

Deficiency of Vitamin D in Allergic Rhinitis: A Possible Factor in Multifactorial Disease

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ABSTRACT

Allergic rhinitis is a common condition affecting 5 to 40% of general population and its prevalence is increasing. It is a chronic condition characterized by inflammation of nasal mucosa. As per recent studies, there is an association between serum vitamin D levels and allergic rhinitis status. Vitamin D has major role in the regulation of calcium metabolism. In addition to this, it also has a number of immunological effects and takes part in immunomodulation, which can significantly affect the outcome of allergic responses like in allergic rhinitis.

Aims and objectives: To establish the correlation between vitamin D3 serum levels and allergic rhinitis.

Materials and methods: Vitamin D levels were assessed in 23 patients with allergic rhinitis diagnosed clinically by allergic rhinitis and its impact on asthma 2008 criteria and results were compared with vitamin D status in the normal population of same region.

Results: The levels of serum vitamin D levels were significantly low in the patients of allergic rhinitis.

Conclusion: Measuring of serum levels of vitamin D could be considered in the routine assessment of patients with allergic rhinitis.

Keywords: Allergic rhinitis, Vitamin D deficiency, Calcitriol.

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INTRODUCTION

Allergic rhinitis is a major atopic condition. Allergic rhinitis is a common health problem caused by inflammatory reaction after allergen exposure and associated with an immunoglobulin E (IgE) mediated immune response against allergen. It is the most common form of the noninfectious rhinitis. It is not a life-threatening condition but in most cases it interferes with the patient's personal life and imposes a substantial burden on public health in economic terms of the quality of life and productivity.¹ There are good treatments available for allergic rhinitis, 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 aero-allergen differences.³⁻⁶ Allergic rhinitis affects between 10 and 30% of all adults and as many as 40% of children. In India, allergic rhinitis (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 One-sixth of Canadians suffer from this disorder.⁸

Low serum 25 (OH) vitamin D levels are prevalent in every region studied (e.g. very low levels are most common in regions such as south Asia and the Middle East).⁹ In recent years, the worldwide increase in allergic diseases has been associated with low vitamin D. Schaubert et al¹⁰ 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.¹¹

Several studies have been designed to investigate the value of vitamin D in the treatment of allergic diseases and asthma, but still the results are controversial.^{10,12,13}

MATERIALS AND METHODS

Study Design and Population

The study included patients with allergic rhinitis, who were referred to department of ENT in our institution, during a 1 year period between December 2011 and December 2012.

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Table 1: TNSS scoring system¹⁴

Score	0 to 3
Rhinorrhea	0 to 3
Obstruction	0 to 3
Sneezing	0 to 3
Itching	0 to 3
Anosmia	0 to 3
TNSS	Out of 15

0: Absent; 1: Mild; 2: Moderate; 3: Severe

Table 3: Age distribution

Age group (years)	No. of patients	Percentage
20-24	2	8.69
25-29	4	17.39
30-34	5	21.7
35-39	3	13.04
40-44	4	17.39
45-60	5	21.7
Total	23	100

- Twenty-three patients of lower and middle class between 15 and 60 years of age both gender having history of allergic rhinitis were included in the study. Inclusion criteria were patients having history of allergic rhinitis (perennial) and diagnosed clinically using allergic rhinitis and its impact on asthma (ARIA) 2008 criteria¹¹ with eosinophilia on blood smear/nasal smear.
- All the patients were thoroughly interviewed and complete ENT examination were done.
- Nasal symptoms score were recorded.
- Serum vitamin D3 levels were measured.
- Exclusion criteria concerned patients who had comorbid disease in addition to allergic rhinitis 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, omega 3 and vitamin D components, such as calcium D were excluded.
- The study results of vitamin D serum levels in allergic rhinitis were compared with the vitamin D serum levels of normal individuals having no history of allergic rhinitis or allergic disease or any other illness that affect serum levels of vitamin D.

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

Table 2: Sex distribution

Sex	No. of patients	Percentage
Male	11	47.82
Female	12	52.18
Total	23	100

Table 4: Distribution of patients according to symptoms score

Total nasal symptom score (TNSS)	No. of patients
>11	9 (39.13%)
7 to 10	13 (56.52%)
3 to 6	1 (4.34%)
0 to 2	0

bothersome but tolerable, 3 = symptoms that is hard to tolerate. Each patients total nasal symptoms scores – TNSS were calculated by summing that patients' nasal symptoms (Table 1).¹⁴ Serum vitamin D3 levels measured using 'Cobas E 411 (fully automated) Hormone-immunoassay analyzer'. Enhanced chemiluminescence method used by this instrument for measurement. Twenty-five (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.¹⁵ Patients with serum vitamin D levels >30 ng/ml were considered as normal. Such patients were two in number.

