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Serum Levels of 25-hydroxyvitamin D in Chronic Urticaria and its Association with Disease Activity: A Case Control Study

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Abstract

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Aim:

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To evaluate the relationship between vitamin D levels and chronic spontaneous urticaria (CSU) and compare with healthy age and sex matched controls.

Material and Methods:

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This was a hospital-based cross-sectional study conducted over a period of 1 year, in which 110 patients with CSU were recruited along with an equal number of sex and age-matched healthy controls. For each patient, urticaria activity score (UAS) was calculated and autologous serum skin test (ASST) was performed. Plasma 25-hydroxyvitamin D [25-(OH)D] was analyzed by chemiluminescence method. A deficiency in vitamin D was defined as serum 25-(OH)D concentrations <30 ng/mL. The statistical analysis was carried out by using appropriate statistical tests.

Results:

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The mean serum 25-(OH)D levels of CSU patients was 19.6 ± 6.9 ng/mL, whereas in control group, the mean level was 38.5 ± 6.7 , the difference being statistically significant ($P < 0.001$). A significant negative correlation was found between vitamin D levels and UAS. ($P < 0.001$). The number of patients with ASST positivity was 44 (40%).

Conclusion:

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The patients with CSU had reduced levels of vitamin D when compared to healthy controls. Furthermore, there was a significant negative correlation between the levels of serum vitamin D and severity of CSU.

Keywords: *Autologous serum skin test, chronic spontaneous urticarial, urticariaactivityscore, 25-hydroxyvitamin D*

Introduction

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Urticaria affects 15–25% of people at least once in their lifetime.[1] It causes severe impairment on the quality of life.[2] In a number of patients, chronic urticaria is associated with various aggravating factors including drugs, food and food additives, infections and infestations, systemic diseases, etc. In spite of extensive laboratory investigations, 50% cases of chronic urticaria remain idiopathic. The circulating antibodies against the high affinity immunoglobulin E (IgE) receptors and anti FC fragment of IgE

receptor Ia (FCεRIa) antibodies have been detected on mast cells in about 30–50% cases. The term autoimmune urticaria is increasingly being accepted for this subgroup of patients.[3]

The diagnostic approach to urticaria includes a comprehensive clinical, chemical, and serological laboratory work-up. The autologous serum skin test (ASST) as defined by Sabroe *et al.* is currently the best *in vivo* clinical test for detection of *in vitro* basophil histamine releasing activity with 65–71% of sensitivity and 78–81% specificity.[2,4] The gold standard laboratory test is the demonstration and measurement of histamine release from target basophils of dermal mast cells.[5]

Vitamin D can exert several immunomodulatory actions in both innate and adaptive immunity primarily by affecting its nuclear vitamin D receptor (nVDR) and plasma membrane receptors (mVDR) on epithelial cells, mast cells, monocytes, macrophages, T-cells, B-cells, and dendritic cells.[6,7] Vitamin D inhibits production of IL-1, IL-6, IL-12, IL-23, interferon-γ (IFN-γ), and regulated on activation, normal T cell expressed and secreted (RANTES).[6,7,8] Interestingly, patients with CSU have increased circulatory levels of IL-1, IL-6, and IL-12.[9] Vitamin D enhances intercellular adhesion molecule 3 (ICAM-3) expression in mast cells which can result in modulation of proliferation, apoptosis, differentiation, function, cytokine production of mast cells in addition to their adhesion to matrix components.[10] Furthermore, vitamin D contributes to the conversion of CD4+ T cells to regulatory T cells. T regulatory cells, which have been shown to play a role in the suppression of pro-allergic mechanisms.[11]

Recently, an increasing body of literature showed paradoxical relationships between vitamin D and allergic diseases like food allergy, rhinosinusitis, recurrent wheeze, asthma, atopic dermatitis, and eczema. [12,13,14] Some studies suggest that vitamin D inhibits development of allergic diseases and can be a potential treatment for allergy whereas others have shown vitamin D supplementation as a possible cause for increased rate of allergy pandemic.[13,14]

In view of these points, we sought to determine whether a relationship between CSU and vitamin D exists.

The aim of the study was to evaluate vitamin D levels in patients of CSU and compare it to a control group and to study its relation to the disease activity. Vitamin D values less than 20 ng/mL are considered as vitamin D deficiency, between 20 ng/mL and 30 ng/mL as vitamin D insufficiency, and values more than 30 ng/mL are categorized as sufficient. Bearing in mind a 10% prevalence of vitamin D deficiency and 50% prevalence of vitamin D insufficiency,[15,16] the current study was designed.

