Dermatology Practical & Conceptual

Correlation Among Serum Calcidiol, Sun Index, and Vitamin D Intake in Individuals With Seborrheic Keratoses Living in Coastal Area

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ABSTRACT

Introduction: Seborrheic keratoses (SK) are benign epidermal tumors with high sun exposure as a major risk factor. Vitamin D deficiency is also thought to play a role in its pathogenesis. There has been no data regarding SK, calcidiol level, vitamin D intake, and sun index (SI) among people living in coastal areas in Indonesia.

Objectives: To assess the correlation between 1) serum calcidiol levels with SI and vitamin D intake and 2) lesion size with SI and serum calcidiol level among SK patients living in a coastal area.

Methods: This is a cross-sectional study. We performed interviews using the sun index questionnaire and semiquantitative food frequency questionnaire for vitamin D; physical examination; dermoscopy to determine the largest SK lesion size; and measurement of serum calcidiol levels in participants with SK living in Cilincing District, North Jakarta. Spearman correlation test was used to assess the relationship between variables.

Results: Thirty-nine participants with SK aged 19–59 years were analyzed. The median of the SK largest diameter, SI, serum calcidiol, and vitamin D intake was 2 (1–10) mm, 3.95 (1.1–23.52), 14.3 (5.25–35.30) ng/ml, and 4.3 (0.1–30.1) mcg/day, respectively. SI and vitamin D intake were not significantly correlated with calcidiol levels. Similarly, SI and calcidiol levels were not significantly correlated with the largest SK lesion size.

Conclusions: We found low calcidiol levels and vitamin D intake in this coastal population. The SI and vitamin D intake had no correlations with calcidiol levels. Furthermore, calcidiol levels and SI had no correlations with the lesion largest diameter.

Introduction

Seborrheic keratoses (SK) are benign epidermal tumors estimated to be present in 20% of adults, especially in the elderly [1,2]. Sun exposure was considered as the main risk factor for SK [1].[1] Genetics, mutations of specific genes, human papillomavirus infection, and vitamin D deficiency were also thought to play a role in the pathogenesis of SK [2,3]. Various studies pointed to the association between vitamin D deficiency and SK, especially gene mutation studies and the use of topical vitamin D analogs to treat SK lesions [4,5].

Vitamin D deficiency is fewer in Brazil and England populations living closer to the sea due to high sun exposure [6,7]. Indonesia is a tropical climate country with many coastal areas. Jakarta, as one of its cities, has a 12-hour duration of sun exposure with the highest average ultraviolet (UV) index of 10-12 [8]. Despite the exposure, vitamin D deficiency was common in various populations in Indonesia [9-11]. In addition to its endogenous synthesis with the aid of sun exposure, 10%–20% of vitamin D in the body is obtained from foods [12,13]. Low vitamin D intake is also a risk factor for vitamin D deficiency [11,14]. Indonesians have darker skin tones from light brown to dark brown (Fitzpatrick skin types 4 and 5).

Objectives

To our knowledge, data on serum calcidiol levels, sun index, and vitamin D intake among people with SK living in Indonesian coastal communities remains limited. Therefore, we aim to obtain baseline data regarding calcidiol level, sun exposure, and vitamin D intake among people with SK who live in coastal areas in Indonesia. Furthermore, we would explore the correlation between serum calcidiol levels with sun exposure and vitamin D intake among this population.

Methods

This cross-sectional study was conducted in the Cilincing district, North Jakarta, Indonesia on 10–12 November 2020. During the study, we implemented protocols for Coronavirus Disease 2019. We reported this study following the STROBE checklist for cross-sectional studies.

Subjects aged 18–59 years with SK lesions based on clinical examination and dermoscopy were enrolled consecutively in this study [15-17]. Impaired vitamin D absorption and metabolism were often found in geriatrics, so this age group was not included in this study [11]. Furthermore, through interview, we excluded subjects who took vitamin D supplements; received therapy for SK in the past month; had routine sunscreen use; had impaired renal or liver function; had a history of malabsorption diagnosis; were pregnant or breastfeeding during the recruitment period; or were grade II or morbid obesity according to the WHO Category for Asia-Pacific Region [18].

The primary outcome measure of this study was the correlation of serum calcidiol level with vitamin D intake and sun index. Furthermore, we would explore the correlation of the largest lesion size with calcidiol level and sun index. We recorded baseline characteristics such as age, sex, and occupation. We also collected basic anthropometric data, food intake, sun index, SK clinical characteristics, and serum calcidiol levels.

