Original Article

Correlation between Serum 25-Hydroxyvitamin-D levels and disease activity in chronic urticaria patients at a tertiary referral hospital in Jakarta, Indonesia

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Abstract

Background Great scientific interest has grown around the role of vitamin D in many chronic diseases, due to its reported immunomodulatory effects and its association with several autoimmune and allergic diseases, including chronic urticaria (CU). Previous studies have shown low serum 25-hydroxyvitamin D [25(OH)D] or calcidiol levels in CU patients, with clinical improvements after vitamin D supplementation. However, data on the correlation between levels of vitamin D in the serum and CU disease activity are still limited, especially in low-middle income tropical countries like Indonesia.

Objective We proposed to investigate the correlation between serum calcidiol levels and clinical disease activity in patients with CU.

Methods We performed an analytic-descriptive cross-sectional study. Disease activity in CU patients, measured using the Urticaria Activity Score 7 (UAS 7) questionnaire, and serum calcidiol levels were assessed in 30 patients aged 18-59 years with CU.

Results Mean UAS7 score was 14.6, median duration of illness was 12 months, and the median serum calcidiol level was 12.1 ng/mL. Most subjects (80%) were vitamin D deficient. We found no statistically significant correlations between serum calcidiol and CU disease activity (r=0.151; p=0.425). However, in subjects with severe vitamin D deficiency, a significant negative correlation was found (r=-0.916; p=0.001). Significant moderate correlation was also found between CU disease activity and illness duration (r=0.391; p=0.033).

Conclusion We found no correlations between serum calcidiol levels and CU activity, however there was a tendency of increased CU disease activity in vitamin D deficient patients.

Key words
Vitamin D, sunlight exposure, disease activity, UAS, chronic urticaria.

Introduction

Urticaria is a skin disorder characterized by cutaneous vascular reactions, which manifest as wheals and flares with or without a surrounding *halo.*[1-3] Urticaria is classified as acute if it resolves under 6 weeks and chronic if it persists over 6 weeks.[1,2] In chronic spontaneous urticaria (CSU), factors that trigger urticaria are often difficult to identify. In chronic inducible urticaria (CIndU), the patient has identifiable

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triggers that are consistent with recurrence of the disease.[1,2,4,5]

Chronic urticaria is the most common disease in 2019 at the Allergy and Immunology Division of the Dermatology and Venereology Outpatient Clinic, Dr. Cipto Mangunkusumo General Hospital, a tertiary referral hospital in Jakarta, Indonesia.[7] The course of chronic urticaria is generally unpredictable and can persist for a long time. Currently, assessing clinical disease activity, efficacy of treatment, quality of life (QoL) of patients, and level of disease control is only based on clinical investigations, including history, physical examination, and questionnaires, such as the validated Urticaria Activity Score 7 (UAS7), and/ or the Angioedema Activity Score (AAS), and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2OL).[1] Several studies reported the benefits of biomarkers to assess disease activity and duration, to monitor response to treatment, and to serve as predictors of disease progression. Potential biomarkers for chronic urticaria are D-dimer, CRP, MMP-9, MPV. Factor VII1, TNF, DHEA-S, and vitamin D.[8-11]

Vitamin D is postulated to have immunomodulatory effects to its influence on both the innate and adaptive arms of the immune system. In the skin, it binds to receptors in the nucleus and plasma membrane of epithelial cells and immune cells, including mast cells, macrophages, dendritic cells, monocytes, B cells, and T cells. Proliferation, function, and differentiation of mast cells are also reported to be influenced, which may explain it's role in allergic and autoimmune skin diseases, including chronic urticaria.[5] In clinical practice, the best indicator for a patient's vitamin D status is the measurement of circulating levels of 25-hydroxyvitamin D [25(OH)D] or calcidiol.

