Effect of Cholecalciferol Supplementation on Disease Activity and Quality of Life of Systemic Lupus Erythematosus Patients: A Randomized Clinical Trial Study

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ABSTRACT

***Background**: Increase in the prevalence and survival rates has led to the assessment of disease activity and quality of life of SLE patients as targets in treatment. Cholecalciferol was considered as having a role in reducing disease activity and improving quality of life.* ***Methods**: A double blind, randomized, controlled trial was conducted on female outpatients aged 18-60 years with SLE, consecutively recruited from September to December 2021 at Cipto Mangunkusumo Hospital. Sixty subjects who met the research criteria were randomized and equally assigned into the cholecalciferol and placebo groups. The study outcomes were measured at baseline and after 12 weeks of intervention.* ***Results**: Out of 60 subjects, 27 subjects in cholecalciferol group and 25 subjects in placebo group completed the intervention. There was a significant improvement on the level of vitamin D (ng/ml) after intervention in the cholecalciferol group, from an average of 15,69 ng/ml (8.1-28.2) to 49,90 ng/ml (26-72.1), and for the placebo group from 15,0 ng/ml (8.1-25,0) to 17.35 ng/ml (8.1-48.3) (p<0,000). Results of the MEX-SLEDAI score showed significant differences in both groups after the intervention, with a significant decrease in the cholecalciferol group from 2,67 (0-11) to 1,37 (0-6), compared to the placebo group from 2,6 (0-6) to 2,48 (0-6) (p<0,001). There were no significant differences on the quality of life in both groups.* ***Conclusion**: Supplementation of cholecalciferol 5000 IU/day for 12 weeks was statistically significant in increasing vitamin D levels and improving disease activity, but did not significantly improve the quality of life of SLE patients.*

***Keywords**: cholecalciferol, disease activity, quality of life, systemic lupus erythematosus.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by autoantibody deposits in tissues, organ damage and various clinical manifestations. SLE is better known as a syndrome than a single disease and the course of SLE is still unpredictable; it can persist, recure, or recover.[1]

The diagnosis and therapy of SLE had improved and made a significant impact on increasing the survival rate of SLE patients.[2] By increasing the survival rate, the target of treatment is not only to control disease activity and prevent organ damage but also to pay attention to the patient's quality of life.[3]

Vitamin D deficiency has a role in the pathogenesis of SLE, especially in the regulation of growth, proliferation, apoptosis, and immune system function. Low vitamin D is associated with decreased Regulatory T-cells (Tregs), which function to increase tolerance to self-antigens. In addition, it also increases the auto reactive activation of B cells to produce autoantibodies, increases the activation and proliferation of Th1 helper cells and produces Interferon-alpha (IFN-α) through plasmatocytoid Dendritic Cells (pDC), producing an excess of pro inflammatory cytokines through macrophages. This process forms immune complexes, which leads to tissue damage and continuous release of self-antigens.[4,5] In vitro studies have shown that 1,25 dihydroxy vitamin D can inhibit the differentiation of Dendritic Cells (DCs), T cell proliferation, cytokine production, activated B cell proliferation and plasma cell formation.[5,6] The relationship between vitamin D and SLE is complex since SLE can cause low levels of vitamin D and vitamin D deficiency further plays a role in the etiology and worsening of SLE symptoms.[6,7] However, the relationship between vitamin D levels and SLE disease activity has been reported to be inconsistent and is still debated.[8] Several studies have shown that vitamin D is associated with SLE disease activity through several mechanisms; meanwhile, other studies have reported that there was no relationship between vitamin D levels and SLE.

Effect of vitamin D supplementation on SLE disease activity is still controversial, and its role on the quality of life of Indonesian SLE patients has never been studied. As a result, this study aims to examine the benefits of vitamin D supplementation on disease activity and quality of life of SLE patients in Indonesia.

