Bone mineral density in the hand as a predictor for mortality in patients with rheumatoid arthritis

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Objectives. BMD in the hand, as evaluated by digital X-ray radiogrammetry (DXR), has been suggested to be a predictor for joint damage in RA. A predictor for long-term prognosis might also predict increased mortality in RA. The aim of the present study was to evaluate BMD in the hand as a predictor for all-cause mortality.

Methods. In 1978, 152 consecutive patients (78% women, mean disease duration: 14.2 years) were enrolled. X-rays of the hands at inclusion were available in 108 patients. Reasons for not evaluating DXR in 24 patients were placement of joint prostheses or severe malalignment. BMD was evaluated by DXR on the same digitized hand X-rays used for scoring radiographic joint damage. Measures of disease activity and damage were used to predict mortality by Cox regression models.

Results. From February 1978 through March 2008, 62 of the 82 patients died, corresponding to a standardized mortality ratio of 2.92 (95% CI 2.19, 3.65) for both sexes combined. In age- and sex-adjusted proportional hazards models, BMD [hazard ratio (HR) = 0.58/1 s.d.; 95% CI 0.37, 0.91], Steinbrocker functional class 3–4 (HR = 4.74/1 step; 95% CI 1.93, 11.64), the physician’s global assessment (HR = 1.38/1 s.d.; 95% CI 1.03, 1.84) and ESR (HR = 1.92/1 s.d.; 95% CI 1.42, 2.58) were significant predictors of mortality, but RF, disease duration, Larsen index, Ritchie articular index and the patient’s global assessment were not.

Conclusion. Low DXR-BMD predicted overall mortality in age- and sex-adjusted analyses, which further supports it as a valid measurement of disease activity or damage and as having prognostic value.

KEY WORDS: Rheumatoid arthritis, Digital X-ray radiogrammetry, Bone mineral density, Mortality, Predictor.

Introduction
RA is associated with inflammation, joint erosions and osteoporosis. Loss of BMD may lead to increased risk of fractures and this is associated with increased mortality. The golden standard to predict fractures is to measure BMD with dual energy X-ray absorptiometry (DEXA) in the hip and in the lumbar spine. In the last few years, it has become possible to measure BMD in the hand by using digital X-ray radiogrammetry (DXR).

It is well known that periarticular bone loss in the hand is a radiological manifestation of RA [1, 2]. Periarticular osteoporosis appearing before erosions is seen on X-ray [3, 4]. Early erosions predict further joint destruction [5, 6]. A pilot study has shown that DXR at 1 year can predict those patients with RA who will become erosive at 4 years [7]. Jawaid et al. [8] found that DXR correlates very well with the Sharp score and the results indicated that DXR may be useful in routine clinical care. A recent study of RA patients, using DXR and followed for 10 years, found that hand bone loss during the first year independently of presence of prevalent erosions and anti-cyclic citrullinated peptide (aCCP), predicted radiographic damage after 10 years [9].

The validity of DXR as a prognostic marker would be enhanced if it could be shown to also predict other long-term consequences of RA, such as mortality, for example. This study is designed to determine if measurement of BMD in the hand, using DXR, can predict increased mortality.

Methods
Patients
From February through March 1978, 152 consecutive outpatients who were given a diagnosis of classical or definite RA according to the 1958 ARA criteria for RA were enrolled [2]. At that time, the city of Malmö had a population of 230 000 inhabitants, and had only one outpatient clinic for secondary and tertiary rheumatological care in the only hospital in the city. The cohort consisted of 33 men (22%) and 119 women (78%), with a median age of 60 years (range 30–83). The median duration since the initial symptoms of the disease at the time of their enrolment in 1978 was 14 years (range 1–52) (Table 1). These patients were followed from 1978 until death or March 2008. During this time, two patients were lost to follow-up (due to emigration). There were missing data on one male RA patient, which leaves 149 patients to the survival analyses. This cohort has been described earlier [10].

