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ORIGINAL ARTICLE

Does replacement of vitamin D reduce the symptom scores and improve quality of life in patients with chronic urticaria?

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Abstract

Background: Vitamin D plays a key role in the immune responses generated by lymphocytes and antigen-presenting cells. Decreased vitamin 25-hydroxyvitamin D (25(OH)D) levels have been implicated in several allergic disorders and association between 25(OH)D levels and chronic urticaria (CU) symptom scores has been evaluated in a few studies. This study was performed to assess the effects of vitamin D supplementation on the symptoms and quality of life scores in chronic spontaneous urticaria (CSU) and to vitamin D levels in CSU patients in comparison with controls. *Patients and methods*: Fifty-eight CSU patients and forty-five controls were included in the study. The patients were divided into two groups according to severity of the disease; as mild/moderate and severe urticaria. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured in serum of CSU patients and compared with the control groups. In patients with 25(OH)D concentrations lower than 30 μg/L, 300 000 IU/month of vitamin D3 supplementation was added to standard therapy. The clinical improvement was evaluated after 3 months with urticaria activity score (UAS4) and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). *Results*: Serum 25(OH)D concentration was significantly lower in CSU group compared to healthy subjects ($p < 0.001$). The prevalence of vitamin D deficiency (<20 (μg/L) and insufficiency (<30 μg/L) was significantly higher in CSU patients than control groups. In addition, 25(OH)D concentrations were significantly lower in both mild-moderate and severe CSU patients than those of the controls ($p = 0.011$ and $p < 0.001$, respectively). Ninety eight percent of patients (25(OH)D < 30 μg/L) were treated with vitamin D3 (300 000 IU/month) supplementation, and after 12 weeks, these patients showed significant improvements in UAS4 and CU-Q2oL scores. *Conclusion*: This study support the contributing and beneficial effects of vitamin D in the treatment of CU. Replacement of vitamin D may provide improvement in both the severity of symptoms and the quality of life scores in these patients.

Keywords

Quality of life, urticaria, urticaria activity score, vitamin D

History

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Introduction

Urticaria is defined as a widespread, fugacious, itchy cutaneous swelling; it is one of the most frequent dermatosis, being its prevalence in general population estimated about 20% (1). Histamine and other mediators are released from mast cells and basophils in urticaria patients. However, the exact mechanism and underlying triggers remain unclear (2).

Vitamin D plays a key role in the immune responses generated by lymphocytes and antigen-presenting cells. Recent studies suggested that vitamin D deficiency contributes to the development of atopic dermatitis and vitamin D as potential immunomodulator of allergic disease because of its role in regulating cathelicidin expression in the skin of subjects with atopic dermatitis (3,4).

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As compared to atopic dermatitis, there are significantly fewer studies that have evaluated the potential link between vitamin D and urticaria.

This prospective study aimed to determine the prevalence of vitamin D deficiency in patients with chronic spontaneous urticaria (CSU), and compare serum vitamin D levels between patients and healthy controls. We also evaluated whether replacement of vitamin D alleviate urticaria symptoms and decrease quality of life scores.

Methods

In a prospective case-control study, we evaluated the levels of 25(OH)D) (25-hydroxyvitamin D) in 58 patients (14 year of age or older) presenting with CSU and in age-matched control group of 45 healthy subjects. CSU is defined as having recurrent wheals occurring at least 3 times per week for more than 6 weeks within the past year. A detailed patient file was recorded for all patients, including the age and sex of the patients, cutaneous symptoms, duration of disease, routine laboratory tests (full blood count, urine analysis, C-reactive protein, stool (for parasites)), hepatitis

serology, thyroid tests and levels of anti-thyroid antibody and total IgE. Patients with physical urticaria and urticarial vasculitis and healthy subjects with significant medical history of low vitamin D levels, those who have taken vitamin D supplements and pregnant were excluded.

