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Generalized Bone Loss as a Predictor of 3-Year Radiographic Damage in African American Patients with Recent-Onset Rheumatoid Arthritis

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Abstract

Objective—To examine the association between baseline bone mineral density (BMD) and radiographic damage at 3-year disease duration in a longitudinal cohort of African Americans (AAs) with recent-onset RA.

Methods—Participants (n=141) included AAs with < 2 years of disease duration. All patients underwent baseline BMD measurement (femoral neck and/or lumbar spine) using DXA. T-scores were calculated using AAs normative data. Patients were categorized as having osteopenia/ osteoporosis (T score ≤ −1) or healthy. Hand/wrist radiographs, obtained at baseline and at 3-year disease duration, were scored using modified Sharp/van der Heijde method. The association between baseline BMD and total radiographic score at 3-year disease duration was examined using multivariable negative binomial regression.

Results—At baseline, the mean age and disease duration were 52.4 years and 14.8 months respectively (85.1% women). Average total radiographic scores at baseline and 3-year disease duration were 2.4 and 5.7. In the final reduced multivariable model adjusting for age, gender, anti-cyclic citrullinated peptide antibody positivity, and the presence of radiographic damage at baseline, the total radiographic score at 3-years of disease duration in patients with osteopenia/ osteoporosis at the femoral neck was twice that in patients with healthy bone density and the difference was statistically significant (p=0.0084). No association between lumbar spine osteopenia/osteoporosis and radiographic score was found.

Conclusion—These findings suggest that reduced generalized BMD may be a predictor of future radiographic damage and support the hypothesis that radiographic damage and reduced generalized BMD in RA patients may share a common pathogenic mechanism.

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Introduction

The progression of radiographic damage in rheumatoid arthritis (RA) is not uniform (1) and despite the advent of biologic agents, RA continues to cause joint destruction in a significant proportion of patients (2–6). Initial radiographic damage, antibodies to cyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP) levels, and other inflammatory markers are currently used to identify patients at greatest risk for developing progressive joint damage in an effort to selectively implement early, aggressive treatment strategies (7–11).

Recent findings among RA patients of European ancestry have suggested that lower bone mineral density (BMD) at various anatomic sites can be used as a predictor of progressive radiographic damage. Significant associations between hand BMD and subsequent radiographic damage in patients with early RA have been reported independently in three longitudinal studies (12–14). Forslind et al showed that generalized bone loss was a significant predictor of radiographic progression at 2-year follow-up (15). In addition to these longitudinal studies, generalized BMD has been shown to be significantly associated with radiographic damage or joint erosions in a number of cross-sectional studies (16–19).

However, it is unknown whether these results can be extrapolated to African American RA patients. Healthy African Americans have higher BMD (20–22) and a significantly lower risk of osteoporosis-related fractures than Caucasians, Asians, and Hispanics (23). African Americans not only achieve a higher peak bone mass but differ from European Americans with respect to skeletal resistance to parathyroid hormone, estradiol and testosterone levels, calcium metabolism, and the rate of bone turnover (24–29).

The objective of this study is to examine whether baseline generalized BMD at the femoral neck and lumbar spine correlates with radiographic joint damage accrued over time in a longitudinal cohort of African American patients with recent-onset RA.

Materials and Methods

The analyses were performed in participants enrolled in the Consortium for the Longitudinal Evaluation of African Americans with Early RA (CLEAR) Registry from 2001 to 2005. The CLEAR Registry has four sites participating in this longitudinal study, including the University of Alabama at Birmingham (Coordinating Site), Emory University, the University of North Carolina, and the Medical University of South Carolina(30). The study was approved by the Institutional Review Board (IRB) at each participating site and all participants provided informed written consent.

