CLINICAL ASSOCIATIONS OF DUAL-ENERGY X-RAY ABSORPTIOMETRY MEASUREMENT OF HAND BONE MASS IN RHEUMATOID ARTHRITIS

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SUMMARY

Hand bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) has potential as a marker of progression in early rheumatoid arthritis (RA). We examined a DXA methodology and studied in a cross-sectional manner 202 patients with RA. Hand BMD correlated inversely with age and was higher in males. Hand BMD correlated with lumbar and femoral sites. In females, BMD of the hand correlated positively with grip strength and negatively with disability. Those with higher C-reactive protein (CRP) had significantly lower hand BMD than those with normal CRP. In patients with a normal CRP, the hand BMD:lumbar BMD ratios were significantly higher in patients with longer disease duration. Hand BMD correlates with measures of disease activity, functional capacity and also with lumbar and femoral BMD. Hand bone loss occurs in early disease, in the absence of detectable systemic disease, and before lumbar BMD loss. It has the potential to be an outcome measure in early disease.

KEY WORDS: Bone density, Rheumatoid arthritis, Hand, DXA.

CONVENTIONAL X-ray examination of the hands and feet is well established as an outcome measure in rheumatoid arthritis (RA) [1, 2]. It is readily available and has been correlated with measures of both disease activity [3, 4] and function [5, 6]. X-ray changes are, however, historical rather than predictive, and there is significant observer variation in quantifying erosive change [7]. Periarticular osteoporosis occurs earlier than erosions, but cannot be quantified accurately using plain radiographs. Dual-energy X-ray absorptiometry (DXA) is an established technique for measuring axial and appendicular BMD, and we have shown previously that lumbar bone density falls in early RA, and correlates with disease activity [8].

The onset of RA is insidious and long-term functional outcome poor [9, 10]. In early disease, suppressive therapy offers the possibility of preventing loss of function. However, conventional markers of disease activity, such as the C-reactive protein (CRP), are frequently normal in early disease, and even if abnormal display wide inter-individual variation [3]. Similarly, disease severity markers such as radiological erosions are absent in more than half of patients with early disease [11]. Thus, they cannot be used to monitor the response to potentially toxic second-line antirheumatic drugs. There is, therefore, a need for a new outcome measure. Such a measure should be simple, cheap, repeatable and alert the clinician to the need for a change or increase in therapy prior to irreversible functional deterioration.

Recently, the use of bone mineral density (BMD) measurement of the hand has been described in patients with chronic RA [12, 13]. The hand is the principal site (in some patients the only site) of inflammation, and is of prime functional importance. Measurement of hand BMD offers quantification of the cumulative effects of local and systemic inflammation, and local immobility. The technique could be of use in the assessment of patients with early RA, in whom conventional measures of disease are unhelpful until disease is (irreversibly) more advanced. We have used a DXA methodology for the measurement of hand BMD using a Lunar DPXL bone densitometer with an analysis package originally developed for the measurement of bone mass of small animals. We have examined the relationship of hand BMD to conventional measurements of disease activity and outcome, and have correlated hand BMD to measures of the axial and appendicular skeleton. We have examined the extent to which loss of axial bone and hand bone occur in disease of differing durations and activity by calculating a ratio of hand BMD/axial BMD.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>N</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>Seropositive</td>
<td>49 (80%)</td>
</tr>
<tr>
<td>Age (yr): median, range</td>
<td>59</td>
</tr>
<tr>
<td>29-82</td>
<td>17-83</td>
</tr>
<tr>
<td>Disease duration (weeks): median, range</td>
<td>85</td>
</tr>
<tr>
<td>6-323</td>
<td>11-300</td>
</tr>
<tr>
<td>Systemic steroid use</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>DMARD use</td>
<td>53 (87%)</td>
</tr>
</tbody>
</table>

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PATIENTS AND METHODS

Consecutive patients with differing disease durations and fulfilling the 1987 ACR criteria for the diagnosis of RA [14] were recruited from the early synovitis clinic, Selly Oak Hospital. The duration of disease ranged from 3 to 60 months. The characteristics of the patients and the therapies used are summarized in Table I.