Urticaria symptom severity and quality of life were assessed based on the Urticaria Activity Score over 4 days (UAS4) and CU-Q2oL (Chronic Urticaria Quality of Life Questionnaire). The Urticaria Activity Score over 4 day (UAS4) was used to measure urticarial severity; this is a composite score (scale, 0–6) calculated as the sum of 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, <20 hives; 2, 20–50 hives; and 3, >50 hives) (5). Chronic Urticaria Quality of Life Questionnaire has been widely used as a quality of life measure for chronic urticaria and has been validated in Turkish language (6,7).

The patients were subdivided into three subgroups, according to the urticarial activity score (UAS4) as follows: mild: (0–8), moderate (9–16) and severe (17–24). Serum 25(OH)D concentration was measured with the use of an automated direct Electrochemiluminescence immunoassay (Elecsys, Roche Diagnostic, Mannheim, Germany). Serum 25(OH)D concentrations were measured at baseline and after 12 weeks. Levels of 25(OH)D were categorized as sufficient (>30 μg/L), insufficient (<30 and >20 μg/L) and deficient (<20 μg/L).

Vitamin D replacement was done for patients with serum levels of 25(OH)D below <30 μg/L. The patients with low vitamin D were treated with 12 weeks of vitamin D3 300 000 IU/monthly and afterwards urticaria activity scores and CU-Q2oL scores were evaluated again.

This study has been approved by the Ethics committee of Okmeydani Research and Training Hospital (2014/April/195). Written informed consent was obtained from all the subjects participating.

The Statistical Package for the Social Sciences (SPSS version 1.2 for Windows, SPSS, Inc., Chicago, IL) computer software was used for all statistical analyses. A $p<0.05$ was considered as statistically significant. The Mann–Whitney *U* test, Wilcoxon test and chi-square test were used to determine associations between patients and control groups. Kruskal–Wallis variance analysis was used to screen differences between the groups.

Results

Fifty-eight CSU patients were enrolled in our study. Forty-five of the patients were female and 13 were male. The age of the patients were between 14 and 75 years (mean age: 40.09 ± 14.59). Duration of the disease ranged between 1.5 months and 50 years (mean duration: 3.44 ± 7.49 years). The control group was composed of 36 females and 9 males.

Three of the 58 patients (5.2%) had mild urticaria, with urticaria activity scores ranging from 0 to 6. Fifteen of the 58 patients (25.8%) had moderate urticaria, with urticaria scores ranging from 10 to 16. Forty of the 58 patients (68.9%) had severe urticaria, with activity scores ranging from 17 to 24.

Anti-thyroglobulin antibody (anti-TG) and anti-thyroid peroxidase antibodies (anti-TPO) were positive in 17.2% and 22.4% of the patients. High levels of total IgE (>87 IU/mL) were found in 69.7% of the patients.

Median vitamin D level was 8.45 μg/L (range 1.1–52.5 μg/L) in patients and 15.3 μg/L in control group. Vitamin D levels were significantly reduced in patients with CSU compared to controls ($p<0.001$) (Table 1).

Vitamin D deficiency was present in 52 (89.7%) patients with chronic urticaria and in 31 (68.9%) of controls. There was a significant difference between CSU and control group regarding the prevalence of vitamin D deficiency (<20 μg/L) ($p=0.017$) (Table 2).

Table 1. Vitamin D levels in the patients group and control group.

	D vitamin (μg/L)		
Groups	Median	Min–Max	*p*
Control ($n=45$)	15.3	3.1–61.0	<0.001
CSU patients ($n=58$)	8.45	1.1–52.5	
Severity of disease			
Control ($n=45$)	15.3	3.1–61.0	0.011
Mild/moderate ($n=18$)	8.95	3.9–23.0	
Control ($n=45$)	15.3	3.1–61.0	<0.001
Severe ($n=40$)	7.1	1.1–52.5	

p Values were calculated with the Mann–Whitney *U*-test.

Table 2. Vitamin D status in patients with CU and control group.