Material and Methods

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This was a hospital-based cross-sectional study involving 110 patients of CSU, attending our outpatient department (OPD) from July 2015 to August 2016. 110 consecutive patients with CSU presenting to us were recruited along with an equal number of sex and age-matched healthy volunteers from hospital visitors with no history of urticaria or those using vitamin supplements as the control group. All our patients showed urticarial symptoms at least twice a week for more than 6 weeks. For each patient, a complete medical history was taken and physical examination was done, and a questionnaire regarding the characteristics of the disease and exacerbating factors was completed. A written and informed consent was obtained from all the participants and the study was approved by ethical committee of the hospital.

Exclusion criteria

- Patients with urticarial lesions lasting more than 24 h
- Those having physical urticaria syndromes or urticaria caused by infection, food allergy, and drug allergy
- Patients who had received antihistamines, systemic steroids, immunosuppressant therapy, and vitamin supplements during the preceding 3 months
- Patients with morbidities like diabetes mellitus, hypertension, kidney diseases, neoplastic disorders, dermatitis herpetiformis, and mastocytosis
- Patients having hypocalcemia or any other calcium disorders or history of bone disease
- Pregnant and lactating females.

ASST was carried out in every patient. A serum induced erythematous wheal with a diameter of 1.5 mm more than the saline induced response within 30 min was taken as a positive test.

Urticaria Activity Score (UAS), which is a clinical tool to assess disease severity based on patient-reported outcomes for symptoms, was calculated in each patient.[17] The patients were subdivided into three subgroups: mild: (0–8), moderate (9–16), and severe (17–24).

Baseline investigations including a full blood count, erythrocyte sedimentation rate, urine analysis, serum glucose, hepatic functions including hepatitis serology, renal function tests, thyroid function tests, serum calcium levels, serum IgE level, C-reactive protein, chest X-ray, and abdominal ultrasound were performed in all the patients.

Serum 25-hydroxyvitamin D level analysis

Blood samples were taken from both cases as well as controls after an overnight fast, and samples were immediately processed by centrifugation of 4000 rpm at room temperature. Plasma 25-hydroxyvitamin D [25-(OH)D] was analyzed by chemiluminescence method/kit method (Siemens USA) as per manufacturers protocol, using Siemens ADVIA Centaur Analyzer. Values less than 20 ng/mL were considered as vitamin D deficiency, between 20 ng/mL and 30 ng/mL as vitamin D insufficiency, and values more than 30 ng/mL were categorized as sufficient.

Statistical analysis

Statistical analysis of the data was performed by using Statistical Package for Social Sciences (SPSS Version 18). The Chi-square test was used to determine association between vitamin D deficiency and the disease. Paired *t*-test was used to compare vitamin D levels between the groups. Pearson test was used to evaluate relationship between vitamin D levels and the disease severity. *P* value < 0.05 was considered statistically significant.

Results

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There was a preponderance of females in both the study as well as the control group. The mean age of patients was 41.82 ± 8.51 years, while as that of controls was 43.11 ± 7.54 years. The characteristic of both patients and control group are presented in [Table 1](#). The duration of the disease ranged from 4 months to 7 years, mean duration was 22.46 months. 88 patients (80%) experienced symptoms of disease activity on a daily basis. Both the cases and controls were normocalcemic, and the difference between the groups was statistically insignificant.

The mean serum 25-(OH)D levels of CSU patients was 19.6 ± 6.9 ng/mL, whereas in control group, the mean level was 38.5 ± 6.7 . The difference in vitamin D (serum 25(OH)D) levels between two groups was statistically significant ($P < 0.001$).

Serum vitamin D deficiency or insufficiency was observed in 87 (79%) patients and 39 (35.45%) controls. Thus, patients with CSU showed a significant reduction in the levels of 25-(OH)D in comparison to the control group ($P < 0.0001$) [[Table 2](#)].

The trend of association between UAS and serum 25-(OH)D levels in patients with CSU was also evaluated. Serum 25-(OH)D levels showed a significant negative trend of association with UAS in patients with CSU ($P < 0.001$; Jonckheere-Terpstra test) [[Figure 1](#)].

In the CSU group, 44 subjects (40%) tested positive in the ASST. The serum 25-(OH)D levels were found to be significantly lower in the ASST positive subjects (19.44 ± 7.33 ng/mL) than in the ASST negative subjects (25.11 ± 7.08 ng/mL) ($P < 0.001$) [[Figure 2](#)].

Among patients of CSU, there was no significant difference in vitamin D level between men and women ($P > 0.05$). There was no significant correlation between vitamin D level and duration of the disease in these patients. ($P > 0.05$).

