Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Meta-Analysis

Association between Vitamin D level and/or deficiency, and systemic lupus erythematosus: a meta-analysis

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Received January 12, 2017; **Accepted** January 25, 2018; **Published** January 31, 2018

Doi: http://dx.doi.org/10.14715/cmb/2018.64.1.2

Abstract: This study aimed to evaluate the relationship between the level of 25-hydroxyvitamin D [25(OH)D] and systemic lupus erythematosus (SLE). We searched the PUBMED, EMBASE, and Cochrane databases and performed a meta-analysis examining the vitamin D level and/or deficiency in patients with SLE, compared with that in healthy controls. In total, 18 studies consisting of 1,083 patients with SLE and 1,273 controls were included. Vitamin D level was significantly lower in the SLE group than in the control group (standardized mean difference [SMD] = −0.938, 95% CI = −1.352 to −0.524, $p = 9.0 \times 10^{-6}$). Stratification by ethnicity showed a significantly decreased vitamin D level in the SLE group in the European and Arab populations (SMD = −1.485, 95% CI = −2.427 to −0.543, $p = 0.002$; SMD = −1.067, 95% CI = −1.251 to −0.883, $p < 1.0 \times 10^{-8}$), and an association tendency between decreased vitamin D level and SLE in the Asian population (SMD = −0.874, 95% CI = −2.073 to −0.324, $p = 0.153$). Subgroup analysis by sample size showed a significantly lower vitamin D level in the SLE group in small- ($n \leq 100$) and large-sample ($n > 100$) populations (SMD = −1.008, 95% CI = −1.672 to −0.344, $p = 0.003$; SMD = −0.863, 95% CI = −1.444 to −0.293, $p = 0.003$). Meta-analysis revealed a significant association between SLE and vitamin D deficiency (RR = 2.321, 95% CI = 1.361–3.960, $p = 0.002$). Stratification by ethnicity showed a significant association between SLE and vitamin D deficiency in European and Arab populations (RR = 2.182, 95% CI = 1.024–4.648, $p = 0.043$; RR = 4.550, 95% CI = 3.471–5.965, $p < 1.0 \times 10^{-8}$). Our meta-analysis demonstrates that compared with controls, patients with SLE show significantly low serum levels of vitamin D, and that a deficiency of vitamin D is associated with SLE.

Key words: Vitamin D; Deficiency; Systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease, characterized by B cell hyperactivity, immune complex deposition, increased production of autoantibodies, and multiple organ damage. Although the exact cause of SLE is not fully understood, it has been established that genetic and environmental factors contribute to its pathogenesis (1).

Vitamin D (25-hydroxyvitamin D [25(OH)D]) alters the expression of genes that affect cellular functions such as proliferation, differentiation, apoptosis, and angiogenesis (2), and it has direct effects on T and B cells (3). Vitamin D ameliorates T cell receptor-induced T cell proliferation and promotes the generation of regulatory T cells; in addition, it inhibits Th1 cell proliferation with a shift toward a Th2 response (4). Vitamin D decreases B cell differentiation, and inhibits antibody secretion and autoantibody production (5). It is known that 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2$ D_3] inhibits the secretion of IFN-γ and negatively regulates the production of dendritic cells (DCs) by IL-12 through downregulating NF-kB (6). Vitamin D promotes the differentiation of monocytes to macrophages and regulates macrophage response, preventing them from releasing inflammatory cytokines (7). When administered *in vivo*, $1,25(OH)_2$ D_3 was found to have a preventative effect on autoimmune diseases (8), and other studies have revealed that vitamin D deficiency is linked to several autoimmune diseases (9,10).

