Bone Geometry Profiles in Women with and without SLE*

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Abstract

Objective—Recent studies have reported an increased risk of fracture among patients with systemic lupus erythematosus (SLE) in comparison to the general population. The aim of this study was to examine associations between SLE status and bone geometry in Caucasian and African American women.

Methods—We compared hip bone mineral density (BMD) and bone geometry parameters among SLE women and controls using hip structure analysis (HSA). 153 DXA scans from the Study of Lupus Vascular and bone Long Term Endpoints (68.7% Caucasian and 31.3% African American) and 4920 scans from the third National Health and Nutrition Examination Survey (59.3% Caucasian and 40.7% African American) were analyzed. Linear regression was used to examine BMD and bone geometry differences by SLE status and by race/ethnicity after adjusting for age and body mass index.

Results—Significant differences were detected between SLE women and control. Among Caucasians, age-adjusted BMD (g/cm^2), section modulus (cm^3) and cross sectional areas (cm^2) were lower among SLE subjects in comparison to control at the narrow neck (0.88 vs. 0.83, 1.31 vs. 1.11 and 2.56 vs. 2.40; p<0.001, <0.01 and <0.0001 respectively), while buckling ratio was increased (10.0 vs. 10.6, p<0.01). Likewise, BMD, section modulus and cross sectional areas were decreased among African American SLE women at all sub regions, while buckling ratios were increased.

Conclusions—There were significant bone geometry differences between SLE women and control at all hip sub-regions. Bone geometry profiles among SLE subjects were suggestive of increased fragility.

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*Part of this work was presented at the 74th Annual Scientific Meeting of the American College of Rheumatology/ 45th Annual Scientific meeting of Association of Rheumatology Health Professionals, Atlanta, Georgia; November 6-11, 2010.

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Keywords

Osteoporosis; Inflammation; Biomechanics; Modeling and Remodeling; Bone densitometry

Introduction

Osteoporotic fracture represents an enormous and growing public health concern [1, 2]. In the United States, 1.5 million fractures are diagnosed annually, with an associated medical cost of 14 billion dollars per year [3, 4]. Osteoporosis is a particular concern among certain populations, including patients with systemic lupus erythematosus (SLE), an autoimmune disease of unknown cause. SLE has a variety of manifestations affecting multiple organ systems and occurs primarily in women in their childbearing years. Treatment for SLE frequently includes corticosteroid to control symptoms, with anti-malarial, immunosuppressive or immunomodulatory medications often added. Supportive therapies to minimize side effects from disease manifestations or from medications include strategies to maintain a normal blood pressure and lipid profile, calcium, 25-hydroxyvitamin D, and other medications to maximize bone health[5].

Data on the prevalence of osteoporotic fracture among patients with systemic lupus erythematosus (SLE) is limited, but recent studies demonstrate that SLE subjects are at a higher risk for fragility fracture than the general population[6-8]. Fractures among patients with SLE can occur at a younger age, including premenopausal females. Furthermore, African American race/ethnicity appears not to be protective against osteoporosis in SLE [9]. There is recent evidence that autoimmunity and its associated inflammation and vitamin D deficiency play key roles in the pathogenesis of adverse skeletal effects in SLE [10]. With recent advances in therapy, life expectancy has improved for patients with SLE [11] and osteoporosis will become an increasingly prevalent complication among patients with SLE.

The gold standard for osteoporosis diagnosis is by performing dual energy x-ray absorptiometry (DXA) scans of the hip and spine [12]. Reduction of hip bone mineral density (BMD) by 1 standard deviation (SD) below age-adjusted mean predicts a 2.4-fold increase of fracture risk [13]. Similarly, BMD improvements measured by DXA have been associated with fracture risk reduction in osteoporosis therapeutic trials [12]. However, many studies have shown that BMD does not fully account for fracture risk [14], and BMD changes with osteoporosis treatment do not fully account for fracture risk reduction [15], suggesting that this clinical assessment does not adequately account for the complex mechanical characteristics of skeletal fragility.

Bones fracture when internal stresses exceed their load-bearing capacity [16,17]. In osteoporosis, fracture occurs with minimal trauma because the load-bearing capacity of the skeleton is compromised. Reduced load-bearing capacity can result from deterioration in the material composition of the skeleton or from changes in the structural geometry of the bones. While there are no reliable non invasive ways to measure the material strength of the skeleton, we are not aware of any evidence suggesting that this parameter is altered in osteoporosis. Thus, changes in internal skeletal stresses are almost entirely a consequence of structural change. Hip structure analysis (HAS) allows for the determination of structural

geometry, from which relevant strength information can be derived[17]. This essential information is not available from conventional DXA.

