time (Table 1).

No vertebral or nonvertebral osteoporotic fractures were reported in any group. One patient had had a previous fracture due to a car accident (Table 1).

In patients with RA, 6.4% were using thiazides, 80% for less than 12 months; 5% used calcium carbonate, 50% for less than 6 months (mean duration of use, 11 ± 8.7 months), mean dose 150 ± 190 mg/day. Use of these drugs was not reported in the control group.

RA patients had lower lumbar spine BMD ($p = 0.011$) and trochanter BMD ($p = 0.041$). Comparison of T-scores showed a significant difference in the areas of the lumbar spine ($p = 0.006$) and trochanter ($p = 0.044$), and in femoral neck it tended to be lower in RA patients ($p = 0.079$; Table 2).

The prevalence ratios for osteopenia were: lumbar spine, 1.5 (95% CI 0.71–3.27); neck, 2.0 (95% CI 0.81–4.91); Ward's triangle, 1.86 (95% CI 0.82–4.19); and trochanter, 2.7 (95% CI 0.85–8.82) and were not statistically different.

Multivariate analysis of variables of RA patients in relation to the T-score in the areas investigated (lumbar spine, neck, Ward's triangle, and trochanter) showed that: (1) no physical activity at work was a risk factor for osteopenia in the 4 areas; (2) use of glucocorticoids for more than 2 years represented a risk only for the lumbar spine; (3) weight < 50 kg represented a risk for lumbar spine and trochanter area; and (4) smoking represented a risk only for osteopenia of Ward's triangle.

Fifty-eight (74.4%) RA patients had used glucocorticoid, and 56 (71.8%) were still using it at the time of the study. Fifty-seven (98.2%) RA patients had used prednisone; just one patient (1.8%) was taking deflazacort. Glucocorticoid use ranged from 1 to 216 months (mean 33.9 ± 47.6 mo). Daily dose ranged from 1 to 30 mg (mean 9.7 ± 5.9 mg/day). Patients using glucocorticoids had significantly higher ESR ($p = 0.027$) and number of tender joints ($p = 0.036$), but not higher CRP ($p = 0.060$), compared to those not taking glucocortidoids, suggesting disease activity in the group using glucocorticoids. BMD in the 3 groups — patients using glucocorticoid, those who did not use it, and controls — was compared through ANOVA. Lumbar spine BMD was significantly lower ($p = 0.049$) in patients using glucocorticoids than in the control group. Similar to the use of glucocorticoids, when comparing the use of MTX in the 3 groups (patients who used MTX, patients who did not use it, and controls), lumbar spine BMD was the only variable that showed a tendency to be lower ($p = 0.073$).

Measures of disease activity and severity are shown in

Table 1. Demographic characteristics of patients with RA and controls. Data are mean ± SD unless indicated otherwise.

Characteristics	RA, n = 78	Controls, n = 39	p
Age, yrs	35.5 ± 6.7	36.0 ± 6.2	0.697
Caucasian, %	82	85	0.706
Weight, kg	59.4 ± 10.8	63.2 ± 14.7	0.159
Height, m	1.58 ± 0.06	1.59 ± 0.06	0.596
Calcium intake, mg/day	542.9 ± 306.7	665.3 ± 389.3	0.080
Current smoking, %	28	23	0.739**
Former smoking, %	18.4	15.4	0.724**
Smoking score (average)	0 (0–38)	5 (0–32)	0.03*
Regular menses, %	91	100	0.093**
Menarche age, yrs	13 ± 1.2	13 ± 1.5	0.897
Not pregnant, %	25	23	0.732**
No. of pregnancies	1.95 ± 1.70	2.05 ± 1.64	0.751
Oral contraceptives use, %	80	87	0.384**
Previous vertebral fractures, n	1	0	—
Family history of fractures, %	21.9	25.9	0.623**
1. Physical activity (daily work), %			
None	21	5	0.030**
Light	66.7	66.7	—
Moderate	12.8	25.6	0.097**
Intense	0	2.6	0.500**
2. No leisure physical activity, %	78	78	0.956**

* Mann-Whitney test. ** Chi-square test.

Table 2. Comparison of densitometry between patients and controls.

Region	RA		Controls		p
	BMD	T Score	BMD	T Score	p BMD/pT Score
Lumbar spine	1.157 ± 0.124	–0.37 ± 1.0	1.223 ± 0.147	0.22 ± 1.2	0.011/0.006
Femur neck	0.940 ± 0.141	–0.33 ± 1.2	0.990 ± 0.137	0.08 ± 1.1	0.075/0.079
Ward's triangle	0.862 ± 0.166	–0.35 ± 1.26	0.913 ± 0.166	0.02 ± 1.28	0.126/0.135
Trochanter	0.767 ± 0.116	–0.2 ± 1.0	0.816 ± 0.122	0.2 ± 1.1	0.041/0.044

