Measurement of hand bone mineral content by dual energy x-ray absorptiometry: development of the method, and its application in normal volunteers and in patients with rheumatoid arthritis

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Abstract

Objectives—To develop a method of measuring hand bone mineral content (BMC) by dual energy x ray absorptiometry (DXA); to apply this method of measuring hand BMC to normal volunteers to ascertain causes of variability; and to measure hand BMC in patients with rheumatoid arthritis (RA) of varying duration and severity.

Methods—The x ray beam of the Hologic QDR 1000 dual energy x ray absorptiometer was hardened by introducing a perspex-aluminium plate and the analysis software altered to allow for the small tissue bulk of the hand compared with the torso. Ninety five volunteers (46 men age 24–81 and 49 women age 20–83) had scans of both hands. Eight volunteers were assessed repeatedly to establish reproducibility and effect of hand position. Fifty six patients (22 men, 34 women, age range 25–86 years) with RA of differing duration and severity, had hand BMC measurement by DXA.

Results—The precision of BMC measurement was 2·3% with no additional variation due to hand position. Hand dominance had no significant effect on BMC. In men, hand BMC correlated with height ($r = 0·57$, $p < 0·0001$), weight ($r = 0·58$, $p < 0·0001$), forearm span ($r = 0·5$, $p = 0·0006$) and hand volume ($r = 0·66$, $p < 0·0001$). In women hand BMC correlated with height ($r = 0·66$, $p < 0·0001$), weight ($r = 0·4$, $p = 0·003$), forearm span ($r = 0·3$, $p = 0·03$) and hand volume ($r = 0·49$, $p = 0·0008$). After correcting for all these variables, male volunteers had significantly higher hand BMC than female volunteers ($p = 0·01$) and patients with RA had lower hand BMC than normal volunteers (total hand BMC in male volunteers 90·9 gms, 95% CI 86·9–95, in male patients 81·7 gms, 95% CI 73·7–89·6, $p < 0·004$, total hand BMC in female volunteers 62·2 gms 95% CI 59·8–64·5, female patients 52·3 gms, 95% CI 48·1–56·5, $p < 0·005$). In patients with RA, the hand BMC showed an inverse correlation with age ($r = -0·44$, $p = 0·01$), disease duration ($r = -0·62$, $p = 0·0003$), Larsen's grades ($r = -0·62$, $p = 0·0002$) and modified Sharp's method score ($r = -0·69$, $p < 0·0001$) in female patients only.

Conclusions—A new, sensitive and reproducible technique of measurement of hand bone mineral content by DXA, has been developed and this method has been applied to normal volunteers and patients with RA. Hand dominance had no significant effect on hand BMC. After correcting for physical size, men have higher hand BMC than women. Hand BMC inversely correlates in women patients with disease duration and other validated methods of assessing radiological outcome in RA. Longitudinal studies are needed to establish its role in monitoring disease progression.

Rheumatoid arthritis (RA) is characterised radiologically by periarticular osteoporosis with subsequent joint space narrowing and erosions. The outcome varies from little joint damage or functional impairment to some cases that progress to severe destructive arthritis with significant disability.[1] The hand is one of the earliest sites to be affected in rheumatoid arthritis.[2] The radiological changes in the hands can reflect the severity and progression of the disease[3] and are used for staging the disease as well as for assessing the efficacy of treatment. The detection of periarticular osteoporosis as one of the earliest signs of RA is dependent on the quality of the radiograph and is subjective. Identification of erosions can be influenced by the hand position at the time of x ray.[4] An objective measurement of bone mass in hands may therefore be a better way to assess the severity and progression of RA.

Dual energy x ray absorptiometry (DXA) is an accurate and reproducible method of measuring bone mineral content (BMC) usually in the spine and hip.[5] It is non invasive and can be safely repeated as the radiation effective dose is small. We have adapted this technique to measure hand BMC and report its application in normal volunteers and in patients with rheumatoid arthritis to establish the relationship of hand BMC with disease

severity assessed clinically, functionally and radiologically.