Several studies show significant decrease in calcidiol levels in chronic urticaria patients. Furthermore, significant negative correlation is found between serum calcidiol levels and chronic urticaria disease activity, indicating the association between low calcidiol levels and worse disease severity.[12-14] Oral supplementation of vitamin D was found to contribute to symptoms improvements in chronic urticaria patients with low serum calcidiol levels.[5] More than half of chronic urticaria cases have unidentified triggers, and the available treatment modalities often yield unsatisfactory results. Thus, other influencing factors of ethiopathogenesis need to be considered, including vitamin D levels, especially in Indonesia, where vitamin D deficiency is prevalent. In this current study, we investigated the relationship between serum calcidiol levels with disease activity in chronic urticaria patients in Indonesia.

Methods

We performed a descriptive-analytic cross-sectional study to analyze the correlation between serum calcidiol levels and disease activity in patients with chronic urticaria, from July to November 2020. The study's target population was chronic urticaria patients aged 18-59 years old at the Allergy-Immunology Division, Dermatovenereology Outpatient Clinic, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. Serum levels of calcidiol were measured at the Southeast Asian Ministers of Education Organization Regional Center for Food and Nutrition (SEAMEO RECFON) laboratory, Department of Nutrition, Faculty of Medicine, Universitas Indonesia. This study has passed ethical review by the Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia. Subjects were recruited using consecutive sampling, as well as informed consent.

Subjects who had signed informed consent forms were evaluated for inclusion and exclusion criteria and had anthropometric measurements (body weight, body height, and body mass index (BMI)) done. Subjects were interviewed using two questionnaires, the Urticaria Activity Score-7 (UAS7) to assess disease activity and the weekly sunlight exposure by Hanley to assess sun exposure.

The collected data was organized and analyzed using Microsoft Excel 2019 and SPSS Statistics 25. Data distribution was determined using the coefficient of variation. For data with normal distribution, mean and standard deviation were used. For data with abnormal distribution, median and minimum-maximum values were used. Spearman's test was used to analyze the correlation between serum calcidiol levels and chronic urticaria disease activity. Correlation was represented by r.

Results

Sociodemographic Characteristics: We recruited 30 subjects who fit our criteria of inclusion and exclusion.. Baseline sociodemographic characteristics of the subjects are shown in **Table 1**.

Clinical Characteristics: Clinical characteristics of the subjects include BMI, disease onset, weekly sun exposure score, and serum levels of calcidiol, as seen in **Table 2**.

Table 1 Baseline sociodemographic characteristics of the study subjects (n=30).

Variable	*n=30*
Sex, n (%)	
Male	6 (20.0)
Female	24 (80.0)
Age (years), mean (SD)	36.14 (9.51)
Education level, n (%)	
Low	1 (3.3)
Moderate	9 (30.0)
High	20 (66.7)
Occupation, n (%)	
Works	23 (76.7)
Does not work	7 (23.3)

Table 2 Clinical characteristics of the study subjects (n=30).

Variable	n=30
BMI, median (min-max)	25.95 (18.77-29.87)
BMI category	
Normal	10 (33.3)
Pre-obesity	20 (66.7)
Time from disease onset (months), median (min-max)	12 (2-120)
Chronic inducible urticaria, n (%)	
Yes	22 (73.3)
No	8 (26.7)
UAS7 Score, mean (SD)	14.63 (7.8)
UAS7 Classification, n (%)	
Mild	17 (56.7)
Moderate	11 (36.7)
Severe	2 (6.7)
Weekly sun exposure score, median (min-max)	8 (2-34)
Weekly sun exposure score, n (%)	
Low	29 (96.7)
Moderate	1 (3.3)
Calcidiol levels (ng/mL), median (min-max)	12.10 (6.85 – 29.87)
Calcidiol levels classification, n (%)	
Deficient	24 (80.0)
Insufficient	6 (20.0)

BMI: body mass index; UAS7: Urticaria Activity Score 7; 1 ng/mL=2.5 nmol/L

Relationship between serum calcidiol with chronic urticaria disease activity: We used Spearman's rank correlation coefficient to analyze the relationship between calcidiol in the serum with UAS7 scores as a proxy for disease activity due to abnormal data distribution. No correlation was found (r=0.151, p=0.425) (**Figure 1**).

