Original Research Article

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

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Abstract

Aim: To study the association of vitamin D- level in patients with chronic severe idiopathic urticaria and correlate their level with severity of disease.**Material and methods:** This was a hospital-based study conducted over a period of 1 year with a sample size of 30 patients diagnosed to have chronic idiopathic urticaria on basis of a recurrent eruption of wheals and flare with or without angioedema for each patient urticaria activity score(UAS) was calculated. Plasma 25-hydroxyvitamin D [25-(OH)D] levels were analyzed. 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**: Serum vitamin D3 level was significantly lower in chronic urticaria subjects. The prevalence of vitamin D deficiency (<30 ng/ml) was significantly higher in patients with chronic urticaria, with the mean value being 14.46ng/ml.**Conclusion**: The present study showed a strong positive correlation between vitamin D deficiency and chronic urticaria. This study also warrants that each subject with chronic urticaria should be screened for serum vitamin D3 levels before initiating treatment.

Keywords: urticaria,vitamin D,angioedema.

Introduction

Urticaria is more commonly known as "hives" is a prevalent disorder that affects between 15-25% of the population at some point in their lifetime[1]. Chronic urticaria is defined as the presence of evanescent wheals which occur for greater than 6 weeks without an identifiable trigger[1]. 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. Thecirculating antibodies against the high affinity immunoglobulin E (IgE) receptors and anti FC fragment of IgE receptor Ia (FCeRIa) 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[2]. Vitamin D is known to have modulatory effects on dendritic cells and monocytes, and the functional impairment of these cells interferes with the production of various cytokines. The impaired function of various immunocytes due to low vitamin D levels might lead to increase of circulating pro-inflammatory cytokines and imbalance of regulatory T-cell cytokine production, which cause worsening of chronic urticarial[1-5]

Method : This study is a descriptive study which was performed in about 30 study subjects with chronic urticaria with a duration more than 6 weeks who attended the outpatient Department of Dermatology in a tertiary care center over a period of 6 months. A detailed written and informed consent was obtained from all the participants and ethical clearance was sought from the institutional ethical committee. For each patient, a complete medical history, detailed physical and cutaneous examination was done.

Inclusion criteria:

1. Patients aged 14-60 years of either sex, with persistent signs and symptoms of urticaria (itching and wheals) for more than 6 weeks.

Exclusion criteria:

1. any underlying diseases or taking any medicine which affects Vitamin-d level
2. Patients with other causes of urticarial (such as physical induced urticaria, drugs- induced urticaria).
3. Patients with urticarial lesions lasting more than 24hr
4. Those having physical urticaria syndromes or urticaria caused by infection, food allergy, and drug allergy.
5. Patients who had received antihistamines, systemic steroids, immunosuppressant therapy, and vitamin supplements during the preceding 3 months.
6. pregnancy and lactation.

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.

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).

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Serum 25-hydroxyvitamin D level analysis

Plasma 25-hydroxyvitamin D [25-(OH)D)] was analyzed, 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 20). The baseline characteristics in the study groups were analysed using ANOVA with 95% confidence interval for

mean and the results were expressed in mean ±standard deviation.

P value < 0.05 was considered statistically significant.

Results:

There was a female preponderance in the study.

The mean age of the patients was 34.60±9.981years. The mean serum 25-(OH)D levels of CSU patients was 14.4690±5.32284 ng/ml.The characteristics of both components are depicted in table 1.

Serum vitamin D levels – 10 patients had mild deficiency with mean value of 20.5620 ± 2.806 ng/ml, 15 patients had moderate deficiency with mean value of 12.9220 ± 1.916ng/ml, 5 patients had severe deficiency with mean value of 6.9240 ± 1.372ng/ml.depicted in 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(figure1).

Table 1:Descriptive statistics

Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Age	30	37	18	55	34.60	9.981
VITAMIN D(mg/ml)	30	20.90	4.90	25.80	14.4690	5.32284
Valid N (listwise)	30					

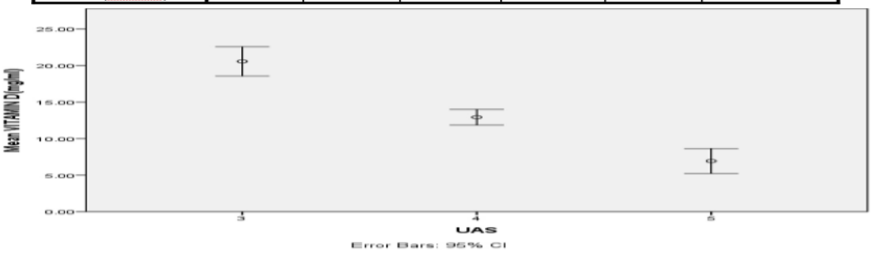

Fig 1: Descriptive statistics

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).