Subjects and methods

DEVELOPMENT OF THE METHOD TO SCAN HANDS

Bone mineral content of the hand was measured by DXA using a Hologic QDR 1000 scanner and modified lumbar spine software. This machine is designed to measure optimally the BMC in the hip and spine with an accuracy of 2%. Measurement of bone mineral content by the standard Hologic lumbar spine software has been shown to be both dependent on the soft tissue thickness at the lower bone mineral content of the hand and to be non-linear for variations in bone mineral content at this lower range. To overcome the dependency on soft tissue thickness, Pye and Law[6] described a method of scanning the hand while positioned on a built up plate consisting of sheets of perspex and aluminium. They optimised the material thickness empirically, by selecting them to reduce the degree of dependence on soft tissue thickness as demonstrated when scanning an aluminium step wedge (with steps at thicknesses resembling the expected BMDs in the hand) positioned in place of the hand. We determined the optimum thickness of aluminium in our situation by adding successive layers of it to a 2 cm perspex plate until values of the Hologic parameters K, which is the function of the tissue attenuation characteristics of the beam, and d-theta, which is used to convert beam attenuation reading to BMC values, matched those obtained by scanning the Hologic spine phantom. For our scanner, a plate thickness of 7 mm aluminium plus 20 mm perspex was found to give closest match to the values of K and d-theta used in the Hologic spine analysis programme. To make the response linear, an aluminium step wedge resembling the bone thicknesses of the hand was scanned on the perspex-aluminium plate and the Hologic linearity coefficients Q1, Q2 and Q3 were altered so that direct proportionality was achieved at the lower BMC of the hand. For our scanner the values are Q1 = 0·203 and 0·226, Q2 = 0·405 and 0·427, Q3 = 0·608 and 0·616. The aluminium wedge was used to provide samples of bone equivalent whose relative thickness were known precisely. A cross calibration at one aluminium thickness was carried out to convert aluminium thickness into an approximately equivalent calcium hydroxyapatite BMD (Pye and Law, personal communication). The threshold which differentiates bone from soft tissue while analysing, was altered to threshold 10, 10, 10 to get the best possible definition of the bone outline without loosing the small bones in the terminal phalanges after testing several values on a number of hand scans. These parameters were included in the analysis software and invoked automatically when scanning hands. It was only necessary for the operator to paint out the first interosseous muscle whose comparative bulk can contribute up to 5% of the apparent bone mass.

SUBJECTS: NORMAL GROUP

Forty six healthy White men and forty nine healthy White women all aged between 20 and 85 years had scans of both hands to determine the hand BMC. Written informed consent was obtained. Most of the volunteers were chosen from the staff members of the hospital and there were no major differences in the use of the hand. None of them were manual labourers. Those suffering with any disease affecting the hands, those who had used steroids any time in their life and in the case of women, those who were pregnant or were likely to be pregnant were excluded. Variables recorded for the healthy volunteers were age, weight, height, forearm span (length of forearm from the ulnar styloid to the olecrenon process measured by a specially made measuring bench on which the forearm was positioned), hand volume (measured as water displaced by hand distal to the ulnar styloid process, the reproducibility of this method was CV = 1·8%), hand dominance and the position of the hand while scanning. The reproducibility of the method was determined by scanning eight hands, each three times. The coefficient of variation (CV) was calculated in the standard fashion ([SD/mean]*100). Five volunteers had their hands scanned in two different attitudes, flat on the plate and with slightly flexed fingers simulating a rheumatoid hand, to see the effect of position on the measurement of hand BMC (figures 1 and 2). The inter-observer variability of the hand BMC analysis was assessed by two observers (AAD and JB) analysing three hand scans each five times.

SUBJECTS: PATIENTS

Fifty six patients (22 men and 34 women) with rheumatoid arthritis of differing severity and duration had both hands scanned to determine BMC. These patients were chosen at random from the outpatient and inpatient departments of the Duke of Cornwall Rheumatology Unit, Truro. Table 1 describes the physical characteristics of this group compared with that of the sex matched volunteers. Hand volume and forearm span could not be measured reproducibly in patients due to limited upper limb movement and deformity. The clinical activity was assessed by the Ritchie Index[7] and a swollen joint score (number of joints with tenderness and synovitis), the functional status by Health Assessment Questionnaire (HAQ) expressed as functional disability index[8] and radiological severity was determined on hand x rays by Larsen's grades[9] and Modified Sharp's method.[10] All patients had BMC mesurement of both hands (figure 3).

