International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 2 Issue 2 // February 2013 // PP.35-40

Vitamin D Serum Level And Disease Activity In Patients With Systemic Lupus Erythematosus

Kusworini Handono[1], Leny Puspitasari[2], Achmad Rudijanto[3], Singgih Wahono[2] and Handono Kalim[2]

[1]*Clinical Pathology Department,* [2]*Rheumato-Immunology Division Internal Medicine Department,*
[3] *Metabolic and Endocrinology Division Internal Medicine Department,*
Medical Faculty Brawijaya University / Saiful Anwar General Hospital Malang, Indonesia

ABSTRACT*: Vitamin D is reported to affect immune system and prevent autoimmunity. Studies showed the low serum level of vitamin D in autoimmune disease patients and its correlation with disease severity. The objective of our study was to determine vitamin D status in patients with SLE and the relationship with disease activity. Our subjects were 63 SLE patients (ACR 1997 criteria) from the Rheumato-Immunology Division, Dr Saiful Anwar Hospital, Malang and 20 healthy controls. Serum vitamin D (25(OH)D_3) level was assessed using ELISA method. SLE disease activity was measured by SLEDAI score. The correlation between vitamin D level and SLEDAI score was analysed with Spearman test .Our study showed that serum level of vitamin D in SLE patients was significantly lower than in healthy controls (20.1 $\pm$ 17.0 ng/mL vs 36.0 $\pm$ 5.7ng/ml ; p=0.000). Thirty eight SLE patients (60.3%) had vitamin D levels <20 ng/mL, fifteen patients (23.8%) had vitamin D levels 20-30 ng/mL and ten patients (15.9%) had normovitamin D level. The level of vitamin D was negatively correlated with SLEDAI score (r = -.659, p = 0.000). Our conclusion was the low level of vitamin D in our SLE patients correlated with increasing disease activity.*

Keywords*: SLE, vitamin D, SLEDAI*

I. INTRODUCTION

Vitamin D is a secosteroid mainly synthesized in the skin from exposure to sunlight [1]. The classic function of vitamin D is to regulate calcium homeostasis and bone formation or resorbtion. Non-classic function of vitamin D is known to involve in the immune system. It is noted since the identification of vitamin D receptor in peripheral lymphocytes, macrophage, and thymus tissue [2, 3], and expression of 1α-OHase in variety of normal human tissue [4]. Many studies have shown that vitamin D has an important role in regulating immune response especially related with T cells [2] and B cell homeostasis [5,6]. Low level of vitamin D is reported to be associated with various autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis and type I diabetes mellitus [7-9], and appears to be critical for autoimmune disease susceptibility and severity [10, 11].

Serum level of vitamin D in SLE patients is reported lower than the normal population [6, 8, 11-14]. This is mainly due to the long-term use of sunscreen by patients with SLE because of photosensitivity, corticosteroid therapy, and lack of dietary intake [6, 15]. It is also reported that SLE patients produce anti-vitamin D antibodies [16]. The low level of vitamin D causes impaired immunological response that is thought to increase disease activity in SLE [13]. The objective of our study was to determine vitamin D status and the relationship between vitamin D level in SLE patients with the disease activity.

II. RESEARCH METHODS

2.1 Subject and study design

The subjects of our study were 63 SLE patients diagnosed based on the criteria of the American College of Rheumatology (ACR) 1997 [17, 18], recruited from the Rheumato-Immunology Division Internal Medicine Department, General Hospital of Dr. Saiful Anwar Malang, Indonesia. The study was performed during the period of January 2011 until June 2011. All of the patients did not consume vitamin D for three weeks or longer. In addition, 20 healthy people matched age were recruited as controls. The study was approved by the ethics committee of Brawijaya University School of Medicine/ Dr Saiful Anwar Hospital Malang, Indonesia and informed consent was obtained from all participants.

All patients underwent baseline investigation for hematologic and biochemical laboratory parameters, urine analysis, chest radiograph and electrocardiogram (ECG). Immunological parameter measurement included

anti-dsDNA antobody and C3 levels. SLE disease activity was measured using SLEDAI score, consist of 24 items with total score 0 – 105 [19, 20]. Vitamin D ($25(OH)D_{3)}$ level was assased using Enzyme Immuno Sorbent Assay in accordance with the manufacturer's instruction (DiaSorin Inc., Stillwater, MN, USA). Vitamin D insufficiency defined as a level 20-30 ng/ml, vitamin D deficiency as level <20 ng/ml, whereas normo vitamin D as level > 30ng/ml [21, 22].

