



Effect of Vitamin D Supplementation in Disease Activity, Activity-Related Markers, Inflammatory Marker and Serum Calcium of Systemic Lupus Erythematosus Patiens: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Effect of additional supplementation of vitamin D toward Systemic lupus erythematosus (SLE) disease activity still differ in results obtained between studies being conducted. The current meta-analysis systematically analyzed the effect of vitamin D supplementation on SLE disease activity with updated literature, also its effect toward other parameters. **Material and Methods:** Relevant literatures were obtained from PubMed database and Google Scholar. The obtained studies were analyzed using fixed effect model or random effect model. **Results:** Five eligible studies with a total of 318 participants were included. Vitamin D supplementation did not affect the total SLEDAI score in SLE patients with pooled mean difference of -0.96 ($p = 0.09$; 95% CI: -2.06 to 0.14). Serum vitamin D level increased after administration of vitamin D with pooled mean difference of 12.67 ($p = 0.001$; 95% CI: 5.04 to 20.29). vitamin D supplementation increase serum calcium levels, with pooled difference of 0.07 ($p = 0.006$; 95% CI: 0.02 to 0.12). Pooled results from two studies obtained vitamin D supplementation did not affect ESR, C3 and C4. **Conclusions:** Current meta-analysis obtained no significant changes in SLEDAI scores due to vitamin D supplementation. In contrast, serum vitamin D and serum calcium levels were increased.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by systemic deposition of complex immune in various body, resulted in release of inflammatory mediators and influx of inflammation cells.¹ Etiology of SLE is still not completely understood, thought as interaction between genetic and environmental factors. SLE marked by loss tolerance of self-antigen and excess

production of autoantibody.²

Vitamin D is a prohormone metabolized in body to its active metabolite, which is 1,25 dihydroxyvitamin D [1,25(OH)₂D]. Two main types of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (*ergocalciferol*), however, only limited foods possess significant amount of D2 and D3, although nowadays it could be obtained from fortified foods or

supplement. The mechanism of vitamin D metabolism in the body mediated by sunlight, occurs in two phases. Phase one occur in liver, forming 25-hydroxy vitamin D [25(OH)D]. Phase two occur in kidney, which formed 1 α ,25-dihydroxyvitamin D [1,25-(OH)2D].³

In SLE patients, there is an increase of prevalence of vitamin D deficiency. Evidence from studies found that vitamin D deficiency contributed to mortality and morbidity of SLE. Condition of SLE also make the patients avoid sunlight exposure due to photosensitivity and potency to flare, hence increasing the likelihood of vitamin D deficiency. The deficiency itself also affect disease activity of SLE.^{4,5}

Vitamin D regulate immune system by inhibit interleukin-2 (IL-2), antibody production and lymphocyte proliferation.⁶⁻⁸ 25-Dihydroxy vitamin D3 (1,25(OH)2 D3)inhibit the secretion of Interferon- γ (IFN- γ).⁹ Inhibition of T cell proliferation and cytokine production, B cell proliferation and activation and formation of plasma cell also affected by 1,25(OH)2 D. Vitamin D and SLE are closely related, in which SLE may decrease the serum level of vitamin D and vitamin D deficiency itself involved in causative factor of SLE severity,¹⁰ hence vitamin D also play a role in

prevention of SLE and SLE disease activity.⁵

Several studies had been conducted to evaluate the effect of vitamin D supplementation to SLE disease activity and other parameters. The supplementation given may in the form of cholecalciferol or ergocalciferol. However, the results obtained still differ.¹¹⁻¹⁵ One meta-analysis by Zheng et al¹⁶ in 2019 found that vitamin D supplementation did not affect SLE disease activity, however they did not analyze other parameters, e.g. erythrocyte sedimentation rate (ESR), complement component 3 protein (C3), complement component 4 protein (C4) and serum calcium levels. This meta-analysis aimed to systematically analyze studies regarding vitamin D supplementation and SLE disease activity, with updated studies included. Other parameters of ESR, C3, C4 and serum calcium also analyzed in this meta-analysis as secondary outcome.

2. Methods

Eligibility Criteria

The eligibility criteria were created based on the PICO framework. PICO criteria can be seen in Table 1.

