The development of bone mineral density and the occurrence of osteoporosis from 15 to 20 years of disease onset in patients with rheumatoid arthritis

H. Hämäläinen, H. Kautiainen, K. Kaarela, A. Kotaniemi

The Rheumatism Foundation Hospital, Heinola, Finland

Abstract

Objective

To ascertain the occurrence of osteoporosis and the development of central bone mineral density (BMD) in long-term rheumatoid arthritis (RA)

Methods

BMD of the lumbar spine (L2-L4) and the femoral neck were measured by dual-energy X-ray absorptiometry in a cohort of 59 patients (49 women and 10 men) with rheumatoid factor-positive RA followed up for 20 years. BMD measurements were obtained at the 15- and 20-year follow-up visits.

Results

At the 15-year check-up the mean age was 61 (SD 13) for men and 54 (SD 11) years for women. Bone densitometry of these patients revealed decreased BMD at both lumbar spine and femoral neck, the mean T-scores being -1.1 [95%CI: -1.6 to -0.6] and -1.3 [95%CI: -1.6 to -1], respectively). Eighteen (31%) patients thus had osteoporosis (BMD T -score ≤ –2.5) and 32 (54%) patients were osteopenic (BMD T-score -1.0 to -2.5). However, when compared with reference values, the decreases in central bone mineral in this patient group were of low degree; the mean Z-score -0.2 [95%CI: -0.7 to 0.2] at the lumbar spine and -0.5 [95%CI: -0.8 to -0.3] at the femoral neck, respectively. After the subsequent five years the mean Z-score increased 0.45 [95%CI: 0.32 to 0.58] at the lumbar spine and the mean T-score decreased -0.20 [95%CI: -0.32 to -0.08] at the femoral neck. ESR, Larsen score, gender and cumulative dose of prednisolone during the 5 year follow-up and HAQ-index were used as explanatory parameters of BMD change between the 15- and 20-year follow-ups. None of these parameters explained the BMD change.

Conclusion

We conclude that in long-term RA central bone densities seemed to be only moderately decreased after 15 years from eruption of RA. No essential change in central BMD was found after the consecutive 5 years.

Key words

Osteoporosis, rheumatoid arthritis, bone density.

Harri Hämäläinen, MD; Hannu Kautiainen, BA; Kalevi Kaarela, MD, PhD; Antero Kotaniemi, MD, PhD.

Please address correspondence and reprint requests to: Harri Hämäläinen, Rheumatism Foundation Hospital, FIN-18120 Heinola, Finland.
E-mail: harri.hamalainen@reuma.fi

Received on June 24, 2004; accepted in revised form on November 30, 2004.

Introduction

Rheumatoid arthritis (RA) is a chronic disorder of unknown cause with a variety of systemic manifestations. Erosive synovitis involving peripheral joints is characteristic of RA (1). The course of RA can vary from mild to severe progressive polyarticular illness. Early peripheral joint destruction may indicate a more severe disease and would appear to be associated with large joint involvement and increased functional disability (2, 3). Disease activity seems to be associated more with functional capacity in early RA, while joint damage is associated with functional capacity in later stages (2, 4, 5). Long-term outcome studies of RA reveal that as many as 80% of hospital inpatients are likely to be moderately or severely incapacitated after 20 years, and that average outpatients with RA have a 30% likelyhood of being severely disabled (6). The functional impairment of patients and the duration of the illness have a negative effect on bone mineral density (BMD) at both the axial and peripheral bone (7-9). In addition, the loss of periarticular bone is one of the classification criteria for RA and it occurs early during the course of the disease (1, 8).

However, treatment of RA and control of disease activity will probably prevent systemic bone loss (10, 11). In a population-based study, an increased number of untreated patients with early RA evinced reduced bone mass in the spine at disease onset, although BMD in spine and hip did not differ from that of the normal reference population (12). In a 2-year follow-up of early community-based patients with RA a lower level of central bone loss was observed than expected (13). When the BMD of axial and peripheral bone in female RA patients was compared to age-matched female patients with osteoarthritis and postmenopausal osteoporosis, there was a relatively preserved bone mass in the axial bone and marked bone loss in the peripheral bone in the case of the RA patients (14). In a longer study the rate of bone loss at the hip joints in RA patients during the first decade of the disease was slower than expected when compared with reference values (15).

