

Role of vitamin D supplementation in allergic rhinitis

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Abstract

Background: Allergic rhinitis (AR) is the most common type of chronic rhinitis, affecting 10-20% of the population. Severe AR has been associated with significant impairments in quality of life, sleep, and work performance. A role for vitamin D in the regulation of immune function was first proposed after the identification of vitamin D receptors in lymphocytes. It has since been recognized that the active form of vitamin D, $1\alpha, 25(\text{OH}) 2\text{D}_3$, has direct effects on naïve and activated helper T-cells, regulatory T-cells, activated B-cells and dendritic cells. There is a growing researches linking vitamin D (serum $25(\text{OH}) \text{D}$, oral intake and surrogate indicators such as latitude) to various immune-related conditions, including allergy, although the pattern of this relationship is still yet to establish. Such effects of vitamin D can significantly affect the outcome of allergic responses like in AR. **Aims and Objectives:** To evaluate nasal symptom scores in patients of AR, pre- and post-treatment with and without supplementation of vitamin D. **Materials and Methods:** Vitamin D levels were assessed in 21 patients with AR diagnosed clinically and evaluated prospectively during the period of 1 year. Pre- and post-treatment vitamin D3 serum levels measured and documented. They received oral vitamin D (chole-calciferol; 1000 IU) for a given period. The results were compared with the patients having AR - treated conventionally without supplementation of vitamin D. **Results:** Improvement in the levels of serum vitamin D levels were significant in post-treatment patients ($P = 0.0104$). As well as clinical improvement in terms of reduction in the total nasal symptom score was also significant in the post-treatment patients ($P < 0.05$). **Conclusion:** Supplementation of vitamin D in such patients alters natural course of AR toward significant clinical improvement.

Keywords: Allergic rhinitis, vitamin D supplementation, immune-modulation

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Introduction



Allergic rhinitis (AR) is the most common type of chronic rhinitis, affecting 10-20% of the population, and evidence suggests that the prevalence of the disorder is increasing. Severe AR has been associated with significant impairments in quality of life, sleep and work performance.^[1] There are good treatments available for AR, including antihistamines and topical corticosteroids.^[2] Yet, there is a need for new treatment options, particularly aiming at new targets and associated with reduced side effects. The prevalence varies among countries, probably because of geographic and aeroallergen differences.^{[3],[4],[5],[6]} In India, AR is considered to be a trivial disease, despite the fact that symptoms of rhinitis were present in 75% of children and 80% of asthmatic adults.^[7]

In recent years, the world-wide increase in allergic diseases has been associated with low vitamin D. Schaubert *et al.*^[8] stated that the association between low serum vitamin D levels and an increase in immune disorders is not coincidental. Growth in populations has resulted in people spending more times indoors, leading to less sun exposure and less cutaneous vitamin D production.^[9]

To investigate the value of vitamin D in the treatment of allergic diseases and asthma, several studies have been designed up to date. However still the results are controversial.^{[8],[10],[11]} Vitamin D deficiency can be treated and further it can prevent AR occurrence and thus reduce morbidity. In the presented study, the vitamin D status of patients with AR was compared pre- and post-treatment with oral vitamin D supplements (chole-calciferol - 1000 IU) and course of AR assessed.

Materials and methods



Study design and population

The study included patients with AR, who were referred to Department of ENT in our institute during a 1 year period between December 2011 and December 2012.

- A total of 21 patients between 15 and 50 years age both gender having a history of AR were included in the study. Inclusion criteria were patients having history of AR (perennial) with eosinophilia on blood smear/nasal smear
- All the patients were thoroughly interviewed and complete ENT examination were done
- Total nasal symptoms score (TNSS) recorded pre- and post-treatment
- Serum vitamin D3 levels were measured pre- and post-treatment
- They received tablet fexofenadine (in patients having TNSS score ≤ 10) and fluticasone nasal spray (in patients having TNSS score ≥ 11) for a short period to relieve acute phase without vitamin D3 which was followed supplementation of oral vitamin D3 (chole-calciferol; 1000 IU) in case of deficiency for 21 days