The value of HSA in predicting skeletal strength has been illustrated by some retrospective analyses of data from large fracture trials [16, 18]. However the clinical applicability of HSA is currently limited by the high intolerance of the technique to skeletal positioning.

These observations are particularly pertinent for patients with SLE because the causes of increased bone fragility in patients with SLE are not fully elucidated. Indeed BMD measurements in patients with SLE who sustain fractures are often higher than those seen in postmenopausal women who sustain fractures[19] In this study, we compared bone geometry parameters in patients with SLE from the Study of Lupus Vascular and bone Long Term Endpoints (SOLVABLE) study [20] to Caucasian and African American women from the third National Health and Nutrition Examination Survey[21] using HSA. We hypothesized that the presence of SLE was associated with bone geometry profiles that predict increased skeletal fragility.

Methods

Study subjects

This study is a retrospective review of DXA and clinical data previously collected on SOLVABLE and NHANES III Caucasian and African American participants. The SOLVABLE cohort consists of women 18 years and older who met at least 4 of the 1982 (or updated 1997) American College of Rheumatology (ACR) classification criteria for SLE[22,23]. Designation of patient race/ethnicity was cultural (by self-declaration) rather than biological. There were three study visits in the protocol for SOLVABLE. The data from the first study visit for SOLVABLE which included interview for osteoporotic risk factors (including self-reported steroid use and 25 hydroxyvitamin D levels), physical examination for anthropometric measurements and SLE disease activity and severity, and imaging for BMD of the hip are included in this report. SOLVABLE patient enrolment occurred between December 2002 and August 2007.

The control population for this study consisted of non-pregnant Caucasian and African American women who participated in the NHANES III study. The NHANES III study was designed to assess the health and nutritional status of the civilian non-institutionalized Caucasian, African American and Mexican American members of the United States population, and was conducted between 1988 and 1994. Data collection was accomplished during household interviews and by direct physical examination at mobile examination centers. Relevant biochemical studies were done, including measurement of serum 25 hydroxyvitamin D levels. Men and non pregnant women 20 years and older in NHANES III who received physical examination and had not fractured both hips were eligible for a DXA scan of the left hip unless there was a history of previous fracture or surgery on the left side (1%), in which case the right side was scanned.

Our study was approved by the Institutional Review Boards of the Medical University of South Carolina and Northwestern University, Feinberg School of Medicine.

Bone Densitometry

Acquisition of DXA data at the hip on SOLVABLE subjects was conducted using a Hologic QDR-4500 (Hologic, Bradford, MA) as specified by the manufacturer with appropriate attention to quality control. Specifically, femur phantoms were measured to assess intra-instrument variation. The intra-instrument coefficient of variation was less than 0.46%. For NHANES, three mobile Hologic QDR1000 DXA scanners (Hologic, Waltham, MA) were used for BMD measurement, with a rigorous quality control program including the use of anthropometric phantoms and close scrutiny of individual scans at a central site. Scans were rejected if they did not meet quality criteria for conventional DXA processing (n=321) or if structural analysis was not possible. Specifically, scans were excluded from structural analysis if they had artifacts or were inappropriately positioned, resulting in excessive ante version or obscured (and cut-off) margins. A total of 2916 Caucasian and 2904 African American scans were available for HSA[21].

Due to the time span between NHANESIII and SOLVABLE studies, our study compares DXA scans obtained using two different DXA generations. Hologic QDR1000 uses pencil beam technology while QDR4500 uses fan beam technology. The main consequence of these differences is a shorter scan time with QDR4500 than with QDR1000. While these technical differences are a potential limitation of the study, comparative studies have shown a high correlation between the two scanners (r^2=0.99, 0.95 and 0.96 at the spine, femoral neck and total hip BMD respectively)[24], implying that the practical consequences of the technical differences are probably minimal. Nevertheless, cross-calibration would have been desirable, but was not practical due to the retrospective nature of our study. For bone geometry measurement, the two scanners are reasonably consistent except at the proximal shaft. (Personal communication from HSA-developer).

Hip Structure Analysis (HSA)

The HSA program is based on a principle first described by Martin and Burr, namely that mineral profiles created during single photon absorptiometry (SPA) bone densitometry are a projection of the corresponding bone cross-section, and can be used to define its geometry at that location[25]. The program uses the distribution of mineral mass in a line of pixels across the bone axis to measure geometric properties of cross-sections in cut planes traversing the bone. Regions of interest include the narrow femoral neck (located at the narrowest point of the femoral neck), the intertrochanteric region (traversing the bisector of the neck and shaft axes), and the shaft (located 1.5 times the neck width distal to the intersection of the neck and shaft axes). These sites are clinically relevant since the majority of hip fractures involve the femoral neck or intertrochanter area.

