Prevalence of Osteoporosis and Osteopenia among African Americans with Early Rheumatoid Arthritis: The Impact of Ethnic-Specific Normative Data

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Purpose: To examine the prevalence of osteopenia and/or osteoporosis among African Americans with early rheumatoid arthritis (RA) and to assess the effect of using race/ethnicity-specific normative data.

Methods: Bone mineral density (BMD) of the hip and spine was assessed in African Americans with early RA. To examine the impact of using different normative data on disease classification, we calculated two sets of T scores, the first using sex-matched reference data from Caucasians and the second using data from African Americans. Osteoporosis was defined as a BMD at either site ≥2.5 SD below the young adult mean. Osteopenia was defined as a BMD ≥1 SD and <2.5 SD below this mean.

Results: Using Caucasian referent data, 33% (n=48) of patients had osteopenia or worse (n=48, 32.9%) and 5% (n=8) were osteoporotic. With the use of African-American normative data, 55% (n=94) were osteopenic or worse, and 16% (n=27) were osteoporotic.

Conclusion: African Americans with RA are at risk of osteopenia and/or osteoporosis. Different diagnostic classifications may occur in this population based solely on the normative data used for assessing fracture risk. These results underscore the need for a standardized approach in defining osteopenia and osteoporosis in African Americans.

Key words: osteoporosis ■ osteopenia ■ African Americans ■ DXA ■ rheumatoid arthritis

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INTRODUCTION

Osteoporosis is increasingly recognized to represent a major source of morbidity for patients with rheumatoid arthritis (RA). Although the availability of dual energy x-ray absorptiometry (DXA) represents a major advance in osteoporosis care in the context of RA, fracture risk assessment in non-Caucasians remains problematic. While there are ample prospective data in postmenopausal Caucasian women that permit bone mineral density (BMD) results to be translated into fracture risk,[1,2] only limited data exist for non-Caucasians. Young, healthy African Americans have approximately 10% greater mean BMD compared to young healthy Caucasians.[3] However, it is unknown whether African Americans have a different fracture threshold than Caucasians, or whether fracture risk is a function of absolute BMD independent of race/ethnicity. As a result, there is little consensus regarding which reference groups are most appropriate for calculating T scores in non-Caucasians.[4,5] This is noteworthy since T scores are the primary factor taken into consideration by healthcare providers when diagnosing osteoporosis and making treatment recommendations.[6]

Further adding to this confusion, DXA manufacturers currently use different approaches to generate T scores for non-Caucasian patients. Of the three major manufacturers, two provide race/ethnicity-adjusted T scores for women, while only one provides race/ethnicity adjustment for men.[5]

Given the association of RA with low bone mass,[7] we examined the prevalence of osteopenia and/or osteoporosis in a group of well-characterized African-American patients with early RA. Because African Americans have higher peak BMD than Caucasians,[3] we were interested in examining the impact of using race/ethnicity-specific normative databases (Caucasian vs. African-American) on osteoporosis disease classification.

METHODS

Patients

Participants were enrollees in the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR).[8,9] Eligible participants self-reported African-American ethnicity, had an established diagnosis of RA as defined by the American College of Rheumatology (ACR) classification criteria[10] and had <2 years of disease duration (from time of symptom onset).[8,9] All patients underwent a comprehensive physical examination and were asked to provide a detailed medical history. RA disease activity was quantified by a board-certified rheumatologist using tender and swollen joint counts in addition to self-reported disability index scores (measured using the Stanford Health Assessment Questionnaire).[11]

Bone Mineral Density Measurement

BMD measurements of the femoral neck and lumbar spine (L1-L4, anterior-posterior) were performed by trained technicians at each participating center using DXA. Quality control of BMD measurement for this study was provided by Synarc Inc. (Maynard, MA) and included the use of a standardized quality-control phantom for each machine on each day a study patient was scanned and at least three times weekly. Femoral neck and lumbar spine measurements were not obtained on a small subset of patients due to the presence of either bilateral total hip replacements (n=3) or other metal hardware interfering with vertebral measurements (n=2). Given the multicenter design of the study,[8,9] BMD values were obtained on machines from all three major manufacturers and included Hologic (n=3 machines), Lunar (n=2 machines) and Norland (n=1 machine).