Briefly, subjects were eligible if their self-reported race was black or African American, if they had a diagnosis of RA as defined by the American College of Rheumatology (ACR) 1987 classification criteria (31), and if the disease duration was less than 2 years from symptom onset. At the baseline visit, questionnaires were administered to collect information on medical history (ACR criteria, extra-articular manifestations, disease duration, current and past use of RA and non-RA medications, co-morbidities) and demographics. All patients underwent a physical examination during which information on height and weight was obtained. The number of tender and/or swollen joints was assessed by trained evaluators; the Joint Alignment and Motion scale was used to assess joint deformity (32); and the Health Assessment Questionnaire (HAQ) Disability Index was used to evaluate functional ability (33). Serum rheumatoid factor (RF-IgM, IU/ml, INOVA Diagnostics, USA) and anti-CCP antibodies (U/ml, Diastat, Axis-Shield Diagnostics Ltd., UK) were measured, as previously reported (34). Plasma high-sensitivity C-reactive protein (hs-CRP, mg/L) concentrations were determined using an immunoturbidimetric assay on the Hitachi

917 analyzer (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN).

Participants were re-evaluated at 3-years disease duration (time elapsed since symptom onset). Because the CLEAR participants were enrolled at any point less than 2 years after disease onset, the disease duration at baseline visit varied from 0–2 years. As a result, the amount of follow-up time also varied among study subjects. Between the baseline and 3-year visits, patients were surveyed via telephone at 6-month intervals to obtain information about medication use since the last study encounter.

The outcome variable of our study was radiographic damage at the 3-year follow-up visit. Radiographs of the hands and wrists were obtained at baseline and at the 3-year visits and radiographic damage was evaluated using the van der Heijde modified Sharp (SvdH) method (35). Baseline BMD at the femoral neck and lumbar spine were measured at each participating center using dual energy x-ray absorptiometry (DXA). BMD measures were standardized to Hologic BMD using published conversion equation (36) and T-scores were calculated using referent data from the general African American population: manufacturer's reference database (lumbar spine) and National Health and Nutrition Examination survey-III data (femoral neck). Details with regard to the collection, standardization, and calculation of T-scores have been previously published (37). Based on baseline T scores, patients were categorized into two groups for each anatomical site: "Osteopenia/Osteoporosis" (T-score less than or equal to −1) or "Healthy" (T-score greater than −1).

Statistical Analyses

Patients in the CLEAR Registry with SvdH score at the 3-year visit and baseline BMD at either femoral neck or lumbar spine were included in the analysis (n=141). The dependent variable was the total SvdH score at the 3-year visit, which was a non-negative integer assuming an over-dispersed Poisson distribution (variance greater than mean). Hence, linear models were not appropriate and negative binomial regressions were used in both univariate and multivariable analyses. The exponentiation of parameter estimate (EPE) of the negative binomial regression model can be interpreted in a multiplicative manner such as in the following example, e.g., an EPE of 3 for female gender indicates that the total SvdH score for a female is 3 times that for a male if the two subjects were the same with regard to all other covariates. An EPE greater than 1 indicates that the presence of the characteristic (or a higher value in the case of a continuous variable, e.g., older age) is associated with greater total 3-year SvdH score and an EPE less than 1 indicate the opposite.

A wide range of baseline characteristics were examined in univariate analyses, including age, gender, body mass index (BMI), disease duration at baseline, baseline plasma hs-CRP level (mg/L), anti-CCP antibody positivity, RF-IgM positivity, presence of radiographic damage (SvdH score > 0), *HLA-DRB1* shared epitope (SE) positivity (the *HLA-DRB1* alleles encoding the SE were: *HLA-DRB1*0101, *0102, *0401, *0404, *0405, *0408, *0413, *1001*, and **1402*), cumulative oral glucocorticoid use (a composite of dose, frequency, and duration) prior to the 3-year visit was categorized approximately into 3 tertiles: never (n=47), low (n=43), and high (n=44), HAQ score, tender and swollen joint counts, number of ACR criteria, number of extra-articular manifestations, and smoking status (never, past, or current smoker).