Five parallel mass profiles, which are spaced about 1 mm apart along the bone axis (corresponding to a 5 mm section thickness) are generated and averaged using an algorithm developed by Thomas Beck[26], to derive the following parameters: 1) bone mineral density (grams per square centimeter), 2) outer cortical diameters (centimeters), 3) bone cross sectional area (square centimeter), and 4) the cross-sectional moment of inertia. The section modulus (cm^3) was calculated as cross-sectional moment of inertia divided by the maximum

distance from the center of mass to the outer cortical margin. To estimate the average cortical thickness and buckling ratios, cortices of the narrow neck, inter-trochanter and shaft were modeled as circular annuli with 60%, 70%, and 100% of the measured mass in the cortex respectively. Buckling ratios were then calculated as the maximum distance from the center of mass to the outer diameter divided by the (estimated) mean cortical thickness. The program also measures neck shaft angle (the angle subtended by the neck and shaft axes) and neck length (the distance between the femoral head and the point of intersection between the neck and shaft axes).

The two studies relied on the same HSA operator, which should reduce systematic measurement error between the two studies. The HSA operator did not know that the SLE patients had SLE or that we would be using the NHANES data for comparison.

Statistical Analysis

Descriptive analyses were performed to examine bone density and geometry parameters among Caucasian and African American women from NHANES III (without SLE) and the SOLVABLE (SLE) studies. Linear regression was used to examine differences in bone density and geometry by SLE status and by race/ethnicity after adjusting for age and body mass index. In addition, the mean difference and 95 % confidence intervals between those with and without SLE were determined by race/ethnicity. Because the NHANES III population was compared to an external clinical population, NHANES sampling weights and design variables were not used to account for the survey design of the NHANES III population[27] Data were analyzed using SAS system (version 9.1; SAS institute; Cary, NC).

Results

A total of 164 Caucasian and African American women from the Chicago Lupus Study were enrolled in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE), from whom 153 hip DXA scans (68.7% Caucasian and 31.3% African American) were adequate for HSA. Patients with analyzable scans (n=153) were of similar age and race/ ethnicity distribution as those whose scans were not analyzable (n=11), with disease markers (C3, C4 and double-stranded DNA antibody levels) also being equally distributed. Smoking status and corticosteroids use were also similar between the two groups. From the NHANES cohort, a total of 4920 DXA scans (59.3% Caucasian and 40.7% African American) were available for analysis.

Demographic characteristics of the SLE patients and NHANES controls are presented in Table 1. Among Caucasian women, NHANES participants were older, had similar BMI and 25-hydroxyvitamin D levels, and were more likely to currently smoke, but less likely to be former smokers than participants with SLE. Among African American women, NHANES participants were a similar age and had similar BMI and 25-hydroxyvitamin D levels, but were more likely to currently smoke than women with SLE. Among women with SLE, disease duration was similar in African Americans and Caucasian women; however, the percent of African American women with American College of Rheumatology/Systemic Lupus International Collaborating Clinics-Damage Index (ACRI/SLICC-DI) scores greater than zero was higher in African American than Caucasian women (80.2% versus 55.7%) as

was the percent with Systemic Lupus Activity Measure (SLAM) greater than 7 (49.0% versus 28.7%). However there were no significant differences in any of the HSA parameters measured in the hip between SLE patients with (SLAM>7) and without (SLAM<=) active disease, or with (SLICC>0) and without (SLICC=0) disease damage. Additionally, among women with SLE, African Americans were slightly (2 +/- SD years) younger with a higher mean BMI and a lower mean 25-hydroxyvitamin D level compared to Caucasians. African American women were also more likely to be current smokers, and less likely to be former smokers than Caucasian women.

After stratifying by SLE status and race/ethnicity, age and BMI-adjusted means were determined for HSA parameters at the femoral neck, trochanter and proximal femoral shaft (Table 2). In general, BMD and bone geometry parameters were significantly different among both Caucasian and African American women with SLE compared to NHANES at all the areas of the skeleton, with some site-specific differences between the race/ethnic groups (figure 1 a, b & c). Specifically, BMD was reduced in both Caucasian and African American women with SLE compared to NHANES controls at all areas, although the difference between Caucasian women did not attain statistical significance at the femoral shaft region.

