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25-Hydroxyvitamin D and Cardiovascular Disease in Patients With Systemic Lupus Erythematosus: Data From a Large International Inception Cohort

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Abstract

Objective—An association between 25-hydroxyvitamin D (25[OH]D; vitamin D) deficiency and increased cardiovascular (CV) risk factors and CV disease (CVD) has been shown in general population studies. Vitamin D deficiency has been noted in systemic lupus erythematosus (SLE), and CVD is a major cause of morbidity and mortality in SLE. The objectives of this study were to estimate the associations of 25(OH)D levels with CV risk factors and to determine whether low baseline 25(OH)D levels predict future CV events in patients participating in an international inception cohort.

Methods—Data were collected on 890 participants, including demographics, SLE activity and damage assessments, CV risk factors and events, medications, laboratory assessments of 25(OH)D levels, and inflammatory markers. Multiple logistic and Cox regressions were used to estimate the associations of baseline 25(OH)D levels with baseline CV risk factors and CVD events. The models were adjusted for age, sex, race, season, and country, with and without body mass index.

Results—Patients in the higher quartiles of 25(OH)D were less likely to have hypertension and hyperlipidemia and were more likely to have lower C-reactive protein levels and lower Systemic Lupus Erythematosus Disease Activity Index 2000 scores at baseline when compared with the first quartile. Vitamin D levels were not independently associated with CVD event incidence; however, hazard ratios for CVD event incidence decreased with successively higher quartiles.

Conclusion—Lower baseline 25(OH)D levels are associated with higher risk for CV risk factors and more active SLE at baseline. There may be a trend toward a lower likelihood of CVD events in those with higher baseline 25(OH)D levels.

INTRODUCTION

25-Hydroxyvitamin D (25[OH]D; vitamin D) deficiency has been associated with increased cardiovascular disease (CVD) (1–4) and CVD risk (5) in the general population. The Third National Health and Nutrition Examination Survey and other cross-sectional cohort studies found serum vitamin D levels to be inversely associated with hypertension, diabetes mellitus, obesity, and hypertriglyceridemia (5,6). Furthermore, there is growing evidence that vitamin D deficiency is associated with an increased prevalence of CVD events, including myocardial infarction (MI), congestive heart failure (CHF), stroke, angina, and peripheral arterial disease (1–4). In the Health Professionals Follow-Up Study, which included 18,225 men, vitamin D levels were found to be an independent risk factor for MI. Furthermore, men with 25(OH)D levels ≤15 ng/ml were at a significantly greater risk for MI than those who had sufficient 25(OH)D levels (>30 ng/ml), even after controlling for confounders (1). Similarly, as noted in the Third National Health and Nutrition Examination Survey, 1,308 men and women with self-reported CVD had a significantly greater frequency

(29.3% versus 21.4%; $P < 0.0001$) of 25(OH)D deficiency (defined as <20 ng/ml) compared to those without CVD (4).

Several studies have established CVD to be a major cause of morbidity and mortality in patients with chronic inflammatory diseases, including systemic lupus erythematosus (SLE; lupus) (7–10). In fact, SLE, like diabetes mellitus, is thought to be an independent risk factor for the development of atherosclerosis (11), and patients with SLE have been found to have a 5-fold increase in MI at a significantly earlier age (49 versus 69 years) (12).

Vitamin D is also thought to have a significant role in several autoimmune diseases, including SLE (13). The vitamin D receptor is expressed in cells involved in the innate and adaptive immune responses, and this receptor is thought to have immunomodulatory, antiproliferative, antibacterial, and antiinflammatory properties (13). Patients with SLE are also known to have lower levels of 25(OH)D, with measurements near or <20 ng/ml (14,15), and in some cases critically low at <10 ng/ml (15,16). Lower levels of vitamin D have been shown to correlate with increased SLE disease activity (17,18), and studies using animal models of SLE (19) demonstrated attenuation of some manifestations with increasing vitamin D intake (19,20). We previously demonstrated significant associations between selected CVD risk factors and 25(OH)D levels in women with SLE, although most of the relationships were partially explained by body mass index (BMI) (21). We extended our studies to further define the relationship between vitamin D and CVD events in a large international inception cohort of women and men with SLE.