Anthropometric data was measured by using a digital scale and microtoise Trained nutritionists assessed macronutrient intake with the 24-hour food recall and vitamin D intake with a semiquantitative food frequency questionnaire (FFQ) under supervision of clinical nutrition specialist (N.R.M.M.). One researcher (I.A.) did the interview to measure sun exposure with the sun index questionnaire. The sun index (SI) is an index for objective sun exposure measurement by multiplying the fraction of body surface area (BSA) by the duration of exposure on weekdays and weekends/holidays [19]. Another researcher who was blinded to the sun index and vitamin D assessment recorded the physical and dermoscopic examination by using a standard camera. Two board-certified dermatolovenereologists (L.P.W. and L.S.S.) oversaw the examination. We measured the SK largest diameter, specified its region, and categorized the lesions based on whether they were sun-exposed or partially exposed. The sun-exposed area was defined as the neck and V-neck area, outer forearms, or back of hands, whereas the partially exposed area included the trunk, upper arms, flexor forearms, legs, and V-neck area. Serum calcidiol levels were measured by using LIAISON® analyzer (DiaSorin) and classified according to the Endocrine Society Classification [20].

Ethics Statement

This study was conducted following the Declaration of Helsinki and approved by the Health Research Ethics Committee Faculty of Medicine Universitas Indonesia (no. KET1003/UN2.F1/ETIK/PPM.00.02/2020). Written informed consent was obtained for all subjects before study enrollment.

Statistical Analysis

We calculated the minimum sample size to detect an r of 0.45 with an α error rate of 5% and 80% power to be 36 subjects. All data were analyzed using SPSS® IBM® ver.20 (IBM Corporation). Subjects with missing outcome data were dropped out from the final analysis. Data distribution was determined using the normality test.

Pearson or Spearman correlation test was performed to assess the correlation of serum calcidiol with the sun index and vitamin D intake. Furthermore, we also assess the correlation of the largest lesion size with the serum calcidiol and sun index. The correlation value was defined using the r correlation coefficient: 0.7–1.0 as a strong correlation, 0.3–0.69 as a moderate correlation, and 0–0.29 as a weak correlation. A P value less than 0.05 was considered statistically significant.

Results

Among 80 assessed for eligibility, 40 subjects were eligible and consecutively enrolled. The blood sample of one subject was lysed, so he was dropped out of the analysis. A total of 39 subjects were included in the final analysis (Figure 1). Most of the subjects were women. The median age was 40.5 (21–59) years. The median BMI was 25.7 (15.81–29.06) kg/m^2. More than half of the subjects were formal employees. The complete sociodemographic and clinical characteristics are described in Table 1.

Most patients (97.4%) had the largest lesion in the sun-exposed areas; only one subject had it on the trunk. There was a significant difference in the largest lesion diameter among age groups: 1 (1–3) mm at the 19–29 years, 2 (1–4) at the 30–39 years, 3 (1–10) mm at the 40–49 years, and 3 (1–7) mm at the 50–59 years group (P = 0.016). There was no significant difference in lesion diameter among subjects with low SI (<4) compared to high SI (>4) (2.00 [1–10] mm *versus* 2 [1–9] mm, P = 0.815). The mean size of lesions in the vitamin D deficient, insufficient, and normal groups was 2 (1–10) mm, 2 (1–9) mm, and 3 (1–5) mm, respectively (P = 0.995).

The mean number of calcidiol levels were similar across all age groups, with the absolute values in the 19-29, 30–39, 40–49, and 50–59 years of age were 14.83 (6.82), 17.33 (9.43), 17.40 (10.03), and 14.08 (4.05) ng/ml, respectively (P = 0.686). Most of the subjects (71.8%) had vitamin D deficiency. However, vitamin D deficiency was more commonly found among the older age group than the younger age group (80% versus 63.2%, P = 0.209). The serum calcidiol had an increasing trend according to the sun exposure duration increment. In the group with sun exposure <14 hours/week, 14-28 hours/week, and >28 hours/week, the serum calcidiol level was 11.3 [10.2–18.7], 14.3 [7.25–26.20], and 15.1 [5.25–35.30] ng/ml, respectively (P = 0.569) (Figure 2). The value of SI in the vitamin D deficient was lower compared than in the insufficient or normal group (3.82 [1.1 –17.64] versus 6.83 [2.21–23.52], P = 0.177) (Figure 3).

