Original Article

Effect of Vitamin D and Calcium Supplementation in Patients with Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus is a chronic autoimmune disease that increases the risk of suboptimal vitamin D levels.

Aim: To determine the effects of vitamin D and calcium supplementation on disease activity, related immune markers and bone mineral density in patients with systemic lupus erythematosus.

Subjects and Methods: Eighty-one patients with systemic lupus erythematosus aged 20–70 years were recruited for this interventional study. Participants were enrolled into the following groups: no corticosteroid treatment (n = 21), corticosteroid treatment but without supplementation (n = 30) and corticosteroid treatment along with oral vitamin D and calcium supplementation (n = 30). Disease activity and laboratory parameters of all participants were measured at baseline and at 6 months. Bone mineral density was assessed using standardized dual-energy X-ray absorptiometry.

Results: At baseline, none of the patients had a normal vitamin D status. There were no significant correlations between vitamin D status and the studied immune markers or disease activity values before and after supplementation. After 6 months, patients who received supplementation showed significant (P = 0.002) improvements in bone mineral density. In addition, frequency of osteopenia decreased from 40% to 16.7% and that of osteoporosis decreased from 26.7% to 13.3%.

Conclusion: Vitamin D and calcium supplementation significantly improved the bone mineral density in vitamin D-deficient patients with systemic lupus erythematosus but did not significantly attenuate immune markers or disease activity. Further investigations are recommended with higher doses of vitamin D and longer durations to normalize the vitamin level and, possibly, achieve better disease control.

Keywords: Bone mineral density, calcium, disease activity, supplementation, systemic lupus erythematosus, vitamin D

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INTRODUCTION

Numerous studies have suggested vitamin D deficiency or insufficiency to be an extrinsic factor capable of modifying the prevalence of autoimmune diseases and affecting their severity.[1,2] In addition to cells involved in mineral and bone homeostasis, vitamin D receptors and vitamin D-activating enzymes have also evolved in other cells associated in immune responses, suggesting that vitamin D has a more diverse role than originally recognized.[3]

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by inflammation of the blood vessels and connective tissues in multiple systems and by the presence of circulating autoantibodies, especially antinuclear antibody and anti-double-stranded DNA (anti-dsDNA) antibodies.[4] In patients with SLE, suboptimal vitamin D levels are common,[5] as they are advised to avoid direct sunlight, a common trigger of disease flares[6] and renal insufficiency. In addition, SLE patients are generally on medications such as glucocorticoids, antimalarials, anticonvulsants and calcineurin inhibitors, all of which affect the metabolism of vitamin D or downregulate the functions of vitamin D receptors.[7]

Corticosteroids are recommended for the treatment of SLE, which in turn can increase the risk of osteoporosis. However, this association needs further validation. Lakshminarayanan *et al*.[8] found that glucocorticoid use in patients with SLE was associated with low bone mineral density (BMD), whereas another study did not find this association after adjusting for disease damage and duration.[9] Further, Lee *et al*.[10] suggested that patients with SLE may have a higher baseline risk of low BMD that is independent of glucocorticoid use or disease duration.

Vitamin D deficiency is a common health problem among Saudis across different age groups.[11,12] SLE patients have a high prevalence of vitamin D deficiency, and its serum levels are found to be inversely associated with disease activity.[7,13-15] This finding has also been reported in Saudi patients.[16,17] However, Kim *et al*.[18] concluded that serum vitamin D is not a useful biomarker for disease activity in SLE. Considering these findings and discrepancies across studies, the current interventional study was conducted to determine the efficacy of vitamin D and calcium supplementation on autoimmune markers, BMD and activity of SLE disease among corticosteroid-treated and untreated individuals in the Makkah region of Saudi Arabia.

SUBJECTS AND METHODS

This prospective interventional study was carried out at Al-Noor Specialty Hospital, Makkah, Saudi Arabia, from April 2014 to September 2015, after obtaining the ethical approval from the Ethics Committee of Umm Al-Qura University (approval number: AMSEC-5-13–9-2013) on September 13, 2013. This study was carried out in accordance with the Declaration of Helsinki, 2013.

