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Evidence that abnormally large seasonal declines in vitamin D status may trigger SLE flare in non-African Americans

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Abstract

Cross-sectional studies have shown that low vitamin D (25-hydroxyvitamin D (25(OH)D)) is associated with increased systemic lupus erythematosus (SLE) activity. This study is the first to assess the temporal relationship between 25(OH)D levels and onset of SLE flare. This assessment was made possible because of the specimen bank and database of the Ohio SLE Study (OSS), a longitudinal study of frequently relapsing SLE that involved regular bimonthly patient follow-up. We identified for this study 82 flares from 46 patients that were separated by at least 8 months from previous flares. Serum 25(OH)D levels were measured at 4 and 2 months before flare, and at the time of flare (a flare interval). We found that for flares occurring during low daylight months (LDM, Oct-Mar), 25(OH)D levels were decreased at the time of flare, but only in non-African American (non-AA) patients (32% decrease at flare, compared to 4 months prior, $p < 0.001$). To control for seasonal effects, we also measured 25(OH)D levels in the LDM "no-flare" intervals, which were intervals that matched to the same calendar months of the patients' LDM flare intervals, but that didn't end in flare ($n = 24$). For these matches, a significant decrease occurred in 25(OH)D levels during the flare intervals (18.1% decrease, $p < 0.001$), but not during the matching no-flare intervals (6.2% decrease, $p = 0.411$). For flares occurring during high daylight months (HDM), 25(OH)D levels changed only in non-AA patients, increasing slightly (5.6%, $p = 0.010$). Analysis of flare rates for the entire OSS cohort ($n = 201$ flares) revealed a tendency for higher flare rates during LDM compared to HDM, but again only in non-AA patients ($p = 0.060$). Flare rates were lower during HDM for non-AA patients compared to AA patients ($p = 0.028$). In conclusion, in non-AA SLE patients, unusually large declines in 25(OH)D during LDM may be mechanistically related to SLE flare, whereas relatively high 25(OH)D levels during HDM may protect against flare.

Keywords

Vitamin D; systemic lupus erythematosus; disease flare

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Introduction

It is widely recognized that low vitamin D status (low levels of vitamin D (25-hydroxyvitamin D, 25(OH)D, calcidiol) is intimately related to bone disorders, especially rickets, osteoporosis, and fractures.^{1,2} Recent discoveries, however, indicate that low vitamin D status is also associated with an increased risk of cardiovascular disease,^{3,4} hypertension,⁵ vascular calcification,^{6–8} and all-cause mortality.^{9–12} The cardiovascular associations may be related to the ability of vitamin D to suppress hypertrophy of cardiomyocytes¹³ and of the renin-angiotensin system.^{14–16} Low vitamin D status is also associated with insulin resistance, diabetes, metabolic syndrome,¹⁷ and the anemia of chronic kidney disease (CKD).¹⁸ Active metabolites of vitamin D, calcitriol and paricalcitol, have been shown to reduce proteinuria in CKD,¹⁹ probably through anti-inflammatory effects of vitamin D.^{20–22} Low vitamin D status is also associated with the hypercoagulable state,^{9,23} several forms of cancer,^{1,24} progression of kidney disease,²⁵ and autoimmune diseases.^{1,26}

The role that vitamin D deficiency appears to play in autoimmunity is likely due both to vitamin D's anti-inflammatory and immunomodulatory effects.^{27,28} For instance, calcitriol can inhibit production of pro-inflammatory/pro-type 1 helper T cell cytokines while promoting type 2 helper T cell cytokines by peripheral blood mononuclear cells,^{29,30} inhibit maturation of dendritic cells,³¹ and inhibit proliferation of activated B cells.³² Among the autoimmune diseases associated with low vitamin D status, the association is particularly strong for Systemic lupus erythematosus (SLE), with many studies showing either low levels of 25(OH)D or its active metabolite (1,25-dihydroxyvitamin D (1,25(OH)₂D, calcitriol), or both being associated with SLE (reviewed in Kamen and Aranow³³). Many of these studies report an inverse correlation between circulating 25(OH)D levels and SLE disease activity. A recent study has shown in a large cohort of Chinese SLE patients an association between vitamin D deficiency and certain cardiovascular risk factors, such as higher low-density lipoprotein cholesterol levels, lower high-density lipoprotein cholesterol levels, higher triglyceride levels and the presence of antiphospholipid antibodies.³⁴ These studies support the notion that vitamin D deficiency is mechanistically related to heightened SLE disease activity, and can possibly serve as a biomarker of disease flare. However, all of the studies to date reporting this association have involved cross-sectional testing, thus making it impossible to determine if low vitamin D status is simply a chronic condition in severe SLE, or develops in relation to SLE flare onset. The present work was designed to address this question, using the data and specimen bank of the Ohio SLE Study (OSS), a longitudinal study involving regular bimonthly testing in a recurrently active SLE patient cohort.

