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Role of Vitamin D Supplementation in Allergic Rhinitis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Allergic Rhinitis (AR) is one of the inflammatory diseases of the nasal mucosa, caused by immunoglobulin E (IgE) after allergens exposure, Severity measurement of the AR symptoms can be conducted subjectively by counting the total nasal symptom score (TNSS) and objectively by counting the serum IgE levels. Vitamin D (VD) plays a significant part in inborn and adaptive immunity; however, this is not completely understood. It is reported that over 900 genes are regulated by VD. The aim of this study is to assess the role of VD supplementation in AR.
Methods: This prospective randomized controlled study was carried out on 90 patients Test group (n = 45): received standard medications and supplementation of oral VD3 (cholecalciferol; 1000 IU) for 3 months. Control group (n = 45): received standard medications without supplementation of oral VD3.
Results: Comparison between both groups showed insignificant difference between both groups in VD level at the start of the study. According to TNSS in test group, there was significant improvement after 3 months compared to before the study. According to TNSS in control group, there was significant improvement after 3 months than before the study. There was significant improvement in test group than control group as regard to TNSS after 3 months.
Conclusions: There was highly significant reduction in the TNSS after VD supplementation. Thus, VD supplementation alters the course of AR towards clinical improvement.

Keywords: Allergic rhinitis; vitamin D; total nasal symptom score.

1. INTRODUCTION

Allergic Rhinitis (AR) is one of the inflammatory diseases of the nasal mucosa, caused by immunoglobulin E (IgE) after allergens exposure, which affects 10-20% of total population and keeps increasing [1].

Severity measurement of the AR symptoms can be conducted subjectively by counting the total nasal symptom score (TNSS) and objectively by counting the serum IgE levels. Moderate to severe AR present in around 67.5% of the AR population and affects the quality of life [2].

Classical symptoms of AR (according to AR and its Impact on Asthma (ARIA)) are nasal itching, sneezing, rhinorrhea and nasal congestion. Ocular symptoms are also frequent, allergic rhino conjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drips and cough [3].

Vitamin D (VD) was usually linked with bone mineralization, calcium level in plasma, and deposition in bone, but now VD is considered to have an immunomodulatory role, especially in allergic diseases. Low serum VD3 level in the body is now considered as a risk factor for many immune-linked diseases such as allergic diseases − for example, asthma and recurrent upper respiratory tract infection. VD plays a significant part in inborn and adaptive immunity; however, it is not completely understood. It is reported that over 900 genes are regulated by VD. This action of VD has gained immense acceptance after the discovery of VD receptor (VDR) in lymphocytes. Several studies have shown that VD prevents the increase of CD41 T-cells and decreases the creation of Th1 cytokines IL-17. However, due to alterations in target cells timing and quantity of vitamin administration, studies have shown contrasting results. Evidence suggests that innate immunity is activated by the production of anti-microbial peptide LL-37 by macrophages. The adaptive immune system increases the production of T-cells and modifies the functions of antigen-presenting cells (APCs), of dendritic cells. In addition, VD has been revealed to improve and inhibit IL-4 production by naive T-cells [4,5].

Vitamin D plays a significant part in inborn and adaptive immunity; however, it is not completely understood. It is reported that over 900 genes are regulated by vitamin D. This action of vitamin D has gained immense acceptance after the discovery of vitamin D receptor (VDR) in lymphocytes. Several studies have shown that vitamin D prevents the increase of CD41 T-cells and decreases the creation of Th1 cytokines IL-17. However, due to alterations in target cells timing and quantity of vitamin administration, studies have shown contrasting results. Evidence suggests that innate immunity is activated by the production of anti-microbial peptide LL-37 by macrophages. The adaptive immune system increases the production of T-cells and modifies the functions of antigen-presenting cells (APCs), of dendritic cells. In addition, vitamin D has been revealed to improve and inhibit IL-4 production by naive T-cells [4,5].

It has been suggested that modernization and westernization have led to vitamin D deficiency among world population. Since, the majority of the population spends time indoors away from sun exposure, leading to vitamin D deficiency. The role of vitamin D in asthma is not yet clear. Few cross-sectional surveys had suggested a probable link between asthma and vitamin D [6].

The aim of this study is to assess the role of VD supplementation in AR.

2. PATIENTS AND METHODS

This prospective randomized controlled study was carried out at the department of otorhinolaryngology, Tanta university hospitals from January 2019 to December 2019. 90 patients were included in this study, with age varying from 15-50 years old, clinically diagnosed AR according to (ARIA criteria [3]).