Age, gender, BMI, cumulative glucocorticoid use, smoking status, and variables that had p-values less than 0.10 in univariate analyses were included in an initial multivariable model. To produce a final parsimonious model, the initial model was then manually reduced by removing variables that had the greatest p-value at each step if they were not statistically

significant at 0.05 significance level and if the removal of the variables did not produce a 10% or greater change in the parameter estimate for femoral neck or lumbar spine osteopenia/osteoporosis (38). Because BMD at femoral neck and lumbar spine were highly correlated, two separate multivariable models were examined for BMD at the two anatomical sites.

All statistical analyses were performed using SAS statistical package (version 9.1, SAS Institute Inc., Cary, North Carolina).

Results

Baseline patient characteristics are shown in Table 1. At the baseline visit, the mean (SD) age and disease duration were 52.4 (13.0) years and 14.8 (7.3) months, respectively. Women accounted for 85.1% of the total study population. Mean (SD) SvdH scores at baseline and 3-year visits were 2.4 (5.4) and 5.7 (11.3), respectively, with an average annual progression rate of 1.5 units.

At baseline, the average BMD (g/cm^2) at lumbar spine and femoral neck were 1.08 and 0.85. At lumbar spine 38.6% of the subjects had either osteopenia or osteoporosis and at femoral neck 44.9% (T-score ≤ -1). Patients with osteopenia/osteoporosis at either anatomical site had higher mean total SvdH scores at baseline and more progression during the follow-up period. At femoral neck, the mean total SvdH scores at baseline and 3-year visits in patients with osteopenia/osteoporosis were 3.31 and 8.16 respectively and in patients who had healthy bone density the means were 1.76 and 3.91. At lumbar spine, the mean total SvdH scores at baseline and 3-year visits were 3.10 and 7.63 in patients with osteopenia/ osteoporosis and were 2.00 and 4.58 in patients who had healthy bone density.

Table 2 presents the results of the univariate analyses and the final reduced multivariable model. Femoral neck osteopenia/osteoporosis at baseline was associated with higher total SvdH score at the 3-year visit (EPE=2.2; p=0.0249). After controlling for other baseline characteristics, femoral neck osteopenia/osteoporosis remained significantly associated with higher total SvdH score in the multivariable analyses (EPE=2.1; p=0.0084). The removal of age and glucocorticoid use from the multivariable model resulted in a 17% increase and a 21% reduction respectively in the parameter estimate for femoral neck osteopenia/ osteoporosis, which exceeded the 10% cut-off point used in the “change in estimate” strategy to evaluate confounding (38). While they were not statistically significant at 0.05 alpha level, they were kept in the final multivariable model (Table 2). To test the robustness of our final model, we built an alternate reduced model retaining only those variables that are significant at 0.05 alpha level and the results were similar. The 3-year total SvdH scores in subjects with reduced bone density at the femoral neck were twice those of subjects with healthy bone density (EPE=2.1; p=0.0035).

Baseline osteopenia/osteoporosis at the lumbar spine was marginally associated with the SvdH score (EPE=1.8; p=0.0897) in the univariate analysis. There was no final reduced multivariable model for lumbar spine BMD. Lumbar spine osteopenia/osteoporosis was not significantly associated with 3-year total SvdH in the full model and was eliminated during variable elimination.

We excluded two subjects whose 3-year SvdH scores were five standard deviations (SDs) above the mean and were osteoporotic at baseline in order to evaluate the sensitivity of the final multivariable model. Reduced bone density at femoral neck remained a significant predictor of total SvdH score (EPE=2.1; p-value = 0.0093).

Given that generalized BMD may be more strongly related to bony erosions than to joint space narrowing or total SvdH scores, we performed additional analyses examining the relationship between femoral neck and hip osteopenia/osteoporosis with erosion scores at 3-years disease duration, using the same method described above. Femoral neck osteopenia/osteoporosis was significantly associated with the 3-year disease duration erosion score in univariate (EPE=2.2; p=0.0279) and multivariable analyses (full model EPE=2.7; p=0.0061). A marginally significant association was observed for lumbar spine osteopenia/osteoporosis in univariate (EPE=2.0; p=0.0535) and multivariable analyses (full model EPE=1.8; p=0.0594). These results are summarized in table 3.