For comparisons within the group, paried *t* test and Wilcoxon matched pair signed ranks test were used depending on the distribution of the variables. Intergroup comparisons were performed by Mann-Whitney U test or unpaired T-test according to distribution of variables. Spearman's correlations were calculated. Partial correlations were calculated to allow for the effects of covariates such as age, height and weight. Differences between groups
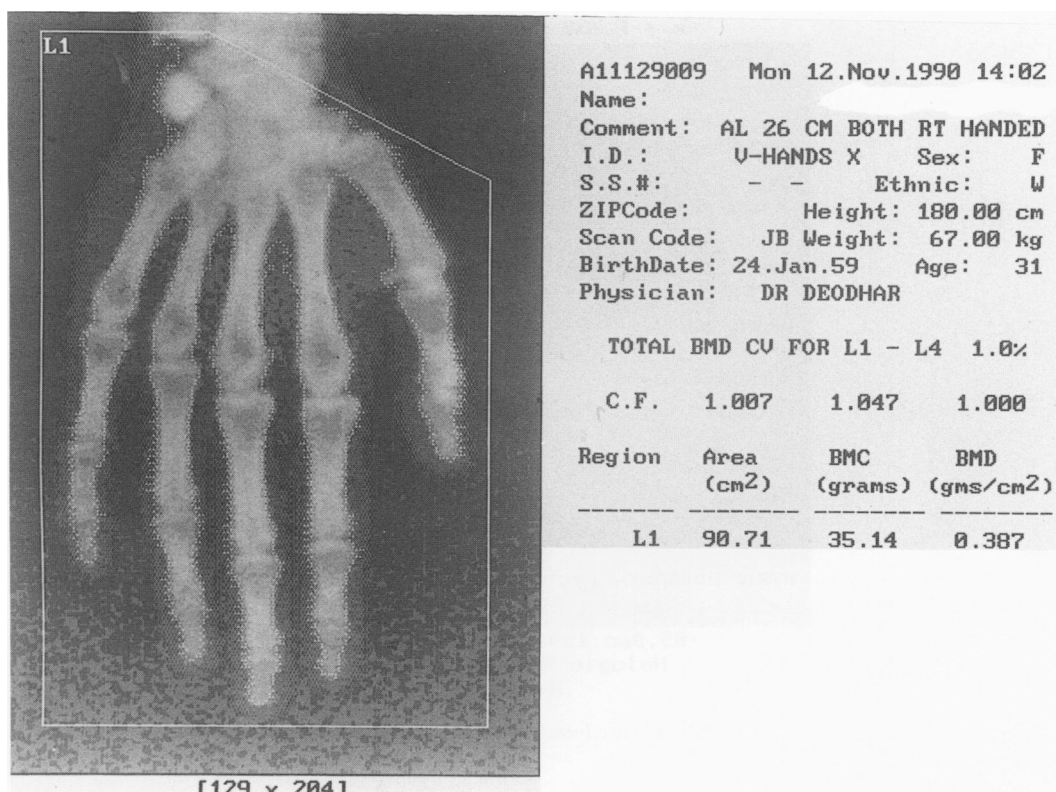
```
A11129009   Mon 12.Nov.1990 14:02
Name:
Comment:  AL 26 CM BOTH RT HANDED
I.D.:     V-HANDS X   Sex:    F
S.S.#:      - -       Ethnic:  W
ZIPCode:        Height: 180.00 cm
Scan Code:  JB Weight:  67.00 kg
BirthDate: 24.Jan.59   Age:   31
Physician:   DR DEODHAR

  TOTAL BMD CV FOR L1 - L4  1.0%

  C.F.    1.007     1.047    1.000

Region   Area      BMC       BMD
         (cm2)    (grams)  (gms/cm2)
------   -------  -------  --------
  L1    90.71     35.14     0.387
```

Figure 1   Hand bone mineral content in a normal volunteer. Hand position: flat.


