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25-Hydroxyvitamin D and Cardiovascular Risk Factors in Women with Systemic Lupus Erythematosus

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Abstract

Objective—Low serum levels of 25-hydroxyvitamin D (25[OH]D, vitamin D) are associated with a higher frequency of cardiovascular disease and risk factors in the general population. Vitamin D deficiency has been noted in systemic lupus erythematosus (SLE). The objective of this study was to evaluate the associations of serum 25(OH)D levels with cardiovascular risk factors in women with SLE.

Methods—Data collected in 181 women with SLE included demographics, SLE activity and damage assessments, cardiovascular risk factors, medications, and laboratory assessments of inflammatory markers and 25(OH)D levels. Multiple linear and logistic regressions were used to estimate the association of 25(OH)D with cardiovascular risk factors.

Results—Mean age and disease duration were 43.2 and 11.9 years, respectively. Mean 25(OH)D was 27.1 ng/ml and 62.2% had 25(OH)D levels <30 ng/ml. In unadjusted analyses, lower 25(OH)D levels were significantly associated with higher diastolic blood pressure, low density lipoprotein cholesterol (LDL-c), lipoprotein (a), body mass index (BMI), and fibrinogen levels, as well as self-reported hypertension and diabetes. Lower 25(OH)D levels were also significantly associated with higher SLE disease activity and damage scores. After adjustment for age, seasonal variation, and race/ethnicity, lower 25(OH)D levels were also significantly related to higher

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fasting serum glucose. With further adjustment for BMI, associations between 25(OH)D and cardiovascular risk factors were no longer significant.

Conclusion—This study demonstrates that vitamin D levels are low in women with SLE and significant associations exist with selected cardiovascular risk factors although most of these associations can be explained by BMI.

Increasing evidence supports an inverse association between vitamin D deficiency and cardiovascular disease (CVD) in the general population (1,2). Low or deficient levels of 25-hydroxyvitamin D (25[OH]D) have been linked to stroke (3), ischemic heart disease (4,5), and heart failure (5), as well as hypertension (6), diabetes(1,6), hypertriglyceridemia (1,6), obesity (7), and the metabolic syndrome (8). The Third National Health and Nutrition Examination Survey (NHANES-III) (6), found that the frequency of selected cardiovascular risk factors including obesity, hypertension, diabetes, and hypertriglyceridemia was significantly higher in the lowest (<21 ng/ml) quartile of serum vitamin D levels compared to the highest (≥37ng/ml). Similarly, a study using NHANES data from 2001–2004 noted that adults with 25(OH)D levels <20 ng/ml compared to those with 25(OH)D levels ≥30 had an increased frequency of CVD including coronary heart disease, heart failure, stroke, and peripheral arterial disease (5).

A link has also been established between vitamin D and the immune system, and vitamin D has been studied as a modifiable environmental factor (9) in autoimmune disease animal models including systemic lupus erythematosus (SLE, lupus) (10), experimental autoimmune encephalomyelitis (a model for multiple sclerosis) (11), rheumatoid arthritis (12), type I diabetes (13), and inflammatory bowel disease (14). Epidemiological evidence also supports an association between vitamin D and the susceptibility and severity of these autoimmune disorders (15–17).

SLE is the prototypical autoimmune disease and patients with SLE are known to have lower levels of 25(OH)D with measurements around or less than 20 ng/mL (16,17) and in some cases critically low at less than 10 ng/ml (17,18). Lower levels of vitamin D have been shown to correlate with increased SLE disease activity (19) and studies using animal models of SLE (10) demonstrated attenuation of some manifestations with increasing vitamin D intake (10,20).

A leading cause of morbidity and mortality in women with SLE, including those who are premenopausal, is CVD (21–23). Patients with lupus have an increased incidence of myocardial infarction up to 5 times that of the general population, with an age-specific incidence in young women up to 50 times higher (21). Evidence has shown that, like diabetes mellitus, SLE itself is an independent risk factor for the development of atherosclerosis (24).