Discussion

RA patients are at increased risk of developing osteoporosis compared with those without RA (39). Increasing evidence suggests a common mechanism for generalized bone loss and localized radiographic joint damage. A number of cross sectional studies have reported a significant correlation between the two types of bone manifestations(16–19) and agents targeting tumor necrosis factor (anti-TNF treatment) has been found to halt generalized bone loss in RA patients in addition to its effect on localized joint damage (40). The mechanism has been postulated to involve inflammatory cytokines in the regulation of osteoclast differentiation and activation. Research interest has focused on the RANK/RANKL (receptor activator of NF-κβ/RANK ligand) pathway and TNF-α (41,42). Our findings of significant associations between reduced BMD (osteopenia/osteoporosis) at femoral neck with 3-year total SvdH score and the erosion score in African American patients with recent-onset RA lends further support to this hypothesis.

Our results raises the question of whether bone density is already reduced in early RA patients compared with general population. We had obtained bone mineral density data on approximately frequency age- and gender-matched African American controls (n=161). Using multivariable linear regression to further control for age and gender, there was a marginally significant difference for femoral neck BMD (p=0.0767). Given the same age and gender, the bone density in RA patient was 0.03 point higher than that in a control. This further suggests that the balance in bone remodeling is already tilted by the disease.

Our findings also have potentially important clinical implications in the treatment of patients with recent-onset RA by suggesting that generalized BMD may be used as a predictor of subsequent radiographic damage. The identification of early RA patients with more a aggressive disease course is of great importance, particularly since prompt initiation of disease modifying treatments have been shown to protect against joint damage and RA-related functional and work disability (43,44). Denosumab, an investigational human monoclonal antibody against RANKL, has been shown to reduce localized joint erosions in RA patients and to increase bone density in postmenopausal women (45,46). Perhaps, given the ability of the new agent to treat both types of bone manifestations, reduced BMD can be used as more than a biomarker to predict future joint damage, but also as a biomarker to identify patients who are likely to benefit most from such new therapy and as an indication to initiate the treatment.

We did not find a significant association between baseline lumbar spine osteopenia/osteoporosis with 3-year SvdH score. The discrepancy that an association was observed between radiographic joint damage with BMD at the hip but not at the lumbar spine has been reported previously in patients of European ancestry (16–18). One likely explanation for the discrepancy is osteoarthritis and/or other vertebral deformities occurring commonly in elderly population. Osteophyte formation, bone sclerosis, and disk space narrowing have been found to correlate positively with lumbar spine BMD whereas such a correlation was

either not observed or observed to a lesser degree with hip BMD (47). The issue that lumbar spine BMD is often falsely inflated is reflected in the clinical guidelines of the National Osteoporosis Foundation (NOF), which recommends hip BMD as the preferred site for the diagnosis of osteoporosis(48).

In our study, peak referent BMD from African Americans was used to derive the T-scores. Because the objective of the study was not to assess fracture risk but to evaluate the association between radiographic damage and reduced bone mass, the use of race-specific referent data allowed us to determine the severity of bone loss and to measure the amount of reduction from the expected peak BMD. We replicated the same models using BMD as a continuous variable. Without adjusting for other variables, femoral neck BMD was marginally associated with the 3-year total SvdH score (EPE=0.21, p=0.0765) and lumbar spine BMD was not (EPE=0.45, p=0.3239). Adjusting for the same covariates as in the final reduced model, femoral neck BMD was again borderline significant at p-value 0.0542 (EPE=0.14). While the association did not reach the 0.05 threshold, the results were consistent with those when the dichotomized measures were used.