Statistical Analysis

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

RESULTS

Among 23 patients, male patients were 11 (47.82%) and female patients were 12 (52.18%) as shown in Table 2. The mean age was 35.3 ± 9.63 years. Distribution of patients according to age is summarized in Table 3.

The mean vitamin D level was 19.52 ± 7.35 ng/ml in 23 patients of allergic rhinitis. Of the 23 patients evaluated, 9 (39.13%) were experiencing severe signs and symptoms of the allergic rhinitis (TNSS >11), 13 (56.52%) were considered to be moderate (TNSS: 7-10) and 1 (4.34%) were classified as mild (TNSS: 3-6) (Table 4).

Twenty-five (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 is defined as 25(OH) D levels between 20 and 30 ng/ml (Table 5).¹⁴

The results of the study when compared to the control group consist of 23 normal individuals of age group ranging from 15 to 60 years having no history of allergic

Table 5: Grading according to vitamin D level¹⁵

Vit. D status	Serum level (ng/ml)	No. of patients
Normal	>30	2 (8.69%)
Insufficient	20-30	6 (26.08%)
Deficient	<20	15 (65.21%)
Total	—	23

rhinitis or other allergic disease or any other illness that can affect serum levels of vitamin D, we found there was significant difference. Mean serum vitamin D level of the normal individuals 34.94 ± 15.65 ng/ml, while it was 19.52 ± 7.35 ng/ml in 23 patients of allergic rhinitis being low with statistically significant at p-value of 0.00059 (<0.05) suggesting deficiency in patients of allergic rhinitis.

Moreover, the deficiency was more pronounced in the patients having severe allergic rhinitis as shown in Table 6, the patients with TNSS > 11 were having mean vitamin D level 16.88 ng/ml.

DISCUSSION

In allergic rhinitis symptoms arise as a result of local inflammation induced by aeroallergens such as pollens, molds, animal dander and house dust mites. The immune response involves the release of inflammatory mediators and the activation and recruitment of different inflammatory cells to the nasal mucosa.¹⁶ Infiltration of inflammatory cells is evident in both seasonal and perennial form, although the magnitude of these cellular changes is somehow different in seasonal and perennial allergic rhinitis.¹⁷

A characteristic feature of allergic inflammation is local accumulation of inflammatory cells including T lymphocytes, mast cells, eosinophils, basophils and neutrophils.¹⁸ Release of various mediators from these cells is responsible for the symptoms of allergic rhinitis.²⁰ Accumulation of additional inflammatory cells such as eosinophils and T cells occurs in response to various chemokines and cytokines.

Vitamin D and Immunomodulation

Vitamin D has immunomodulatory steroid hormone properties and directly affects dendritic cell, monocyte, macrophage, B cell, and T cell functions^{21,22} (Fig. 1: vitamin D effects on immune system).¹⁹

The vitamin D receptor (VDR) and vitamin D metabolizing enzymes are expressed by several cells of the immune system like Th1 and Th2 cells. They are the direct targets of the activated form of vitamin D, 1,25-dihydroxyvitamin D3. Indeed, activation of CD4+ T cells results in a five-fold increase in VDR expression, enabling calcitriol to regulate at least 102 identified genes.²³

Table 6: Correlation of symptoms severity with vitamin D levels

Total nasal symptom score	No. of patients	Mean Vit. D levels in ng/ml
>11	9 (42.85%)	16.88
7 to 10	11 (52.38%)	18.15
3 to 6	1 (4.76%)	26.3
0 to 2	0	0

This regulatory effect has a downstream impact on the levels of circulating chemokines and cytokines. Th1 cells secrete interferon gamma (IFN γ), interleukin (IL)-2, IL-12, and tumor necrosis factor alpha (TNF α), all of which augment the cell-mediated defense against intracellular pathogens. Th2 cells express IL-4, IL-5 and IL-13, which further propagate the Th2 response. These Th2-derived cytokines modulate the immune response against parasites and are also associated with the regulation of atopy and asthma.^{24,25}

Vitamin D exerts suppressive effect on the expression of IL-2 and IFN γ in a VDR-regulated mechanism. The suppression of IL-2 production, in turn, inhibits T-cell proliferation. Addition of exogenous IL-2 can rescue T-cells from the anti proliferative effects of vitamin D.¹ Vitamin D blocks the induction of Th1 cytokines, especially IFN γ , while simultaneously enhancing Th2 responses through the enhancement of IL-4 production.^{26,27} Overall, vitamin D decreases cell-mediated immune responses. This suppressive effect on humoral immunity is facilitated through the effect of vitamin D3 on APC. In APCs, calcitriol inhibits the production of IL-12, a cytokine that normally enhances the Th1 response.²⁷ In effect, vitamin D acts as a physiologic ‘brake’ on humoral immunity.

