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The effect of *Curcuma Xanthorriza* addition to Vitamin D_3 supplementation on fatigue and cytokines serum levels in SLE patients with hypovitaminosis D

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Background: Seventy percent of Lupus patients in Indonesia have hypovitaminosis D. Curcumin is a novel vitamin D receptor (VDR) ligand and has synergic effects with vitamin D.
Objective: This study aimed to determine the effect of *Curcuma xanthorriza* addition to vitamin D_3 supplementation on fatigue, serum IL-6, TGF- β1, and determine the correlation between fatigue, serum IL-6 and TGF-β1 in lupus patients with hypovitaminosis D.
Methods: This was a double blind randomized controlled trial involving 40 SLE patients with hypovitaminosis D (vitamin D<30 ng/ml). The first group consisted of 20 patients who received *Cholecalciferol* 1200 IU/day and placebo, and the other group received *Cholecalciferol* 1200 IU/day and *Curcuma xanthorriza* 60 mg/day. The subjects were followed up at the end of 3 months. Fatigue measured with Fatigue Severity Scale (FSS) and Visual Analogue Scale-Fatigue (VAS-F). Vitamin D, serum IL-6 and TGF-β1 were measured by ELISA.
Result: There was no significant difference between the decrease of FSS ($p = 0.300$) and VAS-F score ($p = 0.085$) in curcuma Vs placebo groups, respectively. The decrease of IL-6 ($p = 0.061$) and increase of TGF-β1 ($p = 0.261$) in curcuma Vs placebo group also did not differ significantly. There was no correlation between fatigue and IL-6 [FSS, r=0.255, p=0.117], [VAS, r=0.086, p=0.625], also between fatigue and TGF-β1 [FSS, r=0.127, p=0.441], [VAS-F, r=0.510, p=0.109].
Conclusion: The addition of *Curcuma xanthorriza* had no significant effect on fatigue and alteration of IL-6, as well as TGF-β1 serum. There were no correlations between fatigue, IL-6 and TGF-β1 serum.

Keywords: *Fatigue,* Hypovitaminosis D, VDR, *Curcuma xanthorriza*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease, characterized by high mortality and morbidity rates.[1] Nowadays, treatment can reduce the mortality rate, but the morbidity is still high. One cause of the high morbidity in SLE is fatigue. Fatigue has been complained by 50-90% SLE patients.[2,3] Fatigue in autoimmune diseases may have multiple risk factors, usually linked by comorbidities of the disease itself (e.g. in anaemia, fibromyalgia, etc) and also linked to inflammation process and dysregulation of immune system. Fatigue also increases low compliance with and negative effects on occupational and social activities, thus reducing patient's quality of life.[4]

Deficiency of vitamin D correlated with fatigue severity in some diseases.[5,6] Irastorza et al showed that 71% of SLE patients have hypovitaminosis D, because they tend to evade sunray exposure by applying sunscreen, and also have inadequate vitamin D intake.[1,7] Patients with SLE who use long term steroid, for mucocutaneus and renal problem, have antibody for vitamin D and vitamin D receptor (VDR). All of that cause hypovitaminosis D in SLE patients.[8] In vivo and in vitro studies show that vitamin D has important immunomodulator activities. Vitamin D could induce chemotaxis, macrophage phagocytosis and activity of Treg cell. It can also inhibit differentiation and proliferation B cell, and production of antibody.[9-11]

Fatigue is associated with increase of proinflammatory cytokines, and one of the most studied cytokines is IL-6. But other cytokines, like transforming growth factor-beta (TGF-β) has negative correlation with fatigue. Vitamin D supplementation increases expression of TGF-β1. This increased TGF-β causes an immune response dominated by Treg, that has an immuneprotective effect by controlling T17.[8,12,13]

There are a lot of studies on the immunomodulator effects of curcumin. One of hypotheses is Curcumin is a novel ligand for vitamin D receptor (VDR). This binding activates transcription genes. Curcumin works synergistically with vitamin D to regulate immune system.[14] Khajehdehi, et

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al in his study showed that providing 22.1 mg of curcumin supplementation, 3 times daily for 3 months in relapse or refractory lupus nephritis patients, significantly decreased proteinuria, hematuria and systolic blood pressure.[2] This study aimed to determine the effect of Curcuma xanthorriza addition to vitamin D3 supplementation on fatigue, serum interleukin-6 (IL-6), TGF-β1, and to study the correlation between fatigue, serum IL-6 and TGF-β1 in lupus patients with hypovitaminosis D.