Eighty-one patients with SLE were recruited for the study after obtaining informed consent. Patients who had malabsorption, renal and liver diseases, chronic diarrheal illnesses and irritable bowel syndrome as well as those who were on antifungal or anticonvulsant medications or received vitamin D and/or calcium supplementation in the past 6 months were not included in this study.

At the onset of this study, trained registered nurses collected the demographic information, anthropometric measurements and medical history from all patients. Then, BMD was determined for all patients at baseline and T-scores were calculated. In total, 60 patients had been treated with a glucocorticoid (prednisone). Of these, 24 patients were osteopenic and 8 were osteoporotic. Of the patients who did not receive corticosteroid treatment, two patients were osteopenic and none were osteoporotic. The participants were categorized into the following three groups: patients with SLE who did not receive corticosteroid treatment ($n = 21$; Group 1), corticosteroid-treated patients who did not receive supplementation ($n = 30$; Group 2) and corticosteroid-treated patients who received vitamin D and calcium supplementation ($n = 30$; Group 3). Groups 2 and 3 both comprised 12 patients who were osteopenic, 4 osteoporotic and 14 with a normal BMD. The three groups were comparable in terms of age, body mass index (BMI), serum vitamin D and calcium levels and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores.

Trained registered nurses educated all patients in Group 3 about the importance of vitamin D and calcium in SLE and the possible side effects of long-term corticosteroid treatment. The method described by Cutillas-Marco *et al*.[19] was followed for supplementation with vitamin D and calcium, wherein patients received 1400 IU of cholecalciferol plus 1250 mg of calcium carbonate tablet per day for 6 months.

Blood sample (5–10 ml) was collected from each patient at baseline and after 6 months. For biochemical and hormonal measurements, blood samples were centrifuged and stored at −20°C or lower. 25-hydroxyvitamin

D (25(OH)-D) was measured using Liaison® IXT (DiaSorin, Saluggia, Italy). Normal serum vitamin D levels were defined as ≥30 ng/ml, insufficiency as 29.9–20 ng/ml and deficiency as <20 ng/ml.[20] White blood cell (WBC) count, hemoglobin (Hb), platelet count and erythrocyte sedimentation rate (ESR) were measured on Coulter LH 750 hematology analyzer (Beckman Coulter, Beijing, China). Calcium and creatinine were measured on ARCHITECT-PLUS ci4100 (Abbott Diagnostics, Shanghai, China). Complement component 3 protein (C3) and complement component 4 protein (C4) were measured on IMMULITE BK-1779 (Siemens Healthcare Diagnostics, New York, United States). Anti-dsDNA was measured on VITROS 350 Chemistry System (Ortho Clinical Diagnostics, Bridgend, UK). SLEDAI scores were determined by experienced rheumatologists and used to assess the disease activity of patients, as described by Sumethkul *et al*.[21] SLEDAI scores of ≥3 indicated moderate-to-high disease activity, while scores of <3 indicated low disease activity. Vitamin D, C3, C4, anti-dsDNA and ESR levels and SLEDAI scores were obtained at baseline and after 6 months.

BMD was measured by dual-energy X-ray absorptiometry (LUNAR Prodigy, Model 8743 BX-1 L; Lunar Corp., Madison, WI, USA),[22] and the reference values were based on the World Health Organization criteria:[23] a T-score between −1 and −2.5 indicates osteopenia, −2.5 and lower indicates osteoporosis and higher than −1 is considered normal.

The data were analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant. The obtained data were nonparametric, and thus the *P* values of differences between groups were determined by Kruskal–Wallis test. Pairwise comparisons for groups with $P < 0.05$ were performed by Mann–Whitney *U*-test. Spearman's correlations were determined between vitamin D and other independent variables. Within each group, differences before and after supplementation were determined by Wilcoxon tests.