	CSU $n=58$		Control $n=45$		*p* Value
Vitamin D insufficient group (<30 μg/L)	57/58	98.3%	39/45	86.7%	0.041
Vitamin D deficient group (<20 μg/L)	52/58	89.7%	31/45	68.9%	0.017

Statistically significant difference ($p<0.05$).

Vitamin D insufficiency was present in 57 (98.3%) patients with CSU and in 39 (86.7%) in controls. There was a significant difference between CSU and control group regarding the prevalence of vitamin D insufficiency (<30 μg/L) ($p=0.041$) (Table 2).

The patients (57 patients) who had low 25(OH)D levels (<30 μg/L) were prescribed vitamin D 300 000 IU/month. There were no significant differences between CSU patients with mild-moderate symptoms and severe symptoms regarding 25(OH)D levels (median: 8.95 versus 7.1 μg/L, $p=0.139$). However, 25(OH)D concentrations were significantly lower in mild-moderate CSU patients than those of the controls (8.95 versus 15.3 μg/L, $p=0.011$) (Table 1). There were significant differences between severe CSU patients and the controls regarding 25(OH)D levels (7.1 versus 15.3 μg/L, $p<0.001$) (Table 1).

Improvement of urticaria symptoms and quality of life were assessed by the Urticaria Activity Score over 4 day (UAS4) and CU-Q2oL in vitamin D-deficient and insufficient groups. A significant decrease in median UAS4 scores (21–6) from baseline to 12 weeks was observed among CSU patients ($p<0.001$). Furthermore, CU-Q2oL scores were significantly improved from 38 (6.5–115.2) to 10.8 (0–43.4) from baseline to 12 weeks ($p<0.001$) (Table 3).

There were no significant differences between vitamin D-deficient or insufficient group regarding CU-Q2oL and UAS4 scores ($p>0.001$). There was no association between the anti-TG and the anti-TPO autoantibodies and the levels of vitamin D in CSU patients ($p=0.641$ and $p=0.373$, respectively). There was no association between the prevalence of high levels of total IgE and the levels of vitamin D in CSU patients ($p=0.5$). The analysis of the association between subject characteristics and serum 25(OH)D concentrations is shown in Table 1.

Discussion

Recent studies have shown vitamin D receptors on distinct cell types such as T cells, B cells, neutrophils and macrophages. Vitamin D affects both innate and adaptive immune mechanisms (8,9). It affects the innate immune system by stimulating the production of cathelicidin which is an anti-microbial peptide that

Table 3. Urticaria activity score over 4 d (UAS4) and Chronic Urticaria Quality of Life score at baselin and after 12 week vitamin D replacement.

		Baseline		After		
	n	Median	Min–Max	Median	Min–Max	*p*
Chronic Urticaria Quality of Life score	57	38	6.5–115.2	10.8	0–43.4	<0.001
Urticaria activity score	57	21	0–42.0	6	0–21.0	<0.001

Wilcoxon Test, statistically significant difference ($p < 0.05$).

is activated through toll-like receptors. Furthermore, 1,25(OH)2D inhibits dendritic cell migration, IL-12 and IL-23 cytokine production, thereby reducing T helper type 1 cells and potentially leading to increased proliferation of allergy-associated T helper type 2 cells. Due to these immunological findings of vitamin D, the studies have been conducted to identify whether vitamin D affects serum levels of immunoglobulin E (3,9,10). Heine et al.'s study showed that stimulated B cells markedly decrease the production of IgE following the administration of vitamin D (11). Most of the studies to assess the effect of vitamin D on allergic skin diseases focused especially on atopic dermatitis. Peroni et al. conducted a study in patients with atopic dermatitis and they found an inverse correlation between serum concentrations of vitamin D and severity of atopic dermatitis (12). Javanbakht et al. demonstrated that administration of vitamin D showed a significant improvement in the SCORAD index as compared to placebo (13).