2.2 Statistical analysis

Correlation between SLEDAI score and vitamin D level was analyzed by Spearman correlation test. Statistical significance was defined as p-value <0.05. Collected data was analyzed with SPSS 16.0 FOR WINDOWS RELEASE version.

III. RESULT

3.1 Patients characteristics

There were no significant differences in age and body mass index (BMI) between groups. The mean age of SLE patients was 31.2 ± 11.2 years, and the healthy subjects was 34.6 ± 4.7 years. A total of 60 patients (95.2%) were women, with the duration of illness was 26.1 ± 25.5 months. Fifty nine patients (93.7%) were of ethnic Javanese. All of SLE patients had received therapy with steroids. Thirty three patients (52.4%) had treatment combination with immunosuppresant such as chloroquine, azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide (table 1).

Table I: Characteristics of SLE patients and healthy controls

Characteristics	***SLE patients N = 63***	***Healthy Control N = 20***
Age (year) (mean± SD)	**31.2 ± 11.2 (14-60)**	**34.6 ± 4.7**
Female (%)	**95.2%**	**100%**
BMI (kg/m^2) (mean±SD)	**20.9 ± 3.74 (12.5 – 31.1)**	**22.3 ± 2.56 (14.6 – 24.1)**
Underweight (%)	**19.0%**	**10%**
Duration of illness (months) (mean±SD)	**26.1 ± 25.5 (0 -102)**	-
SLEDAI score (mean±SD)	**14.4 ± 7.97 (2 -45)**	-
Treatment		
• **Without Immunosuppressant**	**(47.6%)**	-
• **Chloroquin**	**(12.7%)**	-
• **Azathioprin**	**(11.1%)**	-
• **Methotrexate**	**(7.9%)**	-
• **Mycophenolate mofetil**	**(12.7%)**	-
• **Cyclophosphamid**	**(7.9%)**	-

The common clinical manifestations of our patients were anemia (71.4%), nephritis (49.2%), mucosal ulcer (31.7%), and serositis (14.3%) (table 2). The result of hematological and biochemical laboratory measurement are shown in table 3. Mean level of hemoglobin of our SLE patient was 10.96 ± 1.99 g/dl, and 71.4 % had anemia. Mean level of erythrocyte sedimentation rate was 61.6 ± 33.5 mm/h, and other result of hematological and biochemical paremeters showed as normal level.

Table II: Clinical manifestation of SLE patients

Clinical manifestation	***n = 63 (%)***
Anemia	**45 (71.4%)**
Nephritis	**31 (49,2%)**
Skin Rash	**28 (44.4%)**
Mucosal Ulcer	**20 (31,7%)**
Arthritis	**16 (25,4%)**
Serositis	**9 (14,3%)**
Vasculitis	**6 (9,6%)**
Neuro-psychiatric Lupus	**2 (3,2%)**

Table III: Laboratory characteristics of SLE patients

	Mean ± SD (range)	*Abnormal N (%)*
Hemoglobin (gr/dl)	**10,96 ± 1,99 (5.2 – 15.3)**	**45 (71,4)**
ESR (mm/h)	**61,6 ± 33,5 (13-138)**	**61 (96,8)**
Ureum (mg/dl)	**52,93 ± 7,89 (10.4-473)**	**20 (31,7)**
Creatine (mg/dl)	**0,97 ± 1,64 (0.3-12.35)**	**10 (15,9)**
AST (mg/dl)	**34,25 ± 31,6 (11-197)**	**16 (25,4)**
ALT (mg/dl)	**36,25 ± 34,8 (5-197)**	**19 (30,2)**
CPK (mg/dl)	**94,6 ± 223,8 (13-1585)**	**2 (3,2)**

ESR = erythrocyte sedimentation rate. ALT = alanine amino transferase. AST = aspartat amino tranferase. CPK = creatin phosphokinase

3.2 Vitamin D level in study groups

Mean level of vitamin D in SLE patients was 20.1 ± 17.0 ng/ml and healthy control was 36.9 ± 5.3 ng/ml. There was a significant difference between the level of vitamin D in SLE patients and healthy control (p=0.000). Vitamin D insufficiency in SLE patients was found in 15 patients (23.8%) and defficiency in 38 patients (60.3%). Only 10 SLE patients had normo vitamin D level. In healthy control, vitamin D deficiency was found in 1 (6.7%) person (figure 1).