Correlation between levels of calcidiol in the serum with chronic urticaria disease activity according to vitamin D category: We found a majority of subjects (24 out of 30) were vitamin D deficient, therefore we divided subjects with

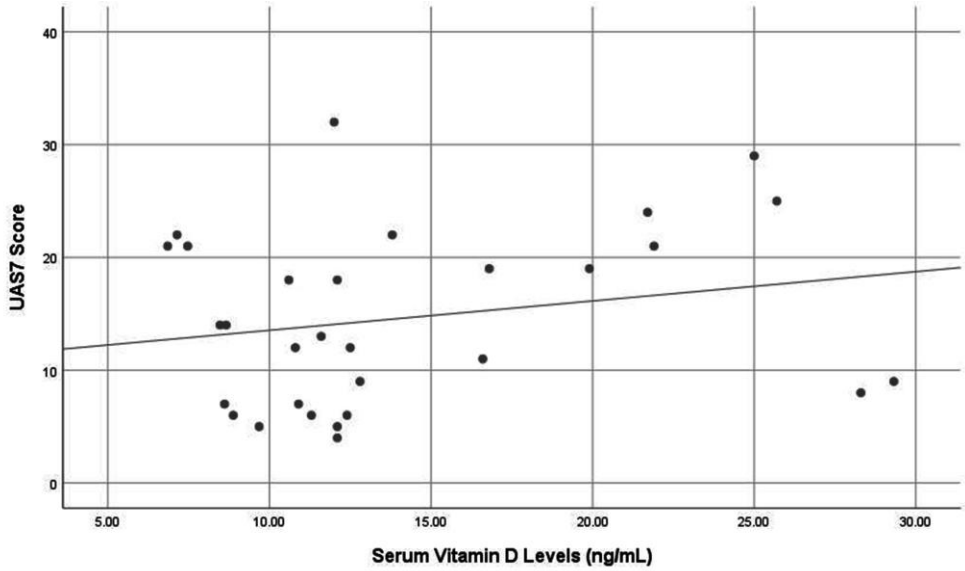

Figure 1 Scatter plot of the correlation between serum vitamin D levels with UAS7 scores.

Table 3 Correlation between serum vitamin D levels with UAS7 score according to vitamin D category.

Variable	*Correlation coefficient (r)*	*p*
Vitamin D category–UAS7 score		
Insufficient (n=6)	-0.486	0.329
Deficient (n=16)	0.223	0.406
Severely deficient (n=8)	-0.916	*0.001

serum calcidiol level ≤10 ng/mL into severely deficient group.[14,15] There were 6 subjects with vitamin D insufficiency, 16 subjects with vitamin D deficiency, and 8 subjects with severe deficiency. Spearman's rank correlation was used to analyze correlations between each group with disease activity (**Table 3**).

We found a strong negative correlation in the severely vitamin D deficient group (r=-0.916; p=0.001),which indicated that in severely deficient subjects, low vitamin D levels correlated with higher UAS7 scores (**Figure 2**).

