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Vitamin D in SLE: Modest Association with Disease Activity and Urine Protein/Creatinine Ratio

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Abstract

Objective—We investigated whether an increase in vitamin D levels in patients with systemic lupus erythematosus was associated with improvement in disease activity.

Methods—1006 SLE patients were followed over 128 weeks. SLE patients with low levels of 25-hydroxy Vitamin D (<40 ng/mL) were supplemented with 50,000 units Vitamin D_2 weekly, with Ca/D_3 200 units twice daily. Longitudinal regression models were used to estimate the association between levels of vitamin D and various measures of disease activity.

Results—The SLE patients were 91% female, mean age 49.6, 54% Caucasian, 37% African-American and 8% other ethnicity. For those with low 25-hydroxy Vitamin D (<40 ng/mL), a 20 unit increase in 25-hydroxy Vitamin D was associated with a decrease in mean SELENA-SLEDAI by 0.22 (CI: −0.41, −0.02) (p= 0.032). This corresponded with a 21% decrease in the odds of having a SELENA-SLEDAI higher than 4 (CI: 1%, 37%). Mean urine protein-to-creatinine ratio decreased 2% (CI: −0.03, −0.01) (p=0.009), corresponding to a 15% decrease in the odds of having a ratio of 0.5 or greater (CI: 2%, 27%).

Conclusion—We found that a 20 ng/mL increase in vitamin D was associated with a 21% decrease in the odds of having a high activity score and a 15% decrease in the odds of having clinically important proteinuria. Though these associations were statistically significant, the clinical importance is relatively modest. There was no evidence of additional benefit beyond a level of 40 ng/mL.

Keywords

Vitamin D; Disease activity; Proteinuria; Systemic lupus Erythematosus

Vitamin D has recently gained attention beyond its traditional role in bone health and calcium homeostasis. Vitamin D levels has been linked to a number of chronic conditions including cardiovascular disease (CVD), malignancy[(1)] and many autoimmune diseases,

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including type 1 diabetes mellitus, inflammatory bowel disease, multiple sclerosis, undifferentiated connective tissue disease, rheumatoid arthritis, and systemic lupus erythematosus (SLE)[2–11].

Several studies have reported a high prevalence of vitamin D insufficiency in SLE[12–18]. The high prevalence of Vitamin D insufficiency in SLE has been partially attributed to sun avoidance[13]. The University of Toronto SLE cohort found that vitamin D insufficiency was related to season, cumulative glucocorticoid dose and serum creatinine[20]. A recent large population study of 33,996 individuals of European descent from 15 non-SLE cohorts reported that genetic variation also contributes to vitamin D insufficiency[21].

Early vitamin D supplementation in murine SLE models demonstrated that vitamin D has immunomodulatory effects. MRL/l mice supplemented with vitamin D had less dermatologic lesions, less proteinuria and lower anti-DNA[22]. A different SLE murine model, however, demonstrated a deleterious effect of vitamin D. F1(NZBxW) mice injected with vitamin D3 showed worsening of renal histopathological findings[23].

Previous studies of vitamin D in SLE are summarized in table 1. In human SLE, several cross-sectional studies have reported an inverse relation between vitamin D insufficiency and SLE disease activity[14–19]. One of the studies also reported an association between vitamin D deficiency and increased aortic stiffness in SLE[19]. However, a recent cross-sectional Brazilian study of SLE patients did not find correlation between vitamin D insufficiency and SLE disease activity[24]. Only one previous intervention study has been reported. In a prospective study of 60 SLE patients conducted by Ruiz-Irastorza et al, SLE patients were treated with oral vitamin D3 for a median period of 24 months (range 7–24 months) at the discretion of the attending physician. They reported a beneficial effect of vitamin D supplementation on fatigue, but no change in disease activity[25].