RESULTS

Of the 81 patients recruited, 66 were females. The mean age and BMI of all participants were 36.4 years (range: 20–70 years) and 24.5 kg/m^2, respectively. At baseline, the average vitamin D level was 18.3 ng/ml. All participants were either vitamin D deficient ($n = 63$) or insufficient ($n = 18$). The disease duration for Groups 1, 2 and 3 was 12.4 ± 3.4, 13.9 ± 4.9 and 13.4 ± 2.9 years, respectively. The corticosteroid treatment duration for Groups 2 and 3 was 10.2 ± 4.1 and 9.4 ± 3.7 years, respectively. The mean dose of prednisone was 7.5 ± 2.3 mg/day for Group 2 and 7.3 ± 3.1 mg/day for Group 3. There were no significant differences in age, weight, height, BMI, WBC and platelet counts, ESR, Hb, vitamin D, calcium, anti-dsDNA, C3 and C4 levels or SLEDAI scores across the three groups. In addition, there were no significant correlations between vitamin D levels and ESR ($r = -0.07$, $P = 0.829$), anti-dsDNA ($r = -0.312$, $P = 0.169$), C3 ($r = 0.147$, $P = 0.502$), C4 ($r = 0.021$, $P = 0.927$) or SLEDAI score ($r = -0.217$, $P = 0.103$) at baseline [Table 1].

After 6 months of treatment, the average vitamin D levels of all participants was 19.7 ng/ml, a nonsignificant improvement compared with baseline. Nevertheless, after 6 months, 17.3% ($n = 14$), 39.5% ($n = 32$) and 43.2% ($n = 35$) of patients had normal, insufficient and deficient vitamin D status, respectively. As expected, Group 3 patients showed a

Table 1: Baseline characteristics of patients according to the study groups

Parameter	Group 1 (mean ± SD) ($n = 21$)	Group 2 (mean ± SD) ($n = 30$)	Group 3 (mean ± SD) ($n = 30$)	*P*
Age (year)	36.4 ± 7.6	35.2 ± 8.7	37.7 ± 8.9	0.501
Weight (kg)	61.5 ± 17.7	63.9 ± 19.4	58.6 ± 10.3	0.342
Height (cm)	162 ± 14.1	159.1 ± 18.1	154.2 ± 13.7	0.467
BMI (kg/m^2)	23.6 ± 5.4	25.6 ± 7.3	24.3 ± 4.9	0.376
WBC (1000/uL)	8.85 ± 2.6	5.9 ± 3.1	3.9 ± 1.1	0.167
Hb (g/dL)	10.9 ± 0.1	11.4 ± 1.5	12.3 ± 2.2	0.49
Platelet (1000/uL)	225 ± 33.9	252.2 ± 73	217.8 ± 70.1	0.627
Vitamin D (ng/ml)	16.9 ± 3.6	19.3 ± 4.1	18.6 ± 4.2	0.209
Calcium (mmol/L)	2.2 ± 0.1	2.2 ± 0.1	2.3 ± 0.2	0.56
ESR (mm/h)	55.1 ± 33.1	51.3 ± 34.3	50.7 ± 44.2	0.579
Anti-dsDNA (IU/ml)	56.1 ± 38.2	51.2 ± 32.1	53.5 ± 29.7	0.873
C3 (mg/dl)	110.7 ± 52.1	97.4 ± 42.6	96.4 ± 47.2	0.264
C4 (mg/dl)	24.6 ± 9.7	17.5 ± 10.6	18.1 ± 15.1	0.308
SLEDAI score	4.9 ± 0.6	4.6 ± 0.7	4.7 ± 0.4	0.35

BMI – Body mass index; WBC – White blood cell; Hb – Hemoglobin; ESR – Erythrocyte sedimentation rate; Anti-dsDNA – Anti-double-stranded DNA; C3 – Complement component 3; C4 – Complement component 4; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; SLE – Systemic lupus erythematosus; SD – Standard deviation. Group 1 – Glucocorticoid-untreated SLE; Group 2 – Glucocorticoid-treated SLE; Group 3 – Glucocorticoid-treated SLE + vitamin D + calcium

significant increase ($P < 0.001$) in vitamin D levels compared with those in Groups 1 and 2. Although in Group 3 patients there was slight attenuation in ESR, anti-dsDNA, C3, C4 and SLEDAI values after 6 months, the differences were not significant between groups [Table 2].

