

## "THE ROLE OF VITAMIN D IN ALLERGIC RHINITIS: A CASE CONTROL STUDY"

### Author:

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### ABSTRACT

**Background:** Allergic rhinitis is a symptomatic disorder of the nose, induced after allergen exposure through IgE-mediated inflammation of the mucosal lining of the nose. Vitamin-D modulates innate immunity and adaptive immunity.

**Aims and Objectives:** The aim of our study was to find out the relationship between vitamin-D and allergic rhinitis.

**Materials and Methods:** Vitamin-D, Total IgE, AEC were assessed in 100 patients with allergic rhinitis diagnosed clinically by ARIA 2008 criteria, then patients were divided in two groups, Group A (given Vit-D) and Group B (given Placebo) along with conventional treatment.

**Results:** On Vit-D supplementation, we found an increase in vit-D serum levels and significant improvement in TNSS in AR cases as compared to controls ( $p < 0.001$ ).

**Conclusion:** Vitamin D supplementation with conventional treatment improves Allergic Rhinitis significantly.

**Key words:** Vitamin-D, Allergic rhinitis, Total IgE, TNSS.

### INTRODUCTION

Allergic rhinitis (AR) is a symptomatic disorder of the nose, induced after allergen exposure through IgE-mediated inflammation of the mucosal lining of the nose. AR is a global health

problem that causes major illness and disability worldwide, affecting patients' social life, sleep, and their school and work performance <sup>[1]</sup>. In recent years, the prevalence of allergic diseases has continued to rise. Allergic rhinitis (AR) is one of the most common allergic conditions. Although AR is not a life-threatening condition, it affects the quality of life, academic achievement and work performance <sup>[2]</sup>. The burden of allergic rhinitis is enormous, constituting about 55% of all allergic diseases. About 20-30% of the Indian population suffers from at least one allergic disease. The reported incidence of Allergic Rhinitis in India also ranges between 20% - 30% <sup>[3]</sup>. The recent classification of allergic rhinitis as suggested by ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines <sup>[4]</sup> is on the basis of:

- (1) Duration as "intermittent" or "persistent" disease,
- (2) Severity of symptoms and quality of life as "mild" or "moderate-severe" (Fig.1).

### ARIA Classification



### Fig. 1 ARIA classification

AR typically presents at a younger age group and more common in boys<sup>[5]</sup>.

Diagnosis of AR is mostly based on symptoms and clinical examination, According to Allergic Rhinitis its Impact on Asthma (ARIA) 2008 criteria, patients report one or more typical symptoms of chronic rhinitis (rhinorrhea, nasal obstruction, sneezing, and nasal itching), and showed positive result to at least one aeroallergen in the multiple allergen simultaneous test or allergy skin test<sup>[4]</sup>.

For many patients, a clear history that fits with allergic rhinitis and a corresponding nasal examination will allow a diagnosis to be made confidently. If there is diagnostic uncertainty, then allergy testing should be performed. This will normally be either a skin prick test or specific IgE in the blood<sup>[6]</sup>.

Patients with Allergic rhinitis are often classified as sneeze runners and blockers because of their distinct clinical profile and need of a different treatment approach. In patients who are predominantly sneezers and runners, the main symptoms are sneezing, anterior rhinorrhoea and itchy nose and eyes. On the other hand, blockers have nasal congestion as predominant symptom, wherein nasal blockage and thick mucus can lead to postnasal drip and breathlessness<sup>[7]</sup>.

Along with a clear genetic basis in allergic diseases, environmental factors, including early neonatal nutrition, may have an important influence on allergy development and thus present an opportunity to prevent or delay the onset of the disease. Vitamin D may be an important environmental factor. Evolutionarily, early humans evolved in sun-rich environments and the increased efficiency of vitamin D production in the skin is thought to be a major driving factor in human skin depigmentation as humans migrated away from the equatorial areas<sup>[8,9]</sup>.

The T-cells infiltrating the nasal mucosa are predominantly T helper (Th)-2 in nature and release cytokines (e.g. 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, rhinorrhoea (runny nose), mucous secretion, and smooth muscle contraction<sup>[10]</sup>.

