

# THE EFFECTS OF VITAMIN D SUPPLEMENTATION ON DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATHOSUS PATIENTS: AN EVIDENCE-BASED CASE REPORT

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### **Abstract**

Background: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production of autoantibodies and multisystem involvement, predominantly affecting women of reproductive age. Vitamin D is known to have immunomodulatory effects, including inhibition of T and B cell activation and suppression of pro-inflammatory cytokine production. Objectives: This evidence-based case report aims to evaluate the effect of vitamin D supplementation on disease activity in SLE. Methods: A literature search was conducted using PubMed, Scopus, and Cochrane. Medical Subject Headings (MeSH) terms and relevant keywords based on the clinical question components were applied. All retrieved literature was screened using predefined eligibility criteria, followed by a critical appraisal of eligible studies. Results: One meta-analysis of randomized controlled trials (RCTs) and two RCTs met the eligibility criteria. Almost all of the included studies recruited patients with SLE who had vitamin D deficiency/insuficiency. The methodological validity of all three studies was considered acceptable. The studies demonstrated heterogeneity in terms of baseline disease activity levels among their study populations. The meta-analysis and one of the RCTs reported non-significant results, while the other RCT showed a significant improvement in disease activity following vitamin D supplementation. Conclusion: Current evidence is insufficient to recommend vitamin D supplementation as an adjuvant therapy for improving disease activity in patients with SLE and further research is needed.

keywords: Disease Activity, SLE, SLEDAI, Vitamin D

#### Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with multisystem involvement, marked by the presence of autoantibodies and a wide range of clinical manifestations. The global prevalence is estimated at 43.7 cases per 100,000 individuals. The condition predominantly affects females, with a female-to-male ratio

from 9:1 to 14:1. Although SLE can occur at any age, it is most frequently diagnosed in individuals between 15 and 40 years of age, the reproductive age group.<sup>2</sup> Vitamin D status has been implicated in the pathogenesis of various autoimmune diseases, including SLE. Notably, among individuals with SLE, 29.7% present with vitamin D insufficiency, while 62.3% exhibit vitamin D deficiency.<sup>3</sup>

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The pathogenesis of systemic lupus erythematosus (SLE) involves multifactorial of genetic interplay predisposition, environmental exposures, hormonal influences, and immunological dysregulation. Vitamin D deficiency has emerged as an important contributing factor in the development of SLE, functioning not only through immunological mechanisms but a modifiable also as environmental determinant.<sup>4</sup> Deficient vitamin D levels have been associated with increased disease activity and cumulative organ damage in patients with SLE.3,5 Vitamin D exhibits immunomodulatory properties, including the suppression of T and B lymphocyte activation, inhibition of proinflammatory cytokine production, and promotion of immune tolerance via the expansion of regulatory T cell populations.6

In patients with systemic lupus erythematosus (SLE), reduced vitamin D levels are frequently attributed to limited sunlight exposure due to photosensitivity concerns, as well as the use of medications such as glucocorticoids, which can disrupt vitamin D metabolism.<sup>7</sup> This deficiency has been associated with heightened disease activity and increased risk of organ damage.3 Disease activity in SLE is commonly evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a validated tool incorporating both clinical and laboratory indicators. Several modified versions of the original index have been developed, including the SELENA-SLEDAI, MEX-SLEDAI, and SLEDAI-2K, to enhance its applicability in different clinical and research settings.

The relationship between vitamin D and systemic lupus erythematosus (SLE) is intricate, as SLE itself can lead to reduced vitamin D levels, while vitamin D deficiency may also contribute to the onset and exacerbation of SLE symptoms.3 However, the association between vitamin D levels and disease activity in SLE remains inconsistent and is a subject of ongoing debate. Some studies have proposed that vitamin D influences SLE disease activity through various immunological mechanisms, whereas other research has found no significant correlation between vitamin D levels and disease activity. This evidencebased case report aims to evaluate the impact of vitamin D supplementation on disease activity in patients with SLE.