METHODS

This study is a double blind randomized controlled trial. Subjects were allocated in each treatment arm using permuted block randomization, with a block size of four and concealed code lists. Investigators, doctors, and subjects were blinded to treatment allocation (double blind).

Study Participants

Women with systemic lupus erythematosus aged 18-60 years old with hypovitaminosis D as inclusion criteria. Exclusion criteria included declining consent to participate, late stage chronic kidney disease (staged 4-5), decompensated liver cirrhosis, consumption of glucocorticoids (equivalent to prednisone 20 mg/day) in the past 30 days, pregnant or lactating, patients with acute infection, hypercalcemic patients, anticonvulsant consumption. Dropout criteria included unwillingness to continue participation in the study, compliance rate <70% for both arms, side effects to vitamin D such as nausea, vomiting, diarrhea, cramps that could not be controlled with medication, hospitalized due to infection, changes in the regiment or dose of immunosuppressant or glucocorticoids (equivalent to prednisone 20 mg/day) during the trial. Subjects were consecutively recruited from September 2021 to December 2021 at Allergy and Immunology Outpatient clinic in Cipto Mangunkusumo Hospital, Jakarta.

Intervention Protocol

After providing written consent, eligible subjects were randomly assigned to either the cholecalciferol (Prove D3 1x5000 IU) or placebo (Saccharum lactis 1x5000 IU) arm. Both the cholecalciferol and placebo tablets were indistinguishable by appearance.

The allocated treatment was dispensed to the subjects every four weeks. The collected data consisted of subjects' demographic data

(age, income, level, duration of illness, Body Mass Index, organ involvement, treatment, comorbidities, initial methylprednisolone dose, initial MEX-SLEDAI score), clinical data (level of hemoglobin, white blood cell, platelets, Erythrocyte Sedimentation Rate, Creatine Kinase (CK), estimated Glomerular Filtration Rate (eGFR), micro-albuminuria, anti-dsDNA, vitamin D levels, blood calcium levels). Quality of life was assessed using the lupus quality of life (Lupus QoL) questionnaire with a 5-point Likert scale.

Measurement of study outcomes was conducted at baseline and after 12 weeks of intervention. Levels of vitamin D were measured using the ELISA kit, and disease activity was measured using the MEX-SLEDAI score, with a score ranging from 0 to 34. Quality of life was assessed using the Lupus Quality of Life (Lupus QoL) questionnaire with a 5-point Likert scale ranging from 0 to 100. All variables were measured initially and 12 weeks after intervention. Adverse events, side effects, and compliance rates were evaluated every four weeks.

Sample Size

The minimum sample size required to assess disease activity of SLE was 10 subjects in each treatment arm. A minimal sample to assess the quality of life was not determined due to the novel nature of the study. Total number of subjects in each treatment group was 30 subjects.

Ethics

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia / Cipto Mangunkusumo Hospital (No. KET-745/UN2F1/ETIK/PPM.00.02/2021). The study procedure was performed in accordance with the Declaration of Helsinki. This study has been registered in clinicaltrial.gov (Registered no. NCT05326841).

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20. Dropout subjects were excluded from the analyses (per-protocol analysis). Mean and standard deviation values were calculated for normally distributed numerical data. Calculation of median and interquartile range values was performed for numeric data with non-normal distributions. Unpaired independent T tests were performed to analyze the changes in the variables between the vitamin D (*Prove D3*) group and placebo when the data distribution was normal. In cases of non-normal data distribution, Mann-Whitney tests were performed.

RESULTS

Despite recruiting 70 SLE subjects to participate in the study, as many as 10 subjects were excluded from this clinical trial, based on the research criteria, which resulted in 60 subjects who were randomized and equally assigned into cholecalciferol (*Prove D3*) and placebo groups. A total of 27 subjects in the cholecalciferol group and 25 subjects in the placebo group had completed the intervention trial (**Figure 1**).