MATERIAL AND METHODS

This double blind randomized controlled trial study was held in Rheumatology Clinic Saiful Anwar Hospital Malang from January 2016 to March 2017 to evaluate the adding effect of *Curcuma xanthorriza* on supplementation of vitamin D_3 in SLE patients with hypovitaminosis D on the degree of fatigue and on alterations in the IL-6 serum and TGF-β. The study was approved by the local ethics committee of Saiful Anwar Hospital. Informed written consent was obtained from all patients prior to their enrolment in this study.

The population included SLE outpatients who underwent treatment in the Rheumatology Clinic of Saiful Anwar Hospital Malang. The inclusion criteria were: 1) Women who had been diagnosed as SLE patients with American College of Rheumatology 1997 criteria, 2) SLE status active (Systemic Lupus Erythematosus Disease Activity Index/ SLEDAI > 3), and 3) Laboratory criteria, vitamin D <30 ng/mL. Exclusion criteria; 1) There were other causes of hypovitaminosis D besides SLE, 2) pregnancy, 3) an ongoing intake of vitamin D. 4) other disorders: a) disorder of liver function (SGOT/SGPT ³2.5 upper limit normal), b) severe renal disorder (GFR < 25 cc/min or oliguria with urine production <400 cc/ day), c) other severe comorbidities, for example, pulmonary tuberculosis, pneumonia, sepsis.

The sample size was 40. The SLE patients were randomized into 2 groups, each comprising 20 patients. The first group of patients had supplementation of Vitamin D_3 and *Curcuma xanthorriza*, while the second group had supplementation of Vitamin D_3 and *placebo,* in addition to their regular SLE treatment. For vitamin D_3 supplementation softgel/cholecalciferol was administered at the dose of 3x400 IU/ day. Extract of *Curcuma xanthorriza* was given at the dose of 3x20 mg/day. The participants were assessed at the end of three months.

Participants had a blood test for vitamin D, IL-6 and TGF-β and had interview sessions to measure the fatigue before study. During the interview, the questionnaire of Fatigue Severity Scale (FSS) was administered. It contained 9 questions, each of which had a score range of 1-7 (1=disagree, 7=strongly agree), and fatigue was classified as severe if the FSS reached the score of >4. Beside FSS, we also measured Visual Analogue Scale-Fatigue (VAS-F) with scores ranging from 0 to10 (0= none, 10=worst possible fatigue). ELISA kit from DiaSorin (ng/ml) was used for measuring vitamin D. ELISA kit from Biolegend (pg/mL) was used for IL-6 and TGF-β. The participants were followed up for 3 months. Participants' complaints, heartbeat, and calcium levels were recorded at each visit. Drug consumption was supervised by patient's family. After 3 months, FSS, VAS-F, serum IL-6 and TGF-β1 were measured.

The data were normalized first with Saphiro-Wilk test, and analysed using paired sample t-test Wilcoxon to study the differences of vitamin D serum, FSS, VAS-F, IL-6 and TGFβ-1 before and after study. Mann Whitney U test later was employed to compare between both groups after experiment. The Spearman rank test was used to study the correlation between fatigue and IL-6, and fatigue and TGF-β1. All of measurements were done using SPSS for Windows 22.

RESULTS

Forty patients participated in this trial, and divided into 2 groups, one person in *Curcuma xanthorriza* group was excluded because non-compliance with supplementation. Finally there were 19 subjects in *Curcuma xanthorriza* groups and 20 subjects in placebo groups. There was no difference of baseline characteristic before study between the two groups (**Table 1**).