PATIENTS AND METHODS

Systemic Lupus International Collaborating Clinics (SLICC) Registry for Atherosclerosis

At the time of this investigation, the SLICC comprised 27 centers from 11 countries in North America, Europe, and Asia. An inception cohort of 1,427 patients had been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis and cardiovascular events. Patients followed at participating centers were enrolled in the registry within 15 months of their date of diagnosis, based on ≥4 American College of Rheumatology (ACR) classification criteria for SLE (22). Demographic data as well as data collected on clinical factors, laboratory factors, cardiovascular events, and coronary artery disease risk factors were submitted to the coordinating center at the University of Toronto at enrollment and once annually using standardized data collection forms. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (23). Damage was measured by the SLICC/ACR Damage Index (24). Laboratory tests necessary to evaluate disease activity and complete disease activity and damage measures were performed locally. Low complement levels were defined as a decrease in CH50, C3, or C4 below the lower limit of normal for the testing laboratory. Double-stranded DNA testing was done locally, with abnormal values defined by the local laboratory parameters. Low-density lipoprotein (LDL) cholesterol, homocysteine levels, and C-reactive protein (CRP) levels were measured in a subset of patients at enrollment. Although the majority of homocysteine levels were measured by a central laboratory, CRP levels were measured in local laboratories. Lupus anticoagulant and IgG anticardiolipin antibody testing was performed at the Oklahoma Medical Research

Foundation. The study has been approved by the research ethics boards of all participating institutions.

Vitamin D measurement

Of the 1,427 patients, 890 had blood samples available for vitamin D testing. After excluding 13 subjects due to pregnancy and 2 subjects with CVD events prior to baseline, 875 subjects were included in our analyses. 25(OH)D was performed by DiaSorin in Toronto through the University Health Network Laboratory Medicine Program. The intraassay coefficient of variation was 10.8% and the interassay coefficient of variation was 9.4%.

Traditional CVD risk factors

Traditional CVD risk factors included hypertension, BMI, hypercholesterolemia, smoking, diabetes mellitus, and postmenopause status. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or taking current treatment for hypertension. Hyperlipidemia was defined as present if LDL cholesterol was ≥130 mg/dl or if the patient was currently receiving lipid-lowering medications. Diabetes mellitus was defined as present if fasting plasma glucose was ≥126 mg/dl or if currently taking medication for diabetes mellitus. Postmenopause status was defined as the absence of menses for 12 months or bilateral oophorectomy. Self-reported alcohol consumption and hours spent in sedentary, slight, moderate, or heavy physical activity on an average day were also collected.

CVD events

Information about incident CVD events, including MI, angina, CHF, peripheral vascular disease, transient ischemic attacks, or strokes (cardiovascular accident), based on definitions previously described, was collected (25). The type and date of event were recorded over the course of 11 years, between 2000 and 2011. Only the first CVD event for each patient was included in the analysis.

Statistical analysis

Means, SDs, percentiles, and ranges were used to describe measured patient characteristics and laboratory values. Multiple linear and logistic regressions were used to investigate associations of baseline 25(OH)D levels by quartiles with each cardiovascular risk factor at baseline, with the first quartile (Q1) as the reference quartile. Linear regression was used for continuous cardiovascular risk factors and logistic regression was used for dichotomous cardiovascular risk factors. The multivariate analyses were further adjusted for age, season (26), white race, country (Korea, UK, US, or other), sex, and BMI. To adjust for season, the lower ultraviolet light season (winter) was defined as having vitamin D levels drawn between October and March, and the higher ultraviolet light season (summer) was defined as having vitamin D levels drawn between April and September (26). Cox proportional hazards models were used to describe the risk of CVD event incidence over time, with Q1 as the reference quartile.

RESULTS

25(OH)D baseline levels were measured in 875 patients (53.6% white, 16.7% African American, 3.1% Hispanic, 22.5% Asian, and 4.6% other) at the time of enrollment. The majority (89.8%) were women, 13% of whom were postmenopausal. Patients were geographically located in Canada (29.4%), the US (26.6%), the UK (22.5%), Korea (15.8%), Sweden (3%), Spain (0.7%), and Switzerland (0.3%). Forty-two percent of subjects were married and subjects had a mean ± SD of 14 ± 3.2 years of education, including secondary and college education. Seventy-two percent of subjects had 25(OH)D levels <30 ng/ml and 27.7% of subjects had 25(OH)D levels ≥30 ng/ml. The mean ± SD 25(OH)D level was 23.8 ± 13.4 ng/ml (Table 1). The first quartile (Q1) of 25(OH)D consisted of levels 4–13 ng/ml, the second quartile (Q2) of 14–21 ng/ml, the third quartile (Q3) of 22–30 ng/ml, and the fourth quartile (Q4) of 31–91 ng/ml.