In order to correct for systematic differences in absolute BMD among the various machine types, measured values were standardized to Hologic BMD using published conversion equations.[12] Application of these standardization formulas has been reported to reduce manufacturer-related variability in bone density to <3%.[12]

Defining Osteopenia and Osteoporosis Prevalence

After the BMD measures were standardized to Hologic values, site-specific T scores were calculated by subtracting the peak referent bone density values from the patient's observed value. This difference was then divided by the corresponding referent standard deviation. For the spine, we used the manufacturer's reference database (Hologic Inc., Bedford, MA). For the hip, we employed reference data collected as part of the National Health and Nutrition Examination Survey (NHANES)-III.[3] The peak reference values and corresponding standard deviation (SD) for both African Americans and Caucasians are shown in Table 1. Normative peak BMD values are approximately 1 SD higher (0.09–0.14 gm/cm^2) in African Americans than Caucasians at both the hip and spine.

We calculated two T scores for each participant. The first set of T scores was generated using peak sex-matched reference data from Caucasians. We then generated a second set of T scores using peak values from referent sex-matched African Americans.

We defined osteopenia and osteoporosis using the

Table 1. Sex-specific bone mineral density values (gm/cm^2) for lumbar spine and femoral neck for study patients (n=175) and normative populations*

Mean ± standard deviation bone mineral density values (gm/cm^2)

	Lumbar Spine		Femoral Neck	
	Men	Women	Men	Women
Study patients†	1.104 (0.20)	1.084 (0.18)	0.879 (0.16)	0.848 (0.16)
Peak normative Caucasians	1.091 (0.11)	1.047 (0.11)	0.934 (0.14)	0.858 (0.12)
Peak normative African Americans	1.197 (0.11)	1.150 (0.11)	1.074 (0.17)	0.950 (0.13)

* Lumbar spine reference data from Hologic Inc. (Bedford, MA); femoral neck reference data from the National Health and Nutrition Examination Survey (NHANES)-III[3]; † Participants in the Consortium for the Longitudinal Evaluation of African Americans with Early RA (CLEAR)[8,9]

T-score thresholds established by the World Health Organization for diagnosis in postmenopausal Caucasian women.[13] Based on these thresholds, osteoporosis was defined as a BMD value ≥2.5 SD below the young adult mean. Osteopenia was defined as a BMD ≥1 SD and <2.5 SD below this mean. Patients were classified as having osteopenia or osteoporosis based on their lowest T score. We examined sex differences in site-specific BMD using Students' t test. Differences in osteopenia and osteoporosis frequency, based on the presence or absence of race/ethnicity adjustment, were assessed using McNemar's test. All analyses were performed with SAS (SAS Inc., Cary, NC).

RESULTS

Patient Characteristics

Characteristics of the 175 study participants are summarized in Table 2. Study participants had a mean age of 51 ± 13 years and were predominantly women (n=144, 82%). Patients had a mean RA disease duration of 14 ± 7 months and a substantial majority of participants (n=145, 83%) had received prior treatment with oral glucocorticoids (mean self-reported prednisone dose = 9.4 ± 9.2 mg/d). Patients had a mean body mass index of 31.3 ± 7.1 kg/m^2 and approximately one-half of patients (n=99, 57%) were either current or past cigarette smokers. Many were receiving either calcium (n=82, 47%) or vitamin D supplements (n=26, 15%) at the time of DXA measurement, but only a small minority had ever used prescription bisphosphonate treatments (n=6, 3%). Overall, patients had moderate-to-severe disease activity as evidenced by mean tender and swollen joints counts in addition to mean disability index scores (Table 2).

Site-Specific BMD Values and T Scores

Sex- and site-specific BMD values are summarized in Table 1. Although differences were not significant, BMD values for both lumbar spine (p=0.6) and femoral neck (p=0.3) were approximately 2–4% higher in men than in women. Using Caucasian reference data, the mean lumbar spine and femoral neck T scores were 0.29 (±1.65) SD and -0.14 (±1.28) SD, respectively. Corresponding T scores were -0.65 (±1.65) and -0.85 (±1.17) for the spine and femoral neck, respectively, when race/ethnicity-matched referent data were used.

Osteopenia and Osteoporosis Prevalence

Results of our primary analyses are summarized in Table 3. Using Caucasian referent data, approximately one-third of patients were classified as having osteopenia and/or osteoporosis (n=48, 32.9%), and eight patients (4.7%) were classified as having osteoporosis. When African-American normative data were used instead, over one-half of patients were classified as having osteopenia or worse (n=94, 55.3%), and 15.9% (n=27) were classified to be osteoporotic.