Materials and methods

Patient population

The OSS is a prospective study of 106 recurrently active SLE patients, 67% with major renal SLE manifestations at or prior to entry into the OSS. Recruitment into the OSS was done following institutional review board-approved informed consent, and the OSS has been performed in accordance with the *Declaration of Helsinki*. The OSS ethnicity consisted of 36% African American (AA), and 64% non-AA (59% European American, 5% Asian or Hispanic). The OSS patients are tested at pre-specified bimonthly intervals within windows of + 1 week, which allows rigorous study of biomarkers that change just prior to or at the time of flare. To date, median follow-up is greater than 44 months, with >90% OSS visit compliance.

Flare adjudication

At approximately yearly intervals, charts were reviewed for each OSS visit to determine, using pre-specified criteria^{35–37} as we have previously reported,^{38–40} if an SLE flare had occurred since the previous OSS visit, and if so, whether it was renal or nonrenal (did or did not involve the renal criteria), and mild, moderate, or severe. The flare criteria are shown in Table 1. If the flare met criteria for both a renal and nonrenal flare, it was classified as a renal flare unless the renal flare was mild and the nonrenal flare was moderate or major. In that case the flare was designated a nonrenal flare. Thus, each visit was classified as a “flare” or “no-flare” visit, and flares were further classified as renal or nonrenal. To date, 201 flares have been identified in the OSS.

Flare intervals

To assess the change in circulating levels of 25(OH)D and related parameters in relationship to flare, assays were performed on serum samples from 4 and 2 months before (–4, of –2) and at the time flare (0). Together these months were termed a flare interval. All flare intervals were tested provided that they had complete data sets (–4, –2, 0 month samples), and were separated by at least 4 months from any other flare interval within the same patient. This resulted in 82 flare intervals to be tested, from 46 patients.

To account for independent seasonal effects on flare intervals in the group that demonstrated 25(OH)D level decreases at flare (see Results), 4-month “no-flare” intervals were also tested in eligible patients. To be eligible for no-flare interval testing, the patient had to have a 4-month interval in which each of 3 consecutive OSS visits were no-flare visits, and the 4-month no-flare interval matched the calendar months of the patient’s flare interval. The matching no-flare interval had to be within 2 years of the flare interval to minimize other confounding variables such as age and life-style changes.

Analytic studies

OSS serum samples are maintained at –80°C. For the present study the selected samples were thawed and then kept on ice until tested. Commercial ELISAs were used to measure serum levels of 25(OH)D (Immunodiagnostic Systems, Fountain Hills, AZ), intact parathyroid hormone (iPTH, MD Bioproducts, St. Paul, MN), phosphate (BioAssay Systems, Hayward, CA) and calcium (BioAssay Systems).

All other assays were performed in the clinical laboratories of The Ohio State University on specimens obtained on the day of patient’s OSS visit.

Statistical analysis

The initial analysis of the temporal relationship between 25(OH)D levels and onset of flare was done using mixed effects models (SAS JMP Version 8, SAS Institute, Cary, NC), with flare interval month as the predictor and 25(OH)D levels as the response. Subjects were used as random effects, which induces equal correlations between the observations within a subject. Other covariates that were included in the analysis were age, body-mass index, race (AA or non-AA), therapy (mean dose of prednisone or hydroxychloroquine during the prior 60 days), and daylight month. Vitamin D supplementation was not included as a covariate because only three of the flare intervals occurred during vitamin D supplementation, and the dose did not change during any of these three intervals. Daylight month was defined as low daylight month (LDM) if the flare occurred during October through March, or high daylight month (HDM) if the flare occurred during April through September. Interactions were included between 25(OH)D and daylight month to account for seasonal effects, and between 25(OH)D and race to account for the natural ultraviolet B (UVB) shielding effects of skin melanin.

