

# Prevalence and factors associated with vitamin D deficiency in systemic lupus erythematosus patients

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## ABSTRACT

**Background:** In addition to the calcium-phosphorus metabolism, vitamin D might also play a role in the immune system. Studies have showed lower levels of vitamin D among SLE patients compared with controls. Researches regarding vitamin D in SLE patients have only been conducted in four seasons' countries (Caucasians subjects in a large part), but no data has been available in tropical countries, particularly Indonesia. The presence of VDR gene polymorphism in different populations will affect the role of vitamin D in the immune system.

**Objectives:** To determine the prevalence of vitamin D deficiency and identify its risk factors such as lack of sunlight exposure, sunscreen usage, long-term corticosteroid therapy, disease activity, insufficient vitamin D supplementation, and obesity in SLE patients with vitamin D deficiency.

**Methods:** A cross-sectional study was conducted on SLE patients who were under treatment at Cipto Mangunkusumo General Hospital or members of Indonesian Lupus Foundation. Then those patients completed questionnaires and their 25(OH)D serum levels were measured. The cut-off value of 25(OH)D levels for vitamin D inadequacy is 75 nmol/L, which then grouped into vitamin D insufficiency (25(OH)D 25 - < 75 nmol/L) and vitamin D deficiency (25(OH)D < 25 nmol/L). SLE activity was assessed with MEX-SLEDAI.

**Results:** During May-June 2008, 80 SLE patients were enrolled with 96.3% female subjects, median age of 26 years (range 17-56 years), 66.3% non-obese, 93.8% using steroid, 62.5% with active disease, and 63.8% have adequate sun exposure. In addition, 81.5% did not use sunscreen and 83.8% did not take vitamin D supplementation. All patients had vitamin D inadequacy with 41.2% in insufficiency level and the other 58.8% in deficiency level. The median of 25 (OH)D levels were 21.85 nmol/L (range 11.5-57.7 nmol/L). It also has been found that vitamin D deficiency occurred more in subjects who were obese, used sunscreens, had lower exposure to sunlight, in a long-term high-dose steroid therapy, had active SLE disease, and had no vitamin D supplements.

**Conclusions:** All SLE patients had vitamin D inadequacy. Vitamin D deficiency occurred more in subjects who were obese, used sunscreens, had lower exposure to sunlight, in a long-term high-dose steroid therapy, had active SLE disease, and had no vitamin D supplements.

Vitamin D has been known to be involved in calcium and phosphorus metabolism, but it also has roles in the immunity system.<sup>1-10</sup> Most studies stated that the immune system, particularly the T cell response, is controlled by 1.25-(OH)-D<sub>3</sub>. Without 1.25-(OH)-D<sub>3</sub>, the immune response that is mediated by T cell will not be effective.<sup>5,10</sup> Besides T cell suppression, 1.25-(OH)-D<sub>3</sub> is also involved in the determination of cytokine secretion system, induction T cell regulations, stimulation of proliferation, and apoptosis.<sup>6,11</sup> Adequate concentration of vitamin D will improve functions of T-helper cells, dendritic cells, and macrophages.<sup>6,10,12</sup> In B cells, vitamin D may inhibit antibody secretion and autoantibody formation. It is been known that immunologic factors also plays an important role in SLE (Systemic Lupus Erythematosus) besides genetic, hormonal, and environment factors.<sup>1-4</sup>

Studies linking Vitamin D deficiency with immunology in SLE were generally conducted in animals and concluded that taking vitamin D decreased SLE symptoms and increased survival rate after.<sup>9, 13-21</sup> Studies in SLE patients had shown that there were lower concentration of vitamin D in patients compared with control group.<sup>22-27</sup> Other studies implied low concentration of vitamin D was associated with severeness of disease activities.