The inclusion criteria: Patients having history of AR (perennial) and clinically diagnosed according to the criteria of AR [3] with serum VD level < 30 ng/ml.

Concerned patients who had co-morbid diseases in addition to AR that could affect VD serum levels (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 VD components such as calcium-D) were excluded.

All patients were subjected to: Complete history, Complete *Ear Nose and Throat* (ENT) examination including endoscopic evaluation with otoscope. VD level: VD was estimated in all subject included in the study by Enhanced Chemiluminescence method on Diasorin Liaison analyzer using "Liaison 25OH VD Total" kits. VD deficiency is defined as 25(OH) D levels <20ng/ml, VD insufficiency was defined as 25(OH) D levels between 20 to 30 ng/ml. Patients with serum VD levels > 30 ng/ml were considered as normal and were excluded from the study.

Subjects were randomly allocated to two groups: Test group (n = 45): received standard medications and supplementation of oral VD3 (cholecalciferol; 1000 IU) for 3 months. Control group (n = 45): received standard medications without oral VD3 supplementation. All subjects in both groups received standard medications in the form of intranasal Azelastine – one spray in both nostrils twice daily. In addition, subjects in the Test group received oral VD3 (Cholecalciferol; 1000 IU) for 3 months while those in Control group received placebo for the same duration.

The TNSS was also evaluated in both the groups before the study and post treatment. The TNSS consists of rating of five nasal symptoms (i.e. Rhinorrhea, Nasal obstruction, Sneezing, Nasal Itching, Anosmia) using four point scale as follows: 0=no symptom evident (Absent), 1= symptom present but not bothersome (Mild), 2= definite symptom that is bothersome but tolerable (Moderate), 3=symptoms that is hard to tolerate (Severe). Each patients total nasal symptoms scores – TNSS was calculated by summing that patients nasal symptoms and scored out of 15 [7]**.**

2.1 Statistical Analysis

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student t-test. Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

3. RESULTS

Regarding patients' characteristics, Comparison between both groups showed insignificant differences as regard to both age and sex.

Table 1. Patients' characteristics in both groups

		Test group (n = 45)	Control group (n = 45)	P value
Age (years)	Mean ± SD	29.9 ± 9.5	31.2 ± 10.8	0.576
	Range	16-50	15-50	
Sex	Male	15 (33.3%)	13 (28.9%)	0.649
	Female	30 (66.7%)	32 (71.1%)	
VD (ng/mL)	Mean ± SD	16.8 ± 3.5	15.4 ± 3.8	0.08
	Range	8.3-24.4	7-20	

Table 2. TNSS in test group

	Before	After	P value
1. Rhinorrhea	3 (1-3)	2 (0-3)	<0.001*
2. Nasal obstruction	2 (0-3)	1 (0-2)	<0.001*
3. Sneezing	2 (0-3)	1 (0-3)	<0.001*
4. Nasal itching	2 (0-3)	1 (0-2)	<0.001*
5. Anosmia	1 (0-3)	0 (0-3)	<0.001*
Total	10 (6-13)	5 (1-8)	<0.001*

Table 3. TNSS in control group

	Before	After	P value
1. Rhinorrhea	3 (1-3)	2 (1-3)	<0.001*
2. Nasal obstruction	2 (1-3)	2 (1-3)	0.002*
3. Sneezing	2 (0-3)	2 (0-3)	0.005*
4. Nasal itching	2 (0-3)	2 (0-3)	0.121
5. Anosmia	1 (0-2)	0 (0-2)	0.563
Total	9 (5-13)	8 (5-12)	<0.001*

Table 4. TNSS before the study and after 3 months in both groups

		Test group (n = 45)	Control group (n = 45)	P value
TNSS before the study	Median	10	9	0.897
	Range	6-13	5-13	
TNSS After 3 months	Median	5	8	<0.001*
	Range	1-8	5-12	

Regarding VD level at the start of the study, Comparison between both groups showed insignificant difference between both groups in VD level at the start of the study Table 1.

According to TNSS in test group, there was significant improvement after 3 months compared to before the study Table 2.

According to TNSS in control group, there was significant improvement after 3 months than before the study Table 3.

Regarding TNSS before the study Comparison between both groups showed insignificant difference between both groups, but there was significant improvement in test group than control group as regard to TNSS after 3 months. Table 4

4. DISCUSSION

AR 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. VD has been shown to play an important role in asthma, and the concept of a unified airway allows extrapolation of VD as a critical player in AR [8].