Both groups show significant improvement of FSS and VAS-F, and increased levels of vitamin D after treatment. A comparison between the two groups after treatment, showed no significant difference in FSS ($p = 0.171$), VAS-F ($p = 0.277$); however, vitamin D levels were significantly higher in the placebo group than in *Curcuma xanthorriza* group ($p = 0.047$) (**Table 2**).

The decrease in the levels of IL-6 and increase of TGF-β1 were significant after treatment. When compared between two groups after treatment there was no significant difference of IL-6 (p=0.061) and TGF-β1 (p = 0.261). In **Table 2** when compared between the two groups of delta after treatment we found no significant difference for the decreased of IL-6 (p = 0.061) and an increase of TGF-β1 (p = 0.261).

There was a relationship between FSS score and VAS-F (p=0.020, r= 0.372). A positive value indicates a relationship in the same direction, where the decreased score of FSS was directly proportional to decreased score of VAS-F. There was no correlation between FSS with IL-6 and TGF-β1 serum (**Figure 1 and Figure 2**, respectively).

DISCUSSION

The youngest age of patients in both study groups was 16 years and the oldest was 50 years old. It can be explained

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Table 1. Characteristic of Subjects

Characteristic	Vitamin D_3 and Curcuma xanthorriza (N=19)	Vitamin D_3 and Placebo (N=20)	*p* value
Age (year), mean ± SD	27.8 ± 7.9	30.3 ± 10.0	0.415
Duration of illness (year), mean ± SD	2.6 ± 2.0	2.6 ± 1.9	0.937
Fatigue Severity Scale (FSS), mean ± SD	5.3 ± 0.9	5.2 ± 0.9	0.914
Visual Analogue Scale-Fatigue (VAS-F), mean ± SD	6.7 ± 1.7	7.2 ± 1.4	0.434
Early Manifestations, n (%)			
- Mucocutaneus	13 (33.3%)	17(43.6%)	0.219
- Arthritis	7 (17.9%)	9 (23.1%)	0.605
- Nephritis	8 (20.5%)	4 (10.3%)	0.135
- Autoimmune Hemolytic Anemia	3 (7.7%)	2 (5.1%)	0.589
- Vasculitis	1 (2.6%)	1 (2.6%)	0.970
- Serositis	1 (2.6%)	1 (2.6%)	0.970
- Cerebral	4 (10.3%)	3 (7.7%)	0.622
Non-Immunosupressant treatment, n (%)			
- Metilprednisolon	19 (48.7%)	19 (48.7%)	0.323
- Calc	15 (38.5%)	19 (48.7%)	0.134
Immunosupressant treatment, n (%)			
- Chloroquine	7 (17.9%)	10(25.6%)	0.408
- Cyclosporin	0 (0%)	2 (5.1%)	0.157
- Cyclophospamide	5 (12.8%)	1 (2.6%)	0.065
- Azathioprin	14 (35.9%)	10 (25.6%)	0.129
Vitamin D (ng/ml), mean ± SD	14.2 ± 6.5	14.9 ± 7.4	0.779
Hb (g/dl), mean ± SD	11.9 ± 1.26	11.2 ± 1.6	0.122
Calcium (g/dl), mean ± SD	8.8 ± 0.4	8.9 ± 0.6	0.630
Ureum (mg/dl), median (min-max)	25.5 (17.6-35.7)	23.7 (15.1-27.4)	0.491
Creatinine (mg/dl), median (min-max)	0.6 (0.4-0.7)	0.6 (0.5-0.8)	0.623
SGOT (U/L), median (min-max)	22 (17-34)	19 (12.7-32.7)	0.641
SGPT (U/L), median (min-max)	20 (15-40)	16.5 (9-32.2)	0.426
Erythrocyte Sedimentation Rate (mm/hour)	49.9 ± 9	41.6 ± 23.3	0.235
IL-6 (pg/ml)	6.8 (4.7-15.5)	11.1 (6.6-18.1)	0.396
TGF-β1 (pg/ml)	279.3 (249.3-313.1)	286.6 (248.8-341.9)	0.627