Observational studies and clinical trials with supplementary vitamin D in the general population have been associated with improved health outcomes[26–29]. Double-blind randomized controlled trials in Switzerland showed greater fall and fracture prevention in patients who attained higher levels of serum 25-hydroxyvitamin D. Prospective cohort data analysis in the same population also suggested benefit in cardiovascular health and colorectal cancer prevention in those who had the highest 25-hydroxyvitamin D levels[26]. Three double-blind, randomized, placebo-controlled studies in 220 patients with stage 3 and 4 chronic kidney disease randomized to paricalcitol or placebo found that reduction in proteinuria was 3.2 times greater in the paricalcitol treated patients[27].

Potential harm of vitamin D supplementation has also been documented. A reanalysis of the Women's Health Initiative Calcium/Vitamin D supplementation study, incorporated in a meta-analysis with eight other studies, found that calcium supplementation, with or without vitamin D, modestly increased the risk cardiovascular events, especially myocardial infarction[30]. This group had also previously reported in a meta-analysis of 15 trials that calcium supplements alone were associated with an increased risk of myocardial infarction[31]. Freedman et al studied three hundred and forty African-Americans with type 2 diabetes and found that 25-hydroxyvitamin D was negatively associated with visceral adiposity, but positively associated with carotid artery and aorta calcified atherosclerotic plaque[32].

In a recently published paper involving twenty-five experts from various clinical disciplines, a target level of at least 30 to 40 ng/mL of 25-hydroxyvitamin D (25(OH)D) serum level was recommended in adult patients with or at risk for fractures, falls, cancer, autoimmune and cardiovascular disease[33]. Therefore, we used 40 ng/mL as our target 25-hydroxy Vitamin D level for routine clinical care. In this study, we analyzed data from a large

prospective cohort to access whether a change in serum 25-hydroxy Vitamin D level was associated with a change in disease activity in SLE.

Patients and Methods

Patients and study design

The Hopkins Lupus Cohort is a clinical cohort of SLE patients regularly seen at Johns Hopkins University. It has been approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. Patients met the American College of Rheumatology (ACR) revised classification criteria for SLE[34, 35].

We conducted a longitudinal observational study of 1006 patients in the cohort from May 2009 to October 2011. During that period, serum 25-hydoxyvitamin D was measured at each visit. If the patient had a 25 hydroxyvitamin D level below 40ng/mL, they were given 50,000 units of vitamin D_2 weekly, as well as calcium/D_3 200 units twice daily, as part of standard care.

Cumulative revised American College of Rheumatology classification of the 1006 patients were: malar rash 60.5%, discoid rash 25.9%, photosensitivity 59.5%, oral ulcers 48.7%, arthritis 80.3%, serositis 53.2%, renal disorder 52.5%, neurologic disorder 15.4%, hematologic disorder 73.4%, immunologic disorder 82.8% and ANA positivity 95.5%. These did not differ, depending on being vitamin D deficient, or not (Table 2).

Variables investigated

Variables in the analyses included: the Physician Global Assessment (PGA, 0–3 visual analogue scale), and the SELENA revision of the Systemic Lupus Erythematosus Disease activity (SELENA-SLEDAI)[36], spot urine protein to creatinine ratio, complement C3, complement C4, anti-double-stranded DNA (by Crithidia), high-sensitivity C-reactive protein (hs-CRP), prednisone and hydroxychloroquine use, and other medication use.

Statistical analysis

Statistical Analysis System (SAS) software was used (SAS Institute Inc. Cary, North Carolina, SAS 9.2). Initially, two different analyses were performed for each outcome variable: A “between-person” analysis and a “within-person analysis”. The “between-person” analysis addressed the question of whether patients who had higher vitamin D tended to have lower disease activity (or other outcomes). To perform this analysis we assessed the association between patient-specific average vitamin D levels, and patient-specific average disease activity levels. The “within person” analysis addressed the question of whether patients tended to have less disease activity when they had higher vitamin D levels. To perform this analysis we create two new variables: 1) the difference between a patient’s observed vitamin D at each visit and that patient’s average vitamin D, and 2) the difference between a patient’s observed level of disease activity at each visit and that patient’s average level of disease activity. Then we assessed the association between those two variables using a longitudinal regression model. If the results of both the “between-person” and “within-person” analyses were consistent, we summarized the results with a single longitudinal regression model of disease activity regressed on vitamin D which draws from both types of relationships.