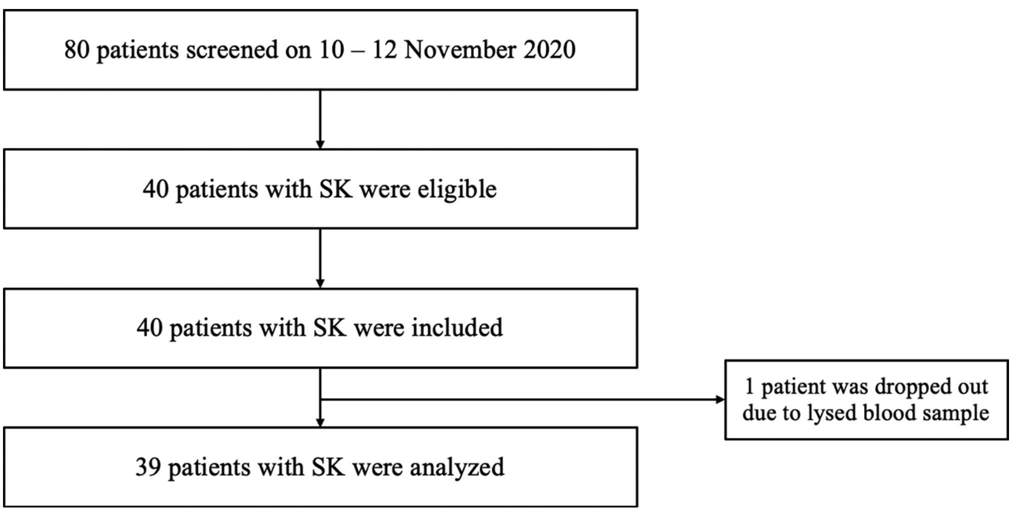

Figure 1. Patient flowchart.
SK = seborrheic keratoses.

Table 1. Sociodemographic and clinical characteristics

Variables	Values
Gender, N (%)	
Men	17 (43.6)
Women	22 (56.4)
Age (year), median (min-max)	40.5 (21–59)
19-29, N (%)	11 (28.2)
30-39, N (%)	8 (20.5)
40-49, N (%)	8 (20.5)
50-59, n (%)	12 (30.8)
BMI category, N (%)	
Underweight	2 (5.1)
Normal	7 (17.9)
Overweight	6 (15.4)
Grade 1 obesity	25 (61.5)
BMI (kg/m^2), median (min-max)	24.82 (3.59)
Occupation, N (%)	
Fishermen	2 (5.1)
Fishmongers	4 (10.3)
Laborers	1 (2.6)
Employees	22 (56.4)
Others (housewives, students, etc.)	10 (25.6)
Sun index	
Sun exposure per week (hour), median (min-max)	24.8 (5.25–84)
Fraction of BSA exposed to sunlight, median (min-max)	0.20 (0.05–0.45)
Sun index[a] median (min-max)	3.95 (1.1–23.52)
Seborrheic keratoses	
Largest lesion diameter (mm), median (min-max)	2 (1–10)
Region, N (%)	
Sun-exposed	38 (97.4)
Partially exposed	1 (2.6)
Calcidiol	
Calcidiol level (ng/ml), median (min-max)	14.3 (5.25–35.3)
Category[b] N (%)	
Deficient (<20 ng/ml)	28 (71.8)
Insufficient (20–29 ng/ml)	9 (23.1)
Normal (30–100 ng/ml)	2 (5.1)
Toxic (>100 ng/ml)	0 (0)

BMI = body mass index; BSA = body surface area.
[a]Hours of sun exposure per week × fraction of BSA exposed to sunlight
[b]According to Endocrine Society [37][37]

Table 2 describes the profile of energy, carbohydrate, fat, protein, and vitamin D intake among study participants. The vitamin D intake in the vitamin D deficient, insufficient, and normal group was 4.2 (0.10–30.10), 4.3 (2.0–28.80), and 15.55 (10.30–20.80) mcg/day (P = 0.226), respectively. Protein intake in subjects with insufficient and normal calcidiol levels was higher than in those with deficient calcidiol levels (54.25 [16.96] versus 48.28 [20.82], P = 0.234). The daily protein intake of subjects with deficient, insufficient, and normal calcidiol levels was 54.0 (12.10–89.0), 51.40 (26.0–76.0), and 67.25 (54.5–80.0) grams/day, respectively (P = 0.440).