We examined our data for differences in skeletal outer diameter to determine if skeletal redistribution was associated with BMD reduction seen among women with SLE. In both Caucasians and African Americans the outer diameter was reduced at all areas (SLE vs. controls) although the difference was not significant at the narrow neck among Caucasians. Since a narrower bone with equivalent bone quantity would have a higher BMD these results suggest that reductions in the quantity of bone, rather than expanded diameter are responsible for the low BMD seen among SLE patients. In support of this theory, low BMD was associated with reductions in bone tissue cross sectional area among African American and Caucasian patients with SLE at all areas analyzed (figure 1, A-C).

We then examined associations between SLE status and skeletal resistance to bending forces, and to local buckling by looking at associations between disease status and section modulus and buckling ratio at common fracture sites (femoral neck and trochanter). Section modulus was reduced in both race/ethnic groups, suggesting reductions in bending resistance among women with SLE. This change was associated with reductions in outer diameter as noted above. At the same time buckling ratio was increased in both race/ethnic groups (non significant difference among Caucasians at the intertrochanter) suggesting an increased tendency for buckling. This finding suggests that cortical thinning proceeds faster among SLE patients than control given that SLE patients have a narrower outer skeletal diameter.

Discussion

Our study presents the first data available comparing bone geometry parameters between women with SLE and controls. Using HSA, we detected the presence of significant bone geometry differences between patients and controls, a finding that has major implications in the management of patients with SLE considering the impact of bone geometry on strength.

Specifically, the presence of reduced section modulus and cross-sectional areas, along with increased buckling ratios at common fracture sites among SLE patients implies that SLE patients are more likely to suffer a hip fracture than the general population in the event of a fall.

This clinically important information, which is not available from conventional DXA is consistent with epidemiological data, and highlights the need for better ways for fracture prediction among patients with SLE. Our findings set the stage for studies to look for factors that underlie the differences in bone geometry and strength, a process which could pave the way for the development of therapeutic agents that specifically target these factors.

It is well documented that SLE is associated with reduced BMD at the hip and spine[28, 29], but the mechanistic explanation for this difference has hitherto been lacking. BMD reduction can result from changes in skeletal mineralization, its distribution or quantity[30]. While we did not look at mineralization, the finding of reduced outer skeletal diameters at the proximal hip among women with SLE suggests that reduced bone quantity rather than skeletal redistribution by radial expansion is the mechanism responsible for reduced BMD at this skeletal site in SLE. This position is additionally supported by the presence of reduced proximal hip cross-sectional areas among the women with SLE.

The dimensional differences seen in our study suggest that the adaptive changes that normally preserve bone strength in the face of aging-associated bone loss may be altered in SLE. Specifically, as BMD declines with age, section modulus (a measure of bending resistance) is maintained by subperiosteal apposition, a process that results in the radial expansion of the skeleton while there is on-going endosteal bone loss, as was documented by Beck et al[21]. Section modulus scales exponentially with changes in bone diameter, making subperiosteal apposition a highly efficient mechanism to preserve bone strength since only a fraction of bone lost on the endocortical surface need be deposited on the subperiosteal surface for biomechanical equivalence. In our study BMD reduction was accompanied by significant reductions of section modulus among SLE patients, implying failure of subperiosteal apposition.

There are several reasons to account for alterations in bone geometry among patients with SLE, including effects of inflammation, corticosteroids, vitamin D deficiency, and altered skeletal loading from arthritis, myositis and/or osteonecrosis.

The finding of low BMD among steroid-naïve SLE patients has led to the hypothesis that inflammation by itself can lead to bone loss and fracture[31], although the mechanisms by which this comes about are yet to be elucidated. In one study, markers of inflammation were correlated with markers of bone turnover, and bone loss was more severe among patients with higher levels of pro-inflammatory cytokines, highlighting the potential role of inflammation in the acceleration of bone turnover[32]. Recent studies using animal models of inflammatory arthritis have shown that inflammation can lead not only to low BMD, but also to unfavorable bone geometry parameters, raising the possibility that both skeletal remodeling and skeletal modeling can be impacted by inflammation[33, 34], ultimately leading to fragility. While we did not directly examine inflammation in our study, the presence of

low BMD and abnormal bone geometry supports the concept that skeletal modeling and remodeling can be simultaneously affected by SLE.

