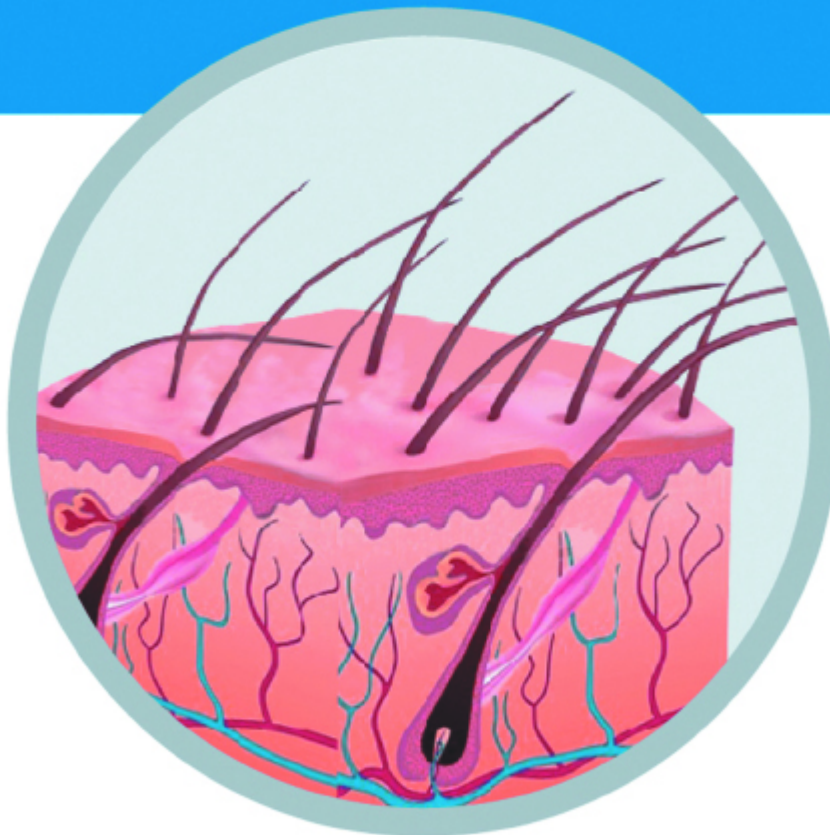


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# Berkala Ilmu Kesehatan Kulit dan Kelamin



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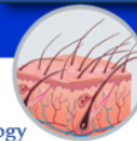
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# The Analysis of Serum Vitamin D (25[OH]D) Level in Psoriasis Patients Comparing with Control Subjects

Ade Fernandes, Muhammad Yulianto Listiawan, Evy Ervianti, Trisniartami Setyaningrum

Department of Dermatology and venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Teaching Hospital Surabaya, Indonesia

## ABSTRACT

**Background:** Vitamin D has been shown to have an immunomodulatory effect, and previous studies have proven that vitamin D deficiency contributed to several autoimmune diseases, including psoriasis. **Purpose:** The purpose of this study was to determine serum vitamin D levels in psoriasis vulgaris patients and compare them with control subjects. **Methods:** The research samples were sixteen adults with psoriasis vulgaris and 16 control subjects. Blood samples were taken, and the serum 25 (OH) D levels were measured using the Chemiluminescent Microparticle Immunoassay method. **Result:** The mean serum vitamin D in psoriasis vulgaris patients and controls were  $14.36 \pm 6.36$  and  $19.92 \pm 7.59$  ng/mL, respectively. No psoriasis vulgaris were observed in patients with normal 25(OH)D levels, and only 3 control subjects with normal serum 25(OH)D levels. These results were not statistically significant ( $p = 0.09$ ). **Conclusion:** Most patients with psoriasis vulgaris were observed having vitamin D deficiency. However, the prevalence of vitamin D deficiency in the control subjects was high as well. Therefore, there were no differences in serum 25(OH)D levels between psoriasis vulgaris and control patients.

