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Hand bone mineral density is associated with both total hip and lumbar spine bone mineral density in post-menopausal women with RA

Sonali P. Desai¹, Ellen M. Gravallese², Nancy A. Shadick¹, Roberta Glass¹, Jing Cui¹, Michelle Frits¹, Lori B. Chibnik¹, Nancy Maher¹, Michael E. Weinblatt¹ and Daniel H. Solomon¹

Abstract

Objective. RA is associated with localized bone loss in the hands, as well as generalized osteoporosis. We evaluated the relationship between hand digital X-ray radiogrammetry BMD (DXR-BMD) and total hip and lumbar spine BMD.

Methods. We conducted a cross-sectional study of 138 post-menopausal women with RA. The DXR-BMD was calculated based on digitized hand radiographs. Measurements of the total hip and lumbar spine BMD were performed by a DXA-BMD (BMDa) scan. Patient and physician questionnaires and laboratory samples supplied information on relevant covariates. Separate multivariate linear regression models were constructed to determine the cross-sectional relationship between hand DXR-BMD (independent variable) and total hip or lumbar spine BMD (dependent variables).

Results. The cohort comprised women with a median age of 61 years and RA disease duration of 13 years. Seventy-six per cent were either RF and/or anti-cyclic citrullinated peptide (anti-CCP) positive and most had moderate disease activity [median disease activity score-28 joint count (DAS28) 3.7]. Hand DXR-BMD was significantly associated with total hip BMD (β = 0.61; P < 0.0001) and lumbar spine BMD (β = 0.62; P < 0.0008) in adjusted models.

Conclusions. This study suggests that hand DXR-BMD is associated with both the total hip and lumbar spine BMD among post-menopausal women with RA. The relationship between bone loss in the hands and generalized osteoporosis should be further explored in longitudinal studies of patients with RA.

Key words: Rheumatoid arthritis, Osteoporosis, Bone mineral density, Digital X-ray radiogrammetry, Hand bone loss.

Introduction

RA is characterized by generalized bone loss in the hands, as well as periarticular demineralization and focal bone erosion. Osteoporosis is a well-recognized feature of RA patients, present at a 2-fold higher rate and associated with significant morbidity [1]. The relationship between hand bone loss in RA and generalized osteoporosis is not clear. By studying this relationship, clues to shared mechanisms may be discovered, perhaps leading to an improvement in the management and treatment of both types of bone loss associated with RA.

Digital X-ray radiogrammetry (DXR) is a technique to measure the hand BMD using digitized hand radiographs [2, 3]. Its utility was initially limited due to imprecision, but adding digitized images to the method with automated regions of interest for BMD calculation improved reproducibility [4, 5]. A recently developed imaging algorithm has improved precision with a coefficient of variation of 0.42% [4].

The DXR-BMD technology has been used to evaluate hand bone loss in RA and measures cortical BMD in the
shaft of the second, third and fourth metacarpal bones, a site distinct from but adjacent to the periaricular region. An automated analysis of the cortical thickness of these regions of interest results in a metacarpal index calculation. These regions of interest have been measured in prior work [6] and found to be reliable and precisely defined. An estimate of the hand DXR-BMD is then obtained by calculating the volume of bone per projected area and adjusting for porosity of the bone, using geometric values to obtain an areal measurement [2]. The hand DXR-BMD measuring cortical metacarpal bone has been shown to strongly correlate with hand DXA-BMD (BMDa) measuring whole-hand cortical and trabecular bone ($r = 0.88$; $P < 0.001$) [7, 8]. The hand DXR-BMD is associated with RA disease severity as measured by radiographic progression [9, 10]. There is emerging evidence for the role of the hand DXR-BMD as a marker of disease activity and potential outcome measure in RA [7, 11]. If hand DXR-BMD is truly a measurement of ongoing bone loss and can predict radiographic progression and/or generalized osteoporosis, it may be a useful tool to help clinicians in the prognostication of RA patients along with currently available data.