Corticosteroids represent a potent therapy for inflammation, and are commonly used in SLE. Corticosteroids have many adverse skeletal effects that can lead to bone loss and ultimately fracture[35]. It has been reported that up to 50% of patients on long term corticosteroids or patients with Cushing's syndrome develop fragility fracture[36-39]. However, a recent meta-analysis looking at fracture risk among corticosteroid-treated patients showed that steroid-associated BMD change did not fully account for the increased fracture risk among steroid treated patients[40]. Moreover, corticosteroid-treated patients tended to fracture at higher BMDs than control[40], suggesting that other skeletal parameters are involved in fragility seen among steroid-treated patients. Kaji et al examined the effect of corticosteroids on bone geometry among middle-aged and elderly women[41]. Using Quantitative Computerized Tomography (QCT) scans of the distal radius, they demonstrated that a variety of bone geometry parameters including total skeletal area, periosteal circumference, cortical area and polar strength-strain index were significantly lower among steroid- treated pre-menopausal women compared to controls, findings that were similar to the effects of endogenous cortisol hyper secretion seen in Cushing's syndrome patients[41]. Moreover, corticosteroid-treated patients with vertebral fractures had lower total area, cortical area, periosteal circumference and polar strength-strain index compared to steroid-treated patients without vertebral fracture[41]. Collectively, these findings suggest that hypercortisolism can bring about changes of bone geometry that resemble the changes we detected among SLE patients.

Vitamin D is known to protect against fracture but its mechanisms of action have not been fully elucidated. A recent meta-analysis showed that supplementation with 700-800 IU of vitamin D significantly reduced the risk of hip and non vertebral fracture (Relative Risk reductions of 26% and 23% respectively)[42]. While these fracture benefits are partly a consequence of improved muscle function with reduced fall risk, it is widely believed that vitamin D also improves bone strength although mechanical studies in support of this assertion have not been available. In a 2 year randomized controlled trial that examined consequences of vitamin D (and calcium) supplementation versus placebo in middle-aged to elderly men using QCT, Daly et al showed that there was expansion of mid-femur medullary area among the placebo subjects, with significant reductions of cross-sectional area, while these parameters were preserved among subjects taking vitamin D and calcium[43]. Preservation of cross-sectional area has a direct consequence on compressional resistance, with potential implications on the buckling susceptibility as well. In addition, there was relative preservation of torsional resistance among the vitamin D and calcium recipients. Increased mid femur medullary area seen among placebo subjects probably resulted from increased endocortical resorption, highlighting the skeletal impact of vitamin D in high turnover situations. Several cross-sectional studies examining skeletal health in SLE have reported low levels of vitamin D[44], raising the possibility that reduced bone strength due to abnormal bone geometry might be a factor in skeletal fragility.

Another potential explanation for the observed differences in section modulus lies in the possibility of differential skeletal loading between SLE patients and control. Mechanical loading of the skeleton is believed to be one of the most potent stimuli for skeletal

adaptation during postnatal life[45], with the greatest effect occurring during growth. According to Frost, muscle forces dominate a bone's postnatal structural adaptations to mechanical usage, modified somewhat by body weight and one's voluntary physical activities[46]. This assertion suggests that without exposure to optimal levels of muscle-generated bone strains one can fail to realize their full (genetically determined) mechanical potential. In SLE, there are a number of factors that can compromise skeletal loading, thereby preventing the full expression of the genetically-specified blueprint of modeling and remodeling, potentially resulting in reduced skeletal strength. These include inflammation, pain and fatigue and steroid-induced myopathy.

Overall, skeletal loading can be expected to have a more localized skeletal effect while the non mechanical factors can be expected to have a more global scope of action. As a result, it is very likely that the bone geometry differences seen at the proximal hip also exist at other skeletal sites, implying a global fracture risk in SLE. Furthermore, it has been suggested that the non mechanical factors act by either altering the mechanical regulation of bone cells (by altering the mechanical set-point of bone) or by a direct effect on bone cells themselves, independent of mechanical stimuli[47]. Accordingly, the non mechanical factors have the potential to affect both the structural and material properties of the skeleton, while skeletal loading would primarily alter the structural properties of bone[47].

While bone geometry trends among SLE patients were in the direction consistent with increased fragility, proximal shaft buckling ratios trended in the opposite direction in our study. The reasons for these unexpected findings are not immediately clear to us although there was a slight difference in the location of this region of interest between the two studies. Additional studies are needed to clarify on the causes of, and consequences of the unexpected proximal shaft buckling ratios.