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k = 1.231  d0 = 125.9(1.000H)
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```
A11199003   Mon 19.Nov.1990 10:45
Name:
Comment:  AL 27CM BOTH RT HANDED
I.D.:     V-HANDS X   Sex:    F
S.S.#:      - -       Ethnic:  W
ZIPCode:        Height:       cm
Scan Code:  JB Weight:        kg
BirthDate: 24.Jan.59   Age:   31
Physician:   DR DEODHAR

  TOTAL BMD CV FOR L1 - L4  1.0%

  C.F.    1.007     1.047    1.000

Region   Area      BMC       BMD
         (cm2)    (grams)  (gms/cm2)
------   -------  -------  --------
  L1    84.21     35.88     0.426
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[118 x 167]
Hologic QDR 1000 (S/N 241)
```
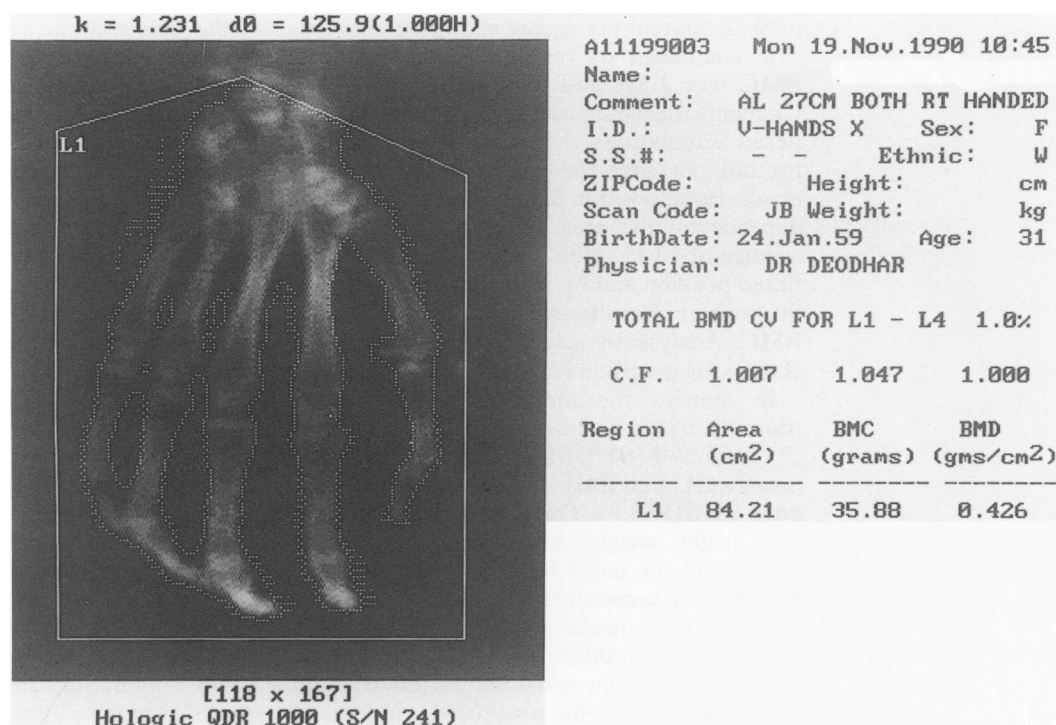
Figure 2   The same hand in fig 1 is scanned in a semi-flexed position, simulating rheumatoid deformity.

Table 1   Physical characteristics of normal volunteers and patients with RA. IQR = Inter quartile range

	Volunteers		Patients	
	Male	female	Male	Female
n =	46	49	22	34
Median (IQR)				
Age	33 (32)	41 (28)	64 (15)	64 (18)
Age Range	24–81	20–83	29–83	25–86
Height	175·7 (8·5)	160 (6·5)	172·25 (7·5)	158 (7)
Weight	74·05 (10·2)	62·4 (11·9)	75·8 (12)	63·7 (16·2)
Body Mass Index	23·93 (3·18)	23·55 (4·63)	25·01 (2·74)	24·85 (5·28)

were corrected for other covariates by using multiple regression. These analyses were carried out using the NCSS statistical package.

Results

NORMAL GROUP

The DXA bone densitometer measures total bone area and total bone mineral content
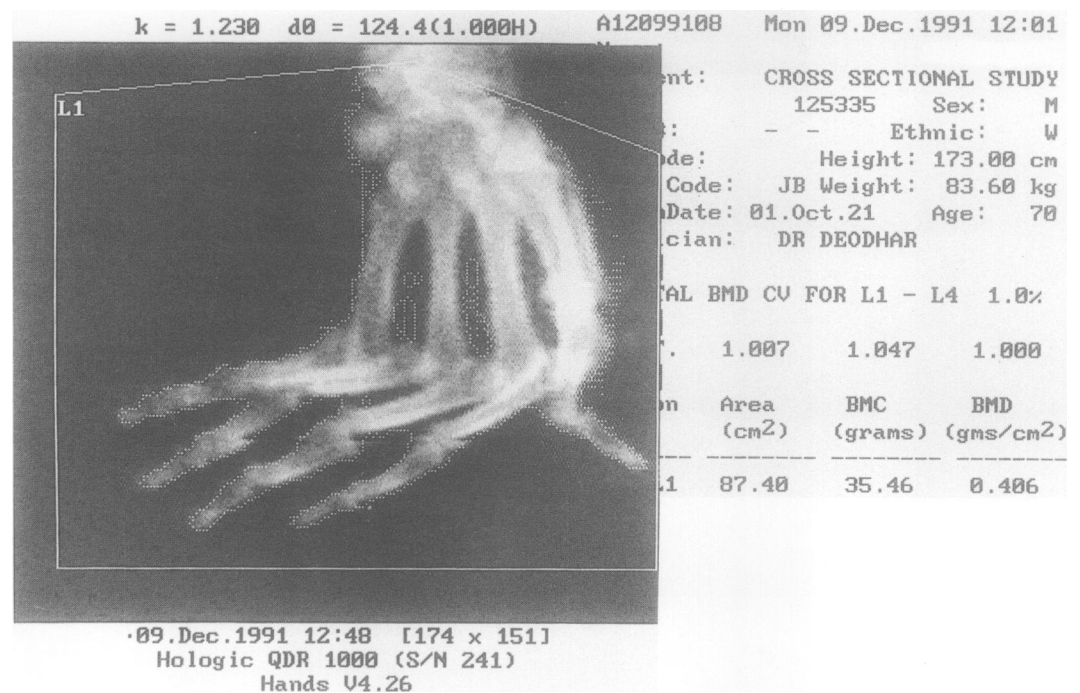
Figure 3   Hand bone mineral content in a patient with rheumatoid arthritis.

(BMC) in the hand. It calculates the bone mineral density (BMD), which is the bone mineral content per square centimetre of area. The coefficient of variation (CV) for hand BMC was 2·3% and for hand BMD 1·3%. Changing the hand position from flat to slightly flexed (simulating a rheumatoid hand) or tight fist did not alter the precision of the BMC result. Hand position did alter the BMD which depends on the area. This increased by an average of 13·1% (figs 1 and 2) in the slightly flexed position and by 30·8% average in a tight fist position. Results are therefore expressed as BMC. Analysis by a second observer did not change the precision of BMC or BMD result.

In females the mean total hand BMC (dominant plus non-dominant) was 62·2 gms (95% CI 59·8–64·5, SD 8·3) and in males the mean total hand BMC was 90·9 gms (95% CI 86·9–95, SD 13·7). The effect of the covariates age, height, weight, forearm span and hand volume on the hand BMC was examined by Spearman's correlation. In males, the total hand BMC correlated with forearm span (r = 0·5, p = 0·0006), height (r = 0·57, p < 0·0001), weight (r = 0·58, p < 0·0001) and hand volume (r = 0·66, p < 0·0001). In females the total hand BMC correlated with forearm span (r = 0·3, p = 0·03), weight (r = 0·4, p = 0·003), hand volume (r = 0·49, p = 0·0008) and height (r = 0·66, p < 0·0001). No signifi-

cant correlation was found in either sex between hand BMC and age.

The hand volume was significantly greater in domiant than non-dominant hands of both males (p = 0·0001) and females (p = 0·005) assessed by Wilcoxon matched pairs signed ranks test. In spite of this difference in the hand volumes, there was no statistical difference between the BMC of the dominant and non-dominant hands in male and female volunteers as shown by paired *t* test.

