EXTENDED REPORT

Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis

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Objectives: (1) To examine the change in regional bone mineral density (BMD), including the hands, and assess its role as a predictor of outcome in patients presenting with an early undifferentiated inflammatory arthritis; (2) to examine for associations with the changes in hand BMD.

Methods: 74 patients with undifferentiated hand arthritis of less than 12 months' duration were examined at baseline and then at three, six, and 12 months follow up, including BMD measurement of the femoral neck, spine (L2–4), and the whole hands using dual energy absorptiometry (DXA).

Results: During the study, 13 patients were diagnosed as having rheumatoid arthritis, 19 as having inflammatory non-rheumatoid joint disorders, and 42 as having non-inflammatory joint disorders. At the femoral neck and lumbar spine no significant bone loss was seen in any of the three subgroups. At the 12 months follow up the mean (95% confidence interval) hand BMD loss in the patients with rheumatoid arthritis was -4.27% (-1.41 to -7.13); in the inflammatory non-rheumatoid group, -0.49% (-1.33 to $+0.35$); and in the non-inflammatory joint disorder group, -0.87% (-1.51 to -0.23). In a multivariate linear regression model (including age, rheumatoid factor, mean C reactive protein, mean HAQ score, and cumulative glucocorticoid dose), only mean C reactive protein ($p < 0.001$) and rheumatoid factor ($p = 0.04$) were independently associated with change in hand BMD during follow up.

Conclusions: Hand DXA provides a very sensitive tool for measuring bone loss in early rheumatoid arthritis and may be useful in identifying patients at high risk of developing progressive disease. Further studies are needed to evaluate the role of hand bone loss as a prognostic factor and outcome measure in rheumatoid arthritis.

There is an increased awareness of the importance of early diagnosis and treatment for patients with rheumatoid arthritis.^{1–2} However diagnosing rheumatoid arthritis in the early stage of the disease can be challenging owing to the lack of acceptable classification criteria for use in early disease, and the difficulty distinguishing rheumatoid arthritis from other disorders with impaired hand function.^{3–4} In rheumatoid arthritis, periarticular bone loss is an early characteristic feature of the disease. Periarticular bone loss and erosions represent the two radiographic criteria in the revised 1997 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis.⁵ Bone densitometry using dual energy x ray absorptiometry (DXA) is known as an objective and precise method for monitoring bone loss, including that in the hands.⁶

Our primary aim in this study was to investigate the change in hand bone mineral density (BMD) in patients presenting with symptoms suggestive of an inflammatory joint disease involving the hands. Subsequently, during follow up, these patients were diagnosed as having rheumatoid arthritis, non-inflammatory joint disorders (for example, polyarthralgia or osteoarthritis), or inflammatory non-rheumatoid disorders (polyarthritis, spondyloarthropathies). Our second aim was to search for potential associations with changes in hand BMD in these patients.

METHODS

Patients

During the period from July 1996 to March 1999, 1877 patients were seen in the Leeds Early Arthritis Project (LEAP)

clinic. One hundred consecutive patients presenting with undifferentiated hand arthritis of less than 12 months' duration were recruited to an observational study including a pragmatic protocol of escalating treatment. Clinical data from this cohort have previously been published and described in detail.⁷ Patients were defined as having an undifferentiated arthritis if they did not satisfy the classification criteria for recognised arthritides but had a characteristic history, examination, or laboratory data suggesting the presence of an inflammatory hand joint disorder.⁸ Patients with definite rheumatoid arthritis or other well defined joint disorders at baseline (for example, osteoarthritis, spondyloarthropathies) were excluded. Synovitis was defined as the presence of at least two of the following three clinical criteria: joint swelling, joint tenderness, decreased range of motion. Seventy four of these 100 patients had bone density measurements and are included in this study.

None of the patients received disease modifying antirheumatic drugs (DMARDs) or prednisolone at baseline or before inclusion. Demographic, clinical, treatment, and hand, spine and hip BMD data were collected at baseline and at three, six, and 12 months follow up. Physical impairment was assessed using the health assessment questionnaire (HAQ)⁹ and disease activity by C reactive protein, swollen joint count, and tender joint count (assessed by MJG and MAQ).

