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Vitamin D supplements improve urticaria symptoms and quality of life in chronic spontaneous urticaria patients

A prospective case-control study

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Abbreviations: CSU, Chronic spontaneous urticaria; UAS7, Urticaria Activity Score 7 days; DLQI, Dermatology Life Quality Index; 25(OH)D, 25-hydroxy vitamin D; ANA, Antinuclear antibody; ASST, Autologous serum skin test; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; TGF-β, Transforming growth factor-β

Vitamin D plays an important role in the immune system; decreased serum vitamin D concentrations have been linked to dysregulated immune function. Low vitamin D status is probably associated with chronic spontaneous urticaria (CSU). We evaluated the prevalence of low vitamin D status, and the clinical response and quality of life following vitamin D supplementation, in a prospective case-control study with 60 CSU patients and 40 healthy individuals. Serum 25-hydroxy vitamin D (25(OH)D) concentrations were measured at baseline and after 6 weeks. For patients with 25(OH)D concentrations < 30 ng/ml, treatment included 20,000 IU/day of ergocalciferol (vitamin D2) and non-sedative antihistamine drugs for 6 weeks. Urticaria symptom severity and quality of life were assessed based on the Urticaria Activity Score over 7 days (UAS7) and the Dermatology Life Quality Index (DLQI). Of the 100 participants, 73% were female; the mean age was 39 ± 16 years. Vitamin D deficiency (measured as 25(OH)D < 20 ng/ml) was significantly higher in the CSU group than the control group. The median 25(OH)D concentration for the CSU group, 15 (7 - 52) ng/ml was significantly lower than for control group, 30 (25 - 46) ng/ml. Overall, 83% (50/60) of CSU patients (25(OH)D < 30 ng/ml) were treated with ergocalciferol (vitamin D2) supplementation; after 6 weeks, these patients showed significant improvements in UAS7 and DLQI scores compared with the non-vitamin D supplement group. This study revealed a significant association of lower serum 25(OH)D concentrations with CSU. Vitamin D supplements might improve symptoms and quality of life in CSU patients.

Background

Chronic urticaria is defined as wheals and/or angioedema lasting more than 6 wks.[1] Chronic urticaria is not lethal, but it affects the quality of life of patients. The disease activity correlates with quality of life impairment.[2] Chronic spontaneous urticaria (CSU) is a common type of chronic urticaria that is endogenous and is not caused by external physical stimuli. The cause is idiopathic in 55% and autoimmune in 45% of CSU cases.[3] Moreover, autoimmune urticaria is associated with higher frequencies of wheals, higher disease activity score, prolonged disease course, and lowered responsiveness to H1-antihistamine.[4-6] Autoimmune urticaria is diagnosed by the autologus serum skin test (ASST) and serum specific anti-FcεRI autoantibody.[7]

Vitamin D (vitamin D2 and vitamin D3) is a fat-soluble vitamin. The body synthesizes vitamin D3 (cholecalciferol) in the skin from the nonenzymatic conversion of provitamin D3 to previtamin D3.[8] Additionally, vitamin D is consumed in the diet, from foods such as oily fish, egg yolks, certain mushrooms, fortified milk, cereals and cheese products. Vitamin D deficiency is a major public health problem worldwide in all age groups.[9] However, vitamin D deficiency is highly prevalent in developed and developing countries.[10-12] Vitamin D plays an important role in the immune system; it activates innate and adaptive immune responses.[13,14] It is know that CSU is often triggered by autoimmune reactions. Since vitamin D deficiency is linked to autoimmune and allergic diseases in addition to type 2 diabetes, cancer and cardiovascular diseases, 25(OH)D levels may be associated with CSU.[15-20] Furthermore, data on chronic urticaria and 25(OH)D levels is limited. Therefore,

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Table 1. Baseline characteristics of study subjects

Characteristic	CSU	control
	n = 60	n = 40
Sex female (%)	46(77)	26(65)
Age (yr)	37 ± 10	43 ± 17
Duration (wk) ± SD	30 ± 13	
Erythrocyte sedimentation rate (min) ± SD	23 ± 13	
Eosinophils (/ml) ± SD	127 ± 50	
Thyroid autoantibodies positive (%)	6(10)	
Anti-nuclear antibodies positive (%)	27(45)	
Skin prick test positive(%)	43(72)	
Autologous serum skin test positive (%)	40(67)	

CSU, chronic spontaneous urticaria

there is a need to investigate whether vitamin D supplementation exerts any beneficial effects on CSU. The primary aim of the study was to evaluate urticaria symptoms and quality of life in CSU patients before and after treatment with vitamin D supplements. We further aimed to determine the incidence of hypo-vitamin D, in order to compare serum 25(OH)D levels between patients with CSU and healthy controls.