Assessment
The evaluation at baseline in 1978 included Steinbrocker functional class, which categorizes the patient’s physical function into four classes (I–IV) [11]; radiographic evaluation of hands and feet with the Larsen index [12], which is a method for numerical grading of joint damage (0–200 arbitrary units); the physician’s and the patient’s global assessment of disease activity on a 10-point scale (0–10), where 0 depicts best possible status and 10 the worst possible status; and Ritchie articular index (RAI) [13] for joint tenderness (0–78 U) and duration of disease.

Blood samples were taken for ESR and IgM RF. ESR was analysed by standard technique. RF was analysed using the sheep cell agglutination test [14]. The patients were considered seropositive when the serum titre was ≥1/32.

Information on comorbidities, present and previous medication with DMARDs and glucocorticosteroids were obtained through a structured review of all the clinical records. Cardiovascular disease (CVD) was defined as inpatient care for acute myocardial infarction or a diagnosis of heart failure based on physical examination during 2 years before examination in 1978.

BMD
DXR. BMD in the hand was measured by DXR using the dxr-online (Sectra, Linköping, Sweden). Standard radiographs of the left hand were scanned and digitalized. The DXR analysis

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engine recognizes the diaphyses of the three middle metacarpals and measures 2.0, 1.8 and 1.6 cm, respectively, of the second, third and fourth metacarpals (Fig. 1). The average cortical thickness and bone diameter are then determined for each metacarpal and then computed into grams per square centimetres.

The DXR technology measures in a region around the waist of the metacarpal shaft and the cortical bone is well defined in this region, also when the joint and metacarpal head has suffered significant damage. Severe joint damage can, however, make it difficult to position the hand of the patient properly with the palm flat on the cassette/detector surface. For example, an elevation of 1 cm of the metacarpals would inflate the measured DXR-BMD by ~1%.

Data were missing for one patient and radiographs were missing for 44 patients. There were 108 radiographs of the hand available. Due to placement of joint prostheses and malalignment, we had to exclude 24 of these. Two patients were lost to follow-up due to emigration, leaving 82 radiographs left to be measured by DXR.

Mortality data

Recording of deaths was assessed through linkage with the continuously updated Swedish Cause of Death Register up until 31 March 2008.

Statistical analyses

Kaplan–Meier survival curves were computed and compared with expected overall mortality in Sweden, adjusting for age, gender and calendar period effects. Standardized mortality ratio (SMR) and the corresponding 95% CIs were calculated, comparing observed rates of death in the cohort with expected rates according to events in the general population of Sweden matched for age, gender and the calendar period of observation. These calculations were performed both for the whole cohort (n = 149) and for the subgroup used for the predictor analyses (n = 82).

To evaluate the predictors for mortality, we used Cox regression models, adjusted for age and gender. In multivariate analysis, we compared the predictive value of DXR, Larsen score and Steinbrocker functional class, all of which reflect cumulative damage, adjusting for age, gender and factors with low multicollinearity (r < 0.35). ESR, RAI, RF, CVD and physician’s global assessment. A P-value of ≤0.05 was considered to indicate a statistically significant difference. All statistics were calculated using the SPSS version 14.0 for Windows (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the two groups of patients. There were no significant differences between the groups for baseline characteristics.

Mortality

The observed number of deaths in the original cohort (149 patients) was 124 and the expected number in the community of Malmö during that 30-year period was 37 (Fig. 2). This resulted in an SMR of 3.39 (95% CI 2.79, 3.98). In the subgroup (82 patients) used for the analyses of predictors for death, the observed number of deaths was 62 and the expected number
was 21 (Fig. 3), resulting in an SMR of 2.92 (95% CI 2.19, 3.65). The mean age of death was 74 years in both groups.

Risk factors

To determine and compare risk factors for mortality in this cohort, we used the Cox regression models to calculate the hazard ratio (HR) for each variable in the subset in which DXR was evaluated (Table 2). We found that ESR, Steinbrocker functional class, DXR, the physician’s global assessment of disease activity and CVD were significant predictors for mortality. In contrast, the RAJ, Larsen score, patient’s global assessment, disease duration and RF were not.

