Low Appendicular Bone Mass Predicts Mortality in Patients with Rheumatoid Arthritis

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Disclosures

• Mr. Algulin is employed by Sectra AB, a Swedish corporation specializing in medical image management.

Background

• Rheumatoid arthritis (RA) patients have:
  • reduced lifespan compared to the general population\(^1\)
  • Increased risk for osteoporosis and fracture risk (included in FRAX)
  • RA patients most often die of cardiovascular causes
  • There may be an association between osteoporosis and increased atherosclerosis\(^2\)

\(^1\)Gonzalez et al. A&R. 2007 Nov 56(11)
\(^2\)Ye et al. PLoS One. 2016 May 5;11(5)

Purpose

• To examine the relationship between appendicular bone mass and mortality risk measured from hand radiographs using Digital X-ray Radiogrammetry in a large cohort of RA patients.

STUDY METHODS

RA Cohort Design

• Recruitment period: January 1996 – April 2001
• Location: 6 rheumatology clinics in San Antonio, Texas
  • county-funded clinic
  • Veterans Affairs clinic
  • private faculty practice
  • private group practice
  • Army clinic
  • Air Force clinic
• Consecutive Patients: diagnosed with RA (in accordance with 1987 ACR criteria)
Mortality Status Assessment

- If unable to contact patient:
  - Family
  - Friends
  - Physicians
  - Neighbors
  - Obituaries
  - Public Health Dept.
  - Online mortality databases
  - Review of medical records

- All reported deaths were confirmed by review of death certificate.

Study Inclusion Criteria from RA Cohort

- 779 patients meeting RA criteria were recruited into the RA Cohort
- 653 patients from the cohort who had hand radiographs were included in the present study
- Must have all variables of interest (listed on previous slide) at baseline assessment
- Must have a DXR-determined bone mineral density
- Must have known mortality status (confirmed living or deceased)

Study Variables

- Patient demographics
  - Age
  - Gender
  - Ethnicity

- Cardiovascular risk factors
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Past/current smoker
  - Body mass index

- RA manifestations/treatment
  - Tender joint count
  - Swollen joint count
  - Measured serum ESR
  - Steroid usage

- RA damage measure
  - Sharp Score

- Appendicular bone mineral density (BMD) via DXR

Evaluation of Bone Mineral Density with DXR

- Digital X-ray Radiogrammetry (DXR) is an established technology used to calculate appendicular BMD using digitized hand radiographs

- Is automated, independent of human operator interventions

- DXR measures the Metacarpal Index (MCI) = ratio of total bone width to cortical thickness

\[ MCI_{dp} = \frac{2 \ T_{dp}}{W_{dp}} \]
Important comments on DXR

- Quantifies peri-articular metacarpal bone loss
- Results correlate with DEXA in assessing total skeletal loss of bone mass
- In RA patients, is more sensitive than DEXA in detecting early bone loss
- Low DXR:
  - Is strongly associated with more RA clinical disease activity
  - Is associated with radiographically significant joint destruction
  - May predict subsequent radiographic damage

Data Analysis

- Cox proportional hazards regression
  - Measure association of predictor variables on primary outcome
  - Adjust for potential confounding factors on our relationship of interest (i.e. BMD and mortality)
- Kaplan-Meier method
  - Produced curve showing survival probability over time based on their reported DXR-BMD

STUDY RESULTS

Distribution of Appendicular Bone Mass

- Mean 5.08 decigram/cm²
- Standard Deviation 1.03 decigram/cm²
- Range 2.65 – 7.75 decigram/cm²

DXR-BMD Quartiles

- 653 Patients with RA
- 85 DXR-BMD measurements
- 2.7 – 4.4
decigram/cm²
- 4.4 – 5.1
decigram/cm²
- 5.1 – 5.9
decigram/cm²
- 5.9 – 7.8
decigram/cm²

Baseline characteristics of patients in each BMD quartile.