Vitamin D modulates innate immunity and adaptive immunity<sup>[11,12]</sup>. The active form of vitamin D, 1,25-hydroxyvitamin D, induces inhibition of DC (dendritic cells) maturation and suppression of antigen presentation. Vitamin D interferes with T-cell proliferation by suppressing Th1 cytokine secretion. Vitamin D decreases IL-12 production; thus it can reduce the differentiation of Th1 cells and increase the differentiation of Th2 cells, which are responsible for allergic reactions. Vitamin D also modulates the secretion of IgE by interrupting the proliferation of B-lymphocytes<sup>[13-15]</sup>.

Today people are spending more time indoors, leading to less sun exposure and less cutaneous vitamin D production. This has led to decreasing Vitamin D levels in the population<sup>[16]</sup>. In recent years several studies have suggested that the worldwide increase in allergic diseases is associated with low vitamin D. The association between low serum vitamin D levels and an increase in immune disorders has also been shown<sup>[17]</sup>.

Genetically, the vitamin D endocrine system may have an association with AR, which may also influence the etiology of AR, additional studies are needed to better understand how vitamin D influences AR.

So, this study was planned to see the effect of vitamin D supplementation in Allergic Rhinitis patients, to measure vitamin D quantitatively and to see the symptomatic improvement.

### Materials and Methods

This prospective randomized Case-Control comparative study was conducted during the period of September 2018 till August 2019 in the

Department of Otorhinolaryngology, Swaroop Rani Nehru hospital and Moti Lal Nehru Medical College, Prayagraj (U.P.). This study was conducted after due clearance from the Institutional Ethics Committee.

Patients were properly informed regarding the nature of the disease process, potential complication, expected outcomes, and alternative treatments. Written informed consent has been taken from patients before their participation in the study.

### Inclusion Criteria

Patients of age group 10 to 40 years with clinical features of Allergic Rhinitis, as per ARIA guideline. Patients having Serum vitamin D level < 30 ng/mL.

### Exclusion Criteria

Patients having Chronic Rhino-sinusitis and nasal mass. Patients having a history of comorbidity like TB, Diabetes, kidney disease. History of other Allergic conditions like Atopy and Asthma. Immunocompromised patients like HIV & chronic ill patients. Patients who have taken Calcium, vitamin D, corticosteroid, antihistaminics within 3 months prior to the start of study.

### Method

Patients were selected by following inclusion criteria:

**A:** Detailed clinical history according to the Total Nasal Symptom Score (TNSS) was also be evaluated in both the groups. The TNSS consists of the rating of five nasal symptoms (i.e. Rhinorrhoea, Nasal obstruction, Sneezing, Nasal Itching, Anosmia) using four-point scale.

**B:** Examination including Anterior Rhinoscopy, Posterior Rhinoscopy and Diagnostic Nasal Endoscopy (DNE).

**C:** Investigations (Serum Vit D, IgE, Absolute Eosinophil count). Serum 25(OH)D was assayed by

an enzyme-linked immunosorbent assay (ELISA) and the value  $\geq 21$  ng/ml to <30 ng/mL would be considered as insufficient, the deficient value would be  $\geq 10$  ng/ml to <21 ng/mL, severely deficient value would be <10 ng/ml and the normal value would be >30 ng/mL<sup>[18]</sup>.

Patients were divided randomly into 2 groups, Group A and Group B.

**Group A-** in which patients of AR were treated with Vitamin D (1000 IU/day) for 20 weeks along with Standard treatment of AR (case).

**Group B-** in which patients of AR were treated with placebo (control) along with standard treatment of Allergic Rhinitis for the same time period.

### Follow-up

Both the group patients have undergone a detailed clinical examination, investigated for Absolute eosinophil count (per mm<sup>3</sup>), Serum vitamin D (ng/ml), Total IgE (IU/ml) and tests were repeated after a period of 1, 3 & 6 months.