Most studies on oral corticosteroid use and loss of BMD in RA have reported inconsistent results (10, 12-22). In the first randomized, placebo-controlled study of the initial effects of low-dose prednisolone on BMD in patients with active RA, lumbar BMD decreased in the prednisolone-treated patients, and this group had a greater mean bone loss than the placebo group between baseline and week 20. After discontinuation of treatment, bone loss appeared to be partially reversible (21). In another placebo-controlled study of effects of low-dose prednisolone on BMD in patients with early active RA there were no significant changes from baseline in BMD of the hips and the lumbar spine in either group during the three years of follow-up (22). In multicentre cross-sectional and population based studies there was a high prevalence of vertebral deformities and clinical manifestations of vertebral fractures in RA patients on corticosteroids as compared to in those without (23, 24). In a recent meta-analysis of corticosteroid-induced osteoporosis, strong correlations were found between the cumulative dose of corticosteroid and the loss of BMD (25).

Recent studies of osteoporosis in RA suggest a more favorable outcome of bone mineral status than expected. However, there are only a few follow-up studies in long-term RA in this area (17-20). To ascertain the occurrence of OP and to determine changes in central bone mineral in late RA, we measured BMD levels at the lumbar spine and the left femoral neck in a series of seropositive RA patients followed up for 20 years.

Materials and methods

A cohort of 108 patients with recent onset (< 6 months) and RF-positive RA have been followed up since 1973-75 at the Rheumatism Foundation Hospital in Heinola, Finland (26). The follow-up examinations took place at 1, 3, 8 and 15 years from entry. A total of 74 patients with RF-positive and erosive RA attended the 15-year follow-up in 1989, when for the first time BMD measurements were available. Viewed

in retrospect they all met the 1987 American College of Rheumatology (ACR) classification criteria for RA.

The study group consisted of those 59 patients (10 men and 49 women), who attended at the 15- and 20-year BMD measurements. Central BMDs were measured by dual-energy X-ray absorptiometry, (DXA); LUNAR DPX, Lunar Radiation Corporation, Madison, WI, and the measurement sites were the 3 lumbar vertebrae L2-L4 in the spine and the left femoral neck (27). The diagnosis of OP was based on a BMD T-score ≤ –2.5, the diagnosis of osteopenia on a BMD T-score -1.0 to -2.5 (28). The precision of the BMD measurements had previously been determined on adults and had proved acceptable: 1.0% for the spine and 1.8% for the femoral neck. Two out of 49 women did not have BMD measured at the left femoral neck due to hip joint endoprothesis. Four out of 49 women and 2 out of 10 men did not have BMD measured reliably at the lumbar spine due to severe osteoarthrotic changes in the spine. Radiographs of the lumbar spine were not taken, because radiographs of both small and large joints were taken at the 15-year follow-up.

The use of disease-modifying antirheumatic drugs (DMARD) were registered. The cumulative dose of prednisolone from entry to 15 years of follow-up and between the 15- and 20-years follow-up visits was evaluated from patient registers simultaneously with the determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

The Larsen method was used to evaluate radiographs of hands and feet, which were taken in the dorsovolar projections at both the 15- and 20-year follow-ups. The joints to be interpreted were compared with standard series on a scale of 0 to 5. Joints with only soft tissue swelling or osteoporosis were assigned a Larsen grade of 0, joints with pre-erosive changes or marked space narrowing a grade of 1, and joints after reconstructive surgery a grade of 5 (29, 30). Grades for the 1st to 5th metacarpophalangeal joints and wrists and the 2nd to 5th metatarsophalangeal joints (20 joints) were summed to form a Larsen score of 0-100 to demonstrate the severity of RA (3). The Health Assessment Questionnaire index (HAQ) was registered at both the 15- and 20-year follow-ups. The highest score for each eight areas of activity in daily living was summed (range 0-24) and divided by eight to yield a continuous scale (0-3) of functional disability index (31). The number and location of large joint replacements were also registered.