**Keywords:** psoriasis, vitamin D serum, vitamin D deficiency.

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## BACKGROUND

Psoriasis is a chronic inflammatory skin disease with a strong genetic basis, characterized by complex changes from the proliferation of the epidermis, immune system, and blood vessels. Psoriasis lesions are characterized by epidermal keratinocyte hyperproliferation associated with inflammatory cell infiltration in the dermis and epidermis. Characteristics of the lesion in the form of erythematous plaques with a clear border covered by squama and plaque can be localized or widespread. Histologically, there are hyperkeratosis, parakeratosis, acanthosis, winding blood vessels, dilated capillaries in the papillary dermis, and inflammation that occur with the presence of a dominant lymphocyte infiltration.<sup>1,2,3</sup>

Psoriasis is a condition that is associated with inflammation, and is chronic and relapsing with a prevalence in the world population between 1 – 4%.<sup>4</sup> Psoriasis vulgaris is the most common form, which ranges from 85 – 90% of all cases. The highest prevalence of psoriasis in the world ever was 11.8%, which was reported in Kazakhstan.<sup>5</sup> In the US and Canada, the prevalence is reported at 4.6% and 4.7%, respectively. Prevalence is lower in several countries in Africa and Norway, which ranges from 0.4% to 0.7%. Meanwhile, in several Asian countries such as Japan, Taiwan, Malaysia, Kuwait, Saudi Arabia, and China,

psoriasis vulgaris have been reported with low prevalence ranging from 0.05% to 5.5%.<sup>2</sup> The frequency of visits of new psoriasis patients to hospitals in Indonesia varies between 0.21% to 2.3%.<sup>6</sup> Medical records of Haji Adam Malik General Hospital Medan in 2011 showed that 0.81% out of 5,644 patients from the Dermatology and Venereology outpatient clinic were diagnosed with psoriasis vulgaris.<sup>7</sup> Data from Dermatology and Venereology outpatient clinic Dr. Hospital Soetomo Surabaya of 2013 showed that 0.46% of 5,454 new patients were diagnosed with psoriasis vulgaris.<sup>8</sup> In 2018, the Dermatology and Venereology outpatient clinic Dr. Hospital Soetomo Surabaya reported that the number of new cases of psoriasis vulgaris increased to 0.78% of 4,197 new patients.

There have been reports in the effects of vitamin D on the pathogenesis of several skin diseases. Significant differences between low levels of vitamin D and psoriasis have been systematically observed. The 25-hydroxyvitamin D (25[OH]D) compound acts as an immunomodulator in both the innate immune system and the adaptive immune system. This changes the gene expression, which affects cellular function, such as proliferation, differentiation, apoptosis, and angiogenesis. In addition, improvement of T cell receptors induces T cell proliferation that will cause

regulatory T cells (Treg) formation, differentiation of monocytes into macrophages, regulate macrophage responses, and prevent macrophages from releasing inflammatory cytokines.

Deficiency of 25(OH)D can contribute to the pathogenesis of psoriasis through decreased antiproliferative, anti-inflammatory, and antiangiogenic activity. In consideration of its role in the proliferation and maturation of keratinocytes, vitamin D has become an important local therapy in the treatment of psoriasis. However, there has been no adequate evidence to support vitamin D intake through diet and supplement for the treatment of psoriasis.<sup>9,10</sup>

Recent studies have shown that vitamin D deficiency is a common condition in psoriasis patients. Research conducted by Bergler and colleagues in 2016 in Poland showed that there were statistically significant differences in serum vitamin D levels between psoriasis patients and control subjects.<sup>11,12</sup> Gisondi and colleagues in 2012 found that 81% of psoriasis patients in winter Italy have serum levels of vitamin D (25[OH]D) <20 ng/mL, compared to 30% of healthy people as controls. They also found that vitamin D deficiency was associated with psoriasis independently based on age, sex, and body mass index (BMI).<sup>13</sup> It was in contrast to the study of Romani and colleagues in 2012 in Spain, which concluded that low levels of vitamin D (25[OH]D) serum, that is <20 ng/mL, often occurs in psoriasis patients and also in control subjects. Moreover, the study found the control subjects had lower serum vitamin D (25[OH]D) levels compared to the psoriasis patients.<sup>14</sup>

The discoveries of several previous studies encourage the researchers to conduct further study on this subject in Dr. Soetomo General Hospital, determining the differences of serum vitamin D levels between psoriasis vulgaris patients and control subjects. This study is also expected to contribute both academically and practically in the management of psoriasis, particularly on the possible use of vitamin D intake for such treatment.