The cardiovascular and autoimmune actions of vitamin D are relevant in the setting of SLE given the significant role CVD can play in the lives of these women. Vitamin D deficiency could be a potential modifiable risk factor in SLE-related CVD as suggested by the clinical observations of vitamin D deficiency and its association with CVD in non-SLE patients (1,6). However, there is minimal information in the literature to document an association between vitamin D levels and cardiovascular risk factors and/or outcomes in SLE. A necessary first step before proposing vitamin D supplementation as a preventive treatment in SLE is to document a relationship between the vitamin D deficient state and CVD risk in SLE. For this study, we examined the association of vitamin D levels with cardiovascular risk factors in women with SLE and propose that lower 25(OH)D levels are associated with an increased risk of cardiovascular risk factors in women with SLE.

Patients and Methods

Study population

All eligible women, aged ≥ 18 years, involved in the Chicago Lupus Database (CLD), a cohort of 515 participants (425 of whom are women) who met at least 4 of the 1982 or updated 1997 American College of Rheumatology classification criteria for SLE (25,26), were invited to participate. The first 181 women to respond were enrolled in SOLVABLE (Study of Lupus Vascular and Bone Long-term Endpoints). This study is an ancillary project of SOLVABLE. The 181 women compared to the remaining 244 women in CLD were similar in race/ethnicity distribution and lupus markers (C3, C4, dsDNA), but had less use of corticosteroids, higher frequency of hydroxychloroquine and immunosuppressant use (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and tacrolimus), were older by approximately seven years, smoked less, and had longer disease duration.

Data collection

A self-administered questionnaire was given to the participant followed by an interview and physical examination by a trained physician during the study visit. Blood and urine were obtained for laboratory tests (e.g. lipids, inflammatory markers, antiphospholipid antibodies). Participant visits also included carotid artery B-mode ultrasound and electron beam computed tomography (EBCT) of the coronary arteries and aorta. All sonographers' training and the carotid ultrasound readings were performed at the University of Pittsburgh Ultrasound Research Laboratory. The coronary artery and aorta calcification scores from the EBCT examinations were read at the University of Pittsburgh Cardiovascular Institute.

The institutional review board of Northwestern University and the University of Illinois at Chicago approved the protocols and all study participants provided informed consent prior to enrollment.

Traditional CVD risk factors

Information on age, demographics, self-reported race/ethnicity, smoking history, family history of CVD (myocardial infarction (MI), stroke), self-reported history of hypertension, diabetes and hypercholesterolemia, CVD events (MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), transient ischemic attack (TIA), stroke), current estrogen use, current aspirin use, and menopause status were obtained from the questionnaire. Menopause status was confirmed by follicle stimulating hormone (FSH) measurements if the subject's status was uncertain (e.g. irregular menses or hysterectomy without oophorectomy). Blood pressure was measured twice and the mean of the two measurements was used for analysis. Height, weight, and waist/hip measurements were obtained in standard fashion.

Laboratory tests

CVD and Inflammatory markers—Laboratory tests included fasting lipids (total cholesterol, high density lipoprotein cholesterol (HDL-c) and triglyceride), homocysteine, fasting glucose, insulin, and lipoprotein (a) measured in the Lipid Laboratory at the University of Pittsburgh Graduate School of Public Health and Prevention. The Friedewald equation was used to estimate low density lipoprotein cholesterol (LDL-c), unless the triglyceride level was >400 mg/dl in which case LDL-c was measured directly. Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. C-reactive protein (CRP) was measured using an immunonephelometric assay at the Laboratory for Clinical Biochemistry Research at the

University of Vermont. Inflammatory markers included fibrinogen (modified clotrate assay), which was measured at the Laboratory for Clinical Biochemistry at the University of Vermont, albumin (dye binding assay) measured at the Lipid Laboratory in the University of Pittsburgh, and erythrocyte sedimentation rate (ESR using standard Westergren's method) measured locally.

Antibodies (phospholipid, double stranded DNA) and Complement (C3, C4)— Antiphospholipid antibodies, anticardiolipin (ACL) antibodies (IgG and IgM; Diasorin, Stillwater, MN), and lupus anticoagulant (partial thromboplastin time or Russell's viper venom time with mix) were measured at the Coagulation Laboratory at the University of Pittsburgh Medical Center. ACL IgG was considered positive if the result was >10 IgG phospholipid units and ACL IgM was considered positive if >15 phospholipid units, as per laboratory standards. C3 and C4 were measured locally by nephelometry and double stranded DNA (dsDNA) antibodies were measured using the Crithidia luciliae method. dsDNA antibodies were considered positive if the titer was ≥ 1:10.

