

BONE DENSITOMETRY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract- Osteoporosis (OP) is a frequent complication of rheumatoid arthritis (RA) and longitudinal studies have documented increased rate of bone loss in RA patients. To determine the frequency of low bone mass as well as the influence of disease duration and corticosteroid use on bone mass in patients with RA, 88 patients with RA and 112 age matched controls were studied. Bone densitometry was performed by a single dual X-ray absorptiometry equipment in the lumbar spine (LS) and femoral neck (FN). The mean age of patients and controls were 52.6 and 54.6 years, respectively. The mean disease duration was 7.0 years and 79.5% of patients were taking 5.0 mg prednisolone daily for a mean period of 4.6 years. At the FN, 45% of patients had OP compared to 30.4% in the controls ($P < 0.05$). At the LS the frequency of OP in patients was non-significantly lower than in the controls. OP was more frequent in corticosteroids treated patients compared to non-corticosteroids treated patients both at the FN (43.5% vs 39%) and LS (26% vs 22%) but the differences were not significant. Disease duration longer than 10 years in comparison to disease duration of less than two years was associated with bone mineral density change of -10.9% at the FN ($P = 0.05$) and -10.4% at the LS (P not significant). The results of this study indicate that a significant proportion of patients with RA have OP at the FN and LS, and disease duration longer than 10 years is associated with a significant increase in bone loss.

Acta Medica Iranica, 43(2): 99-104; 2005

Key words: Rheumatoid arthritis, bone loss, bone densitometry, osteoporosis, bone mass, corticosteroid

INTRODUCTION

Osteoporosis (OP) has been frequently described in patients with rheumatoid arthritis (RA) and longitudinal studies have documented increased rate of bone loss in RA patients (1, 2). Several cross-sectional studies have also shown lower bone mass in RA patients compared to controls (2, 3). The etiology of reduced bone mass in RA is multifactorial, including life-style risk factors and disease-related determinants. Persistently high levels of inflammation, low levels of physical activity and use of corticosteroids are associated with increased risk of bone loss (2-9). Bone loss at the spine and hip is

more severe in patients with active disease with high levels of CRP or ESR compared to patients with inactive disease (7). Low bone mass is a risk factor for fracture which is the clinically relevant consequence of osteoporosis. An increased risk of fracture at spine and the hip has been shown in patients with RA, in particular those treated with corticosteroids (10, 11).

Both RA and OP are common among postmenopausal women, so these patients are at an increased risk of bone loss. Moreover, use of corticosteroids exacerbates bone loss in these patients. Therefore, RA patients and in particular those with chronic steroid dependent disease are at an increased risk of future fractures.

Despite the lower than normal values of bone mineral density (BMD) at the appendicular as well as axial bones in RA patients, there is a considerable controversy whether RA is associated with more extensive OP; in particular, the results of studies

Received: 7 Feb. 2004, Revised: 6 July 2004, Accepted: 31 Aug. 2004

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concerning the influence of disease duration, physical disability and disease activity on bone mass of RA patients are not similar, even the reducing effect of steroid on bone mass varies according to site of BMD measurement (2, 5, 6, 8, 9, 13-14).

With regard to different results and controversies in the frequency of low bone mass in RA, the present study was performed to determine the frequency of OP as well as the effect of corticosteroid therapy and disease duration on the bone mass of patients with RA.

MATERIALS AND METHODS

A total of 88 patients with RA who presented for regular clinical examination to an outpatients clinic or hospital, and 112 age-matched healthy controls entered the study. Control subjects were selected among the subjects without prior history of RA or other inflammatory arthritides who presented with upper respiratory infection or dyspepsia. These subjects attended the same clinic or hospital. We obtained informed consent from all participants of this study.

Sample size was determined with a confidence interval level of 95% and power of 80% to detect 15% difference between patients and controls. On the basis of statistical analysis, 75 samples for each group were needed to detect a significant difference between patients with RA and controls. Diagnosis of RA was confirmed by the 1987 American College of Rheumatology Revised Criteria (15). Data were provided regarding disease duration and use of corticosteroids. BMD was measured with a single dual X-ray absorptiometry (DXA) equipment (Norland Excell) in the lumbar spine (LS) at the L2-L4 and in the femoral neck (FN) areas. All densitometries were performed by the same technician.

The results of bone densitometries were compared with the reference data supplied by the manufacturer's DXA system and expressed as BMD (gr/cm^2), T-score and Z-score. Diagnosis of OP and osteopenia were confirmed according to World Health Organization (WHO) criteria (16). Patients and controls were compared regarding BMD values, the frequency of OP, the frequency of low bone mass

defined as having a Z-scores ≤ -1 , and the frequency of subjects with severe reduced bone mass defined as a Z-score ≤ -2 .

Patients were categorized by disease duration and corticosteroid use. The effect of corticosteroid therapy on bone mass was assessed by comparing the results of bone densitometry between patients with and without corticosteroid treatment. The influence of disease duration on BMD was assessed by comparison of the BMD values between patients with disease duration of less than two years with those with disease duration of 2-10 years as well as with patients with disease duration longer than 10 years. In statistical analysis Chi square test and *t* test were used for group comparison.