Ethics

The subjects' written consent was obtained according to the Declaration of Helsinki. The design of the work was approved by the local ethical committee of The Rheumatism Foundation Hospital, Heinola.

Statistics

Results are expressed as mean or median, standard deviation (SD) or interquartile range (IQR), and 95 per cent confidence intervals (95% CI). Statistical significance was evaluated by t-test. Hommel's adjustments were performed to correct significance levels for the multiple test. The normality of variables was evaluated by Shapiro-Wilk statistics and correlation coefficients were calculated by the Spearman method. The α level was set at 0.05 for all tests. Regression analyses with biased corrected bootstraping (10,000 replications) confidence intervals was used to model the relationship between BMD change and predictor variables.

Results

A total of 59 patients (10 men and 49 women) had their BMD measured at the lumbar spine and/or the left femoral neck. The mean age was 61 (SD 13) years for men and 54 (SD 11) years for women at 15 years from the onset of RA. The main figures for the measured clinical parameters, the number of prednisolone users are shown in Table I. In this stage the inflammatory activity proved to be fairly low, but Larsen score determinations revealed that the joint destruction was substantial at the peripheral joints. Between the 15- and 20-year follow-up visits the median difference of ESR, CRP and Larsen score was 2 [95%CI: -6 to 2], p = 0.32, 2 [95%CI: -2 to 4], p = 0.53 and 6 [95%CI: 4 to 6], p < 0.001, respectively. At the end-point, a total of 22 large joint replacements (LJR) had been performed for one man and nine women. The median (IQR) HAQ-index was 0.62 (0.37, 1.00) for men and 0.37 (0.00, 0.75) for women, respectively. Since disease onset, 1973-1975, 90% of these patients had been treated initially with gold sodium thiomalate, hydroxychloroquine, penicillamine and/or prednisolone or their combinations. Sulfasalazine was introduced in the treatment regimen after 1982. Only six patients used methotrexate periodically during the years 1991-96 (3). At the 15-year evaluation point four out of 10 men and 15 out of 49 women were using prednisolone, the median (IQR) daily dose being 5.0 mg (1.25, 7.5) and respectively at the 20-year check-up four out of 10 men and 24 out of 49 women were using prednisolone, the median (IQR) daily dose being 5.0mg (0.50, 10). From entry to the 15-year follow-up the median (IQR) cumulative dose of prednisolone was 8.0g (0.00, 15) for men and 1.0g (1, 9) for women, respectively. Between 15- and 20-year check-ups the median (IQR) cumulative dose of prednisolone was 0.50g (0.00, 6.12) for men and 1.00g (0.00, 6.75) for women, respectively.

At the 15-year measurements, the mean lumbar BMD was 1.06g/cm^2 [95%CI: 1.00 to 1.22] reflecting a mean T-score of -1.13 [95%CI: -1.62 to -0.65] and a Z-score -0.22 [95%CI: -0.67 to 0.24]. For comparison at the femoral neck the mean BMD was 0.84g/cm^2 [95% CI: 0.80 to 0.87], and the mean T-score was -1.29 [95%CI: -1.57 to -1.00], and the Z score -0.52 [95%CI: -0.76 to -0.27]. One man out of 10 (10% [95% CI: 0 to 45]) and 3 women out of 49 (6% [95% CI: 1 to 17]) had OP at both the lumbar spine and the femoral neck. Altogether 18 (31% [95% CI: 19 to 44]) patients out of 59 (17 women and one man) had central osteoporosis, and altogether 32 (54% [95% CI: 41 to 67]) patients out of 59 (23 women and 9 men) were considered to have osteopenia.

After subsequent 5 years the mean BMD changes were of low degree gen-

Table I. Demographic and clinical data on RA patients at 15 years of follow-up.