25(OH)D—The serum 25(OH)D concentration was measured in the Mineral Metabolism Research laboratory at Children's Memorial Hospital and determined by the 25(OH)D ^{125}I Radioimmunoassay kit made by Diasorin (Stillwater, MN). The intraassay coefficient of variation was 10.8% and the interassay coefficient of variation was 9.4%. Samples were measured in duplicate and the average value was reported.

SLE-related factors

Validated measures of lupus disease activity, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), as well as disease damage, Systemic Lupus International Collaborating Clinics Damage Index (SLICC/ACR Damage Index), were completed by trained physicians. Disease duration was calculated using the date the subject fulfilled the 4th ACR classification criteria for lupus (25,26). Participants provided information on corticosteroid treatment (current use and duration of treatment), as well as current use of hydroxychloroquine and immunosuppressants (which included cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus). Renal disease (51,52) was defined as being present if the subject had fulfilled ACR classification criteria for lupus renal involvement (greater than 0.5 gm/day or 3+ proteinuria and/or the presence of cellular casts) or had a renal biopsy with evidence of WHO class IIb, III, IV, or V lupus nephritis.

Subclinical CVD Outcome Measures

Subclinical CVD was measured in the carotid arteries using B-mode ultrasound by trained sonographers. Carotid plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas and was measured at 8 sites (bilateral internal carotid, external carotid, common carotid and carotid bulb). The outcome measure used for analysis was the presence or absence of plaque (plaque ≥1 versus plaque = 0). Intima-media thickness (IMT) was measured using specialized reading software across 1 centimeter segments of both the right and left sides of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and internal carotid artery. The mean of all average IMT readings across the 8 sites was used for analysis. The reproducibility of carotid duplex scanning using this technique has been previously documented in both a non-SLE population and a SLE population (27,28).

In the coronary arteries and aorta, electron beam computed tomography (EBCT) scanning was performed to measure vascular calcium, using the Imatron C150 Ultrafast CT scanner (General Electric Medical Systems, South San Francisco, CA, USA). Calcium scores were

calculated with a densitometric program available on the Imatron C-150 scanner using the Agatston method. The outcome measures used for analyses were the absence or presence of coronary artery calcification (CAC) and the absence or presence of aortic calcium (AC) (29). CAC and AC were dichotomized with absence being CAC≤10 and AC≤100, and CAC>10 and AC>100 signifying presence.

Statistical Methods

Means, standard deviations, percentiles, and ranges were used to describe measures of subclinical CVD, patient characteristics and laboratory values. Mean 25(OH)D levels in those with and without subclinical CVD were compared using t-tests.

Multiple linear and logistic regressions were used to estimate associations of 25(OH)D with cardiovascular risk factors. Linear regression was used for continuous variables and logistic regression for dichotomous variables. It should be noted that the traditional cardiovascular risk factors related to smoking, BMI, and waist/hip measurements were not a focus of this study since they are unlikely to be influenced by 25(OH)D levels. For measures of subclinical cardiovascular disease, carotid IMT was analyzed as a continuous variable, while plaque, CAC, and AC were dichotomized as absent versus present.

The multivariate analyses were further adjusted for season (30), age, race/ethnicity (white versus other), and then in addition BMI. To adjust for season, the lower ultraviolet light season (winter) was defined as having had a vitamin D level drawn between October and March and the higher ultraviolet light season (summer) between April and September (30). Adjustment was performed for age and BMI because both are strongly related to subclinical CVD as well as 25(OH)D and many of the traditional CVD risk factors.

To assess possible non-linearity of associations, squared terms in 25(OH)D were added to all models that included only 25(OH)D. The squared term was not significantly related to any of the cardiovascular risk factors, SLE factors, or subclinical markers of cardiovascular disease, and thus was not included in any of the adjusted model analyses.