FSS: Fatigue Severity Scale (FSS), VAS-F: Visual Analogue Scale-Fatigue, IL-6: Interleukon-6, TGF-β1: Transforming growth factor-beta1

that epidemiologically SLE can affect all ages although women of childbearing age (15-44 years) are most at risk.[3] The patients were suffering from SLE for lengths between 1 and 4 years, whereby the first 5 years after diagnosis SLE, patients still need to be in control for awareness of incidence of flare. FSS value of the average patient between 4-7 and VAS-F grades 3-10. All patients enrolled in this study experienced severe fatigue with the average value of FSS> 4, and degree of VAS ranged from mild to very severe. Levels of vitamin D in both groups ranged between 5 and 26.8 ng/ml, which shows some degree of hypovitaminosis D from severe deficiency to insufficiency. Initial manifestations dominant in both groups

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Table 2. Several comparison of different variable in both groups

Variable	Vitamin D_3 and Curcuma xanthorriza (N=19)			Vitamin D_3 dan Placebo N=(20)			p*
	Pre	Post	p	Pre	Post	P	
FSS, mean ± SD	5.3 ± 0.9	2.9± 1.3	0.000	5.2 ± 0.9	2.3 ± 1.2	0.000	0.171
VAS-F, mean ± SD	6.7 ± 1.7	3.2 ± 1.5	0.000	7.2±1.4	2.7 ± 1.7	0.000	0.277
IL-6 (pg/ml), median (min-max)	6.8 (4.3-74.9)	5.2 (2-9.4)	0.013*	11.0 (4.1-24.6)	3.65 (1.6-18.1)	0.001*	0.061
TGF-β1 (pg/ml), median (min-max)	279.3 (14.2-360.7)	348.4 (9.5-490.2)	0.011*	286.6 (11.3-432.4)	352.2 (150.3-490.2)	0.000*	0.261
Vitamin D (ng/ml), mean ± SD	14.3 ± 6.5	22.7±5.4	0.003	14.9 ± 7.4	26.8 ± 3.7	0.000	0.047*

FSS: Fatigue Severity Scale (FSS), VAS-F: Visual Analogue Scale-Fatigue, IL-6: Interleukon-6, TGF-β1: Transforming growth factor-beta1