From 27 subjects who completed the intervention in the cholecalciferol group, the mean age was 32,9 (20-40) years old, and most (60%) had an education level of up to senior high school. Eighteen subjects (40%) had a duration of disease greater than 5 years. Most subjects (30%) weighed within normal ranges of BMI. In the placebo group, the mean age was 29.5 (19-49) years old, with a majority (56.7%) having middle school education level. A plurality (46.7%) of subjects in this group had a duration of disease greater than 5 years, and normal weight was observed in 13 subjects (43.3%).

In the cholecalciferol group, mucocutaneous organ involvement was found in all subjects, followed by musculoskeletal involvement in 29 subjects (96.7%). Hydroxychloroquine (HCQ) was the most commonly prescribed treatment, given to 21 subjects (70%), followed by Myfortic (63.3%) and Imuran (23.3%). Most patients had at least one comorbidity with 5 subjects (31.3%) having only one. In the placebo group, mucocutaneous involvement was present in 29 subjects (96.7) followed by musculoskeletal involvement in 25 subjects (83.3%). Treatment by HCQ was standard for 23 subjects (76.7%), followed by myfortic in 17 subjects (56.7%) and imuran in 3 subjects (10%). Ten subjects (33.3%) had one comorbidity, with most having more than one. Results of the demographic characteristics are summarised in **Table 1**.

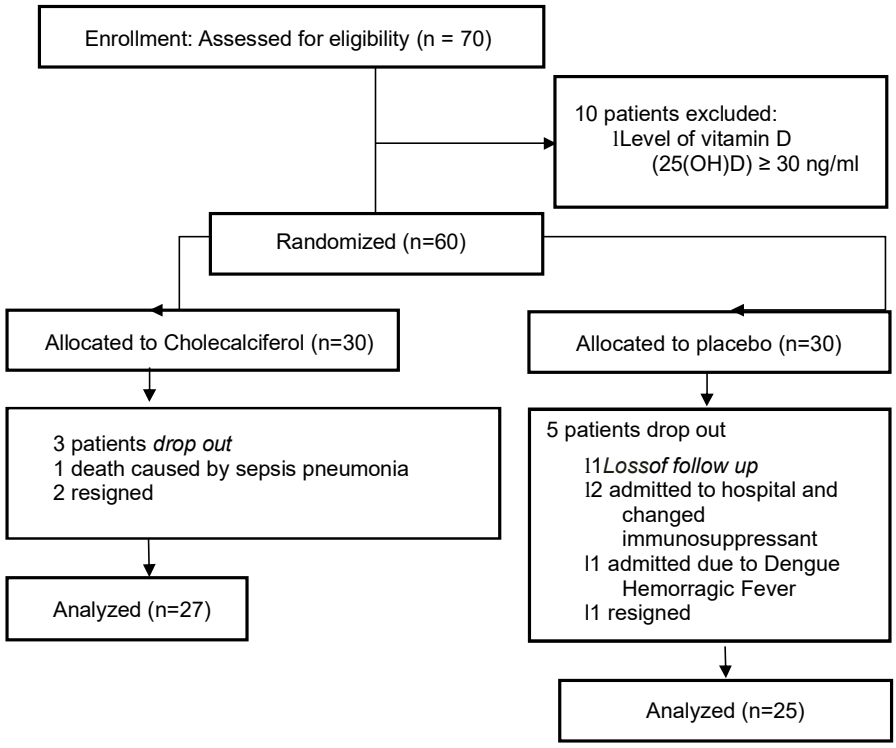

Figure 1. Flow diagram of randomized control trial.

Table 1. Characteristic study subjects.