Discussion

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Vitamin D deficiency is a major health problem in both children and adults across the globe as well as in the Indian sub-continent.[18,19] Our study population was ethnic, consistent with the region and had vitamin D deficiency or insufficiency. A high percentage (87%) of CSU patients had insufficient or

deficient vitamin D levels against 62.5% of the healthy controls, suggesting a possible role of vitamin D deficiency in the pathogenesis and exacerbation of CSU.

The finding of our study is in accordance with the findings of Thorp *et al.*[20] on 25 patients with CSU. Goetz *et al.*[21] reported a case series of 63 patients with idiopathic pruritus, rash, and urticaria and low levels of vitamin D whose cutaneous manifestations improved upon vitamin D supplementation. Recently, Sindher *et al.*[22] reported resolution of CSU following treatment with vitamin D in a patient with severe vitamin D deficiency. Another study conducted by Rorie *et al.*[23] showed that vitamin D3 supplementation decreased the symptoms of CSU as well as increases the quality of life of such patients. A study by Grzanka *et al.*[24] 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, $P = 0.02$). Furthermore, a study by Chandrashekar *et al.*[25] reported a significant lowering of mean 25(OH)D levels between the CSU and control groups (13 vs. 24 ng/mL, $P < 0.001$). Boonpiyathad *et al.*[26] revealed a significant rate of low serum 25(OH) concentrations in patients with CSU. They further went on investigating the effect of vitamin D replacement in those patients based on the measurement of UASs and Dermatology Life Quality Index scores. They concluded that vitamin D supplementation might improve symptoms and quality of life in CSU patient.

In the present study, the ASST-positive patients were found to have significantly lower levels of 25-(OH)D3 when compared with the ASST-negative patients. Our finding was in conformity with the study of Chandrashekar *et al.*[25] who observed that the mean 25-(OH)D3 level was significantly lower in the ASST-positive group. However, Thorp *et al.*[20] and Grzanka *et al.*[24] observed no differences in the levels of 25-(OH)D3 between the two groups.

In our study, a negative correlation between serum 25-(OH)D3 concentration and disease severity as indicated by UAS was seen. Certainly, the guidelines for managing CSU do not include serum 25-(OH)D level testing. On the basis of our findings, we speculate that treatment of vitamin D deficiency would not only preserve mineral homeostasis but, due to possible immunomodulatory and anti-inflammatory effects of vitamin D, might have a beneficial impact on CSU activity. Vitamin D supplementation may provide an important and viable complement to the already existing CSU therapy.

Since our populace belonged to a culturally conservative, temperate area with a high altitude, the role of several factors like limited ultraviolet exposure, seasonal changes and altitude, level of activity, pattern of clothing, and dietary intake of vitamin D need to be assessed to justify the vitamin D level in these patients in further studies.

Limitations of the study

Our study had a small sample size, with a nonrandomized controlled design. ASST, a test with low sensitivity and specificity, was used to determine the autoimmune nature of urticaria instead of using the gold standard *in vitro* test. Furthermore, no therapeutic trial with vitamin D was given to the study subjects.

Conclusion

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The present study showed a significant reduction in the levels of vitamin D3 in patients with CSU as compared to healthy controls. Further, randomized controlled studies are needed to evaluate the etiopathogenesis of vitamin D with regard to the immune response in patients of CSU and to prove the benefit of vitamin D supplements in these patients.

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Conflicts of interest There are no conflicts of interest.