Although the benefit effects of vitamin D for SLE patients has been known, the prevalence shows that vitamin D deficiency was mainly caused by the lack of sun exposure, long term steroid therapy, and low vitamin D consumption. Sun exposure is the main source of vitamin D activation and can provide 90% of the body's requirement of vitamin D, but it is also can worsen SLE so the patients are advised to avoid it.<sup>1-4</sup>

Furthermore, vitamin D receptor gene polymorphism found in different population could influence role of vitamin D in the immune system hence influencing SLE disease activities. Recently, studies regarding vitamin D and SLE have been conducted in four seasons' countries with most subjects being Caucasian, but no available data about the prevalence of vitamin D deficiency and SLE in tropical countries, particularly Indonesia. This study aimed to know the prevalence and associated factors of Vitamin D deficiency in SLE patients.

## METHODS

### Study Design and Patients

This was a cross-sectional study conducted in Cipto Mangunkusumo Hospital, Jakarta and Indonesian Lupus Foundation between May and June 2008. Samples were collected using consecutive method. The inclusion criteria were SLE patients diagnosed according to 1982 American College of Rheumatology Revised Criteria for SLE. Exclusion criteria were patients with chronic kidney disease and liver function disturbance, alcohol ingestion, any conditions related to fat malabsorption (pancreatitis, intestine resection, Crohn's disease), pregnancy, and breastfeeding. All patients were asked to give informed consent. To obtain necessary data, we performed complete anamnesis and questionnaires filling, physical examinations, and laboratory tests (complete blood count, serum creatinine, urinalysis, 24-hour quantitative urine protein, and 25(OH)D serum concentration).

### Analytical Statistics

Data obtained were processed electronically using SPSS 10.0 to produce frequency and contingency tables based on the purpose of study. Mean and standard deviation (SD) is used for quantitative data with normal deviation while median and range are used for data with abnormal deviation.

### Assessment

A total of 80 SLE patients were included in this study, characteristics of subjects were collected from questionnaires including gender, education, ethnic, participation in Indonesian Lupus Foundation, history of sunscreen usage, duration of sun exposure, steroid dosage per day, other immunosuppressive drugs, and vitamin D consumption. Disease activity were assessed in score based on MAX-SLEDAI.

Currently there is no agreement for the definition of Vitamin D deficiency. Most scientists define vitamin D deficiency as concentration of 25(OH)D < 20 ng/mL (50 nmol/L), relative insufficiencies as concentration of 25(OH)D ranging 21-29 ng/mL, and adequate levels of vitamin D as concentration of 25(OH)D  $\geq$ 30 ng/mL. Other opinions define vitamin D inadequacy as concentration of 25(OH)D < 30 ng/mL (75 nmol/L), vitamin D insufficiency as the concentration of 25(OH)D 10 - < 30 ng/mL (25 - < 75 nmol/L), and vitamin D deficiency as concentration of 25(OH)D < 10 ng/mL (25 nmol/L).<sup>12, 28</sup> This study defined adequate as concentration of 25(OH)D > 30 ng/mL (75 nmol/L) and inadequate as concentration of 25(OH)D < 30 ng/mL (75 nmol/L).

## RESULTS

Most subjects were women (96.3%) with a median age of 26 years old (range 17-56 years old). The median duration of illness was 28 months (range 0-216 months). Description of other data can be seen in the Table 1 and Table 2.

**Table 1** Characteristics of patients

Characteristic	N	%
<b>Gender</b>		
Male	3	3,8
Female	77	96,3
<b>Education</b>		
Elementary school	3	3,8
Junior high school	6	7,5
Senior high school	41	51,3
College	30	37,5
<b>Member of LFI</b>		
Yes	18	22,5
No	62	77,5
<b>Ethnicity</b>		
Java	57	71,3
Sumatera	21	26,4
Sulawesi	1	1,3
Kalimantan	1	1,3
<b>Protection Utilization History</b>		
Sunscreen	7	8,8
Umbrella	7	8,8
Hijab (hood)	22	27,5
Hat	4	5,0
$\geq$ 2 protectors	25	31,4
No protector	15	18,8
<b>Sunlight exposure sufficiency</b>		
Inadequate	29	36,3
Adequate	51	63,8
<b>Steroid therapy (dosage per day)</b>		
Prednisone 15 mg/day or more	36	45,0
Prednisone less than 15 mg/day	39	48,8
Without steroid	5	6,3
<b>Immunosuppressive therapy (exclude steroid)</b>		
Yes	36	45,0
No	44	55,0
<b>SLE Disease Activity (MEX-SLEDAI)</b>		
Score < 2 (inactive)	30	37,5
Score $\geq$ 2 (active)	50	62,5
<b>Vitamin D Intake (minimal 8 weeks)</b>		
No (<400 IU/day)	72	90
Yes ( $\geq$ 400 IU/day)	8	10
<b>Body Mass Index</b>		
Underweight	10	12,5
Normal	27	33,8
Overweight	16	20,0
Obese	27	33,8