Results

25(OH)D levels were measured in 181 women (62% Caucasian, 27% African-American, 6.1% Hispanic and 5.5% Asian) with a mean and standard deviation (SD) of 27.1 ± 11.9 ng/ml (Table 1). Twenty percent of subjects had extremely deficient levels of 25(OH)D (≤ 15 ng/ml) and 62.2% of subjects had insufficient 25(OH)D levels (<30 ng/ml).

The mean and SD for age and disease duration were 43.2 ± 10.6 years and 11.9 ± 8.6 years, respectively. Of the 181 women, 35.9% were post-menopausal, 30.2% had renal disease at some time during their disease course, and 11.1% reported they were current smokers. Self-reported cardiovascular risk factors included 39.8% with hypertension, 7.7% with diabetes, 26.5% with hypercholesterolemia, and 7.2% with a history of a CVD event. In addition, 10.9% of the study subjects were positive for lupus anticoagulant and 29% were positive for anticardiolipin IgM or IgG. Medications included corticosteroids in 40% (current mean daily dose was 11.8 ± 9.03 mg in 72 patients), hydroxychloroquine in 72%, immunosuppressants in 34.8%, vitamin D in 33% (mean dose was reported to be 597 IU in 59 patients), bisphosphonates in 11%, and teriparatide in 1%. The means and SD for the SLEDAI and SLICC-DI, excluding CVD events, were 4.0 ± 3.6 and 1.6 ± 1.7, respectively, consistent with low disease activity and damage.

In the unadjusted model for the associations of 25(OH)D levels with cardiovascular risk factors (Table 2), lower 25(OH)D levels were significantly associated with higher diastolic

blood pressure, LDL-c cholesterol, lipoprotein (a), fibrinogen levels, and self-reported hypertension and diabetes. Lower 25(OH)D levels were also significantly associated with higher SLICC-DI and SLEDAI scores. A higher 25(OH)D level was significantly associated with a higher HDL-c cholesterol. Though not significant, lower 25(OH)D levels were found with higher systolic blood pressure, total cholesterol, homocysteine, triglycerides, self-reported hypercholesterolemia, and CRP.

After adjustment for age, seasonal variation, and race/ethnicity, the inverse association between lower 25(OH)D and higher fasting serum glucose became significant, and the association with LDL-c, self-reported diabetes, fibrinogen, and SLEDAI remained significant (Table 2). With further adjustment for BMI, all of the associations between 25(OH)D and cardiovascular risk factors were no longer significant. Further analyses (not shown) that examined cardiovascular risk factors which are unlikely to be influenced by vitamin D found that BMI was significantly associated with 25(OH)D levels but smoking, waist/hip ratio were not associated.

We also examined the associations of subclinical imaging markers of disease with vitamin D levels. Within our cohort, mean IMT was 0.60 ± 0.12 (N=179), mean plaque was 0.70 ± 1.17 (66/179 (37%) had plaque≥1), mean CAC was 42.96 ± 152.09 (35/178 (20%) had CAC>10), and mean AC was 476.30 ± 1686 (36/139 (26%) had AC>100). None of these subclinical imaging markers were found to have a significant association with 25(OH)D levels after adjustment for age, season, and race/ethnicity (Table 3). Adjustment was not made for BMI or other cardiovascular risk factors, because of the relatively small numbers of women with CAC>10 or AC>100, and because none of these outcomes was significant after adjustment for age, season, and race.

Mean 25(OH)D levels were similar in women with lupus with CAC present (>10) versus absent (28.0±12.8 mg/dl versus 27.0±11.8), plaque present (≥1) versus absent (26.9±1.5 mg/dl versus 27.1±1.12 mg/dl), and AC present (>100) versus absent (26.4±2.31 mg/dl versus 28.1±1.17 mg/dl).

Discussion

This is the first study to demonstrate significant associations between selected CVD risk factors and 25(OH)D levels in women with SLE where most of the relationships are partially explained by BMI. Lower 25(OH)D levels were also significantly associated with higher SLICC-DI and SLEDAI. Consistent with other studies (17,31), many subjects had extremely deficient levels of 25(OH)D with 20% less than or equal to 15 ng/ml and 62.2% less than 30 ng/ml. The definition of vitamin D insufficiency is controversial but the preferred range is a 25(OH)D level greater than 30 ng/ml or 75 nmol/l, a level at which the risk of secondary hyperparathyroidism is decreased (1).