Prior work [6] has demonstrated a correlation between hand DXR- and DXA-BMD measurement of the total femur BMD ($r = 0.59$; $P < 0.01$) and lumbar spine BMD ($r = 0.45$; $P < 0.01$), but this study was limited by lack of information on glucocorticoid usage and serological status. The hand DXR-BMD has been associated with osteoporotic fracture risk both in non-RA and RA populations [10, 12]. However, detailed analysis of the association between hand DXR-BMD and generalized osteoporosis as measured by both total hip and lumbar spine BMD is lacking.

By comparing the measurement of hand BMD by DXR with the measurement of generalized osteoporosis by conventional DXA, important relationships between the two types of bone loss may be better elucidated. We examined the relationship of hand DXR-BMD with total hip and lumbar spine BMD in a cohort of postmenopausal women with established RA. We hypothesized a direct relationship between hand DXR-BMD and both total hip and lumbar spine DXA-BMD, and that this relationship would be stronger in specific subgroups.

Methods

Study design

The study population consisted of women with RA who received their rheumatological care at an academic medical centre. All eligible patients were enrolled in the Brigham Rheumatoid Arthritis Sequential Study (BRASS); a longitudinal RA patient registry. Our study population represents a subset of the BRASS cohort, including only 138 post-menopausal women who had had bilateral hand radiographs and a total hip and/or lumbar spine DXA done within 2 years of each other (Fig. 1). The Institutional Review Board (Partners Human Research Committee) approval was obtained for this study. All patients in the BRASS cohort provided informed patient consent for participation in the BRASS, and our study population represents a subset of the BRASS cohort.

Hand DXR-BMD measurements

The hand DXR-BMD was measured at the metacarpal bones of the second, third and fourth digits, using a methodology developed by Sectra (Sweden) [6]. Regions of interest were defined on hand radiographs at fixed distances of 2.0 cm for the second, 1.8 cm for the third and 1.6 cm for the fourth metacarpals. Digitized hand radiograph images were collected every 2 years as part of the BRASS. The digitized image of the hand radiograph closest in time to the DXA was analysed using the DXR-online service (Sectra Imtec AB, Linkoping, Sweden).

Total hip and lumbar spine DXA measurements

All patients underwent a DXA scan on a Hologic QDR 4500 densitometer (Hologic, Bedford, MA, USA). Lumbar levels with artefact from sclerosis or compression fracture were removed from the reading. Short-term in vivo reproducibility for the posteroanterior spine is 0.026 gm/cm$^2$ and for the lateral spine is 0.034 gm/cm$^2$. Long-term in vivo reproducibility, determined by calculating the residual variation around a line connecting measurements made at 0, 3 and 6 months for each patient in before study, is between 1 and 2% for the total hip and lumbar spine DXA, and the reproducibility is independent of the patient's absolute BMD. Readers of the bone density measurement were blinded to the patient's clinical status.

Covariates

Participants completed a questionnaire with the assistance of a trained interviewer at baseline and then annually. The questionnaire included information about past and present arthritis medications, non-arthritis medications, comorbidities, smoking history and surgeries. In an additional semi-annual self-administered questionnaire, patients provided demographical information, new medical conditions, medication use, new symptoms, health-care resource use and assessed functional status with the multidimensional HAQ (MDHAQ) [13]. Rheumatologists completed a questionnaire documenting the ACR criteria for RA diagnosis, the 28-joint count, comorbid conditions, overall disease activity on a numerical rating scale of 0–100 and medication changes made at the visit [14].

Laboratory tests performed at baseline include the RF with anti-cyclic citrullinated peptide (anti-CCP) antibody performed annually. Hand radiographs are performed at baseline and every 2 years. Glucocorticoid use was measured as the self-reported cumulative lifetime dose with high glucocorticoid usage defined as >5 g over a lifetime (the 75th quartile of cumulative lifetime glucocorticoid usage) [15]. Since the baseline hand radiograph and the total hip and/or lumbar spine DXA measurements were not performed at the same time point, a time difference variable was defined to account for the time lag between...
the two measurements. The time difference was the time in months between the date of the hand radiograph and the date of the total hip and/or lumbar spine DXA.