Results

Characteristics of subjects

A total of 100 subjects (60 CSU patients and 40 controls) were recruited into the study (**Table 1**). No statistically significant differences were noted in the distribution of baseline characteristics between the two studied groups for sex and age. The mean age of the study subjects was 39 ± 16 y, and the majority of the subjects were female. The average duration of hives was 29 ± 13 wk, and the mean erythrocyte sedimentation rate (ESR) was 23 ± 13 min. Patients testing positive for thyroid antibody and anti-nuclear antibody (ANA) comprised 10% and 45% of the total study participants, respectively. In addition, the skin prick test and autologous serum skin test results were positive in 71% and 66% of the patients. Regarding vitamin D status, 32% of the subjects had 25(OH)D levels in the insufficiency range (< 30 ng/ml and > 20 ng/ml), whereas 41% had vitamin D deficiency (< 20 ng/ml) (**Figure 1A**). Among the vitamin D deficiency subjects, 9% had a 25(OH)D levels of less than 10 ng/ml. The prevalence of vitamin D insufficiency was higher in the healthy control group, but not significantly different (45% vs. 28%, $P = 0.38$). However, vitamin D deficiency was prevalent in more than half of CSU patients; 55% showed significant differences when compared with healthy subjects ($P < 0.001$).

25(OH)D levels and clinical associations

The median 25(OH)D levels at baseline in the CSU group were lower than those in the healthy control group, 15 (7–52) ng/ml and 30 (25–46) ng/ml, respectively; $P < 0.001$ (**Figure 1B**). Further, 83% (50/60) of CSU patients had low 25(OH)D levels (< 30 ng/ml); these patients were each prescribed a vitamin D2 supplement, ergocalciferol (vitamin D2) 20,000 IU per day. At the end of the study, the median 25(OH)D concentration in the CSU patient group, 39 (28–62) ng/ml was significantly higher than in the control group 29 (20–55) ng/ml, $P < 0.001$(**Figure 1B**). Improvement of urticaria symptoms and quality of life were assessed by the Urticaria Activity Score over 7 d (UAS7) and Dermatology Life Quality Index (DLQI). The difference in median UAS7 scores between baseline, 27 (6–42) and after 6weeks, 15 (2–44) decreased significantly ($P < 0.001$) among CSU patients (**Figure 2A**). Furthermore, DLQI scores were significantly better between baseline, 12 (4–31) and after 6weeks, 7 (1–27), $P < 0.001$ (**Figure 2B**). The analysis of the association between subject characteristics and serum 25(OH)D concentrations is shown in **Table 2**. Significant correlation was noted between ESR and 25(OH)D levels ($P = 0.001$, r = 0.43). However, UAS7 and DLQI scores showed no association with 25(OH)D levels.

25(OH)D levels in the CSU group

Data from patients in the CSU group were analyzed. Baseline median 25(OH)D levels in CSU patients receiving vitamin D supplements (25(OH)D < 30 ng/ml) and those not receiving supplements (25(OH)D ≥ 30 ng/ml) were 13 (8 – 29) ng/ml and 37 (33 – 52) ng/ml, respectively (**Figure 2A**). After 6 wk of vitamin D supplementation, 98% (49/50) showed complete restoration of 25(OH)D levels (≥ 30 ng/ml). The median 25(OH)D concentration for the vitamin D supplement group, 40 (28 – 62) ng/ml was higher than that in the vitamin D non-supplement group 38 (33 – 52) ng/ml (**Figure 3A**). The median UAS7 scores at baseline in the vitamin D supplement group were not significantly different from those of the vitamin D non-supplement group 27 (6 – 38) and 26 (18 – 42), respectively; $P = 0.28$ (**Figure 2B**). After 6weeks, the median UAS7 scores were significantly better in the vitamin D supplement group 15 (2 – 33) than in the vitamin D non-supplement group 26 (16 – 44), $P < 0.001$(**Figure 3B**). In addition, the median DLQI scores at baseline in the vitamin D supplement and non-supplement groups were not significantly different 13 (4 – 31) and 12 (5 -28), respectively; $P = 0.86$ (**Figure 3C**). The median DL(QI score at the 6-wk follow-up was significantly improved in the vitamin D supplement as compared with the vitamin D non-supplement group, 6 (1 -20) vs. 14 (3 -27), $P < 0.001$ (**Figure 3C**). The changes in UAS7 and DLQI scores at the end of the treatment were also more pronounced in the vitamin D supplement group (-46.3% and -52%) than in the vitamin D non-supplement group (-2% and 13%), respectively (**Figure 3D**). This difference reached statistical significance ($P < 0.001$ and $P < 0.001$, respectively). However, none of the patients in the vitamin D

