Hand bone densitometry in rheumatoid arthritis, a five year longitudinal study: an outcome measure and a prognostic marker

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Objective: To investigate whether hand bone mineral content (BMC) measurement is an outcome measure for RA and whether the early changes in hand BMC predict functional disability.

Methods: Tender and swollen joints in hands and body, HAQ score, Larsen score on hand radiographs, serum CRP, and hand BMC measurement by DXA were studied every six months for five years in 40 patients with early RA. At the final visit, patients completed the SF-36 and Duruoz hand function questionnaires.

Results: All patients completed two years and 29 completed five years' follow up. Hand BMC worsened over the first three years (percentage loss from baseline: mean (SD) −5.5 (7.2), −7.5 (8.4), −9.8 (9.4)) and stabilised over last two years (−9.9 (8.8), −10 (7.8)). Baseline disease activity and function correlated with hand BMC loss at five years (swollen joints in hands: $r=-0.38$, $p=0.043$; swollen joints in body: $r=-0.47$, $p=0.01$; HAQ: $r=-0.52$, $p=0.004$). Percentage change in hand BMC over five years correlated with SF-36 physical function ($r=0.61$, $p<0.01$), hand function ($r=-0.64$, $p<0.01$), HAQ score ($r=-0.63$, $p<0.01$) at five years. Relative risk of bad hand functional outcome at five years was significantly higher for patients with hand BMC loss of ⩾1.17 g (smallest detectable difference) than for patients with less bone loss within the first six months (OR=6.9, 95% CI 1.3 to 34.5, $p<0.02$).

Conclusion: Early loss of hand BMC in patients with RA is a composite marker of disease activity and functional status and can predict poor functional outcome.

The increasing focus on treating rheumatoid arthritis (RA) early and aggressively has been accompanied by the recognition that this approach is best employed in patients with a high probability of rapidly progressive disease.[1][2] Its rational use requires prognostic indicators that predict the outcome in an individual patient in the early stages of the disease.

We have previously described and validated an objective and reproducible technique (coefficient of variation = 2.3%) for measuring hand bone mineral content (BMC) by dual energy x ray absorptiometry (DXA) to monitor progression of RA in the early stages.[3] A prospective 12 month study showed that hand BMC continued to worsen despite an improvement in overall disease activity.[4] The question is whether these early changes in hand bone density can predict future disability.

We carried out a five year longitudinal study of hand BMC measurements in an inception cohort of patients with early RA and explored two key questions:

- How does the "cumulative loss of hand BMC" over a five year period compare with other validated outcome measures?
- Is the loss of hand BMC within the first six months a prognostic marker of disability at five years?

PATIENTS AND METHODS

Forty consecutive patients with a diagnosis of RA based on the American Rheumatism Association criteria,[5] were enrolled in a longitudinal study of hand BMC measurement after informed consent. All patients had had symptoms of RA for <2 years. Patients with diseases of bone metabolism and female patients who might be pregnant during the study period were excluded. All 40 patients completed six-monthly assessments for two years and 29 of these completed a five year follow up.

At every visit the following clinical assessments were made: number of tender and swollen joints and visual analogue score for pain in hands and in the whole body, Ritchie articular index, Health Assessment Questionnaire (HAQ),[6] C reactive protein and x ray examination of both hands. All patients underwent measurement of hand BMC of the right hand by DXA (Hologic QDR 1000) according to the protocol described earlier.[3] A single observer (JB) performed all the scans (coefficient of variation = 2.3%). The hand x ray findings were scored by Larsen's technique[7] at the end of the study by a single observer (AAD) (intraobserver variability: correlation coefficient = 0.93, interobserver variability between AAD and DLS: correlation coefficient = 0.87). At the final visit, each patient completed a Short Form-36 (SF-36)[8] and the Duruoz hand function questionnaire.[9] The Duruoz hand index (DHI) is derived from 18 validated questions to assess functional disability and handicap due to hand involvement in RA. Each answer is scored on a scale of 0 (no difficulty) to 5 (impossible to do), with a maximum score of 90. A higher score indicates worse disability or handicap.

All decisions about treatment were left to the treating doctor.