Variable	Females (n = 49)		Males (n = 10)	
Mean (SD) age, years	54	(11)	61	(13)
Median (IQR) ESR, mm/h	20	(11, 41)	32	(18, 48)
Median (IQR) CRP, mg/L	2	(2, 24)	14	(3, 63)
Median (IQR) Larsen score (0-100)	33	(17, 61)	44	(32, 62)
Median (IQR) physical function, HAQ†	0.37	(0.00, 0.75)	0.62	(0.37, 1.00)
Number of prednisolone users (%)	15	(31)	4	(40)

† Health Assessment Questionnaire.

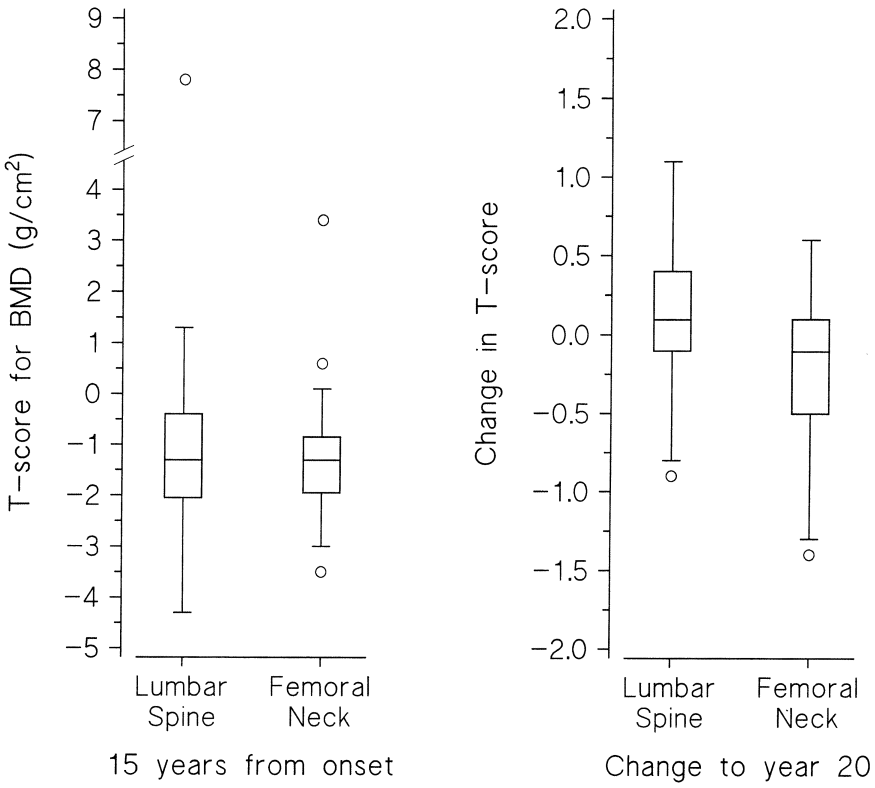

Fig. 1. T-scores for central bone mineral density (BMD) at the 15-year follow-up and the change in T-score for BMD from the 15-year to 20-year follow-ups in 59 RA patients.

Table II. Central bone mineral density (BMD) at the 15-year follow-up and the change in BMD to the 20-year follow-up in 59 RA patients.

	15 years from onset Mean (SD)	Change to year 20 Mean (95% CI)	p value†
Lumbar spine:			
BMD (g/cm²)	1.06 (0.21)	0.01 (-0.00 to 0.03)	0.10
BMD T-score	-1.13 (1.76)	0.13 (0.01 to 0.26)	0.082
BMD Z-score	-0.22 (1.66)	0.45 (0.32 to 0.58)	<0.001
Femoral neck:			
BMD (g/cm²)	0.84 (0.13)	-0.02 (-0.04 to -0.01)	0.002
BMD T-score	-1.29 (1.07)	-0.20 (-0.32 to -0.08)	0.002
BMD Z-score	-0.52 (0.93)	0.01 (-0.10 to 0.12)	0.84