A few studies such as Jung et al., 2013 [9] have hinted at a link between VD deficiency and AR. VD seems to have an immune-modulator effect by specifically regulating the mechanism which suppresses the inflammatory response. VD harbors actions more akin to hormones and pro-hormones. The discovery of VD 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 VD plays an integral role in induction of cell differentiation, inhibition of cell growth, immunomodulation and regulation of other hormonal systems. VD deficiency is very common in India across all ages and both sexes, with a prevalence of 70%-80%.

Many studies such as Gupta et al., 2011 [10] have explored the link between serum VD levels and atopy, allergy and asthma but have yielded ambiguous and even contradictory results. Some of them demonstrate a link between VD deficiency and presence of AR/atopy, with a poor control and/or frequent exacerbations of concomitant symptoms in those with VD deficiency.

Other authors such as Gale et al., 2008 [11] however, question the existence of a relationship and present a contrary picture. Wjst and Hypponen, for instance, found an increase in prevalence of AR with higher VD levels, at all ages. Supplementation of VD in water soluble form has been shown to be associated with an increased risk of AR up to the age of four years.

Our results were supported by study of Hembrom et al., 2019 [12] as they reported that there was no statistically significant difference between their studied groups as regard age and sex. The age of control group was 40.18±7.81years whereas in Test group the mean age± SD was 39.40±7.58 years. The total no. of male was 27 (42.18%) and female was 37 (57.81%) in this study.

In the study of Velankar et al., 2019 [13] all 166 patients who were VD deficient were enrolled into the randomized, double-blind, placebo-controlled study for investigating the possible role of oral VD supplementation in potentiating the efficacy of intranasal steroid spray for treatment of AR. The enrolled patients had an average age of 30 years. The male to female ratio was 1:1.40.

In recent years, the world-wide increase in allergic diseases has been associated with low VD. Schauber and Gallo 2008 [14] stated that the association between low serum VD 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 VD production.

Our results were supported by study of Hembrom et al., 2019 [12] as they reported that there was no statistically significant difference between their studied groups as regard serum VD3. The serum VD3 level was 21.24±2.30 IU/ml in control group and 18.25±3.34 IU/ml in test group respectively.

Our results were in contrary with study of Velankar et al., 2019 [13] as they demonstrated a significant VD deficiency among Indian patients with AR, which could reflect lower sun exposure due to their urban lifestyle and poor dietary intake because of a predominantly vegetarian diet. Arshi et al., 2012 [15] have reported a high prevalence of VD deficiency in AR patients as compared to the normal population in Iran. They also found a high incidence (83%) of VD deficiency in AR patients in their 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 [16].

In a study performed by Moradzadeh et al., 2008 [17] the prevalence of severe VD 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 VD levels and AR status. Also, Malik et al., 2015 [18] demonstrated that patients of AR showed deficiency in VD levels. The mean VD level in Test group was 17.32+8.26 ng/ml and in Control group was 18.19±4.66 ng/ml. Fifty subjects of AR were randomised into two groups. The test group received oral VD (chole-calciferol; 1000 IU) for thirty days while the Control group received placebo.

In the study of Modh et al., 2014 [19] patients of AR showed deficiency in VD indicated by mean VD level of 18.03 ± 5.61 ng/ml before treatment. This result suggests the importance of assessing VD levels in patients of AR. There are other studies recently coming in support of this fact as stated by Arshi et al., 2012 [15] The prevalence of severe VD deficiency was significantly higher in patients with AR than the normal population. Furthermore, Menon, 2016 [20] revealed that patients of AR showed deficiency in VD indicated by mean VD level of 17.32+8.26 ng/ml in Test group and 18.19+4.66 ng/ml in Control group.

Additionally, the self-reported prevalence of AR in eleven major cities in mainland China by Cheng and Chen, 2012 [21] ranged from 8.7%–24.1%. Therefore, AR has become a large burden in society worldwide. Although clinical practice guidelines for the management of AR that have been developed over the past decade have improved the care of patients with AR, the exact pathogenesis of AR remains unclear. It is believed that both environmental factors and genetic susceptibility play a role in the etiology of AR.