Table 1. PICO criteria of the study

Patient	Systemic Lupus Erythematosus
Intervention	Vitamin D Supplementation
Comparator	Placebo
Outcome	Disease activity using SLEDAI

Type of studies

Studies included in the current systematic review and meta-analysis were studies with full-text available in English. Article of case report, anatomic, animal, economic, qualitative, review and cadaveric studies were excluded. Studies without the required information needed also excluded. Articles written by the same author within similar institution were evaluated in order to prevent duplication of sample.

Type of participants

This review included studies with SLE patients irrespective of ages and gender who receive vitamin D administration. All patients, whether in stable condition or flare up condition were included in this review. The disease activity assessed using SLEDAI scores.

Type of intervention

The reviewed intervention is administration of vitamin D. We included studies which administered vitamin D for any doses and any duration. However, we noted both the doses and

the duration of vitamin D given for each studies.

Type of outcomes

The primary result investigated in this review was the SLE disease activity. In this regard, we use SLEDAI scores to determine the disease activity of the patients. The SLEDAI score was reported as numerical value, rather than as classification. The secondary objective in this review were vitamin D levels, which represented as 25(OH)D (ng/ml), ESR (mm/h), C3 (mg/dl), C4 (mg/dl), and serum calcium levels (mmol/L).

Information sources

The eligibility criteria, as depicted in PICO, were extracted into keywords using Boolean operator. In this study, we used keywords (Systemic Lupus Erythematosus OR SLE) AND (Vitamin D OR Vitamin D3 OR Cholecalciferol) AND (Disease activity OR SLEDAI OR Systemic Lupus Erythematosus Disease Activity Index) in PubMed database and Google Scholar as search engine to find eligible journals.

Study selection

Study selection performed by GK, DAS and PKK in order to decrease the likelihood of disposing the relevant studies. When disagreement occurred, consideration between GK, DAS and PLL was considered. Study selection started with removal of duplicate records. Screening of title and abstract then performed to exclude the irrelevant studies. All articles that pass the first screening then evaluated to assess its compliance toward the inclusion and exclusion criteria. The final step was to evaluate the articles' quality before included in the study.

Data Collection Process

Electronic data collection form was used to collect data from each author. The collected data by each author was merged and managed with

software Review Manager 5.4.

Data items

The data items were the author's name, year of publication, type of study, population, doses of vitamin D, duration of vitamin D administration, sample size, age and baseline disease activity. The mean of SLEDAI score after administration of vitamin D and without administration of vitamin D for respective duration were performed the meta-analysis. The secondary parameters analyzed were vitamin D, ESR, C3, C4 and serum calcium.

Assessment of quality of study

All studies that in accordance with the eligibility criteria were evaluate for their quality in order to ensure its validity and reliability. Two authors, DAS and PKK, performed this process. The evaluation performed with a standardized critical appraisal tool, which is Joanna Briggs Institute (JBI) critical appraisal tool based on study design. Consensus was performed with the third reviewer (GK) was done when disagreement occurred. To determine the quality of the study, cut off point was determined. We use the cut off point of half of the total score in each JBI critical appraisal checklist. Low-quality study was study with core under the cut off point, while others regarded as high quality study.

Synthesis of result

The mean of SLEDAI score, serum vitamin D level, ESR, C3, C4 and serum calcium level in SLE patients with administration and without administration of vitamin D were pooled and analysed. Meta-analysis was conducted using software Review Manager 5.4.

3. Results

Study selection

We found a total of 171 studies with the initial

searching strategy. Subsequently, 160 articles were excluded based on the title and abstract screening, left us 11 relevant studies. Studies which not provided all the information needed for this meta-analysis or being retracted were

excluded. We obtained 5 articles that further used in this study after screening and qualitative evaluation were done. PRISMA study flow diagram is described in Figure 1.