Abbreviations: ACR, American College of Rheumatology; BMD, bone mineral density; CV, coefficient of variation; DXA, dual energy x ray absorptiometry; DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; RF, rheumatoid factor; SDD, smallest detectable difference

Table 1 Demographic variables, disease related, and treatment variables

Variable	n	All (n = 74)	Non-inflammatory (n = 42)	Inflammatory non-rheumatoid (n = 19)	Rheumatoid arthritis (n = 13)	p Value*
<i>Baseline variables</i>						
Age (years)	74	44.1 (12.4)	43.6 (11.5)	39.2 (9.8)	52.7 (15.1)	0.01**
Female	74	65 (87.8)	38 (90.5)	16 (84.2)	11 (84.6)	0.73
Duration of hand symptoms (months)	74	5.7 (3.7)	6.0 (4.1)	5.1 (3.0)	5.5 (3.4)	0.64
C reactive protein (mg/l)	74	4.7 (0 to 55)	4.3 (0 to 42)	1.5 (0 to 14)	10.5 (0 to 55)	0.04**
RF positive	74	12 (16.2)	1 (2.4)	1 (5.3)	10 (76.9)	<0.001§**
HAQ (0 to 3)	73	0.55 (0 to 2.4)	0.56 (0 to 2.4)	0.47 (0 to 1.2)	0.62 (0 to 1.9)	0.73
Arthritis at baseline†	74	37 (50.0)	13 (31.0)	14 (73.7)	10 (76.9)	0.001§¶
Swollen 56 joint count	74	4.8 (0 to 28)	3.7 (0 to 24)	7.1 (0 to 28)	4.9 (0 to 14)	0.14
Tender 56 joint count	73	14.3 (0 to 52)	16.3 (0 to 52)	12.7 (1 to 46)	10.2 (0 to 25)	0.24
<i>Treatment given at baseline</i>						
Number of patients given						
IM steroid injection	74	27 (36.5)	17 (40.5)	6 (31.6)	4 (30.8)	0.72
IA steroid injection in hands	74	11 (14.9)	1 (2.4)	5 (26.3)	5 (38.5)	0.002§¶
IA steroid injection in other joints	73	17 (23.3)	5 (12.2)	5 (26.3)	7 (53.8)	0.008¶
<i>Clinical variables during follow up‡</i>						
Mean C reactive protein (mg/l)	74	4.7 (0 to 102)	3.0 (0 to 19)	1.2 (0 to 5.8)	15.5 (0 to 102)	0.002**
Mean HAQ (0 to 3)	74	0.48 (0 to 2.0)	0.46 (0 to 2.0)	0.50 (0 to 1.1)	0.52 (0 to 1.45)	0.90
Mean swollen joint count (0 to 56)	74	3.5 (0 to 16)	2.5 (0 to 11)	4.4 (0.8 to 16)	5.3 (0 to 15.8)	0.02¶
Mean tender joint count (0 to 56)	73	10.6 (0 to 28)	11.0 (0 to 28)	9.7 (0.3 to 21.5)	11.0 (1 to 21.5)	0.81
<i>Treatment variables during follow up‡</i>						
Number of patients with						
Antiresorptive osteoporosis treatment	74	2 (2.7)	1 (2.4)	1 (5.3)	0	0.45
DMARD	74	23 (31.1)	2 (4.8)	10 (52.6)	11 (84.6)	<0.001§¶
Oral prednisolone use	73	4 (5.5)	1 (2.4)	2 (10.5)	1 (7.7)	0.41
IM steroid injection	74	30 (40.5)	18 (42.9)	6 (31.6)	6 (46.2)	0.64
IA steroid injection (hand joints)	74	15 (20.3)	4 (9.5)	6 (31.6)	5 (38.5)	0.03§¶
IA injection (other joints)	73	21 (28.8)	6 (14.6)	7 (36.8)	8 (61.5)	0.003¶
Mean methylprednisolone dose (mg)						
Intramuscular	30	151.7 (69.6)	128.9 (51.0)	173.3 (65.3)	198.3 (99.7)	0.07
IA (hand joints)	15	46.7 (0 to 160)	36.3 (0 to 80)	29.2 (10 to 60)	76.0 (0 to 160)	0.22
IA (other joints)	15	43.8 (26.9)	41.0 (30.1)	40.6 (31.6)	48.3 (25.6)	0.89
Total	52	125.1 (0 to 560)	102.7 (0 to 240)	124.1 (2.5 to 280)	175.0 (0 to 560)	0.09

Mean (SD) for continuous variables with normal distribution and mean (range) for continuous variables with non-normal distribution; n (%) for counts.

*p values of the overall group comparison (ANOVA for continuous variables; χ^2 test for categorical variables); in case of a significant difference in the overall comparison of groups, differences between individual groups are presented.