Approximately 32% of subjects consumed alcohol on an average day, with mean ± SD consumption of 1.17 ± 3.44 units daily. Those in the higher 25(OH)D quartiles were more likely to consume alcohol on an average day ($P = 0.004$ by analysis of variance [ANOVA]; data not shown); however, it should be noted that the number of persons consuming alcohol was small.

Participants spent more time in an average day in sedentary activity (mean ± SD 7.02 ± 3.96 hours) than in heavy activity (mean ± SD 0.49 ± 1.31 hours). Time spent in various activity levels did not differ between 25(OH)D quartiles, nor was it related to 25(OH)D level (data not shown).

The mean ± SD age and disease duration at enrollment were 39.3 ± 13.5 years and 0.5 ± 0.4 years, respectively. The mean ± SD SLEDAI-2K score was 5.6 ± 5.5; lower quartiles exhibited higher mean SLEDAI-2K scores ($P < 0.001$ by ANOVA), with a mean SLEDAI-2K score of 7.0 in Q1 and 4.7 in Q4. One-hundred fifty-seven patients (20.3%) were positive for lupus anticoagulant and 8.8% were positive for IgM or IgG anticardiolipin antibodies at moderate to high levels (≥14.1–50 IgM phospholipid/IgG phospholipid units, respectively) (Table 2).

At baseline, corticosteroids were used in 67.4% (mean ± SD daily dose 23.3 ± 15.9 mg), hydroxychloroquine in 66.4%, and immunosuppressants (including azathioprine, cyclophosphamide, methotrexate, cyclosporine, and mycophenolate mofetil) in 37.8% of patients. Cohort members in the lower 25(OH)D quartiles were more likely to be taking a corticosteroid at baseline ($P < 0.001$ by ANOVA; data not shown); of the 219 patients in Q1, 174 (79.5%) were taking a corticosteroid at baseline, and of the 216 patients in Q4, 125 (57.9%) were taking a corticosteroid. However, the mean daily corticosteroid dose did not differ between quartiles ($P = 0.70$ by ANOVA; data not shown). Those in the lower 25(OH)D quartiles were also less likely to be taking an antimalarial at baseline ($P < 0.001$ by ANOVA; data not shown). Those in our lower 25(OH)D quartiles were also less likely to be taking an antimalarial medication at baseline ($P < 0.001$ by ANOVA; data not shown). Of the 219 patients in Q1, 124 (56.7%) were taking an antimalarial, and of the 216 patients in Q4, 155 (71.7%) were taking an antimalarial. Of the women, 7.7% had used hormone

replacement therapy and 49.3% had used oral contraceptives. Although 25.3% reported taking vitamin D supplements, the mean dose was not known. Bisphosphonate use at baseline was present in 8.7% of patients.

Hypertension was present in 34.5%, hyperlipidemia in 15.7%, diabetes mellitus in 6.5%, and current smoking in 15.4% of patients at baseline (Table 3). Mean ± SD objective cardiovascular risk factor measurements included systolic blood pressure of 119.9 ± 17.3 mm Hg, diastolic blood pressure of 74.9 ± 11.2 mm Hg, BMI of 25.1 ± 5.9 kg/m^2, fasting glucose of 91.6 ± 31.9, total cholesterol of 189.3 ± 57.1 mg/dl (with LDL cholesterol of 106.6 ± 45.4 mg/dl), creatinine of 0.86 ± 0.79 mg/dl, and CRP level of 0.8 ± 1.7 mg/dl (Table 2). Eighty-four percent of patients had normal CRP levels (<1.0 mg/dl). Renal disease, as defined by the ACR revised classification criteria, was present in 26.2% at baseline (22).

In the unadjusted model for the associations of 25(OH)D levels with cardiovascular risk factors (Tables 4 and 5), lower 25(OH)D levels were significantly associated with the presence of hypertension, the presence of hyperlipidemia, higher CRP levels, and higher SLEDAI-2K scores. After adjustment for age, season, white race, country (Korea, UK, US, or other), and sex, these associations remained significant. Further correcting for BMI did not abrogate these associations. 25(OH)D levels were not associated with the presence of diabetes mellitus. Post hoc adjustment with glucocorticoid and antimalarial use did not affect the relationship between SLEDAI-2K and 25(OH)D (data not shown).