For each analysis, we fit two models: 1) a model that assumed a linear relationship between vitamin D and disease activity (“one-slope model”), and a model that allowed for the linear relationship between vitamin D and disease activity to change after vitamin D reached 40

mg/nL (two slope models). These models were based on exploratory analyses that suggested that the relationship between some variables and vitamin D changed at that point. In all models we controlled for race, age, age squared, sex, use of prednisone, use of hydroxychloroquine and date. Correlations between multiple observations from the same patients were modeled using mixed effects models with random intercepts and an auto-regressive correlation structure for the residuals. Dependent variables considered included PGA, SELENA-SLEDAI, complement C3, complement C4, anti-dsDNA, hs-CRP, and log-transformed urine protein/creatinine ratio. We also fit models with binary dependent variables (e.g. PGA≥1) to determine the association between vitamin D levels and the odds of high disease activity.

Results

Demographic and other baseline variables

From May 2009 to October 2011. 1006 SLE patients in the cohort contributed 5935 visits with serum 25-hydroxyvitamin D measurements. They were 91% female with mean age 49.6 (SD = 13.2). 54% were Caucasian, 37% African-American and 8% other ethnicities. 110 (11%) contributed 1 visit, 313 (31%) had 2–5 visits, 517 (51%) had 6–9 visits, and 65 (6%) had 10–16 visits.

At the first visit when vitamin D was measured (prior to supplementation), seven hundred and sixty three patients (76%) had levels of 25-hydroxy vitamin D below 40 ng/mL (insufficient) (Table 3). This percentage was significantly higher among African-Americans (85%, p<.0001) and among those aged 30–50 (79%, p=.0070).

Changes associated with increases in vitamin D (Table 4)

For all dependent variables other than C3 and C4, the “between-person” analysis was consistent with the “within-person” analysis. Therefore, the results are summarized below based on a model that combines both types of relationships. In the one-slope model, there was a statistically insignificant decrease in the mean PGA of 0.01 per 20ng/mL increase in vitamin D (CI: −0.03, 0.01) (p= 0.21). Similarly, there was a small decrease in the mean SELENA-SLEDAI of 0.02 per 20ng/mL increase in vitamin D (CI: −0.11, 0.07) (p= 0.65). However, in exploratory analysis we observed that the association between changes in vitamin D and disease activity were more pronounced among those with vitamin D below 40. Accordingly, we fit a two-segment linear spline and found that for those with vitamin D below 40 ng/mL, a 20 unit increase in 25-hydroxy Vitamin D was associated with a statistically significant decrease in mean physician global assessment of 0.04 (CI: −0.08, −0.01) (p= 0.026). This corresponded to an estimated 13% decrease in the odds of having a PGA score of 1 or more (CI: 0%, 22%). Similarly, below 40 ng/mL, a 20 unit increase in vitamin D was associated with a decrease in mean SELENA-SLEDAI of 0.22 (CI: −0.41, −0.02) (p= 0.032), corresponding to a 21% decrease in the odds of having a SLEDAI score of 5 or more (95% CI, 1%, 37%).

A 20 ng/mL increase in vitamin D was associated with a 2% decrease in urine protein to creatinine ratio (CI: −0.03, −0.01) (p< 0.0001) based on a one-slope model. This corresponded to a 15% decrease in the odds of having a urine protein-to-creatinine ratio of greater than 0.5 (CI 2%, 27%). When this analysis was restricted to those patients with a history of proteinuria and adjusted for use of ACE inhibitors and immunosuppressants, we found a somewhat larger association. Specifically, a 20 ng/mL increase was associated with a 4% decrease in urine protein-to-creatinine ratio (CI: 2%,5%), and the odds of having a ratio greater than 0.5 was decreased again by 15% (CI: 1%, 28%).

The relationships between vitamin D levels and complement were somewhat paradoxical (Table 5). The results of a "between person" analysis differed qualitatively from the results of a "within-person" analysis. From the "between person" analysis we found that patients with higher average vitamin D had a lower average complement C3 (−10.5 units per 20 ng/mL difference, p<.0001). However, within patients, when their vitamin D was higher, their complement was higher (1.17 units per 20 ng/mL increase in vitamin D, p=.0010). Similar results were seen for C4.

