

The Role of Vitamin D Deficiency and Its Supplementation in the Treatment of Allergic Rhinitis

Dr. Haritosh K. Velankar¹, Dr. Yogesh G. Dabholkar², Dr. Prajakta Deshmukh³,
Dr. Bhavika Verma Bhatt⁴

¹Professor, ²Professor and Head, ³Intern, ⁴Senior Resident,
Department of ENT, D. Y. Patil University School of Medicine.

Corresponding Author: Dr. Yogesh G. Dabholkar

ABSTRACT

Purpose: Many studies have suggested Vitamin D to be a critical player in allergic rhinitis, however this association yet remains uncertain. In this study, the incidence of vitamin D deficiency in allergic rhinitis patients was compared to normal population and the role of Vitamin D in potentiating the action of a steroid spray in allergic rhinitis was evaluated.

Methods: 200 subjects with allergic rhinitis were tested for serum vitamin D levels. A two arms study was carried out in allergic rhinitis patients with vitamin D deficiency wherein one group received treatment with steroid spray and vitamin D while the other group received treatment with steroid spray and placebo for a period of two weeks. The response in both the groups was compared by their total nasal symptom scores. The unpaired 't' test was used for comparison of the two groups.

Results: There was a high prevalence (83%) of vitamin D deficiency in the allergic rhinitis patients. There was a significantly better response in the group which received vitamin D along with a steroid spray.

Conclusion: There is higher prevalence of vitamin D in allergic rhinitis patients and that vitamin D supplementation in these patients potentiates the effect of steroid sprays.

Keywords: Vitamin D, deficiency, allergic rhinitis

INTRODUCTION

Allergic rhinitis and asthma are considered as different manifestations of the same disease under the 'One Airway-One Disease' concept. Along with atopic dermatitis, and the life threatening anaphylaxis, these two are categorized as allergic diseases and have the same underlying mechanism of IgE mediated immune response and hypersensitivity. Vitamin D has been shown to play an important role in asthma, and the concept of a unified airway allows extrapolation of vitamin D as a critical player in allergic rhinitis. [1, 2] A few studies have hinted at a link between vitamin D deficiency and allergic rhinitis. [3, 4] Vitamin D seems to

have an immune-modulator effect by specifically regulating the mechanism which suppresses the inflammatory response. Vitamin D harbors actions more akin to hormones and pro-hormones. [5] The discovery of vitamin D receptor (VDR) has stimulated more research into the nature of this vitamin which has, subsequently, been shown to be a steroid hormone. Investigators have found that vitamin D plays an integral role in induction of cell differentiation, inhibition of cell growth, immunomodulation and regulation of other hormonal systems. [6]

Vitamin D deficiency is very common in India across all ages and both sexes, with a prevalence of 70%-80%. [7-9]

The proposed causes of vitamin D deficiency in India are low dietary calcium and vitamin D intake due to changing food fads or food habits; genetic factors; modern lifestyle which has reduced sun exposure; and cultural and traditional habits of dressing in women which reduce their sun exposure. [10] In India, widely consumed food items such as dairy products are rarely fortified with vitamin D. Consequently, subclinical vitamin D deficiency is highly prevalent in both urban and rural settings, and across all socioeconomic and geographic strata. The role of vitamin D deficiency in the very high prevalence of rickets, osteoporosis, cardiovascular diseases, diabetes, cancer and infections such as tuberculosis in India, is being investigated.

Many studies have explored the link between serum vitamin D levels and atopy, allergy and asthma but have yielded ambiguous and even contradictory results. Some of them demonstrate a link between vitamin D deficiency and presence of allergic rhinitis/atopy, with a poor control and/or frequent exacerbations of concomitant symptoms in those with Vitamin D deficiency. [4, 11, 12]

Other authors, however, question the existence of a relationship and present a contrary picture. Wjst and Hypponen, for instance, found an increase in prevalence of allergic rhinitis with higher vitamin D levels, at all ages. [13] Supplementation of Vitamin D in water soluble form has been shown to be associated with an increased risk of allergic rhinitis up to the age of four years. [14-16]

There is a need for further research in light of these contrasting findings.

This study was undertaken to assess the prevalence of vitamin D deficiency in allergic rhinitis patients, and whether supplementation of Vitamin D will help in the treatment of these patients. After estimating serum vitamin D levels in allergic rhinitis patients, a two arms study was carried out in allergic rhinitis patients

with vitamin D deficiency. Subjects were randomly allocated to two groups. One group received treatment with steroid spray and vitamin D while the other group received treatment with steroid spray and placebo, for a period of two weeks. The primary outcome was taken as the improvement in the total nasal symptom scores. Comparison of the outcome in the two groups showed a significant improvement in both groups with a statistically better response in vitamin D group.