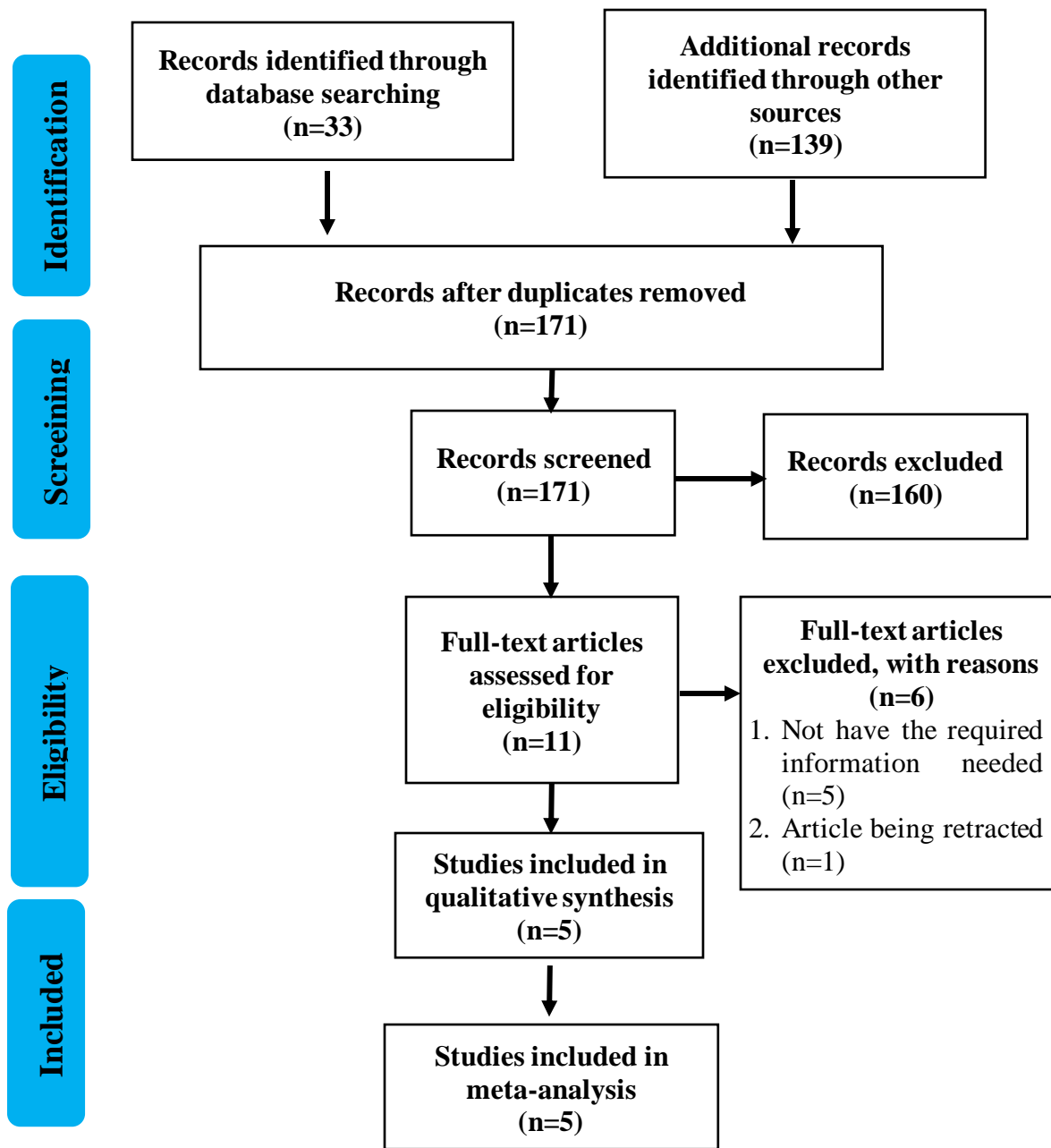


Figure 1. PRISMA flow diagram

Study characteristics

We included five full-text articles which consist of four Randomized Control Trial (RCT) and one cohort study. The publication year of

these articles varied between 2016 to 2020 with a total of 159 samples for intervention group and 159 samples for placebo group. The experiment group receive vitamin D supplementation in

varying doses and duration, while the control group receive placebo, except for a study by Pakchotanon et al¹⁵ in which the control group also receive daily 800 U of cholecalciferol while the experiment group receive additional vitamin D supplementation. Either glucocorticoid,

hydroxychloroquine, or immunosuppressive drugs were given for experiment or control group. The summary of finding and studies characteristics can be seen in Table 2.