### Statistical analysis

Data were analysed using SPSS software (Version 21.0; SPSS, USA). After clinical observations, the data collected was tabulated and all observed results were then subjected to various statistical analyses as per requirement. A p-value <0.05 was considered as statistically significant.

### Results

A total of 112 patients of Allergic Rhinitis were included, out of these, 5 patients took treatment for allergic rhinitis within 3 months prior to the study, 3 patients had Vitamin D >30 ng/ml, 1 patient was diagnosed as Diabetes Mellitus and 3 patients did not turn up in the follow-up period. Hence, as mentioned in the exclusion criteria, they were excluded from the study. The final study was carried out on 100 patients. The mean age of the patients was  $26.35 \pm 7.31$  years (range 10-40

years). Group A included 19 (38.0%) Females and 31 (62.0%) Males, while Group B included 17 (34.0%) Females and 33 (66.0%) Males.

Table:1

	Group A	Group B	Total
Sex			
Male	31(62%)	33(66%)	64
Female	19(38%)	17(34%)	36
Age(Mean±SD)	26.02±6.72	26.68±6.77	26.35±7.18

Table 2 shows that in Group A improvement in TNSS scoring occurred to a greater extent than Group B. In Group A all 50(100%) patients came under normal TNSS score(1-2) after treatment with Vit D while in Group B 21(42%) came under mild (3-6) and 29(58%) under normal ( $\leq 2$ ) after treatment with placebo.

Table:2 TNSS Distribution in Groups according to Grading

TNSS	Group A(n=50)				Group B(n=50)			
	Baseline	1 <sup>st</sup> Follow up	2 <sup>nd</sup> follow up	3 <sup>rd</sup> follow up	Baseline	1 <sup>st</sup> Follow up	2 <sup>nd</sup> follow up	3 <sup>rd</sup> follow up
Severe ( $\geq 11$ )	4(8%)	0(0%)	0(0%)	0(0%)	5 (10%)	0(0%)	0(0%)	0(0%)
Moderate (7-10)	40(80%)	0(0%)	0(0%)	0(0%)	39(78%)	1 (2%)	0(0%)	0(0%)
Mild(3-6)	6(12%)	37 (74%)	7 (14%)	0(0%)	6 (12%)	45 (90%)	24 (48%)	21 (42%)
Normal ( $\leq 2$ )	0 (0%)	13 (26%)	43 (86%)	50 (100%)	0(0%)	4 (80%)	26 (52%)	29 (58%)

Fig:2 TNSS distribution in Groups

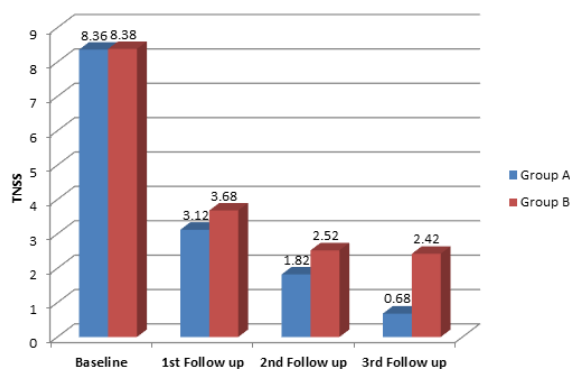


Table 3: Comparison of TNSS Values between the groups

TNSS	Group A		Group B		t-value	p-value
	Mean	SD	Mean	SD		
Baseline	8.36	1.52	8.38	1.86	0.06	0.953
1st Follow up	3.12	0.96	3.68	0.98	2.89	<b>0.005</b>
2nd Follow up	1.82	0.75	2.52	0.91	4.21	<b>&lt;0.001</b>
3rd Follow up	0.68	0.59	2.42	0.64	14.15	<b>&lt;0.001</b>

On comparing the TNSS values between the groups, it was found that at Baseline the mean TNSS of Group A and B were almost the same, whereas at 1st follow up (1 month), the mean TNSS of Group A was less than the Group B and difference was found statistically significant (p value=0.005), and at 2nd follow up (3 month), the mean TNSS of Group A was less than the Group B and difference was found to be statistically significant (p value<0.001).