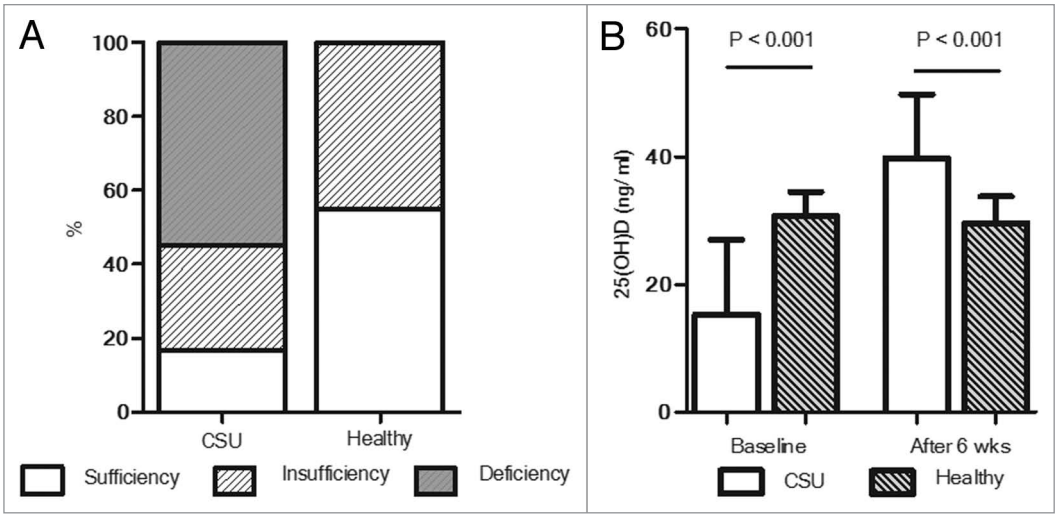


Figure 1. (A) Percentage of vitamin D status in chronic spontaneous urticaria (CSU) and healthy control. (**B**) 25(OH)D levels for CSU and healthy control compared at baseline and after 6 wk. At baseline, patients with low 25(OH)D concentrations (< 30 ng/ml) were treated with vitamin D supplements.

supplement group were symptom-free at the optimal vitamin D level.

Safety

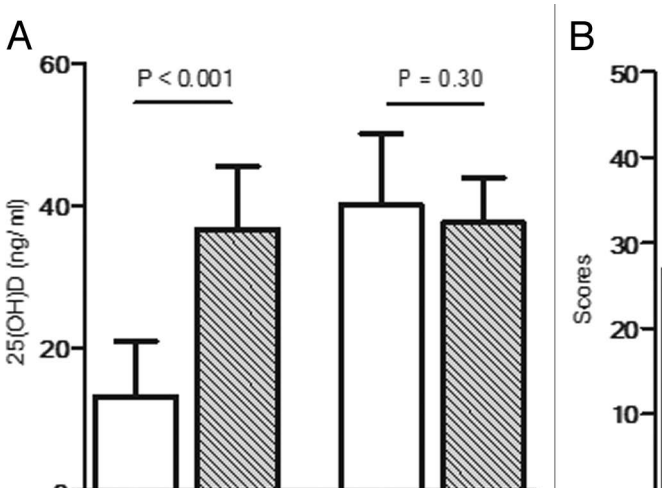
The occurrence of adverse events was monitored in the study. Ergocalciferol (vitamin D2) 20,000 IU/day was well-tolerated and effective, and no adverse effects were reported from the patients who received vitamin D supplements. All subjects who received ergocalciferol (vitamin D2) supplements completed the 6-wk study. No drug interactions were reported between ergocalciferol (vitamin D2) and non-sedative anti-histamine drugs.