Table 2. Summary of findings and studies characteristics

Author	Type of Study	population	Doses of Vitamin D	Duration	Sample Size, experiment vs control	Age, mean ± SD	Initial Condition of Disease Activity using SLEDAI, mean ± SD or median (IQR)
Lima <i>et al.</i> (2016) ¹¹	Randomized, double-blind, placebo-controlled trial	Juvenile onset SLE	Oral cholecalciferol of 50,000 IU/week	6 months	20 vs 20 subjects	18.5 ± 3.5 (experiment) 19.3 ± 3.3 (control)	4 (0, 8) (experiment) 3 (0, 12) (control)
Rifa'i <i>et al.</i> (2016) ¹²	Open label clinical trial	SLE patients	vitamin D3 softgel/cholecalciferol 1200 IU/day or 30 mg/day	3 months	20 vs 19 subjects	28.25± 6.97 (experiment) 27.26±6.76 (control)	12.65±4.85 (experiment) 10.74±2.75 (control)
Karimzadeh <i>et al.</i> (2017) ¹³	randomized, double-blind, placebo-controlled trial	Vitamin deficient SLE patients	D- 50,000 unit/weekly Vitamin D for 12 weeks and then 50,000 unit/monthly for 3 months	6 months	45 vs 45 subjects	33.78±6.2 (experiment) 35.69±6.8 (control)	3.09±2.36 (experiment) 3.09±1.25 (control)
Al-Kushi <i>et al.</i> (2018) ¹⁴	Prospective interventional study	systemic lupus erythematosus aged 20–70 years	1400 IU of cholecalciferol	6 months	30 vs 30 subjects	37.7 ± 8.9 (experiment) 35.2 ± 8.7 (control)	4.7 ± 0.4 (experiment) 4.6 ± 0.7 (control)
Pakchotanon <i>et al.</i> (2020) ¹⁵	Randomized, double-blinded, placebo-controlled study	SLE at least 18 years of age. Not pregnant or nursing if female	100.000 IU ergocalciferol weekly for 4 weeks followed by 40,000 IU of ergocalciferol weekly for 20 weeks and daily 800 U of cholecalciferol . The control group receive placebo however also receive daily 800 U of cholecalciferol	24 weeks	44 vs 45 subjects	41.15 ± 13.31 (experiment) 43.67 ± 13.19 (control)	4.0 (2, 6) (experiment) 4.0 (1, 4) (control)

SLE: Systemic lupus erythematosus; IU: International unit

Risk of bias within studies

The risk of bias was analysed using JBI critical appraisal tool for cohort and RCT

studies. All 5 articles included in this study were passed the quality evaluation. Complete result of bias risk was described in Table 3.

Study (Year)	Question no.													Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Reviewer: DAS														
Lima <i>et al.</i> (2016)	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	12/13
Rifa'i <i>et al.</i> (2016)	Y	UC	Y	UC	UC	UC	Y	Y	UC	Y	Y	Y	Y	8/13
Karimzadeh <i>et al.</i> (2017)	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	12/13
Al-Kushi <i>et al.</i> (2018)	Y	Y	Y	N	UC	Y	Y	Y	Y	UC	Y			8/11
Pakchotanon <i>et al.</i> (2020)	Y	Y	Y	Y	Y	UC	Y	UC	UC	Y	Y	Y	Y	10/13
Reviewer: PKK														
Lima <i>et al.</i> (2016)	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	12/13
Rifa'i <i>et al.</i> (2016)	Y	UC	Y	Y	UC	UC	Y	Y	UC	Y	Y	Y	Y	9/13
Karimzadeh <i>et al.</i> (2017)	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	12/13
Al-Kushi <i>et al.</i> (2018)	Y	Y	Y	UC	N	Y	Y	Y	Y	UC	Y			8/11
Pakchotanon <i>et al.</i> (2020)	Y	Y	Y	Y	UC	UC	Y	N	UC	Y	Y	Y	Y	9/13

Effect of vitamin D supplementation on disease activity, vitamin D level, ESR, C3 and C4