- Exclusion criteria concerned patients who had co-morbid disease in addition to AR that could affect vitamin D serum levels. Such diseases included rheumatoid arthritis, cystic fibrosis, multiple sclerosis, ulcerative colitis, Crohn's disease, celiac disease, rickets, osteomalacia, sarcoidosis and thyroid dysfunctions, and individuals who had received medications including corticosteroids, barbiturates, bisphosphonates, sulfasalazine, omega3 and vitamin D components such as calcium-D were excluded
- Another 21 patients of lower and middle class between 15 and 50 years of age both gender having a history of AR were assessed in the similar way for pre-treatment TNSS and treated using similar criteria i.e. fexofenadine (in patients having TNSS score ≤ 10) and fluticasone nasal spray (in patients having TNSS score ≥ 11) for a short period but without supplementation of vitamin D and followed similarly after given period. Post-treatment TNSS assessed and compared.

Measurements

- Before and after treatment, patients rated their nasal symptoms (i.e., rhinorrhea, nasal blockage, sneezing, nasal itching, anosmia) using four point scale as follows: 0 = No symptom evident, 1 = symptom present but not bothersome, 2 = definite symptom that is bothersome but tolerable, 3 = symptoms that is hard to tolerate. Each patient's TNSS were calculated by summing that patients' nasal symptoms [Table 1] ^[12]
- Serum vitamin D3 levels measured using "Cobas E 411 (fully automated) hormone-immunoassay analyzer." Enhanced Chemi-luminance method used by this instrument for measurement. 25(OH) D levels greater than 30 ng/ml is considered as normal
- While vitamin D deficiency is defined as 25(OH) D levels <20 ng/ml, vitamin D insufficiency defined as 25(OH) D levels between 20 and 30 ng/ml [Table 2]. ^[13] Patients with serum vitamin D levels >30 ng/ml were considered as normal and excluded from the study. Such patients were two in number
- Follow-up Clinical assessment for nasal symptom score and serum vitamin D levels were obtained after 21 days during which patients with deficient vitamin D levels were supplemented with oral vitamin D3 (chole-calciferol; 1000 IU).

Score	0-3	Table 1: Total nasal symptoms scoring system
Rhinorrhea	0-3	
Obstruction	0-3	
Sneezing	0-3	
Itching	0-3	
Anosmia	0-3	
TNSS	Out of 15	
0 - Absent, 1 - Mild, 2 - Moderate, 3 - Severe, TNSS - Total nasal symptoms score		
Vitamin D status	Serum level (ng/ml)	Table 2: Vitamin D status - grading
Normal	>30	
Insufficient	20-30	
Deficient	<20	

Statistical analysis

Data were analyzed using SPSSR software (version 17.0; SPSS, USA). Descriptive statistical analysis and non-parametric statistical tests were used.

Results



Initially there were 23 patients. 2 of them were having levels > 30 ng/ml i.e. normal in our study. Hence they were excluded. Of the 21 patients enrolled in the study, 11 (52.38%) were men and 10 (47.61%) were women [Table 3]. The mean age of the patients was 34.47 ± 9.25 years. Distribution of patients according to age is summarized in [Table 4].

Sex	No. of patients	Percentage
Male	11	52.38
Female	10	47.61
Total	21	100

Table 3: Sex distribution of disease

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Age group (years)	No. of patients	Percentage
20-24	2	9.52
25-29	4	19.04
30-34	5	23.8
35-39	2	9.52
40-44	4	19.04
45-49	4	19.04
Total	21	100

Table 4: Age distribution of disease

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The mean vitamin D level was 18.03 ± 5.61 ng/ml in 21 patients of AR before treatment. Post-treatment mean vitamin D level was 28.92 ± 6.21 ng/ml in 15 patients (71.42%) in which vitamin D level was increased following supplementation of oral vitamin D3 (chole-calciferol; 1000 IU). Rest of the 6 patients (28.57%) showed decrease in the vitamin D level.

Of the 21 patients evaluated, 8 (38.09%) were experiencing severe signs and symptoms of the AR (TNSS > 11), 10 (47.61%) were considered to be moderate (TNSS: 7-10) and 1 (4.76%) were classified as mild (TNSS: 3-6) and 2 (9.42%) were with TNSS: 0-2 [Table 5]. In this group of patients overall mean pre-treatment TNSS score was 10.6 ± 2.65 and post-treatment mean TNSS score was 2.76 ± 1.6 [Table 6].