Many causes of vitamin D deficiency exist (1) with some of the more common causes being reduced skin synthesis and absorption of vitamin D due to sunscreen use, darker skin pigment, aging, season, latitude, and time of day (1,32). These causes are particularly relevant in patients with lupus because of disease-related photosensitivity and increased use of sunscreen. Other lupus-related factors that may contribute to vitamin D deficiency include renal disease (17), use of steroids which are thought to alter the metabolism of vitamin D (33), and hydroxychloroquine, an anti-malarial commonly used to treat lupus (34).

The findings in this study noting an association between CVD risk factors and low vitamin D are consistent with those reported in the general population (6,35). Data from the NHANES III survey (6) showed that patients within the lowest quartile (<21ng/ml) of vitamin D had a significantly increased prevalence of selected CVD risk factors (including a

history of diabetes and elevated blood pressure, fasting blood glucose, BMI, and triglyceride levels) when compared to the highest quartile (≥37 ng/ml). In addition, several studies have shown an inverse relationship between 25(OH)D, CVD events, and all-cause and CVD mortality (3,4,36) even after adjusting for traditional CVD risk factors (4). Data from NHANES between 2001–2004 revealed that hypovitaminosis D was more prevalent in adults at highest risk for CVD, especially if the person had both coronary heart disease and heart failure even after adjusting for age, race, and gender (5).

Within the SLE population, no studies have documented an association between vitamin D levels and CVD risk factors or outcomes. In our study we found trends similar to those in the general population. Lower vitamin D levels were associated with higher BMI, diastolic blood pressure, LDL cholesterol, and self-reported hypertension and diabetes. However, it is difficult to compare the magnitude of the associations between our study and the NHANES III study (6), because of the difference in methods and the inclusion of both genders in NHANES III.

It is not clear why BMI abrogates most of the relationships between CVD risk factors and 25(OH)D. One explanation may be that BMI acts as a mediator between the two by contributing to the “inflammatory load” of women with SLE. When adjusting for BMI, we did note that the associations between fibrinogen and 25(OH)D became insignificant and that between CRP and 25(OH)D became even weaker.

No significant relationship was found between CVD events and 25(OH)D in this study but the number of events were too few (N=12) to consider this an accurate assessment. We did, however, look at the relationship between 25(OH)D and markers of subclinical atherosclerosis (plaque, IMT, CAC, and AC). This is important because the presence or extent of carotid plaques, increased IMT, and aortic calcification have been found to predict risk of cardiovascular events including myocardial infarction (37). Similarly, increased IMT and CAC scores have been found to predict risk of angina and stroke (38,39) in the general population. Low vitamin D levels have also been associated with increased coronary artery calcification in non-SLE patients at moderately high risk for coronary heart disease (40). Though our study did not show an association between 25(OH)D and these subclinical markers of atherosclerosis, this is an important area that needs further investigation because SLE patients tend to have prevalent vascular and valvular calcifications (41) which can predict atherosclerotic risk (42,43).

We also found that lower 25(OH)D levels were associated with increased lupus disease activity and damage indices which is consistent with most other studies (19). This is important because vitamin D may have a beneficial role in preventing or attenuating some manifestations of SLE. In fact, treatment with various levels of $1,25(OH)_2D_3$ in animal models of lupus reduced dermatologic lesions of lupus such as alopecia, proteinuria, as well as serum anti-dsDNA antibodies (10). Two other studies using the MRL/lpr spontaneously developing lupus mouse model found $1,25(OH)_2D_3$ to prevent proteinuria with effects similar to that of high-dose corticosteroids (44), and prolong the average the lifespan of the lupus mouse (20). The physiologic and clinical effects of using vitamin D to modulate SLE disease activity and damage are not known at this time and there are currently no prospective studies looking at the effects of vitamin D supplementation in SLE. However, given the relative safety of vitamin D and the multiple immunologic and cardiovascular benefits, further clinical trials are warranted in patients with SLE.