Variables	Intervention (n=30)	Placebo (n=30)
Age (year), median (IQR)	32.9 (20-46)	29.5 (19-49)
Level of education, n (%)		
Low	3 (10.0)	3 (10.0)
Middle	18 (60.0)	17 (56.7)
High	9 (30.0)	10 (33.3)
Income, n (%)		
<UMR	16 (53.3)	19 (63.7)
>UMR	14 (46.7)	11 (37.3)
Disease of duration, n (%)		
<1 year	6 (20.0)	7 (23.3)
1-5 year	6 (20.0)	9 (30.0)
>5 year	18 (40.0)	14 (46.7)
IMT, n (%)		
Underweight	6 (20.0)	4 (13.3)
Normoweight	9 (30.0)	13 (43.3)
Overweight	8 (26.7)	8 (26.7)
Obesity	7 (23.3)	5 (16.7)
Organ involvement, n (%)		
Mucocutaneous	30 (100)	29 (96.7)
Musculosceletal	29 (96.7)	25 (83.3)
Renal	18 (40.0)	10 (33.3)
Hematology	15 (50.0)	8 (26.7)
Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)	1 (3.3)	2 (6.7)
Serositis	2 (6.7)	0
Treatment, n(%)		
Hydroxyichloroquine (HCQ)	21 (70.0)	23 (76.7)

Myfortic	19 (63.3)	17 (56.7)
Imuran	7 (23.3)	3 (10.0)
Methotrexate (MTX)	0	1 (3.3)
Comorbidity, n (%)		
None	3 (18.8)	11 (36.7)
One	5 (31.3)	10 (33.3)
Two	3 (18.8)	4 (13.3)
Three	2 (12.5)	4 (13.3)
Four	2 (12.5)	3 (3.3)
Five	1 (6.3)	0 (0.0)
Initial dose of methylprednisolone mg/day, median (IQR)	3.53 (0-16)	5.13 (0-16)
Initial MEX-SLEDAI score, median (IQR)	2.67 (0-11)	2.6(0-6)

IQR: Interquartile Range ; n= total subjects

Quality of life in the two groups had similar median values across the 8 domains. In the physical health domain, the average cholecalciferol group score was 79.6 (50-100), which was slightly higher than the average placebo group, which was 79.0 (21-100). Pain scores in the cholecalciferol group (median 73.3 [33-100]) were on average lower than the placebo group (median 78.5 [25-100]). On average, the planning score in the cholecalciferol group was 79.1 (25-100), which was lower than the placebo group score of 84.4 (25-100). The median intercourse score in the cholecalciferol group was 86.2 (12.5-100), which was higher than the placebo group (median 81.4 [0-100]). Emotional health scores in the cholecalciferol group (median 65.4 [8-95]) were lower than the placebo group (median 75.4 [25-100]), and median self-image scores in both groups were 66.4 (15-100) and 77.1 (15-100) for the cholecalciferol and placebo arm respectively. Fatigue score in the intervention group (median 57.7 [12.5-93]) was lower on average, compared to the placebo group (median 70.2 [18-100]). Quality of life scores is summarised in **Table 2**.

The initial levels of vitamin D 25 (OH) in the two groups before intervention were similar. After an intervention, the cholecalciferol group had an increase of average vitamin D 25(OH) levels from 15.69 ng/ml (8.1-28.2) to 49.90 ng/ml (26-72.1), resulting in an average increase of 33.8 ng/ml. In the placebo group, average vitamin D levels also increased slightly by 2.5ng/ml from 15.0 ng/ml (8.1-25,0) to 17.35 ng/ml (8.1-48.3). The difference in the increase in average vitamin D 25(OH) levels between the two groups was statistically significant ($p<0.000$). Results of initial laboratory values and analysis of vitamin D changes are summarised in **Table 3** and **Table 4**, respectively.

The effect of giving cholecalciferol on SLE disease activity, based on the MEX-SLEDAI results, showed a significant difference between the cholecalciferol group and the placebo group. An average decrease in the MEX-SLEDAI value of about 1.29 in the intervention group was observed, compared to the average decrease of 0.12 in the MEX-SLEDAI value of the placebo group. This indicates that the intervention with cholecalciferol provided an improvement, in the

Table 2. Characteristic initial quality of life.