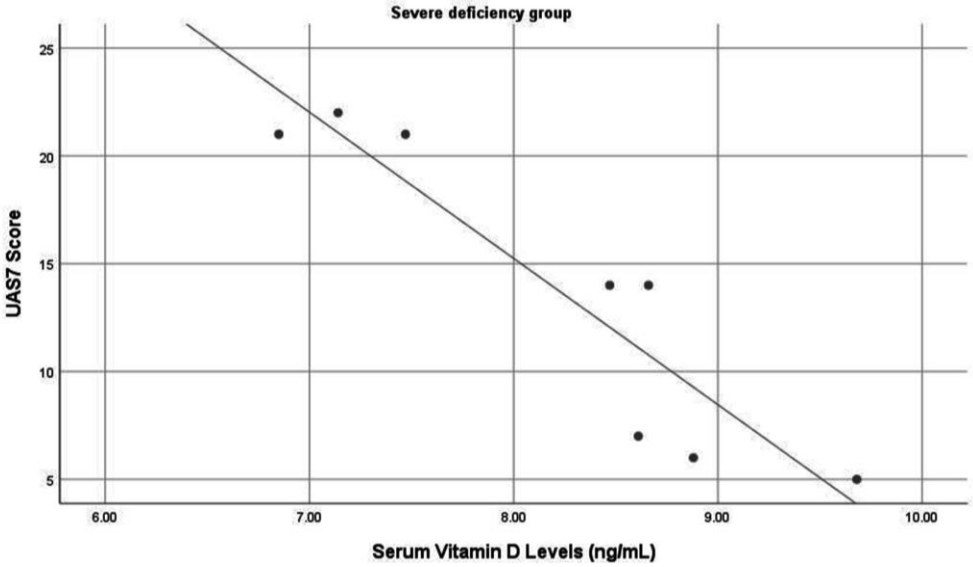

Figure 2 Scatter plot of the correlation between serum vitamin D levels with UAS7 score in severely deficient subjects.

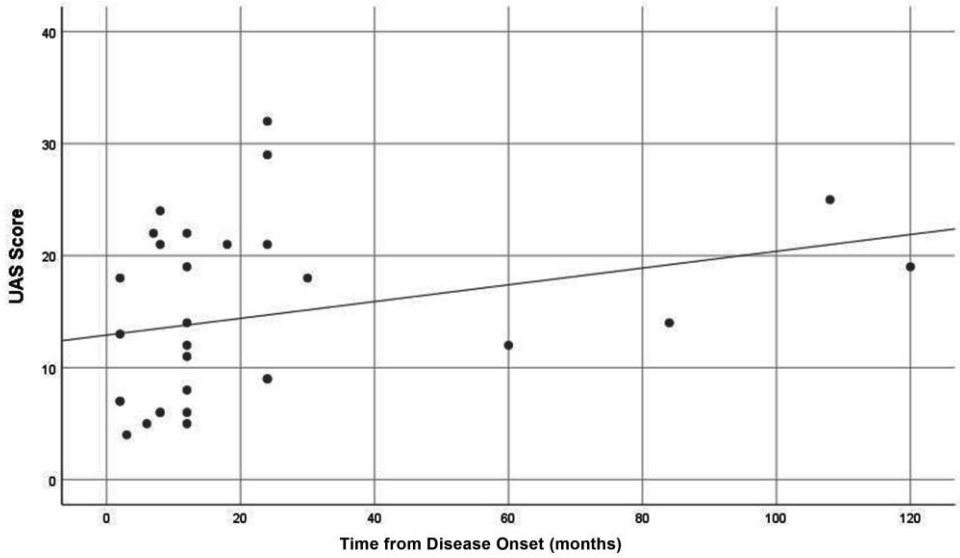

Figure 3 Scatter plot of the correlation between disease duration with UAS7 score.

Table 4 Comparison of sun exposure duration scores and number of sun-exposed body parts between subjects with different vitamin D levels.

Variable	*Vitamin D Level*		*p*
	Insufficient	*Deficient*	
Score for duration of sun exposure, median (min-max)	7 (2-10)	7 (2-14)	0.852*
Score for number of sun-exposed body parts, median (min-maks)	11 (7-18)	7 (2-14)	0.031*

*Mann Whitney test

Correlation between disease duration and chronic urticaria disease activity: We performed the Spearman's rank correlation test to investigate the correlation between disease duration, calculated based on disease onset (in months) and disease activity (UAS7 scores). We found a moderate positive correlation (r=0.391; p=0.033); **(Figure 3)**, showing longer disease duration was correlated with worse UAS7 scores.