**Table 2** Distribution of subjects characteristic based on mean, median, standard deviation, and range (minimal and maximal)

Characteristic	Mean	Median	Standard Deviation (SD)	Range	
				Minimal	Maximal
Age (years)*		26		17	56
BMI	23,40		4,62		
Duration of illness (months)*		28		0	216
Steroid dosage per day (mg)*		10		0	250
MEX-SLEDAI*		3,5		0	14
Vitamin D concentration (nmol/L)*		21,85		11,5	57,7

\* Abnormal distribution

### Prevalence of Vitamin D Deficiencies in SLE Patients

It was found that all subjects had vitamin D inadequacy, in which 33 subjects (41,2%) had vitamin D insufficiency and 27 subjects (58,8%) had vitamin D deficiency. The 25(OH)D median is 21,85nmol/L (range 11,5 – 57,7 nmol/L) (table 3).

**Table 3** Prevalence of vitamin D deficiency in SLE Patients

Vitamin D Concentration	Category	N	%
≥75 nmol/L	Adequate	0	0
25 - <75 nmol/L	Insufficient	33	41,2
<25 nmol/L	Deficient	47	58,8

### Factors Affecting Vitamin D Deficiencies in SLE Patients

Vitamin D deficiency occurred more frequently in subjects who used sunscreens compared with those who did not. Details of factors influencing vitamin d deficiency in SLE patients can be viewed in Table 4.

**Table 4** Factors affecting Vitamin D Deficiency in SLE Patients

Variable	Deficiency	Insufficiencies	
		N	%
Sunscreens	– Yes	40	61,5
	– No	7	46,7
Exposure to sunlight	– Inadequate	20	69
	– Adequate	27	52,9
Steroid therapy	– Prednisone 15 mg/day or more	23	63,9
	– Prednisone less than 15 mg/day or no steroid	24	54,5
SLE disease activity (MEX-SLEDAI)	– Active	33	66
	– Inactive	14	46,7
Vitamin D intake	– No	43	59,7
	– Yes	4	50
BMI	– Obese	17	63
	– Non Obese	30	56,6
	– Overweight	12	75
	– Underweight + normal	18	48,6

Further investigation shows the median of Vitamin D concentration were lower in patients who were obese, used sunscreens, had lower exposure to sunlight, had steroid therapy more than 15 mg per day, had an active SLE disease, and did not have vitamin D supplementation. For more details refer to Table 5.

**Table 5** The difference in vitamin D concentration median of factors that affect vitamin D deficiency in SLE patients

Factors that affect vitamin D deficiency in SLE patients	Vit D median and concentration range (nmol/L)	
Sunscreens	- Yes	21,1 (13,4-57,7)
	- No	28,4 (11,5-54,5)
Sunlight exposure sufficient	- Adequate	23,6 (15,7-57,,7)
	- Less	19,7 (11,5-54,5)
Steroid therapy	- Prednisone equivalent ≥15 mg/day	21,1 (11,5-57,7)
	- Prednisone equivalent <15 mg/day or no steroid	23,4 (13,4-54,5)
SLE disease activity (MEX-SLEDAI)	- Active	19,7 (11,5-54,8)
	- inactive	25,6 (13,4-57,7)
Vit D intake	- Yes	22,1 (14,6-54,8)
	- No	21,9 (11,5-57,7)
BMI group	- Obese	19,4 (15,4-54,4)
	- Non-obese	23,6 (11,5-57,7)

## DISCUSSIONS

There was an interesting finding in which most of the subjects had enough exposure to sunlight even though they knew that it may cause disease recurrence and should be avoided. They felt safe by using protections, such as sunscreen, umbrellas, hoods, hats, or others. This meant most patients understood the importance of avoiding sun exposure to prevent recurrence. This attitude may be supported by sufficient level of education. However, awareness towards the importance of vitamin D consumption was majorly low, which showed lack of knowledge regarding the significance of vitamin D intake in SLE, especially since they need to avoid a direct exposure to sunlight.