## METHODS

This was an observational cross-sectional study, and it aimed to determine the difference between serum vitamin D (25[OH]D) levels in psoriasis vulgaris patients and control subjects. This study involved 16 psoriasis patients and 16 control subjects who have met the acceptance and rejection criteria. Psoriasis vulgaris patients were adults, both new and old patients, 18 – 70 years old, have been diagnosed clinically and histologically, have not received or have received topical or systemic therapy, having results of liver and kidney function examinations within normal limits,

willing to take part in the research, and have signed the informed consent. The control group consisted of healthy subjects with the closest matching characteristics of the study sample per their age, sex, and indoor or outdoor occupation. The rejection criteria were study subjects who took vitamin D supplements or received topical vitamin D analog therapy in the past month, took drugs that affect vitamin D such as systemic corticosteroids, bisphosphonates, or calcium supplementation in the past 1 month, received phototherapy therapy, have a history of atopy, have a history of bone fractures, or hyperthyroidism.

The study began with examinations of patients who visited Dr. Soetomo Surabaya. History taking, clinical, and histopathological examinations were performed to diagnose psoriasis vulgaris. Interested and eligible patients were then being explained about the current research and its implication in the medical field and scientific development. Once the patient signed the written consent, the researcher began to check the kidney and liver function of the patient. Should the result be within normal limits, the patient underwent the next examination on serum vitamin D (25[OH]D) levels. Vitamin D (25[OH]D) serum levels of the patients were examined using the Chemiluminescent Microparticle Immunoassay (CMIA) method with reagents from the Architect at Prodia Clinical Laboratory, Surabaya. The normal value of vitamin D in the blood ranges from 30-100 ng/mL, vitamin D deficiency is <20 ng/mL, and vitamin D insufficiency is 20-29.9 ng/mL. The ethics committee of RSUD Dr. Soetomo Surabaya approved this study.

## RESULT

This study involved 32 research subjects who have met the criteria of acceptance and rejection. Sixteen patients were clinically and histopathologically diagnosed with psoriasis vulgaris, and sixteen control subjects were selected in consideration of the characteristics of research subjects. The criteria were age, sex, and indoor or outdoor occupation. The sampling technique was a consecutive sampling method. All study samples that met the requirements and were willing to participate in the study were asked to sign information for consent, informed consent, and medical action approval sheets. Each subject was recorded, and blood samples were taken for measurement of 25(OH)D serum levels.

Demographic data of research subjects from each group are presented in Table 1. The data show that this study involved more male than female subjects, but the sex data of the psoriasis vulgaris group and the control subjects were homogeneous ( $p = 1.000$ ). The subjects

were aged >21 years old, with the youngest being 24 years old and the oldest 62 years old. The mean age of the two study groups was 46.06±12.00 years old. The age group between the psoriasis vulgaris group did not differ from the control group with a p-value = 0.954.

The most Fitzpatrick skin type found was type IV, with 59.37%. The statistical test obtained p-value = 0.719, and there was no difference in Fitzpatrick skin type between the psoriasis vulgaris and the control group. The highest formal education level was high school with 59.37% and 56.25% of the research

subjects reside in Surabaya. Most research subjects having indoor occupation, which was 87.5, and 65.63% of research subjects earn below the regional minimum wage. The assessment of sunlight protection was scored, and each item adds one score. The items were covered clothing, umbrellas, hats/headscarves, and sunscreen. This study found that 46.87% of the research subjects obtained 3 scores (3 protectors). There was no difference in the protection score between the psoriasis vulgaris and control groups with a value of p = 0.057.