† Hommel's adjusted p-values.

erally, at the lumbar spine was 0.01g/cm² [95%CI: -0.00 to 0.03] and at the femoral neck it was -0.02 g/cm² [95% CI: -0.04 to -0.01]. Simultaneous mean T-score and Z-score changes were 0.13 [95%CI: 0.01 to 0.26] and 0.45 [95% CI: 0.32 to 0.58] at the lumbar spine and -0.20 [95%CI: -0.04 to -0.01] and 0.01 [95%CI: -0.10 to 0.12] at the femoral neck, respectively (Fig. 1, Table II). Concerning the clinical data none of the explanatory variables was found as a statistical predictor of BMD change at the lumbar spine and femoral neck from 15- to 20-year check-ups (Table III).

Discussion

Few studies concerning central BMD and changes of BMD in long-term (mean disease duration over 10 years) RA have been conducted. In these studies BMD values seem to be only slightly reduced or close to that of controls in the lumbar spine and femoral neck (16-20). Sambrook *et al*. assessed BMD values as BMD percentage of normal mean in female RA patients at the lumbar spine and femoral neck and these BMD values were 6.9% and 8.9% reduced from that of controls, respectively (17). Cortet *et al*. measured BMD values also in men and assessed the difference of central BMD values in long-term RA patients versus healthy controls at the lumbar spine and femoral neck and found the differences in BMD to lie 14.8% and 17.7% lower in RA patients at the measurements sites, respectively (18). In our study at the 15-year check-up the decreases in BMD were only moderate at the lumbar spine and femoral neck when compared with values in the reference population at the same age and sex (32-34).

Sambrook *et al*. found no differences in changes of BMD in long-term (mean disease duration over 10 years) RA patients versus in healthy controls at the lumbar spine and femoral neck in a 2-year follow-up study. These BMD changes assessed as change of percentage per year had the magnitude from 1% to 2% at the femoral neck and even less at the lumbar spine (17). Haugeberg et al found the mean BMD reduction as percentage of change in RA

Table III. Main results of multivariate analyses modelling the relationship between BMD changes and clinical variables in 59 patients with RA.

Explanatory variables	Regression model					
	Lumbar spine			Femoral neck		
	β †	(95% CI ‡)	P-value	β †	(95% CI ‡)	P-value
Sex (male)	4.37	(-4.95 to 12.02)	0.082	2.74	(-2.65 to 7.34)	0.18
Age, years	-0.08	(-0.27 to 0.11)	0.34	-0.14	(-0.27 to -0.00)	0.053
ESR, mm/h	0.08	(-0.06 to 0.18)	0.095	0.04	(-0.04 to 0.13)	0.34
Median (IQR) physical function, HAQ*	0.15	(-4.80 to 5.61)	0.95	-0.17	(-.561 to 4.12)	0.93
Cumulative prednisolone dose # (g)	0.23	(-0.22 to 0.60)	0.26	0.00	(-0.29 to 0.24)	0.98
Larsen score (0 – 100)	-0.04	(-0.17 to 0.05)	0.28	-0.04	(-0.14 to 0.05)	0.21
Constant	3.95			5.93		

† Coefficients multiplied by 100.
‡ 95% confidence interval obtained by bias-corrected bootstrapping (10,000 replications).
* Health Assessment Questionnaire.
# Cumulative prednisolone dose between 15-20 years of disease onset.

patients not using any OP treatment to lie 0.64% at the femoral neck and 0.43% at the lumbar spine in a population-based cohort of RA patients followed up for two years (20). In our study the Z-score increased at the lumbar spine and there were no change at the femoral neck from 15 to 20 years of disease duration.