The immunosuppressive and immunoregulatory activities of vitamin D may have a role in SLE (11,12). A previous study showed a 67%prevalence of vitamin D deficiency, and vitamin D deficiency has been considered as a potential environmental factor for SLE (13). However, studies on serum vitamin D levels in patients with SLE compared with healthy controls, and on the relationship between vitamin D deficiency and SLE have shown inconsistent results (14-31). The reasons for this disparity may be small sample sizes, low statistical power, and/or clinical heterogeneity (32-34). Therefore, in order to overcome the limitations of individual studies, we performed a meta-analysis. The present study aimed to determine serum vitamin D concentrations and vitamin D deficiency in patients with SLE and to compare the levels with those in healthy controls, using the meta-analysis approach.

Materials and Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined vitamin D status in patients with SLE, and controls. The PUBMED, EMBASE, and Cochrane databases were searched to identify all available articles (up to December 2017). The following key words and

subject terms were used in the search: "vitamin D," "level," "deficiency", "systemic lupus erythematosus," and "SLE". All references cited were also reviewed to identify additional studies not indexed by the electronic databases. Case-control studies, and studies that provided data on vitamin D levels and/or vitamin D deficiency in patients with SLE and in healthy controls were included. Healthy controls were defined as normal people without any disease. No language restriction was applied. Studies containing overlapping or insufficient data and review articles or case reports were excluded. Data on methods and results were extracted from original studies by two independent reviewers. Any discrepancies between reviewers were resolved by consensus, and the meta-analysis was conducted in accordance with PRISMA guidelines (35). The following information was extracted from each study: first author, year of publication, country, ethnicity, number of participants, adjustment for age and/or sex, vitamin D level, vitamin D deficiency, and cut-off level. If the standard error of mean (SEM) was reported, the SD was calculated using a statistical formula. When the data given were medians, interquartile ranges, or ranges, the mean and standard deviation (SD) were computed using previously described formulae (36,37). We scored the quality of each study included in the meta-analysis based on the Newcastle–Ottawa Scale (38). Scores ranging from 6–9, with 9 being the highest score possible indicated high methodological quality.

Evaluation of statistical associations

We performed meta-analyses examining the relationship between serum 25(OH)D level and SLE, and between vitamin D deficiency and SLE. The serum 25(OH)D level is a reliable indicator of the vitamin D status. For continuous data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between two groups by the pooled SD, and were used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of SMD was considered as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect (39). Within- and between-study variations and heterogeneities were assessed using Cochran's Q-statistics (40). When the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis (41); otherwise, the fixed effects model was used. The fixed effects model assumes that all studies estimate the same underlying effect and considers only within-study variations (40). The effect of heterogeneity was quantified using I^2 value, where I^2 measured the degree of inconsistency among the studies (42). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity test, and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, subgroup analysis and meta-regression analysis were performed using the following variables: ethnicity, sample size, adjustment, data type, and publication year. Sensitivity analysis was also performed to assess the influence of each study on the pooled OR by omitting each study. While funnel plots are often used to detect publication bias, they require diverse studies of varying sample sizes, and the interpretation of the plots involves subjective judgment. Considering this, we evaluated the publication bias using Egger's linear regression test (43), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included in the meta-analysis

We identified 261 studies by using electronic and manual search methods, 21 of which were selected for full-text review based on the title and abstract; three of these were excluded because they provided insufficient data on vitamin D levels in case and control groups. Thus, 18 articles met the inclusion criteria (14-31). One report contained data on two different groups (31), and these studies were analyzed independently. Therefore, in total, 19 separate studies were considered in the meta-analysis, which contained 1,083 patients with SLE and 1,273 controls (Table 1). All of the 19 studies examined the vitamin D level in the SLE and control groups, and eight of these studies provided the frequency of vitamin D deficiency in the SLE and control groups. The quality assessment score of each study ranged between 5 and 8 (Table 1). Selected characteristics of these studies on the relationship between vitamin D level and/or deficiency and SLE are summarized in Table 1.