The overall prevalence of osteoporosis increased significantly for both lumbar spine (p<0.001) and femoral neck (p=0.008) when race/ethnicity-matched referent data were used compared to the use of Caucasian normative data. Likewise, the prevalence of osteopenia and/or osteoporosis (T scores <-1 SD) at the lumbar spine (p<0.001) and femoral neck (p<0.001) was significantly greater with the use of race/ethnicity-matched normative data (Table 3).

Recognizing the current controversy in applying the World Health Organization's criteria to men and premenopausal women, we restricted our analyses to postmenopausal women and obtained similar results (data not shown). Among postmenopausal women (n=88), four (4.6%) were classified to be osteoporotic at both the lumbar spine and femoral neck with the use of normative data from Caucasian women. With the use of race/ethnicity-adjusted T scores, the preva-

Table 2. Osteoporosis risk factors and rheumatoid arthritis-related characteristics of study patients (n=175)*

	Mean ± SD or frequency (%)
Osteoporosis Risk Factors	
Age (Years)	51 ± 13
*Sex**	
Premenopausal women	55 (31)
Postmenopausal women	88 (50)
Men	31 (18)
Body mass index, kg/m^2	31.3 ± 7.1
Ever glucocorticoid use	145 (83)
*Smoking Status**	
Never	75 (43)
Past	45 (26)
Current	54 (31)
Ever use of bisphosphonate therapy	6 (3)
Rheumatoid arthritis-related characteristics	
Disease duration, months	14 ± 7
Rheumatoid factor positivity	119 (68)
Rheumatoid nodules	26 (15)
Erosive disease‡	52 (30)
Tender joints (range 0–32)	11.2 ± 11.4
Swollen joints (range 0–32)	5.5 ± 7.1
HAQ disability index score (range 0–3)†	1.59 ± 0.94

* Denominator as noted (n=175) with the exception of missing data for menopausal (n=1) and smoking status (n=1); † HAQ: Health Assessment Questionnaire[11]; ‡ Based on physician documentation at the time of study enrollment

lence of osteoporosis at the spine (n=15, 17%) and femoral neck (n=8, 9%) for postmenopausal women was higher ($p<0.05$ for differences).

DISCUSSION

To our knowledge, this is the first study to examine the prevalence of low bone density in African-American patients with RA (including patients with either early or established disease). Depending on the race/ethnicity of the reference population used, we found that approximately one-third to half of patients were osteopenic or worse, and 5–16% were osteoporotic with <2 years of disease duration.

Although low bone mass was not infrequent, these prevalence rates do not appear to be disproportionately higher than that seen in African Americans without RA. Among population-based postmenopausal African-American women,[14] 5% have osteoporosis of the femoral neck with the use of Caucasian reference data, identical to the 5% prevalence noted in our study. This is consistent with previous studies involving Caucasians with early RA,[15,16] suggesting that BMD is relatively preserved in the early stages of the disease.

In the absence of a documented insufficiency fracture, there is no accepted standard regarding the best approach to the diagnosis of osteoporosis in non-Caucasians.[5] Our findings confirm that African Americans with RA are at risk of receiving different diagnostic classifications based solely on the normative data used for assessing fracture risk. In comparison to the use of Caucasian reference data, the use of race/ethnicity-specific T scores resulted in a three-fold increase in osteoporosis prevalence among African Americans with early disease. Compared to femoral neck values, the impact of using different normative data was particularly striking for the lumbar spine where the site-specific frequency of osteoporosis increased nearly five-fold with the use of ethnicity-matched data.

Given the present reliance on T scores for clinical decision-making,[6] these findings have implications in terms of healthcare utilization and health outcomes for African Americans. If the use of race/ethnicity-adjusted normative data were to provide the most informative fracture risk assessment, then the use of normative data from Caucasians would lead to an underestimation of fracture risk in African Americans and unacceptably high levels of undertreatment. Approved antiresorptive therapies reduce hip and vertebral fracture risk by as much as 50%.[17] The proven efficacy of bisphosphonate therapy in African Americans,[18] coupled with the fact that such fractures lead to disproportionately poor outcomes among minorities,[19-21] underscores the potential importance of undertreatment in this population.