**Table 1.** Demographic data of research subjects of psoriasis patients and control

Variable	Patients (n = 16)	Controls (n = 16)	Total (n = 32)	P
Sex				1.000
Male	9 (56.25)	9 (56.25)	18 (56.25)	
Female	7 (43.75)	7 (43.75)	14 (43.75)	
Age (Years)	46.18±12.36	45.93±12.03	46.06±12.00	0.954
Fitzpatrick Skin				0.719
Type IV	9 (56.25)	10 (62.5)	19 (59.37)	
Type V	7 (43.75)	6 (37.5)	13 (40.63)	
Formal Education				0.943
Primary School Graduate	4 (25)	4 (25)	8 (25)	
Middle School Graduate	1 (6.25)	1 (12.5)	2 (6.25)	
High School Graduate	10 (62.5)	9 (50)	19 (59.37)	
Bachelor Degree	1 (6.25)	2 (12.5)	3 (9.38)	
Residency				0.033
Surabaya	6 (37.5)	12 (75)	18 (56.25)	
Non- Surabaya	10 (62.5)	4 (25)	14 (43.75)	
Occupation				1.000
Indoor Work	14 (87.5)	14 (87.5)	28 (87.5)	
Outdoor Work	2 (12.5)	2 (12.5)	4 (12.5)	
Income				0.264
Below minimum wage	12 (75)	9 (56.25)	21 (65.63)	
Above minimum wage	4 (25)	7 (43.75)	11 (34.37)	
Protection from sunlight				0.057
1 Protection	0	4 (25)	4 (12.5)	
2 Protections	6 (37.5)	7 (43.75)	13 (40.63)	
3 Protections	10 (62.5)	5 (31.25)	15 (46.87)	

Table 2 shows the average age of onset of psoriasis vulgaris at 35.31 ± 15.19 years old. In this study, the proportion of patients with psoriasis vulgaris was almost the same in all groups. The data shows that psoriasis vulgaris patients have been ill for <5 years, 5 – 10 years, and > 10 years, 31.25%, 37.5%, and 31.25%, respectively. Joint involvement in psoriasis vulgaris patients in this study was observed in 56.25% of patients, whereas nail involvement was observed in 25% of patients.

A family history of psoriasis vulgaris is only observed in 12.5% of patients. The severity was assessed using a Psoriasis Area and Severity Index

(PASI) score, and the result was that 62.5% of patients had a moderate-severe PASI score. The mean PASI score in psoriasis vulgaris patients was 11.79 ± 6.17. The use of systemic methotrexate therapy was found in 81.25% of patients, and topical corticosteroid therapy was found in all patients.

The results of the study are shown in Table 3. Deficiency of serum 25(OH)D levels was found in 81.5% in psoriasis patients, and none had serum 25(OH)D levels within normal limits. The control subjects in this study also showed a high prevalence of 25(OH)D serum deficiency, which was 68.75%, and only 18.75% of the control subjects had normal



25(OH)D serum value. The results of the Mann-Whitney U-test statistical test showed a statistically insignificant difference between serum 25(OH)D

levels of psoriasis vulgaris patients and control subjects with a p-value of 0.090.