It is generally agreed with Osguthorpe, 2013 [22] that a shift from a Th1 to Th2 phenotype in the proliferation of CD4+ T cells contributes to the pathogenesis of AR; however, the exact mechanism is still under investigation. Recent studies indicate that Th17 and Treg cells are important in the disease course of AR. VD inhibits the proliferation of T cells; induces a switch from Th1 to Th2 by enhancing the development of Th2 cells; facilitates the induction of Foxp3+ Treg cells; and suppresses the differentiation, maintenance, bioactivity, and transcription of Th17 cells. These data indicate there is a relationship between VD and AR morbidity.

Our results were supported by study of Velankar et al., 2019 [13] as they demonstrated that VD supplementation had a favorable impact on the treatment of AR with steroid sprays. There was significantly more reduction in the TNSS in the group which received VD 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, VD supplementation can be recommended for a faster onset of action of an intranasal steroid spray in AR patients with VD deficiency.

The exact mechanism of VD augmenting the action of inhaled corticosteroids is not known but increasing evidence points to an immunomodulatory action of VD in IgE mediated allergy. Pichler et al., 2002 [23] reported an immunoregulatory action of VD in IgE mediated allergy. VD could improve allergy symptoms directly or indirectly by potentiating the anti-inflammatory effects of the medications used to treat allergy [23]. Searing et al., 2010 [24] have suggested the possibility of a VD effect on glucocorticoid pathway and stated that VD insufficiency promotes the need for higher doses of glucocorticoids to achieve treatment effect. Poon et al., 2004 [25] have identified mutations in VD receptor genes as genetic risk factors for asthma/atopy suggesting that VD receptor may function as a regulator of susceptibility to asthma and atopy.

Steroid sprays are the first-line anti-inflammatory treatment for AR. 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. 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 VD. The role of VD in potentiating effect of steroids has already been demonstrated in asthma. These studies suggest that VD supplementation will improve patients' response to inhaled corticosteroids [26].

Also, Malik et al., 2015 [18] revealed that the TNSS score was 9.92±1.37 in Test group and 10.17±2.90 in Control group. The Post treatment mean VD level was 29.71±2.28 ng/ml in test group and 18.67±4.75 ng/ml in Control group and the TNSS scores was 2.81±3.04 and 5.42±7.78 respectively. This difference between groups was significant. There was significant correlation between the severity of disease as represented by the different TNSS groups and VD levels.

In the study of Modh et al., 2014 [19] they supplemented the patients of AR having deficient serum VD levels with oral VD supplements (chole-calciferol-1000 IU) and such patients were followed to evaluate their clinical status regarding AR. There was an improvement in the TNSS and serum VD level in such patients as it is concluded from this study. When the clinical improvement compared in the control group in which VD supplements were not given, they showed a difference of 6.34 in TNSS score which is lower than their 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.

The improvement in the allergic status reported by Akbar and Zacharek, 2011 [27] can be attributed to the immunomodulator effects of VD on the immune system: VD regulates the activity of various immune cells, including monocytes, dendritic cells, T and B lymphocytes, as well as immune functions of epithelial cells. Furthermore, some immune cells express VD -activating enzymes facilitating local conversion of inactive VD into active calcitriol with subsequent paracrine and autocrine effects.

As 25(OH) D serum levels are low in individuals and VD 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 VD plays a role in allergy development. First scientist who hypothesized a link between nutritional intake of VD and allergies were Wjst and Dold in 1999 [7]. Furthermore, Menon, 2016 [20] revealed that the TNSS score was 9.92+1.37 in Test group and 10.17+2.90 in Control group. After the study period, mean VD level was 29.71+2.28 ng/ml in test group and 18.67+4.75 ng/ml in Control group. The Post treatment TNSS scores were 2.81+3.04 in test group and 5.42+7.78 in Control group. This difference between groups was statistically significant. There was significant correlation between the severity of disease as represented by the different TNSS groups and VD levels.

In the study of Hembrom et al., 2019 [12] the ASS (Allergy symptom score) score was 14.06±1.01 in test group and 13.93±1.01 in control group and the post treatment ASS score was 2.65±1.12 and 6.06±0.87 respectively. This difference between groups was significant ($p<0.001$).

The main limitation of this study is the small sample size and single centered study, so we cannot generalize our findings on the whole population. Also Lack of more previous research studies on the topic.

5. CONCLUSIONS

There was highly significant reduction in the TNSS after VD supplementation. Thus, VD supplementation alters the course of AR towards clinical improvement.

CONSENT

Written informed consent was obtained from all the subjects of the study.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of faculty of medicine, Tanta university.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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