§Non-inflammatory v inflammatory non-rheumatoid arthritis.

¶Inflammatory v rheumatoid arthritis.

**Inflammatory non-rheumatoid v rheumatoid arthritis.

†Defined as the presence of at least two of the following clinical criteria: joint swelling, joint tenderness, decreased range of motion.

‡Values collected at baseline and at 3, 6, and 12 months of follow up.

DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; IA, intra-articular; IM, intramuscular; RF, rheumatoid factor.

Rheumatoid factor (RF) was measured as IgM RF by nephelometry (positive if the titre was ≥ 40 IU/ml). Treatment data were collected before inclusion and during follow up including osteoporosis treatment, DMARDs, and the use of corticosteroids, both oral and by intra-articular or intramuscular injection.

During follow up the clinical diagnoses were determined by experienced rheumatologists. For analyses the patients were finally divided into the three groups: non-inflammatory joint disorder (for example, polyarthralgia, osteoarthritis), inflammatory non-rheumatoid arthritis disorder (such as polyarthritis and spondylarthropathies), and rheumatoid arthritis (fulfilling the ACR 1987 revised classification criteria for rheumatoid arthritis).⁵

BMD measurements

Standardised BMD measurements at the left and right femoral neck, spine (L2–4, anterior-posterior view), and left and right hands were carried out by one technician (SS) using the same DXA equipment (Lunar Expert, Madison, Wisconsin, USA). Hand DXA included measures of all bones distal from the wrist joint. The short term in vivo precision of hip, spine, and hand BMD measurements was assessed from duplicate measurements in 48 healthy volunteers and expressed as a percentage coefficient of variation (CV%).

Short term CV% was 2.75% at femoral neck and 2.33% at spine L2–4 and 1.07% at hand. The long term spine phantom precision for the whole study period calculated from daily measurements was 0.80%. The DXA measurements were expressed as BMD (g/cm^2), and for femoral neck and hand we used the mean values from the left and the right side.

Statistical tests

Paired two tailed Student's *t* test, analysis of variance (ANOVA) test (ad hoc test, Bonferroni), and the Pearson χ^2 test were used as appropriate. Probability (p) values ≤ 0.05 were considered significant. BMD loss was assessed on both a mean group level and an individual level, applying the method of Bland and Altman,¹⁰ calculating the smallest detectable difference (SDD) for hand DXA BMD with 95% detection limit using the formula as described by Ravaud,¹¹ and by using the duplicate hand BMD measurements from the 48 healthy volunteers described above. SDD was calculated to be $0.013 \text{ g}/\text{cm}^2$ for the hand. Univariate and multiple linear regression analyses were undertaken using all the baseline and longitudinal variables listed in table 1 to predict hand bone loss at follow up. Based on the results of the corresponding univariate analysis ($p < 0.20$) and supposed clinical relevance, variables were added to the multiple linear regression model. The multiple regression analyses were

Figure 1 Hand bone mineral density (BMD) change from baseline at 3, 6, and 12 months of follow up in patients finally diagnosed as having non-inflammatory joint disorder ("arthralgia"), inflammatory non-rheumatoid arthritis disorder (No-RA), and rheumatoid arthritis (RA). (A) Mean percentage values with SEM; p values from overall analysis of variance. (B) Percentage of patients with hand BMD loss exceeding smallest detectable difference (SDD); p values from Pearson χ^2 test.

carried out as enter, backward and enter, forward procedures. Missing data were handled by last observation carried forward.

All analyses were carried out with the SPSS (Statistical Package for Social Sciences) program, version 11.0.

RESULTS

Patient characteristics

During the 12 month follow up period, 13 patients fulfilled ACR criteria for rheumatoid arthritis, 19 had a final diagnosis of inflammatory non-rheumatoid arthritis disorder (14 polyarthritis, five spondylarthropathies), and 42 were considered to have a non-inflammatory joint disorder (14 osteoarthritis, 22 polyarthralgia, six miscellaneous).

Table 1 gives baseline demographic and clinical variables, mean values of follow up clinical data, and treatment variables during follow up. A significant difference between two or all three groups was found for age, RF, C reactive protein, and arthritis at baseline, and during follow up for mean C reactive protein, mean swollen joint count, and frequency of patients having intra-articular steroid injection.