Patients were referrals from primary care physicians and were treated according to clinical indications. Clinical assessments were made at the first visit, 3 and 6 months, and thereafter annually. A detailed history and examination included height, weight and occupation. The date of onset of disease was recorded and the patients completed a modified Stanford Health Assessment Questionnaire (HAQ) [15]. This questionnaire has been validated for use in RA and reflects the individual's functional ability with particular emphasis on hand function. It is a self-administered questionnaire and questions are directed at patients' functional ability in eight areas of daily activity, such as dressing, hygiene, grip and mobility. Zero indicates no disability and 24 the maximally disabled score (this figure is conventionally divided by eight to yield a maximum score of three). Grip strength was measured using an inflatable grip meter. The highest of three readings was recorded. IgM rheumatoid factor and biochemistry profile were performed at the first visit. CRP assay was performed at every visit using a semi-automated ELISA. Patients were grouped into those who had persistently normal CRP at all visits (CRP < 14 mg/l, 95% confidence level for upper limit) and those who had experienced either persistent or intermittent CRP elevation.

Statistical methods used for data analysis were correlation and regression analysis, analysis of variance and analysis of covariance.

DXA scans were all performed on a Lunar DPXL densitometer in the Department of Nuclear Medicine, Queen Elizabeth Hospital. Scans of the femoral neck, greater trochanter, Ward's triangle and the lumbar spine were carried out at the same visit as the hand scans. As there is currently no dedicated software for the analysis of hand BMD, software originally developed for the measurement of the bone and soft tissue composition of small animals supplied by the manufacturer (Lunar Corporation, Madison, WI, USA) was used. There are special features of this software which are essential to the successful measurement of BMD of the hand. Firstly, a lower current (150 μA) is employed which allows scanning of the hand without the additional use of bolus material, such as the alloy and perspex plates used in previous studies [12, 13]. Higher tube currents require this because of problems of pulse pile-up in the detector. Secondly, both a fine collimator (0.2 mm) and a higher number of scan pixels are chosen. The improved resolution and image quality should allow a more accurate measurement of bone.

There were two choices of scan pixel size, 'high' and 'detail', and each has two choices of speed, 'slow' and 'medium'. The 'detail' mode had pixels of 1.2 × 2.4 mm, whilst the 'high' mode had pixels that were 0.6 × 1.2 mm.

In vitro measurements

A cadaver hand was measured on five occasions in each of the four acquisition modes. The interval between successive measurements was at least 24 h, thus ensuring that the precision results represented true daily variation in the machine. Scan times varied from 6 to 40 min. Selection of smaller pixel size and of the 'slow' setting resulted in longer scan times, while either selection of larger pixel size or the 'medium' speed setting reduced scan time. Longer-term precision was assessed using an aluminium phantom containing four gradations of varying mass measured over 6 months on 30 occasions. An attempt to estimate the accuracy of bone mineral content (BMC) measurement was made by placing known amounts of calcium hydroxyapatite on the cadaver hand. This simulated higher and known increments of bone mineral content.

In vivo measurements

The subjects sat at the end of the scanning table and placed their dominant hand directly on it. The operator ensured that the hand was placed along the longitudinal centre line of the scan field and that the hands were as flat (extended) as practicable. No operator intervention was necessary during the scan acquisition.

Precision was estimated by scanning the dominant hand of four volunteers on five occasions over a 2 week period. Three of these volunteers were also scanned with the hands in differing positions, varying from flat (extended) to a loosely closed fist, to simulate the effect of deformity. The longer scan acquisition times were impracticable, and all patients were therefore scanned in the 'detail' mode at slow speed which resulted in scan times of ~10 min, depending on hand size.

Lumbar and femoral measurements

The other sites measured were the femoral neck, the greater trochanter and Ward's triangle bilaterally, and the second to fourth lumbar vertebrae. Means of the right and left measurements were calculated for each of the femoral neck, the greater trochanter and Ward's triangle. The ratio of the hand to other sites was calculated by dividing hand BMD by femoral neck, greater trochanter and lumbar BMD. This was performed in order to examine clinical and serological variables as determinants of the relative bone density at different sites measured.