Comparison of sun exposure duration scores and amount of skin exposed scores between subjects with different vitamin D levels: The weekly sun exposure questionnaire consisted of two variables: duration and amount of skin exposed. Scores of each variable were obtained across seven days. Subjects with vitamin D insufficiency had significantly higher scores for number of sun-exposed body parts compared to subjects with vitamin D deficiency (p=0.031), shown in **Table 4**.

Discussion

Sociodemographic characteristics: The mean age of subjects in this study was 36.14±9.51 years, with the youngest subject being 20 years old and the oldest 58 years old. The subjects' age range was in line with the literature which reported chronic urticaria patients to be 20 to 59 years old.[16] A study by Woo et al.[14] on 72 patients with chronic urticaria reported a median age of 37.9 years, closely resembling our study. Age may influence QoL in chronic urticaria patients assessed with the Chronic Urticaria Quality of Life Questionnaire (CU-Q2OL); studies found younger patients with chronic urticaria had especially affected daily activities, caused discomfort due to itch. and shame, while

older patients felt quality of sleep and eating problems were affected more.[17]

Most subjects were female, in agreement with many epidemiological studies which show women are twice more likely to have chronic urticaria than men.[1,2,4] Women are also reported to have longer disease duration and worse quality of life.[17] The high prevalence and disease severity in women gave rise to speculation that sex hormones play a role in chronic urticaria, but further studies are needed.[16] In our study, 23 subjects (76.7%) employee and 7 subjects unemployed. Stress can be considered a trigger for chronic urticaria. A study by Bansal et al.[18] reported stress and mood disorders contributed to CSU but the underlying mechanisms are yet to be elucidated. Conversely, chronic urticaria can cause stress and disrupt quality of life.

Clinical Characteristics: The median for BMI in this study was 25.95 (18.77–29.87), with the highest proportion of subjects classified as pre-obese. A study by Zbiciak-Nylec et al.[19] on 85 CSU patients reported a significant relationship between CSU and high body weight and BMI. Furthermore, BMI also influences vitamin D levels, due to vitamin D accumulation in adipose tissues, causing low serum levels. In our current study, subjects with obesity were excluded. The median duration from disease onset in this study was 12 months, with the shortest being 2 months and the longest 120 months. Our finding was consistent with previous epidemiological studies which reported most cases of chronic urticaria persisted for more than 12 months. Other studies described 50% of patients with chronic urticaria can be declared as disease-free after 3 months, but 11% of patients may still experience symptoms after 5 years.[14,16] Disease duration was also reported to be associated with disease severity, as described by Toubi et al.[20] who found patients with severe chronic urticaria had greater disease duration and positive autologous serum skin test (ASST).

We found 22 out of 30 subjects had CIndU, with each subject having more than one triggering factors. The most common inducing factor was delayed pressure urticaria in 19 out of 22 subjects, followed by dermographism in 11 out of 22 subjects. Our findings are in line with the high reported prevalence (10–50%) of CIndU in patients with chronic urticaria (most common types are symptomatic dermographism and delayed pressure urticaria). Chronic urticaria in combination with CIndU was associated with longer duration of disease and lower remission rates.[16]

The average UAS7 score in our study was 14.6; 17 out of 30 subjects (56.7%) had mild disease, 11 subjects (36.7%) had moderate disease, and 2 subjects (6.7%) had severe disease. A study by Rosandi[9] in 30 subjects found similar distribution of disease severity, in which 43.3% subjects had mild disease, 33.3% had moderate disease, and 23.3% had severe disease. In contrast, a study by Woo et al.[14] reported moderate-to-severe disease in 70% subjects. Utilization of UAS7 scores in this study can suitably represent disease severity because of the prospective nature of the questionnaire– subjects fill in the questionnaire everyday for 7 consecutive days. The study team also sent reminders to subjects to report their daily UAS scores through an instant messaging application to prevent recall bias.