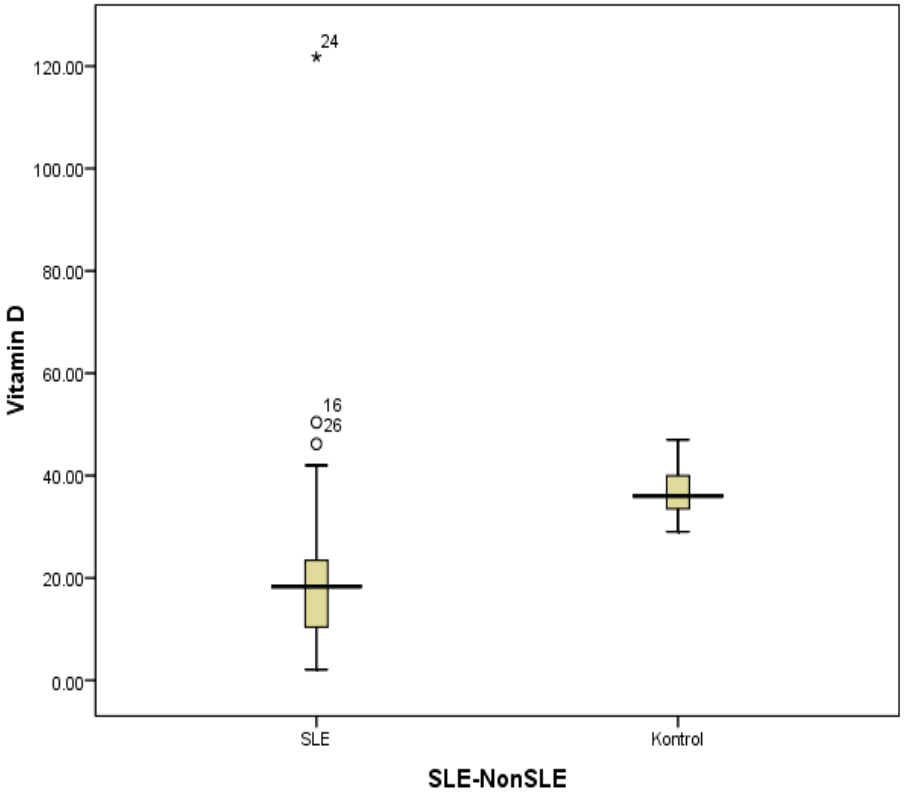

Figure 1: Serum vitamin D level in SLE and healthy control. P value determined by students T test (p= 0.000).

3.3 Vitamin D (25(OH)D_3) level and correlation with disease activity

Mean SLEDAI score among sixty three SLE patients in this study was 14,14 ± 7,97. There was negatively correlation between serum levels of vitamin D with SLEDAI score (r=-0.659; p=0.000) (figure 2).

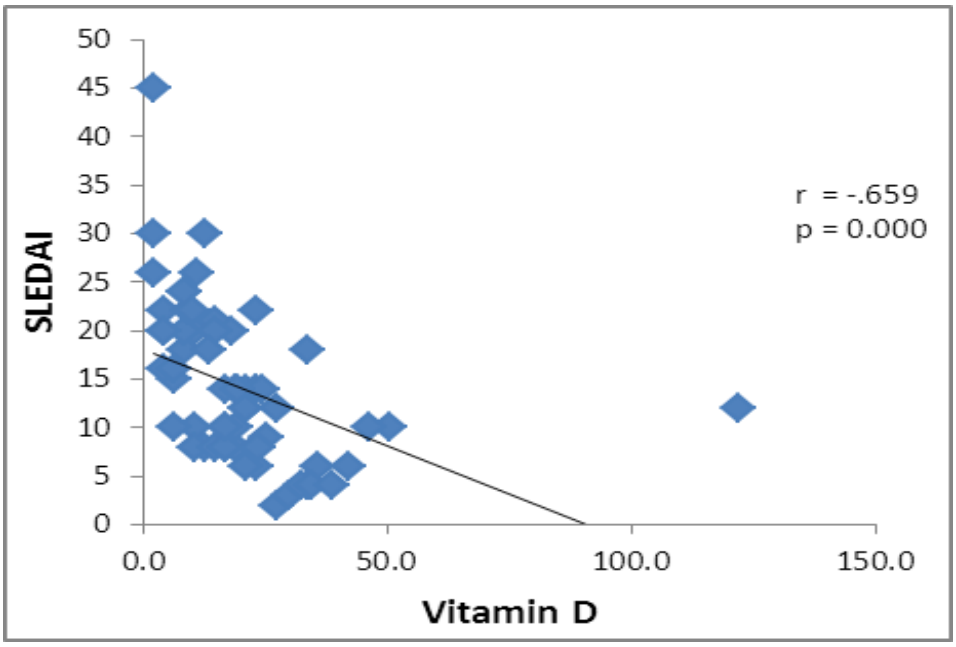

Figure 2: Correlation of vitamin D and SLEDAI

IV. DISCUSSION

This was an observational study of vitamin D level in Indonesian SLE patients. This study was conducted in a tropical-climate country with nearly year-round excessive sun exposure, that is sufficient for vitamin D synthesis [23]. However, our study showed that the average vitamin D level in our SLE patients was below normal (20.1 $\pm$ 17.0 ng/ml), and significantly lower in comparison to the healthy control. Our result confirmed those of Kim et al. [24], who also found significant lower vitamin D level of SLE patient in comparison to the healthy control.