Of the 875 subjects, 36 had reported incident CVD events after enrollment. Only 1 CVD event was fatal. Mean ± SD followup time was 5.72 ± 3.03 years. Three subjects were excluded because of events attributed to postpartum cardiomyopathy, overhydration, and shrinking lung syndrome. An additional subject was excluded due to an unknown event date, which led to a final 32 subjects for analysis. Seven subjects reported MI, 6 reported angina, 4 reported peripheral vascular disease, 4 reported CHF, 7 reported transient ischemic attacks, and 4 reported cerebrovascular accident. Mean ± SD time to an event was 3.13 ± 2.19 years. Of the 32 subjects, 9 were in 25(OH)D Q1, 13 were in 25(OH)D Q2, 5 were in 25(OH)D Q3, and 5 were in 25(OH)D Q4 at baseline. A statistically significant association was not demonstrated between 25(OH)D levels and risk for CVD events (Table 6). However, a trend was present that suggests those in higher quartiles are less likely (lower hazard ratios) to develop any CVD event when compared with the lowest quartile. Of the 32 subjects with incident events, 25 were taking corticosteroids. However, adjusting for current use of an antimalarial or current use of a corticosteroid did not affect the Cox model results (data not shown).

DISCUSSION

We have investigated the relationship of baseline serum 25(OH)D levels with baseline cardiovascular risk factors and risk for future cardiovascular events. To our knowledge, this is the first investigation of risk for future cardiovascular events in a large international cohort of SLE patients. We have found that lower 25(OH)D levels are independently associated with the presence of hypertension, hyperlipidemia, and increased CRP levels after

controlling for age, season, sex, race, country, and BMI. We have also found that those with lower 25(OH)D levels exhibit a trend toward increased risk for future cardiovascular events.

In concordance with previous studies (27–32), we found that the mean 25(OH)D level was low, with 72.3% being <30 ng/ml. In our cohort, those in the lower 25(OH)D quartiles were more likely to have hypertension and hyperlipidemia compared with the highest quartile, even after controlling for age, season, sex, race, country/location, and BMI. Similar findings have been repeatedly noted in the general population (5,33,34) and are thought to be related to the effects of vitamin D on the renin–angiotensin system. Studies have demonstrated elevated renin levels in vitamin D deficiency in both animal and human models (35,36).

The explanation for the association of lower 25(OH)D levels and higher CRP levels is not as clear; controlling for BMI did not affect this relationship significantly. In the general population, studies have reported inconsistent findings with regard to CRP. Hyppönen et al reported an association between 25(OH)D levels and preclinical variations in CRP levels even when controlling for age, month, and sex, but this relationship did not persist after adjusting for lifestyle factors and adiposity (6). Shea et al, however, noted no association between 25(OH)D and CRP, and even after vitamin D supplementation, found no significant change in CRP level per 2-fold increase in 25(OH)D level (37). In our previous study of SLE patients, CRP was not associated with 25(OH)D, but the CRP level in that population was higher than in this international inception cohort (mean ± SD 4.2 ± 10.2 versus 0.8 ± 1.7 mg/dl) (21). While CRP level often increases with age (the mean age in this cohort was 39.3 years versus 43.2 years in our previous study), in the general population, CRP level is thought to double from ~1 mg/dl in ages 25–34 years to ~2 mg/dl in ages 55–64 years, suggesting that age alone cannot account for the increase in CRP level. The mean 25(OH)D level in our previous study was 27.1 ng/ml compared with 23.8 ng/ml, and some studies have suggested that an inverse relationship between CRP and 25(OH)D exists only in 25(OH)D levels <21 ng/ml and that CRP levels may actually increase with 25(OH)D levels ≥21 ng/ml in the general population (38). Akin et al also reported an inverse association between 25(OH)D and CRP only in those with deficient 25(OH)D levels <20 ng/ml (34), and it may be that the 25(OH)D levels in this cohort were low enough to show an association.

We found the higher 25(OH)D quartiles to be more likely to have lower SLEDAI-2K scores when compared with the lowest quartile, even after controlling for cardiovascular risk factors. This is consistent with several recent studies (28,30,31,39,40). Of interest, in a study of Thai SLE patients, Sumethkul et al found that 25(OH)D levels were inversely correlated with the SLEDAI-2K, but not with the adjusted SLEDAI-2K (excluding nephritis variables), which suggested that lupus nephritis is a major predictor of low 25(OH)D (32). Ruiz-Irastorza et al did not find a correlation between 25(OH)D and SLEDAI scores, but 53% of their population had a SLEDAI score of 0, 28% had a SLEDAI score of 1–3, and 19% had a SLEDAI score of >3 (27), whereas our population had much higher disease activity at baseline, with 18.2% with a SLEDAI-2K score of 0, 18.7% with a SLEDAI-2K score of 1–3, and 62.0% with a SLEDAI-2K score of >3. Some have found that those with SLEDAI scores >3 had the lowest 25(OH)D levels (28), and it may be that the association is more apparent given the more active disease in our population.