RESULTS

Seventy five female and 13 male RA patients with mean age of 52.6 (± 14.6) years and 112 age-matched controls (105 females and 7 males) with mean age of 54.6 (± 9.0) years entered the study. Characteristics of the patients and controls are shown in table 1. The mean disease duration was 7.0 (± 6.9) (range 0.25-30) years. The mean menopausal duration of patients and controls were 11.3 (± 9.5) and 10.7 (± 15) years, respectively.

None of the patients were treated for osteoporosis; 79.5% of patients were taking 5.0 mg prednisolone daily for a mean duration of 4.6 (± 5.0) (range 0.8-5.2) years. With respect to findings presented in table 2,

Table 1. Characteristics of the study patients with rheumatoid arthritis and age-matched controls*

Characteristic	Patients (n=88)	Controls (n=112)	P value†
Age (years)	52.6 (14.6)	54.6 (9)	NS
Female gender ‡	84	90.2	NS
Postmenopausal women‡	69	69.3	NS
Menopausal duration (year)	11.3 (9.5)	10.7 (15)	NS

Abbreviation; NS, not significant.

* Data are given as mean \pm SD unless specified otherwise.

† Compared with student *t* test and chi square test.

‡percent.

Table 2. Comparison of the results of bone densitometry in patients with rheumatoid arthritis and age-matched controls*

Results of bone densitometry	Patients	Controls	P value†
Femoral neck			
BMD, g/cm ²	0.71 (0.14)	0.74 (0.15)	NS
Mean T-score	-2.2 (1.38)	-1.86 (1.44)	0.09
Osteoporosis (T-score < -2.5)‡	40 (45.5)	34 (30.4)	0.05
Osteopenia (-1 < T-score > -2.5) ‡	35 (39.8)	57 (51)	NS
Mean Z-score	-1.86 (1.04)	-0.71 (1.05)	0.01
Z-score ≤ -1‡	53 (60)	46 (41)	0.01
Z-score ≤ -2‡	18 (20.5)	15 (13.5)	NS
Lumbar spine			
BMD g/cm ²	0.82 (0.16)	0.80 (0.15)	NS
Mean T-score	-1.64 (1.44)	-1.47 (1.14)	NS
Osteoporosis (T-score < -2.5) ‡	22 (25)	16 (14.3)	NS
Osteopenia (-1 < T-score > -2.5) ‡	42 (48)	61 (54)	NS
Mean Z-score, mean	-1.26 (1.17)	-1.47 (1.14)	NS
Z-score ≤ -1‡	53 (59)	61 (69.3)	NS
Z-score ≤ -2‡	21 (24)	18 (16.2)	NS

Abbreviations: BMD, bone mineral density; NS, not significant.

* Data are given as mean ± SD unless specified otherwise.

†Statistical analysis was performed using *t* test and Chi square test.

‡ Number (percent).

the frequency of OP at the FN was significantly higher in patients than controls ($P < 0.05$). At the LS region the frequency of OP was also higher in patients than in controls but the difference did not reach a significant level ($P < 0.06$).

At the FN the mean Z-score value was significantly lower in patients than in the controls. The mean T-score value at the FN was also lower in the patients but the difference was not significant. At the LS the mean Z-score value and the mean T-scores values were also nonsignificantly lower in RA patients than in controls.

The frequency of patients with low bone mass (T-score ≤ -1) in corticosteroid treated and non-corticosteroid treated RA patients were 74% and 83% at the FN and 73 and 72.2% at the LS, respectively.

The frequency of OP (T score ≤ -2.5) at the FN was 43% in corticosteroid treated patients and 39% in non-corticosteroid treated patients ($P = NS$). At the LS the frequency of OP in corticosteroid treated and non-corticosteroid treated patients were 26% and

22%, respectively ($P = NS$).

The mean (±SD) BMD values at FN in corticosteroid treated and non-corticosteroid treated patients were 0.72 (±0.14) and 0.70 (±0.13) g/cm² and the mean (±SD) BMD at LS were 0.82(0.17) and 0.79 (±0.15) g/cm² respectively. In corticosteroid treated patients FN BMD increased by 2.85% and LS BMD increased by 3.8% ($P = NS$).

The mean (±SD) BMD value at FN in 28 patients with disease duration of less than two years was 0.73 (±0.13) gr/cm², in 37 patients with disease duration of 2-10 years was 0.71 (±0.15) g/cm², and in 23 patients with disease duration longer than 10 years was 0.65 (±0.12) gr/cm². The respective mean BMD values at LS were 0.86 (±0.18), 0.82 (±0.16), and 0.77 (±0.16) g/cm². Compared to patients with disease duration of less than two years, after 2-10 years the mean BMD at FN decreased by 2.7% and at LS by 4.6%; after 10 years the mean BMD at FN and at LS decreased by 10.9% ($P < 0.05$) and 10.4% ($P = NS$), respectively.