After stratifying the data by race and by monthly daylight at flare (LDM vs HDM), differences among -4, -2, and 0 measurements were analyzed by repeated measures analysis of variance (Tukey for normally distributed data, Friedman for data not normally distributed) (Figures 1 and 2). Because many of these datasets were not normally distributed, all of the flare interval 25(OH)D levels are shown graphically as median levels.

For matching flare and no-flare intervals in non-AAs during LDM flare intervals (Figure 3), two-tailed one-sample *t* tests were done to determine if changes in 25(OH)D from -4 month to 0 month were different from zero. These data were also analyzed by two-tailed paired *t* test to determine if the decrease in the mean % from -4 month to 0 month for the flare interval was greater than the no-flare intervals.

Results

Baseline demographic data

Table 2 shows the demographic and clinical characteristics at OSS entry of the 46 patients whose SLE flares met the criteria for inclusion in this study.

Change in 25(OH)D during flare

The purpose of this study was to determine whether circulating levels of 25(OH)D changed during the flare interval, defined as 4 months before flare (-4), 2 months before flare (-2), and at flare (0). The data were first analyzed by a mixed effects model. This allowed assessment of other variables that may influence 25(OH)D levels, including age, body mass index (BMI), therapy (prednisone or hydroxychloroquine), race, and monthly daylight. The monthly daylight term was determined by whether the flare occurred during low or high daylight months (LDM or HDM, as defined in Methods). The rationale is that the exposure of the individual patients to daylight will, on average, be related to the amount of available daylight in the given LDM or HDM. The data on daylight levels were collected for central Ohio from the US Naval Observatory, with the LDM months (October through March) having an average of 10.5 hours of daylight, and the HDM months (April through September) having an average of 13.9 hours of daylight.

Using the mixed effects models, we found that individual predictors of serum 25(OH)D levels included age (direct correlation; $p = 0.049$), body mass index (BMI, indirect correlation; $p = 0.002$), and race (higher in non-AAs, compared to AAs; $p < 0.001$), but not prednisone (0.671), hydroxychloroquine ($p = 0.940$), monthly daylight ($p = 0.093$), or the flare interval month (-4, -2, or 0; $p = 0.730$). However, there was a significant interaction between flare interval month and monthly daylight ($p = 0.003$), and between flare interval month, monthly daylight, and race ($p = 0.005$).

To better understand the interactions between race, monthly daylight, and flare interval month, the data were stratified by race (non-AA vs AA) and by whether flare occurred during LDM or HDM, and then tested by repeated measures analysis to determine whether 25(OH)D levels changed during the flare interval. Figure 1 shows the median 25(OH)D levels during the LDM flare intervals in non-AA and AA patients. For the flares occurring in non-AA patients ($n = 38$), there was a significant decrease in median 25(OH)D levels at the time of flare (32% compared to -4 month level, $p < 0.001$, Figure 1A and 1B), with the at-flare value being significantly lower than the levels at -2 months ($p < 0.05$) and -4 months ($p < 0.001$). The decrease in 25(OH)D was significant for both nonrenal flares ($p = 0.019$) and renal ($p = 0.022$) flares. By contrast, for LDM flares occurring in the AA patients ($n = 13$), no significant differences were observed at any of the time points of the flare interval (Figure 1C and 1D).

Figure 2 shows the median levels in 25(OH)D levels during the HDM flare intervals. In the non-AA patient flares ($n = 20$), there was a small (5.6%) but significant increase in the median 25(OH)D levels at the time of flare, compared to the -4 month level ($p = 0.010$, Figure 2A and 2B). This increase appeared to be mainly due to increases at nonrenal flares ($p = 0.057$). For the AA patient flares ($n = 11$), no significant differences were observed at any of the time points of the flare interval (Figure 2C and 2D).

Table 3 shows the summary statistics for the serum 25(OH)D levels, stratified for each category of flare.