RESULTS

In vitro measurements

The precision results of scanning the cadaver hand at differing acquisition settings are shown in Table II, and varied from 0.6 to 1% for BMC and from 0.2 to 0.8% for BMD, depending on resolution and speed.
TABLE II

Precision (% CV) with varying scan parameters

<table>
<thead>
<tr>
<th>Scan resolution and speed</th>
<th>Mean acquisition time (min)</th>
<th>Total BMC</th>
<th>Total area</th>
<th>Total BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>'High' resolution, slow speed</td>
<td>40</td>
<td>0.8</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>'High' resolution, medium speed</td>
<td>25</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>'Detail' resolution, slow speed</td>
<td>10</td>
<td>0.9</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>'Detail' resolution, medium speed</td>
<td>6</td>
<td>1.0</td>
<td>0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

On addition of increasing known amounts of hydroxyapatite (0-40 g) placed over the cadaver hand, a linear fit of measured BMC (MBMC) vs actual BMC (ABMC) yielded the equation: MBMC = (ABMC) x (1.1 ± 0.05) - (4.09 ± 1.99) and there was a high correlation between MBMC and ABMC (r = 0.997). The MBMC was plotted against ABMC (see Fig. 5). This shows that the technique is linear and suggests that the accuracy is high in the physiological range.

In vivo measurements

The 'detail' resolution and slow speed settings were selected for all control and patient measurements. Precision at these settings for the entire hand was 1.6% for BMC and 0.6% for BMD, with lower precision for the regions of interest within the hand than for the hand as a whole (data not shown).

Patient measurements

Hand, lumbar spine and femoral scans were performed on 202 patients with RA.

Effect of sex, weight, height and age. Mean hand BMD was significantly higher in males (0.48 vs 0.40 g/cm², P < 0.0001). There was a trend for increased hand BMD with increased height and weight in both sexes (r = 0.1-0.3), but this only reached statistical significance for hand BMD vs weight in females (r = 0.3, P < 0.001). In female patients, there was a negative correlation between age and both hand BMD (Fig. 1, r = -0.4, P < 0.001) and BMD at other sites (femoral neck r = -0.3, P < 0.001; Ward's triangle r = -0.4, P < 0.001; greater trochanter r = -0.2, P < 0.01; lumbar spine r = -0.3, P < 0.01). In male patients, similar significance was observed for hand, femoral neck and Ward's triangle, but not for greater trochanter and lumbar spine. There was a weak negative correlation between disease duration and hand BMD in both sexes (males —0.1, females —0.1), but this did not reach statistical significance. Similar results were observed for the femoral and lumbar sites. In female patients, when the ratios of hand to other sites were examined using regression analysis in relation to age, the ratio of hand BMD to Ward's triangle BMD was significantly associated with age (Fig. 2; ratio higher with older age, P = 0.01). ESR, CRP and disease duration were examined in a similar manner, but hand/axial ratios did not vary significantly with these variables.

Correlation of hand BMD with BMD at other sites. There was correlation between the hand and all other sites measured, with highly significant r values in females for the lumbar spine (Fig. 3; r = 0.67, P < 0.001), Ward's triangle (Fig. 4; r = 0.63, P < 0.001).
Correlation of hand BMD with measures of hand function. In female patients \((n = 141)\), correlation was also found between hand BMD and the measures of hand function (Table IIIa) both HAQ \((r = -0.2, P < 0.05)\) and grip strength \((r = 0.3, P < 0.01)\). Higher HAQ score indicates greater disability and correlated with lower BMD. A closer correlation was observed when a restricted HAQ score was used which only included the areas of relevance to the hand \((r = -0.3, P < 0.01)\). Analysis of male patient clinical data yielded weaker correlations and these did not reach statistical significance.

Using partial correlation analysis, the relationship of hand BMD with both HAQ and grip strength was corrected for BMD at other sites. This demonstrated a relationship between both hand BMD and BMD at other sites with HAQ. Correlation between hand BMD and HAQ was \(-0.22\), and between BMD at any other site and HAQ it was \(-0.18\).

**Correlation with disease activity.** Patients in the group with an elevation of the CRP at or before the time of measurement had significantly lower hand BMD than those with lower CRP (males \(0.45 \text{ vs } 0.5 \text{ g/cm}^2, P = 0.009\); females \(0.39 \text{ vs } 0.42 \text{ g/cm}^2, P = 0.003\); Table IIIb). Similar results were obtained when the patients were divided on the basis of the ESR, which reflects the acute-phase response indirectly. Analysis of covariance demonstrated that age was not a significant factor in the relationship between CRP and hand BMD.