- Mean ± SD
- *P<0.001
- †P<0.05
- §P<0.01

<table>
<thead>
<tr>
<th>Quartile</th>
<th>BMD Q1</th>
<th>BMD Q2</th>
<th>BMD Q3</th>
<th>BMD Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD years</td>
<td>64 ± 9†</td>
<td>60 ± 12†</td>
<td>54 ± 13 †</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>No. (%) Man</td>
<td>183(21)*</td>
<td>180(22)*</td>
<td>163(19)</td>
<td>163(19)</td>
</tr>
<tr>
<td>No. (%) Caucasian</td>
<td>373(23)*</td>
<td>366(22)*</td>
<td>163(19)</td>
<td>163(19)</td>
</tr>
<tr>
<td>CV Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>35(21)*</td>
<td>26(16)*</td>
<td>18(11)</td>
<td>13(8)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>89(54)§</td>
<td>93(57)†</td>
<td>71(44)</td>
<td>63(39)</td>
</tr>
<tr>
<td>Hypercholesteremia, no. (%)</td>
<td>14(9)</td>
<td>13(8)</td>
<td>9(6)</td>
<td>15(9)</td>
</tr>
<tr>
<td>Past or current smoker, no. (%)</td>
<td>79(48)†</td>
<td>98(60)‡</td>
<td>97(60)‡</td>
<td>115(71)</td>
</tr>
<tr>
<td>BMI, mean ± SD kg/m²</td>
<td>28 ± 7§</td>
<td>29 ± 8</td>
<td>30 ± 6</td>
<td>30 ± 7</td>
</tr>
<tr>
<td>RA Manifestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender joint count, mean ± SD</td>
<td>17 ± 13</td>
<td>14 ± 12</td>
<td>16 ± 13</td>
<td>13 ± 12</td>
</tr>
<tr>
<td>Tender joint count, mean ± SD</td>
<td>9 ± 7</td>
<td>8 ± 6</td>
<td>9 ± 7</td>
<td>8 ± 7</td>
</tr>
<tr>
<td>ESR, mean ± SD mm/hour</td>
<td>49 ± 28†</td>
<td>48 ± 28†</td>
<td>35 ± 24</td>
<td>35 ± 22</td>
</tr>
<tr>
<td>SR Crystalline Measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp score</td>
<td>123 ± 63§</td>
<td>98 ± 61‡</td>
<td>73 ± 46‡</td>
<td>47 ± 38</td>
</tr>
</tbody>
</table>
### Mortality by Quartile

<table>
<thead>
<tr>
<th>BMD Q1</th>
<th>BMD Q2</th>
<th>BMD Q3</th>
<th>BMD Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) deaths</td>
<td>100 (61)†</td>
<td>71 (44)†</td>
<td>38 (23)</td>
</tr>
<tr>
<td>Person-years</td>
<td>1921</td>
<td>2127</td>
<td>2343</td>
</tr>
</tbody>
</table>

Total No. of Deaths = 252

†P≤0.001. †P≤0.05. §P≤0.01.

### Kaplan-Meier Curve

- Analysis Time (years)
- BMD Quartiles (decigrams/cm²)
- Survival Probability
- Mortality by Quartile

### All-Cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>Mortality Hazard Ratio (per 1 decigram/cm² BMD)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.5638</td>
<td>1.3870 – 1.7632</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.5687</td>
<td>1.3489 – 1.8242</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.6079</td>
<td>1.3784 – 1.8756</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.4691</td>
<td>1.2463 – 1.7317</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.3345</td>
<td>1.1043 – 1.7128</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Assessing Potential Confounders

- Sequence of Cox Proportional Hazard Models
  - Model 1: DXR-BMD + demographic variables
  - Model 2: Model 1 + cardiovascular risk factors
  - Model 3: Model 2 + clinical RA manifestation measures + steroid use
  - Model 4: Model 3 + Sharp Score

### Conclusions

- RA patients with low appendicular BMD have greater mortality independent of potential confounders
- DXR can be useful tool in assessing mortality risk in patients with RA
- More research is needed to examine the mechanism underlying the association between low BMD and increased mortality
Study Limitations

- Only all-cause mortality was considered in this study without analysis of more specific causes.
- Glucocorticoid dosing was not evaluated in the present study as a potential mortality confounder.
- Did not address potential mechanisms associated with low BMD which could contribute to increased mortality such as fractures.

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