#### Case Ilustrasi

A 28-year-old female patient, Mrs. N, presented with a primary complaint of progressive bilateral lower limb weakness, which had persisted for five months and worsened over the last two weeks prior to her admission. She had been diagnosed with systemic lupus erythematosus (SLE) one year prior and was compliant with her prescribed medications. There was no known family history of SLE. The patient's clinical history revealed chronic neurologic symptoms,

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including tingling, weakness, and a sensation of heaviness in the lower extremities during ambulation. Comprehensive history taking, physical examination, and additional diagnostic testing were performed. The patient was subsequently diagnosed with transverse myelitis and polyneuropathy, complications associated with SLE. Based on her clinical evaluation, the patient was assigned a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score of 14, indicating high disease activity. Her serum 25-hydroxyvitamin D level was found to be deficient at 12.1 ng/mL. Management consisted of intravenous methylprednisolone (1000 mg daily for 5 days, followed by a tapering regimen), hydroxychloroquine (200 mg daily), and mycophenolate sodium (360 mg twice daily). Additionally, the patient was prescribed vitamin D3 supplementation at a dose of 5000 IU per day.

#### **Problem Formulation**

In adult patients diagnosed with SLE, can vitamin D supplementation reduce disease activity?

Based on the clinical question, the following PICO was created:

P (Patient): adult patient with a diagnosis of SLE

I (Intervention): vitamin D supplementation

C (Comparison): placebo

O (Outcome): disease activity

Type of clinical question : therapy.

#### Methods

A literature search was conducted on June 15, 2025, across three databases: PubMed, Cochrane, and Scopus, utilizing the search terms "Vitamin D supplementation AND Disease Activity AND Systemic Lupus Erythematosus." Advanced search features were employed, incorporating MeSH terms and Boolean operators ("OR" and "AND") as detailed in Table 1.

## **Eligibility Criteria:**

- Adult patients (≥18 years) with a confirmed diagnosis of systemic lupus erythematosus (SLE).
- Studies with randomized controlled trial (RCT) or systematic review/metaanalysis designs that included RCTs.
- 3. The intervention group received vitamin

  D supplementation, while the control
  group received either a placebo or
  standard therapy.
- 4. Studies that reported outcomes using the SLE Disease Activity Index (SLEDAI) scores.
- **5.** Articles published in English or Indonesian.

#### **Exclusion Criteria:**

1. Studies not conducted in human populations.

2. Studies where the full manuscript was inaccessible.

The titles and abstracts of all retrieved articles were reviewed to assess their relevance to the clinical question. Studies that met the eligibility criteria were further screened. In cases where an RCT was already included in a systematic review or meta-analysis, it was excluded to prevent duplication. A critical appraisal of the included studies was conducted using the Oxford Centre for Evidence-Based Medicine (OCEBM) assessment tool, evaluating each article for Validity, Importance, and Applicability (VIA).

#### **Results**

A total of 202 articles were retrieved from PubMed, Cochrane, and Scopus (Table 1). These articles were subsequently filtered to assess the relevance of their titles and abstracts in relation to the PICO framework. After screening, three studies met the eligibility criteria (Figure 1), including one meta-analysis of randomized controlled trials (RCTs) and two RCT-based studies. Detailed study characteristics, including research design, population, intervention, and outcomes assessed, are summarized in Table 2. Critical evaluations of each study are provided in Tables 4, 5, and 6.

Table 1, Article Search Strategy Method

Database	Search strategy	Number
Pubmed	(((((systemic lupus erythematosus[MeSH Terms]))) OR (SLE[Title/Abstract])) AND (((24 hydroxylase, vitamin d3[MeSH Terms]) OR (vitamin d[Title/Abstract])) OR (vitamin d supplementation[Title/Abstract])))) AND ((disease activity[Title/Abstract]) OR (SLEDAI[Title/Abstract])) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (humans[Filter]))	17
Cochrane	#1 MeSH descriptor: [Lupus Erythematosus, Systemic] #2 MeSH descriptor: [Vitamin D] #3 (sledai) OR ("SLE disease activity index") #4 #1 AND #2 AND #3	18
Scopus	(((TITLE-ABS-KEY (systemic lupus erythematosus) OR TITLE-ABS-KEY (systemic lupus erythematosus) OR TITLE-ABS-KEY (SLE))) AND ((TITLE-ABS-KEY (vitamin d supplementation)) AND ((TITLE-ABS-KEY (disease activity) OR TITLE-ABS-KEY (sledai))) AND NOT (TITLE-ABS-KEY (children)) AND (LIMIT-TO (SRCTYPE, "j"))	167