**Table 2.** Distribution data of research subjects of psoriasis vulgaris

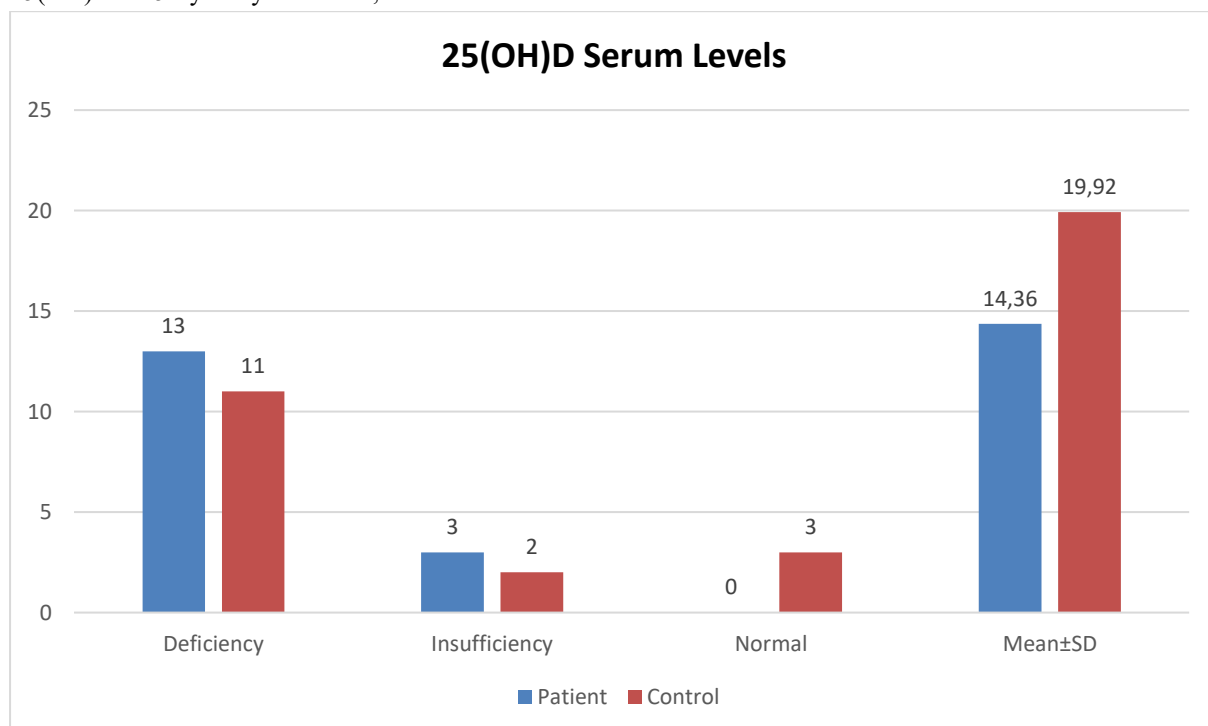
Variable	Patients (n = 16)
Age of Onset	35.31±15.19
Duration of Onset	<5 Years
	5 – 10 Years
	>10 Years
Joints Involvement	Yes
	No
Nail Involvement	Yes
	No
Family History of Psoriasis Vulgaris	Yes
	No
Severity	Mild (<10)
	Moderate – Severe (>10)
PASI Score	11.79±6.17
Methotrexate Systemic Therapy	Yes
	No
Topical Steroid Therapy	Yes
	No

PASI = Psoriasis Area and Severity Index

**Table 3.** 25(OH)D Serum Levels in Psoriasis Vulgaris Patients and Control Subjects

Variable	n (32)	25(OH)D Serum Levels			Mean±SD	p
		Deficiency (< 20)	Insufficiency (20 – 29.9)	Normal (30 – 100)		
Patients	16	13(81.25)	3 (18.75)	0	14.36±6.36	0.090
Controls	16	11(68.75)	2 (12,5)	3(18.75)	19.92±7.59	

25(OH)D = 25-hydroxyvitamin D; SD = Standard deviation



**Picture 1.** 25(OH)D Serum Levels in Psoriasis Vulgaris Patients and Control Subjects

## DISCUSSIONS

The control subjects were purposively selected in consideration of the research samples' age, sex, and occupation. Each group consisted of 9 males (56.25%) and 7 females (43.75%). The age rate of the psoriasis vulgaris group was  $46.18 \pm 12.36$  years, while in the control group was  $45.93 \pm 12.03$  years. As much as 37.5% of the psoriasis vulgaris patients have been ill for 5 – 10 years with an average PASI score of  $11.79 \pm 6.17$ . Family histories of psoriasis vulgaris were only observed in 12.5% of patients. Research conducted by Han and colleagues in 2017 in Korea found that the prevalence of psoriasis increased at the age of 50 and decreased after the age of 60. There were more males than female psoriasis vulgaris patients with 56% and 44%, respectively.<sup>15</sup> Maleki and colleagues' research in 2016 in Iran found that the average duration of illness was  $10.37 \pm 9.87$  years, with an average PASI score of  $12.15 \pm 11.76$ , and 34% had a family history of psoriasis vulgaris.<sup>16</sup>

