Bone mineral density in nonsteroid treated early rheumatoid arthritis

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Abstract

Objectives—To determine whether significant reduction in bone mass is detectable in early disease in patients with rheumatoid arthritis (RA) and to examine the possible influences of disease activity and physical disability on bone mineral density (BMD) of the lumbar spine (LS) and femoral neck (FN).

Methods—LS and FN BMD values were measured and Z scores determined in a cross-sectional study of 104 patients with RA of less than five years duration. BMD values were also compared between a subgroup of 64 patients and a normal control group matched for age, sex, menopausal status and body mass. BMD values and Z scores were correlated with disease activity, measured by the Stoke Index, disability, measured by HAQ score, and disease duration.

Results—Premenopausal female patients with RA had significantly reduced mean FN Z scores (-0.62 , 95% CI -0.30 to -0.94) which correlated with HAQ scores (R_s 0.358 , $p=0.05$) and age (R_s 0.397 , $p=0.03$). There were no significant changes of BMD in males or postmenopausal females. Disease duration and disease activity did not correlate with BMD changes.

Conclusion—BMD is reduced in premenopausal female patients with early RA possibly related to the attainment of peak bone mass. No significant reduction of BMD was found in males or postmenopausal females with early disease. Physical disability but not disease activity appears to play a role in the reduction of FN bone mass.

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With the advent of precise methods of measuring bone mineral density (BMD) there is good evidence that generalised osteoporosis occurs in rheumatoid arthritis (RA).^{1–10} Potential aetiological factors include corticosteroid treatment, decreased physical activity with progressive disease and a direct effect of inflammatory mediators on bone turnover.^{2 4–6 9–11} Current controversies include whether all, or only some, patients with RA are affected and the nature and contribution of various aetiological factors. The influence of these factors is likely to be most clearly defined early in the disease process, when bone mass

is highest and change most easily quantified, and there is less influence of previous treatment and functional impairment on bone turnover.

This study examines a cohort of patients with RA not treated with corticosteroids with a disease duration of less than five years to determine whether significant reduction in bone mass is detectable in early disease and to examine the possible influence of disease activity, and physical activity on the BMD of the lumbar spine (LS) and femoral neck (FN).

STUDY POPULATION

(A) RA Group

A total of 104 patients with RA (ARA criteria 1987)¹² of less than five years duration were enrolled over a period of 18 months. Thirty seven males, 30 premenopausal females and 37 postmenopausal females were recruited from a general rheumatology outpatient or early synovitis clinic. Patients of unknown menopausal status or who were perimenopausal, defined as the onset of menopausal symptoms within the previous five years or a perimenopausal hormone profile on blood testing, were excluded. Other exclusion criteria were current or previous treatment with oral corticosteroids, hormone replacement therapy, thyroxine, vitamin D, abnormal thyroid function tests previous fragility fracture and coexistent disease associated with altered bone metabolism. Patients with marked BMD scan abnormalities known to falsely elevate BMD values, including marked scoliosis, marked osteophyte formation and vertebral crush fractures, were excluded. Plain radiographs of the lumbar spine and hip were not routinely performed to exclude these changes or coexistent aortic calcification.

(B) Control Group

Sixty four of the RA patients comprising 23 males, 20 premenopausal females and 21 postmenopausal females, were matched for age (within five years), sex, menopausal status and body mass (within 10%) with 64 normal individuals recruited from hospital staff and spouses and a retirement group. These individuals did not have any diseases nor were taking any drugs known to affect bone turnover nor did they have a history of osteoarthritis. Exclusion criteria were as for the RA group but thyroid function tests were not performed.

Methods

Each patient underwent a detailed history and examination with details of age, menopausal

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status, duration of disease, current and previous drug treatment, current and previous illnesses, weight, height, duration of early morning stiffness (EMS), joint count, Ritchie Index¹³ and modified Stanford Health Assessment Questionnaire (HAQ)¹⁴ being recorded. Blood was taken for erythrocyte sedimentation rate (ESR), C reactive protein (CRP), thyroid function tests and sex hormone profile including LH, FSH and oestradiol where appropriate. Control group details included drug therapy, current and previous illnesses, height and weight.

BMD was measured in the L1 to L4 lumbar vertebrae (LS) and the left femoral neck (FN) region by dual x-ray absorptiometry using an Hologic QDR 1000 machine.