At 3rd follow up (6 months) the mean TNSS of Group A was less than Group B and difference was found statistically significant (p value<0.001).

Table 4: Vit D Distribution in Groups according to Grading Vit D	Group A(n=50)				Group B(n=50)			
	Baseline	1 <sup>st</sup> Follow up	2 <sup>nd</sup> follow up	3 <sup>rd</sup> follow up	Baseline	1 <sup>st</sup> Follow up	2 <sup>nd</sup> follow up	3 <sup>rd</sup> follow up
Normal(=30)	0(0%)	15(30%)	49(0%)	50(100%)	0(0%)	1(2%)	2(4%)	1(2%)
Insufficient (=20-730)	12(24%)	27(54%)	1(2%)	0(0%)	15(30%)	15(30%)	14(28%)	18(36%)
Deficient(=10-720)	21(42%)	8 (16%)	0 (0%)	0(0%)	24(28%)	26(52%)	28 (56%)	25 (50%)
Severely Deficient (<10)	17 (32%)	0 (0%)	0 (0%)	0 (0%)	11(22%)	8 (16%)	6 (12%)	6 (12%)

Table 4 shows that in Group A, Vit D level significantly improved and all the 50 patients came into normal Vit D level. While in Group B only 1(2%) patient achieved the normal Vit D level, and 18(36%) were in insufficient group, 25(50%) in deficient and 6(12%) were in severely deficient group.



Figure 3: Change in Vit D in Groups

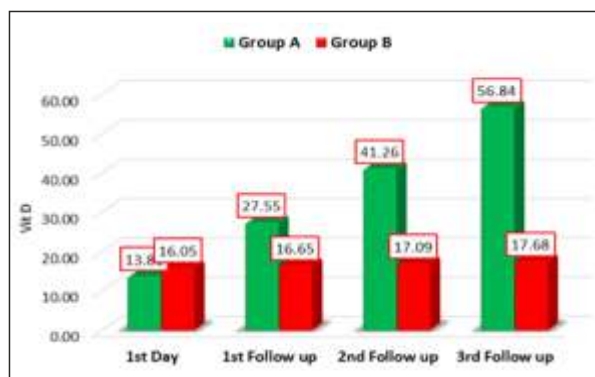


Figure 3 shows that the improvement in Vit D level is much more in Group A comparatively Group B.

Table 5: Comparison of AEC Changes from Baseline (1<sup>st</sup> Day) to different Duration of Study in Groups

AEC	Group – A				Group – B			
	Mean	SD	t-value	p-value	Mean	SD	t-value	p-value
Baseline	351.82	283.56			490.94	547.32		
1st Follow up	305.04	181.77	0.98	0.328	473.04	531.31	0.16	0.869
2nd Follow up	268.54	142.82	1.85	0.067	442.18	455.76	0.48	0.629
3rd Follow up	242.36	126.55	2.49	<b>0.014</b>	427.08	401.43	0.66	0.507

Table 5 shows that in Group A, the mean changes in AEC from Baseline to 1st and 2nd follow-ups were statistically insignificant with p value=0.328 and p value=0.067 respectively while in 3rd follow up it is statistically significant p value=0.014. In Group B, the mean changes in AEC from Baseline to 1st, 2nd, and 3rd follow-ups were statistically insignificant with p value=0.869, p value=0.629 and p value=0.507 respectively. The magnitude of change in group A was more than group B, as the t-value of 3rd follow up in group A was greater than group B (t=2.49 vs t=0.66).