Discussion

In this study, the incidence of low 25(OH)D levels (25(OH)D < 30 ng/ml) was high, especially in CSU patients, and the median vitamin D concentration was lower than the normal level. This study reveals the prevalence of low vitamin D status in 45% of the healthy control group, as seen in a recent study in a normal population.[21] Thailand, a Southeast Asian country, is located close the Equator and generally has a tropical rainforest climate. This low vitamin D status may be caused by sun protection behaviors such as application of sunscreen and lifestyle. In addition, vitamin D intake among Thais is generally low, because few natural vitamin D-rich food sources are available in Thailand and foods are not fortified with vitamin D.[22]

Throp et al. reported that the mean 25(OH)D concentration was reduced in chronic urticaria patients as compared with the control group (29 vs. 40 ng/ml), but failed to show significant differences.[23] In addition, they showed that the proportion of all subjects with vitamin D deficiency and insufficiency (25(OH)D < 30 ng/ml) in chronic urticaria was not significantly different between the chronic urticaria group (48%) and the control group (28%; $P = 0.24$).[23] A study in Poland by Grzanka et al. reported that the median serum 25(OH)D concentration was significantly lower in the CSU group than in normal subjects (26 vs. 31 ng/ml, $P = 0.02$).[24] Similar to this study, they showed that the prevalence of vitamin D deficiency was significantly higher in the CSU group than the healthy subjects group ($P = 0.02$), whereas the prevalence of insufficiency was not significantly different between CSU patients and normal subjects ($P = 0.41$).[24] Furthermore, a study in India by Chandrashekar et al. reported a significant lowering of mean 25(OH)D levels between the CSU and control groups (13 vs. 24 ng/ml, $P < 0.001$).[25] Their study subjects exhibited lower mean vitamin D concentrations than those in the present and previous studies. The above studies indicate that patients with CSU may be associated with lower vitamin D concentration during the active period of the disease.[24] Moreover, the widespread prevalence of vitamin D deficiency makes it difficult to conclude that decreased 25(OH)D levels are the cause of CSU.

Although our study was unsuccessful in finding correlations between serum 25(OH)D concentrations and disease severity, the UAS7 score and the quality of life metric, the DLQI score, improved. The study revealed a slight correlation between serum 25(OH)D concentrations and ESR, an inflammatory marker.



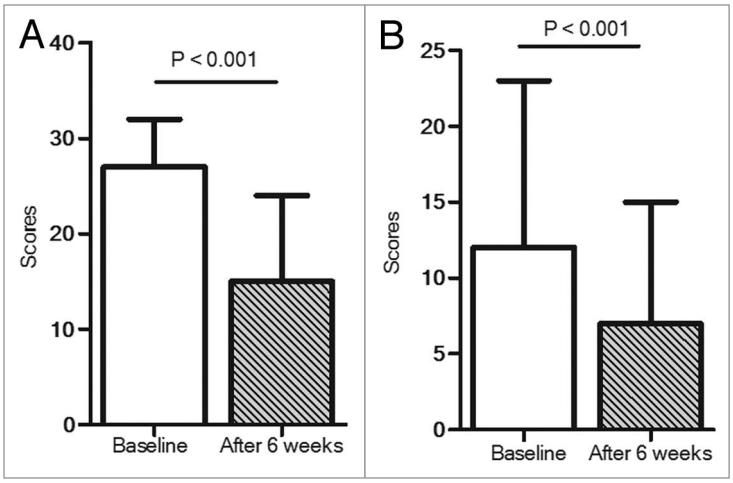


Figure 2. (A) Urticaria Activity Score over 7 d (UAS7) and **(B)** Dermatology Life Quality Index (DLQI) score at baseline and after 6 wk in CSU patients.