We recognize that our study has several limitations that should be taken into consideration when evaluating our results. This cohort included 181 women and only 77% (N=139) had an aorta calcium score measured. Due to the limited sample size, we likely did not have

adequate power to detect associations between 25(OH)D and surrogate imaging markers of subclinical CVD. In addition, there were also too few CVD events (N=12) to accurately assess the relationship between CVD events and 25(OH)D. We also did not measure physical activity during this study though increased BMI and low vitamin D levels may also be markers of poor general health and mark out a population with lower levels of physical activity.

We also did not control for certain confounders, including renal disease and medication use, which may have affected both vitamin D levels and CVD risk factors. Two medications that may have influenced results were corticosteroids and hydroxychloroquine. The data on whether corticosteroids are pro- or anti-atherogenic is controversial but some suggest that progression of subclinical atherosclerosis based on serial carotid ultrasounds correlate with lower mean dose of corticosteroids and less aggressive immunosuppressive therapy (45). However, corticosteroid use has also been associated with higher IMT and frequency of carotid plaque in patients with rheumatoid arthritis (46) and is also thought to increase the catabolism of vitamin D thus lowering serum levels (1,32). The data on hydroxychloroquine's effects on vitamin D are also controversial (34,47). Hydroxychloroquine is suspected to inhibit the conversion of 25(OH)D to its more biologically active form $1,25(OH)_2D$ (16,34) but has also been found to protect against vitamin D deficiency (47). In terms of cardiovascular effects, hydroxychloroquine has been shown to be protective against thrombosis and cardiac disease (45).

We did not control for renal disease because the correlation between 25(OH)D and GFR was 0.004 so it was very unlikely to be a confounder of any associations between 25(OH)D and CVD risk factors. In addition, for many or our outcomes, our sample size of 181 was inadequate to control for any more variables that those already included. We were unable to do a subgroup analysis on those with the most severe renal disease because only 5 had a GFR<30.

Though the majority of studies support an inverse association between serum vitamin D levels and CVD risk and events, a few studies report evidence to the contrary. One study in South Indian patients claimed that high levels of 25(OH)D can be arteriotoxic. The authors reported that high 25(OH)D levels greater than 89 ng/ml or 222.5 nmol/l were associated with an increased risk of ischemic heart disease (48). Another study through the Women's Health Initiative (49) found that calcium and vitamin D supplementation in 36,282 healthy postmenopausal women aged 50–79 years neither increased nor decreased the risk of myocardial infarction, coronary heart death, or stroke over a period of 7 years. However, the amount of vitamin D supplementation in this study was 400 IU daily and may be lower than what is necessary to reduce CVD risk factors and events. Although the Institute of Medicine (50) recommends 400 IU daily for adults 51 to 71 years of age, most other sources believe adults lacking adequate sun exposure should take 800–1000 IU daily (1,32).

In this study, we found an association between lower 25(OH)D levels and increased CVD risk factors as well as increased SLE disease activity and damage indices in women with SLE. Vitamin D is relevant in lupus because of its immunomodulatory, anti-inflammatory, and possibly anti-atherogenic properties based on animal models and epidemiological studies in the general population. The known effects of vitamin D in lupus to date are that patients generally have deficient or severely deficient levels which may also be associated with increased disease activity. However, very little is known about the effects of vitamin D on cardiovascular disease in SLE. We have demonstrated an association between lower 25(OH)D levels and increased cardiovascular risk factors exists in women with SLE though this may be mediated by BMI. Future studies are needed to determine whether vitamin D

levels can predict the progression of subclinical atherosclerosis, as measured by surrogate imaging markers, as well as cardiovascular events in patients with lupus.