**Statistical analysis**

We examined the cross-sectional relationship between the baseline hand DXR-BMD and both total hip and lumbar spine DXA-BMD. These relationships were analysed in two separate linear regression models, with the dependent variables being total hip and lumbar spine DXA-BMD. Variables tested as possible confounders or effect modifiers included age, disease duration, BMI, glucocorticoid use, smoking (in pack-years), MDHAQ score, disease activity score-28 joint count (DAS28), RF and CCP status and current osteoporosis medications [16]. Variables that changed the hand DXR-BMD parameter estimate in bivariate models by $>10\%$ were placed in the multivariate models as these were deemed to be clinically relevant. Differences in $R^2$ were used to quantify the effect of adding and subtracting variables from the models.

To elucidate potential relationships between hand DXR-BMD and both total hip and lumbar spine BMD, we stratified by age, seropositivity, smoking status, cumulative glucocorticoid usage and disease duration. Our goal was to assess whether these factors modified the relationship between hand DXR-BMD and total hip and lumbar spine DXA-BMD. All statistical analysis was performed using SAS (version 9.1, Cary, NC, USA).

**Results**

**Patient characteristics**

Our study cohort consisted of 138 post-menopausal women with RA with a mean age of 61 years. The median duration of RA was 13 years with 19% having...
coid use is defined as a cumulative lifetime exposure of
given between 25th and 75th percentiles. High glucocorti-
total hip BMD analysis consisted of 99 patients. IQR is
516
26 (23–30)
118 (86)
1 (0–17)
41 (30)
41 (30)
19 (14)
13 (7–23)
26 (19)
105 (76)
88 (64)
87 (63)
0.6 (0.2–1.0)
3.7 (2.5–4.9)
7 (1–14)
0.52 (0.09)
0.85 (0.11)
0.97 (0.16)

Lumbar spine BMD analysis consisted of 129 patients; total
hip BMD analysis consisted of 99 patients. IQR is
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coid use is defined as a cumulative lifetime exposure of
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Variable created to account for time difference (in months)
between date of total hip or lumbar spine DXA for BMD
measurement.

<table>
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<th>Variables</th>
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Variable created to account for time difference (in months)
between date of total hip or lumbar spine DXA for BMD
measurement.

≤5-year duration (Table 1). The majority of patients
were positive for RF and/or anti-CCP (76%). Eighty-six
per cent were on DMARD therapy at baseline. The
median DAS28 score was 3.7, reflecting moderate
disease activity, and the median MDHAQ score was 0.6 (range 0–3). The sample had a median BMI of
26 kg/m².

Association of hand DXR-BMD with total hip and
lumbar spine DXA-BMD

We found that hand DXR-BMD was associated with
both total hip and lumbar spine DXA-BMD. The parameter
estimate (β-coefficient) for hand DXR-BMD in the
unadjusted total hip model was 0.57 (P < 0.0001). The
parameter estimate (β-coefficient) for hand DXR-BMD
and in the unadjusted lumbar spine model was 0.45
(P = 0.004). After adjusting for relevant confounders,
the multivariate linear regression models found that hand
DXR-BMD was still significantly associated with
DXA-BMD, having a β-coefficient of 0.61 in the total hip
model (P < 0.0001) and 0.62 in the lumbar spine model
(P = 0.0008) (Tables 2 and 3). The R² of the total hip
model was 0.34 and lumbar spine model was 0.17.

Modification of effect by seropositivity, disease
duration and age >61 years

To further delineate the relationships between hand
DXR-BMD and both total hip and lumbar spine
DXA-BMD, we stratified the models by serological status
(positive or negative), disease duration (≤5 and >5 years)
and age (≤61 or >61 years). We did not find evidence of
effect modification by seropositivity, disease duration or
age in the hip model, nor did we find evidence of effect
modification by seropositivity or disease duration in
the spine model. There was effect modification of the
relationship between hand DXR-BMD and spine
DXA-BMD by age (P < 0.05). There was no effect
modification with smoking (pack-years) or cumulative
glucocorticoid use.