Biological markers such as C-reactive protein (CRP), interleukin-17 (IL-17), and transforming growth factor-β1 (TGF-β1) were studied to monitor the relationship between the severity of chronic urticaria and vitamin D status. Serum CRP concentrations were significantly higher in CSU patients than in healthy subjects (7 vs. 0.8 mg/L, $P < 0.001$) but no significant correlations were found between serum concentrations CRP and 25(OH)D levels.[24] The levels of IL-17 (48 vs. 5 ng/mL) and TGF-β1 (55 vs. 31 ng/mL) were raised significantly in patients with CSU as compared with controls ($P < 0.001$), and ESR was significantly higher in the CSU group as compared with the control (17 vs. 13 mm/h, $P = 0.03$).[25] A significant negative correlation was found between serum 25(OH)D levels and urticaria symptom scores (r = 0.95, $P < 0.001$), while the cytokines TGF-β1 (r = -0.9, $P < 0.001$), IL-17(r = -0.9, $P < 0.001$),and ESR (r = -0.3, $P = 0.002$) correlated negatively with serum 25(OH)D concentrations.[25] Currently, CSU is directly linked to immune inflammatory disease. Both ESR and CRP tests show the possible elevation of these levels by a few points in CSU. However, high ESR levels and positive ANA should be related to systemic diseases such as systemic vasculitis and other autoimmune diseases, rather than CSU.

This study demonstrated the potential beneficial effects for vitamin D supplementation as an addition to standard treatments for CSU to improve hives symptoms and quality of life. The ergocalciferol (vitamin D2) supplementation dose of 20,000 IU/day was rather high in compared with common existing treatments; however, no complications appeared after 6 wk of treatment. Treating vitamin D deficiency by vitamin D2 supplementation, typically with 50,000 IU once weekly for 8 wk or three times weekly for 1 mo often achieves a 25(OH)D concentration of 30 ng/ml.[26] A regimen consisting of > 60,000 IU of ergocalciferol (vitamin D2) for a mean of 40 ± 60 d results in sufficiency without causing vitamin D toxicity.[27] Of the CSU patients in the study who exhibited low vitamin D status, 98% were treated successfully with serum 25(OH)D concentrations reaching ≥ 30 ng/ml. Goetz reported a retrospective case series consisting of patients with urticaria/angioedema with low 25(OH)D concentrations; 61% of these patients exhibited complete resolution of symptoms with vitamin D treatment.[28] The mean time for the resolution of symptoms was 4 wk.[28] The beneficial role for supplemental vitamin D3 in CSU has been reported by Rorie et al.[29] Add-on therapy with high-dose vitamin D3 (4,000 IU/day) demonstrated a more pronounced trend toward lower urticaria severity scores at 12 wk than with low-dose treatment (600 IU/day; $P = 0.52$).[29] However, the patients in the high-vitamin D3treatment group showed a nearly normal mean level of 25(OH)D (29 ng/ml) and those in the low-vitamin D3treatment group exhibited a slightly higher than normal mean level of 25(OH)D (37 ng/ml) at baseline.[29] Vitamin D2 supplementation has been reported to be less-effective than vitamin D3 in raising total serum levels of vitamin D.[30-32] Vitamin D2 is perhaps metabolized more rapidly that reasonable for vitamin D2 is less effective in increasing 25(OH)D concentrations.[33] It has been assumed that vitamin D2 may be less toxic than vitamin D3 when provided in large amounts.[33]

Certainly, the guidelines for managing CSU do not include serum 25(OH)D levels for complete laboratory investigation.[1] Further research is needed to establish the benefit of using vitamin D to treat patients with CSU and low vitamin D status. This study has some limitations including the small sample size in the vitamin D non-supplement group, the fact that it is a non-randomized controlled study, and the lack of follow-up of 25(OH)D levels after the study period. Further transitional studies are required to evaluate the etiopathogenesis of vitamin D with regard to the immune response, such as the functions of T lymphocyte cells, basophils, and mast cells in CSU patients. Cytokines, such as IL-10, IL-17 and TGF-β, may play a role in monitoring the changing immunoregulatory effects of vitamin D and the immune system.