Multivariate analyses were performed to elucidate whether measures of cumulative damage such as DXR, Steinbrocker functional class and Larsen articular index were predictors independent of not only age and gender, but also of measures more reflective of acute activity, such as ESR, the physician’s global assessment of disease activity, RAJ and RF. In these models, the HR for DXR per 1 S.D. increase was 0.67 (95% CI 0.42, 1.08; \( P=0.098 \)) and for Steinbrocker functional class 3–4 HR was 5.40 (95% CI 1.88, 15.58; \( P=0.002 \)) (Table 3). Steinbrocker functional class 3–4 was the only independent significant risk factor for increased mortality.

We also found that DXR was a significant predictor in separate models, adjusted for age and gender and then adjusting for ever use of DMARDs (HR = 0.58; 95% CI 0.37, 0.91; \( P=0.018 \)), ever use of corticosteroids (HR = 0.60; 95% CI 0.38, 0.96; \( P=0.033 \)) or CVD (HR = 0.59; 95% CI 0.36, 0.94; \( P=0.028 \)). In the multivariate analysis adjusting for age and gender and including ever use of DMARDs, ever use of corticosteroids, DXR (HR = 0.60; 95% CI 0.37, 0.97; \( P=0.037 \)) and CVD (HR = 2.9; 95% CI 1.3, 6.2; \( P=0.007 \)), the latter two were significant predictors for mortality.

Discussion

We found that mortality was significantly increased among these consecutively seen RA patients followed from the 1970s and that DXR, ESR, Steinbrocker functional class and physician’s global assessment were significant predictors in age- and gender-adjusted analyses. Medication (DMARDs or corticosteroids) or a history of CVD did not alter the predictive ability of DXR.

This is the first report evaluating bone loss of DXR as a predictor for mortality. Bone loss of the metacarpal bones has, however, been measured previously. Before the development of DXR as a method, different methods were used. In early studies, cortical thickness was evaluated manually by measuring the cortical thickness of the second metacarpal as suggested by Chan et al. [15]. More recently, bone loss of the hand measured with DEXA has been used [16–18]. In the metacarpal bones, DXR has been found to better capture bone loss [18], to be a better predictor [16] and have a stronger association with joint destruction [17] compared with DEXA. Furthermore, it has been demonstrated that DXR-BMD decrease parallel to joint destruction in randomized controlled trials [19]. In observational studies, hand bone loss during the first year has been shown to predict joint destruction after 2 years (Forslid K et al., Abstract 07-A-1744-ACR 2007) and after 5 and 10 years, independently of the occurrence of baseline erosions and presence of aCCP antibodies [9].

There seems to be a high correlation between DXR and DEXA in the hand, but not between DXR in the hand and DEXA in the total hip and spine in an RA population [16]. The same study also demonstrated that hand bone loss measured by DEXA was shown only in the first years of the disease, while DXR can detect bone loss in all stages of RA. In addition, the bone loss in patients with a high disease activity score (DAS28) was higher than in patients with low DAS28 [16]. This agrees with previously published results from our clinic [20].

DXR appears to be a useful predictor for long-term prognosis in RA, in that it predicts both joint destruction and, as we have demonstrated, all-cause mortality in bivariate analyses. In the multivariate analysis, DXR did not reach statistical significance as a predictor for death, in contrast to the Steinbrocker functional class. This may be influenced by the limited sample size, which increases the risk of type II statistical errors. The fact that the Steinbrocker functional class was a strong independent mortality predictor is not surprising, since it captures multiple dimensions of disease severity. Our study also illustrates that it is applicable to historical digitized radiographs, with the exception of the subgroup of patients that had joint prostheses in the MCP joints or severe malalignment. It is not possible to know how the exclusion of these subjects affected our results, but one could speculate that it might have led to an underestimation of the DXR association with mortality, since these patients are likely to have a more severe disease and thus a higher mortality risk.