We observed no association between vitamin D levels and measures of either anti-double-stranded DNA or hs-CRP (Table 4).

Risks

There were two cases of asymptomatic hypercalcemia due to unrecognized hyperparathyroidism.

Discussion

ANA-positive healthy controls have been found to be more deficient in vitamin D than ANA-negative controls. Vitamin D insufficiency is associated with both autoantibody production and the interferon gene signature, part of the pathogenesis of SLE[37]. Thus, there is great interest in the role of vitamin D in both the pathogenesis and maintenance of SLE.

We found a statistically significant improvement in urine protein to creatinine ratio, with higher levels of 25-hydroxy vitamin D. Improvement in proteinuria, even if modest (as found here) could have clinical implications. A prospective study of 631 patients by Reich et al concluded that persistent proteinuria in SLE patients contributed to an increased risk of progressive chronic kidney disease[38]. The financial burden of renal disease in SLE is also of importance. A four year Canadian study on health care use and productivity loss in 715 SLE patients found higher direct costs in SLE patients with renal damage[39]. Our study results suggest that vitamin D supplementation may play a small role in reducing renal morbidity and, ultimately, the financial burden in renal SLE patients.

An inverse relation of serum vitamin D levels with SLE disease activity has been reported in a number of cross sectional studies[14–19], but not in all[24]. We were able to find a statistically significant relationship between change in serum 25(OH) vitamin D and global SLE clinical disease activity, using the Physician Global Assessment or the SELENA-SLEDAI, in our prospective study design, but the clinical relevance is modest. This change was found mainly among SLE patients with serum 25(OH) vitamin D levels below 40ng/mL. Increasing 25(OH) vitamin D levels once the patient was above 40ng/mL did not appear to have an effect on disease activity. One previous study in 60 SLE patients examined the role of intervention with vitamin D. It failed to achieve adequate serum 25(OH) vitamin D levels post vitamin D supplementation, with as many as 57 patients still having levels below 30 ng/mL[25]. We were able to achieve an average serum 25(OH) vitamin D level of 41.1 ng/mL.

Vitamin D levels were not associated with anti-dsDNA. Any effect on complement was small, and required complex statistical modeling to document. The lack of marked benefit on serologies is surprising, as vitamin D insufficiency appears to be associated with the interferon gene signature. The interferon gene signature in SLE is strongly associated with serologic tests[40].

We recognize the limitations of our analysis. Since we explored the relationship between disease activity and vitamin D changes (not vitamin D supplementation), the small observed association does not directly imply that vitamin D supplementation would be reduce disease activity. However, our analyses adjusted for prednisone and hydroxychloroquine use. Reverse causality or residual confounding might be responsible for the observed relationship between low circulating vitamin D and the variables studied. In a recent article on rheumatoid arthritis and increased vitamin D supplementation, caution was advised before widespread adoption of supplementation with vitamin. They suggested, and we agree, that well-conducted large randomized controlled trials are necessary to establish the role of vitamin D[41]. This caution is especially important given that there is still controversy about the role of calcium and vitamin D in cardiovascular disease[30–32].

Ours is the second longitudinal analysis of vitamin D in SLE. The first[25] was likely too small to find the small difference we report. Our study has the strengths of large numbers, ethnic balance (both Caucasians and African-Americans), long followup, and achievement of desirable (≥ 40 ng/mL) 25-OH vitamin D levels. Vitamin D supplementation is not completely safe, with rare risk of hypercalcemia (usually due to hyperparathyroidism) and renal stones.

Our study followed clinical care guidelines to achieve 25-OH vitamin D levels of 40 ng/mL or above. We did not find any benefit of 25-OH vitamin D levels above 40 ng/mL. Future research, including clinical trials of vitamin D supplementation, could now be considered in SLE. Longer follow up of our cohort, to determine if higher 25-OH vitamin D levels lead to standard clinical improvement in disease activity, is underway.