The majority of subjects in this study had low weekly sun exposure scores. This finding might be caused by the subjects' characteristic as urban dwellers with mostly indoor activity. Furthermore, the COVID-19 pandemic caused governments to advise citizens to stay at home, which may indirectly influence sun exposure.

Levels of Calcidiol in The Serum: All subjects

in our study had lower-than-normal calcidiol levels, with a median of 12.1 ng/ml, concurrent with previously reported calcidiol levels in chronic urticaria patients of 11.86±7.16 ng/ml.[14] Based on vitamin D deficiency cut-offs, we found 80% of the subjects to be vitamin D deficient and 20% were vitamin D insufficient. This low level of vitamin D is in line with Modi et al.'s[13] study on 114 patients with chronic urticaria, which found 75.4% of subjects to be vitamin D deficient, 15.8% insufficient, and 8.8% had normal vitamin D levels.

The lack of subjects with normal vitamin D levels represents the high prevalence of vitamin D deficiency in Indonesia. Studies reported 50% of active, productive women aged 45-55 years had vitamin D deficiency.[21] Another study in Bogor, West Java, found a large proportion of working women of reproductive age had vitamin D deficiency, with an average serum level of calcidiol of 15.75 ng/ml.[22] A study in Jakarta and its surroundings 936 reported a prevalence of 35.1% for vitamin D deficiency in subjects aged 60-75 years.[23] We classified subjects who had calcidiol serum levels ≤10 ng/ml as severely deficient, and 8 subjects (26.7%) fell into that category, which slightly differed from another study which reported 49% of subjects with chronic urticaria as severely vitamin D deficient.[14]

The low weekly sun exposure score in most subjects may explain why calcidiol levels were low. The subject who scored moderate in their weekly sun exposure questionnaire was also the subject with the highest calcidiol level in the study, almost reaching normal levels at 29.32 ng/ml. Aside from sun exposure, there are evidence of the role of skin color in calcidiol levels, due to higher levels of melanin in darker skin colors that can act as natural sunscreen, including in Asian skin tones. Melanin can disrupt vitamin D production in the skin by absorbing ultraviolet (UV) radiation. This may cause lower calcidiol levels in individuals with darker skin tones who live in the tropics.[24] Unfortunately, our study did not collect data on skin color. Serum levels of calcidiol can be influenced by many factors and we tried to control for several confounding factors, such as obesity, renal disease, and liver disease. Vitamin D intake from consumed foods also play a role, but it was beyond the scope of our study.

Relationship between serum calcidiol levels and chronic urticaria disease activity: We found no relationship between serum calcidiol levels and disease activity in patients with chronic urticaria (r=0.151; p=0.425), showing low levels of calcidiol did not correlate with increased disease activity. Previously published studies reported significant negative correlations with varying degree of corrrelation. A study on 110 patients with chronic urticaria found significant negative correlation between serum vitamin D levels and urticaria disease activity (r=-0.488, p=0.001), and the subjects' median UAS score was 27.33±1.29 (severe).[25] The study excluded factors that may influence disease activity, such as medications, foods, infections, physical urticaria, and systemic disease.[25]

Chandrashekar et al.[12] reported significant strong negative correlation (r=-0.95, p<0.0001) between serum vitamin D levels and disease activity. Studies by Rasool et al.[26] and Rather et al.[27] also reported significant negative correlations between the two variables, but subjects in the two studies had CSU with mostly moderate-to-high disease activity. Several studies on CSU patients described significantly lower levels of calcidiol in subjects with positive ASST.[12,27] Our study did not choose CSU patients as subjects due to limitation to diagnose CSU and exclude CIndU, and to investigate triggering factors. Vitamin D was found to be a factor in not only CSU, but also in CindU.[28] On

the contrary, a study by Movahedi et al.[13] found a positive correlation between calcidiol levels and UAS scores (r=0.2, p=0.042). The majority of their study subjects had mild urticaria and analysis based on vitamin D deficiency classification was not performed.