Influence of low daylight months on 25-hydroxyvitamin D levels: Flare versus no-flare intervals

It is well established that variations occur in 25(OH)D levels due to seasonal variations in sun exposure.⁴¹ For this reason we tested whether the association reported here, decreased 25(OH)D levels during LDM flares in non-AAs (Figure 1A), was observed simply because the flare occurred during LDM. This analysis was carried out in the non-AA SLE patients whose LDM flare intervals could be matched, in the same patient, to LDM “no-flare” intervals. Matching required that the no-flare intervals occurred in the same calendar months as the flare interval, and within 2 years of the given flare interval, as described in Methods. The hypothesis is that, if an abnormally large decrease in 25(OH)D during LDM is mechanistically related to SLE, it should be possible to show that the decrease in 25(OH)D during LDM flare intervals is significantly greater than the decrease in 25(OH)D during matching no-flare intervals.

Using this approach, we identified 24 flare intervals with matching no-flare intervals in 16 non-AA patients. The percent change in serum 25(OH)D from 4 months prior to the time of flare was calculated for each flare and no-flare interval. In 4 instances, there were 2 flares occurring in a patient in the same calendar month and within 2 years of each other, and for these individuals the percent change for the 2 flares was averaged. Thus 20 matching flare/no-flare intervals were available for this analysis.

Figure 3 shows that, for these flare intervals, the percent change in 25(OH)D from -4 months to 0 months was significantly different from zero (18.1% mean decrease, $p < 0.001$). By contrast, the percent change in 25(OH)D levels during the matching no-flare intervals was not significantly different from zero (6.2% mean decrease, $p = 0.411$). When analyzed in a pair-wise fashion, the difference between matching flare and no-flare 25(OH)D changes did not reach significance ($p = 0.124$). However, this difference did reach significance ($p = 0.026$) if the two outliers (Figure 3, shaded symbols) were removed from the analysis.

Influence of race and monthly daylight status on SLE flare rates

The temporal relationship between decreased vitamin D levels during LDM and onset of flare in non-AA patients led us to two hypotheses concerning the relationship between SLE flare rate, race and LDM/HDM status. First, we hypothesized that flare rates would be higher in non-AA patients, but not AA patients, during LDM compared to HDM. Second, because vitamin D levels were chronically low in AA SLE patients, we hypothesized that HDM flare rates would be lower in non-AA compared to AA SLE patients.

To address these hypotheses, we determined the flare rates for the entire OSS cohort ($n = 201$ flares), for non-AA and AA patients, during LDM and HDM. As shown in Table 4, there was a trend for an overall higher flare rate in non-AA patients during LDM, compared to HDM ($p = 0.060$), with the effect being predominantly for renal flares. In contrast, there was no difference in flare rates in AA patients between LDM and HDM. In addition, while the flare rates were the same between non-AAs and AAs during LDM months, the overall

flare rate was lower for non-AAs during HDM ($p = 0.028$), again with this effect being predominantly for renal flares.

Other factors related to 25-hydroxyvitamin D levels

There was no relationship between 25(OH)D levels and serum creatinine level or 24-hour proteinuria. The latter is relevant because it is well established that heavy proteinuria can cause low serum 25(OH)D levels due to urinary loss of 25(OH)D bound to vitamin D binding protein.⁴²

Serum calcium, phosphate, and iPTH were analyzed in the non-AA SLE patient cohort during LDM flare intervals. No significant changes were observed (data not shown).

Discussion

The present study examines, for the first time, the temporal relationship between serum 25(OH)D levels and SLE flare in SLE patients with recurrently active SLE. This analysis was made possible because of the availability of regular bimonthly serum samples from the OSS specimen bank. For this study, 82 flares were tested (51 renal flares) using samples at 4 and 2 months prior to flare and at the time of flare. This study also took into account the seasonal effect of sunlight exposure and skin pigmentation, two factors known to influence the levels of circulating vitamin D.^{41,43}

The major finding of this study was that in non-AA SLE patients, there was a highly significant decrease in 25(OH)D serum levels at the time of flare for those flares occurring during LDM. This was observed in both nonrenal and renal flares. Importantly, this decrease was about 3-fold larger than could be accounted for by the usual reduction in 25(OH)D levels during LDM, as determined for the matching “no-flare” intervals that occurred in the same calendar months. Taken together, the present work is consistent with the hypothesis that during LDM, a larger than usual decline in vitamin D status is a mechanism of SLE flare. The mechanism may involve a reduction in the roles played by vitamin D in modulating both the immune response and the inflammatory response.^{27,44,45}