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Study identification based on Studies were excluded search strategies from three before the screening process: databases: (n=202) Duplication of articles PubMed: 17 (n=22)Cochrane Library: 18 ScienceDirect: 167 Studies that were Title not relevant (n=122) screened by title/abstract: (n=180)Title and abstract screening: Articles after screening Articles not relevant to PICO criteria (n=50) (n=58)Articles included in SR/MA (n=5) Inclusion Number of articles included (n=3) MA(n=1)RCTs (n=2)

Figure 1 Flowchart of Literature Search Strategy

**Table 2. Study characteristics** 

Research er (year)	Design	Population	Intervention	Outcome	Conclusion
Zheng, et al <sup>(8)</sup> (2019)	Meta Analysis of RCTs	5 RCT studies (n=490) with SLE patients	Vitamin D supplementat ion≥ 1200 IU/day for at least 3 months	Serum 25(OH)D levels, SLEDAI, anti- dsDNA positivity, fatigue severity score (FSS), and adverse events	Vitamin D supplementation was relatively safe, significantly increased serum 25(OH)D levels, and improved fatigue in SLE patients, but did not decrease antidsDNA positivity and SLEDAI.
Fiblia, et al <sup>(9)</sup> (2022)	RCT	SLE patients (n=60) aged 18- 60 years with hypovitaminosis D.	Vitamin D3 supplementat ion 5000 IU/day for 12 weeks	Vitamin D levels, MEX- SLEDAI, Lupus QoL	Vitamin D3 supplementation at a dose of 5000 IU/day for 12 weeks significantly increased vitamin D levels and improved disease activity, but did not significantly improve the quality of life of SLE patients.
Lomarat, et al <sup>(10)</sup> (2022)	RCT	SLE patients aged > 18 years, serum 25(OH)D level > 10 ng/mL (n=104)	Ergocalcifero l supplementat ion 100,000 IU/week for 4 weeks followed by 40,000 IU for 20 weeks	Serum 25(OH)D, SLEDAI-2K, inflammatory markers, urine protein creatinine ratio (UPCR), health assessment questionnaire (HAQ)	Administration of high doses of ergocalciferol was not significant in improving SLE disease activity. However, the supplementation could increase vitamin D levels to normal.

Table 3. Summary of Critical Validity Review

Question	Zheng, et al.	Fiblia, et al.	Lomarat, et al.
SR/MA study	et al.	et al.	
Does the SR describe the clinical question (PICO) and is it used in article search and selection?	+		
Did the search find all relevant evidence?	+		
Were the selected studies subjected to critical review?	+		
Did it include only high quality studies?	-		
Were results of studies summarized in tables and diagrams?	+		
And was heterogeneity between studies assessed?	+		
RCT studies			
Were study participants randomized? And is the randomization table hidden?		+	+
Were the characteristics of the two groups comparable before the intervention?		+	+
Was each group given the same treatment?		+	+
Were all patients who participated in the clinical trial included in the final analysis?		-	?
Are measurements made objectively or are both patients and doctors blind to the therapy provided?		+	+

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Table 4, Summary of Importance Critical Review