The overall prevalence of hypovitamin D in SLE patients in this study was 84.1%, with 60.3% patients had vitamin D deficiency, significantly higher in comparison to the prevalence of low vitamin D level in healthy control (6.7%). This finding showed that low vitamin D level was frequent in SLE patients, and indicated that SLE patients had higher risk of insufficient vitamin D. The high prevalence of SLE patients who have vitamin D level below normal was similar with other studies, with percentages between 50-75%, however those studies were performed in different latitude and ethnicity [14, 24, 25-27]. Low concentration of vitamin D in SLE patients is not surprising mainly because SLE patients often have risk factor of low vitamin D level such as the use of long-term sunscreen, lack of dietary intake, [6, 15] and the use of full covered clothing [23, 27]. SLE patients tend to avoid the sun because of photosensitive rashes and potential of disease flare [28]. It is also known that the SLE patients produce antibodies anti-vitamin D [16]. In this study we did not perform evaluation of dress type, duration of sun exposure, the use of sunscreen, serum anti- vitamin D antibody and dietary intake in patients.

Our study demonstrated also that serum vitamin D was negatively correlated with disease activity measured by SLEDAI. This finding was similar with a recent study in China that involved 290 SLE patients which also showed a reciprocal relationship between vitamin D level and SLEDAI score, independent of age, sex, disease duration, and the use of vitamin D supplement and immunosupresive agent [29]. Other large multi-centered study conducted in Europe and Middle East involving 378 SLE patients [30] and a study in Brazil involving 36 SLE patients [12] also found similar correlation. These similarities were found in many SLE patients in different places and different ethnicity, which supported the fact that vitamin D is important for disease severity in SLE patients. This observational finding supported the fact that low vitamin D level was important as a risk factor for severe disease activity in SLE patients. This finding also supported the hypothesis that vitamin D deficiency might represent a new possible risk factor for the progression of autoimmunity in to well defined autoimmune diseases [11].

However, some other studies failed to show this correlation. A study performed by Sung in Korea showed that vitamin D did not correlate with disease activity, but this may be caused by SLE patients in this study were relatively well controlled [24]. Other study that compared SLE patients with active disease and less active disease conducted by Reynolds showed that patients with active disease had significant lower vitamin D level [31]. This result suggest that the association between vitamin D level and disease activity is strongest in patient with more active disease.

Moreover, our study did not find significant difference of serum vitamin D level between patients taking antimalaria drug and those who were not. This finding may be caused by the vitamin D level measured in this study was $25(OH)D_3$ which not yet converted to $1,25(OH)_2D$. Other immunosuppressant treatment also showed no significant different (data not shown). This study showed that immunosuppressant drug did not influence vitamin D level, consistent with other study.

Low vitamin D level was found as strong predictor of cutaneous lupus [32]. Vitamin D deficiency is also associated with higher degree of fatigue [33], and vascular stiffness [31]. This finding showed that eventhough in several studies vitamin D level did not directly correlate with disease activity but vitamin D affected other systems in SLE patients. Among these clinical manifestations, the presence of renal disorder in SLE is one of the most consistent clinical manifestation that had significantly lower vitamin D level than those without renal manifestation.

Vitamin D is an important factor in SLE patients, not only related with disease activity, but also with specific clinical manifestation and cardiovascular risk factor as lipid and aortic stiffness. Vitamin D is also important in bone metabolism. Eventhough many experts have recommended additional vitamin D to overcome vitamin D deficiency in SLE patients [29], the effect of vitamin D suplementation is still not yet established. Further interventional studies to determine the therapeutic value of vitamin D are still needed.

V. CONCLUSION

SLE patients have been proven to have several risks of vitamin D deficiency, thus vitamin D deficiency has been frequently found in SLE studies. Our SLE patients had lower vitamin D level in comparison to the healthy cotrol. Low level of vitamin D was negatively correlated with disease activity.

ACKNOWLEDGEMENTS

The Government of the Republic of Indonesia c/q Ministry of National Education, Research Development Unit Faculty of Medicine, Brawijaya University for funding this research.

Conflict of Interests

No conflict of interest has been declared by the authors

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