The active metabolite of 25(OH)D is 1,25-dihydroxyvitamin D (1,25(OH)₂D), and the effect of low 25(OH)D is likely mediated through low 1,25(OH)₂D levels. Though 1,25(OH)₂D levels were not measured in the present study, iPTH levels, which increase in the face of decreased circulating 1,25(OH)₂D, were measured and were found not to change. This suggests that if the effect of low 25(OH)D on flare is due to low 1,25(OH)₂D production, the effect is on the local production of 1,25(OH)₂D. Such local effects are not unexpected, as cell types known to express the enzyme that converts 25(OH)D to 1,25(OH)₂D (CYP27B1) include macrophages,⁴⁶ dendritic cells,⁴⁷ and B lymphocytes,³² all involved in the pathogenesis of lupus.

In contrast to LDM flares, flares occurring during HDM in non-AA SLE patients were associated with a small but significant increase in the median 25(OH)D level. This increase is likely related to the normal seasonal increase in circulating 25(OH)D that is driven by ultraviolet B (UVB) radiation from greater exposure to direct sunlight.⁴⁸ Thus, if normal 25(OH)D levels contribute protection against SLE flare, the mechanism of this protection is overridden during HDM by other flare mechanisms. Excessive UV exposure, which is a well-established mechanism of SLE flare, may represent one such mechanism, and account for the apparent paradox of SLE flare occurring in the face of rising 25(OH)D levels. Indeed, SLE patients are often advised to avoid excessive sunlight in the summer. Our study indicates that there is potential disadvantage to this management approach if it leads to

vitamin D insufficiency, and suggests that such an approach should include vitamin D supplementation.

The associations that we demonstrate between LDM, vitamin D levels and SLE flare were statistically significant only for the non-AA patients. The reasons for this are likely related to the lower levels known to occur in AAs⁴⁹ and shown in this study, and the relative insensitivity of these levels to seasonal effects,⁵⁰ both of which are due to the UVB screening effects of pigmentation in the skin. Thus any vitamin D-related risk for flare in the AA patients may be obscured because their vitamin D status is already low, and less likely to change during LDM. On the other hand, the chronically low 25(OH)D levels may indicate a risk that is year-round, with additional decreases not adding additional risk. Finally, the role of vitamin D in instigating SLE activity may differ between AA and non-AA patients. This appears to be the case for rheumatoid arthritis⁵¹ and stroke risk.⁵² Interestingly, the cross-sectional studies that have examined the relationship between low vitamin D status and SLE activity have not noted a difference in this relationship between AA and non-AA patients.⁴⁴

If large decreases and/or chronically low vitamin D levels contribute to SLE flare pathogenesis, flare rates should reflect this relationship. Analysis of all of the 201 flares in the OSS (Table 4) suggests this to be true, with a trend in non-AA patients for a higher overall flare rate during LDM than during HDM ($p = 0.060$). In contrast, in AA patients, the flare rate during LDM was no different than during HDM. Comparing flare rates between races showed LDM flare rates to be similar, while the overall HDM rate was significantly lower in non-AA patients compared to AA patients. Interestingly, the differences in overall flare rate appeared more so for renal flare, although the differences for non-renal flare may become statistically significant with a larger sample size. Taken together, the results of analyzing OSS flare rates support a role for decreased vitamin D levels as a mechanism for SLE flare. In addition, these data may explain in part differences in disease activity between AA and non-AA patients.^{53,54}

In summary, the present study suggests that greater than usual decreases in 25(OH)D during LDM are mechanistically related to SLE flare, further supporting a role for vitamin D in lupus disease pathogenesis. To rigorously test this hypothesis would require a prospective, controlled, randomized trial. Currently, one such Phase II trial is underway (ClinicalTrials.gov). Our data suggest that it will be important for randomized trials to take into account not only race, but also seasonal effects. These may be different for SLE patients residing in southern climates compared to those in northern climates. It may be important for randomized trials to consider an additional study arm in which a subset of those randomized to vitamin D supplementation would receive increased vitamin D supplementation during LDM.