At baseline, the BMD T-score was 0.4 ± 0.4 in Group 1, −1.2 ± 1.3 in Group 2 and − 1.1 ± 1.2 in Group 3, with no significant difference between the groups. After 6 months, Group 3 patients showed significant ($P = 0.002$) improvements in T-scores [Table 3]. Further, in the same group, the frequency of osteopenia decreased from 40% ($n = 12$) at baseline to 16.7% ($n = 5$) after 6 months of treatment, while that of osteoporosis decreased from 26.7% ($n = 8$) to 13.3% ($n = 4$). In Group 2, after 6 months of treatment, osteopenia prevalence increased from 40% ($n = 12$) to 46.7% ($n = 14$), while there was no change in the number of osteoporotic patients; however, one patient had a fracture after a minor trauma due to severe osteoporosis. In Group 1, osteopenia increased from two to three patients.

DISCUSSION

Vitamin D deficiency is high among SLE patients, but measuring its levels as an indicator of disease activity has shown contrasting results.[7,13-15,18] In addition, patients with SLE tend to have a lower BMD,[8-10] but the effect of vitamin D on improving the BMD in these patients was yet unclear. This study found that supplementation with 1400 IU cholecalciferol plus 1250 mg calcium carbonate tablet per day for 6 months significantly improves the BMD of vitamin D-deficient SLE patients; however, immune markers and disease activity are not affected.

As vitamin D regulates several genes involved in innate and adaptive immunity, it possibly plays a role in SLE through its immunomodulatory effects, which include downregulating Th1 immune responses, modulating the differentiation of dendritic cells, reducing the proliferation of activated B-cells, upregulating regulatory T-cells and preserving innate immune responses.[6,24,25] Further, vitamin D has also been found to hinder the production of interferon alpha, which is known to play a key role in the etiology and pathogenesis of SLE.[6,13]

At the start of the current study, all included patients were either vitamin D deficient or insufficient. High vitamin D deficiency rates of about 70%–90% have been reported in several studies,[6,13,16] although lower deficiency rates of about 40% have also been reported.[1] The high vitamin D deficiency rates are likely because SLE patients are often photosensitive and, consequently, advised to avoid sunlight, the main source of vitamin D.[6]

In this study, no significant correlations were found between vitamin D levels and other indicators at baseline. In contrast, Attar and Siddiqui[17] found a significant positive correlation between 25(OH)D and C4 ($r = 0.25$, $P = 0.014$) but not C3 ($r = 0.14$, $P = 0.191$), and a significant negative correlation between anti-dsDNA and 25(OH)D levels ($r = −0.38$, $P < 0.001$). However, Fragoso *et al*.[1] found no significant associations between 25(OH)D insufficiency/deficiency and anti-DNA, which is in line with our results. Similarly, Muñoz-Ortego *et al*.[26] reported a nonsignificant relation between anti-dsDNA and vitamin D levels. The discrepancies in results could be explained by the fact that the anti-dsDNA serological biomarker is specific for disease activity but less sensitive for serum levels of vitamin D.[26]

Table 2: Disease activity and autoimmune biomarkers after the 6-month study period

Parameter	Group 1 (mean ± SD) ($n = 21$)	Group 2 (mean ± SD) ($n = 30$)	Group 3 (mean ± SD) ($n = 30$)	*P*
Vitamin D (ng/ml)	15.4[b] ± 2.9	17.1[b] ± 5.3	26.5[a] ± 7.9	<0.001
ESR (mm/h)	56.7 ± 17.4	46.6 ± 13.7	45.2 ± 16.5	0.241
Anti-dsDNA (IU/ml)	55.2 ± 31.9	50.6 ± 22.4	50.6 ± 28.8	0.681
C3 (mg/dl)	134 ± 42.6	100.3 ± 52.5	96.7 ± 48.2	0.074
C4 (mg/dl)	23.9 ± 8.8	18.3 ± 9.2	18.5 ± 8.1	0.224
SLEDAI scores	5.1 ± 0.6	4.5 ± 0.6	4.5 ± 0.5	0.103

[a,b]A significant ($P<0.05$) difference between means. ESR – Erythrocyte sedimentation rate; Anti-dsDNA – anti-double-stranded DNA; C3 – Complement component 3; C4 – Complement component 4; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; SLE – Systemic lupus erythematosus; SD – Standard deviation. Group 1 – Glucocorticoid-untreated SLE; Group 2 – Glucocorticoid-treated SLE; Group 3 – Glucocorticoid-treated SLE + vitamin D + calcium.