In contrast, if we assume that the use of normative data from Caucasians provides for the most informative T scores in African Americans, then it follows that the use of race/ethnicity-adjusted T scores may lead to inappropriate overtreatment. If healthcare providers, for instance, were to use a T-score threshold of ≤-2.5 SD to initiate therapy, regardless of the DXA machine used, our results suggest that >10% of all African-American RA patients could be overtreated with antiosteoporosis medications. This number would be even higher with the use of lower treatment thresholds (i.e., T score <-1 or -2 SD).

Recognizing the "lack of consistency" and "near absence of consensus guidelines" for the diagnosis of osteoporosis in non-Caucasians, the International Society of Clinical Densitometry convened a Position Development Conference in July of 2001 to address this issue.[5] The resulting position statement recommended that a uniform Caucasian reference database be employed for the DXA diagnosis of osteoporosis in non-Caucasians. This recommendation was based on two well-founded assertions:

1) the best-available fracture data exists for Caucasians (specifically, postmenopausal Caucasian women), and

Table 3. Site-specific frequency of osteopenia and osteoporosis in study patients based on peak normative reference data used to calculate T scores, number (%)

	Race/Ethnicity of Reference Data Used to Calculate T Score			
	Caucasian Reference Data		African-American Reference Data‡	
	Femoral Neck†	Lumbar Spine	Femoral Neck	Lumbar Spine
Healthy*	131 (76%)	136 (79%)	91 (53%)	107 (62%)
Osteopenia	37 (22%)	31 (18%)	70 (41%)	41 (24%)
Osteoporosis	4 (2%)	6 (3%)	11 (6%)	25 (14%)

* Disease classifications: healthy equivalent to T score > -1 standard deviation, osteopenia equivalent to T score ≤-1 standard deviation and >-2.5 standard deviation, osteoporosis equivalent to T score ≤-2.5 standard deviation; † n=172 patients for femoral neck, n=173 for lumbar spine; ‡ prevalence of osteoporosis higher for both lumbar spine ($p<0.001$) and femoral neck ($p=0.008$) with the use of African-American reference data compared to the use of Caucasian reference data; prevalence of osteopenia and/or osteoporosis higher for lumbar spine ($p<0.001$) and femoral neck ($p<0.001$) with the use of ethnic-matched data.

2) satisfactory databases for all ethnic groups are not likely to be available in the near future.

Using Caucasian reference data, 5% of postmenopausal African-American women were noted to be osteoporotic in the National Health and Nutrition Examination Survey.[14] This estimate closely approximates the lifetime risk of hip fracture in older African-American women[22] (far lower than the fracture rate observed in age-matched Caucasian women), suggesting that the use of Caucasian normative data provides more meaningful T scores in African Americans and that fracture risk may indeed be a function of absolute bone density independent of race/ethnicity.

Although the controversy surrounding osteoporosis diagnosis in non-Caucasians is yet to be resolved, prior investigations have provided insight into possible sources of interethnic variation in BMD. DXA provides a measure of areal bone density (gm/cm^2), values that are confounded by skeletal size. Indeed, when skeletal size and bone diameter are adjusted for, race/ethnicity-specific differences in bone density are either reduced or eliminated.[23-25] Based on this knowledge, it might be possible to use volumetric or three-dimensional BMD (gm/cm^3) as a means of circumventing the race/ethnicity issue. However, validated technologies for volumetric bone density measurement are limited in availability and suffer from a lack of normative data. Moreover, the relationship between volumetric bone density and fracture risk has not been quantified in large, population-based studies.

There are limitations to this study. BMD assessment in this study was restricted to African-American RA patients residing in the southeastern United States. As a result, our prevalence estimates may not be generalizable to other populations. Although we employed routine quality-control measures and standardized measures to limit machine-related variability, BMD values were ascertained on different DXA machines by a number of different technicians, raising the possibility of diagnostic misclassification. Additionally, the standardization equations used in this study were originally developed using pencil-beam DXA technology (as opposed to contemporary fan-beam technology) scanning L2-L4 in the spine rather than L1-L4 used in our study.[12] Despite these limitations, important inferences can be drawn from our work. Namely, physicians and healthcare providers ordering bone density measurements in non-Caucasian subjects need to be aware of the precise reference data being used in order to ensure a meaningful interpretation of individual T scores.

Some have advocated for less reliance on arbitrary T-score thresholds in diagnosing osteoporosis with a move towards assessments of absolute fracture risk,[4] perhaps justifiable given the problems of using T scores in non-Caucasians. However, medical practice and third-party payers often mandate dichotomous disease classifications. Additionally, there is a paucity of data in non-Caucasians that would allow providers to accurately infer absolute fracture risk based on BMD. Until the issue of race/ethnicity in the context of absolute fracture risk assessment can be addressed with much-needed research, it is paramount that a standardized approach to T-score calculation be universally adopted in non-Caucasian patients.