Discussion

Bone disease in RA has at least two components: first,
local inflammation leads to both erosions and periarticular
osteopenia; secondly, generalized osteoporosis results
from multiple factors [17, 18]. Osteoporosis carries the
risk of fracture, and localized joint destruction leads to
pain, disability and a decrease in functional status.
Systemic bone loss in RA is related to RA-specific factors
such as disease duration, disease severity and medication
use (such as glucocorticoids), as well as other determi-
nants of osteoporosis such as post-menopausal status
and race [19]. Similarly, hand bone loss in RA may be
from RA-specific factors and generalized osteoporosis
disease determinants, although these complex relations-
ships are yet to be fully determined. Low BMI is an estab-
lished risk factor for osteoporosis [20]. In our population
of post-menopausal women with established RA, we
found that hand DXR-BMD was a significant predictor of
both total hip and lumbar spine BMD, even after adjusting
for multiple confounders. Disease duration and BMI
were also important predictors of the total hip and
lumbar spine BMD.

The relationship between hand DXR-BMD and lumbar
spine DXA-BMD was modified by age. Our study included
only post-menopausal women ranging in age from 51 to
71 years. Our models stratified by age revealed that
among women who were aged <61 years, the hand
DXR-BMD was more highly associated with the lumbar
spine BMD. This finding of an increased association of
hand BMD with spine BMD in younger women also
implies that the effect of increasing age plays a more
prominent role in determining generalized bone loss
at the spine as other data have suggested [21]. Future
studies may enroll pre-menopausal women with RA to
examine this relationship in further detail and to ascertain
the extent that RA disease-specific factors may influence
generalized osteoporosis.

Hand bone loss in RA occurs early in the course of
disease, whereas generalized osteoporosis may take
longer to develop [22–24]. The hand DXR-BMD has
been associated with radiographic progression, which
manifests as the disease duration increases [25]. Thus, it

Sonali P. Desai et al.

Table 1: Patient characteristics

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</table>
is possible that the hand DXR-BMD has more utility in predicting generalized osteoporosis among post-menopausal women who have longer disease duration, compared with those with early RA; however, our analysis was limited by the smaller number in the early RA group with disease duration ≤5 years (n = 26). To investigate this hypothesis more thoroughly, a prospective longitudinal study of the baseline hand DXR-BMD and serial measurements of the total hip and lumbar spine BMD would be necessary.

DXA is traditionally measured at sites that include the trabecular bone, particularly those involved in clinically significant morbidity from fractures such as the spine and femur. Inaccuracies in measurements at the lumbar spine may be due to the degenerative joint disease that is unrelated to RA disease activity. In addition, sclerotic changes from the degenerative joint and disc disease in the lumbar spine may create artefact that falsely increases the overall lumbar spine BMD. The DXA measurement in our study attempted to account for such inaccuracies by

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**Table 2** Linear regression analyses of hand DXR-BMD, covariates and total hip BMD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate parameter estimate (β-coefficient)</th>
<th>P-value</th>
<th>Multivariate parameter estimate (β-coefficient)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Hand DXR-BMD</td>
<td>0.57</td>
<td>&lt;0.0001</td>
<td>0.61</td>
<td>&lt;0.0001</td>
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<td>Age at hand radiograph, years</td>
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<td>0.007</td>
<td>-a</td>
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<tr>
<td>Disease duration, years</td>
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<td>0.37</td>
<td>0.002</td>
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<td>BMI, kg/m²</td>
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<td>0.0003</td>
<td>0.006</td>
<td>&lt;0.00002</td>
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<td>0.16</td>
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<td>High glucocorticoid useb</td>
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</table>

Total hip BMD model consisted of 99 patients. In the multivariate model, all variables listed in Table 1 were tested for entry into the model and remained if there was a >10% change in the hand DXR-BMD parameter estimate. R² is found to be 0.34. aVariables not included in the multivariate model. bHigh glucocorticoid use defined as a cumulative lifetime exposure of >5g. cVariable created to account for time difference (in months) between date of hand radiograph for hand DXR measurement and date of total hip or lumbar spine DXA for BMD measurement.