Epidemiological survey of psoriasis in Japan conducted by Ito and colleagues in 2017 found 9,290 cases of psoriasis from 2009 to 2012. As much as 67.6% were male patients, and 32.4% were females. The study also found that 18.6% of subjects had onset of disease of 30 – 39 years, 17% at the age of 60 – 69 years, and 15.5% at the age of 50 – 59 years. Various complications were also observed, including symptoms in joints (13.6%), nail involvement (25.7%), mucous membrane involvement (0.8%). For about 33.3% of psoriasis cases were treated with systemic therapy. The most used agents were cyclosporine (33.6%), followed by etretinate (19.5%), methotrexate (8.6%), and corticosteroids (6.4%). Phototherapy was used in 30.9% of cases. The topical therapies that were widely used in Japanese studies included topical corticosteroids in 89.7% of cases and vitamin D3 ointment in 78.0% of cases.<sup>17</sup> Different results were reported by Chang and colleagues in 2009 in Taiwan that 13.6 % of psoriasis vulgaris patients received systemic therapy included methotrexate (7.3%), retinoids (6.2%), and cyclosporine (1.2%). Topical steroids were used in 98.4% of cases, while vitamin D3 ointment was only used in 25.1% of cases.<sup>18</sup> These results indicate that, unlike in Japan, steroids are the main topical therapy in Taiwan. The study also showed joint involvement in 56.25% of the patients, and nail involvement in 25% of the patients. Methotrexate was prescribed in 81.25% of patients, and all patients received topical steroid therapy.

The mean of serum 25(OH)D levels was  $14.36 \pm 6.36$  ng/mL in psoriasis vulgaris patients and  $19.92 \pm 7.59$  ng/mL in controls. About 81.25% of the psoriasis vulgaris patients had vitamin D deficiency, comparing

of 68.75% in the control group. There was no significant difference in serum 25(OH)D levels between psoriasis vulgaris patients and control subjects with a p-value = 0.90. Research conducted by Filoni and colleagues in 2018 in Italy involving 170 psoriasis patients and 340 healthy people as controls found that levels of 25(OH)D serum in psoriasis patients was lower than the control subjects with a mean value of 21.8 ng/mL and 34.3 ng/mL (p = 0.0007) respectively. For about 45.8% of patients had vitamin D deficiency, and 38.9% of patients had vitamin D insufficiency.<sup>19</sup> There has been no definitive evidence in the correlation between psoriasis and vitamin D. Initial observations suggested that psoriasis patients had significantly lower vitamin D levels compared to the control subjects. Another study found the opposite. A cross-sectional study by Maleki and colleagues in 2016 conducted at the Dermatology Outpatient Clinic of University Hospital in Mashhad, Iran, involving 50 psoriasis vulgaris patients and 50 control subjects found that there was no significant difference in serum vitamin D levels between the two groups (p = 0.06). The mean of vitamin D levels was  $14.92 \pm 6.31$  ng/mL in psoriasis patients and  $12.52 \pm 4.54$  ng/mL in the control group. The prevalence of vitamin D deficiency was 84.0% in psoriasis patients and 93.0% in the control group. There was no statistical difference in vitamin D levels between the psoriasis patients and the control group (p = 0.21). However, it was found that females had higher vitamin D levels than males (p = 0.04).<sup>16</sup>

Similar research was conducted at the General Hospital dr. Cipto Mangunkusumo (RSCM) Indonesia from November 2016 to May 2017, comparing the difference of serum 25(OH)D levels in multiple sclerosis patients and healthy people. The study took place in Jakarta at 6° 12' south latitudes and 106° 48' east longitude.<sup>20</sup> The temperature ranged from 26 – 31°C, indicating that all healthy individuals should have sufficient UV exposure throughout the year to aid vitamin D production. There was no difference in vitamin D levels between the multiple sclerosis patients (p = 0.73) and there was a significant difference (p < 0.001) in the control group. Although it was not the optimal method for evaluating sun exposure, the same method was used in both groups.<sup>20</sup>

Vitamin D synthesis depends on the factors of UV index, including exposure time, blocking clouds, smoke, shadows, reflections from the nearest water, sand, or snow, latitude, altitude, and season. Individual factors, such as age, body mass index, clothes, and surface skin area.<sup>21,22,23</sup> All of the research subjects resided in Surabaya. Geographically, Indonesia is located at the equator, and Surabaya is at 7° 9' – 7° 21'

south latitude and 112° 36' – 112° 57' east longitude.<sup>24</sup> The geographical condition affects sun exposure. Thus, individuals who reside in Surabaya should have sufficient UV exposure to aid vitamin D3 throughout the year. More than 90% of vitamin D synthesis depends on UV exposure through skin synthesis. It was hypothesized that psoriasis patients had lower vitamin D levels than healthy people due to a series of factors. Low serum 25(OH)D levels can cause or be the consequence of psoriasis. Patients tend to cover the skin area with psoriasis, preventing sun exposure. If this lasts for years, it can prevent UV-aided vitamin D synthesis. Therefore, those who have long-standing psoriasis and have not undergone phototherapy are more susceptible to decreased serum vitamin D levels.<sup>19</sup>