Variables	Intervention (n=30)	Placebo (n=30)
Lupus QoL, median (IQR)		
Physical health	79.6 (50-100)	79.0(21-100)
Pain	73.3 (33-100))	78.5 (25-100)
Planning	79.1 (25-100)	84.4 (25-100)
Intimate relationship	86.2 (12.5-100))	81.4 (0-100)
Burden to others	63.0 (7-100)	72.1 (10-100)
Emotional health	65.4 (8-95)	75.4 (25-100)
Body image	66.4 (15-100)	77.1 (15-100)
Fatique	57.7 (12.5-93)	70.2(18-100)

Table 3. Initial laboratory characteristics.

Variables	Intervention (n=30)	Placebo (n=30)
Hemoglobin (g/dl), median (IQR)	11.9 (7.2-14.1)	12.0 (7.8-14.3)
White Blood Cell (/uL), median (IQR)	6639 (4100-10670)	7048 (3190-13110)
Platelets (/uL), median (IQR)	298966 (202000-396000)	320066 (139000.0-549000)
LED (mm), median (IQR)	38.1 (0-140)	41.8 (0-144)
CK (U/L), median (IQR)	66.0 (16.0-167.0)	54.7(16-178)
eGFR (ml/min/1.73m^2), median (IQR)	111 (68-140)	105.7 (12-131)
Microalbuminuria (mg/g kreatinin), median (IQR)	169 (0-2085)	118.3 (0-792)
Anti dsDNA (IU/mL), median (IQR)	266.7 (1.1-1235)	223.1 (1.9-967.0)
Initial Vitamin D (ng/ml), median (IQR)	15.69 (8.1-28.2)	15.0 (8.1-25.0)
Calsium level mg/dl, mean (SD)	9.27 (0.49)	9.40(0.30)

IQR= Rentang Interquartile; SD= Standard Deviation

Table 4. Changes in pre and post intervention vitamin D Levels.

Variables	Group [Mean (SD)]		P
	Intervention (n=30)	Placebo (n=30)	
Vitamin D (ng/ml)	33.8 (SD 12.04)	2.5 (SD 10.58)	<0.000

Unpaired T-test.

form of a decrease in SLE disease activity (p = 0.015). The analysis of the SLE disease activity post intervention is described in **Table 5**.

The effect of giving cholecalciferol compared to placebo on the Lupus Quality Of Life (Lupus Qol) scores showed that there was no significant difference in the quality of life between the two groups across all domains including physical health, pain, planning, intimate relationships, burden to others, emotional health, self-image and fatigue **(Table 6)**.

Table 5. Effect of cholecalciferol supplementation on SLE disease activity using MEX-SLEDAI.

Variable	Group [Median (IQR)]		p
	Intervention (n=30)	Placebo (n=30)	
MEX-SLEDAI	-1.29 (-5.0; 4.0)	-0.12 (-5.0; 6.0)	0.015

Table 6. Changes in the total quality of life of SLE patients pre and post intervention.

Lupus QoL	Intervention (n=30)	Placebo (n=30)	p
Total QoL Mean (SD)	21.32 (90.57)	14.4 (78.2)	0.773

DISCUSSION

In this study, the results in the vitamin D group showed a significant increase in 25(OH) D levels when compared to the placebo group. These results are in accordance with the randomized trial by Abou-Raya et al. where SLE patients receiving vitamin D 2000 IU/day and had a greater increase in post-intervention vitamin D 25(OH)D levels, compared to the placebo group. On average, the vitamin D 25(OH) level was greater by 17.9 ng/ml with a mean of 37.8±16.3 ng/ml in the intervention group, compared to 19.9±16.2 ng/ml in the placebo group ($p<0.05$).[9]