Table 6: Comparison of AEC values between the groups

AEC	Group A		Group B		t-value	p-value
	Mean	SD	Mean	SD		
Baseline	351.82	283.56	490.94	547.32	1.59	0.114
1st Follow up	305.04	181.77	473.04	531.31	2.11	<b>0.037</b>
2nd Follow up	268.54	142.82	442.18	455.76	2.57	<b>0.012</b>
3rd Follow up	242.36	126.55	427.08	401.43	3.10	<b>0.002</b>

In Table 6 on comparing the AEC values between the groups, it was found that at Baseline the mean AEC values of Group B was relatively more than the Group A and difference was not found statistically significant (p value=0.114), whereas at 1<sup>st</sup> follow up the mean AEC values of Group A was less than the Group B and the difference was found statistically significant (p value=0.037). At 2<sup>nd</sup> follow up the mean AEC values of Group A was less than the Group B and the difference was found statistically significant (p value=0.012), and at 3<sup>rd</sup> follow up the mean AEC values of Group A was less than the Group B and the difference was found statistically significant (p value=0.002).

## Discussion

In our study the mean age of the AR patients was 26.35±7.18 years, which closely resembles with similar studies of **Saba Arshi et al**<sup>[19]</sup>, **Vijay Kumar et al**<sup>[20]</sup>, **Manuprita Sharma et al**<sup>[21]</sup> 26.2±1.1 years, 29.36 years and 29.68±7.82 years respectively.

In our study the number of males (64%) was higher than the number of females (36%) similar to the other studies conducted by **Datt Modh et al**<sup>[18]</sup>, out of the 21 patients enrolled, 11 (52.38%) were men and 10 (47.61%) were women, another study conducted by **Balakrishnana Menon et al**<sup>[22]</sup>, out of 48 patients 25 (52.08%) were male and 23 (47.92%) were female. Study by **Hai-Yan Wu et al**<sup>[23]</sup> showed that the majority of the participants were male (92%), and studies by **Manuprita Sharma et al**<sup>[21]</sup> and **Sunita Agarwal et al**<sup>[24]</sup> showed male preponderance.

In post treatment the mean TNSS values of Group A and B were 0.68±0.59 and 2.42±0.64

respectively ( $p$  value < 0.001). i.e. statistical comparison between these two groups was highly significant. In a similar study of **DattModh et al**<sup>[18]</sup> overall mean pre-treatment TNSS score was  $10.6 \pm 2.65$  and post-treatment mean TNSS score was  $2.76 \pm 1.6$ . Another similar study of **Upadhyay P and Jain R**<sup>[25]</sup>, showed that there was significant reduction in the TNSS in the post-Vitamin D supplemented group.

In this study the pre-treatment mean serum Total IgE level was  $503.82 \pm 428.44$  IU/ml in Group A (cases, who were given Vitamin D along with conventional treatment) and post treatment the mean serum Total IgE level was  $365.80 \pm 311.30$  IU/ml, while in Group B (controls, who were given Placebo along with conventional treatment) Total IgE level was  $514.66 \pm 463.47$  IU/ml in pre-treatment and  $467.09 \pm 415.0$  IU/ml in post-treatment respectively. This shows that Vit D supplementation lower down the Total IgE level, but it was statistically insignificant ( $p$  value = 0.170).

In our study the pre-treatment mean AEC (Absolute eosinophil count) was  $421.38 \pm 441.49/\text{mm}^3$  in total patients, while in group A and B the pre-treatment mean AEC were  $351.82 \pm 283.56/\text{mm}^3$  and  $490.94 \pm 547.32/\text{mm}^3$  respectively, and in post-treatment the total mean AEC was  $334.72 \pm 311.83/\text{mm}^3$ , while in group A and in group B post-treatment mean AEC were  $242.36 \pm 126.55/\text{mm}^3$  and  $427.08 \pm 401.43/\text{mm}^3$  respectively. On comparing the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> follow ups of Group A and Group B, the difference was found statistically significant as the  $p$ -values were 0.037, 0.012 and 0.002 respectively.

**Conclusion:** Our study concluded that Allergic Rhinitis is associated with low Vitamin D level and after Vitamin D supplementation with conventional treatment improves Allergic Rhinitis significantly.

Allergic Rhinitis has a multifactorial aetiopathogenesis, multiple prognostic markers (TNSS, Vit D, Total IgE, AEC) should be considered

rather than single marker for diagnosis and treatment.

Vitamin D should be given along with conventional treatment in Allergic Rhinitis patients.

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