This study has some limitations that may have affected the results. First, we have used a 2-dimensional technique to determine cross-sectional diameters and assess bending properties in the image plane[48]. It is very likely that there are significant differences between patients and controls in other planes as well, which we are unable to capture. Second, cortical thickness component of this study is modeled on the assumption that the cortex occupies a fixed percentage of the wall, and that bone loss in SLE affects the cortical and trabecular components to the same degree as occurs with aging. Accordingly, our study would overestimate cortical thickness (and underestimate buckling ratios) if the percent involvement of the cortex is greater than it is the general population, and vice versa. Thirdly, BMD differences at the femur could also result from differences in fat distribution around the femur between patients and control[49], however this is made less likely by the lack of a significant difference in BMI after controlling for race/ethnicity. Moreover, we were unable to perform scanner cross-calibration by scanning recommended hip phantoms at each of the DXA machine as has been recommended. Furthermore, slight incompatibilities exist between software versions used in NHANES and our study which could have affected geometry estimates.

Another area of potential concern pertains to the use of medications among the SOLVABLE population. Use of bisphosphonates in this young population was rare out of concerns for

pregnancy. Steroids were used in less than half of the patients and the average dose is low. So though steroids can affect bone health, the low dose and reduced use in this population should minimize this concern.

In conclusion, our findings show that SLE is associated with changes in bone geometry that are suggestive of increased fracture risk. These changes are not captured by conventional DXA, and highlight the importance of including bone geometry on fracture-prediction models for patients with SLE. Our study focuses on the structural composition of the skeleton. Other aspects of bone quality including bone micro architecture, bone turnover and material composition which are known to influence bone strength were not studied. Considering that SLE patients often have multiple osteoporosis risk factors which could potentially alter these parameters, it will be worth examining these parameters in future studies to determine their impact on fracture risk in SLE.

Acknowledgments

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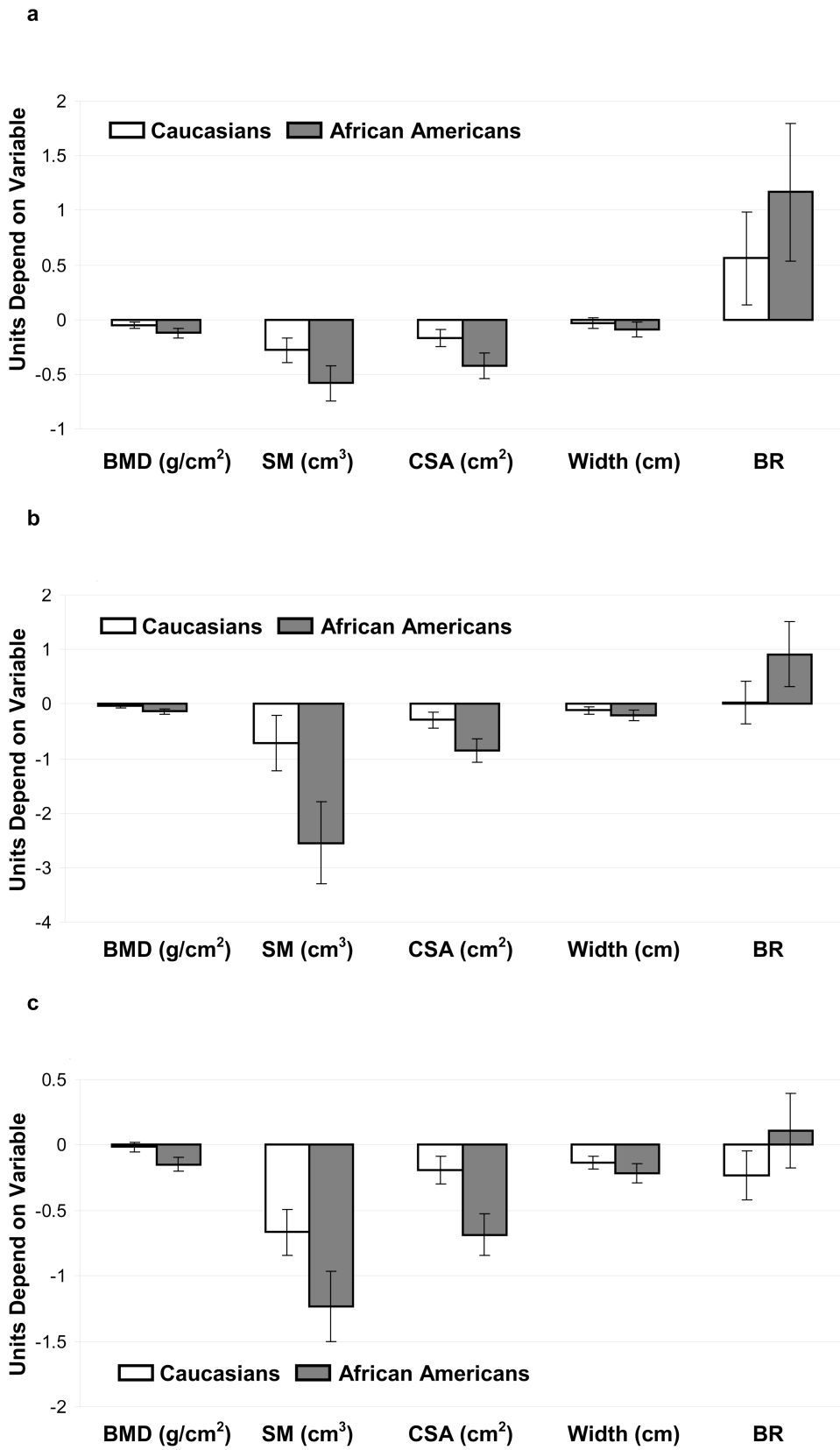
a