Statistical analysis

The SPSS statistical package was used for the analysis. The smallest detectable difference for hand bone densitometry was calculated according to the method described by Ravaud *et al*[10] and by using normative data from a previous publication.[3] The value of 1.17 g was the smallest detectable difference for our measurement technique. Odds ratio, paired *t* test, and Pearson's correlation (two tailed) were used to

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Table 1 Change in clinical variables over five years (n=29)

Parameter	Baseline value (n=29)	Five year value (n=29)	p Value
Ritchie index	14.0 (10.1)	9.8 (6.4)	0.001
Number of swollen joints in both hands	5.6 (4.0)	7.8 (5.3)	0.042
Number of swollen joints in the body	6.7 (4.7)	8.6 (5.6)	0.09
Grip: right hand	36.0 (20.2)	32.3 (17.6)	0.35
Plasma viscosity	1.8 (0.2)	1.7 (0.2)	<0.001
C reactive protein	43.5 (52.9)	18.4 (24.0)	0.02
HAQ score	1.1 (0.9)	1.3 (0.8)	0.24
Larsen score	10.9 (13.5)	38.8 (22.1)	<0.001
Hand BMC	35.8 (9.5)	32.1 (8.6)	<0.001

evaluate changes and correlation in various clinical measurements over five years. Multiple regression analysis was used to assess predictors of hand bone loss over five years.

RESULTS

Forty patients completed a two year period and 29 completed the five year follow up. By the end of five years, all patients were being treated with disease modifying antirheumatic drugs (DMARDs; injectable gold 4, plaquenil 4, methotrexate 8, methotrexate plaquenil combination 1, sulfasalazine 10, D-penicillamine 2). Over the five year period, seven patients received intra-articular corticosteroid injections and seven others received short courses of oral corticosteroids. No patients were receiving oral corticosteroids for more than four weeks during the study period.

There was no significant difference between those who dropped out after two years and those who completed five years, either at baseline or on completion of two years (data not shown). Table 1 gives the results for the 29 patients who completed the five year study.

All measures of disease activity showed significant improvements in the first year. The Larsen score showed a progressive worsening over five years, while the HAQ score showed no significant change from baseline throughout the study. Despite early improvement in the markers of disease activity, hand BMC declined progressively over the first three years (percentage loss of hand BMC from baseline: mean (SD) at

one year −5.5 (7.2), at two years −7.5(8.4), at three years −9.8(9.4)). This hand bone loss stabilised over the last two years (at four years −9.9 (8.8), at five years −10 (7.8)) (fig 1).

The percentage change from baseline to five years (cumulative over five years) in hand BMC showed significant inverse correlation with the baseline markers of disease activity and function (correlation with number of swollen joints in hands: $r=-0.38$, p=0.043, number of swollen joints in body: $r=-0.47$, p=0.01, HAQ score: $r=-0.52$, p=0.004). The cumulative loss of hand BMC over five years correlated significantly with the loss of hand BMC within the first six months ($r=0.63$, p<0.0001). These results indicate that the predictors of hand BMC loss over five years are baseline disease activity, functional status, and the hand BMC loss within the first six months.

The time integrated factors influencing percentage loss in hand BMC over the full five year period were examined by multiple regression analysis. It showed that the average HAQ score and the average number of swollen joints in the whole body and the hands predicted the percentage loss in hand BMC at five years (multiple $R=0.71$, adjusted $R^2=0.45$), indicating that persistently high disease activity and poor function lead to worse hand BMC loss.