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References

1. Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. Anticancer Res. 2006; 29:3699–3704. [PubMed: 19667167]
2. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–281. [PubMed: 17634462]
3. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis. 2007; 66:1137–1142. [PubMed: 17557889]
4. Maruotti N, Cantatore FP. Vitamin D and the immune system. J Rheumatol. 2010; 37:491–495. [PubMed: 20080911]
5. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab. 2008; 93:3927–3935. [PubMed: 18682515]
6. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med. 2008; 168:1340–1349. [PubMed: 18574092]
7. Zold E, Szodoray P, Gaal J, Kappelmayer J, Csathy L, Gyimesi E, et al. Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther. 2008; 10:123. [PubMed: 19090978]
8. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol. 2008; 68:261–269. [PubMed: 18510590]
9. Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev. 2010; 9:507–510. [PubMed: 20146942]

10. Cutillas-Marco E, Morales-Suárez-Varela M, Marquina-Vila A, Grant W. Serum 25-hydroxyvitamin D levels in patients with cutaneous lupus erythematosus in a Mediterranean region. Lupus. 2010; 19:810–814. [PubMed: 20305048]
11. Hyppönen E. Vitamin D and increasing incidence of type 1 diabetes-evidence for an association? Diabetes Obes Metab. 2010; 12:737–743. [PubMed: 20649624]
12. Cutolo M. Vitamin D and autoimmune rheumatic diseases. Rheumatology (Oxford). 2009; 48:210–212. [PubMed: 18930963]
13. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology (Oxford). 2008; 47:920–923. [PubMed: 18411213]
14. Becker A, Fischer R, Schneider M. Bone density and 25-OH vitamin D serum level in patients with systemic lupus erythematosus. Z Rheumatol. 2001; 60:352–358. [PubMed: 11759235]
15. Borba VZ, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporos Int. 2009; 20:427–433. [PubMed: 18600287]
16. Amital H, Szekanecz Z, Szücs G, Dankó K, Nagy E, Csépány T, et al. Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? Ann Rheum Dis. 2010; 69:1155–1157. [PubMed: 20439290]
17. Bonakdar ZS, Jahanshahifar L, Jahanshahifar F, Gholamrezaei A. Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. Lupus. 2011; 20:1155–1160. [PubMed: 21680639]
18. Yeap SS, Othman AZ, Zain AA, Chan SP. Vitamin D levels: its relationship to bone mineral density response and disease activity in premenopausal Malaysian systemic lupus erythematosus patients on corticosteroids. International Journal of Rheumatic Diseases. 2011; 10 1756-185.
19. Reynolds JA, Haque S, Berry JL, Pemberton P, Teh LS, Ho P, Gorodkin R, Bruce IN. 25-Hydroxyvitamin D deficiency is associated with increased aortic stiffness in patients with systemic lupus erythematosus. Rheumatology. 2011; 10:1093.
20. Toloza SM, Cole DE, Gladman DD, Ibañez D, Urowitz MB. Vitamin D insufficiency in a large female SLE cohort. Lupus. 2010; 19:13–19. [PubMed: 19897520]
21. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010; 376:180–188. [PubMed: 20541252]
22. Lemire JM, Ince A, Takashima M. 1,25-Dihydroxyvitamin D3 attenuates the expression of experimental murine lupus of MRL/l mice. Autoimmunity. 1992; 12:143–148. [PubMed: 1617111]
23. Vaisberg MW, Kaneno R, Franco MF, Mendes NF. Influence of cholecalciferol (vitamin D3) on the course of experimental systemic lupus erythematosus in F1 (NZBxW) mice. J Clin Lab Anal. 2000; 14:91–96. [PubMed: 10797606]
24. Souto M, Coelho A, Guo C, Mendonça L, Argolo S, Papi J, Farias M. Vitamin D insufficiency in Brazilian patients with SLE: prevalence, associated factors, and relationship with activity. Lupus. 2011; 20:1019–1026. [PubMed: 21646315]
25. Ruiz-Irastorza G, Gordo S, Olivares N, Egurbide MV, Aguirre C. Changes in vitamin D levels in patients with systemic lupus erythematosus: Effects on fatigue, disease activity, and damage. Arthritis Care Res (Hoboken). 2010; 62:1160–1165. [PubMed: 20235208]
26. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int. 2010; 21:1121–1132. [PubMed: 19957164]
27. Agarwal R, Acharya M, Tian J, Hippensteel RL, Melnick JZ, Qiu P, et al. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney Int. 2005; 68:2823–2828. [PubMed: 16316359]
28. Prietl B, Pilz S, Wolf M, Tomaschitz A, Obermayer-Pietsch B, Graninger W, Pieber TR. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? Isr Med Assoc J. 2010; 12:136–139. [PubMed: 20684175]

29. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009; 20:315–322. [PubMed: 18629569]
30. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011; 342:d2040. [PubMed: 21505219]
31. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010; 341:c3691. [PubMed: 20671013]
32. Freedman BI, Wagenknecht LE, Hairston KG, Bowden DW, Carr JJ, Hightower RC, et al. Vitamin d, adiposity, and calcified atherosclerotic plaque in african-americans. J Clin Endocrinol Metab. 2010; 95(3):1076–1083. [PubMed: 20061416]
33. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev. 2010; 9:709–715. [PubMed: 20601202]
34. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982; 25:1271–1277. [PubMed: 7138600]
35. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40:1725. [PubMed: 9324032]
36. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005; 353:2550–2558. [PubMed: 16354891]
37. Ritterhouse LL, Crowe SR, Niewold TB, Kamen DL, Macwana SR, Roberts VC, et al. Vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus. Ann Rheum Dis. 2011; 70:1569–1574. [PubMed: 21586442]
38. Reich HN, Gladman DD, Urowitz MB, Bargman JM, Hladunewich MA, Lou W, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int. 2011; 79:914–920. [PubMed: 21248713]
39. Clarke AE, Panopalis P, Petri M, Manzi S, Isenberg DA, Gordon C, et al. SLE patients with renal damage incur higher health care costs. Rheumatology (Oxford). 2008; 47:329–333. [PubMed: 18238790]
40. Kirou KA, Lee C, George S, Louca K, Peterson MG, Crow MK. Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis Rheum. 2005; 52:1491–1503. [PubMed: 15880830]
41. Welsh P, Peters MJ, Sattar N. Is vitamin D in rheumatoid arthritis a magic bullet or a mirage? The need to improve the evidence base prior to calls for supplementation. Arthritis Rheum. 2011; 63:1763–1769. [PubMed: 21400480]

Table 1

Previous Vitamin D Studies in Systemic Lupus Erythematosus

Study	Year	Number of SLE Patients	Study Design	Measures of Disease Activity	Association with Disease Activity.
Becker A.[14]	2001	57	Cross-sectional	SLAM[1]	P = 0.02
Borba VZ.[15]	2009	36	Cross-sectional	SLEDAI[2]	P = 0.0005
Amital H.[16]	2010	378	Cross-sectional	SLEDAI-2K[3] and ECLAM[4]	P = 0.018
Ruiz-Irastorza G.[25]	2010	60	Prospective Cohort	SLEDAI[2]	NS.
Bonakdar ZS.[17]	2011	40	Cross-sectional	BILAG[5]	P = 0.001
Yeap SS.[18]	2011	38	Cross-sectional	SLEDAI	P = 0.033
Reynolds JA.[19]	2011	75	Cross-sectional	SLEDAI-2K[3]	P = 0.031
Souto M.[24]	2011	159	Cross-sectional	SLEDAI-2K[3]	NS.

[1]SLAM: Systemic Lupus Activity Measure.

[2]SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

[3]SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000.

[4]ECLAM: European Consensus Lupus Activity Measurement.

[5]BILAG: British Isles Lupus Assessment Group.

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Table 2

Cumulative American College of Rheumatology Criteria with Normal versus Low 25-Hydroxy Vitamin D.