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Figure 1.

Individual and median 25-hydroxyvitamin D (25(OH)D) serum levels for flares that occurred during low daylight months (LDM) in non-African American (AA) patients (Panels A and B), and African American (AA) patients (Panels C and D). As shown, in non-AA patients, 25(OH)D levels are decreased significantly by the time of flare (0 month of the flare interval). By contrast, in AA patients, there are no significant changes in 25(OH)D over the flare interval. F = flares, NRF = non-renal flares, RF = renal flares.

Figure 2.

Individual and median changes in 25-hydroxyvitamin D (25(OH)D) levels for flares that occurred during the high daylight months (HDM) intervals. As shown in non-African American (AA) patients (Panels A and B), there is a significant increase in 25(OH)D levels by the time of the flare when all flares are considered together. By contrast, the changes in the African American (AA) patients during the flare interval were not statistically significant (Panels C and D). F = flares, NRF = non-renal flares, RF = renal flares.

Figure 3.

Percent change in 25-hydroxyvitamin D (25(OH)D) levels from -4 months to 0 months of the no-flare intervals compared to that of the matching flare intervals. The mean percent decrease in 25(OH)D during the flare intervals is significant (18.1%, $p < 0.001$), while the mean percent decrease in 25(OH)D during the no-flare intervals is not (6.2%, $p = 0.411$). Individual patients are shown as open or shaded circles, with dotted lines matching the no-flare and flare values for each patient. The mean values are shown as closed circles. The horizontal dashed line indicates zero change.

Table 1**Adjudication criteria for SLE Flare**

Renal – the development of the following symptoms	
<i>Mild</i>	<ul style="list-style-type: none"> – increase in glomerular hematuria from <5 to >15 red blood cell (RBC)/high-powered field (hpf), with >2 acanthocytes/hpf, and/or – recurrence of >1 RBC cast, white blood cell cast (no infection), or both
<i>Moderate</i>	<ul style="list-style-type: none"> – if baseline creatinine <2 mg/dl, an increase of 0.2–1.0 mg/dl – if baseline creatinine >2 mg/dl, an increase of 0.4–1.5 mg/dl – if baseline urine protein/creatinine (Pr/Cr) <0.5, an increase to 1 – if baseline urine Pr/Cr 0.5–1, an increase to 2 – if baseline urine Pr/Cr >1, an increase of 2-fold with absolute Pr/Cr <5
<i>Severe</i>	<ul style="list-style-type: none"> – if baseline creatinine <2 mg/dl, an increase of >1 mg/dl – if baseline creatinine ≥ 2 mg/dl, an increase of >1.5 mg/dl – an absolute increase in urine Pr/Cr >5
Nonrenal – the development of the following symptoms, and an increase in therapy.	
<i>One or more of the following:</i>	
<i>Mild</i>	typical rash, symmetrical mild to moderate arthralgias, fever, thrombocytopenia 50,000 to 100,000/mm ³ , significant fatigue, oral ulcers, mild to moderate hair loss
<i>Moderate</i>	serositis, hemoglobin 9 to 11, thrombocytopenia 25,000 to 50,000/mm ³ , neutrophil count <1,500 /mm ³ , severe migraine requiring narcotics for management, seizures in the absence of neurological deficit, uveitis, retinal cytoid bodies, severe alopecia, pericarditis (no tamponade), extensive mucosal ulceration.
<i>Severe</i>	pulmonary hemorrhage, vasculitis involving abdominal viscera or brain, severe myositis, platelet count < 25,000/mm ³ , hemolytic anemia with hemoglobin < 9, severe rash involving > 2/9th body surface area, aseptic meningitis, transverse myelitis, cerebritis, myocarditis, pericarditis with tamponade.