We investigated the cumulative loss of hand BMC (corrected for sex and menopausal state) and its relation to other outcome measures at five years. The percentage change in hand BMC at five years showed a significant correlation with the SF-36 physical function module score ($r=0.61$, p<0.01)
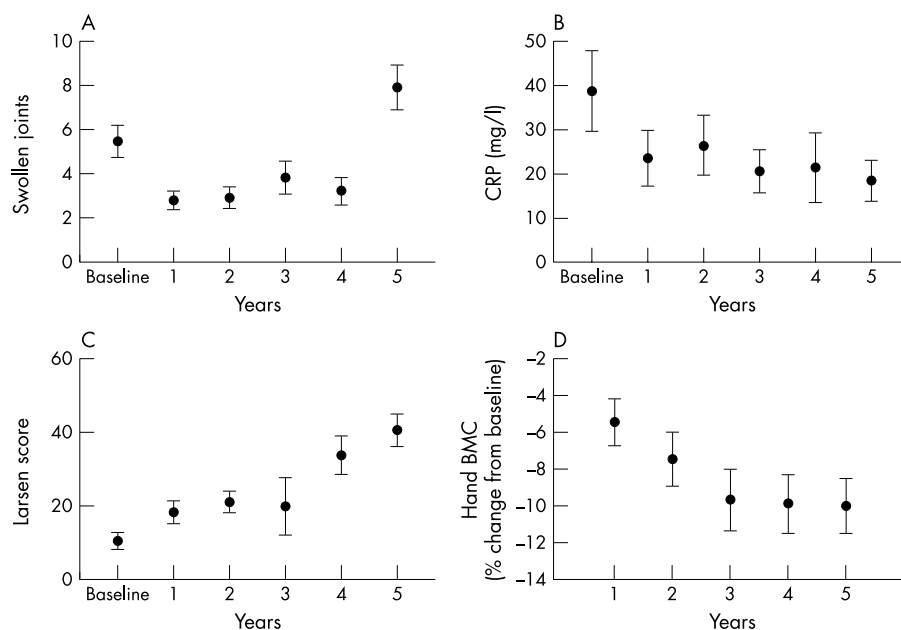
Figure 1 Changes in (A) number of swollen joints, (B) C reactive protein (CRP), (C) Larsen score, and (D) percentage loss of hand BMC from baseline over five years. Mean (SE).
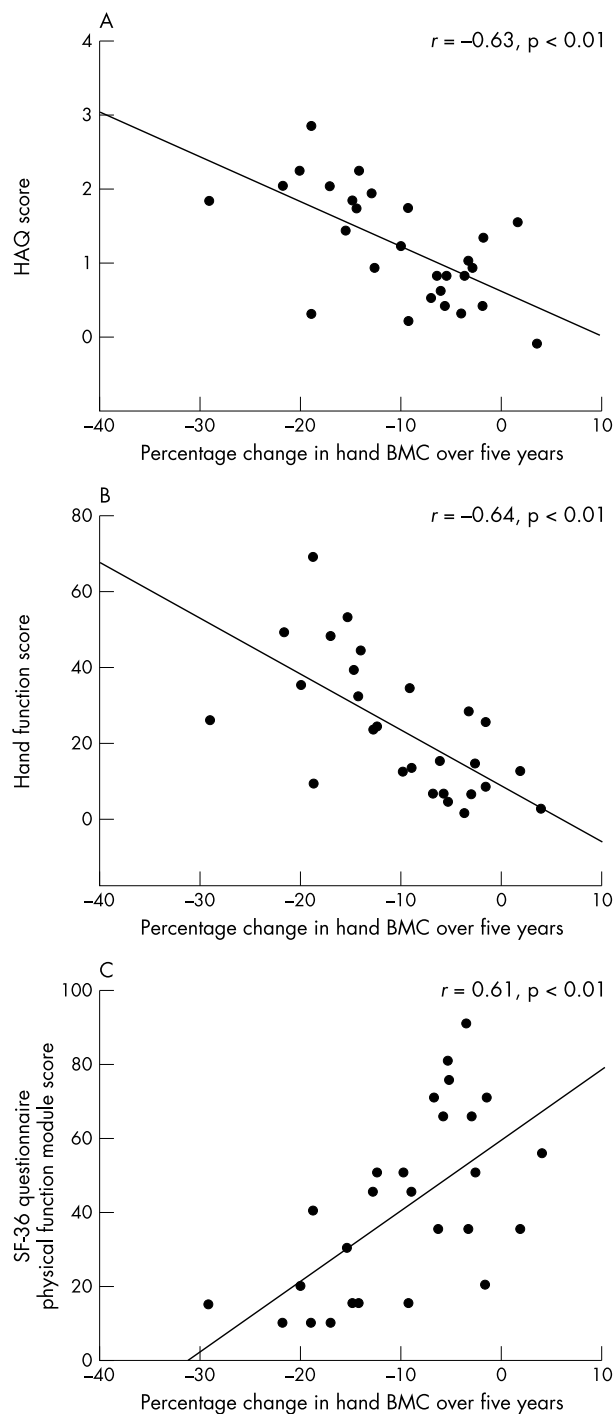
Figure 2 Correlation between cumulative loss of hand BMC over five years and other measures of outcome.

and a significantly negative correlation with the DHI ($r=-0.64$, p<0.01), and HAQ score ($r=-0.63$, p<0.01), indicating that patients who lose more bone mass also have worse function (fig 2). There was no significant correlation between the loss of hand BMC and the Larsen score at five years.

To investigate whether the early hand bone loss predicts future disability, patients were divided into two groups based on the smallest detectable difference (1.17 g) of bone loss at six months ("high" bone loss group = hand BMC loss of ≥1.17 g, n=15, "low" bone loss group = hand BMC loss of <1.17 g, n=14). Those with high bone loss within the first six

months had a significantly increased bad hand functional outcome at five years when compared with those with low bone loss (DHI odds ratio 6.9, 95% confidence interval 1.3 to 34.5, p<0.02). There was no statistically significant difference in the final HAQ score, Larsen score, or the SF-36 physical function between the "high" and the "low" bone loss group.