ACR Criteria	All N=1006	25- Hydroxy Vitamin D <40ng/mL N=763	25- Hydroxy Vitamin D >=40ng/mL N=243	P-value[1]
Malar rash	60.5%	60.3%	61.3%	0.78
Discoid rash	25.9%	26.5%	24.3%	0.50
Photosensitivity	59.5%	60.8%	55.6%	0.15
Oral Ulcers	48.7%	48.4%	49.8%	0.56
Arthritis	80.3%	80.7%	79.0%	0.19
Serositis	53.2%	53.2%	53.0%	0.97
Renal disorder	52.5%	51.8%	54.7%	0.42
Neurologic disorder	15.4%	14.7%	17.7%	0.26
Hematologic disorder	73.4%	73.8%	72.0%	0.59
Immunologic disorder	82.8%	82.3%	84.4%	0.46
ANA positivity	95.5%	95.3%	96.3%	0.51

[1]Comparison between the patients with low vitamin D and those with normal vitamin D

Table 3

Mean 25-Hydroxy Vitamin D and Proportion with low 25-Hydroxy Vitamin D at the First Assessment, by Demographic Characteristics.

Characteristic	Mean (SD) Vitamin D	P-value	Number (%) with Vitamin D below 40 ng/mL	P-value
Overall	29.8 (14.8)		763 (76%)	
Sex				
Female (n=920)	29.7 (15.0)	0.50	698 (76%)	0.95
Male (n=86)	30.8 (13.2)		65 (76%)	
Race				
White (n=545)	33.2 (13.7)	<0.0001	382 (70%)	<0.0001
Black (n=377)	24.4 (14.5)		321 (85%)	
Other (n=84)	32.1 (16.3)		60 (71%)	
Age Group				
<30 (n=157)	31.1 (16.1)	0.0042	109 (69%)	0.0070
30–44 (n=349)	28.4 (14.8)		273 (78%)	
45–49 (n=364)	29.2 (14.1)		289 (79%)	
60+ (n=136)	33.5 (14.6)		92 (68%)	

Table 4

Effect of Change in 25 Hydroxy Vitamin D on SLE Disease Activity (Longitudinal Regression Models with One or Two-Slopes).

Disease Measure	One-slope Model		Model allowing slope to differ before and after 40 ng/mL			
	Slope[1] (95% CI)	P-value	Slope[1] over range of 0–40 ng/mL (95% CI)	P-value	Slope[1] over range of 40+ ng/mL (95% CI)	P-value
Physician Global Assessment	−0.01 (−0.03, 0.01)	0.21	−0.04 (−0.08, −0.01)	0.026	0.01 (−0.02, 0.04)	0.50
SLEDAI-SLEDAI	−0.02 (−0.11, 0.07)	0.65	−0.22 (−0.41, −0.02)	0.032	0.12 (−0.01, 0.24)	0.065
Log Urine Protein/Creatinine	−0.02 (−0.03, −0.01)	<0.0001	−0.03 (−0.05, −0.02)	0.0004	−0.01 (−0.01, 0.00)	0.24
Log HSCRP	−0.02 (−0.09, 0.06)	0.64	−0.06 (−0.20, 0.09)	0.45	0.02 (−0.12, 0.15)	0.82
Log Anti-dsDNA	0.01 (−0.03, 0.04)	0.78	0.04 (−0.04, 0.11)	0.32	−0.02 (−0.07, 0.04)	0.55

[1]Slopes are interpretable as difference in mean level of disease per 20ng/mL increase in vitamin D.

Table 5

Association between 25 Hydroxy Vitamin D and Complement, Adjusting for Age, Sex, Race, Date, Prednisone, and Plaquenil.

Marker	Association between Individual mean Vitamin D and Individual mean Complement: Slope (95% CI)[1]	P-value	Association between Individual variation in Vitamin D and Individual variation in complement. Slope (95% CI)[1]	P-value
C3	−10.5 (−13.6, −7.3)	<0.0001	1.17 (0.28, 2.06)	0.010
C4	−1.9 (−2.8, −1.0)	<0.0001	0.37 (0.16, 0.58)	0.0005

[1] Slopes are interpretable as difference in mean level of disease per 20ng/mL increase in vitamin D.