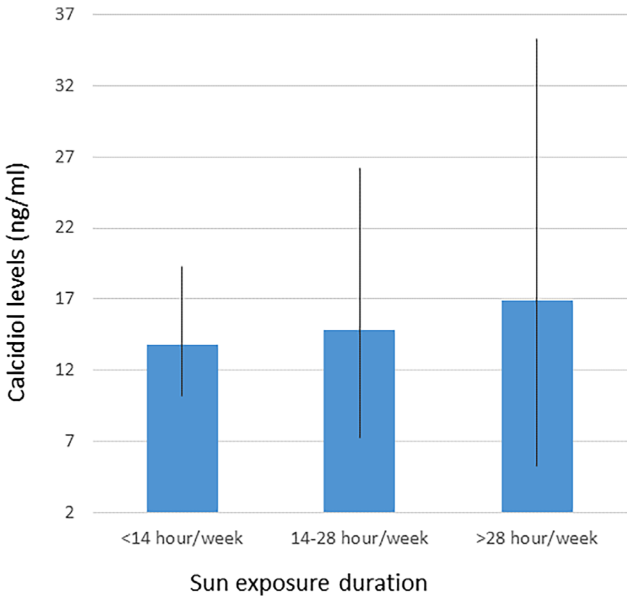

Figure 2. Serum calcidiol levels according to sun exposure duration group.

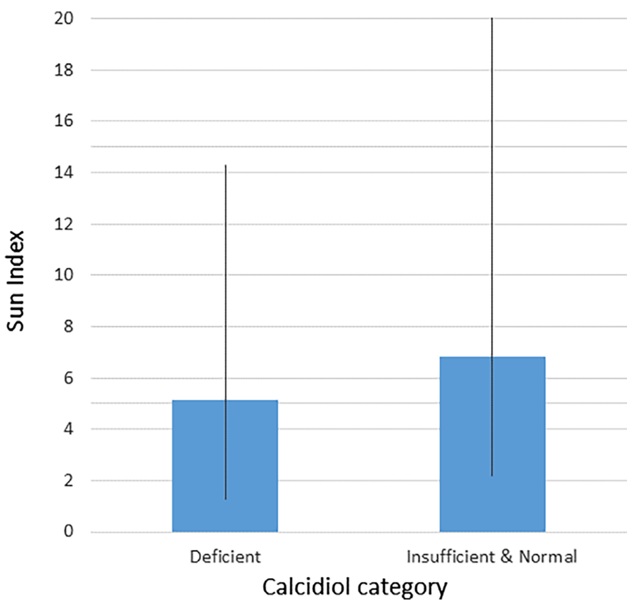

Figure 3. Sun index according to calcidiol category group.

Finally, we found that there was no significant correlation between the largest lesion diameter and SI (r = -0.057, P = 0.731) nor serum calcidiol (r = 0.108, P = 0.513). Exploratory analysis showed a weak negative correlation between lesion size and calcidiol level in the 19–39 years age group (r = -0.270, P = 0.250), and a significant positive correlation in the 40–59 years age group (r = 0.523, P = 0.018). There was also no significant correlation between calcidiol level and SI (r = 0.188, P = 0.253), vitamin D intake (r = 0.042, P = 0.801), or daily protein intake (r=0.113, p=0.495).

Table 2. **Profile of energy, carbohydrate, fat, protein, and vitamin D intake**

Variable	Value	Daily needs
Energy (kcal/day), median (min-max)	1189 (267–2357)	1800–2650 kcal/day[a]
Carbohydrate (%), mean (SD)	53.14 (11.11)	45–65%[b]
Fat (%), median (min-max)	31.57 (3.13–50.4)	20–30%[b]
Protein (grams/day), median (min-max)	54 (12.10–89)	60–65 grams/day[a]
Vitamin D (mcg/day), median (min-max)	4.3 (0.1–30.1)	15 mcg/day[a]
Vitamin D intake category, N (%)		
Deficient	34 (87.2)	
Sufficient	5 (12.8)	

SD = standard deviation.
[a]According to Indonesian Recommended Dietary Allowance 2019
[b]According to Indonesian Balanced Nutrition Guidelines

Conclusions

This study is among the first to describe the demographic and clinical characteristics of people living with SK in coastal areas of Indonesia and explore their SI, vitamin D intake, and serum calcidiol levels. Among this coastal population, we found no correlations between SI, calcidiol levels, and the size of the largest SK lesion. We also did not find any correlations between SI, vitamin D intake, and calcidiol levels.

Among our population, the median SI was greater than a similar study in Malaysia which found a median SI of 0.72 (0.26–1.28) in the urban population and 0.89 (0.42–1.83) in the rural population [20]. Nevertheless, despite the high SI, most of the subjects (71.8%) had vitamin D deficiency. This figure is within the reported prevalence of vitamin D deficiency in Southeast Asia, which ranges from 22%–87% [21-23]. We found that people with vitamin D deficiency were older and had higher BMIs. Older age is associated with decreased vitamin D metabolism due to decreased hepatic and kidney function [24], whereas in young age, vitamin D level is associated with higher vitamin D binding protein (DBP) levels, resulting in higher vitamin D levels [25]. Among overweight and obese individuals, vitamin D distribution into the fat tissue will reduce its total half-life and lower its serum level [26,27].