Meta-analysis comparing the vitamin D levels between patients with SLE, and controls

Vitamin D level was significantly lower in the SLE group than in the control group (SMD = −0.938, 95% CI = −1.352 to −0.524, $p = 9.0 \times 10^{-6}$) (Table 2, Figure 1). Stratification by ethnicity showed a significantly decreased vitamin D level in the SLE group in European and Arab populations (SMD = −1.485, 95% CI = −2.427 to −0.543, $p = 0.002$; SMD = −1.067, 95% CI = −1.251 to −0.883, $p < 1.0 \times 10^{-8}$), and an association tendency between decreased vitamin D level and SLE in the Asian population (SMD = −0.874, 95% CI = −2.073 to −0.324, $p = 0.153$) (Table 2). Subgroup analysis by

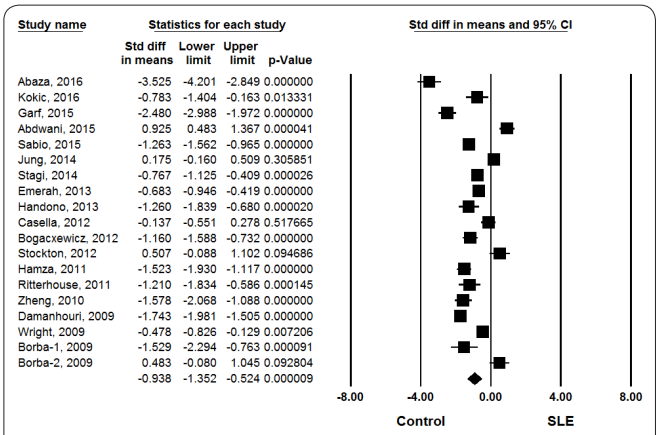

Figure 1. Meta-analysis of the relationship between vitamin D level and systemic lupus erythematosus (SLE)

Table 1. Characteristics of individual studies included in the meta-analysis.

Authors	Country	Ethnicity	No. of patients		Vitamin D level (ng/mL)		Vitamin D deficiency, frequency		Cut-off (ng/mL)	Adjustment for	Data type	Quality
			SLE	Control	SLE	Control	SLE	Control				
Abaza, 2016(14)	Egypt	Arab	60	30	17.60	79.00	na	na	Original	Age, sex	Original	6
Kokic, 2016(15)	Croatia	European	22	21	17.85	22.88	18	6	Calculated	Age, sex	Calculated	6
Garf, 2015(16)	Egypt	Arab	70	40	12.00	21.00	28	0	Original	Age, sex	Original	7
Abdwani, 2015(17)	Oman	Arab	27	97	61.00[a]	46.00	na	na	Original	na	Original	6
Sabio, 2015(18)	Spain	European	106	101	21.35	23.75	9	2	Calculated	Age*	Calculated	7
Jung, 2014(19)	Korea	Asian	102	52	12.10	11.00	na	na	Original	Age, BMI	Original	7
Stagi, 2014(20)	Italy	European	45	109	20.70	28.30	17	42	Original	Age, sex	Original	7
Emerah, 2013(21)	Egypt	Arab	107	129	27.40[a]	38.10[a]	na	na	Original	Age, sex	Original	7
Handono, 2013(22)	Indonesia	Asian	41	20	23.00	36.00	na	na	Original	Age, sex, BMI	Original	6
Casella, 2012(23)	Brazil	Mixed	57	37	21.44	22.54	31	18	Original	Age, sex, BMI	Original	7
Bogacxewicz, 2012(24)	Poland	European	49	49	18.47	31.27	na	na	Original	Age, sex	Original	6
Stockton, 2012(25)	Australia	Unknown	24	21	73.90[a]	62.60[a]	na	na	Original	Age*, BMI*	Original	6
Hamza, 2011(26)	Egypt	Arab	60	60	26.33	42.66	na	na	Original	Age, sex	Original	7
Ritterhouse, 2011(27)	USA	European	32	18	16.80	28.20	22	4	Calculated	Age, sex	Calculated	6
Zheng, 2010(28)	China	Asian	42	42	54.34[b]	89.99[b]	na	na	Original	Age*, sex*	Original	6
Damanhouri, 2009(29)	Saudi Arabia	Arab	165	214	23.50[a]	64.50[a]	148	43	Original	Age, sex	Original	8
Wright, 2009(30)	USA	Mixed	38	207	18.00	22.30	25	78	Calculated	na	Calculated	6
Borba-1, 2009(31)	Brazil	Mixed	12	26	17.40	37.80	na	na	Original	Age	Original	5
Borba-2, 2009(31)	Brazil	Mixed	24	26	44.60	37.80	na	na	Original	Age	Original	5