DISCUSSION
As far as we know this is the first study that investigates hand bone densitometry as an outcome measure and a prognostic marker for RA. We have shown that the loss of hand BMC over five years was related to the baseline and cumulative disease activity and the functional status. Control of the disease activity was associated with the rate of loss of hand BMC, though there was a lag period of three years.

The total loss of hand BMC over five years correlated well with other validated functional outcome measures such as HAQ, SF-36, and the DHI. However, over the five year period, there was no significant change in HAQ score. The value of HAQ scores as an outcome measure has been questioned recently and it is thought that the HAQ score may be a marker of process rather than outcome.[11] The Larsen score progressively worsened over five years despite treatment with DMARDs. The Larsen score is rarely used in routine clinical practice as it continues to have problems of precision, sensitivity, and reproducibility and requires interested and trained observers.[12] Despite these problems, radiological changes in the hands and feet are considered to be the "gold standard" outcome measure in RA. Hand BMC measurement is not a substitute for radiological measurements but it might be complementary because of its better precision and sensitivity in the early pre-erosive stage of the disease. Hand BMC measurement is also a "user-friendly" procedure that can be ordered on existing bone densitometry machines in most practices. After the first three years, the Larsen score is a better tool for monitoring outcome.

In our study both the Larsen score and hand BMC loss over five years correlated significantly with the final HAQ score ($r=0.51$, and $r=-0.63$, p<0.01) but did not correlate with each other. This may indicate that these two measures explain two different aspects of the overall functional outcome. The Larsen score is a composite measure of joint space narrowing and number of erosions; and an increase in the Larsen score depicts worsening hand deformities. Progressive loss of hand BMC precedes and continues after the development of erosions and deformities, and depends on disease activity, use of corticosteroids, menopausal state, and deteriorating function.

Our data suggest that serial measurements of hand bone densitometry could be used as a prognostic marker. Patients who lost more than 1.17 g of hand BMC within the first six months had a significantly worse DHI at five years than those who lost less. However, the HAQ score, Larsen score, and SF-36 were not different at five years in the low bone loss and high bone loss group, indicating that these outcome measures may not be sensitive enough to reflect the impact of the early hand bone changes of RA.

There are many limitations to our study. It was designed to be an observational study, had a small number of patients, and a large dropout rate. Very few patients received "combination therapy" or the newer biological agents. We feel that our data justify a study with a larger number of patients treated more aggressively to clarify the effect of combination therapy or new biological agents on hand bone loss in RA.

Hand bone densitometry is an objective and reproducible investigation obtained on equipment that is readily available in most rheumatology practices. Our work shows that this technique possesses qualities that could make it a marker of both "prognosis" and "outcome".

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REFERENCES

1 **Verhoeven AC**, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systemic review. Br J Rheumatol 1998;37:612–19.
2 **Young A**, van der Heijde DMFM. Can we predict aggressive disease? Baillieres Clin Rheumatol 1997;11:27–48.
3 **Deodhar AA**, Brabyn J, Jones PW, Davis MJ, Woolf AD. Measurement of hand bone mineral content (BMC) by dual energy x-ray absorptiometry (DXA) development of the method, and its application in normal volunteers and in patients with rheumatoid arthritis. Ann Rheum Dis 1994;53:685–90.
4 **Deodhar AA**, Brabyn J, Jones PW, Davis MJ, Woolf AD. Longitudinal study of hand bone densitometry in rheumatoid arthritis. Arthritis Rheum 1995;38:1204–10.
5 **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
6 **Fries JF**, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
7 **Larsen A**, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radio Diagn (Stockh) 1977;18:481–91.
8 **Ware JE Jr**. Standards for validating health measures: definition and content. J Chronic Dis 1987;40:473–80.
9 **Duruoz MT**, Poiraudeau S, Fermanian J, Menkes CJ, Amor B, Dougados M, et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. J Rheumatol 1996;23:1167–72.
10 **Ravaud P**, Reny JL, Giraudeau B, Porcher R, Dougados M, Roux C. Individual smallest detectable difference in bone mineral density measurements. J Bone Miner Res 1999;14:1449–56.
11 **Wolfe F**. The long term outcome of RA: limitations of the HAQ model of disability [abstract]. Arthritis Rheum 1999;42(suppl):S75.
12 **Brower AC**. Use of radiographs to measure the course of rheumatoid arthritis: the gold standard versus fool's gold. Arthritis Rheum 1990;33:316–23.