Table 2

Demographic and clinical characteristics at Ohio SLE Study (OSS) entry

No of patients	46
Age, mean	35
Gender (female, male)	45, 1
Race ^a (Cau, AA, Asian)	29, 15, 2
% with lupus nephritis	76
% on Prednisone	85
% on immunosuppressives	70
C3, mg/dl ^b	96 ± 38
C4, mg/dl ^b	16 ± 10
% anti-dsDNA positive	13
Serum creatinine, mg/dl ^a	1.08 ± 1.42

^aCau = Caucasian, AA = African American;^bMean + SD

Table 3

Summary statistics for serum 25(OH)D levels in flare interval samples (months -4, -2, and 0 (at flare)) for flares occurring during low daylight months (LDM) and high daylight months (HDM)

Serum 25(OH)D, ng/ml																	
Nonrenal flares						Renal flares				Nonrenal and renal flares							
		-4	-2	0	P value			-4	-2	0	P value			-4	-2	0	P value
LDM Flares	Non-AA	N	20					18					38				
		Median	28.3	24.3	19.2	0.019 ^a		30.2	30.5	25.4			29.0	27.7	19.7	<0.001 ^a	
		Mean	30.2	28.8	25.9			32.7	28.1	24.8	0.022 ^b			31.4	28.5	25.4	
		SD	14.5	13.6	14.5			17.8	13.1	12.6				16.0	13.2	13.4	
	AA	N	8					5					13				
		Median	16.0	22.9	17.5			17.0	14.4	14.2	0.691 ^a			17.0	20.0	14.6	
		Mean	17.3	21.5	18.6	0.425 ^b		16.2	15.5	14.0				16.9	19.2	16.9	0.463 ^b
		SD	9.0	10.8	10.1			4.3	6.8	3.7				7.4	9.7	8.4	
	All races	N	28					23					51				
		Median	24.2	23.4	19.2	0.010 ^a		24.0	24.2	18.9				24.0	23.7	19.1	<0.001 ^a
HDM Flares	Non-AA	N	15					5					20				
		Median	23.4	21.2	23.9	0.057 ^a		23.5	30.1	29.8				23.4	24.6	24.7	0.010 ^a
		Mean	25.6	26.9	29.5			22.7	31.0	30.5	0.182 ^b			24.9	27.9	29.8	
		SD	14.1	14.8	13.9			10.5	7.4	7.3				13.1	13.3	12.4	
	AA	N	8					3					11				
		Median	11.8	11.7	12.1			18.2	10.7	11.0				15.5	10.7	11.0	
		Mean	15.6	17.1	17.5	0.312 ^b		16.4	11.3	12.2	0.256 ^b			15.8	15.5	16.0	0.928 ^b
		SD	9.7	12.2	12.4			3.9	5.0	4.1				8.3	10.8	10.8	
	All races	N	23					8					31				
		Median	20.7	21	22.6			8.6	6.6	8.8				19.8	21.2	22.6	
	Mean	22.1	23.5	25.4	0.008 ^b		20.4	23.6	23.6	0.563 ^b			21.7	23.5	24.9	0.019 ^b	
	SD	13.4	14.5	14.3			8.9	11.9	11.2				12.3	13.7	13.4		

^aLevel of significance by Friedman's nonparametric repeated measures analysis of variance (ANOVA).

^bLevel of significance by Tukey repeated measures ANOVA.

Table 4

Flare rates for the Ohio SLE Study (OSS), according to race (non African Americans (non-AA) versus AA) and low daylight months (LDM)/high daylight months (HDM) categories

Patient race		number during LDM	LDM flare rate ^a	number during HDM	HDM flare rate ^a	LDM flare rate/HDM flare rate	P value LDM vs HDM ^b	P value vs AA LDM ^c	P value vs AA HDM ^c
Non-AA	Follow-up visits	816		787					
Non-AA	All flares	73	8.9%	53	6.7%	1.33	0.060	0.528	0.028
Non-AA	Nonrenal flares	42	5.1%	34	4.3%	1.19	0.254	0.279	0.229
Non-AA	Renal flares	31	3.8%	19	2.4%	1.57	0.073	0.278	0.030
AA	Follow-up visits	406		383					
AA	All flares	36	8.9%	39	10.2%	0.87	0.306		
AA	Nonrenal flares	17	4.2%	21	5.5%	0.76	0.247		
AA	Renal flares	19	4.7%	18	4.7%	1.00	0.560		

^a Flare rate is the average rate for each category (race, flare type, LDM/HDM), defined as the # flares / # follow-up visits.

^b Level of significance by one-tailed Fishers exact test, for differences between LDM and HDM flare rates.