The effect of cholecalciferol supplementation on SLE disease activity, showed that there was a greater decrease in average MEX-SLEDAI values of the intervention group compared to the placebo group. The results of this study are concordant with the research by Kalim et al, where a double-blinded randomized clinical trial was conducted involving 20 SLE patients who were given vitamin D supplementation of 1200 IU/day for 3 months, compared to 19 SLE patients who received a placebo. The results of this study showed a significant decrease in the SLEDAI scores from an average of 12.65 ± 4.85 to 6.20 ± 2.67 in the vitamin D group, compared to the slight decrease in SLEDAI scores of the placebo group (10.74±2,75 to 9.68±2.26).[10]

Vitamin D plays a role in regulating Treg cells through the process of tolerogenic induction of dendritic cells, which will produce IL-10 through CD4+ T cells and Treg-specific antigens. High levels of vitamin D can stimulate the transcription factor FOXP3, which plays

a role in the formation and enhancement of Treg function. High vitamin D levels are also associated with anti-inflammatory lymphoid polarization. Tregs stimulated by vitamin D will function to control the immune response of T cells, both alloreactive or autoreactive, by producing inhibitory cytokines, namely IL-10 and TGF-beta, through the release of granzyme and perforin or expression of CTLA-4 to prevent antigen presentation or proinflammatory response. Vitamin D can increase Tregs both directly or indirectly. The results of the study showed that there was a relationship between high Treg levels and immunosuppressive phenotypes. Vitamin D supplementation can decrease SLE activity. This is due to the role of vitamin D in inhibiting Th1, Th17 and increasing Tregs and Th2. Vitamin D also decreases the differentiation and proliferation of B cells.[12]

After the intervention, there was an increase in the Lupus QoL score in the cholecalciferol and the placebo group, but the differences between the two results were not significant (p=0.773). This was due to the good baseline quality of life in both groups since both groups had a median score greater than 50 in each domain prior to intervention. In addition, several factors can affect the quality of life in this study such as age, duration of illness, level of education, disease activity. In this study, the difference in age between the two groups was not much different and on average subjects were relatively young. In addition, the duration of illness and level of education may also play a role in the quality of life since a patient with longer duration of disease may have better physical health, mental health and emotional regulation. Higher education levels on average will lead to a better quality of life. Quality of life in this study was good and not related to disease activity and organ involvement.[14]

Although there were three serious adverse events (SAEs) reported in the vitamin D group (nausea, pneumonia, iron deficiency anemia), further investigation showed that they were not related to vitamin D administration.

The advantage of this study was that it used a double-blinded randomized trial design, with a long observation time of 12 weeks. In addition, the use of cholecalciferol tablets in this study at a dose of 5000 IU was in accordance with the guidelines of the European Food Safety Authority, which recommends the use of vitamin D at a daily average of 4000 IU/day (100µg/day) for adults and the elderly with normal weights. The tablet preparations taken are also small, tasteless, and odorless, making it easier for patients to consume. This study was also successful in increasing vitamin D levels, achieving sufficient values, and succeeded in significantly improving disease activity. The study also succeeded in improving the quality of life of the subjects, albeit slightly.

The weakness of this study is a large number of tablets that have to be consumed per day and the absence of specific inflammatory marker examinations that can explain the decrease in SLE disease activity. With respect to the quality of life study, the sample size needs to be increased, and the research time needs to be longer than at least 6 months.

CONCLUSION

In this study, the results showed that daily cholecalciferol (5000 IU) supplementation for 12 weeks improved disease activity, but did not significantly improve the quality of life of SLE patients.

From this study, it can be proven that cholecalciferol (5000 IU)/day supplementation for 12 weeks increases vitamin D levels and improves disease activity in SLE patients. However, it is necessary to conduct an assessment in the form of inflammatory markers that are more specific for inflammatory conditions in the LES so that they can explain the activity of the LES. And related to the role of cholecalciferol supplementation on the quality of life of SLE patients, it is still not significant in this study, so further research is needed with a larger sample size and a longer time of at least 6 months.

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