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REFERENCES

1. Bauer D, Gluer C, Cauley J, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 1997;157:629-634.

2. Black D, Nevitt M, Cummings S. Bone densitometry and spine films. In: Cummings S, Cosman F, Jamal S, eds. *Osteoporosis: An Evidence-Based Guide to Prevention and Management.* Philadelphia: American College of Physicians; 2002:29-58.

3. Looker A, Wahner H, Dunn W, et al. Updated data on proximal femur bone mineral levels of U.S. adults. *Osteoporosis Int.* 1998;8:468-489.

4. Cummings S, Bates D, Black D. Clinical use of bone densitometry. *JAMA.* 2002;288:1889-1897.

5. Binkley N, Schmeer P, Wasnich R, et al. What are the criteria by which a densitometric diagnosis of osteoporosis can be made in males and non-Caucasians? *J Clin Densitom.* 2002;5(Suppl):S19-S27.

6. Fuleihan G, Stock J, McClung M, et al. A national random survey of bone mineral density reporting in the United States. *J Clin Densitom.* 2002;5:3-9.

7. Mikuls T, Saag K. Rheumatoid arthritis comorbidity. *Rheum Dis Clin North Am.* 2001;27:283-303.

8. Sokka T, Willoughby J, Yazici Y, et al. Databases of patients with early rheumatoid arthritis in the USA. *Clin Exp Rheumatol.* 2003;21(Suppl 31):S146-S153.

9. Bridges SJ, Hughes L, Mikuls T, et al. Early rheumatoid arthritis in African Americans: the CLEAR Registry. *Clin Exp Rheumatol.* 2003;21(Suppl 31):S138-S145.

10. Arnett F, Edworthy S, Bloch D, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31:315-324.

11. Fries J, Spitz P, Kraines R, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum.* 1980;23:137-145.

12. Genant H, Grampp S, Gluer C, et al. Universal standardization for dual X-absorptiometry: patient and phantom cross-calibration results. *J Bone Miner Res.* 1994;9:1503-1514.

13. Kanis J, Melton LI, Christiansen C, et al. Perspective: the diagnosis of osteoporosis. *J Bone Miner Res.* 1994;9:1137-1141.

14. Looker A, Orwoll E, Johnston CJ, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res.* 1997;12:1761-1768.

15. Keller C, Hafstrom I, Svensson B. Bone mineral density in women and

men with early rheumatoid arthritis. *Scand J Rheumatol.* 2001;30:213-220.

16. Shenstone B, Mahmoud A, Woodward R, et al. Longitudinal bone mineral density changes in early rheumatoid arthritis. *Br J Rheumatol.* 1994; 33:541-545.

17. Seeman E. The antifracture efficacy of alendronate. *Int J Clin Pract Suppl.* 1999;101:40-45.

18. Bell N, Bilezikian J, Bone H, et al. Alendronate increases bone mass and reduces bone markers in postmenopausal African-American women. *J Clin Endrocrinol Metab.* 2002;87:2792-2797.

19. Furstenberg A, Mezcy M. Differences in outcome between black and white elderly hip fracture patients. *J Chronic Dis.* 1987;40:931-938.

20. Kellie S, Brody J. Sex-specific and race-specific hip fracture rates. *Am J Public Health.* 1990;80:326-328.

21. Jacobsen S, Goldberg J, Miles T, et al. Race and sex differences in mortality following fracture of the hip. *Am J Public Health.* 1992;82:1147-1150.

22. Barrett J, Baron J, Karagas M, et al. Fracture risk in the U.S. Medicare population. *J Clin Epidemiol.* 1999;52:243-249.

23. Cundy T, Cornish J, Evans M, et al. Sources of interracial variation in bone mineral density. *J Bone Miner Res.* 1995;10:368-373.

24. Bhudhikanok G, Wang M-C, Eckert K, et al. Differences in bone mineral in young Asian and Caucasian Americans may reflect differences in bone size. *J Bone Miner Res.* 1996;11:1545-1556.

25. Marcus R, Greendale G, Blunt B, et al. Correlates of bone mineral density in the postmenopausal estrogen/progestin interventions trial. *J Bone Miner Res.* 1994;9:1467-1476. ■

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