A study by Huisman et al<sup>26</sup> about vitamin D concentration in women with SLE and fibromyalgia suggested that most of them were suffering from vitamin D deficiency (25(OH)D < 50 nmol/L) with the average concentration of 25 (OH)D 46.5 nmol/L.<sup>26</sup> A study by Muller et al<sup>29</sup> which assessed vitamin D3 in patients with inflammation diseases (SLE, Rheumatoid Arthritis and Osteoarthritis), found that the 25(OH)D concentrations in SLE patients were significantly different compared with controls and RA patients, with the median 25(OH)D concentration of 13 ng/mL or 32.5 nmol/L.

Another study by Kamen et al<sup>30</sup> which measured the concentration of vitamin D in newly-diagnosed SLE patients found that most of them had 25(OH)D concentration of less than 30 ng/mL. Kamen et al<sup>30</sup> also analyzed the concentration of vitamin D in 200 SLE patients from various ethnicities and found that the concentrations of vitamin D in African-American and Hispanic races were statistically lower than those of Caucasians and Asians. The concentration of vitamin D in African-American race was 15.5 ng/mL  $\pm$  9.4 while the Caucasian race had 31.3 ng/mL  $\pm$  4.9.

A study by Irastorza et al<sup>28</sup> found that the prevalence of vitamin D deficiency was lower than this study, although most of the subjects suffered from vitamin D insufficiency (25(OH)D < 75 nmol/L). There were differences in their characteristics, such as younger age, shorter duration of disease, higher prednisone dosage, and lower vitamin D intake compared with Irastorza's study.

Sheng et al<sup>25</sup> found that the concentration of 25(OH)D was significantly lower than the control with mean concentration of 11.5 ng/mL (28.75 nmol/L)  $\pm$  1.5 ng/mL. This study also suggested no correlation found between 25(OH)D concentration and clinical parameters of SLE, disease activities, or steroid consumption. The subjects of this study were younger, had shorter disease duration, and lower steroid consumption. Regarding disease activity, this study was similar with Sheng's study.

The difference of vitamin D concentration between SLE patients in Indonesia and the ones in western countries may be related to their race in addition to inadequate intake of vitamin D. The correlation between race and vitamin D concentration was supported by Muller et al<sup>29</sup> who analyzed 25D concentrations in SLE patients from different ethnicities (African-American, Hispanic, Caucasian, and Asian). The study found that concentrations of 25D in African-American and Hispanic patients were significantly lower than those

of Caucasians and Asians. Huisman et al<sup>26</sup> found that SLE patients who had no vitamin D supplementation also had lower vitamin D concentration compared with the ones who did.

Further inspection of the factors affecting vitamin D deficiency using median concentration found lower concentration of vitamin D occurred in patients who were obese, used sunscreens, had lower exposure to sunlight, 15 mg/day or more prednisone therapy, active SLE disease, and no vitamin D supplementation.

Another thing that needs attention is the lack of research and definition of vitamin D deficiency, especially in Indonesian younger population. The 25 nmol/L parameter that was used in this study was based on a study on SLE patients in Spain.<sup>28</sup> The geographical condition that allowed a lot of exposure to sunlight or low consumption of vitamin D in Indonesia would affect the parameter in defining vitamin D deficiency.

In this study, we know that all SLE patients had vitamin D inadequacy, so they needed vitamin D. Sunlight exposure is the main source of vitamin D for the majority of people, but SLE patients have to avoid sunlight so they get vitamin D from various food sources such as fatty fish (salmon, sardines, mackerel, tuna), fortified cereal, fortified milk, eggs, and cheese.

## CONCLUSION

All SLE patients in this study suffered from vitamin D inadequacy and it happened more often in patients who were obese, used sunscreens, and had lower sunlight exposure, high dose steroid, active SLE, and no vitamin D supplementation.

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