b

c

Figure 1.

(A): Comparisons (SLE vs. NHANES) for bone mineral density (BMD) and bone geometry parameters (Section modulus-SM, cross-sectional area-CSA, Width and Buckling ratio-BR) were made for Caucasian(open bars) and African American(grey bars) subjects. Units depend on variable.

a. Narrow Neck: differences (95% Confidence Interval) between SLE and NHANES in Caucasians and African Americans adjusted for age and body mass index

(B): Comparisons (SLE vs. NHANES) for bone mineral density (BMD) and bone geometry parameters (Section modulus-SM, cross-sectional area-CSA, Width and Buckling ratio-BR) were made for Caucasian(open bars) and African American(grey bars) subjects. Units depend on variable.

b. Intertrochanter Region: differences (95% Confidence Interval) between SLE and NHANES in Caucasians and African Americans adjusted for age and body mass index

(C): Comparisons (SLE vs. NHANES) for bone mineral density (BMD) and bone geometry parameters (Section modulus-SM, cross-sectional area-CSA, Width and Buckling ratio-BR) were made for Caucasian(open bars) and African American(grey bars) subjects. Units depend on variable.

c. Femoral Shaft Region: differences (95% Confidence Interval) between SLE and NHANES in Caucasians and African Americans adjusted for age and body mass index

Table 1

Age-adjusted levels (95% CI) of population characteristics stratified by race and SLE status.

	White Women		Black Women	
	NHANES (n=2916)	SLE (n=105)	NHANES (n=2004)	SLE (n=48)
Age [*] (years)	53.8 (53.2, 54.5)	44.8 (41.3, 48.3)	43.4 (42.6, 44.2)	42.3 (37.2, 47.4)
Menopausal [*,a] (%)	55.1 (53.3, 56.9)	40.0 (31.1, 49.6)	34.6 (32.5, 36.7)	39.6 (26.9, 53.9)
Age at menopause [†,b] (years)	47.4 (47.1, 47.8)	43.1 (41.0, 45.3)	46.0 (45.5, 46.6)	39.0 (35.8, 42.2)
Years since menopause [†,c] (years)	21.9 (21.3, 22.5)	11.4 (7.8, 14.9)	16.8 (15.9, 17.6)	11.5 (6.3, 16.7)
BMI (kg/m^2)	26.3 (26.1, 26.5)	26.3 (25.1, 27.5)	29.2 (28.9, 29.5)	29.4 (27.6, 31.2)
25-hydroxyvitamin D (ng/ml)	29.9 (29.5, 30.3)	31.1 (29.1, 33.1)	17.7 (17.3, 18.2)	16.4 (13.4, 19.4)
Obese [d] (%)	22.8 (21.3, 24.4)	20.5 (13.8, 29.4)	38.9 (36.8, 41.1)	43.9 (30.5, 58.3)
Severe vitamin D Deficient [e] (%)	1.1 (0.8, 1.6)	2.9 (0.9, 8.5)	11.0 (9.6, 12.5)	19.7 (10.5, 33.7)
Current Smoker (%)	23.2 (21.6, 24.8)	4.9 (2.2, 10.6)	24.4 (22.5, 26.3)	14.0 (7.0, 25.8)
Former Smoker (%)	21.6 (20.1, 23.2)	33.6 (25.1, 43.2)	12.8 (11.4, 14.4)	26.7 (15.9, 41.2)
SLE Duration (years)	----	12.0 (10.4, 13.7)	----	13.5 (11.0, 15.9)
SLICC > 0 (%)	----	55.7 (45.6, 65.3)	----	80.2 (66.6, 89.2)
SLAM > 7 (%)	----	28.7 (20.8, 38.1)	----	49.0 (35.1, 63.0)