We did not find statistically significant negative correlations, which may be due to the small number of subjects with severe disease activity, in contrast with the studies that reported significant negative correlations.[14,26] In order to reduce bias, we implemented strict inclusion and exclusion criteria, including discontinuation of antihistamines 10 days prior to blood draws and stopping corticosteroids or other immunosuppresants 12 days prior to blood draws. Other studies which had a majority of subjects with moderate-to-high disease activity did not exclude antihistamine and corticosteroids use.[14] This study was performed at a tertiary, national referral hospital, thus most of the patients had moderate-to-severe disease activity who needed high dose antihistamines or addition of immunosuppresants, or had comorbidities, and therefore were excluded from this study. Furthermore, this study was not designed to differentiate disease activity categories.

Further analysis based on level of vitamin D insufficiency showed a strong negative correlation (r=-0.916; p=0.001) between serum levels of calcidiol and UAS7 scores in severely vitamin D deficient subjects, which showed very low vitamin D levels (≤10 ng/mL) can be correlated with disease activity in chronic urticaria. Our findings are consistent with Woo et al.'s study[14] which reported significant negative correlation between calcidiol and UAS scores (p<0.001). They also reported a significantly higher number of severe vitamin D deficiency in subjects with moderate-to-high disease activity compared to subjects with mild disease.[14]

Correlation between disease duration and disease activity in chronic urticarial: In our study, a significant moderate relationship between disease duration (measured from disease onset to time of study) and chronic urticaria activity was found (r=0.391, p=0.033). This finding is supported by Toubi et al. study[20] which described chronic urticaria patients with longer duration of disease and positive ASST had more severe disease activity. Longer disease duration and lower remission rates are also found in chronic urticaria with CIndU;[20] 73.3% of our subjects had CIndU.

Comparison of sun exposure duration scores and amount of skin exposed scores between vitamin D categories: None of our subjects scored high in the sun exposure questionnaire, which seemed to be discordant with Indonesia's tropical climate and perennial sunshine. We analyzed each variable in the weekly sun exposure questionnaire (duration of sun exposure and amount of skin exposed variables) to determine which variable played the bigger role in the subjects' low sun exposure scores. In the vitamin D insufficient group, the median score for amount of skin exposed was significantly higher than in the group with vitamin D deficiency (p=0.031), which may be due to sun avoidance or customs of wearing modest clothing that can hinder sun exposure; 19 out of 30 subjects described only the face and hands were exposed to the sun. These customs may explain the low calcidiol levels in all subjects, as also observed in studies from Morocco, Saudi Arabia, and Kuwait, which are countries with year-long sun, customary modest clothing, and high prevalence of vitamin D deficiency.[29-31]

The recommended amount of sun exposure to fulfil vitamin D needs has been described by several papers. Sun exposure on legs and arms for 5-30 minutes (duration may depend on time,

latitude, season, and skin color) between 10.00 and 15.00 twice a week has been reported as adequate.[32] Others argue sun exposure in the summer on people wearing bathing suits for 20 minutes can produce 15.000-20.000 IU of vitamin D.[33] Holick found 6-8 minutes of sun exposure on arms, hands, face, and legs 2-3 times can sufficiently fulfil our vitamin D needs.

Conclusion

There was no correlation between serum calcidiol levels and disease activity, however there was a tendency of increasing disease activity in chronic urticaria patients with severe vitamin D deficiency.

Measuring calcidiol levels can be recommended for chronic urticaria patients, especially in patients with severe disease. Disease activity tends to worsen in patients with longer disease duration, thus early diagnosis and management are needed to prevent disease progression. Furthermore, chronic urticaria patients need to be informed on the importance of sun exposure duration and amount of sun-exposed areas in promoting vitamin D sufficiency. More studies are needed to investigate causal relationships between levels of vitamin D and chronic urticaria and efficacy of treatment with vitamin D in chronic urticaria patients.

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