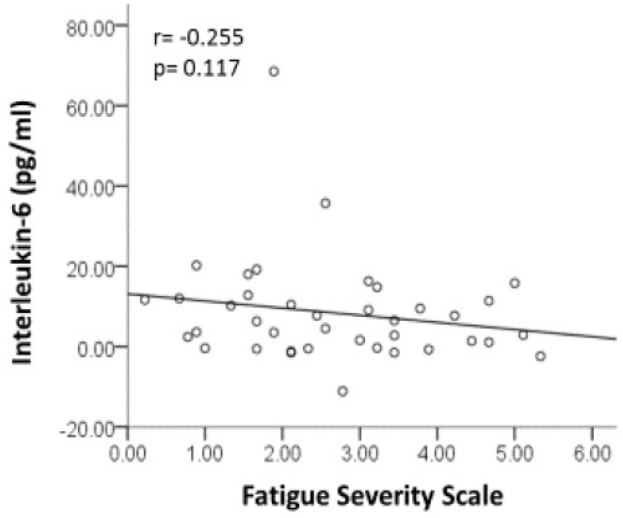

Figure 1. Correlation of FSS with IL-6 serum

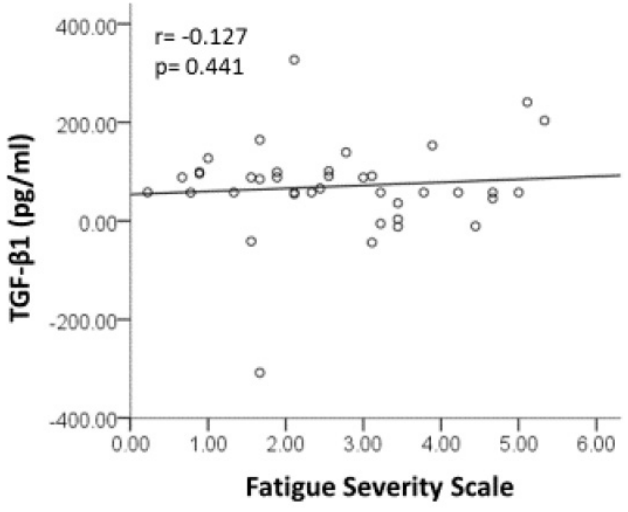

Figure 2. Correlation of FSS with TGF-β1 serum

were mucocutaneous. These patients tended to avoid the sun and to use sunscreen, for which the production of vitamin D in the skin is inhibited.[4] Corticosteroid therapy also increases incidence hypovitaminosis D, because as sparing agent steroid increases the catabolism of vitamin D and also causes an increase in fat tissue mass. As vitamin D is fat soluble, the level of vitamin D in the circulation becomes less.[5]

Vitamin D_3 (Cholecalciferol) 1200 IU/ day for 3 months with *Curcuma xanthorriza* or with placebo gave effect on increasing of vitamin D serum, but we could not achieve target vitamin D 30 ng/mL. This may be because the low serum level of vitamin D before supplementation. There were 26% and 25% patients with 25(OH)D serum less than 10 ng/ml or severe deficiency, in the curcumin and placebo groups respectively. Cholecalciferol 1000 IU could increase vitamin D level for 10 ng/mL in 3-4 months, but if there was no sunray exposure, cholecalciferol dose must be increased to 2000 IU to achieve the same increase of vitamin D level. ACR recommended 50.000 IU/week loading dose vitamin D for 8 weeks, continued with 2000-4000 IU/day for maintenance, and also stated 2000 IU/day of vitamin D was sufficient to achieve optimal vitamin D status in normal subjects.[6]

No side-effects were found due to increased vitamin D in both groups after treatment with median calcium group level of 9.1 (8.9-9.6) mg/dl in placebo group and 9.3 (8.9-9.5) mg/dl in *Curcuma xanthorriza* group. Intoxication due to vitamin D intake is when the consumption exceeds 10,000 IU/ day and the level of vitamin D> 150 ng / ml.[7]

Fatigue, measured by FSS and VAS, in previous trial negatively correlated with of vitamin D serum. Our trial shows that supplementation of vitamin D (cholecalciferol) even though it didn't reach its normal range in circulation still has anti fatigue effects. Lorentzen in his study 2014, show that fatigue in SLE patient is correlated with decrease of social, physical and mental function. FSS has high validity

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and reliability and has been translated into several languages, including Indonesian.[10] While Visual VAS-F can also be used to measure fatigue where accuracy and response are good.[8,10,11]

Decrease of fatigue is caused by elevated levels of vitamin D. Vitamin D supplementation improved fatigue.[5,6] The symptoms that often arise from vitamin D deficiency are fatigue, musculoskeletal disorders, sleep disturbances, concentration disturbance, and headache. Hypovitaminois D itself is one of the causes of fatigue in SLE patients.[9]

The binding of vitamin D with VDR results in decrease of IL-6. It is explained by an increased syntheses of mitogen-activated protein kinase phosphatase 5 (MKP5). MKP5 inactivates protein p38 that was important in synthesis IL-6.[12]

Increase of TGF-β1 was because of vitamin D formed ligand with VDR and through SMAD3 pathway will increase expression of TGF-β1.[12] Increase ratio of TGF-β1/IL-6 will cause the balance of Treg (anti-inflammatory)/Th17 (pro-inflammatory) change to anti-inflammatory through expression of FOXP3 and also RORγt. This anti-inflammatory effect is protective for SLE patient.[12,13]

In the different test of each delta of IL-6 and TGF-β1 after treatment in both groups there was no difference in the Curcuma xanthorriza group compared with the placebo group.