Table 3. There was a negative correlation between duration of disease and BMD in the lumbar spine and trochanter. Body weight, height, and serum calcium showed a positive correlation with BMD in all areas investigated. Duration of glucocorticoid use showed a negative correlation with BMD in the 3 proximal femur areas. Age at disease onset showed a positive correlation with BMD in lumbar spine and trochanter. Multivariate analysis (Table 4) identified (1) weight ≤ 50 kg as a risk factor for low BMD in lumbar spine and in trochanter; (2) ESR > 20 and severe alterations with joint destruction in hand radiographs (stage III) as risk factors for osteopenia in the 3 areas of the proximal femur; and (3) functional disability (Steinbrocker class III) as a risk factor for osteopenia in femoral neck and Ward's triangle. Anemia was also a risk factor for osteopenia in the area of the trochanter. Although most patients had active disease, only 25% presented deformities. Only one case of symptomatic atlantoaxial subluxation was reported, and its treatment was surgical. In the multivariate analysis, no variable was a risk or protective factor independent from other variables.

Calcium, phosphorus, osteocalcin, and alkaline phosphatase were within the normal ranges. Calcium levels had a negative correlation with BMD in all areas investigated, particularly in the area of the trochanter.

DISCUSSION

Women have a higher risk of osteoporosis, and the intensity of bone loss secondary to estrogen deficiency is individual, probably due to genetic influences[26]. To avoid the influence of this variable, we studied only premenopausal women. Seronegative RA has a presentation and progress with a better prognosis[22]. In order to study a group of patients with a clinical presentation as uniform as possible, only patients with detectable rheumatoid factor were included, excluding those with severe disability of functional class IV. Some patients did not have a relative who could be referred to the control group, and on this account this group had fewer participants.

The group of 78 patients with RA presented lower bone mass than the control group of 39 healthy women. Osteopenia was found in 20 (25.6%) of our patients. Even in

Table 3. RA patients' characteristics.

Disease characteristics	
Age at onset, yrs	30 ± 7.3
Duration of disease (months)	48 ± 51
Steinbrocker functional class (%)	
I	46 (59)
II	23 (29.5)
III	9 (11.5)
Radiographic stage, hands	
I	40 (51.5)
II	29 (37.0)
III	9 (11.5)
Radiographic stage, feet	
I	44 (56.4)
II	27 (34.6)
III	7 (9.0)
Fatigue	52 (67)
Anorexia	26 (33)
Weight loss	26 (33)
Morning stiffness, min	
< 15	26 (33.0)
> 15 to 30	9 (11.5)
> 30 to 60	24 (30.7)
> 60	19 (24.3)
No. tender joints	
0	10 (12.8)
1	8 (10.3)
≥ 2	60 (76.9)
No. swollen joints	
0	20 (25.6)
1	10 (12.9)
≥ 2	48 (61.5)
VAS (mean)	6.0 ± 3.0
Patient global evaluation	5.5 ± 2.5
Physician global evaluation	5.7 ± 2.7
ESR above normal value	39 (50.0)
CRP above 10	19 (24.3)
Anemia (hematocrit < 35)	23 (29.5)
Weight (≤ 50 kg)	39 (50)

premenopausal women with RA, there is significant bone loss compared to healthy women in the same menopausal period. Women with RA are reported to experience later menarche[22]; this short time of bone tissue under estrogenic protection could explain the bone loss. However, this was not what we found when we compared this variable in the 2 groups. Age of menarche can be genetically determined; since the women in the 2 groups were relatives, this may be the reason why no significant difference was found.

Eighty percent of the development of peak bone mass occurs between the ages of 16 and 20 years; the other 20% may be gained until the age of 30 years, and involutional bone loss begins around 40 years of age. Caucasians have a higher risk of osteoporosis[15]. Two-thirds of the patients with RA in our study were between 25 and 40 years of age, and 82% were Caucasian, thus defining a homogeneous group. Age at onset of disease corresponded also to the peak of BMD (80% between age 20 and 40 years). These patients had already reached the peak of bone mass, but they had not yet begun the involutional bone loss, when the mechanisms associated with RA determined reduction of BMD, suggesting that RA is a risk factor for bone loss independent of age and race.

Low height and weight are considered risk factors for osteoporosis[17], and this finding was confirmed in our study. Reduced weight and height were found to be correlated with osteopenia in all regions investigated, except for the Ward's triangle area, where only height showed this correlation. Weight < 50 kg was found to be a risk factor for osteopenia in the lumbar spine and in the trochanter area.

Patients with RA are reported to exercise less[27], and this is known to be a risk factor for osteoporosis[11]. No physical activity at work was the only variable that presented a significant difference between patients and controls in our study, thus confirming it as a risk factor for osteopenia in all areas studied. Possibly, these are the patients with the most severe disease and with inflammatory activity: in the multivariate analysis, when the activity and severity of disease variables were controlled, it did not remain as an independent variable for risk.

Patients with severe, active disease or with disease that begins at an earlier age present a greater reduction in BMD. Their altered microarchitecture and weakening of the bone tissue, and increase of risk of fractures[28], may be due to anorexia and resulting nutritional disorders, or mainly through local and systemic release of inflammatory cytokines. These inflammatory cytokines act on parent cells of the bone marrow and on osteoblasts and osteoclasts, diminishing bone formation and increasing bone resorption.