Table 3: Group-wise comparison of bone mineral density (*T*-score) at baseline and after 6 months

Parameter	Group 1 (mean ± SD) ($n = 21$)	Group 2 (mean ± SD) ($n = 30$)	Group 3 (mean ± SD) ($n = 30$)
At baseline	0.4 ± 0.4	−1.2 ± 1.3	−1.1 ± 1.2
After 6 months	0.4 ± 0.5	−1.3 ± 1.5	−0.7 ± 0.9
P	0.759	0.598	0.002

Group 1 – Glucocorticoid-untreated SLE; Group 2 – Glucocorticoid-treated SLE; Group 3 – Glucocorticoid-treated SLE + vitamin D + calcium. SLE – Systemic lupus erythematosus; SD – Standard deviation

In the current study, vitamin D supplementation for 6 months nonsignificantly improved the immune markers and disease activity: SLEDAI, ESR, C3, C4 and anti-dsDNA. In a systematic review, Antico *et al*.[27] found that administration of cholecalciferol to patients with SLE did not improve or reduce the symptoms, radiological assessment of lesions or number of relapse episodes. Further, vitamin D supplementation was also found to not influence the clinical onset of SLE or its immunological progression. Similarly, AlSaleem *et al*.[28] also did not find any significant improvement in the clinical or laboratory parameters of 14-year-old children with SLE who received vitamin D (cholecalciferol 2000 IU/day) supplementation for 3 months. On the other hand, Abou-Raya *et al*.[29] reported that in SLE patients, oral vitamin D supplementation (cholecalciferol 2000 IU/day) for 12 months significantly decreases the inflammatory and hemostatic marker levels and disease activity. These inconsistencies in findings could be caused by differences in the dosing and/or duration of vitamin D supplementation. The current study found nonsignificant improvements in immune markers and disease activity after 6 months of vitamin D supplementation; however, these may significantly improve with a longer period of supplementation.[29]

Low BMD associated with SLE is multifactorial in origin and caused by a lack of motor activity, disturbance of hormonal balance, increased inflammatory cytokines, kidney impairment, nutritional disorders, vitamin D deficiency and medications such as corticosteroids.[30] The most commonly used drugs for the treatment of SLE are corticosteroids, long-term use of which is implicated as a major factor that decreases BMD and increases the risk of fracture.[31] In addition, long-term use of corticosteroids may induce osteoporosis in patients with SLE by affecting their bone turnover, increasing bone resorption and decreasing bone formation, preventing the formation of collagen and osteocalcin as well as affecting the bone matrix mineralization.[32] Recent studies have shown that low-dose vitamin D and calcium supplementation (<1000 IU vitamin D and <800 mg calcium) does not improve BMD in pediatric SLE patients.[33,34] However, long-term supplementation with different doses of vitamin D (400–1200 IU) and calcium (1–1.5 g) can have a better effect on the BMD of postmenopausal osteoporotic women.[35] The results of the present study indicate that supplementation with higher doses of vitamin D and calcium improves BMD and decreases the rates of osteopenia and osteoporosis in corticosteroid-treated patients. The BMD improvement could be because 1,25(OH)-D can activate osteoblast and bone formation as well as decrease bone resorption through inactivation of osteoclasts.[36] In addition, a high calcium supplementation may improve the bone matrix and, consequently, prevent its destruction.[32]

A major limitation of this study is the short supplementation period and using a single-dose therapy in all patients of Group 3. In addition, as the patients were all vitamin D deficient, the results may not be applicable to vitamin D-sufficient patients.

CONCLUSION

Supplementation with vitamin D and calcium for 6 months significantly improves the BMD of vitamin D-deficient SLE patients, but the immune markers and disease activity are not affected. Further studies are recommended with different doses of vitamin D over longer durations to determine if normal vitamin D levels can be achieved and if inflammatory markers and disease activity can be attenuated.

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Conflicts of interest

There are no conflicts of interest.

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