Participants in the lower 25(OH)D quartiles were more likely to be taking a corticosteroid at baseline and had higher mean SLEDAI-2K scores. Higher prevalence of current corticosteroid use could reflect the higher amount of disease activity, and concurrently, the mean corticosteroid dose in our cohort was >23 mg daily, which is significantly higher than most other studies. Glucocorticoid use has been documented to be associated with lower 25(OH)D levels (41) and is thought to be related to an increase in 24α-hydroxylase activity (42). It is not known if this is a dose-dependent relationship; however, the mean daily corticosteroid dose did not differ between quartiles.

Evidence regarding a relationship between antimalarial use and 25(OH)D levels is inconclusive. Hydroxychloroquine has been suspected to inhibit the conversion of 25(OH)D to its biologically more active form 1,25-dihydroxyvitamin D (43), and as such, Ruiz-Irastorza et al reported that hydroxychloroquine was associated with higher 25(OH)D levels (27). However, Huisman et al (14) and Toloza et al (29) et al did not find any association between 25(OH)D levels and antimalarial use.

Although both glucocorticoids and antimalarials have been shown to independently affect 25(OH)D levels and in our case may be related to disease activity/SLEDAI-2K scores, adjusting for each did not affect the relationship between SLEDAI-2K and 25(OH)D. Of note, 43% (n = 377) were taking both an antimalarial and a corticosteroid.

We did not find a statistically significant relationship between baseline 25(OH)D level and risk for cardiovascular event occurrence over the 11-year followup; however, those in the higher 25(OH)D quartiles (Q3 and Q4) were less likely to develop an incident cardiovascular event when compared to those in Q1. Those in Q2 had more cardiovascular events when compared with the other quartiles, but the reason for this observation remains to be determined.

In non-SLE populations, there are reports of low 25(OH)D levels in association with cardiovascular events (1–3,33,34). This has prompted investigation into a relationship between 25(OH)D levels and subclinical atherosclerosis. Low levels of 25(OH)D also have been shown to be associated with incident coronary artery calcium (CAC) in the Multi-Ethnic Study of Atherosclerosis (44). In SLE populations, Reynolds et al reported that lower 25(OH)D levels were associated with an increase in arterial pulse wave velocity that persisted, although slightly attenuated, even after adjusting for SLEDAI-2K score (31). Our previous study did not find a relationship between 25(OH)D and carotid intima-media thickness (CIMT), carotid plaque, CAC, and aorta calcium, before or after adjusting for age, season, and race. Similarly, Reynolds et al did not find a relationship between 25(OH)D and CIMT or plaque (31). Ravenell et al, however, did find that 25(OH)D levels were lower in those with higher total plaque areas (45). Such findings suggest that low 25(OH)D levels may infer a greater risk for CVD and events in SLE populations, and that the lower levels of 25(OH)D seen in SLE populations when compared with the general population may be a contributing factor to the early cardiovascular morbidity and mortality seen in SLE patients.

Those cohort members in the higher 25 (OH)D quartiles were more likely to be taking an antimalarial medication, and it has been reported that ever use of hydroxychloroquine is

protective against CAC (46), which may have contributed to the decreased risk for a cardiovascular event in the higher quartiles. Of the 32 subjects with incident events, 15 were taking an antimalarial medication and 16 were not. Data on whether or not corticosteroids contribute to atherosclerosis are controversial, but some studies suggest that treating inflammation may decrease the progression of subclinical atherosclerosis. For example, one study followed serial carotid ultrasounds and found that progression of subclinical atherosclerosis was associated with lower mean doses of corticosteroids and less aggressive immunosuppressive therapy (47). However, we did not find that adjusting for antimalarial use or current corticosteroid use affected the Cox model results.

Given these findings, the question remains whether supplementation with vitamin D should be more aggressively pursued in the management of SLE. Abou-Raya et al reported improvement in SLEDAI scores after 12 months of 2,000 IU daily oral cholecalciferol when compared with placebo, despite noting that 1 of 3 in the intervention group did not reach optimal 25(OH)D levels (40). Petri et al gave 50,000 IU of vitamin D_2 and calcium/D_3 200 IU twice daily to patients with 25(OH)D levels <40 ng/ml over a period of approximately 2.5 years. They reported that a 20-IU increase in 25(OH)D level resulted in a 21% decrease in the odds of having a Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI score ≥5 (48). While these reports suggest that supplementation may be beneficial in reducing disease activity, interventional studies investigating incident cardiovascular event risk would be useful, since literature in the general population has not supported the utility of supplementation for cardiovascular risk reduction. In the Women's Health Initiative (WHI) study, Hsia et al reported no effect on coronary or cerebrovascular risk in 36,282 postmenopausal women over 7 years of calcium/vitamin D supplementation, although they acknowledged that it was possible the supplementation dose was not high enough (49). Another study through the WHI noted that CAC scores were not significantly worse in those taking moderate dosages (1,000 mg/day) of calcium and vitamin D (400 IU/day) (50).