[*] Unadjusted;

[†] Limited to those who went through menopause;

[a] Menopause is defined by the following algorithm. A women is considered menopausal if no menses in last 12 months (and not currently breastfeeding and no surgery done which could complicate interpretation of menopausal status); total hysterectomy and bilateral salpingo-oophorectomy; if no menses and had a hysterectomy, ovary status unknown or known to have at least one ovary, FSH >23 IU/L; or if menopausal status unknown and FSH unknown and age 50 years. Age 50 years is the median age of menopause in NHANES women who have not had a hysterectomy or oophorectomy;

[b] Age of menopause is defined as age at last menses, or when a hysterectomy was preformed prior to menopause, age when FSH was measured > 23 IU/L or at 50 years of age;

[c] Years since menopause, was defined as current age minus age at menopause plus 1 with the 1 added to differentiate between women who went through menopause the same year as their examination and women who are not menopausal;

[d] Obesity is defined as BMI 30kg/m^2;

[e] Severely vitamin D deficient is defined as less than 10 ng/ml.

Table 2

Age- and BMI-adjusted mean (95% CI) bone mineral density and bone structure levels stratified by race and SLE status.

	Whites		Blacks	
	NHANES (n=2916)	SLE (n=105)	NHANES (n=2004)	SLE (n=48)
Narrow Neck Region				
BMD(g/cm^2)	0.88 (0.88, 0.89)	0.83 (0.80, 0.86)†	0.96 (0.95, 0.96)	0.83 (0.79, 0.87)‡
Section Modulus(cm^3)	1.31 (1.30, 1.32)	1.11 (1.06, 1.17)*	1.38 (1.37, 1.40)	1.01 (0.93, 1.09)‡
Cross Sectional Area (cm^2)	2.56 (2.55, 2.58)	2.40 (2.32, 2.47)‡	2.74 (2.72, 2.76)	2.32 (2.20, 2.44)‡
Width (cm)	3.07 (3.06, 3.08)	3.04 (3.00, 3.09)	3.03 (3.02, 3.04)	2.94 (2.87, 3.01)
Buckling Ratio	10.0 (9.94, 10.1)	10.6 (10.2, 11.0)*	9.13 (9.03, 9.23)	10.3 (9.67, 10.9)†
Intertrochanter Region				
BMD (g/cm^2)	0.86 (0.86, 0.87)	0.82 (0.79, 0.85)*	0.94 (0.93, 0.94)	0.80 (0.75, 0.84)‡
Section Modulus (cm^3)	3.76 (3.74, 3.79)	3.54 (3.40, 3.68)*	3.81 (3.78, 3.85)	3.03 (2.81, 3.24)‡
Cross Sectional Area (cm^2)	4.35 (4.32, 4.37)	4.05 (3.91, 4.20)‡	4.61 (4.58, 4.65)	3.76 (3.55, 3.97)‡
Width (cm)	5.31 (5.30, 5.32)	5.19 (5.13, 5.26)†	5.20 (5.18, 5.22)	4.98 (4.89, 5.08)‡
Buckling Ratio	9.25 (9.17, 9.32)	9.27 (8.88, 9.66)	8.58, 8.49, 8.67)	9.49 (8.90, 10.1)*
Femur Shaft Region				
BMD (g/cm^2)	1.29 (1.29, 1.30)	1.28 (1.24, 1.31)	1.34 (1.33, 1.35)	1.19 (1.14, 1.25)‡
Section Modulus (cm^3)	2.26 (2.25, 2.28)	1.93 (1.85, 2.00)	2.32 (2.30, 2.34)	1.67 (1.55, 1.79)‡
Cross Sectional Area (cm^2)	3.78 (3.76, 3.80)	3.59 (3.48, 3.69)‡	3.91 (3.89, 3.94)	3.23 (3.06, 3.39)†
Width (cm)	3.09 (3.08, 3.10)	2.95 (2.90, 3.00)‡	3.08 (3.07, 3.09)	2.86 (2.79, 2.94)‡
Buckling Ratio	3.62 (3.59, 3.70)	3.39 (3.21, 3.57)	3.46 (3.42, 3.51)	3.57 (3.29, 3.86)

P-values are for comparisons within racial group between NHANES participants and individuals with SLE:

* p-value <0.01;

† p-value <0.001;

‡ p-value <0.0001.