ANALYSIS

Disease activity was measured by the Stoke Index¹⁵ an algorithm incorporating joint count, duration of EMS, ESR, Ritchie Index and CRP to give a value ranging between 1 (minimum) activity to 17 (maximum) activity. The HAQ score was used as a measure of disability and scored giving a value ranging between 0 (normal) to 3.0 (severe disability).

BMD results were expressed both as an absolute value in gHA/cm² as well as the Z score where the absolute value is compared with an age and sex matched reference population and the value expressed as a multiple of standard deviation values.

Analysis was performed by subgroups based upon sex and menopausal status. Individual LS and FN BMD and Z scores were correlated with disease duration, Stoke Index, and HAQ scores. The mean LS BMD and FN BMD value were compared with the matched control group. The parametric statistical tests applied included analysis of variance, Pearson's correlation test and the nonpaired *t* test. The non parametric tests included Spearman's rank correlation and the Mann Whitney U test.

Results

The characteristics of the RA cohort with subgroups based on sex and menopausal status are shown in tables 1 and 2. LS and FN Z scores in normal premenopausal individuals did not differ significantly from zero [LS mean (SEM) 0.34 (0.18), FN mean (SEM) -0.26 (0.16)]. LS and FN BMD values of the RA groups did not differ significantly from age, sex and body mass matched normal individuals (table 3). Although FN scores in premenopausal females were significantly reduced (table 2), there was no significant difference between the FN Z scores compared with the matched controls. In premenopausal females with RA LS Z values correlated with age (Rs 0.541, *p*0.002) and body mass index (Rs 0.399, *p*0.03) and FN Z values correlated with age (Rs 0.397, *p*0.03), body mass index (Rs 0.390, *p*0.03) and HAQ scores (Rs 0.358, *p*0.05). The HAQ score was an independent predictor of FN Z score in premenopausal patients under age 35, but not those over age 35, after correction for age and body mass. LS and FN Z score decreases were more marked in younger premenopausal female RA patients than older patients (figure A and B). The younger patients did not have more severe disease nor a lower body mass than the older premenopausal RA patients. There was no correlation of LS Z scores with disease duration, Stoke Index or HAQ scores in any of the subgroups.

Discussion

There was no significant reduction of bone mass in male and postmenopausal females with early RA compared with normal individuals in this study. There were sufficient numbers to have a 90% probability of detecting a greater than 8% decrease in BMD values in RA patients compared with normal matched individuals at the *p* < 0.05 level of significance, or a Z score decrease of greater than 0.4,

Table 1 Characteristics of RA Cohort

	Male	Premenopausal female	Postmenopausal female	Total
Number enrolled	37	30	37	104
Number taking SAARDs	20	14	13	47
Age* (years)	58 (12)	36 (7)	67 (7)	55 (16)
Body mass index* (kg/m ²)	26 (4)	25 (4)	25 (5)	25 (4)
Disease duration** (months)	24 (9-42)	21 (9-36)	14.5 (3-29)	24 (8-36)
HAQ score**	0.38 (0-0.98)	0.68 (0.31-1.19)	0.88 (0.13-0.98)	0.63 (0.25-1.25)
Stoke Index**	5 (1-8)	3.5 (1-5.5)	5 (1-7.8)	4.5 (1-8)

*Mean (SD).

**Median (Interquartile range).

SAARDs = slow acting anti-rheumatic drugs.

HAQ = health assessment questionnaire.

Table 2 Mean BMD values and Z scores for the RA cohort

	Male Mean (SEM)	Premenopausal female Mean (SEM)	Postmenopausal female Mean (SEM)	Total Mean (SEM)
Number	37	30	37	104
LS BMD (gHA/cm ²)	1.043 (0.025)	1.029 (0.019)	0.870 (0.022)	0.975 (0.015)
FN BMD (gHA/cm ²)	0.803 (0.020)	0.804 (0.015)	0.683 (0.020)	0.758 (0.012)
LS Z Score	0.10 (0.25)	0.01 (0.20)	0.39 (0.21)	0.18 (0.13)
FN Z Score	-0.06 (0.18)	-0.62* (0.16)	0.08 (0.19)	-0.18 (0.11)

**p* = <0.001.

Table 3 Comparison of LS and FN BMD values in RA patients and controls matched for age, sex and body mass