In subsequent years, Goetz et al. sought to determine whether a relationship between vitamin D and chronic urticaria exists. They evaluated 50 patients with CU and determined that vitamin D levels were significantly reduced in patients compared with controls (14). Similarly we found that, the prevalence of vitamin D deficiency was high in our CSU patients group (89.7%).

Earlier studies reported that the vitamin D replacement decreased disease activity in urticaria patients (14). Goetz et al. studied to identify whether vitamin D supplementation can improve health outcomes in patients with pruritus, rash and CU. Ninety percent of patients had low vitamin D levels and 61% of 28 patients with urticaria/angioedema resolved cutaneous symptoms with vitamin D supplementation in their study (15). Boonpiyathad et al. revealed a significant rate of low serum 25(OH) concentrations in patients with CSU. And they investigated the effect of vitamin D replacement in those patients based on the measurement of urticaria activity scores and Dermatology Life Quality Index scores. They concluded that vitamin D supplementation might improve symptoms and quality of life in CSU patients (16). We detected similar findings in our study. After vitamin D supplementation, urticaria activity scores and CU-Q2oL scores significantly decreased ($p < 0.001$).

Grzanca et al. showed that the rate of vitamin D deficiency proved significantly higher in CSU patients. But, they found no significant differences in the prevalence of 25(OH)D insufficiency between CSU patients and normal subjects (17). Thorp et al. reported that the frequency of vitamin D deficiency and insufficiency in CU patients was not significantly different from the control group ($p = 0.24$) (18). The prevalence of vitamin D deficiency was 89.7% and vitamin D insufficiency was 98.3% in our study. In contrast to former studies, we found a significant difference between the prevalence of vitamin D deficiency or insufficiency in patients with CSU and control groups ($p < 0.05$). In addition, 25(OH)D concentrations were significantly lower in mild-moderate CSU and severe CSU patients than those of the controls ($p = 0.011$ and $p < 0.001$ respectively).

Although some data demonstrated that 25(OH)D levels are associated with an increased activity/severity of the inflammatory diseases, Thorp et al. detected that the levels of vitamin D in urticaria patients did not correlate with duration or severity of the disease (4,17). Similarly, the levels of vitamin D did not significantly differ between mild-moderate CSU and severe CSU patients in our study. These findings suggest that vitamin D does not affect the clinical progress, alone. Other factors may play a role in the etiopathogenesis.

The cause of CSU remains unclear. But over the years, a number of direct and indirect measures of immune activation, complement activation, histamin release or neuroendocrine function have been suggested as a cause of CSU. Furthermore, it has been argued that the presence of thyroid autoantibodies play a role in the etiopathogenesis of CSU (19). Verneuil et al. compared the frequency of anti-thyroid antibodies in healthy individuals and patients with CSU, demonstrating a statistical association between anti-TPO or anti-TG antibodies and CSU; the frequency of these antibodies in CSU patients was 26.7% compared to 3.3% in healthy subjects ($p < 0.01$) (20). In our study, the percent of anti-TG and anti-TPO were 17.2% and 22.4%, respectively. We determined that the prevalence of anti-thyroid antibodies was significantly higher in our CSU patients. With respect to association between vitamin D and thyroid autoantibodies, we did not find a positive correlation.

Urticaria results from the activation of cutaneous mast cells. The release of mast cell-derived mediators may be caused by both immune and nonimmune mechanisms. Huilan et al. demonstrated that total IgE significantly increased in acute and CU patients (21). Sixty-nine percent of our patients had high levels of Ig E. But, there was no association between the total Ig E and the vitamin D.

In conclusion, we revealed two significant findings in this study. First, there was a high incidence of vitamin D deficiency or insufficiency among Turkish urticaria patients. Secondly, urticaria activity scores and CU-Q2oL scores in the vitamin D-deficient or insufficient group decreased in response to vitamin D replacement. Vitamin D supplementation seems to significantly improve hives symptoms and quality of life in CSU patients. We believe, immunomodulator and anti-inflammatory effects of vitamin D possibly provided these consequences.

Declaration of interest

Authors have no conflict of interest.

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