After correcting for height, weight, volume and forearm span, male volunteers had significantly more bone mass than female volunteers (p = 0·01).

Patients with rheumatoid arthritis

Demographic and disease characteristics of the patients with rheumatoid arthritis are described in tables 1 and 2. Four out of 34 women were premenopausal. Thirteen (23%) patients had taken oral corticosteroids at some stage.

In patients with RA, the mean total hand BMC in male patients was 81·7 grams (95% CI 73·7–89·6, SD 17·8) and in female patients was 52·3 grams (95% CI 48·1–52·5, SD 12). There was no statistical difference between the dominant and non-dominant hand BMC in male and female patients with RA by the paired *t* test. The hand BMC inversely correlated with age in female (r = –0·44, p = 0·01) but not in male patients.

The Mann-Whitney test was used to compare age, height and weight in volunteers and patients since these were not matched for these covariates. Age was significantly higher in patients when compared with volunteers (males p = 0·0001, females p < 0·0001), height was lower in male patients than male volunteers (p = 0·01) but weight was not

Table 2   Patients with rheumatoid arthritis

Disease characteristics	Median (range)
Duration	9 years (0·75–40)
Early morning stiffness	30 minutes (0–300)
Ritchie Index	10 (0–51)
Active joint count	2·5 (0–13)
HAQ score	1·5 (0–3)
Larsen's score	30 (1–137)
Modified sharp's method score	97 (4–309)

significantly different in either sexes in these two groups. The total hand BMC (dominant and non-dominant) in patients was therefore corrected for height and age in male patients and for age in female patients by using multiple regression with group and the covariates as independent variables. Male patients (corrected for age and height) had lower hand BMC than male volunteers (p = 0·005) and female patients (corrected for age) had significantly lower hand BMC than female volunteers (p < 0·005).

Six female and 7 male patients had used oral corticosteroids at some stage of their disease but there were no statistically significant differences in hand BMC between steroid users and non users of either sex using Mann-Whitney test.

To allow for the confounding effect of other variables, partial correlations (Spearmans) of patients total hand BMC were used eliminating the effect of age, height and weight. The hand BMC showed inverse correlation with disease duration (r = −0·62, p = 0·0003), Larsen score (r = −0·62, p = 0·0002) and Sharp's score (r = −0·69, p < 0·0001) in females. In male patients the hand BMC also showed an inverse but much weaker and not significant correlation with disease duration (r = −0·23, p = ns), Larsen score (r = −0·24, p = ns) and Sharp's score (r = −0·31, p = ns). Ritchie index, swollen joint score, EMS or HAQ did not show any significant correlation with the hand BMC.

A comparison of hand BMC values in normal volunteers and patients with RA is shown in fig 4.

Discussion