Similarly, vitamin D also inhibits the innate immune system. Vitamin D inhibit the differentiation, maturation, and immune-stimulating ability of dendritic cells by downregulating the expression of MHC class II molecules.²⁰ Immature dendritic cells promote T-cell tolerance, whereas mature dendritic cells activate naive T cells. Physiologic levels of vitamin D inhibit the maturation of dendritic cells and maintain an immature and tolerogenic phenotype with inhibition of activation markers such as MHC class II, CD40, CD80 and CD86 and up regulation of inhibitory molecules.

Vitamin D concurrently suppresses IL-12 and enhances IL-10 production in these dendritic cells.²⁸ The net response is a decrease in Th1 responses and proliferation of T regulator cells which act as a further ‘check’ on the immune response. The immune response is skewed toward a Th2 response with a significant suppression of the Th1 response.^{26,27} Thus, vitamin D may have a suppressive effect on inflammation at the level of the nasal mucosa, potentially influencing the



development and propagation of CRS. Interestingly, vitamin D has also been shown to have a stimulatory effect on monocytes *in vitro*, suggesting a complex role in immune homeostasis rather than a purely suppressive effect on the immune system.²⁰ The extent of this physiologic balance has yet to be fully elucidated.

In our study, patients of allergic rhinitis showed deficiency in vitamin D indicated by mean vitamin D level of 19.52 ± 7.35 ng/ml. This result suggests the importance of assessing vitamin D levels in patients of allergic rhinitis. There are other studies recently coming in support of this fact as stated by Saba Arshi et al²⁹ The prevalence of severe vitamin D deficiency was significantly higher in patients with allergic rhinitis than the normal population. In a study performed by Moradzadeh et al³⁰ the prevalence of severe vitamin D deficiency was significantly greater in patients with allergic rhinitis than the normal population (30% vs 5.1%; $p = 0.03$) demonstrating that there is an association between serum vitamin D levels and allergic rhinitis status. These results may indicate subtle differences in terms of vitamin D metabolism or sensitivity in allergic patients, as hypothesized by Wjst et al.³¹

As Bruce W Hollis stated 'The assessment of vitamin D is rapidly becoming an important tool in the diagnosis and management of much diverse pathology'³² therefore measuring serum levels of vitamin D could be considered in the routine assessment of patients with allergic rhinitis.

Hypponen et al³³ showed that IgE concentrations were higher for participants with low 25(OH) D (<25 nmol/l) and with very high 25(OH) D serum levels (>135 nmol/l) compared with a reference group (100-125 nmol/l). Thus very low and very high levels are associated with elevated IgE levels in adults. For allergic diseases like chronic rhinosinusitis, current clinical studies have shown that such patients had 25(OH) D serum levels that were 40 to 50% lower than the serum 25 (OH) D levels in the control group.^{34,35} In contrast, the incidence of allergic rhinitis correlated with increasing 25 (OH) D levels in early studies from 1930 to 1962 long before vitamin D re-entered the spotlight as an allergy influencing factor.³⁶ But still, vitamin D intake above current dietary recommendations was not related with an increased risk of adverse events.³⁷

Although, our results are extremely compelling, the study suffers from a small sample size. Future work may extrapolate these data to a larger patient set up and their study, mainly through a prospective study, which would help us to understand the role of vitamin D in the pathophysiology of allergic inflammation. Serum vitamin D levels could, potentially, be added to the routine workup of patients suffering from allergic rhinitis and these data

could be used to help determine the disease severity and possibly even treatment.

CONCLUSION

There is a correlation between serum vitamin D levels and allergic rhinitis. The level of vitamin D is being low in patients of AR. Therefore measuring of serum levels of vitamin D could be considered in the routine assessment of patients with allergic rhinitis. To further evaluate vitamin D and its relationship to allergic rhinitis, Randomized controlled trials are needed. These findings may then guide researchers to pursue clinical trials aimed at evaluating vitamin D and its analogs as potential therapeutic interventions and addition of vitamin D in the therapeutic regimen for treatment of allergic rhinitis can possibly reduce the severity of the disease and may control the frequent attacks of allergic rhinitis.

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