Study group	TNSS	Vitamin D (21 patients)
Pre-treatment	10.6 ± 2.65	18 ± 5.61
Post-treatment	2.76 ± 1.6	23.91 ± 9.73
Difference	7.84	5.91
TNSS - Total nasal symptoms score		

Table 5: Distribution of patients according to severity- pre and post treatment

Study group	TNSS	Vitamin D (21 patients)
Pre-treatment	10.6 ± 2.65	18 ± 5.61
Post-treatment	2.76 ± 1.6	23.91 ± 9.73
Difference	7.84	5.91
TNSS - Total nasal symptoms score		

Table 6: Pre and post treatment comparison of disease severity and vitamin D levels

Post-treatment improvement in the TNSS were indicated by shifting of patients to a lower TNSS as shown in [Table 6]. The mean vitamin D levels post-treatment were 22.1; 21.22 and 25.86 in the group of patients having TNSS 7-10; 3-6 and 0-2 respectively.

Improvement in the levels of serum vitamin D levels were significant using paired "*t*-test" in our study group ($P = 0.0104$). The clinical improvement in terms of reduction in the total nasal symptom score was assessed using Wicoxan signed rank test for pre- and post-treatment in our study group where value of $P = 0.0001$. Which shows statistically significant differences between these two group [Table 6].

The patients with TNSS > 11 were having mean vitamin D level 16.88 ± 4.65 ng/ml. These patients were improved following treatment suggested by the post-treatment TNSS (mean) 3.77 ± 1.92 . The improvement in the level of vitamin D were also noted in this group with a mean level of 21.54 ± 9.17 ng/ml which was statistically significant ($P < 0.05$). This observation correlates the link of severity of AR with vitamin D deficiency.

In another control group of patients without supplementation vitamin D, the mean pre-treatment TNSS score was 11.04 ± 1.93 which get improved following anti-allergic treatment applying same criteria as for study group and mean post-treatment TNSS score was 4.66 ± 1.99 . In the control group, this improvement in TNSS was also significant when assessed by Wicoxan signed rank test suggested by value of $P = 0.0001$ [Table 7].

Treatment modality	TNSS		Difference
	Mean pre-treatment	Mean post-treatment	
Anti-allergic treatment followed by vitamin D supplementation	10.6 ± 2.65	2.76 ± 1.6	7.84
Anti-allergic treatment only without vitamin D supplementation	11.04 ± 1.93	4.66 ± 1.99	6.34
TNSS - Total nasal symptoms score			

Table 7: Effect of vitamin D supplementation

Discussion

In AR, numerous inflammatory cells, including mast cells, CD4-positive T-cells, B-cells, macrophages, and eosinophils, infiltrate the nasal lining upon exposure to an inciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, molds, and pollens). [14] During the early phase of an immune response to an inciting allergen the mediators and cytokines are released which trigger a further cellular inflammatory response over the next 4-8 h (late phase inflammatory response) which results in recurrent symptoms (usually nasal congestion). [15] Infiltration of inflammatory cells is evident in both seasonal and perennial form, though the magnitude of these cellular changes is somehow different in seasonal and perennial AR. [16]

The T-cells infiltrating the nasal mucosa are predominantly T helper (Th) 2 in nature and release cytokines (e.g. interleukin [IL]-3, IL-4, IL-5, and IL-13) that promote immunoglobulin E (IgE) production by plasma cells. IgE production, in turn, triggers the release of mediators, such as histamine and leukotrienes, which leads to arteriolar dilation, increased vascular permeability,

itching, rhinorrhea (runny nose), mucous secretion, and smooth muscle contraction. ^[1]

In our study, patients of AR showed deficiency in vitamin D indicated by mean vitamin D level of 18.03 ± 5.61 ng/ml before treatment. This result suggests the importance of assessing vitamin D levels in patients of AR. There are other studies recently coming in support of this fact as stated by Arshi *et al.* ^[17] The prevalence of severe vitamin D deficiency was significantly higher in patients with AR than the normal population. In a study performed by Moradzadeh *et al.* ^[18] the prevalence of severe vitamin D deficiency was significantly greater in patients with AR than the normal population (30% vs. 5.1%; $P = 0.03$) demonstrating that there is an association between serum vitamin D levels and AR status. These results may indicate subtle differences in terms of vitamin D metabolism or sensitivity in allergic patients, as hypothesized by Wjst and Hyppönen. ^[19]