Zheng, et al.		
The measure used was standardized mean		
difference (SMD). Vitamin D		
* *		
score by 0.507. Based on the p value there is		
Results are presented with a forest plot.		
Not statistically significant (n=0.070)		
Not statistically significant (p=0.070).		
Fiblia et al <sup>9</sup>	Lomarat, et al. <sup>10</sup>	
ribila, et al.	Lomai at, et al.	
The decrease in MEX-SLEDAL in the	The change in median value (IOR) of	
The decrease in MEX-SLEDAI in the intervention group was 1.29 and in the	The change in median value (IQR) of SLEDAL score in the intervention group was	
intervention group was 1.29 and in the	SLEDAI score in the intervention group was	
intervention group was 1.29 and in the placebo group was 0.12. These results were	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the	
intervention group was 1.29 and in the	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group	
intervention group was 1.29 and in the placebo group was 0.12. These results were	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group from 4.0 (1, 4) to 2.0 (0, 2) at the end of the	
intervention group was 1.29 and in the placebo group was 0.12. These results were	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group from 4.0 (1, 4) to 2.0 (0, 2) at the end of the intervention. This result was not statistically	
intervention group was 1.29 and in the placebo group was 0.12. These results were statistically significant ( $p=0.015$ ).	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group from 4.0 (1, 4) to 2.0 (0, 2) at the end of the intervention. This result was not statistically significant ( $p = 0.101$ ).	
intervention group was 1.29 and in the placebo group was 0.12. These results were statistically significant ( $p = 0.015$ ).  This study did not report confidence	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group from 4.0 (1, 4) to 2.0 (0, 2) at the end of the intervention. This result was not statistically significant ( $p = 0.101$ ).  This study did not report confidence	
intervention group was 1.29 and in the placebo group was 0.12. These results were statistically significant ( $p=0.015$ ).	SLEDAI score in the intervention group was from 4.0 (2, 6) to 0.0 (0, 4) at the end of the intervention. While in the placebo group from 4.0 (1, 4) to 2.0 (0, 2) at the end of the intervention. This result was not statistically significant ( $p = 0.101$ ).	
	The measure used was standardized mean difference (SMD). Vitamin D supplementation decreased the SLEDAI	

Table 5, Summary of Applicability Critical Review

Question	Zheng, et al.	Fiblia, et al.	Lomarat, et al.
Are your patients very different from the	No	No	No
study population?			
Is the therapy available at your facility?	Yes	Yes	Yes
Will the benefits of the therapy outweigh	Yes	Yes	Yes
the harms for your patients?			

## Discussion

The literature search identified three relevant studies addressing the clinical question concerning the impact of vitamin D supplementation on SLE disease activity, as measured by the SLE Disease Activity Index (SLEDAI). Of these, one was a meta-analysis of randomized controlled trials

(RCTs), while the other two were individual RCTs. These three studies were subsequently analyzed to evaluate the effectiveness of vitamin D supplementation as an intervention for modulating disease activity in patients with systemic lupus erythematosus (SLE).

The validity of the evidence presented in the three studies warrants

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careful consideration. Zheng et al.'s metaanalysis8 included studies with a high risk of bias, which may have compromised the overall quality of the evidence. The randomized controlled trials (RCTs) by Fiblia et al.9 and Lomarat et al.10 generally demonstrated strong validity; however, the potential for bias remains. Specifically, the study by Fiblia et al.9 employed a perprotocol analysis, while Lomarat et al.10 did not clarify whether they used a per-protocol or intention-to-treat analysis. This lack of clarity raises the possibility of attrition bias, which could result in an overestimation of the intervention's effect in the broader population.

study by Fiblia et al.9 The demonstrated that vitamin D supplementation resulted in a significant reduction in SLEDAI scores. In contrast, the studies by Zheng et al.8 and Lomarat et al.<sup>10</sup> reported a reduction in SLEDAI scores following the intervention, but the results were not statistically significant. Zheng et al.'s meta-analysis8 included only four studies and exhibited high heterogeneity (I<sup>2</sup> = 73.3%, p = 0.010), which undermined the reliability of the effect estimate and limited the clinical applicability of the findings. Additionally, the studies by Zheng et al.8, Fiblia et al.9, and Lomarat et al.10 all involved populations with heterogeneous characteristics, further complicating the

interpretation and generalizability of the results.

The characteristics of the study populations primarily consisted of adult individuals with systemic lupus erythematosus (SLE). However, it is important to highlight that one of the studies included in Zheng et al.'s metaanalysis8, specifically the study by Lima et al.11, focused on adults with juvenile-onset SLE—defined as SLE diagnosed before the age of 18. Juvenile-onset SLE is a distinct subset, as patients with early-onset disease typically experience more severe disease activity, a more aggressive clinical course, and a higher risk of organ damage compared to those with adult-onset SLE.11 The inclusion of juvenile-onset SLE patients introduces additional heterogeneity to Zheng et al.'s meta-analysis8, which may limit the generalizability of the findings regarding the effects of vitamin D supplementation to the broader adult-onset SLE population.