Table 2. Age- and gender-adjusted Cox regression models with mortality as outcome (n = 82)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR  (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, mm/1h</td>
<td>1.92 (1.42, 2.58)</td>
<td>0.001</td>
</tr>
<tr>
<td>Steinbrocker functional class 1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Steinbrocker functional class 2</td>
<td>2.01 (1.00, 4.04)</td>
<td>0.051</td>
</tr>
<tr>
<td>Steinbrocker functional class 3–4</td>
<td>4.74 (1.93, 11.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DXR*, g/cm²</td>
<td>0.58 (0.37, 0.91)</td>
<td>0.12</td>
</tr>
<tr>
<td>Physician’s global assessment, 0–10</td>
<td>1.38 (1.03, 1.84)</td>
<td>0.032</td>
</tr>
<tr>
<td>RAJ, 0–7</td>
<td>1.27 (0.97, 1.67)</td>
<td>0.080</td>
</tr>
<tr>
<td>Larsen score, 0–200 U</td>
<td>1.27 (0.95, 1.71)</td>
<td>0.199</td>
</tr>
<tr>
<td>Patient’s global assessment, 0–10</td>
<td>1.23 (0.93, 1.63)</td>
<td>0.124</td>
</tr>
<tr>
<td>Disease duration, 1–46, years</td>
<td>1.16 (0.91, 1.48)</td>
<td>0.223</td>
</tr>
<tr>
<td>RF seropositivity</td>
<td>1.43 (0.74, 2.76)</td>
<td>0.282</td>
</tr>
<tr>
<td>DMARDs ever</td>
<td>0.81 (0.42, 1.58)</td>
<td>0.641</td>
</tr>
<tr>
<td>Corticosteroids ever</td>
<td>1.66 (0.90, 3.08)</td>
<td>0.105</td>
</tr>
<tr>
<td>CVD</td>
<td>3.23 (1.57, 6.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Per 1 S.D.

Table 3. Cox regression models with mortality as outcome for Steinbrocker functional class, DXR and Larsen articular index, adjusted for age, gender, ESR, RAJ, RF and physician’s global assessment in multivariate analysis (n = 82)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR  (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinbrocker functional class 1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Steinbrocker functional class 2</td>
<td>1.90 (0.91, 3.97)</td>
<td>0.087</td>
</tr>
<tr>
<td>Steinbrocker functional class 3–4</td>
<td>5.40 (1.88, 15.58)</td>
<td>0.002</td>
</tr>
<tr>
<td>DXR</td>
<td>0.67 (0.42, 1.08)</td>
<td>0.098</td>
</tr>
<tr>
<td>Larsen articular index</td>
<td>1.27 (0.93, 1.72)</td>
<td>0.131</td>
</tr>
</tbody>
</table>
This limitation is likely to be much less important in an early RA cohort, in which abnormalities are rare.

This report also supports several earlier reports regarding the increased mortality in RA with a long disease duration [21]. Our estimates are in the higher range of what has previously been reported [10]. Possible explanations for this may be the long duration of disease at inclusion and the long follow-up. It has previously been suggested that the increase in mortality may be more apparent after 10 years of disease duration [22]. Furthermore, almost all our cohort, being started as long as 1978, was not treated with TNF-α inhibitors and with few exceptions not treated with MTX, both of which have been suggested to decrease mortality in RA patients [23, 24].

The strengths of the present study are the long and complete follow-up, low drop-out rate and the fact that radiographs and measures of disease severity and activity were available at baseline.

Limitations that may affect the general applicability of these results are possible left censorship since it was based on a cohort of prevalent cases and possible selection bias of more severe cases as they were seen at the only specialist clinic in the city at that time, the University Hospital of Malmö. Another limitation is the limited sample size, which may increase the risk of type II errors.

In conclusion, we found that low BMD, as measured by DXR in age- and gender-adjusted analyses, predicted overall mortality, in a similar or more accurate manner than other measurements of disease damage such as radiographic damage and functional disability. This supports the concept that diaphysial local bone loss in the hand is a valid measurement of disease activity or damage and has prognostical importance.

Rheumatology key messages

- Low BMD in the hand as measured by DXR predicted overall mortality.
- Bone loss in the hand is a valid measurement of disease activity or damage.

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