SLE: Systemic lupus erythematosus, USA: United States of America, na: Not available, [a]: nmol/L, [b]: pmol/L, *: Not age-matched, but no statistical difference in age between SLE and control groups, BMI: Body mass index.

Table 2. Meta-analysis of the association between vitamin D level and SLE.

Groups	Population	No. of Studies	Test of association SMD*	95% CI	*p*-val.	Test of heterogeneity Model	*p*-val.	I^2
All	Overall	19	−0.938	−1.352 to −0.524	9.0×10^{-6}	R	0.000	94.7
Ethnicity	European	5	−1.067	−1.251 to −0.883	$<1.0 \times 10^{-8}$	F	0.235	27.9
	Arab	6	−1.485	−2.427 to −0.543	0.002	R	0.000	97.4
	Asian	3	−0.874	−2.073 to −0.324	0.153	R	0.000	95.0
Sample size	N ≤ 100	10	−1.008	−1.672 to −0.344	0.003	R	0.000	93.0
	N > 100	9	−0.863	−1.444 to −0.293	0.003	R	0.000	96.2
Adjustment[a]	Yes	17	−1.076	−1.488 to −0.665	3.0×10^{-7}	R	0.000	93.9
	No	2	0.217	−1.158 to 1.591	0.757	R	0.000	95.8
Data type	Original	15	−0.942	−1.463 to −0.422	3.9×10^{-4}	R	0.000	95.7
	Calculated	4	−0.928	−1.373 to −0.483	4.3×10^{-4}	R	0.007	75.4

SMD: Standard mean difference, [a]: Adjustment for age- and/or sex, F: Fixed effects model, R: Random effects model. *Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect.

sample size showed a significantly lower vitamin D level in the SLE group in small- (n ≤ 100) and large-sample (n > 100) populations (SMD = −1.008, 95% CI = −1.672 to −0.344, $p = 0.003$; SMD = −0.863, 95% CI = −1.444 to −0.293, $p = 0.003$) (Table 2). Stratification by adjustment for age or sex revealed a significantly lower vitamin D level in the SLE group (SMD = −1.076, 95% CI = −1.488 to −0.665, $p = 3.0 \times 10^{-7}$), but not in the group without adjustment (SMD = 0.217, 95% CI = −1.158 to 1.591, $p = 0.757$) (Table 2). Subgroup analysis by data type showed a significantly lower vitamin D level in the SLE group by original and calculated data populations (Table 2).

Meta-analysis comparing vitamin D deficiency between patients with SLE, and controls

Our meta-analysis revealed a significant association between SLE and vitamin D deficiency (RR = 2.321, 95% CI = 1.361–3.960, $p = 0.002$) (Table 2, Figure 2). Stratification by ethnicity showed a significant association between SLE and vitamin D deficiency in European and Arab populations (RR = 2.182, 95% CI = 1.024–4.648, $p = 0.043$; RR = 4.550, 95% CI = 3.471–5.965, $p < 1.0 \times 10^{-8}$) (Table 2, Figure 2).