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Table 1

Description of the SLE population at enrollment*

Demographics	
Age, mean ± SD	43.2 ± 10.6
Race, %	
Caucasian	61.9
African American	26.5
Hispanic	6.1
Asian	5.5
Menopausal, %	35.9
Vitamin D levels, ng/ml	
25(OH)D, mean ± SD	27.1 ± 11.9
25(OH)D < 30, %	62.2
25(OH)D ≤ 15, %	20
Self-reported cardiovascular risk factors, %	
Hypertension	39.8
Diabetes	7.7
Hypercholesterolemia	26.5
History of cardiovascular event†	7.2
Family history heart attack/stroke	52.2
Current Smoking‡	11.1
Cardiovascular risk factors and Lab Values	
Systolic blood pressure, mean ± SD *mmHg*	117.5 ± 14.9
Diastolic blood pressure, mean ± SD *mmHg*	73.5 ± 9.5
Total Cholesterol, mean ± SD *mg/dl*	187.2 ± 37.4
Fasting glucose, mean ± SD *mg/dl*	91.0 ± 17.5
HDL cholesterol, mean ± SD *mg/dl*	55.5 ± 15.1
LDL cholesterol, mean ± SD *mg/dl*	106.8 ± 31.3
Trigylcerides, mean ± SD *mg/dl*	126.2 ± 81.0
Lipoprotein (a), mean ± SD *mg/dl*	46.1 ± 43.3
Fibrinogen, mean ± SD *mg/dl*	332.3±105.5
C-reactive protein, mean ± SD *mg/dl*	4.2 ± 10.2
Homocysteine, mean ± SD *μmol/L*	11.4 ± 4.9
Lupus anticoagulant, %	10.9
Anticardiolipin IgG or IgM, %	29
Creatinine, mean ± SD *mg/dl*	1.0 ± 1.3
Glomerular Filtration Rate, mean ± SD *ml/min*	81.6 ± 25.8
Body Mass Index, mean ± SD kg/m^2	27.5 ± 7.4
Waist/hip ratio mean ± SD‡	0.8 ± 0.1
Cardiovascular medications, %	
Statins	8

Aspirin	16
Anti-hypertensive meds	47
SLE related factors	
Disease duration, mean ± SD *years*	11.9 ± 8.6
Receiving corticosteroids, %	40.0
Current corticosteroid dose (n=7), mean ± SD *mg*	11.8 ± 9.03
Receiving hydroxychloroquine, %	72
Receiving immunosuppressants %[§]	34.8
Renal Disease,%	30.2
SLEDAI score mean ± SD	4.0 ± 3.6
SLICC-DI score mean ± SD[¶]	1.6 ± 1.7
C4, mean ± SD *mg/dl*	19.4 ± 8.9
C3, mean ± SD *mg/dl*	97.7 ± 28.1
+dsDNA, *Crithidia method*, %	47
Bone medications	
Estrogen (HRT[o] and OCPs[o])	14 (7.8%)
Calcium	83 (46%)
Vitamin D	59 (33%)
Bisphosphonates	19 (11%)
Teriparatide	2 (1%)

[*] Continuous variables are the mean ± SD and categorical variables are the percentage. SLE = systemic lupus erythematosus; 25(OH)D = 25-hydroxyvitamin D; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI = Systemic Lupus International Collaborating Clinics Damage Index; dsDNA = double-stranded DNA; HRT = hormone replacement therapy; OCPs = oral contraceptive pills.

[†] Including stroke, myocardial infarction, and percutaneous transluminal coronary angiography.

[‡] Unlikely to be influenced by 25(OH)D levels.

[§] Including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and tacrolimus.

[¶] Excluding cerebrovascular accident, myocardial infarction, and coronary artery bypass graft.