Our results characterized the group under study as composed predominantly of patients with active disease but no evidence of significant severity or serious forms of disease. Patients in our study remained for a long time under the harmful effect of the inflammatory disease activity: 83% had disease duration of more than one year, and more than half for more than 4 years. Longer duration of disease was found to be correlated with osteopenia in the 3 areas of the proximal femur. Low body weight can be considered as an indicator for inflammatory disease activity, according to Harris[22], and as a risk factor for osteoporosis in patients with RA[29]. There is a correlation between tumor necrosis factor-α concentrations and loss of body mass and arthritis activity, particularly in patients with more aggressive disease[30]. In our study, low body weight was correlated with reduced bone mass in all areas studied, except for the Ward's triangle, and this might be a useful indicator of active disease and/or risk of osteoporosis.

The variables that evaluate inflammatory activity and severity of disease are primarily correlated to reduced BMD in femoral areas, and this region may be a more reliable indicator of the harmful effect of the disease on bone mass, possibly because the region has more cortical bone than the

Table 4. Osteopenia in the 4 regions associated with all disease characterisitcs was evaluated by multivariate analysis (only statistically significant data are shown).

	T Score < –1 (%)	T Score ≥ –1 (%)	p
L2–L4			
No physical activity at work	29 (38.1)	11 (14.3)	0.030
Weight (kg) ≤ 50.0	29 (50.0)	10 (12.5)	0.002
Duration of glucocorticoid use > 2 yrs	47 (60.0)	22 (28.6)	0.030
Neck			
No physical activity at work	31 (40.0)	11 (14.3)	0.015
Hand radiograph stage III	24 (30.0)	3 (3.8)	0.001
Steinbrocker functional class III	19 (25.0)	4 (5.4)	0.011
ESR above normal values (> 20)	70 (90.0)	35 (44.6)	0.001
Ward's triangle			
Smoking	37 (47.6)	16 (21.2)	0.024
No physical activity at work	32 (40.9)	10 (13.2)	0.013
Hand radiograph stage III	18 (23.8)	5 (6.0)	0.039
Steinbrocker functional class III	18 (22.7)	4 (5.1)	0.044
ESR above normal values (> 20)	60 (77.3)	38 (49.1)	0.024
Height (m) > 1.58 (median)	21 (27.3)	41 (52.8)	0.040
Trochanter			
No physical activity at work	44 (56.3)	9 (12.1)	0.001
Hand radiograph stage III	4 (5.1)	24 (31.2)	0.006
ESR above normal values (> 20)	68 (87.5)	39 (50.0)	0.007
Anemia (hematocrit < 35)	34 (43.8)	13 (17.2)	0.040
Weight ≤ 50 kg	14 (18.7)	40 (51.7)	0.021

vertebra, and it is less vulnerable to the action of other factors such as glucocorticoids. Similar findings are reported in other studies[31-35].

The comparison between RA patients using MTX with controls showed an almost significant correlation with reduced BMD in the lumbar spine. These patients were using glucocorticoids concurrently. Use of this therapy was not an isolated or significant factor of bone loss, and the duration of administration was only correlated negatively with the BMD of the femoral neck, reinforcing what is reported in the literature[36,37].

Glucocorticoid use as a cause of osteoporosis in patients with RA is a controversial issue[38-40]. In our study, glucocorticoid was not an independent determinant factor of bone loss. Duration of glucocorticoid administration was the variable associated with reduction of bone mass in the lumbar spine, an area known to be richer in trabecular bone and thus more sensitive to the action of glucocorticoids[35]. Longterm use of glucocorticoids was correlated with osteopenia in the 3 regions of the proximal femur. Administration for over 2 years, however, was a risk factor for osteopenia only in the lumbar spine. Patients using glucocorticoids had more active disease, as comparison of patients with and without use of glucocorticoids showed there was a significant difference in the ESR and number of tender joints, with higher values for the group using glucocorticoids. In the analysis of the 3 groups — those using and not using glucocorticoids and the controls — there was found to be a significant reduction in bone mass of the lumbar spine in the group using glucocorticoids compared to controls.

Similar to other reports[41-44], the mean daily dose of prednisone was not an isolated risk factor in out study, probably because most patients used low doses. It seems that the most important factor in preventing bone loss in patients with RA is to control the inflammatory activity of the disease. If prednisone must be used, its use for more than 2 years should be avoided.

RA occurs preferentially after the fourth decade of life. It is a disease that causes early bone loss, even in premenopausal women. Effective therapy is essential as a preventive measure. Independent exposure factors for the development of osteoporosis in RA were not found in our study; the disease activity was the major risk factor for bone loss. Glucocorticoid was not an independent risk factor for bone loss. Our findings should be verified in other populations, and followup of patients and controls will lead to a better understanding of disease progression in RA and risk factors for late bone loss.

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