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Therapeutic effect of vitamin D supplementation on allergic rhinitis

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Abstract

Purpose In this study, we aimed to determine whether short-term (2 months) vitamin D supplementation could improve the allergic symptoms in AR patients.

Methods A randomized double-blind placebo-controlled clinical trial was performed on allergic rhinitis patients with vitamin D deficiency from Nov. 2017–2018. 80 cases with allergic rhinitis and vitamin D deficiency were divided into two groups and vitamin D plus routine antihistamine medication (cetirizine) was prescribed for the study group, whereas the control group received cetirizine plus placebo. The clinical symptoms questionnaire was completed at baseline and after 4 and 8 weeks of treatment initiation. Vitamin D levels were re-measured at the end of the 8-week treatment course.

Results In total, 80 patients with allergic rhinitis and vitamin D deficiency were enrolled. Among them, 35 cases and 33 controls visited the clinic after 8 weeks; the mean age in the aforementioned groups was 29.68 years and 29.13 years demonstrating no meaningful difference ($P > 0.05$). At study initiation, the mean vitamin D level was 14 ng/ml and 14.67 ng/ml in the study and control groups, respectively, indicating no significant difference ($P = 0.189$). The mean serum vitamin D level at 8 weeks of treatment in the study group (24.08 ng/ml) indicated a statistically meaningful difference with the mean vitamin D level at baseline ($P < 0.001$). Comparison of the mean scores of symptoms severity showed no significant difference between the two groups at study initiation and 4 weeks later ($P = 0.073$), whereas a significant difference was obtained between baseline and 8 weeks of treatment initiation ($P = 0.007$).

Conclusion Based on the findings of the present study, it can be concluded that vitamin D supplementation along with antihistamines can result in relative symptoms improvement in AR patients with vitamin D deficiency.

Keywords Vitamin D · Allergic rhinitis · Serum level of vitamin D

Introduction

Allergic rhinitis (AR) is one of the most common chronic childhood diseases with a rising prevalence worldwide. Based on various reports, its prevalence in Asia ranges from 27% in South Korea to 32% in the United Arab Emirates [1]. In a cross-sectional, population-based survey, the prevalence of clinically approved AR was reported as 16.9–28.5% in Europe [2]. Today, AR is a global health problem imposing high costs on both societies and governments. It also has a remarkable impact on the patients' social life, sleep, and school as well as work performance [3, 4].

Vitamin D which is a member of the steroid hormones family has recently been mentioned in several studies regarding its role in the development of allergic diseases [5–7]. These studies have been mainly focused on the non-calcemic effects and immunologic aspect of vitamin D.

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Vitamin D affects both innate as well as adaptive immunity and almost all types of immunologic cells, including T, B, and dendritic cells. Moreover, monocytes and macrophages are influenced by the regulation of 1, 25 (OH) 2D. In addition to its effects on immune cells by modulating a variety of cytokines, vitamin D may have a key role in the pathogenesis of many allergic disorders [8, 9]. Therefore, in recent years, the potential protective effects of vitamin D supplementation has been the highlight in research regarding AR [10, 11].

Based on a review study conducted by Tian and Cheng in 2017, maternal vitamin D intake (food-based) seems to reduce the risk of AR in childhood; however, infant and maternal vitamin D supplementation may have no significant impact on reducing the rate of AR in adulthood and childhood, respectively [8]. Despite a large number of studies in the field of prevention, very few studies have assessed the therapeutic effect of vitamin D on allergic rhinitis. Therefore, this study aimed to investigate the effect of short-term vitamin D supplementation on allergic symptoms in AR patients.

Materials and methods

This randomized double-blind placebo-controlled clinical trial was performed on allergic rhinitis patients visiting the Otorhinolaryngology Clinic during November 2017–2018. This study was conducted on all patients aged 18–40 years with AR diagnosed by the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline [12] and confirmed by skin prick testing who also had a vitamin D level of 10–20 ng/ml, considered as vitamin D deficiency based on the Endocrine Society Clinical Practice Guideline [13].

Patients with a concomitant chronic disease causing a disorder in vitamin D level, its absorption or secretion, a history of vitamin D supplements consumption in the past 3 months, pregnancy, breastfeeding, and the use of corticosteroids and antiepileptic drugs (which impair vitamin D absorption) were excluded from the study.

The study sample size was calculated as 80 individuals (40 persons per group) based on previous studies and by considering $\alpha = 0.05$, a confidence interval of 95%, and possible sample attrition.

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran, and registered by the code of 30659. All participants were informed of the study protocol and a written informed consent was obtained from each individual prior to the study.

Vitamin D level was measured using the electrochemiluminescent method in a single laboratory. All cases with vitamin D deficiency were divided into two groups based on the table of random numbers. Since the patients visited the clinic on a gradual basis, group randomization was performed by encoding.