**Relationship of hand to lumbar BMD in patients with normal acute-phase response: short vs long duration.** Amongst female patients with normal CRP, there was a significantly higher hand/lumbar spine ratio at disease durations <24 months compared to female patients with normal CRP with disease duration >24 months \((0.38 \text{ vs } 0.35, P = 0.029)\). Correcting these values for age using analysis of covariance resulted in a slight enhancement of the significance value \((P = 0.025)\). In patients in whom the CRP was elevated at or before the scan date, the ratio of hand to lumbar spine did not vary with disease duration.

No similar relationship was found for the ratios of hand BMD to the femoral sites measured.

**DISCUSSION**

There is a need for new markers of disease progression in the assessment of RA patients. Outcome measures which have been used in the past include the development of erosions and disability. Whilst these are useful in comparing efficacies of different therapies between study groups, they are not suitable for monitoring the progress of individual patients since they are irreversible, and the aim of therapy should be to prevent the development of these sequelae of disease. In individual patients, therefore, the monitoring of treatment has been based on the patient’s response, and on markers of inflammation such as ESR and CRP, both of which are frequently normal in early and limited disease. The use of BMD measurement by imaging is attractive since it is objective and repeatable. This study suggests that a measurable change in hand
BMD occurs in early disease when the other indices of disease activity may be normal. If confirmed by longitudinal study, this raises the possibility of this technique being of value in the monitoring of early disease activity.

The use of plain X-ray examination as an outcome measure in RA is well established, but has serious shortcomings. Even rigid scoring systems such as those of Larsen or Sharp are subject to positional error [16] and significant inter- and intra-observer variation [7]. MRI has been used to image erosions, but while it is more sensitive than plain X-ray, it is difficult to quantify consistently.

The development of secondary osteoporosis in RA is long established and has been the subject of recent comprehensive review [17, 18]. Previous attempts to quantify the loss of bone mass in patients with RA have used techniques such as plain radiographs [19], quantifiable computed tomography [20], single-photon absorptiometry [18] and, more recently, DXA. The examination of plain radiographs yields very poor precision in estimating bone mass. Quantitative CT is limited by the availability of machines and precision that is inferior to newer techniques. Single-photon absorptiometry, which gave a coefficient of variation of 1.9% in the measurement of hand BMC [21], has been superseded by the superior reproducibility of DXA.

A previous study of DXA measurement of hand BMD [12] examined a principal study population of 70 female patients with long disease duration (minimum 3 yr) all receiving oral corticosteroids. Amongst these patients with established disease, no relationship between hand BMD and function was found. A group of 20 patients with shorter disease duration (6-156 months) was examined and a weak relationship found between BMD and both grip strength and HAQ score. This relationship failed to reach statistical significance, perhaps unsurprisingly in view of the small number of patients in this subgroup. Another study using different methodology measured BMC rather than BMD in 56 patients with RA [13]. A relationship was found between hand BMC and age, disease duration and erosive scores, but this study did not address functional capacity.

The present paper represents the largest series to date of hand BMD measurement using DXA in patients with RA, and the first using the technique described above. The duration of disease in this study was shorter, and corticosteroid use limited to a small minority of the subjects. We related hand BMD to two important aspects of disease, namely disease activity and the patient's hand function. We have previously described loss of axial skeletal bone mass in RA patients significantly associated with an elevated CRP [8], and this study extends this finding to hand BMD. A previous DXA study has demonstrated a negative correlation between BMD at the neck of the femur and in the whole body with function as expressed by the HAQ [22], and these findings were consistent with the study of Sambrook et al. [23] in which BMD measurements of the lumbar spine and femoral neck using dual-photon absorptiometry were found to correlate with physical activity in patients with RA. The partial correlation analysis in the present study demonstrated a stronger association between low hand BMD and poor functional outcome than between BMD at other sites and function. In addition, the finding that the ratio of hand to lumbar spine BMD varies inversely with disease duration in patients with a normal CRP suggests that in early disease, when synovitis is often confined to the small joints and CRP is normal, hand bone loss is greater than axial. This is consistent with our previous study which associated CRP (i.e. systemic inflammation) with lumbar bone loss [8], as where local disease alone is present and CRP is normal, hand density would be expected to fall whereas spine density would not, and therefore the ratio of hand to spine BMD to decrease. Loss of hand BMD in the absence of evidence of systemic inflammation (i.e. CRP normal) at a time when local inflammation is present is consistent with previous work suggesting that bone loss in early RA is predominantly in the vicinity of affected joints [24]. It is likely that our patients with normal CRP had predominantly localized hand involvement, with insufficient disease mass to produce sufficient cytokines to stimulate hepatic CRP production, but sufficient to result in local bone loss. These findings add to evidence that active RA is a catabolic state [25], both locally and systemically.