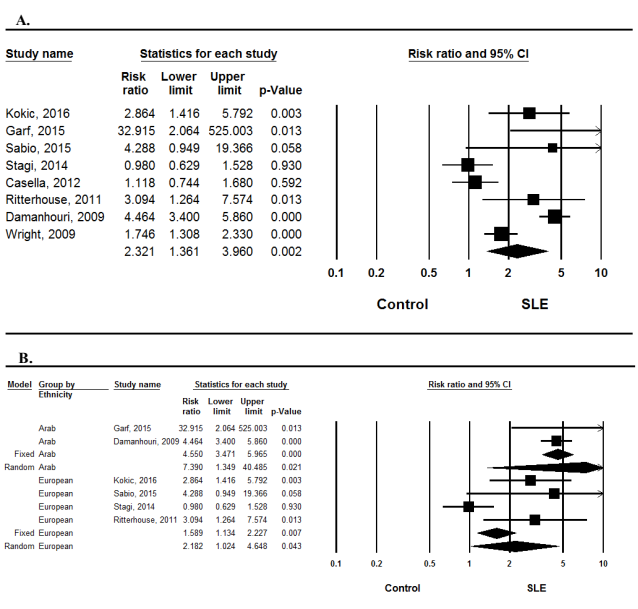

Figure 2. Meta-analysis of the relationship between vitamin D deficiency and systemic lupus erythematosus (SLE) in overall (A) and specific ethnic groups (B).

Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneity was identified during the meta-analyses of vitamin D levels in patients with SLE (Table 2). Meta-regression analysis showed that ethnicity ($p < 0.001$), adjustment ($p < 0.001$), and publication year ($p < 0.001$), but not sample size ($p = 0.760$), and data type ($p = 0.771$), had a significant impact on the heterogeneity in the meta-analysis of the vitamin D levels in patients with SLE. Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating that the results of this meta-analysis are robust. Funnel plots to detect publication bias showed symmetry, and Egger's regression analysis showed no evidence of publication bias for the meta-analyses of vitamin D (Egger's regression test *p*-values > 0.1) (Figure 3).

Discussion

Given the immunosuppressive effects of vitamin D and the potential link between vitamin D deficiency and autoimmune diseases (44), the potential role of vitamin D in the pathogenesis of SLE has been studied (45).

In this meta-analysis, we reviewed combined data on vitamin D level and deficiency in patients with SLE, compared with the corresponding levels in healthy controls. This analysis of 18 studies showed that patients with SLE had significantly lower vitamin D levels

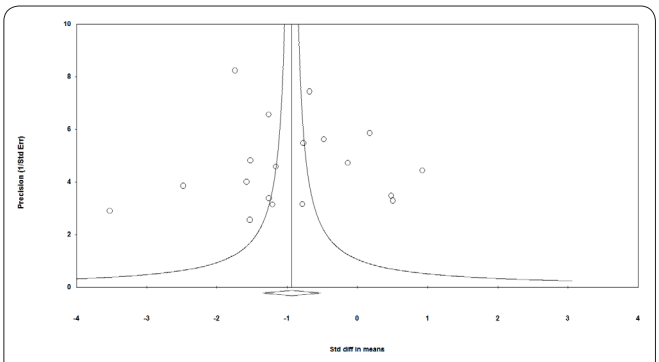

Figure 3. Funnel plot of studies that examined the association between vitamin D levels and systemic lupus erythematosus (SLE) (Egger's regression *p*-value = 0.953).

Table 3. Meta-analysis of the association between vitamin D deficiency and SLE.

Groups	Population	No. of Studies	Test of association			Test of heterogeneity		
			RR	95% CI	*p*-val.	Model	*p*-val.	I^2
All	Overall	8	2.321	1.361–3.960	0.003	R	0.000	87.3
Ethnicity	European	4	2.182	1.024–4.648	0.043	R	0.012	72.8
	Arab	2	4.550	3.471–5.965	$<1.0 \times 10^{-8}$	F	0.159	49.4

RR: Relative risk, F: Fixed effects model, R: Random effects model.

than the levels observed in controls, and that vitamin D deficiency is associated with SLE. These data suggest that serum vitamin D level may definitively influence the pathogenesis of SLE.