Vitamin D supplementation did not affect the total SLEDAI score in SLE patients. Based in random effect model (I²=82%; $\chi^2 = 22.66$; $p = 0.0001$), pooled mean difference between vitamin D supplementation and without vitamin D supplementation was -0.96 ($p = 0.09$; 95% CI: -2.06 to 0.14) (Figure 2). Serum vitamin D level increased after administration of vitamin D, based in random effect model (I²=97%; $\chi^2 = 124.78$; $p < 0.00001$), pooled mean difference

between vitamin D supplementation and without vitamin D supplementation was 12.67 ($p = 0.001$; 95% CI: 5.04 to 20.29) (Figure 3). As for ESR, C3 and C4, the pooled result indicated that vitamin D supplementation did not affect all parameters, based on fixed effect model (Figure 4, Figure 5, and Figure 6, respectively). As for calcium, pooled result from two studies found that supplementation of vitamin D in SLE patients increase serum calcium levels by 0.07 ($p = 0.006$; 95% CI: 0.02 to 0.12) based in fixed effect model (I²=0%; $\chi^2 = 0.94$; $p = 0.33$) (Figure 7).

Figure 2. Forest plot of disease activity

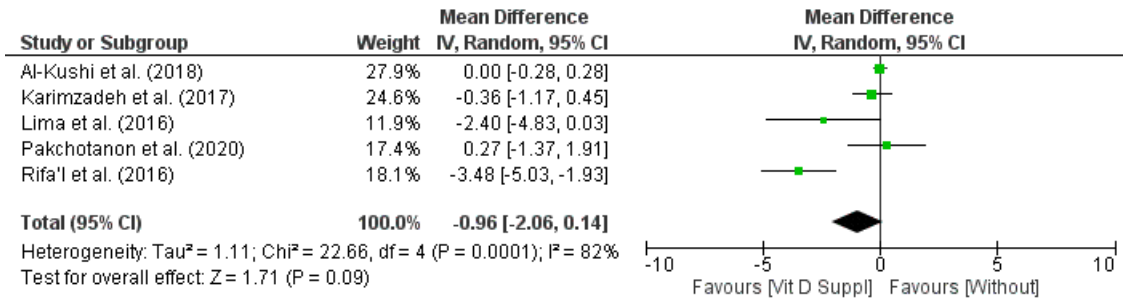


Figure 3. Forest plot of vitamin D level

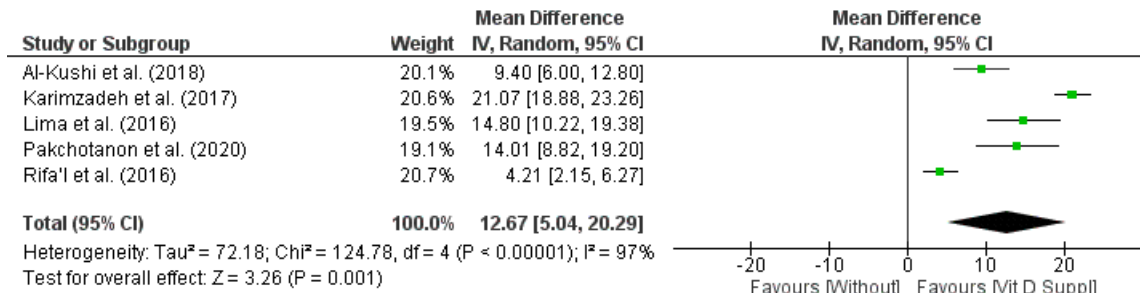


Figure 4. Forest plot of ESR

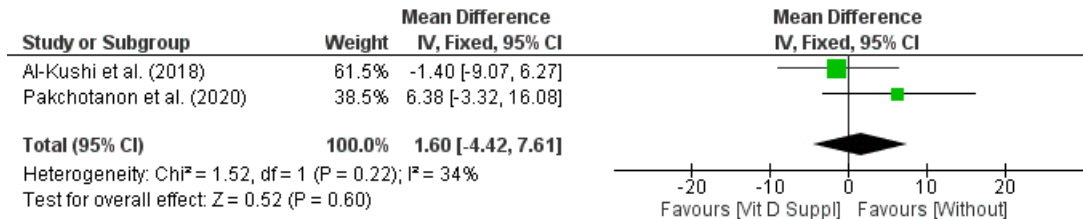


Figure 5. Forest plot of C3

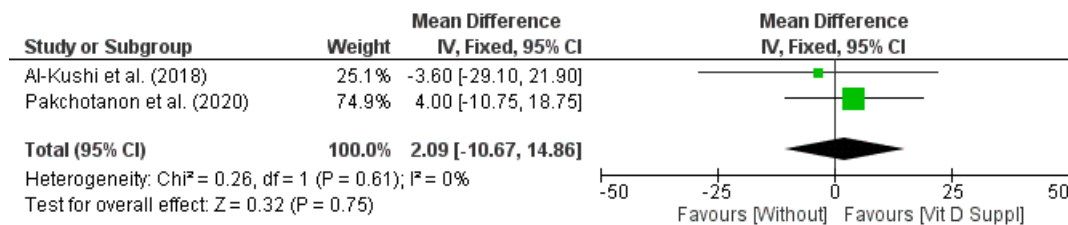


Figure 6. Forest plot of C4

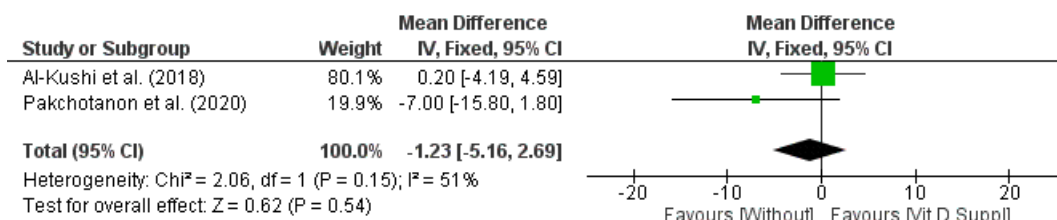
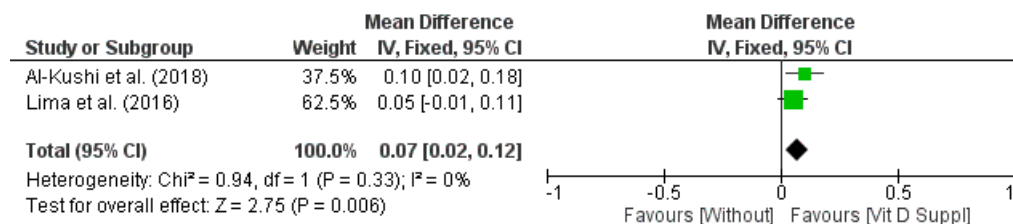


Figure 7. Forest Plot of serum calcium



4. Discussion

The pooled result from current meta-analysis found that vitamin D supplementation had no significant effect to reduce the disease activity of SLE. In addition, this supplementation increase serum vitamin D levels and pooled result from two studies obtain significant effect on serum calcium levels, in which supplementation of vitamin D may increase serum calcium levels in SLE patients. However, vitamin D supplementation did not had toward ESR, C3 and C4 serum levels.