	RA mean (SD)	Controls mean (SD)
Total (64)		
Age (years)	53 (16)	54 (17)
Body Mass Index (kg/m ²)	25 (3)	25 (3)
LS BMD (gHA/cm ²)	0.982 (0.141)	0.999 (0.156)
FN BMD (gHA/cm ²)	0.759 (0.015)	0.783 (0.015)
Males (23)		
AGE (years)	57 (11)	57 (11)
Body Mass Index (kg/m ²)	25 (3)	25 (2)
LS BMD (gHA/cm ²)	1.024 (0.139)	1.022 (0.163)
FN BMD (gHA/cm ²)	0.780 (0.131)	0.798 (0.120)
Premenopausal females (20)		
Age (years)	34 (8)	34 (8)
Body Mass Index (kg/m ²)	23 (3)	23 (3)
LS BMD (gHA/cm ²)	1.025 (0.106)	1.060 (0.128)
FN BMD (gHA/cm ²)	0.809 (0.092)	0.847 (0.110)
Postmenopausal females (21)		
Age (years)	68 (6)	68 (6)
Body Mass Index (kg/m ²)	27 (4)	26 (3)
LS BMD (gHA/cm ²)	0.896 (0.139)	0.920 (0.142)
FN BMD (gHA/cm ²)	0.690 (0.107)	0.707 (0.091)

SD = standard deviation.
LS = lumbar spine.
FN = femoral neck.
BMD = bone mineral density.

Premenopausal patients with RA.

equivalent to a 5% decrease of absolute BMD values compared to the Hologic reference values. Other studies have shown a significant decrease in LS and FN BMD values in RA patients¹⁻¹⁰ but have included patients with longstanding disease, greater functional disability with resultant decreased physical activity, and patients taking oral corticosteroids which accelerate bone loss. This study excluded patients taking oral corticosteroids and included patients with a relatively short disease duration (mean duration of two years) to avoid the potential effects of prolonged disability on bone mass.

LS and FN BMD values in the normal population are influenced by age, sex and menopausal status¹⁶⁻¹⁷ and because of this the cohort was divided into subgroups based on sex and menopausal status for analysis.

Perimenopausal patients were excluded because of the greater variability of bone loss between individuals during this period which may obscure more subtle changes due to the disease process. Z scores are not affected by sex and menopausal status as these reflect the relationship of an individual value with an age and sex matched reference population with the result expressed as a multiple of standard deviation values from the mean with a normal value equal to zero. A mean value which is negative indicates that a group has a lower than predicted mean BMD. The usefulness of Z scores rely on the Hologic database being comparable with normal individuals from the population being studied. Reference data from France, Belgium and Australia have been shown to closely correlate with North American values within $\pm 2\%$ over the whole BMD range for spines.¹⁸⁻²⁰

Normal premenopausal female Z scores did not differ significantly from zero in this study indicating that Z scores are a valid reference for this subgroup. Premenopausal female RA patients had significantly reduced FN BMD values particularly affecting the younger patients which was also reflected in the lumbar spine. These findings reflected by the correlation of Z score changes with age, suggest that the effect of the disease process is more marked before the attainment of peak bone mass during the period of net bone formation. The correlation of body mass with LS and FN Z scores indicates that premenopausal patients of slighter build are more susceptible to the effects of disease. Age and body mass correlated with each other but were also independent predictors of the femoral neck Z score.

HAQ scores but not the Stoke Index correlated with FN Z scores in premenopausal RA patients suggesting that disability, with a concomitant reduction in physical activity, is responsible for the reduction rather than a direct effect of inflammatory mediators related to disease activity. Other studies have also shown an association of FN BMD values with disability^{6 10} and physical activity measures.² HAQ score values in the other RA subgroups were comparable but were not associated with FN Z score changes suggesting that mild disability has much less impact on FN BMD in these groups. The lack of association of HAQ scores with LS Z changes either indicates no direct effect of disability on LS BMD or that greater disability is required before there is sufficient change in physical activity to affect the lumbar spine.

No significant association of Z scores was found with disease duration indicating that there was no large cumulative bone loss occurring in the cohort. Other studies have not found an association but two have indicated that bone loss may be greatest during the first years of disease.^{6 10} The lack of association of Stoke Index with Z score changes indicates that disease activity did not directly affect bone density in this cohort. Both disease activity and Z score changes, however, were low and the lack of association may reflect the difficulty of comparing on a crossectional basis variables

which fluctuate daily or weekly with those reflecting cumulative changes over months to years.

In summary, no significant changes of BMD were found in the RA patients except in the femoral neck of premenopausal females which were associated with physical disability, younger age and lower body mass. No relationship of reduction of bone mass with disease activity was found.

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