We have developed a reproducible method of measuring hand bone mineral content using dual energy x ray absorptiometry, by modifying the existing technique of measuring BMC in the spine. By hardening the x ray beam with the perspex aluminium plate and establishing linearity, the method gave a measurement of hand BMC with a coefficient of variation of 2·3% with no additional inter-observer variation.

As RA progresses, the consequent deformity results in a change in hand position but the precision of measuring total hand BMC was unchanged in any hand position. In contrast, BMD measurement depends on the area of the hand which, if altered by changing the position of the hand, shows a wide variation in the results. Bone mineral content rather than bone mineral density should therefore be used for further longitudinal studies of the hand.

This method takes 10 minutes to scan one hand and a further three to four minutes to analyse it. All volunteers and most of the patients found the position of scanning quite comfortable. Patients with rheumatoid involvement of the shoulder with poor abduction found most difficulty positioning the hand on the machine but by adjusting the height of the chair they were able to find a satisfactory position for the duration of the scan.

Hand BMC correlated in both sexes with indices of body size like forearm span, height, weight and hand volume. In volunteers it did not correlate with age in contrast to the BMC in spine or hip, which is known to reduce after menopause in females. This apparent difference in age related changes to other parts of the skeleton could be explained by the 're-generative changes' of osteoarthritis. Some of the classic changes of osteoarthritis include sclerosis of bone margins and development of new bone such as the Heberden's and Bouchard's nodes in the hands. In DEXA measurements of the spine, the osteophyte formations coupled with the sclerotic changes are known to give higher results of BMC.[11] None of our volunteers had clinical evidence of osteoarthritis but asymptomatic osteoarthritis in the hands is quite common with advancing age. We did not, however, perform plain hand x rays of our volunteers.

Exercise is known to stimulate bone growth[12] but our study found no difference between the BMC of the dominant and non-dominant hand in the volunteers. There were not however manual workers but principally hospital staff.

After correcting for physical size, patients with RA had significantly lower hand BMC than normal volunteers. There are several possibilities why patients with RA had significantly lower hand BMC. Certain cytokines like Interleukin 1, Interleukin 6 and tumour necrosis factor which are potent stimulators of bone resorption, have been implicated in the juxta-articular as well as generalised bone loss in rheumatoid arthritis.[13] Treatment with corticosteroids and reduced mobility have also been suggested as possible important factors[14 15] but in this study we could not find any appreciable effect of steroid use although the numbers were small. The subject of generalised osteoporosis in inflammatory arthritis has been extensively studied though most of the studies have

Normal volunteers v patients with rheumatoid arthritis

Legend:
- • Male vol.
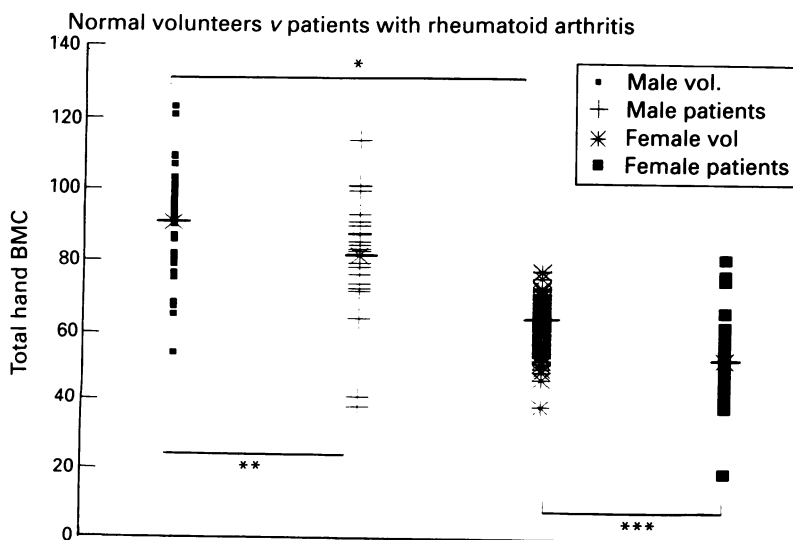- + Male patients
- * Female vol
- ■ Female patients