Hyperactivity of DCs, T cells and B cells, reduced Treg suppression, and increased inflammatory cytokines lead to autoimmunity (46). Vitamin D exerts regulatory effects on the immune system by affecting the processing of self-antigens by antigen-presenting cells, persistence and hyperactivation of B and T cells, and maintenance of immunoregulatory systems (2). The low levels of vitamin D can be either the cause or consequence of SLE. Low vitamin D levels and a high prevalence of vitamin D deficiency in SLE may be attributed to the lack of exposure to sunlight; frequent use of sunscreen; common use of drugs that interfere with vitamin D metabolism, such as glucocorticoids, hydroxychloroquine, and immunosuppressive agents; or a limited intake of vitamin D. Thus, vitamin D status may act as a potential environmental factor involved in SLE. However, the exact relationship between vitamin D levels and SLE is still unclear. An immunomodulatory effect of vitamin D may be involved in the pathogenesis of SLE. Vitamin D has a suppressive effect on the differentiation of DCs and T-helper (Th) 1 CD4 + T cells, leading to suppression of autoimmune disease (6). The suppression of autoimmunity may entail increased T regulatory cells, decreased autoantibody production, diminished inflammatory mediator release, and perhaps tolerance re-establishment (7). In addition, vitamin D was found to directly affect the function of B-cells in lupus (5). Vitamin D may play an important role in autoantibody production and in the pathogenesis of SLE. The pleiotropic effects of vitamin D are mediated through its binding to the vitamin D receptor (VDR). VDR polymorphisms, which may influence VDR activity, have been studied as potential causes of autoimmune diseases including SLE (47,48). A previous meta-analysis revealed a significant association between VDR polymorphism and susceptibility to SLE. [44] Thus, low levels of vitamin D may be associated with the development of SLE. Sensible sun exposure and increased dietary and supplemental vitamin D intakes are needed to guarantee vitamin D sufficiency (49). The wide variety of effects of vitamin D on the immune system might suggest a role of vitamin D in the future therapeutic strategies (50,51). Vitamin D supplementation was associated with decrease in inflammatory cytokines and ESR in SLE patients (51).

The present study has some shortcomings that should be considered. First, most of the studies included in this meta-analysis had small sample sizes; thus, many of the individual studies that constitute this meta-analysis may have been underpowered. Second, the studies included in the meta-analysis were heterogeneous in the demographic characteristics and clinical features of the patients. The heterogeneity and confounding factors such as body mass index, body fat distribution, disease activity and the drugs used (*e.g.*, immunosuppressive agents, hydroxychloroquine, corticosteroids) may have affected our results, which may be compounded by the limited information provided on the clinical status and disease activity. This limited data did not allow further analysis, although we performed a sensitivity test and a meta-regression analysis. However, we could not adjust treatment medications for SLE in this analysis owing to insufficient information.

Nevertheless, this meta-analysis has its strengths. The number of patients from individual studies ranged from 12 to 165, but our pooled analysis included 1,083 patients. Compared to individual studies, our study was able to provide more accurate data on the relation between vitamin D levels and SLE by increasing the statistical power and resolution through pooling of the results of independent analyses.

In conclusion, our meta-analysis suggests that compared with controls, serum vitamin D level is significantly low in patients with SLE, and that vitamin D deficiency is associated with SLE. Our meta-analysis indicates that low vitamin D level may be a risk factor for SLE or a consequence of SLE. Our meta-analysis indicated that low vitamin D level likely plays an important role in the pathogenesis of SLE. Further studies are necessary to elucidate whether decreased vitamin D levels directly contribute to the pathogenesis of SLE.

Acknowledgements
This study was supported in part by NRF-2017M3A9B4050335, Republic of Korea.

Conflict of interest statement
The authors have no financial and non-financial conflicts of interest to declare.

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