Table 2:Descriptives

Descriptives

VITAMIN D(mg/ml)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Mild	10	20.5620	2.80678	.88758	18.5542	22.5698	17.28	25.80
Moderate	15	12.9220	1.91668	.49488	11.8606	13.9834	8.50	15.24
Severe	5	6.9240	1.37225	.61369	5.2201	8.6279	4.90	8.50
Total	30	14.4690	5.32284	.97181	12.4814	16.4566	4.90	25.80

ANOVA

VITAMIN D(mg/ml)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	691.780	2	345.890	71.913	.000
Within Groups	129.866	27	4.810		
Total	821.645	29			

Discussion

Chronic urticaria, a heterogenous group of skin disease with diverse etiological factors, at times the cause is almost not found, which severely debilitates the day to day activities of the individuals. However in 40 % of cases, chronic urticaria is found to be autoimmune in nature with circulating autoantibodies against IgE and its receptors signifies the role of vitamin D as immunomodulator in the pathogenesis of chronic urticaria.

Role of Vitamin D3 In the pathogenesis of chronic urticaria

Vitamin D, a fat-soluble vitamin, exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol)[1].Vitamin D2 has been found in some mushrooms, e.g., shiitake mushrooms and button mushrooms. Vitamin D3 is commonly found in halibut, mackerel, eel, salmon, beef liver, and egg yolks. Within the human body, only the skin can produce vitamin D3.Vitamin D plays a major role in mineral homeostasis.Besides its role in bone physiology, it also has a role on cutaneous immunity by binding to its nuclear receptors and plasma membrane receptors of epithelial cells, and to various cells such as mast cells, monocytes, macrophages, T-cells, B-cells, and dendritic cells[1,2]n the innate immune system, vitamin D contributes to improving antimicrobial defenses by stimulating the expression of antimicrobial peptides such as cathelicidin and human β-defensin.[1] In the adaptive immune system, in vitro study showed that physiologic (in vivo) concentration of 25(OH)D3 in serum-free medium can activate T cells to express CYP27B1 and then convert 25(OH)D3 to 1,25(OH)2D3. (active form of vitamin D).

Vitamin D can exert immunomodulatory actions in both innate and adaptive immunity primarily by modifying vitamin D receptors (VDR) receptors on mast cells, inhibiting mast cell differentiation and inducing mast cell apoptosis thereby reducing the recurrent episodes of urticaria[6].Mast cells express VDR and respond to 1-25(OH)2D3. Mechanism of action for 1-25(OH)2D3 in inhibiting mast cell activity is by means of down-regulating mast cell development, differentiation, and eventually function via VDR, inhibition of IL3, which is a crucial cytokine involved in mast cell survival, proliferation and maturation, induction of apoptosis of bone marrow mast cell precursors ,inhibits the release of inflammatory mediators by bone marrow mast cells stimulated by FcεRI cross-linking.

Calcitriol also plays a role in mast cell activation and produces interleukin 10 (IL-10) without causing degranulation. Calcitriol

maintains mast cell stability and reduces histamine production. Generated IL-10 will inhibit the production of immunoglobulin E-dependent pro-inflammatory mediators. Mediators will reduce leukotriene C4 involved in eosinophil activation process[11-13]

Hence, Vitamin D is considered now as a marker for chronic inflammatory disease, but also for the acute phase of inflammation it could be suspected that low vitamin D levels among patients initially presenting with acute urticaria may provide a marker for predicting higher probability to progression to the chronic form[3]In our study, the mean age in the study group was found to be 34.60±9.981years.This is similar to previous study done by Chandrasekar et al.In our study, chronic urticaria patients were predominantly females.This female preponderance in chronic urticaria subjects in our study was very similar to previous studies done by Chandrasekar et al. Our study showed significantly lower serum vitamin D levels with mean value being 14.4690±5.3228. The finding of our study is in accordance with the Boonpiyathad et al. revealed a significant rate of low serum 25(OH) concentrations in patients with CSU.Our study showed a strong positive correlation between vitamin D deficiency and chronic urticaria. This is similar to previous studies by Rather et al. who showed a significant reduction in the levels of vitamin D3 in patients with CSU. Wu et al. showed that the majority of people with urticaria (54.6%) had vitamin D levels below normal limits. Rasool et al. (Randomized case–control study) showed Low serum 25(OH)D levels in 91% of CSU patients. Chandrashekar et al. proved Significant lower vitamin D levels among chronic urticaria patients and controls[13]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 study, if vitamin D deficiency's corrected, 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 a viable complement to the already existing CSU therapy. Which is proved in study done by, Sindher et al. reported resolution of CSU following treatment with vitamin D in a patient with severe vitamin D deficiency. Another study conducted by Rorie et al[7] showed that vitamin D3 supplementation decreased the symptoms of CSU as well as increases the quality of life of such patients[12-17]