Objectives:

1. To determine the incidence of vitamin D deficiency in patients diagnosed with allergic rhinitis.
2. To study the possible role of oral vitamin D in augmenting the efficacy of intranasal steroid spray for treatment of allergic rhinitis.

MATERIALS AND METHODS

Prior institutional ethical clearance was obtained before the study.

200 men and women between 15 and 60 years of age, with documented allergic rhinitis for more than 2 years were recruited for the study. All patients provided written informed consent before being included in the study. At screening, the study subjects were assessed for inclusion and exclusion criteria, medical history, physical examination and severity of allergic rhinitis. The period of June- July was selected as the weather in this period is cloudy with very little sunshine.

Inclusion and Exclusion Criteria:

Patients were considered for study inclusion if they were between 15 and 60 years of age, had a history of allergic rhinitis symptoms of at least 2 years' duration, and had a positive skin test response to 1 or more allergens (house dust mite, cockroach, mold, and animal dander) within the previous 12 months. At the screening visit, they were required to have allergic rhinitis symptoms with a total nasal symptom score (TNSS) of at least 8 (maximum score 12).

Table 1. Severity score for individual signs and symptoms of perennial allergic rhinitis

Severity score (For each of Sneezing, Rhinorrhoea, Itching and Congestion)	
0 = None	No signs or symptoms present
1 = Mild	Signs/symptoms clearly present but minimal awareness of them; tolerable
2 = Moderate	Clear awareness of signs/symptoms; bothersome but tolerable
3 = Severe	Signs/symptoms difficult to tolerate; might cause interference with activities of daily living, sleeping, or both

Inclusion Criteria:

Patients were required to be in good general health, as confirmed by history, physical examination and routine laboratory tests. Women of childbearing potential were required to have a negative serum pregnancy test at screening and to use a medically accepted method of contraception before screening and during the study.

Exclusion criteria were structural abnormalities interfering with nasal airflow, an upper respiratory tract or sinus infection requiring antibiotic treatment within 14 days before screening, a viral upper respiratory tract infection during the 7 days before screening, and current or past history of recurrent or chronic sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, or asthma that necessitated the regular use of inhaled corticosteroids or use of systemic corticosteroids. Patients with seasonal allergic rhinitis triggered by an allergen pollinating during the time of the study were also excluded. Patients with co-morbid diseases, that affect vitamin D serum levels like rheumatoid arthritis, cystic fibrosis, multiple sclerosis, ulcerative colitis, Crohn's disease, celiac disease, rickets, osteomalacia, sarcoidosis and thyroid dysfunctions, were excluded. Also pregnant women, children (age <14 years) and individuals who were on medications like corticosteroids, barbiturates, bisphosphonates, sulfasalazine, omega3 and vitamin D components such as calcium-D were excluded. Medications prohibited during the study included cromolyn, nedocromil, oral corticosteroids, antihistamines, leukotriene modifiers, intranasal ipratropium bromide, ocular or intranasal saline or systemic antibiotics. Pseudoephedrine was permitted on an as a rescue medication for relief of severe nasal block. Appropriate washout times were required for previous use of prohibited

medications. Patients receiving allergen immunotherapy were excluded. Pregnant or nursing women were also excluded.

All study subjects underwent blood investigation for serum vitamin D levels using the fully automated electrochemiluminescence analyzer COBAS e411, Roche Hitachi. A vitamin D level between 30ng/mL to 100ng/mL was considered normal and vitamin D levels below 30ng/mL deficient. To determine the incidence of vitamin D deficiency in allergic rhinitis patients, the proportion of allergic rhinitis patients with vitamin D deficiency was calculated as percentage of all allergic rhinitis patients.

To study the role of vitamin D supplementation in potentiating the efficacy of intranasal steroid spray all allergic rhinitis patients diagnosed with vitamin D deficiency were enrolled in a randomized, placebo-controlled, double-blind, parallel group study and were randomly allocated to one of the following treatment groups-

1. Placebo Group: treated with intranasal steroids along with placebo
2. Active Group: given oral vitamin D supplements along with intranasal steroids

Thus, all patients were asked to self-administer 27.5 microgram fluticasone furoate nasal spray into each nostril two puffs daily and alternate patients received oral treatment with Vitamin D 60,000 IU sachets or placebo once weekly for 14 days. All the subjects in both groups in second arm of study underwent serum Vitamin D estimation on day 8 and day 14 of study. The overall severity of allergic rhinitis was assessed jointly by investigators and participants at baseline and at subsequent visits by using a 4-point scale (0 = none to 3 = severe). Each symptom was assessed on a 4-point scale (0 = not noticeable, 1 = mild symptoms, 2 = moderate symptoms and 3 =

severe symptoms). Total nasal symptom scores were obtained by adding symptom scores (sneezing, rhinorrhea, nasal obstruction and nasal itching). The total nasal symptom scores on the 1st, 8th and 14th day were taken into consideration for analysis.