There is an increase prevalence of vitamin D deficiency in SLE patients. Several reasons including avoidance toward exposure to sunlight, renal insufficiency, use of glucocorticoids, antimalarial agent. The use of those medications could alter the metabolism of vitamin D, in addition to decrease function of vitamin D receptor.⁵

Vitamin D and SLE have two-way relationship, in which SLE may lead to vitamin D deficiency, while the deficiency itself may aggravate the activity of SLE. Vitamin D deficiency may enhance the risk for higher disease activity, increased susceptibility to infections, reduction in type 2 muscle fibers, which may lead to muscle weakness and fatigue

in patients with SLE. Two relevant studies revealed a significant inverse relationship between levels of 25(OH)D3 and disease activity scores.^{17,18} Another study involving Australian patients with SLE revealed that vitamin D insufficiency associated with increase in disease activity. Furthermore, the rise of serum vitamin D associated with decrement of disease activity.¹⁹

The active form of vitamin D acts by interacting with its receptor, vitamin D receptor (VDR). VDR is a member of large family of nuclear hormone receptor. It is broadly distributed, and its existence on most cells of immune system may explained its effect to immunomodulatory system. The polymorphism in VDR may deliberate susceptibility to immune-related illness, e.g., SLE and rheumatoid arthritis.^{20,21} In-vitro study revealed 1,25(OH)₂D may alter the differentiation of dendritic cells and modulates the function and phenotype of T cell.²² It also may alter generation of plasma cells, prevent T cell proliferation and cytokine production, and inhibit proliferation of activated B cells.^{23,24} The other effect of vitamin D is its curative effects, including immune-inflammatory-modulatory effects. It may modify endothelial function and repair mechanism,

improves immune health, regulates cell cycle progression, apoptosis and apoptosis related molecules.⁵ Considering the beneficial effects of vitamin D, including its well-tolerated price, it is logical to infer the use of vitamin D as disease suppressing intervention for SLE patients.