We recognize that our study has several limitations that should be taken into consideration when evaluating our results. Our results suggest an association between low 25(OH)D levels and higher risk for certain cardiovascular risk factors; however, causality cannot be implied. Low 25(OH)D may be a marker of overall poor health, as evidenced by physical inactivity with lack of sunshine, rather than itself a cause of CVD. The number of incident cardiovascular events was small and we did not control for renal disease, which may have affected both vitamin D levels and CVD risk factors. However, only 26.2% fulfilled the ACR criteria for renal disease at enrollment. In addition, we did not control for estrogen use, nor did we specifically control for antimalarial or corticosteroid use. However, the post hoc exploratory analyses described earlier did not change the Cox model results.

This study supports an association between lower 25(OH)D levels and certain cardiovascular risk factors. We have also reported a possible association between lower 25(OH)D levels and increased risk for a future cardiovascular event. Specific attention to maintaining optimal 25(OH)D levels may be beneficial in the management of SLE.

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Significance & Innovations

- Systemic lupus erythematosus (SLE) patients with higher 25-hydroxyvitamin D (25[OH]D) levels are more likely to have lower SLE disease activity.
- SLE patients with higher 25(OH)D levels are less likely to have hypertension and hyperlipidemia.
- An association may exist between higher baseline 25(OH)D levels and lower risk for future cardiovascular disease events.

Table 1

Demographics of the Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis cohort at enrollment*

	All (n = 875)	Women (n = 786)	Men (n = 89)
Age, mean ± SD years	39.3 ± 13.5	38.9 ± 13.1	42.9 ± 16.4
Women, %	89.8		
Ethnicity, %			
White	53.6	52.5	62.9
African American	16.7	16.8	11.2
Hispanic	3.1	3.2	2.2
Asian	22.5	22.5	22.5
Other	4.6	5.0	1.1
Country, %			
Canada	29.4	28.2	32.6
Iceland	2.4	2.5	1.1
Korea	15.8	15.8	15.7
Spain	0.7	0.8	0
Sweden	3.0	2.9	3.4
Switzerland	0.3	0.3	1.1
UK	22.5	23.0	18.0
US	26.6	26.5	28.1
Married, %	41.9	41.3	47.2
Education, mean ± SD years	14.0 ± 3.2	14.0 ± 3.2	13.2 ± 3.2
Vitamin D levels			
25(OH)D, mean ± SD ng/ml	23.8 ± 13.4	23.8 ± 13.6	23.7 ± 11.6
25(OH)D <30 ng/ml, %	72.3	71.6	78.7
25(OH)D ≥30 ng/ml, %	27.7	28.4	21.3
Lifestyle factors			
Daily alcohol use, % (n)	32.0 (862)	30.3 (775)	30.3 (87)
Amount, mean ± SD units	1.17 ± 3.44	0.92 ± 2.23	3.41 ± 8.23
Sedentary activity, mean ± SD hours/week	7.02 ± 3.96	6.92 ± 3.94	7.98 ± 4.03
Slight activity, mean ± SD hours/week	5.23 ± 3.15	5.33 ± 3.14	4.34 ± 3.09
Moderate activity, mean ± SD hours/week	2.48 ± 2.91	2.52 ± 2.91	2.14 ± 2.84
Heavy activity, mean ± SD hours/week	0.49 ± 1.31	0.48 ± 1.3	0.60 ± 1.39
Cardiovascular medications			
Hyperlipidemia therapy, %			
Current	9.0	8.9	10.1
Past	1.9	2.0	1.1
Aspirin, %	14.2	13.9	16.9
Antihypertensive medications, %			
Current	10.2	24.4	39.3
Past	25.9	10.1	11.2