Statistical Analysis:

The results were analyzed by GraphPad In Stat using student's unpaired t-test for comparison of total nasal symptom scores between two groups. A *p* value of <0.05 was considered as statistically significant. After exiting the study each patient with Vitamin D deficiency received Vitamin D supplementation for a total of 6 weeks. All subjects after exiting the study received complete treatment of allergic

rhinitis with antihistamines and steroid sprays to induce a remission.

RESULTS

Out of 200 subjects with allergic rhinitis, 166 had a vitamin D deficiency (serum vitamin D level <30 ng/mL). Thus the incidence of Vitamin D deficiency in the subjects with allergic rhinitis was found to be 83%.

All 166 patients who were Vitamin D deficient were enrolled into the randomized, double-blind, placebo-controlled study for investigating the possible role of oral vitamin D supplementation in potentiating the efficacy of intranasal steroid spray for treatment of allergic rhinitis. The enrolled patients had an average age of 30 years. The male to female ratio was 1:1.40.

Table 2. Baseline Demographics:

	Steroid Spray + Vitamin D (n = 84)	Steroid Spray + Placebo (n = 82)
Sex, n (%)		
Women	46 (54.76%)	52 (63.41%)
Men	38 (45.23%)	30 (36.59%)
Mean age, y (range)	33.21 (15-59)	34.26 (15-60)
Mean Vitamin D Level (pre-treatment)	15.89	16.75
Mean Vitamin D Level (post treatment)	22.41	16.23

At baseline, the average level of serum Vitamin D was about 16.31 ng/ml. By the end of the study, the average Vitamin D level of the patients randomized to take weekly vitamin D had increased significantly, while the average levels in the patients in the placebo group had not changed significantly from baseline.

After 2 weeks into the study, the day time total nasal symptom scores fell by an average of 10.65 points in the placebo group compared to 11.59 in the active group, a significant statistical difference. The total nasal symptom score fell dramatically lower in the active group during the 1st week of the study as well as during the second week. In contrast, scores fell more gradually for the placebo group and by the final 14th day of the study there was a statistical difference in the mean day time total nasal symptom score between the 2 groups.

The student's unpaired 't' test was used for comparison between two groups which showed no difference in pre-treatment total nasal symptom scores but significant difference in post treatment total nasal symptom score both after 1 week (*p* value < 0.0001) and after 2 weeks (*p* value < 0.0001). Thus, the post 2 week improvement in total nasal symptom score was significantly better in active group compared to placebo group.

Table 3. Comparison of Total Nasal Symptom Score in the vitamin D and placebo group.

	Test Mean±SD (Range)	Placebo Mean±SD (Range)
Pre- treatment TNSS	11.92 ± 0.28 (11.00-12.00)	11.94 ± 0.24 (11.00-12.00)
8 th Day Post treatment TNSS	6.43 ± 1.33 (4.00-8.00)	7.74 ± 0.7504 (5.00-10.00)
14 th Day Post treatment TNSS	0.33 ± 0.61 (0.00-3.00)	1.29 ± 1.581 (0.00-6.00)

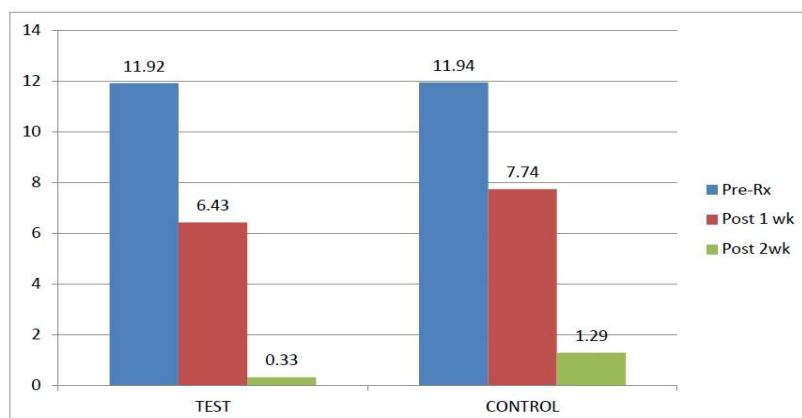


Figure 1: Comparison of Total Nasal symptom scores pre-treatment and post-treatment

