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# Association of Osteoporosis and Cardiovascular Disease in Women With Systemic Lupus Erythematosus

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***Objective.*** **Young women with lupus are at increased risk for premature osteoporosis and cardiovascular disease. Experimental evidence suggests that inflammation and immune-mediated mechanisms, key factors in the pathogenesis of lupus, play a role in osteogenesis and atherogenesis. This study investigated whether bone mineral density (BMD) was associated with the carotid plaque index, intima media thickness (IMT), or coronary artery calcium score in lupus patients.**

***Methods.*** **In this pilot study, 65 women with lupus underwent carotid B-mode ultrasound to measure the carotid plaque index and IMT, and dual x-ray absorptiometry to measure BMD at the lumbar spine and hip. As part of a feasibility study, 13 of these 65 patients also underwent electron-beam computed tomography to assess coronary artery calcification.**

***Results.*** **The carotid plaque index was higher (1.00, 1.00, and 0.38, respectively) in the patients in the lowest and middle tertiles of hip BMD when compared with patients in the highest tertile of hip BMD. The correlation coefficient between the coronary artery calcium score and lumbar spine BMD was −0.57 ($P$ = 0.04), and between the coronary artery calcium score and hip BMD was −0.55 ($P$ = 0.05).**

***Conclusion.*** **These results demonstrate an association between decreased BMD and both an increased carotid plaque index and presence of coronary artery calcification in a small cohort of young women with lupus.**

Systemic lupus erythematosus (SLE) is the prototypic systemic, inflammatory autoimmune disease that affects predominantly young, premenopausal women. Because survival has improved over the last 2 decades, attention is now focused on complications leading to late mortality and progressive morbidity. Increasing numbers of young women with SLE are experiencing fracture, stroke, and myocardial infarction, complications typically associated with aging in non-SLE populations of women. The risk of fracture was increased 5-fold in a large cohort of lupus patients whose mean age was <45 years (1). Similarly, the risk of myocardial infarction reached 50 times higher than expected in women with SLE who were ages 35–44 years, a population that should otherwise be protected from such risks (2).

Clinical evidence supports an association between low bone mineral density (BMD) and vascular calcifications in postmenopausal women (3). These findings, that women with SLE are at increased risk for both clinical osteoporotic and cardiovascular outcomes at a much younger age, suggest that this group of women may provide an ideal population in which to study the underlying relationship between these conditions independent of age. Clearly, there is a role for traditional risk factors, such as sedentary lifestyle, hypertension, and hyperlipidemia, in the premature development of osteoporosis and atherosclerosis in patients with SLE. Furthermore, corticosteroids, commonly used in the treatment of SLE, likely contribute to these morbidities. However, we hypothesize that the underlying link to osteoporosis and cardiovascular disease is also related to the nature of SLE.

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Inflammation, which plays an important role in both osteoporosis (4) and atherosclerosis (5), and immunologic factors are likely candidates, considering the inflammatory and immunologic nature of SLE. New information linking the role of inflammation and tumor necrosis factor (TNF) superfamily members in atherosclerosis (5,6) and osteoporosis (4), respectively, may be particularly relevant in the setting of SLE, a disease characterized by inflammation. Macrophages play an essential role in the initiation and progression of atherosclerosis and, once activated, secrete cytokines and chemokines. In addition, up-regulation of TNF superfamily members, including the receptor activator of nuclear factor κB (RANK), the ligand for RANK (RANK-L), and osteoprotegerin, which serves as the decoy receptor for RANK-L, contribute to bone resorption and osteoporosis by increasing osteoclast function and differentiation. These superfamily members may also play a role in vessel calcification, which may be an early event in the development of atherosclerotic lesions (7). Endothelial cell injury and autoantibodies to oxidized low-density lipoprotein (ox-LDL) as well as anticardiolipin antibodies are increased in SLE patients compared with controls (8). The uptake of ox-LDL is a key event in promoting atherogenesis and was recently noted to inhibit bone cell differentiation (7).

Ongoing collaborative studies at Northwestern University Medical School and the University of Pittsburgh School of Medicine are examining the prevalence of bone fracture, stroke, and myocardial infarction, as well as surrogate markers for these outcomes, including BMD, carotid plaque index, intima media thickness (IMT), and coronary artery calcification, in women with SLE. Even though the risk for bone fracture and overt cardiovascular outcomes in this population is high, the actual numbers of these events are too small to adequately determine whether there is an association between them. An alternative strategy is to examine bone and vascular status as defined by imaging techniques or surrogate markers for these outcomes. We investigated whether BMD was associated with the carotid plaque index, IMT, or coronary artery calcium score in women with SLE.

## PATIENTS AND METHODS

**Patients.** As part of 2 funded studies designed to examine the prevalence and risk factors associated with cardiovascular disease in women with lupus conducted at the University of Pittsburgh, B-mode carotid ultrasound was performed on 289 women. Near the end of the studies, consecutive women were invited to undergo dual x-ray absorptiometry (DEXA) scans to assess BMD. Sixty-five women completed the DEXA-scan evaluation. Similarly, as part of a feasibility pilot study, 13 of these 65 women also underwent electron-beam computed tomography to assess coronary artery calcification. All patients provided informed consent for their participation (see Table 1 for a description of the study participants).