Similarly with the increase in level of vitamin D after study, decrease of fatigue, decrease of IL-6 and increase of TGF-β1 were not significantly different compared with that of placebo group. The role of *Curcuma xanthorriza* has not been proved in the study. It may be explained by the use of a lower dose, low bioavailability, low affinity for VDR, and binds to alternative pocket while vitamin D binds to genomic pocket. Vitamin D and *Curcuma xanthorriza* competes in occupying VDR (Vitamin D Receptor). When Curcuma xanthorriza successfully occupies VDR, it requires larger doses up to 10-1000x; doses up to 8 grams/day can be used. The cells treated with both of Vitamin D and *Curcuma xanthorriza* cause lower VDR content than vitamin D alone.[14-16] One way to increase *Curcuma xanthorriza* bioavailability is adding piperine, which will inhibit glucoronidation of *Curcuma xanthorriza* in liver and small intestine.[17] Alternatives are the use of nanoparticles and various encapsulation.[18]

There was no correlation between fatigues in SLE patient with IL-6, possibly because etiology of fatigue in SLE are multifactorial, it includes decrease of physical activity, obesity, low quality of sleep, mood disturbance, cognitive disorder, hypovitaminosis D or drugs for SLE . Ahn and Ramsay proposed that proinflammatory cytokines that play a role in the occurrence of fatigue are not only IL-6, but also TNF-α, IL-2, IL-10, IFN-Y, and low C4 values.[19] Nishimura, et al showed that fatigue correlated with anxiety and did not correlate with IL-6.[20]

In SLE patient, decrease of TGF-β1 is correlated to increase of fatigue, but in our study even though the fatigue was decreased and TGF-β1 increased. The correlation was not significant. In immunological diseases such as SLE, fatigue is influenced by central and peripheral mechanisms. In peripheral mechanisms, low level of TGF-β1 was found in SLE, when there was an improvement of SLE the levels will increase so that the balance of TGF-β1/IL-6 will affect the balance of Treg/Th17.[12,13] But in the brain tissue, high level of TGF-β1 found in fatigue conditions and will inhibit DHEA production and interfere with the metabolism of acetylcarnitine and glutamate biosynthesis resulting in an autonomic imbalance and fatigue. Thus, in the brain tissue with fatigue improvement, the level of TGF-β1 decreases.[21] It is different with peripheral inflammation where TGF-β1 increases with SLE improvement. No association between fatigue and TGF-β1 is also due to fact that fatigue in multifactorial in SLE other than inflammation, brain cytokines did not reflect peripheral inflammation, and psychosocial factor is a dominant predictor for fatigue.[22]

From our trial, we found weak correlation between FSS and VAS (r=0.372, p = 0.020). Our trial showed that VAS as a single indicator of fatigue could be used as a possible alternative measurement to measure fatigue, because it is simpler than FSS.[23]

This study has several weakness and limitation because we used raw extract of Curcuma xanthoriza, which contains low active ingredients. We did not measure Curcumin level in circulation, and we did not include other factors that may cause fatigue (such as physical activity, depression, anxiety, mood disorder) in our analysis. We need larger dose of *Curcuma xanthorriza*. If vitamin D pre trial < 10 ng/mL, we need a loading dose or increased dose. We also need to measure Curcumin level in circulation. For fatigue we need to include other factors that affect fatigue in analyses, and futher research with 3 groups, where one of them should be curcumin only, to show the real effect of Curcumin.

CONCLUSION

Addition of Curcuma xanthorriza to vitamin D3 in SLE patient with hypovitaminosis D had no significant difference compared to vitamin D3 alone in the decrease of fatigue, decrease of IL-6 serum, and increase of TGF-β1 serum. There was no correlation between fatigue, IL-6 and TGF-β1 serum.

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