**Table 3** Linear regression analyses of hand DXR-BMD, covariates and lumbar spine DXA

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<td>DAS28</td>
<td>-0.006</td>
<td>0.54</td>
<td>-a</td>
<td>-a</td>
</tr>
<tr>
<td>Seropositive (RF and/or anti-CCP)</td>
<td>-0.03</td>
<td>0.38</td>
<td>-a</td>
<td>-a</td>
</tr>
<tr>
<td>Current osteoporosis medications</td>
<td>-0.027</td>
<td>0.51</td>
<td>-a</td>
<td>-a</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>0.001</td>
<td>0.93</td>
<td>0.001</td>
<td>0.47</td>
</tr>
<tr>
<td>Aged &gt;61 years</td>
<td>-0.014</td>
<td>0.62</td>
<td>-a</td>
<td>-a</td>
</tr>
<tr>
<td>Time difference measurementc</td>
<td>-0.001</td>
<td>0.39</td>
<td>-0.002</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Total hip BMD model consisted of 99 patients. In the multivariate model, all variables listed in Table 1 were tested for entry into the model and remained if there was a >10% change in the hand DXR-BMD parameter estimate. R² was found to be 0.17. aVariables not included in the multivariate model. bHigh glucocorticoid use defined as a cumulative lifetime exposure of >5g. cVariable created to account for time difference (in months) between date of hand radiograph for hand DXR measurement and date of total hip or lumbar spine DXA for BMD measurement.
removing any sclerotic artefact from the reading. About 27% of the patients had four or less vertebrae in the analysis. RA does not typically involve the lumbar spine, but can involve the total hip, particularly with secondary OA and the cervical spine. In our analysis, we found that there was a similar relationship between hand DXR-BMD and both total hip and lumbar spine DXA-BMD, as indicated by the parameter estimates (β-coefficients) of 0.61 in the total hip and 0.62 in the lumbar spine models. Prior study [26] has found that radiographic joint damage in RA as measured by the Larsen score correlates with the BMD of the total hip but not the lumbar spine [26]. The $R^2$ of the total hip model was 0.34 compared with 0.17 in the lumbar spine, indicating that the explanatory power of the model to account for the variability was higher in the total hip vs the lumbar spine. This increased explanatory power of the total hip model as compared to the lumbar spine model is consistent with some prior studies noting that RA radiographic damage is associated more with the total hip compared with lumbar spine BMD.

Several important limitations of our study need to be discussed. This study was an analysis of cross-sectional data. Hand radiographs performed to measure the hand DXR-BMD and the DXA scans were not done on the same day. Although the time between the studies was taken into account in our analysis through the time difference variable, this may have affected our results. Despite this drawback, we still found a strong association between hand DXR-BMD and total hip and lumbar spine DXA-BMD. We did not have data on current physical activity level or vitamin D at the time of the hand DXR-BMD measurement and it is known that low activity level is a putative risk factor for the development of osteoporosis [27]. Vitamin D serum levels were also not available but may play a role in both RA disease activity and osteoporosis [28]. Lastly, measurement of the hand DXR-BMD and the total hip and lumbar spine DXA-BMD in a population of healthy post-menopausal women would serve as an important comparison group and may be the subject of future research.

The regions of interest used in our study were areas of active joint inflammation, but not contained within the joint itself. Our analysis demonstrates that in this cohort of post-menopausal women with established RA, hand DXR-BMD is significantly associated with both total hip and lumbar spine BMD, after adjustment for multiple confounders. Other studies have shown that hand DXR-BMD may be a better predictor of radiographic progression in patients with early RA as compared with patients with longer disease duration, and there may be a role for serial measurements of hand DXR-BMD over time to evaluate the change in DXR-BMD as a predictor of the DXA-BMD and radiographic progression [29]. Future prospective studies might focus on RA patients with both early and established disease and women who are pre- and post-menopausal, as these results may have implications for osteoporosis-prevention strategies [30, 31]. Since hand radiographs are routinely used in the management of patients with RA, DXR-BMD may have a role in assessing both the RA-specific bone effects and generalized osteoporosis, among patients with RA.

### Rheumatology key messages

- The hand DXR-BMD is significantly associated with both the total hip and lumbar spine BMD.
- This association was seen among post-menopausal women with RA after adjustment for several key confounders.
- In RA, hand DXR-BMD may play a role in elucidating hand bone loss and generalized osteoporosis.

### Acknowledgements

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### References

Hand BMD is associated with hip and spine BMD