Reduced BMD values seem to be met in patients with long-term RA receiving corticosteroids when compared to those of controls or RA patients not receiving corticosteroids (16-20). Buckley *et al*. found significantly lower BMD values at the lumbar spine in RA patients receiving over 5mg daily dose of prednisolone (19). Haugeberg *et al*. found similar results also at the femoral neck (20). Sambrook et al and Cortet *et al*. explained that it is difficult to distinguish the effects of disease duration and severity of RA from effect of corticosteroid treatment on central BMD in RA patients (16, 18). We emphasize that the daily dose of prednisolone is 5mg in majority of cases in our hospital to achieve a favorable benefit to risk ratio as discussed recently by Strand and Simon (35). Forslind *et al*. and Berglin *et al*. have suggested that reduced BMD in RA is associated with radiologic progression (36, 37). However, in our study Larsen score beared no correlation with BMD change. In addition, disease activity, age or HAQ beared no correlation with BMD change. Cortet *et al.* found age to have negative correlation to central BMD values (18). Cortet *et al*. and Buckley *et al*. found HAQ-index to be associated with BMD in the lumbar spine and femoral neck (18,19).

We conclude that in RA central BMDs seem to be only moderately decreased after 15 years from eruption of the disease. No essential change in central BMDs were found in this series of RA patients between the 15- and 20-year check-ups.

References

1. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
2. SCOTT DL, PUGNER K, KAARELA K *et al.*: The links between joint damage and disability in rheumatoid arthritis. *Rheumatology* 2000; 39: 122-32.
3. JÄNTTI JK, KAARELA K, BELT EA, KAUTIAINEN HJ: Incidence of severe outcome in rheumatoid arthritis during 20 years. *J Rheumatol* 2002; 29: 688-92.
4. WELSING PMJ, VAN GESTEL AM, SWINKELS HL, KIEMENEY LALM, VAN RIEL PLCM: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
5. SOKKA T, KRISHNAN E, HÄKKINEN A, HANNONEN P: Functional disability in rheumatoid arthritis patients compared with a community population in Finland. *Arthritis Rheum* 2003; 48: 59-63.
6. DONNELLY S, SCOTT DL, EMERY P: The long-term outcome and justification for early treatment. *Baillière's Clin Rheumatol* 1992; 6: 251-61.
7. ALS OS, GOTFREDSEN A, RIIS BJ, CHRISTIANSEN C: Are disease duration and degree of functional impairment determinants of bone loss in rheumatoid arthritis ? *Ann Rheum Dis* 1985; 44: 406-11.
8. SHENSTONE BD, MAHMOUD A, WOODWARD R *et al.*: Longitudinal bone mineral density changes in early rheumatoid arthritis. *Br J Rheumatol* 1994; 33: 541-5.
9. HANSEN M, FLORESCU A, STOLTENBERG M *et al.*: Bone loss in rheumatoid arthritis. *Scand J Rheumatol* 1996; 25: 367-76.
10. COUGH AKS, LILLEY J, EYRE S, HOLDER RL, EMERY P: Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994; 344: 23-7.
11. DOLAN AL, MONIZ C, ABRAHA H, PITT P: Does active treatment of rheumatoid arthritis limit disease-associated bone loss ? *Rheumatology* 2002; 41: 1047-51.
12. KELLER C, HAFSTRÖM I, SVENSSON B: Bone mineral density in women and men with early rheumatoid arthritis. *Scand J Rheumatol* 2001; 30: 213-20.
13. ÅMAN S, HAKALA M, SILVENNOINEN J, MANELIUS J, RISTELI L, RISTELI J: Low incidence of osteoporosis in a two-year follow-up of early community-based patients with rheumatoid arthritis. *Scand J Rheumatol* 1998; 27: 188-93.
14. SHIBUYA K, HAGINO H, MORIO Y, TESHIMA R: Cross-sectional and longitudinal study of osteoporosis in patients with rheumatoid arthritis. *Clin Rheumatol* 2002; 21: 150-8.
15. KROOT E-JJA, NIEUWENHUIZEN MG, DE WAAL MALEFIJT MC, VAN RIEL PLCM, PASKER-DE JONG PCM, LAAN RFJM: Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. *Arthritis Rheum* 2001; 44: 1254-60.
16. SAMBROOK PN, EISMAN JA, YATES MG, POCOCK NA, EBERL S, CHAMPION GD: Osteoporosis in rheumatoid arthritis: safety of