Conclusions

In summary, CSU is associated with low 25(OH)D concentrations and a higher prevalence of vitamin D deficiency. The results of this study reveal a correlation between serum 25(OH)D levels and the inflammatory marker, ESR. We suggest monitoring serum 25(OH)D at baseline, because the potential of vitamin D supplementation to improve hives symptoms and quality of life in CSU patients. Randomized controlled studies are needed to prove the benefit of vitamin D supplements in patients with CSU and low vitamin D status.

Methods

Study population

The study population was composed of patients diagnosed with CSU who visited the Allergy Clinic in Phramongkutklao Hospital, Bangkok, between May 2012 and July 2013.Bangkok's latitude and longitude are 13° 45′ North and 100° 31′ East, respectively. All subjects underwent a case control and cross-sectional study for 25(OH)D levels. We enrolled adults (18 y of age or older) with a clinical history of urticaria lasting more than 6

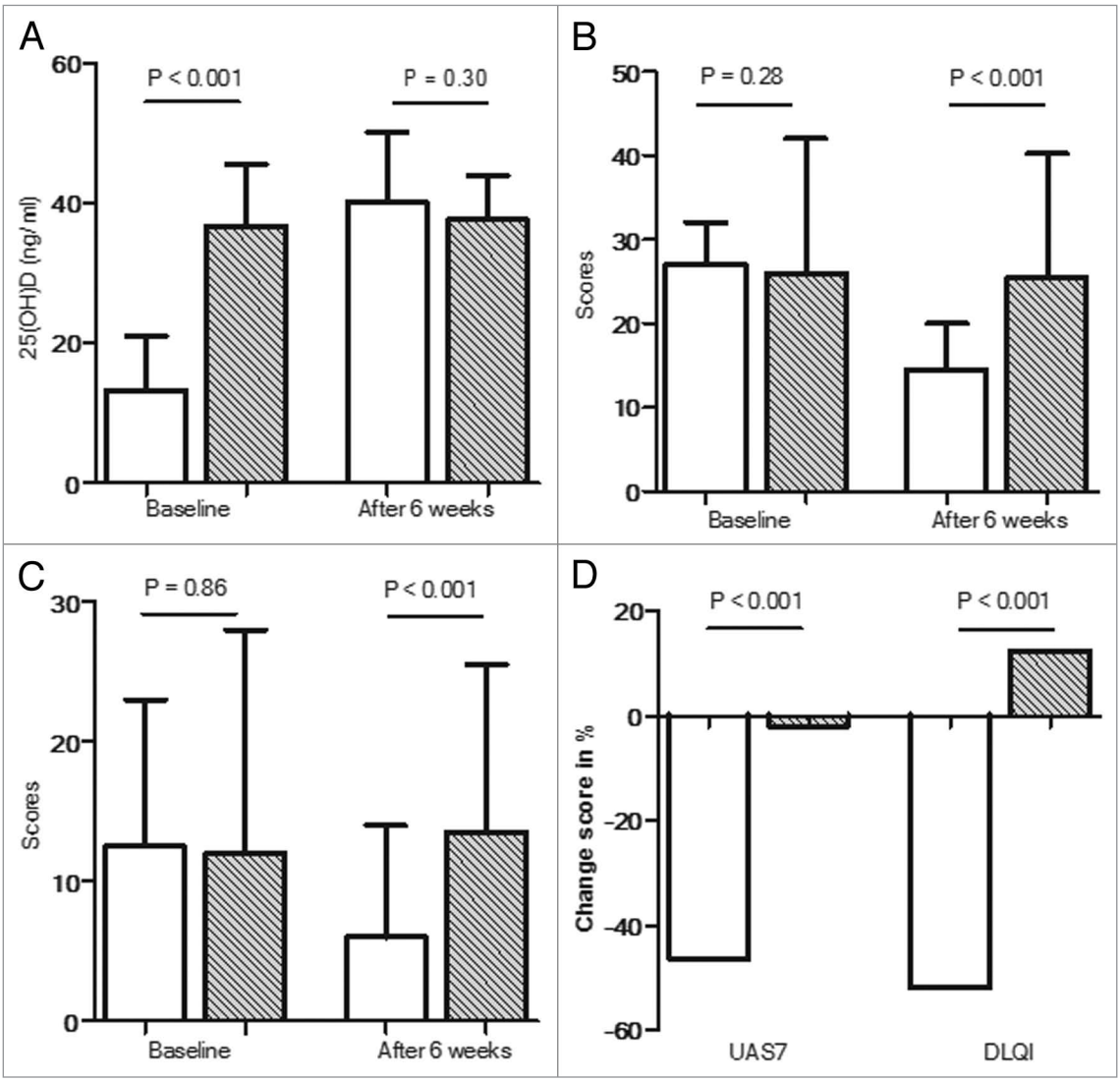


Figure 3. (A) Vitamin D levels in the Vitamin D supplement group (25(OH)D < 30 ng/ml; white bars) and the Vitamin D non-supplement group (25(OH) D ≥ 30 ng/ml; shaded bars) compared at baseline and after 6 wk. **(B)** Urticaria Activity Score over 7 d (UAS7) at baseline and after 6 wk in the the Vitamin D supplement (white bars) and the Vitamin D non-supplement (shaded bars) groups. **(C)** Dermatology Life Quality Index (DLQI) score at baseline and after 6 wk in the Vitamin D supplement (white bars) and the Vitamin D non-supplement (shaded bars) groups. **(D)** Percent change in UAS7 and DLQI scores between baseline and the end of treatment for the Vitamin D supplement (white bars) and the Vitamin D non-supplement (shaded bars) groups.

wk and hives more than 3 d in a week. Subjects with significant medical history of low 25(OH)D levels, those who had taken vitamin D supplements, and those with physical urticaria and urticarial vasculitis were excluded. The control subjects were adults without history of chronic illness. Subjects in this study provided written informed consent. The study was reviewed and approved by the hospital's ethics committee.

Study design