There are a number of limitations in our study. First and foremost, the relatively small sample size (n=141) is likely to have resulted in the exclusion of a number of baseline characteristics from entering the multivariable analyses. To address this issue, the change-in-estimate approach has been used to evaluate possible confounders and to fit the final multivariable model. Perhaps more importantly, because under-powered early studies tend to report over-inflated effect size (49), the magnitude of the association found in our study will need to be evaluated and interpreted with caution.

Another limitation of our study concerns the accuracy of the patients' self-reported cumulative oral glucocorticoid use. Patients were asked to provide detailed information on the dose, duration, and type of glucocorticoid used and were then categorized into tertiles of cumulative glucocorticoid use. While previous research has shown robust agreement between quartiles of cumulative glucocorticoid dose from self-report and medical records review (50), it is possible that the self-reported information was inaccurate and patients were misclassified into the wrong group regarding this important exposure. Misclassification may result in uncontrolled confounding and inflation of the magnitude of the association between generalized BMD and radiographic damage we found in our study.

The association between generalized BMD and radiographic damage may be confounded by multiple factors. In addition to glucocorticoid use, physical inactivity due to impaired function, body mass index (BMI), disease activity, and medications may all influence the relationship. A study by Solomon et al. (16) found that the relationship between focal bone erosions and generalized BMD was stronger among patients with shorter disease duration and lower cumulative oral glucocorticoid use, suggesting that in patients with longer disease duration, the other factors exerted greater influence on the relationship between bony erosions and generalized BMD.

Despite the limitations discussed above, our study is the first to examine the relationship between generalized BMD and radiographic damage in African American patients with recent-onset RA. African Americans are under-represented in RA research and the known racial/ethnic differences in the skeletal system render it unclear whether the previously reported results apply in this population.

In summary, the findings from our study suggest that generalized bone density may be a predictor of radiographic damage and provide further support for the hypothesis that the two types of bone manifestations share a common mechanism. The elucidation of such mechanism responsible for the imbalance in bone remodeling in future research will not

only lead to a better understanding of the pathogenesis of RA but also one more step toward individualized medicine and development of novel treatment therapies that have the potential of addressing both types of bone involvement.

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Table 1

Baseline characteristics of African Americans with recent-onset rheumatoid arthritis (n=141)

Baseline Characteristics	Mean ± SD or n (%)
Women	120 (85.1)
Age (years)	52.4 ±13.0
Disease duration since symptom onset (months)	14.8 ± 7.3
BMI (kg/m^2)	31.2 ± 6.7
Patient assessment of pain (on a visual analog scale)	5.9 ± 3.0
HAQ score	1.4 ± 0.8
Number of Swollen Joints (range; 0–38)	5.7 ± 7.5
Number of Tender Joints (range; 0–42)	10.9 ± 11.3
Rheumatoid nodules	19 (13.7)
Number of ACR criteria (range; 4–7)	5.0 ± 0.8
CRP, mg/L	12.3 ± 30.3
IgM RF positive	104 (77.6)
Anti-CCP positive	89 (66.9)
HLA-DRB1 shared epitope positive	69 (50.0)
Presence of baseline radiographic damage (SvdH score >0)	48 (34.5)

*BMI, body mass index; HAQ, Health Assessment Questionnaire; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; HLA-DRB1 shared epitope positivity (0101, 0102, 0401, 0404, 0405, 0408, 0413, 1001, and 1402); SvdH, modified Sharp/van der Heijde score

Table 2

Univariate and multivariable models between baseline characteristics and 3-year van der Heijde modified Sharp score among African Americans with recent-onset rheumatoid arthritis (n=141)