Almost all studies recruited patients with hypovitaminosis D, and all vitamin D supplementation interventions were effective in increasing mean or median serum vitamin D levels to normal levels by the end of the study period. Therefore, the findings from this evidence-based case report can only be generalized to SLE patients with hypovitaminosis D. The effect of interventions in patients with normal

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vitamin D levels at baseline is unknown and has not been included in the studies available to date.

The level of baseline disease activity in patients varied among the three studies. The studies of Fiblia et al.9, Lomarat et al.<sup>10</sup>, and the majority of studies in the meta-analysis of Zheng et al.8had low baseline mean/median SLEDAI scores of <5. In populations with mild disease activity, the maximum effect interventions may be difficult to detect due to limited room for improvement, a condition known as the floor effect. There was only one study in the Zheng et al. metaanalysis 8, which was the Rifa'I et al. study <sup>12</sup>with a high mean baseline SLEDAI score of 12.65+ 4.85. Although the statistical significance of the results of the three studies varied, all studies showed a decrease in the mean/median SLEDAI score after vitamin D supplementation.

Vitamin D, whether obtained through diet or synthesized endogenously, binds to the Vitamin D Binding Protein (VDBP) before undergoing hydroxylation in the liver to form 25-hydroxyvitamin D (25[OH]D). This is followed by a second hydroxylation step in the kidneys, converting it into its active form, 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub>D), also known as calcitriol.<sup>3</sup> Calcitriol exerts its effects through the vitamin D receptor

(VDR), which is expressed on a variety of cell types, including immune cells such as T cells, B cells, and dendritic cells.<sup>13</sup>

A theoretical framework supports the role of vitamin D in modulating systemic lupus erythematosus (SLE) disease activity. Vitamin D has been shown inhibit the activation of inflammatory Th1 and Th17 pathways while promoting the expansion of antiinflammatory regulatory T cells (Tregs). Additionally, vitamin D reduces the expression of cytokines, including IL-6, IL-17, and TNF-α, which are implicated in SLE flares and organ damage.14 At the molecular level, vitamin D suppresses the transcription of proinflammatory and autoimmune-related genes. As a result, correcting vitamin D deficiency is believed to mitigate disease activity, which can be quantified using the SLE Disease Activity Index (SLEDAI).15

The expression of the vitamin D receptor (VDR) and vitamin D binding protein (VDBP) is regulated by various factors, including genetic polymorphisms such as the Taql and Fokl variants, which can influence individual responses to vitamin D supplementation. <sup>16</sup>, <sup>17</sup> Beyond genetic factors, nutritional status, the level of systemic inflammation, and the severity of the disease also play significant roles. <sup>1,7</sup>, <sup>8</sup> These factors contribute to inter-individual

variability in the physiological response to vitamin D supplementation, affecting aspects such as the required dose, duration of administration, and overall therapeutic outcomes.<sup>19</sup>

The evidence regarding the efficacy of vitamin D supplementation in reducing disease activity in adult patients with systemic lupus erythematosus (SLE) remains inconclusive and inconsistent. The observed high heterogeneity, the limited number of studies, and the suboptimal validity of the included studies all contribute to the limitations in drawing strong recommendations for clinical practice.

#### **Conclusions and Recommendation**

The review of the three selected studies indicates that the evidence supporting the effectiveness of vitamin D in reducing disease activity in SLE patients is not robust. Additional high-quality randomized controlled trials (RCTs) are warranted, particularly those involving SLE populations with moderate to severe disease activity.

#### **Conflict of Interest**

The authors declare that there are no conflicts of interest related to the studies in this manuscript.

#### **Author Contributions**

Author 1 - generated the clinical question, conducted the search and critical review, analyzed the data and synthesized the evidence, and drafted the manuscript.

Author 2 - provided academic supervision, directed the process of data analysis and interpretation, and reviewed and edited the manuscript.

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