The current meta-analysis analyze five studies. Each studies give intervention of vitamin D supplementation with various dosages and durations toward SLE patients. The results obtained from the studies found decrease of SLEDAI score after administration of vitamin D supplement. However, they did not find significant relationship before and after administration of vitamin D supplement. It should be noted that several studies only compare the serum level of vitamin D levels in the treatment group only. In this meta-analysis, we compare the vitamin D levels between intervention and placebo group after several weeks of vitamin D administration, not the vitamin D levels value before and after vitamin D duration in the treatment group only. Lima et al found no significant difference of SLEDAI after six months of vitamin D supplementation between intervention group and placebo group.¹¹ This finding also consistent with the result from a study by Al-Kushi et al, in which they did not find any significant difference of SLEDAI scores after six months of vitamin D supplementation between intervention group and placebo group.¹⁴ A study by Karimzadeh et al found no significant difference of SLEDAI before and after vitamin D supplementation for six months in the intervention group. However, they did not provide the significancy value for SLEDAI scores between intervention and placebo groups. It should be noted that the SLEDAI scores after 6 months of vitamin D administration in the intervention group was lower than control group.¹³ The study by Rifa'i et al found significant decrease of SLEDAI score after three months of supplementation in intervention group. However, they did not analyze the

significancy of SLEDAI scores between intervention and placebo group.¹² Lastly, Pakchotanon et al found no significant difference in SLEDAI scores between intervention and placebo group.¹⁵

One meta-analysis also analyze the effect of vitamin D supplementation to disease activity of SLE.¹⁶ The result of the study also found the same conclusion, vitamin D supplementation did not decrease SLE disease activity, using SLEDAI. However, they did not analyze its effect toward calcium levels.

One study involving large numbers of SLE patients with control found that SLE patients were two-fold likelihood to experience episodes of hypocalcemia compared to controls, with OR of 2.34.²⁵ In SLE patients, the total serum calcium level is negatively correlated with SLE disease activity ($r = -0.394$, $P = 0.001$).²⁶ Thus, the increase of serum calcium level may followed by the reduce of SLE disease activity.

The decrease of calcium in SLE patients may be related to vitamin D deficiency which may occur in SLE patients. The main function of vitamin D is to increase calcium and phosphorus absorption in intestine, and needed for formation of bone matrix.²⁷ In this meta-analysis, the supplementation of vitamin D may increase serum calcium levels. However, the it should be noted whether the increase of only 0.07 mmol/L would be significantly affect clinically or not.

Active SLE is associated with decreased in complement proteins; hence complement activation is part of an important mechanism in SLE. The importance of complement in SLE pathogenesis makes it included in SLE classification criteria. Also, monitoring serum levels of C3 and C4 still recommended to measure SLE disease activity. It should be noted that a decrease in its levels not always associated with flare of SLE. It also bears several disadvantages to measure complement levels, including synthesis variability and genetic

polymorphism.²⁸ In the current meta-analysis, vitamin D supplementation did not have any effect on either ESR, C3 and C4. Studies have explored the relationship between vitamin D and complement in patients with SLE. One study found a positive correlation between vitamin D and C4 levels for C3 levels.²⁹ Other studies also obtained similar results.³⁰ It also has been known that low concentration of C3 and C4 were strong predictors for vitamin D deficiency in SLE patients. Thus, it has been assumed that vitamin D supplementation may affect serum complement levels.

5. Conclusions

The current meta-analysis found no significant effect of vitamin D supplementation on SLE disease activity, also with ESR, C3 and C4. However, in relation to the condition of vitamin D deficiency in SLE patients, supplementation of vitamin D may increase serum vitamin D. In addition, along with supplementation of vitamin D, calcium levels also increase in SLE patients.

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