DISCUSSION

Our study demonstrated a significant vitamin D deficiency among Indian patients with allergic rhinitis, which could reflect lower sun exposure due to their urban lifestyle and poor dietary intake because of a predominantly vegetarian diet. Saba Arshi et al [4] have reported a high prevalence of vitamin D deficiency in allergic rhinitis patients as compared to the normal population in Iran. We also found a high incidence (83%) of vitamin D deficiency in allergic rhinitis patients in our study. However this is not significantly higher when viewed in light of the otherwise high incidence found in normal population by other researchers in India. [7-9]

Our study demonstrated that vitamin D supplementation had a favorable impact on the treatment of allergic rhinitis with steroid sprays. There was significantly more reduction in the total nasal symptom scores in the group which received vitamin D supplementation in addition to steroid sprays as compared to the group which received treatment with steroid spray along with placebo. As this difference in two groups was more marked in the first week, vitamin D supplementation can be recommended for a faster onset of action of an intranasal steroid spray in allergic rhinitis patients with vitamin D deficiency.

The exact mechanism of vitamin D augmenting the action of inhaled corticosteroids is not known but increasing evidence points to an immunomodulatory action of vitamin D in IgE mediated allergy.

Pichler et al reported an immunoregulatory action of vitamin D in IgE mediated allergy. [17] Vitamin D could improve allergy symptoms directly or indirectly by potentiating the anti-inflammatory effects of the medications used to treat allergy. Searing et al. have suggested the possibility of a vitamin D effect on glucocorticoid pathway and stated that vitamin D insufficiency promotes the need for higher doses of glucocorticoids to achieve treatment effect. [18] Poon AH, Laprise C, et al have identified mutations in vitamin D receptor genes as genetic risk factors for asthma/atopy suggesting that vitamin D receptor may function as a regulator of susceptibility to asthma and atopy. [19]

Steroid sprays are the first-line anti-inflammatory treatment for allergic rhinitis. Their multiple inhibitory properties, including inhibition of Th2 cytokine synthesis, are likely to contribute to clinical efficacy. Glucocorticoids also enhance IL-10 production in vitro by human CD4+ and CD8+ T cells. [20] IL-10 has a potent anti-inflammatory and immunosuppressive effect leading to profound inhibition of Th1 cell-mediated immunity. The expression of IL-10 by B cells is enhanced by not only exogenous, but also autocrine calcitriol, the bioactive metabolite of vitamin D. The role of Vitamin D in potentiating effect of steroids has already been demonstrated in asthma. [18, 21, 22] These studies suggest that vitamin D supplementation will improve patients' response to inhaled corticosteroids.

While clearly effective in the management of allergic rhinitis, corticosteroids come with a variety of potential side effects. Consequently, treatment options for allergic rhinitis that reduce steroid dose can minimize the risk of these adverse effects. Thus, vitamin D supplementation can be prescribed to allergic rhinitis patients according to status of deficiency. This could improve allergy symptoms by enhancing anti-inflammatory effects of medications used to treat allergy

If the prevalence of Vitamin D in general population is brought down we may succeed in arresting the recent pandemic of allergy and asthma and in fact bring down the incidence of allergic diseases. Although, there is adequate sunshine in India, high temperatures during daytime and sultry and humid climate in many areas are deterrents to follow the advice about sun exposure. Hence, food fortification with Vitamin D is a good option to solve this issue. At the same time one must be careful not to overenthusiastically over treat Vitamin D deficiency without actually monitoring Vitamin D levels and land up with hypervitaminosis D. Hypercalcemia, constipation, decreased appetite, lethargy, dehydration, failure to thrive(in children), polyuria, polydipsia, nausea, vomiting, abdominal pain, nephrocalcinosis and headache can be the common clinical features of hypervitaminosis D.

CONCLUSION

Our study has shown that there is a high prevalence of vitamin D deficiency in allergic rhinitis patients in India. Vitamin D supplementation in allergic rhinitis patients with vitamin D deficiency enhances the action of intranasal steroid spray and brings about a faster recovery.

Suggestions and Future Directions:

Our finding that Vitamin D supplementation enhances the effect of intranasal steroid therapy has important implications on potential future directions in allergic rhinitis. While further research is required to explore the link between vitamin D

and allergic rhinitis, we recommend serum vitamin D level estimation in all allergic rhinitis patients and treatment of vitamin D deficiency in these patients. Large multi-center prospective studies are required to confirm the beneficial effect of vitamin D supplementation in the treatment of allergic rhinitis patients.

Compliance with Ethical Standards:

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest:

The authors declare no conflicts of interest with respect to the research and publication of this article.

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