DISCUSSION

In this study the status of bone mass was evaluated with regard to severity of bone loss and the frequency of low bone mass. The results showed that low bone mass was more frequent in RA than in controls, furthermore the frequency of severe reduced bone mass defined as a Z-score of -2 and lower as well as a T-score of -2.5 and lower were also higher in RA patients. It was also found that disease duration longer than 10 years was associated with a significant bone loss whereas corticosteroid therapy for a mean period of nearly 5 years was not associated with bone loss.

The results of the present study are somewhat different from other published studies; however, in most other similar studies the prevalence of OP in RA has been higher than expected. Haungeberg *et al.*, in a study of RA patient aged 20-70 years with a mean disease duration of 13 years, found OP at FN and at LS in 14.7% and 16.8% of cases, respectively. The prevalence of reduced bone mass ($Z \leq -1$) was 27.6% at FN, and 31.6% at LS. A two-fold increased frequency of OP was observed in RA patients compared with the reference population. Similar to our study, there was no significant difference between the frequency of reduced bone mass at the LS in patients and in controls (17). In another study in RA patients with mean disease duration of 30 months, low bone mass ($Z \leq -1$) was found in 32% of patients in the LS and 24.2% in the hip. In that study low bone mass was more frequent in RA than in healthy age and sex-matched controls (18). Saario *et al.* in 57 patients with advanced RA who were on long-term corticosteroid therapy found that 47% of patients had low bone mass (Z -scores ≤ -1) at the LS (19). Gukasian *et al.* showed that 60% of premenopausal women with RA had low bone mass (T -scores ≤ -1) at the FN, and 33% at the LS (20). Aman *et al.* over a two years follow-up of early RA found that only 10% of 52 patients developed OP by Z scores ≤ -1 definition) (21). In another study of RA patients from Khozestan, Iran, 40.4% of cases had OP (22). In that study the frequency of OP at the FN and LS were 34.9% and 25%, respectively.

In comparison to previous studies the prevalence of low bone mass in the present study was higher

both in patients and controls. This finding could be attributed to an inclusion of a high proportion of menopausal participants, which comprises about two-thirds of the study population. OP and RA are common in postmenopausal patients. Several factors have been associated with development of OP in RA as well as in postmenopausal women (2, 3, 4, 8, 9, 23).

We have shown a significant difference in the frequency of low bone mass in RA patients. However, the mean BMD between the patients and controls at the FN was not different significantly. This discordance can be attributed to heterogeneity of RA patients according to disease duration and use of corticosteroids. The mean BMD at FN in patients with disease duration of lower than two years as well as corticosteroid treated patients were nearly similar to the mean BMD at FN of the controls whereas in patients with disease duration of longer than ten years the mean FN BMD was significantly lower than controls. For this reason despite the significantly higher than expected frequency of OP in RA patients, the difference between the mean FN BMD of patients and controls did not reach a significant level. In contrast to FN, there was no discordance between BMD and frequency of low bone mass at the LS. Kroger *et al.* in a cross-sectional study of RA patients and controls without any other disease showed that the mean spinal and FN BMD was significantly lower in patients with RA than controls. At the spine the difference was significant only in patients having corticosteroid treatment, whereas at the FN patients with non-steroid treatment also had significantly lower BMD (2). In the study by Hansen *et al.* lumbar spine BMD did not differ from age-matched healthy controls, but distal forearm BMD and metacarpal BMD were significantly lower in RA patients, which was attributed to impaired physical activity related to disease activity. In that study, similar to our study, corticosteroid therapy had no effect in BMD of axial or appendicular skeleton (9). Shenstone *et al.* found no significant difference in BMD changes between RA patients and controls overall (1), but significant changes in bone mass was observed in patients with disease duration of less than six months at the FN (-3.9%) compared to the remainder of cohort (-0.2%) and controls.

Regarding the findings of present study, treatment with corticosteroids for a mean period of 4.6 years was not associated with bone loss either at the FN or LS. The effect of corticosteroids on bone mass of RA patients has been discussed in several studies. While many studies have shown a significant bone loss in patients using corticosteroids both at the FN and LS (4, 5, 8, 17, 24), in other studies the difference of BMD between corticosteroid treated and non-corticosteroid treated patients has not been significant (2, 9). Two reasons have been identified for the discrepancies in the literature. First, non-randomized studies are subject to selection bias because RA itself and its concomitant decreased mobility may cause bone loss. Second, the negative effect of corticosteroids on bone mass may be most pronounced in the initial phase of therapy (11). Furthermore the anti-inflammatory effect of corticosteroids leads to clinical improvement which may counteract the expected negative effect of these drugs on bone in RA (9).

In addition to RA, other responsible factors of postmenopausal OP which have been reported from another study in Iran (23), may also contribute to the development of OP in RA as well as in controls. The higher than expected rate of OP in the control group is in favor of this concept.

In conclusion, the results of this study indicate that a significant proportion of patients with RA have OP. Using low dose corticosteroids at least for a mean period of 55 months may not cause bone loss, but disease duration of more than 10 years is associated with bone loss in particular at FN. Regarding the increased risk of fracture in subjects with low bone mass, these findings show that RA patients are at an increased risk of FN fracture. Early bone densitometry is essential for diagnosis of low bone mass and initiation of appropriate preventive program or anti-osteoporotic therapy seems mandatory.

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