This work describes a relationship between hand BMD, the HAQ score (both global and when biased toward hand function) and grip strength. This may suggest that local bone loss can also be associated with inactivity, but it is difficult to separate this effect from the effect of localized inflammation. The relationship may be useful in patients with early RA in whom the CRP is normal. If loss of bone mass precedes irreversible loss of function, the clinician may be alerted to ongoing disease requiring initiation of immunosuppressive therapy.

Some of these findings were not reproduced in male patients, specifically the correlation of hand BMD with hand function, and the relationship of hand BMD/lumbar spine BMD ratio to disease duration in the absence of an elevated CRP. Possible reasons for this might be a greater functional reserve in males, an effect of occupation, or a different distribution of affected joints in these patients. Sex has been shown to be a determinant of functional outcome [26], and previous investigators have demonstrated better HAQ scores in male patients with similar disease activity to a matched set of female patients [27]. In the present study, the male group is only half as large as the female, and this will reduce the power to detect real changes. The fact that height and weight also fail to correlate with hand BMD tends to support this possibility.

In the course of this study, we evaluated the precision of our protocol for the measurement of BMD. As expected, variations in BMD were observed with changes in resolution and scan speed settings (Table II). Each pixel is interpreted as either bone...
or soft tissue, depending on the total attenuation within it. Decreasing resolution (increasing pixel size) decreases precision due to an ‘edge effect’ occurring at sites where a single pixel contains bone and adjacent soft tissue which may be misinterpreted as soft tissue only. Precision depends ultimately on the number of photon counts in the generation of the scan, and is therefore superior at lower speeds. The poorer precision in in vivo measurements is not surprising because of the errors associated with hand repositioning. This problem could be greater in patients with established RA and progressive hand deformity, and thus less tight reproducibility could be anticipated than in the volunteers scanned to assess reproducibility in this study. Indirect assessments of accuracy using known increments of hydroxyapatite placed over the cadaver hand suggested a high degree of accuracy and linearity up to the addition of 15 g of the material.

DXA offers, for the first time, a reproducible measure of BMD that is quick and therefore relatively cheap to perform. It administers a radiation dose at least 50 times lower than a conventional X-ray and is well tolerated by patients with RA. It has the potential to be the preferred method of monitoring patients with early RA. It would be feasible to construct a cheap hand DXA unit, making routine serial measurements an office-based procedure. At the time of the acquisition of the scans reported in this study, a hand scan took ~10 min to perform, and complete measurement of the other sites a further 20 min. Newer densitometers can now scan the hand in <30 s, and this compares favourably both in terms of convenience and administered radiation dose with contemporary scanning of other sites, which can now be completed in ~10 min. Furthermore, the images are stored digitally, eliminating costly and cumbersome storage of films.

In summary, this study presents evidence that hand BMD measurement by DXA may be a useful routine clinical measure of disease activity and progression. Using our protocol, it was found to be accurate, repeatable and sensitive enough to detect bone loss even in early disease. In addition, it detects local disease activity where no systemic features are evident, and may be a useful predictor of disability. It is possible, therefore, that hand DXA bone densitometry may become a valuable adjunct in monitoring disease progression and therapeutic efficacy at all stages of RA, but longitudinal studies are necessary to assess the validity of this proposal.

ACKNOWLEDGEMENTS

The authors wish to thank Sister Valerie Arthur S.R.N., Selly Oak Hospital, for her invaluable contribution to the research clinic and Mr John Truscott, Senior Research Fellow, Centre for Bone and Body Composition Research, University of Leeds, and Mr Christopher Ngeh, Department of Nuclear Medicine, Queen Elizabeth Hospital, for assistance with analysis and technical advice.

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