**Table 1.** Comparison of characteristics between 65 SLE patients participating in both the cardiovascular and osteoporosis studies and 224 SLE patients participating in the cardiovascular study only*

| Characteristic | Dual-study participants (n = 65) | Single-study participants (n = 224) | *P* |
|---|---|---|---|
| Age at study visit, years | 44.6 ± 11.4 | 45.1 ± 10.8 | 0.77 |
| Age at menopause, years† | 43.7 ± 7.7 | 42.2 ± 8.5 | 0.44 |
| Menopause, % | 40 | 41.5 | 0.83 |
| Race, % white | 93.9 | 86.2 | 0.10 |
| Body mass index, kg/m$^2$ | 26.1 ± 6.5 | 28.0 ± 6.6 | 0.04 |
| Waist:hip ratio | 0.83 ± 0.08 | 0.85 ± 1.3 | 0.10 |
| Heart rate per minute | 76.9 ± 9.6 | 75.8 ± 8.9 | 0.40 |
| Systolic blood pressure, mm Hg | 119.5 ± 17.0 | 120.9 ± 18.7 | 0.60 |
| Diastolic blood pressure, mm Hg | 77.9 ± 9.0 | 78.3 ± 10.8 | 0.77 |
| Antihypertensive medications, % | 20 | 29.5 | 0.13 |
| Albumin, mg/dl | 4.6 ± 0.4 | 4.7 ± 0.4 | 0.39 |
| Median C-reactive protein, mg/dl | 2.1 | 2.1 | 0.50 |
| Fibrinogen, mg/dl | 305.5 ± 67.0 | 296.9 ± 75.9 | 0.24 |
| Cholesterol, mg/dl | 184.5 ± 39.1 | 196.6 ± 41.4 | 0.04 |
| LDL cholesterol, mg/dl | 104.4 ± 29.2 | 113.3 ± 34.4 | 0.06 |
| HDL total cholesterol, mg/dl | 53.8 ± 14.6 | 57.3 ± 16.7 | 0.14 |
| Triglycerides, mg/dl | 127.7 ± 77.4 | 128.4 ± 88.6 | 0.95 |
| Lipid-lowering agents, % | 3.2 | 4.6 | 1.00‡ |
| Current smoking, % | 13.9 | 14.3 | 0.93 |
| Total calcium intake, mg | 1,156.5 ± 702.5 | NA | – |
| Oral contraceptive use ever, % | 55.4 | 62.1 | 0.33 |
| Estrogen replacement, %† | 38.5 | 44.7 | 0.57 |

* Except where otherwise indicated, values are the mean ± SD. SLE = systemic lupus erythematosus; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NA = not available.
† Includes postmenopausal women only.
‡ By Fisher's 2-tailed exact test.

**Outcome measures.** DEXA densitometry was used to measure BMD of the total hip and lumbar spine using a QDR-2000 bone densitometer (Hologic, Waltham, MA). The scans were performed following the manufacturer's recommendations. The scan requires <15 minutes, and patient exposure to radiation is maintained at <7 mR. The coefficient of instrument variation for total bone mineral content was 0.6% at the lumbar spine and 0.6% at the hip, measured as part of a standard quality control exercise administered by Synarc (Bedford, MA). All measurements were within acceptable limits for all phantom studies (9).

The carotid plaque index and IMT were assessed by carotid B-mode ultrasound using a Toshiba SSA-270A scanner

equipped with a 5-MHz linear array imaging probe. Plaque was defined as a distinct focal area protruding into the vessel lumen and was assessed in 4 areas: proximal common, distal common, carotid bulb, and internal carotid. For each segment, the degree of plaque was graded using the following criteria: grade 0 = no observable plaque, grade 1 = 1 small plaque (<30% of the vessel diameter), grade 2 = 1 medium plaque (between 30% and 50% of the vessel diameter) or multiple small plaques, grade 3 = 1 large plaque (>50% of the vessel diameter) or multiple plaques with at least 1 medium plaque. The grades were summed to create a variable called the carotid plaque index, a measure of the extent of eccentric plaque that has been found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations (10).

Measurement of IMT was performed using a work station consisting of a Macintosh Quadra 650 computer, an image capture board, an optical disk drive, a super-VHS video cassette recorder with a high-resolution monitor and graphics card, and specialized reading software (11). Measures were taken from the near and far walls of the distal common carotid artery (1 cm proximal to the carotid bulb) as well as the far walls of the carotid bulb (the point where the near and far walls of the common carotid artery are no longer parallel, extending to the flow divider) and the internal carotid artery (from the flow divider to 1 cm distal to this point). To measure the average IMT of a segment, digitized B-mode images are displayed on the monitor and 2 lines are electronically drawn, one along the lumen–intima interface and one along the media–adventitia interface. Interfaces are identified across a 1-cm segment. The computer then generates 1 measurement for each pixel over this area, for a total of ~140 measurements. The average, standard deviation, minimum, and maximum for these measurements are then recorded. The mean of all average readings across the 8 locations (4 on each side) is used. The mean of all maximum readings is calculated.