Table 2

25(OH)D, cardiovascular risk factors, and SLE activity/damage*

	Unadjusted 25(OH)D model			Adjusted 25(OH)D model 1†			Adjusted 25(OH)D model 2‡		
Self-reported CV risk factor	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Hypertension	0.68	(0.49, 0.93)	0.016§	0.72	(0.49, 1.1)	0.090	0.80	(0.54,1.2)	0.253
Diabetes	0.49	(0.26, 0.94)	0.032§	0.48	(0.25, 0.91)	0.026§	0.68	(0.33,1.4)	0.294
High cholesterol	0.74	(0.52, 1.0)	0.085	0.68	(0.46, 1.0)	0.061	0.71	(0.46, 1.1)	0.107
CV events¶	0.83	(0.45, 1.53)	0.560	NA#	NA#	NA#	NA#	NA#	NA#
CV risk factor	**β coeff**	**95% CI**	**P value**	**β coeff**	**95% CI**	**P value**	**β coeff**	**95% CI**	**P value**
Systolic BP‡	−2.01	(−4.19, 0.16)	0.069	−1.83	(−4.23, 0.56)	0.132	−1.26	(−3.76,1.25)	0.324
Diastolic BP‡	−1.49	(−2.87, −0.12)	0.034§	−1.31	(−2.82, 0.46)	0.099	−1.1	(−2.82, 0.46)	0.158
Total Cholesterol	−3.57	(−9.06, 1.93)	0.202	−4.13	(−10.22, 1.94)	0.181	−1.55	(−7.85, 4.75)	0.628
Fasting glucose	−1.88	(−4.46, 0.69)	0.150	−3.07	(−5.97, −0.17)	0.038§	−1.23	(−4.14, 1.68)	0.406
HDL cholesterol	2.80	(0.60, 4.99)	0.013§	2.15	(−0.35, 4.65)	0.091	0.653	(−1.87, 3.18)	0.610
LDL cholesterol	−5.60	(−10.19, −1.00)	0.017§	−5.81	(−11.0, −0.64)	0.028§	−3.27	(−8.58, 2.04)	0.226
Triglycerides	−8.43	(−20.30, 3.44)	0.163	−6.81	(−20.40, 6.85)	0.326	0.839	(−13.1, 14.76)	0.905
Lipoprotein (a)	−7.29	(−13.59, −0.99)	0.024§	−6.56	(−13.80, 0.68)	0.075	−6.22	(−13.87, 1.43)	0.110
Fibrinogen	−37.25	(−51.8, −22.69)	0.000§	−24.7	(−41.0, −8.41)	0.003§	−14.13	(−30.35, 2.09)	0.087
CRP	−1.17	(−2.67, 0.33)	0.126	−1.03	(−2.77, −0.71)	0.244	−0.75	(−2.58, 1.08)	0.418
Homocysteine	−0.29	(−1.02, 0.44)	0.429	−0.26	(−1.08, 0.55)	0.527	−0.362	(−1.22, 0.50)	0.406
SLE factors	**β coeff**	**95% CI**	**P value**	**β coeff**	**95% CI**	**P value**	**β coeff**	**95% CI**	**P value**
SLEDAI	−0.876	(−1.40, −0.35)	0.001§	−0.715	(−1.30, −0.13)	0.018§	NA	NA	NA
SLICC DI**	−0.376	(−0.62, −0.13)	0.003§	−0.210	(−0.49, 0.07)	0.136	NA	NA	NA

*25(OH)D = 25-hydroxyvitamin D; SLE = systemic lupus erythematosus; OR = odds ratio; 95% CI = 95% confidence interval; CV = cardiovascular; NA = not applicable; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC DI = Systemic Lupus International Collaborating Clinics Damage Index.

†Controls for age, season, and white race, except for diabetes mellitus, controls for age only.

[‡] Controls for age, season, white race, and body mass index (BMI), except diabetes mellitus (controls for age and white race only) and BMI, SLEDAI, and SLICC-DI (controls for age, season, and white race only).

[§] Significant.

[¶] Including myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, transient ischemic attack, and stroke.

[#] Adjusted models 1 and 2 were not done due to the small number of events (N=12).

[**] Excluding cerebrovascular accident, myocardial infarction, and coronary artery bypass graft.

Table 3

25(OH)D and subclinical markers of cardiovascular disease*

	Unadjusted 25(OH)D model			Adjusted 25(OH)D model 1†		
Imaging study	**β coeff**	**95% CI**	**P value**	**β coeff**	**95% CI**	**P value**
IMT	0.0006	(−0.018, 0.019)	P=0.948	−0.0008	(−0.016, 0.015)	P=0.918
Imaging study	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
CAC	1.1	(0.75, 1.6)	P=0.684	1.0	(0.66,1.7)	P=0.842
Plaque	0.98	(0.72,1.3)	P=0.912	1.2	(0.80,1.7)	P=0.420
AC	0.88	(0.60,1.3)	P=0.493	0.75	(0.45,1.3)	P=0.275

*IMT = intima-media thickness; CAC = coronary artery calcification; AC = aorta calcium; see Table 2 for additional abbreviations.

†Controls for age, season, and white race.