Figure 4 Total hand BMC in grams in normal volunteers and patients with RA (Vol = Volunteers). After correcting for body size, male volunteers had significantly higher BMC than female volunteers and patients had significantly lower hand BMC than sex matched volunteers. p = 0·01*, p = 0·005**, p < 0·005***.

measured bone density at the lumber spine and femoral neck to examine the effect of inflammation at these distant sites.[13] [14] [16] [17] As the hip is not always, and lumbar vertebrae are very rarely, involved directly by the disease process in RA, the changes in BMC at these sites largely indicate the generalised changes in bone metabolism caused by an inflammatory disorder. Our method, however, is not aimed at only assessing these more generalised changes but in addition assessing what is happening at a site of widespread disease involvement and of functional impairment. The hand with its multiple joints and periarticular bone involvement in RA combined with the functional effects of disease on its usage may act as a site for composite assessment of overall disease progression by measurement of the bone mineral content.

Radiological changes in the hands have been used for many years to assess the outcome of RA but significant problems exist in quantifying them.[4] The global scoring method of Larsen,[9] where a single score is given for all the radiological abnormalities in the joint under consideration, and the detailed scoring method of Sharp,[10] where a separate score is given to each radiological abnormality in the joint concerned, have the problem of poor sensitivity to monitor change. Change of hand position can alter the assessment of joint space and erosions by plain radiographs.[4] These methods can therefore be either imprecise and coarse or too cumbersome and time consuming. They require interested and trained observers. In contrast, measurement of hand BMC is quantitative, reproducible even on changing hand position and automated to avoid the observer error.

In patients with RA, hand BMC correlated variably with parameters of disease severity but not with parameters of disease activity. Hand BMC did not show significant correlation with the Ritchie Index, swollen joint count or duration of early morning stiffness, loose indicators of ongoing inflammatory disease process. Correlation was, however, better with disease duration and with the radiological scores. It is not surprising to find the poor correlation between the measures of disease activity with a single measurement of hand BMC as logically one would expect this to be an outcome measure and the better correlation with the disease duration and radiological measures of disease outcome might be expected.

Hand BMC measurement with DXA is a reproducible method, free of observer bias that has the potential to be performed on standard equipment available in many hospitals. It provides quantitative data for assessing and monitoring RA. The future of this method lies in longitudinal studies to see whether the early loss of hand bone mass in patients with RA can predict erosions and subsequent disability and whether early pharmacological interventions can prevent this bone loss.

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