BMD

No statistically significant differences for mean (SD) baseline BMD (g/cm^2) values between the three groups (rheumatoid arthritis, inflammatory non-rheumatoid arthritis, and non-inflammatory) was found at the femoral neck (0.946 (0.166), 1.032 (0.144), and 1.030 (0.140) g/cm^2 , respectively ($p = 0.17$)); lumbar spine (1.136 (0.181), 1.215 (0.153), and 1.252 (0.168) g/cm^2 ($p = 0.09$)); and hand (0.404 (0.071), 0.438 (0.041), and 0.439 (0.052) g/cm^2 ($p = 0.11$)). At the 12 month follow up none of the three patient groups (rheumatoid arthritis, inflammatory non-rheumatoid arthritis, and non-inflammatory joint conditions) had a significant reduction (mean (95% CI)) in BMD at the femoral neck (-0.30% (-1.95 to $+1.35$), -0.42% (-1.47 to $+0.63$), and -0.50% (-1.28 to $+0.28$), respectively ($p = 0.96$)) or lumbar spine ($+0.63\%$ (-2.71 to $+3.97$), -0.57% (-2.63 to $+1.49$), and -0.31% (-1.75 to $+1.12$) ($p = 0.78$)). As shown in fig 1A, at 12 months a pronounced hand BMD loss (mean (95% CI)) of -4.27% (-1.41 to 7.13) was seen in the rheumatoid arthritis group, whereas in the inflammatory non-rheumatoid group hand BMD loss was only -0.49% (-1.33 to $+0.35$) and in the non-inflammatory joint disorder group it was -0.87% (-1.51 to -0.23). At an individual level, at the 12 month follow up 46% of the rheumatoid group, 11% of the inflammatory non-rheumatoid group, and 12% of the non-inflammatory group had loss of hand BMD exceeding the SDD (fig 1B).

Factors associated with hand BMD reduction

In univariate testing the following variables listed in table 1 were significantly ($p < 0.05$) associated with hand BMD reduction: age, RF, baseline C reactive protein, baseline HAQ, mean C reactive protein, mean HAQ, and cumulative methylprednisolone dose. The following variables had a p value < 0.20 and ≥ 0.05 : mean tender joint count during follow up, intra-articular hand joint injections. In the final multiple regression model we included age, RF, mean C reactive protein, mean HAQ, and cumulative methylprednisolone dose. Only RF and mean C reactive protein during follow up were independently associated with hand BMD loss (table 2). The same result was found when carrying out the multiple linear regression analysis both in a forward and a backward manner.

DISCUSSION

There are two main findings in our study. First, hand bone loss in patients presenting with an undifferentiated arthritis occurs rapidly in those patients diagnosed as having rheumatoid arthritis during follow up, but not in patients with other inflammatory joint disorders or with non-inflammatory hand joint disorders. Second, the presence of RF and inflammation assessed by the C reactive protein were independent predictors of hand bone loss in this group of patients.

Table 2 Multiple linear regression analysis of 12 month hand BMD (g/cm^2) loss (dependent variable), demographic, disease and variables (independent variables)

	12 Month hand BMD loss			
	β	SE	95% CI	p Value
Age (years)	-1.56^{-4}	0.000	0.000 to 0.000	0.15
Rheumatoid factor (no/yes)	-7.9^{-3}	0.004	-0.015 to 0.000	0.04
Mean C reactive protein (mg/dl)	-4.84^{-4}	0.000	-0.001 to 0.000	< 0.001
Mean HAQ (0-3)	-5.47^{-4}	0.000	-0.001 to 0.000	0.08
Cumulative methylprednisolone (mg)	1.77^{-4}	0.000	0.000 to 0.000	0.29
Constant	5.72^{-3}	0.005	-0.004 to $+0.015$	0.24
R^2				41

R^2 , percentage of total variance explained in the model.

BMD, bone mineral density; CI, confidence interval; HAQ, health assessment questionnaire.

BMD loss in patients with rheumatoid arthritis^{6 12 13} has been shown to occur early in the disease process and to be more pronounced at the hands than at the hip or the lumbar spine.^{6 14 15} BMD can be measured using different methods and at different sites. Various bone measurement tools have been used to assess hand bone mass in rheumatoid arthritis, including DXA,^{6 12 14–17} quantitative ultrasound,^{18 19} and measures of cortical thickness at the metacarpal bones.^{20–22} DXA is known to measure BMD with good precision,⁶ especially in the hand, which makes it possible to also assess BMD at an individual level.