	All (n = 875)	Women (n = 786)	Men (n = 89)
SLE-related factors			
Disease duration, mean ± SD years	0.5 ± 0.4	0.4 ± 0.3	0.5 ± 0.3
Taking corticosteroids, %			
Current	67.4	66.4	82.0
Never	24.2	25.0	14.6
Current corticosteroid dose, mean ± SD mg	23.3 ± 15.9	23.1 ± 16.1	25.0 ± 14.5
Taking antimalarials, %	66.4	67.0	60.7
Taking immunosuppressants, %			
Current	37.8	36.1	52.8
Never	59.3	60.8	46.1
Renal disease, %	26.2	25.2	34.8
SLEDAI-2K score, mean ± SD (n)	5.6 ± 5.5	5.6 ± 5.5 (783)	6.0 ± 5.2 (89)
Low complement, % (n)[†]	42.1	42.0 (709)	42.7 (82)
Positive dsDNA, % (n)[‡]	41.8	41.2 (701)	46.3 (82)
Bone medications			
Estrogen use ever, % (n)			
HRT	7.7 (779)		
OCPs	49.3 (781)		
Calcium, %	32.2	32.4	30.3
Vitamin D, %	25.3	25.3	24.7
Bisphosphonates, %	8.7	8.1	13.4

[*] 25(OH)D = 25-hydroxyvitamin D; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; dsDNA = double-stranded DNA; HRT = hormone replacement therapy; OCPs = oral contraceptives.

[†] Defined as a decrease in CH50, C3, or C4 below the lower limit of normal for the testing laboratory.

[‡] Increased DNA binding above the normal range based on local testing laboratory parameters.

Table 2

Objective and laboratory measures of the Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis cohort at enrollment*

	All		Women (n = 786)		Men (n = 89)	
Cardiovascular risk factor	**Value**	**N**	**Value**	**N**	**Value**	**N**
Systolic blood pressure, mm Hg	119.9 ± 17.3	864	119.0 ± 17.0	775	127.9 ± 17.9	
Diastolic blood pressure, mm Hg	74.9 ± 11.2	585	74.6 ± 11.0	769	77.6 ± 11.9	
Body mass index, kg/m^2	25.1 ± 5.9	845	25.1 ± 6.0	762	25.4 ± 4.7	85
Fasting glucose, mg/dl	91.6 ± 31.9	733	91.3 ± 32.9	659	94.2 ± 20.6	74
Total cholesterol, mg/dl	189.3 ± 57.1	776	189.7 ± 57.7	697	185.7 ± 52.3	79
HDL cholesterol, mg/dl	55.2 ± 26.7	408	55.5 ± 26.6	370	52.7 ± 28.5	38
LDL cholesterol, mg/dl	106.6 ± 45.4	336	106.2 ± 46.1	304	110.7 ± 39.0	32
Triglycerides, mg/dl	136.4 ± 85.7	755	132.7 ± 82.4	680	169.2 ± 106.1	75
Lipoprotein(a), mg/dl	36.5 ± 40.7	17	40.0 ± 44.23	14	20.1 ± 7.2	3
Fibrinogen, mg/dl	436.4 ± 126.0	11	407.12 ± 133.5	8	514.3 ± 67.3	3
C-reactive protein, mg/dl	0.8 ± 1.7	655	0.76 ± 1.7	587	0.65 ± 1.2	68
Homocysteine, μmoles/liter	12.9 ± 43.5	489	13.3 ± 45.9	436	11.8 ± 3.7	53
Lupus anticoagulant, %	20.3	772	19.0	691	32.1	81
Moderate/high aCL positive, %†	8.8	729	8.7	652	9.1	77
Creatinine, mg/dl‡	0.86 ± 0.79	436	0.85 ± 0.82	402	0.97 ± 0.17	34

*Values are the mean ± SD unless indicated otherwise. HDL = high-density lipoprotein; LDL = low-density lipoprotein; aCL = anticardiolipin antibody.

†Defined as ≥14.1–50 IgM phospholipid/IgG phospholipid units.

‡Three outliers removed (creatinine >15 mg/dl).

Table 3

Percentage of subjects with cardiovascular risk factors at enrollment

	%
Hypertension (n = 301/873)	34.5
Women (n = 251/786)	31.9
Men (n = 50/89)	56.2
Hyperlipidemia (n = 137/875)	15.7
Women (n = 121/786)	15.4
Men (n = 16/89)	18.0
Diabetes mellitus (n = 56/861)	6.5
Women (n = 50/786)	6.4
Men (n = 6/89)	6.7
Current smoker (n = 135/875)	15.4
Women (n = 115/785)	14.6
Men (n = 20/89)	22.5
Ex-smoker (n = 181/875)	20.7
Women (n = 157/784)	20.0
Men (n = 24/89)	27.0
Never smoker (n = 559/875)	63.9
Women (n = 514/786)	65.4
Men (n = 45/89)	50.6
Postmenopausal (n = 102/786)	13.0