Limitations of the study

Our study had a small sample size. Further large-scale studies are needed to replicate this association. Since Hypovitaminosis D has been recently established in the healthy Indian population, low serum vitamin D levels in most of our chronic urticaria subjects is whether due to inadequate diet, less sunlight exposure, pattern of clothing is unclear.

Furthermore, studies are needed to evaluate the etiopathogenesis of vitamin D and its association in chronic urticaria.

Conclusion

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.

Conflict of Interest: Nil
Source of support: Nil

References

1. Bracken SJ, Abraham S, MacLeod AS. Autoimmune Theories of Chronic Spontaneous Urticaria. Front Immunol. 2019;10:627.
2. Godse KV. Autologous serum skin test in chronic idiopathic urticaria. Indian J Dermatol Venereol Leprol. 2004;70:283-4.
3. Woo YR, Jung KE, Koo DW, Lee JS. Vitamin D as a Marker for Disease Severity in Chronic Urticaria and Its Possible Role in Pathogenesis. Ann Dermatol. 2015;27(4):423-30.
4. Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med. 2011;364:248–254. doi: 10.1056/NEJMcp1009570
5. Ko JA, Lee BH, Lee JS, Park HJ. Effect of UV-B exposure on the concentration of vitamin D2 in sliced shiitake mushroom (Lentinus edodes) and white button mushroom (Agaricus bisporus) J Agric Food Chem. 2008;56:3671–3674. doi: 10.1021/jf073398s.
6. Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J. 2001;15:2579–2585
7. Yu C, Fedoric B, Anderson PH, Lopez AF, Grimbaldeston MA. Vitamin D(3) signalling to mast cells: a new regulatory axis. Int J Biochem Cell Biol. 2011;43:41–46.
8. Hata TR, Kotol P, Boguniewicz M, Taylor P, Paik A, Jackson M, et al. History of eczema herpeticum is associated with the inability to induce human beta-defensin (HBD)-2, HBD-3 and cathelicidin in the skin of patients with atopic dermatitis. Br J Dermatol. 2010;163:659–661.
9. Kongsbak M, Schjerling P, Woetmann A, Odum N, et al. Vitamin D-binding protein controls T cell responses to vitamin D. BMC Immunol. 2014;15:35.
10. Movahedi et al. Vitamin D Deficiency in Chronic Idiopathic Urticaria. Iranian journal of allergy, asthma, andimmunology 2015:1
11. Baroni E, Biffi M, Benigni F et al. VDR-dependent regulation of mast cell maturation mediated by 1, 25-dihydroxyvitamin D3. J Leukoc Biol. 2007;81:250–262.
12. Astri Adelia, Larisa Paramitha Wibawa, Adhimukti T Sampurna, Windy K Budianti, Farida Zubier. The role of oral vitamin D in several skin diseases J Gen Proceed Dermatol Venereol Indones. 2017;2(1):18-23.
13. Chandrashekar L, Rajappa M, Munisamy M et al. 25-Hydroxy vitamin D levels in chronic urticaria and its correlation with disease severity from a tertiary care centre in South India. Clinical Chemistry and Laboratory Medicine (CCLM). 2019;52(6):e115-e118 .
14. Boonpiyathad T, Sangasapaviriya A. Vitamin D supplements improve urticaria symptoms and quality of life in chronic spontaneous urticaria patients: A prospective case-control study. Dermatoendocrinology. 2014;6:e29727.
15. Tuchinda, Papapit et al. "Relationship between vitamin D and chronic spontaneous urticaria: a systematic review." Clinical and translational allergy, 2018:1
16. Sindher SB, Jariwala S, Gilbert J, Rosenstreich D. Resolution of chronic urticaria coincident with vitamin D supplementation Ann Allergy Asthma Immunol. 2012;109:359-60.
17. Rorie A, Goldner WS, Lyden E, Poole JA. Beneficial role of supplemental vitamin D3 treatment in chronic urticaria: A randomized controlled study. Ann Allergy Asthma Immunol. 2014;112:376-82.