This longitudinal study supports the view that hand BMD loss, even at the earliest stage of the disease process, is related to measures of disease activity and severity in rheumatoid arthritis. Our finding is consistent with data from previously published cross sectional^{6 14 16 17 23} and longitudinal studies in populations of patients with rheumatoid arthritis.¹²

There was no change in BMD in the hip or lumbar spine in the three subgroups. Ardicoglu *et al* also found a significant difference in hand BMD between rheumatoid patients and healthy controls but not for axial BMD measurements.¹⁴ This may partly be explained by the small number of patients included and the poorer precision of spine (CV = 2.33%) and femoral neck (CV = 2.75%) BMD measures compared with the good precision at the hand (CV = 1.07%). However, the significant hand BMD loss seen only in the rheumatoid arthritis patients in our study is most probably related to different pathophysiological disease mechanisms between the study groups and the higher rate of hand BMD loss at a comparatively early stage of the disease.

In rheumatoid arthritis it has been suggested that the osteoclast cell is the common cellular mechanism for both erosions and osteoporosis at a periarticular level, in addition to the observed generalised loss.²⁴ In a study by Gough *et al* assessing biochemical markers of bone turnover, osteoclastic activation rather than suppression of bone formation was found to be the dominant process leading to bone loss in early rheumatoid arthritis.²⁵

Harrison *et al*²³ found that periarticular hand bone loss in early disease, as assessed by DXA, occurred both in patients with rheumatoid arthritis and in those with psoriatic arthritis. However, an association between periarticular osteoporosis and measures of joint inflammation was seen only in the patients with rheumatoid arthritis. In contrast, in the inflammatory non-rheumatoid arthritis disorder group in the present study, including 14 patients with polyarthritis and five with spondylarthropathies, no significant hand BMD loss was observed.

The use of intra-articular and intramuscular corticosteroids in our study was not associated with reduced hand BMD. Iwamoto *et al*²⁶ found that functional disability and ESR, but not the dose of prednisolone, were independently associated with distal radius BMD reduction in 470 postmenopausal patients with rheumatoid arthritis. Both studies suggest that inflammation is the dominant process associated with periarticular bone loss in rheumatoid arthritis. The role of inflammation in the bone destruction of rheumatoid arthritis has also been shown in a recent magnetic resonance imaging study, assessing individual metacarpophalangeal joints in patients with early disease.²⁷ This study showed that bone damage was associated with the level of synovitis and did not occur in the absence of joint inflammation.

To assess periarticular osteoporosis in the hands we used mean global hand BMD of both hands, and not the regions around the finger joints (MCP and PIP joints). Theoretically DXA measures of bone adjacent to an inflamed joint—for example, around finger joints—would be the best measurement site to capture disease related hand bone loss in rheumatoid arthritis. In a study by Alenfeld *et al*,²⁸ BMD

measured around the finger joints was reduced by 23% in women and by 19% in men, compared with 16% in women and 12% in men when measured at the whole hand. However, in the same study it was shown that the precision for DXA measures was poorer for regions around the finger joints (range 2.7 to 3.2 CV%) compared with the whole hand (0.9 CV%). Furthermore, whole hand DXA also captures disease related bone loss in the carpal and metacarpal bones. Thus taking into account taking feasibility, the global measurement of all hand bones, and the precision of the two different DXA measurement sites, whole hand DXA seems to be the most useful.

In the light of our study showing rapid hand bone loss in rheumatoid arthritis, it is relevant that an association has been found between radiographic joint damage and hand bone mass in rheumatoid arthritis.^{14–16 18 21 22 29} In addition, erosive disease has been shown to be independently associated with measures of generalised bone loss assessed by DXA at the hip and lumbar spine in patients with rheumatoid arthritis,³⁰ further suggesting a close relation between bone loss and joint damage in this disease. Recently, Deodhar *et al*³¹ also reported that hand bone loss in the first six months in patients with early rheumatoid arthritis predicted poor hand function at a five year follow up, with an odds ratio as high as 6.9.

Our finding that hand bone loss is a sensitive early outcome marker in rheumatoid arthritis is of particular interest in the light of preliminary data reporting that hand bone loss predicts subsequent radiographic damage during follow up in the early course of the disease.³²

We conclude that hand DXA provides a sensitive tool for measuring bone destruction in early rheumatoid arthritis and may be useful for identifying patients at high risk of developing progressive disease. Further studies are needed to evaluate the role of hand bone loss as an outcome measure and predictor of prognosis in patients with rheumatoid arthritis.

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