Table 4

25(OH)D quartiles and binary CV risk factors at enrollment *

	Unadjusted model		Adjusted model 1†		Adjusted model 2‡	
CV risk factor	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Hypertension						
Q2	0.84	0.58, 1.24	0.81	0.55, 1.21	0.83	0.55, 1.25
Q3	0.60§	0.41, 0.89§	0.66	0.43, 1.00	0.69	0.44, 1.06
Q4	0.43§	0.29, 0.65§	0.44§	0.28, 0.68§	0.49§	0.31, 0.77§
Diabetes mellitus						
Q2	1.14	0.56, 2.31	0.98	0.47, 2.03	0.93	0.43, 1.99
Q3	0.54	0.22, 1.22	0.52	0.21, 1.21	0.57	0.22, 1.35
Q4	0.81	0.37, 1.73	0.66	0.29, 1.45	0.71	0.31, 1.63
Hyperlipidemia						
Q2	0.87	0.55, 1.38	0.76	0.47, 1.22	0.80	0.49, 1.29
Q3	0.31§	0.17, 0.54§	0.28§	0.15, 0.51§	0.30§	0.16, 0.55§
Q4	0.48§	0.28, 0.79§	0.43§	0.24, 0.74§	0.50§	0.28, 0.87§

*25(OH)D = 25-hydroxyvitamin D; CV = cardiovascular; OR = odds ratio; 95% CI = 95% confidence interval; Q = 25(OH)D quartile.

†Adjusted model 1: controlled for age, season, white race, sex, and country (Korea, UK, US, or other), except for diabetes mellitus, which controls for age, white race, sex, and season only.

‡Adjusted model 2: controlled for same as model 1 plus body mass index.

§Statistically significant.

Table 5

25(OH)D quartiles and continuous CV risk factors at enrollment *

	Unadjusted model		Adjusted model 1†		Adjusted model 2‡	
CV risk factor	β§	95% CI	β§	95% CI	β§	95% CI
CRP						
Q2	−0.12	−0.48, 0.24	−0.11	−0.47, 0.25	−0.10	−0.47, 0.26
Q3	−0.30	−0.66, 0.06	−0.30	−0.68, 0.08	−0.30	−0.69, 0.08
Q4	−0.38¶	−0.76, −0.01¶	−0.44¶	−0.84, −0.04¶	−0.44¶	−0.85, −0.03¶
Homocysteine						
Q2	0.10	−0.04, 0.25	0.077	−0.07, 0.23	0.08	−0.08, 0.23
Q3	−0.02	−0.16, 0.13	−0.04	−0.20, 0.12	−0.03	−0.20, 0.13
Q4	−0.01	−0.16, 0.14	−0.04	−0.21, 0.12	−0.03	−0.21, 0.14
Creatinine						
Q2	0.14	−0.09, 0.38	0.12	−0.12, 0.36	0.13	−0.11, 0.37
Q3	0.13	−0.10, 0.36	0.09	−0.15, 0.32	0.10	−0.15, 0.34
Q4	0.06	−0.16, 0.28	0.02	−0.22, 0.25	0.03	−0.21, 0.27
SLEDAI-2K						
Q2	−1.22¶	−2.24, −0.20¶	−1.44¶	−2.43, −0.46¶	−1.38¶	−2.37, −0.38¶
Q3	−1.88¶	−2.90, −0.86¶	−2.15¶	−3.17, −1.12¶	−2.16¶	−3.19, −1.12¶
Q4	−2.27¶	−3.30, −1.25¶	−2.22¶	−3.26, −1.18¶	−2.37¶	−3.25, −1.31¶

*25(OH)D = 25-hydroxyvitamin D; CV = cardiovascular; 95% CI = 95% confidence interval; CRP = C-reactive protein; Q = 25(OH)D quartile; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

†Adjusted model 1: controlled for age, sex, season, white race, and country (Korea, UK, US, or other).

‡Adjusted model 2: controlled for same as model 1 plus body mass index. When looking at women and men, model controlled for only age, season, white race, and country.

§Represents the mean difference in risk factor between Q1 and Q2, Q3, and Q4.

¶Statistically significant.

Table 6

25-Hydroxyvitamin D quartiles (Q) and cardiovascular disease events at followup*

	No. of events	HR	95% CI
Q2	13	1.15	0.46, 2.84
Q3	5	0.68	0.21, 2.13
Q4	5	0.63	0.20, 1.97

* Q1 is the referent quartile, with 9 events. HR = hazard ratio; 95% CI = 95% confidence interval.