low dose corticosteroids. *Ann Rheum Dis* 1986; 45: 950-3.
17. SAMBROOK PN, COHEN ML, EISMAN JA, POCOCK NA, CHAMPION GD, YEATES MG: Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. *Ann Rheum Dis* 1989; 48: 535-8.
18. CORTET B, FLIPO R-M, BLANCKAERT F, DUQUESNOY B, MARCHANDISE X, DELCAMBRE B: Evaluation of bone mineral density in patients with rheumatoid arthritis. *Rev Rhum* [Engl Ed] 1997; 64: 451-8.
19. BUCKLEY LM, LEIB ES, CARTULARO KS, VACEK PM, COOPER SM: Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. *J Rheumatol* 1995; 22: 1055-9.
20. HAUGEBERG G, ØRSTAVIK RE, UHLIG T, FALCH JA, HALSE JI, KVIEN TK: Bone loss in patients with rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 1720-8.
21. LAAN RFJM, VAN RIEL PLCM, VAN DE PUTTE LBA, VAN ERNING LJTHO, VAN'T HOF MA, LEMMENS JAM: Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. *Ann Intern Med* 1993; 119: 963-8.
22. VAN EVERDINGEN AA, SIEWERTSZ VAN REESEMA DR, JACOBS JWG, BIJLSMA JWJ. Low-dose glucocorticoids in early rheumatoid arthritis: Discordant effects on bone mineral density and fractures ? *Clin Exp Rheumatol* 2003; 21: 155-60.
23. DE NIJS RNJ, JACOBS JWG, BIJLSMA JWJ *et al.*: Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. *Rheumatology* 2001; 40: 1375-83.
24. HOOYMAN JR, MELTON LJ III, NELSON AM, O'FALLON WM, RIGGS BL: Fractures after rheumatoid arthritis. A population based study. *Arthritis Rheum* 1984; 27: 1353-61.
25. VAN STAA TP, LEUFKENS HGM, COOPER C: The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002; 13: 777-87.
26. KAARELA K: Prognostic factors and diagnostic criteria in early rheumatoid arthritis. *Scand J Rheumatol* 1985; 14 (Suppl. 57): 1-54.
27. GENANT HK: Interpretation of bone densitometry. *J Clin Rheumatol* 1997; 3 (Suppl. 2): 22-27.
28. WORLD HEALTH ORGANIZATION: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *Technical report series* 843. Geneva, WHO, 1994.
29. LARSEN A, DALE E, EEK M: Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn* 1977; 18: 482-91.
30. LARSEN A: How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in longterm studies ? *J Rheumatol* 1995; 22: 1974-5.
31. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
32. LAITINEN K, VÄLIMÄKI M, PEKKA K: Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. *Calcif Tissue Int* 1991; 48: 224-31.
33. KRÖGER H, HEIKKINEN J, LAITINEN K, KOTANIEMI A: Dual-energy X-ray absorptiometry in normal women: a cross-sectional study of 717 Finnish volunteers. *Osteoporos Int* 1992; 2: 135-40.
34. KRÖGER H, LAITINEN K: Bone mineral density measured by dual-energy X-ray absorptiometry in normal men. *Eur J Clin Invest* 1992; 22: 454-60.
35. STRAND V, SIMON LS: Low dose glucocorticoids in early rheumatoid arthritis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S186-90.
36. FORSLIND K, KELLER C, SVENSSON B, HAFSTRÖM I: Reduced bone mineral density in early rheumatoid arthritis is associated with radiological joint damage at baseline and after 2 years in women. *J Rheumatol* 2003; 30: 2590-6.
37. BERGLIN E, LORENZON R, NORDMARK L, NILSSON-SOJKA B, RANTAPÄÄ DAHLQVIST S: Predictors of radiological progression and changes in hand bone density in early rheumatoid arthritis. *Rheumatology* 2003; 42: 268-75.