A face-to-face interview and examination by a research physician provided data on demographic characteristics. A self-administered questionnaire evaluated urticaria symptom severity and quality of life. The Urticaria Activity Score over 7 d (UAS7) was used to measure urticarial severity; this is a composite score (scale, 0–6) calculated as the sum of the daily average morning and evening scores for itch severity (0, none; 1, mild; 2, moderate; and 3, severe) and number of hives (0, none; 1, 1–6 hives; 2, 7–12 hives; and 3, > 12 hives).[34] The Dermatology Life Quality Index (DLQI) was used as a quality of life measure for dermatological diseases.[35] The complete blood count (number of eosinophils), erythrocyte sedimentation rate (ESR), thyroid autoantibodies, and antinuclear antibody (ANA) levels were determined at baseline. Skin prick tests were performed with 28 standardized allergen extracts (ALK-Abello). The skin prick test was positive when the size of the wheal was more than 3 mm in diameter, larger than the negative control. The autologous serum skin test (ASST) was performed by the intradermal injection of 50 µl autologous serum, and a positive ASST was defined as the appearance of a serum-induced wheal 1.5 mm in thickness, or more than the saline-induced response at 30 min.[36]

The serum level of 25-hydroxy vitamin D (25(OH)D) was considered the best biomarker of vitamin D nutritional status. Serum 25(OH)D was quantified by high-performance liquid chromatography-tandem mass spectrometry and categorized as sufficient (≥ 30 ng/ml), insufficient (< 30 and > 20 ng/ml), and deficient(< 20 ng/ml). Subjects' blood samples were taken to measure25 (OH)D levels at baseline. During the study period, the subjects were treated with an approved dose of non-sedative H1-antihistmines. Allowable non-sedative H1-antihistmines were 10 mg cetirizine twice per day, 10 mg loratadine twice per day, 5 mg levocetirizine twice per day, 5 mg desloratadine twice per day, and 180 mg fexofinadine twice per day. If the serum level of 25(OH)D was less than 30 ng/ml, the subjects were treated with ergocalciferol (vitamin D2) supplement at a dose of 20,000 IU per day. After 6 wk, subjects were evaluated again for serum 25(OH)D, UAS7, and DLQI.

Statistical Analyses

In evaluating the clinical characteristics of subjects, data were analyzed by the *t* test and chi-square test. The Mann-Whitney U test was used to assess primary end-points and compare serum 25(OH)D levels between groups. In addition, changes in serum 25(OH)D levels, UAS7,and DLQI from baseline to week 6 were assessed using the Wilcoxon Signed Ranks Test. All analyses were performed using Stata version 11.0 (StataCorp LP, Texas, USA). A *P* value less than 0.05 was considered statistically significant.

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