Electron-beam computed tomography was used to measure coronary artery calcification using an Imatron C-150 Ultrafast computed tomography scanner with a standard protocol. The total coronary artery calcium score was calculated with a densitometric program available on the Imatron C-150 scanner using the widely accepted Agatston method (12). Briefly, coronary artery calcium scores are generated using the computer program, which extracts the pixels above 130 units within an operator-defined region of interest in each of 3 mm–thick images of the coronary arteries. All pixels >130 units and larger than 1 mm within the coronary arteries are considered to be calcium. The calcium score is then calculated for each region of interest by multiplying the area of all significant pixels by a grade number of 1, 2, 3, or 4, indicative of the peak computed tomography number units. The individual region of interest scores are then summed to determine the total coronary artery calcium score.

**Statistical analysis.** The demographic variables, potential risk factors, and outcome measures were analyzed using descriptive statistics. We compared the mean values of the carotid plaque index or IMT across tertiles of hip or spine BMD. In the small convenience sample of women with SLE who also had coronary artery calcium scores, we report our findings in terms of the association between BMD at the spine or hip and coronary artery calcium score as correlation coefficients.

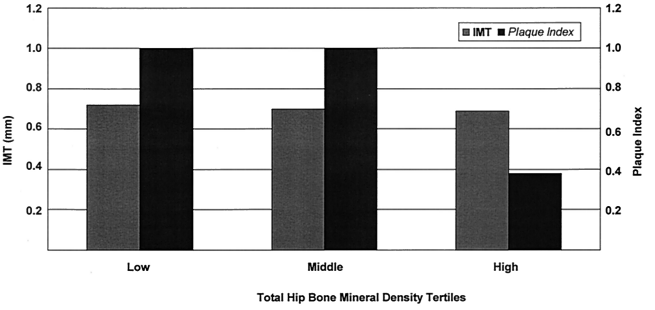


**Figure 1.** Mean intima media wall thickness (IMT) and carotid plaque index, stratified by tertiles of hip bone mineral density in 65 women with systemic lupus erythematosus.

## RESULTS

The mean age of the 65 study participants was 44.6 years, and the mean disease duration was 9.8 years. Ninety-four percent of the women were white and 40% were menopausal (Table 1). The mean (±SD) lumbar spine and total hip BMD were 1.00 ± 0.14 gm/cm$^2$ and 0.87 ± 0.13 gm/cm$^2$, respectively. The mean carotid plaque index was 0.8. The carotid plaque index in the carotid arteries was higher (1.00 versus 1.00 versus 0.38, respectively) in the patients in the lowest and middle tertiles of total hip BMD when compared with patients in the upper tertile of hip BMD (Figure 1). There was no relationship between the carotid plaque index and lumbar spine BMD among the tertiles.

There were no significant differences in IMT across BMD tertiles for the lumbar spine or total hip. There was no significant difference in the current mean prednisone dose among patients in each BMD tertile for the lumbar spine (low 5.8 mg, middle 4.3 mg, high 2.2 mg; $P = 0.17$) or total hip (low 2.8 mg, middle 5.6 mg, high 4.0 mg; $P = 0.33$).

Among the 13 patients who also underwent electron-beam computed tomography scanning, the mean BMD for the lumbar spine was 1.00 ± 0.12 gm/cm$^2$, and for the total hip was 0.86 ± 0.16 gm/cm$^2$. The mean coronary artery calcium score in these 13 women was 65 (range 0–405). The correlation coefficient between the coronary artery calcium score and lumbar spine BMD was −0.57 ($P = 0.04$), and between the coronary artery calcium score and total hip BMD was −0.55 ($P = 0.05$).

## DISCUSSION

These preliminary data in women with SLE are consistent with the data from postmenopausal women

that support the association between a surrogate marker for cardiovascular disease (coronary artery calcification) and osteoporosis (low BMD). Although these data were collected from samples of convenience obtained from a small number of patients, these women appear to be representative of our larger cohort of lupus patients in Pittsburgh. Our findings lend scientific rationale to the suggestion that factors related to the inflammatory and immune-mediated nature of SLE or its treatment may play a role in the premature cardiovascular disease and osteoporosis experienced by these patients.

The current observations raise additional hypotheses regarding possible important differences in the relationship between vascular and bone surrogate markers as they relate to the site of BMD (hip versus spine), method of vascular imaging (IMT versus carotid plaque index or coronary artery calcium score), or disease-related factors such as disease activity and prednisone dose. Larger studies designed to examine this group of young, high-risk women with SLE for an association between cardiovascular disease and osteoporosis are necessary to confirm our findings.

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