	Univariate analyses		Final Reduced Multivariable Model	
Baseline Characteristics	**EPE†**	**P-Value**	**EPE†**	**P-Value**
Demographics				
Age	1.02	0.1693	1.02	0.1513
Gender (Female)	0.60	0.2745		
Smoking status#				
Never	1.50	0.3312		
Current	1.11	0.8244		
Laboratory measures				
Positive IgM RF	2.88	0.0109		
Positive anti-CCP	2.38	0.0188	2.80	0.0028
CRP	1.01	0.2230		
Other RA-related measures				
Disease duration	1.02	0.3865		
Number of ACR criteria	1.25	0.2552		
Number of extra-articular manifestations	1.28	0.2261		
Number of tender joints	1.00	0.9072		
Number of swollen joints	1.03	0.2097		
Pain	1.09	0.1681		
HAQ score	1.30	0.2440		
BMI	0.98	0.4165		
Cumulative oral glucocorticoid use				
Low	1.25	0.5994	1.40	0.3667
High	0.88	0.7575	0.79	0.4698
Presence of radiographic damage (SvdH score >0)	9.43	<.0001	9.60	<.0001
HLA DRB 1	1.01	0.9776		
Femoral neck osteopenia or osteoporosis (vs. healthy)	**2.15**	**0.0249**	**2.10**	**0.0084**

† EPE, exponentiation of parameter estimate

* BMI, body mass index; HAQ, Health Assessment Questionnaire; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; HLA-DRB1 shared epitope positivity (0101, 0102, 0401, 0404, 0405, 0408, 0413, 1001, and 1402); SvdH, modified Sharp/van der Heijde score

** Baseline variables included in the initial multivariable model included: age, gender, body mass index, smoking status, IgM-rheumatoid factor positivity, anti-CCP positivity, cumulative glucocorticoid use, presence of radiographic damage, and presence of femoral neck osteopenia/ osteoporosis.

Reference group was past smokers

Table 3

Univariate and multivariable models between baseline characteristics and 3-year erosion score among African Americans with recent-onset rheumatoid arthritis (n=141)

	Univariate analyses		Femoral Neck Full Multivariable Model		Lumbar Spine Full Multivariable Model	
Baseline Characteristics	**EPE†**	**P-Value**	**EPE†**	**P-Value**	**EPE†**	**P-Value**
Demographics						
Age	1.02	0.0470	1.01	0.4105	1.02	0.1785
Gender (Female)	0.97	0.9440	2.91	0.0218	2.77	0.0311
Smoking status#						
Never	1.33	0.5062	0.41	0.0434	0.44	0.0651
Current	0.73	0.5284	0.47	0.0936	0.54	0.1658
Laboratory measures						
Positive IgM RF	5.69	0.0002	5.02	0.0051	5.16	0.0054
Positive anti-CCP	4.54	0.0001	2.57	0.0365	2.21	0.0760
CRP	1.00	0.7097				
Other RA-related measures						
Disease duration	1.04	0.1347				
Number of ACR criteria	1.47	0.0698	1.20	0.3250	1.22	0.2920
Number of extra-articular manifestations	1.41	0.1360				
Number of tender joints	1.01	0.6021				
Number of swollen joints	1.06	0.0352	1.05	0.0404	1.03	0.1384
Pain	1.09	0.1744				
HAQ score	1.35	0.1740				
BMI	0.97	0.2946	0.97	0.2946	0.96	0.1186
Cumulative oral glucocorticoid use						
Low	1.55	0.3141	0.97	0.9453	0.71	0.3620
High	0.82	0.6548	0.74	0.3986	0.72	0.3679
Presence of erosion (erosion score >0)	6.45	<.0001	9.61	<.0001	10.66	<.0001
HLA DRB 1	0.81	0.5607				
Femoral neck osteopenia or osteoporosis (vs. healthy)	**2.17**	**0.0279**	**2.71**	**0.0061**		
Lumbar spine osteopenia or osteoporosis (vs. healthy)	**1.99**	**0.0535**			**1.81**	**0.0594**

[†] EPE, exponentiation of parameter estimate

[*] BMI, body mass index; HAQ, Health Assessment Questionnaire; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; HLA-DRB1 shared epitope positivity (0101, 0102, 0401, 0404, 0405, 0408, 0413, 1001, and 1402); SvdH, modified Sharp/van der Heijde score

[#] Reference group was past smokers