In presented study, we supplemented the patients of AR having deficient serum vitamin D levels with oral vitamin D supplements (chole-calciferol-1000 IU) and such patients were followed to evaluate their clinical status regarding AR. There was an improvement in the total nasal symptom score and serum vitamin D level in such patients as it is concluded from the presented study. When the clinical improvement compared in the control group in which vitamin D supplements were not given, they showed a difference of 6.34 in TNSS score which is lower than our study group which showed a difference of 7.84 in TNSS score. When both groups compared statistically using Mann-Whitney U-test, $P = 0.0001$, which shows a significant difference between study group and control group.

As per internet medical database there is no similar study done previously. Our study and its result are more important than other studies mentioned above suggesting a correlation between AR and vitamin D as they did not compare the pre- and post-treatment levels and its clinical correlation.

The improvement in the allergic status can be attributed to the immunomodulator effects of vitamin D on the immune system: Vitamin D regulates the activity of various immune cells, including monocytes, dendritic cells, T and B lymphocytes, as well as immune functions of epithelial cells. ^[20] Furthermore, some immune cells express vitamin D-activating enzymes facilitating local conversion of inactive vitamin D into active calcitriol with subsequent paracrine and autocrine effects. ^{[21],[22]}

As 25(OH) D serum levels are low in individuals and vitamin D influences allergy mediating immune cells such as T-cells and immune functions of cells forming the barriers against allergies such as epithelial cells, one might speculate that vitamin D plays a role in allergy development. First scientist who hypothesized a link between nutritional intake of vitamin D and allergies were Wjst and Dold in 1999. ^[23]

Effect of vitamin D on innate immunity

Innate immune responses comprise all mechanisms that resist infection, but do not require specific recognition of the pathogen. Several aspects of innate immunity are affected by vitamin D.

The expression of pattern recognition receptor, which activates innate immune responses such as Toll-like receptors (TLRs) on monocytes are inhibited by Vitamin D, which leads to suppression of TLR-mediated inflammation. ^[24] Vitamin D induces autophagy in human macrophages, which helps in the defense against opportunistic infections. ^[25] The endogenous antimicrobial peptide in resident epithelial cells in the skin and lung are induced by Vitamin D, thereby strengthening the innate barriers against environmental allergens. ^{[26],[27]}

Effect of vitamin D on adaptive immunity

Lymphocytes such as T-cell with Th1 and Th2 polarization are major players in adaptive immunity and vitamin D modulates their functions.

Pro-inflammatory cytokine release from peripheral mononuclear blood cells in general and from T-cells in particular are decreased by vitamin D. ^{[28],[29]} In addition, T-cell proliferation is suppressed by vitamin D through decreased Th1 cytokine production. ^{[30],[31]} Vitamin D increases IL-10 and decreases IL-2 production, thereby promoting the state of hypo responsiveness in T regulatory cells - an effect which is also seen with anti-allergic therapies such as corticosteroids or allergen immunotherapy. ^{[28],[30]}

Effect of vitamin D on IgE secretion, mast cells and eosinophils

Vitamin D also affects B lymphocytes functions and modulates the humoral immune response including secretion of IgE. ^[31]

Allergy-mediating cells such as mast cells and eosinophils are also vitamin D targets: Increased cutaneous vitamin D synthesis increases IL-10 production in mast cells, which leads to suppression of skin inflammation ^[32] also vitamin D treated mice showed reduced airway hyperresponsiveness and decreased infiltration of eosinophils in the lung. ^[33]

As chronic AR is a decays old problem, management of which is a difficult task for most of clinicians including physicians and otolaryngologists in the current scenario, supplementation of vitamin D to alter the allergic course has emerged as ray of hope.

Conclusion



There is a correlation between serum vitamin D levels and AR. The level of vitamin D being low in patients of AR. Supplementation of vitamin D in such patients alters natural course of AR toward significant clinical improvement. Although more studies with a larger number of patients should be conducted to validate the role of vitamin D supplementation therapy along with initial anti allergic treatment.

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