We originally hypothesized that lesion diameter would be associated with SI and calcidiol level. However, we found that there was no correlation between SI and SK largest diameter. The lesion size significantly increased along with the increment in age decades, as also found in the Korean population study. This finding might be caused by increased cumulative UV exposure in people with older age [28]. We also found no correlation between lesion diameter and calcidiol level. Vitamin D was found to play a role in the pathogenesis of SK in mice studies, including research on FGFR3, PIK3CA, and EGFR mutations. The topical administration of vitamin D analogs i.e. calcipotriol and tacalcitol, has been shown to reduce lesion size [29,30]. However, in the 19–39 years age group, there was a negative weak correlation between serum calcidiol level and the largest diameter, although this correlation was not significant. The opposite result was shown in individuals aged over 40 years, wherein we found a significant positive correlation between calcidiol levels and the largest diameter of SK. In this group, the higher the calcidiol, the larger the lesion size. We suspected that even though high sun exposure might cause higher calcidiol levels, it also increased the risk of SK, which was also a sign of photodamage.

We found that calcidiol level had no correlations with SI, even though the mean SI in subjects with insufficient and normal calcidiol was greater than in the deficient one. Moreover, there was an increment in calcidiol levels according to the increase in sun exposure duration. High sun exposure in the coastal community is among the many factors causing higher vitamin D levels in this community compared to the urban community. This finding is also similar to the study in England, which found that the average calcidiol levels of the population living closer to the coast were higher than in the people living within a radius of 40 km of the coastal area.[7] But still, the high sun exposure (median 24.8 [5.25–84]) hours per week) in the area with high UV index, did not prove to be adequate to increase calcidiol levels in this population. A study on a population of pregnant women in West Sumatra, Indonesia, also found that there was no relationship between outdoor activity and vitamin D deficiency, with an odds ratio of 0.986 (95% confidence interval: 0.972–1.001) [13].

There are also other factors affecting vitamin D production with the help of sunlight, including the amount of UV exposure, the use of sunscreen and protective clothing, and Fitzpatrick skin type [20]. Although food is not the primary source of vitamin D, the lack of vitamin D intake from food is one of several factors causing vitamin D deficiency in Indonesia [11,13]. The lack of vitamin D intake in subjects is caused by the lack of food containing vitamin D consumption, including fish, shrimp, crab, milk, and dairy products. In our study, the mean vitamin D intake in the deficient group was lower than in the insufficient and normal levels groups. However, we found no correlation between vitamin D intake and calcidiol levels. Calcidiol levels are influenced by metabolizing enzymes and the polymorphisms of DBP-regulating genes and vitamin D receptor genes, which were beyond the scope of this study [24,31]. The VDR polymorphisms were found in a group of healthy women with vitamin D deficiency and insufficiency in North Sumatra, Indonesia [32].

In addition, the median intake of daily energy, carbohydrates, and protein was below the nutrient requirement. Protein intake, as one of the main nutrients, is thought to play a role in vitamin D deficiency. DBP is a protein derivative that transports 85%–88% of vitamin D in the blood [25,33]. To our knowledge, there is no known research subjecting protein intake to DBP formation and the influence of protein intake on vitamin D deficiency. In this study, the median protein intake was below the Indonesian 2019 recommended daily allowance. Protein intake in subjects with insufficient and normal vitamin D levels was higher than in deficient ones, but no correlation was found between protein intake and calcidiol levels.

Our study has several limitations. Firstly, this study did not compare subjects with SK and without SK in the coastal area. We also did not include the calculation of lesion number to shorten the examination time during the COVID-19 pandemic. Furthermore, our study utilized a 24-hour food questionnaire, which might be prone to recall bias and flat-slope syndrome [34,36]. Flat-slope syndrome is the reduction in food intake reported by overweight individuals or the increase in food portions reported by underweight ones [37]. Further study with a larger sample size may be conducted to provide external validity for our result.

In conclusion, we found low levels of serum calcidiol and vitamin D intake among people with SK living in the coastal area of Indonesia. There were no correlations between SI, calcidiol levels, and the size of the largest SK lesion, as well as correlations between SI, vitamin D intake, and calcidiol levels in this coastal population.

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