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Figures and Tables

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Table 1

Clinical characteristics of patients and controls

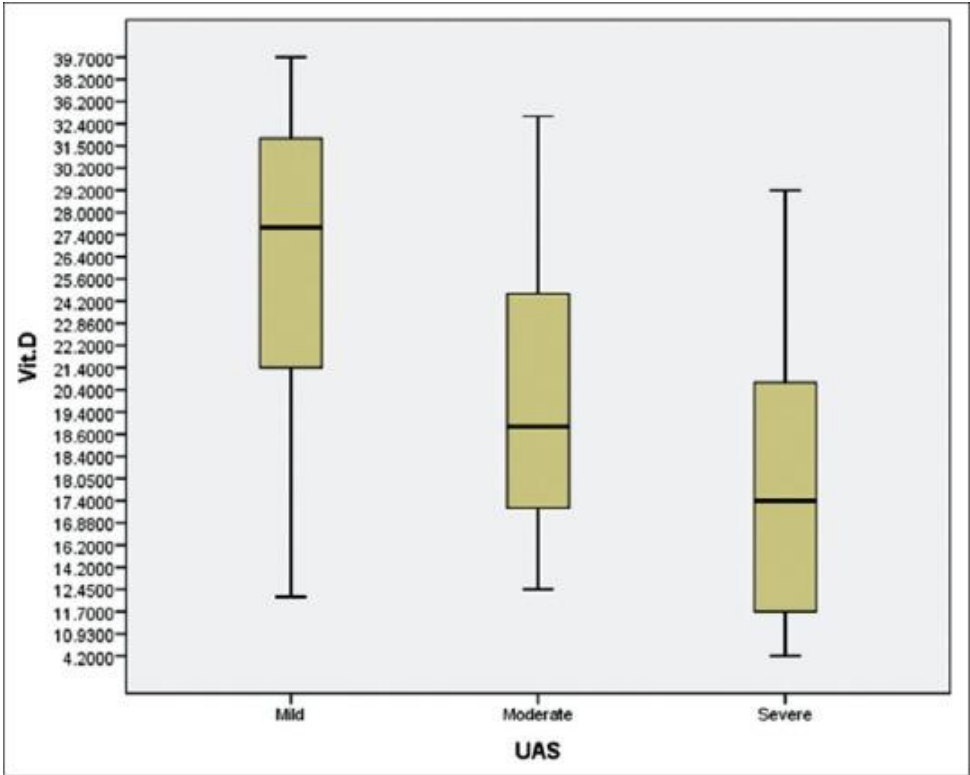
Characteristics	Patients (N=110)	Controls (N=110)	P
Age (y), (mean±SD)	41.82±8.51 years	43.11±7.54	Insignificant
Gender (Male/Female)	38 M; 72F	40 M; 70 F	Insignificant
UAS (mean±SD)	14.9±2.15	-	-
Family history of urticaria	22 (20%)	-	-
History of angioedema	44 (40%)	-	-

Table 2

Vitamin D status in patients and controls

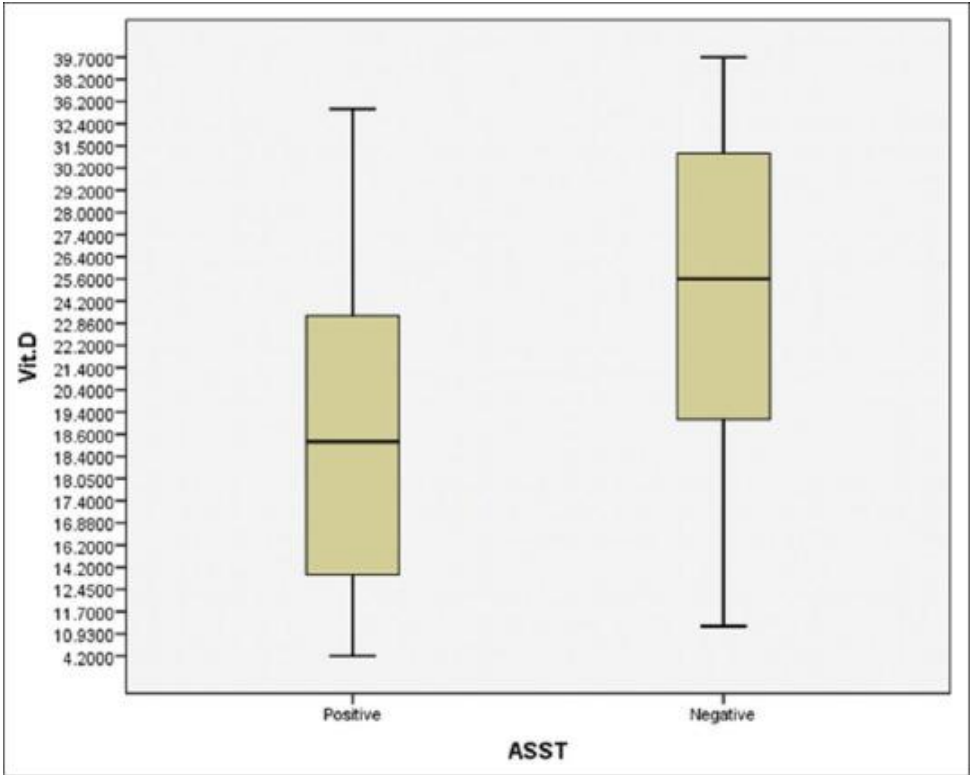
Characteristics	Patients (N=110)	Controls (N=110)	P
Vitamin D deficiency	70 (63.64%)	15 (13.64%)	P<0.0001
Vitamin D insufficiency	17 (15.45%)	24 (21.82%)	
Vitamin D sufficiency	23 (20.91%)	71 (64.54%)	

Figure 1



The trend of association between urticaria activity score (UAS) and serum 25-hydroxy vitamin D 25-(OH)D3 levels in patients with chronic urticaria

Figure 2



25-hydroxy vitamin D Serum 25-(OH)D3 levels of chronic urticaria patients according to autologous serum skin test (ASST) results

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