A study involving 1,255 older adults showed that the amount of daily physical activity, both indoors and outdoors, was positively related to serum 25(OH)D levels. Several types of outdoor physical activities with high intensity, such as gardening and cycling, are associated with a higher 25(OH)D serums.<sup>25</sup> A study conducted by Filoni and colleagues in 2018 in Italy found that 18.2% of psoriasis patients worked indoors, while 88.5% of healthy people worked indoors. The study also showed that vitamin D deficiency occurred in indoor workers, even in locations with high UV radiation exposure.<sup>19</sup> Cargill and colleagues in 2013 found a weak correlation between the duration of outdoor work and the actual sun exposure. This study found that 87.5% of subjects in each group had an indoor occupation, which can be a contributing factor to vitamin D deficiency, even in areas with high UV radiation.<sup>26</sup> The relationship between sun exposure and level of vitamin D serum was limited as it was calculated using a self-reported questionnaire.

The temperature of Surabaya is around 33°C – 34°C with the ultraviolet index of 9-11; therefore, the ultraviolet light index is very strong. Outdoor activities also affect the UVB-aided vitamin D formation in the skin. A cross-sectional study involving Malaysia, Thailand, Indonesia, and Vietnam reported variations between serum 25(OH)D levels in relation to sun exposure. Subjects from Sarawak have an average amount of sun exposure of 6 hours/day. However, the serum 25(OH)D levels were higher among other Malaysian regions with more prolonged sun exposure. The central region of Vietnam showed much lower serum 25(OH)D levels with average sun exposure of 6.8 hours/day. However, the survey found no sun exposure information in Indonesia.<sup>27</sup>

There is no definitive recommendation for a sufficient duration of sun exposure. A report stated that 15 minutes of sun exposure throughout the body

increases vitamin D levels up to 20,000 IU, depending on skin pigmentation, geographical location, season, time, and skin area exposed to UVB. The body surface area needed for the adequate synthesis of 25(OH)D is not confidently known. However, the recommended body surface area needed to maintain an adequate level of 25(OH)D is >27%.<sup>25</sup>

A supplement is the most important factor in vitamin D intake. Several studies reported that people who regularly take vitamin D supplements had higher vitamin D levels.<sup>28</sup> Most nutritionists recommended vitamin D3 instead of vitamin D2 to treat and prevent vitamin D deficiency, as several studies have reported that it has a higher efficacy in increasing 25(OH)D serum concentration. Although there are significant variations between individuals due to differences in body weight, sun exposure, and calcium intake, it is thought that daily intake of 1000 IU vitamin D3 supplement can increase 25(OH)D levels by around 10-20 ng/mL. Several studies have looked at safety issues related to vitamin D supplementation doses. However, oral vitamin D intake up to 10,000 IU daily is not associated with any harmful effects as it is proportional to the maximum skin vitamin D production. In this regard, IOM and the European Food and Safety Authority (EFSA) recommends a daily intake of 4,000 IU vitamin D for adults, including pregnant and breastfeeding women. A general guide is 400 – 1,000 IU per day with or without calcium or in a multivitamin, 10,000 IU per week or 10 days, or 50,000 IU per month. To achieve a stable condition, after 2 – 3 months of vitamin D supplementation, repeated measurements of 25(OH)D serum levels are needed. Therefore, vitamin D supplementation should be considered for populations with high-risk vitamin D deficiency, such as psoriasis patients. There is no consistent and sufficient evidence for an extraskeletal effect of vitamin D to date. Therefore, the recommended vitamin D intake is based on a beneficial effect on bone health.<sup>1,9,11</sup>

This research concluded that there was no significant difference between serum 25(OH)D levels in psoriasis vulgaris patients and the control group. Although no significant differences were found, the 25(OH)D serum levels in psoriasis vulgaris patients were lower than the control group. The higher rate of 25(OH)D serum deficiency in groups can be influenced by several factors such as age, skin type, duration of sun exposure, outdoor time, and sun protection.

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