In the next step, a classified questionnaire consisting of demographic data and clinical symptoms including rhinorrhea, nasal itching, sneezing, nasal obstruction, reduced sense of smell, postnasal drip, eye redness, eye pruritus, and eyelid edema was completed for each participant [14]. Based on the code designated to each questionnaire, vitamin D plus routine antihistamine medication (cetirizine) was prescribed for the intervention group, whereas the control group received cetirizine plus placebo with the same dose, shape, and package.

Weekly Pearl 50,000 IU of vitamin D was administered for 8 weeks based on the Endocrine Society Clinical Practice Guideline [13]. The clinical symptoms questionnaire was completed at baseline and after 4 and 8 weeks of treatment initiation. Vitamin D levels were re-measured at the end of the 8-week treatment course. Nevertheless, following study termination, the appropriate treatment regimen was prescribed for the control group.

The precisely recorded data at each time visit were analyzed in SPSS software (version 23). The Shapiro–Wilk test was employed regarding the normality distribution of data for a sample size below 100. In addition, paired sample's *t* test and independent *t* test were utilized for quantitative variables. *P* value less than 0.05 was considered statistically significant.

Results

In total, 80 patients with AR and vitamin D deficiency were enrolled in this study; however, 38 and 36 cases in the intervention and control groups visited the clinic after 4 weeks, respectively. Following that, the same figures reduced to 35 and 33 after 8 weeks. The mean ages of the intervention and control groups were 29.68 and 29.13 years, respectively, indicating no meaningful difference between the two groups regarding the age ($P > 0.05$). Moreover, the two groups were homogenous in terms of gender ($P > 0.05$).

The mean values of serum vitamin D level in the outdoor and indoor occupation groups were 14.67 and 14.16 ng/ml, respectively, revealing no significant differences between the two groups ($P > 0.05$). The results obtained from skin prick testing on 52 allergens revealed the highest rate of sensitivity for mites (65%).

The mean values of serum vitamin D level at the onset of the study were 14 and 14.67 ng/ml in the intervention and control groups, respectively, indicating no significant differences between the two groups ($P = 0.189$). At 8 weeks of treatment, the vitamin D level was estimated at 24.08 ng/ml in the intervention group ($n = 33$) indicating a statistically

significant difference between the baseline and 8 weeks post-treatment ($P < 0.001$) (Table 1).

The mean scores of symptom severity at baseline according to nine specified criteria in the questionnaire were 26.43 and 26.78 in the intervention and control groups, respectively. Consequently, no significant differences were observed between the two groups regarding this variable ($P = 0.861$).

Furthermore, there was no significant differences at baseline between the two groups regarding clinical symptoms. However, the intervention group revealed a significant decrease in the scores of rhinorrhea, nasal itching, sneezing, and postnasal drip after 8 weeks of intervention (Table 2).

There was also no significant difference between the two groups at the onset of the study and 4 weeks later regarding the mean scores of symptom severity ($P = 0.073$), whereas a significant difference was obtained between the two groups in terms of symptom severity at baseline and 8 weeks post-treatment ($P = 0.007$, Table 3).

Table 1 The serum vitamin D level in the control group (cetirizine alone) and intervention group (vitamin D in addition to cetirizine) at the end of the study

Group statistics				
Group	N	Mean	Std. deviation	Sig. (two-tailed)
Final Vitamin D				
Control	35	15.06	2.213	0.001
Intervention	33	24.08	3.940	

Discussion

In contrast to the major interest in the nutritional role of vitamin D in the past, in recent years, much emphasis has been placed on its hormonal characteristics. Vitamin D is a member of the steroid hormones family and its nuclear vitamin D receptor manifests in various cells and tissues [15]. This hormonal form of vitamin D affects a wide range of immune cells and cytokines and is recognized as an immune system modulator [8]. Therefore, there is a growing increase

Table 2 The comparison of allergic symptoms between control group (cetirizine alone) and intervention group (vitamin D in addition to cetirizine) at the study initiation and after 8 weeks and the significance of difference in clinical symptoms between two groups after 8 weeks of intervention

Group	Study initiation			After 8 weeks			
	N	Mean	Std. deviation	N	Mean	Std. deviation	*P* value
Rhinorrhea							
Control	40	3.70	1.244	35	3.74	0.898	< 0.001
Study	40	3.70	1.137	33	2.76	1.173	
Nasal pruritus							
Control	40	3.00	1.320	35	3.38	0.985	0.001
Study	40	3.20	1.203	33	2.45	1.201	
Sneeze							
Control	40	3.20	1.305	35	3.38	1.045	0.001
Study	40	3.23	1.187	33	2.42	1.146	
Nasal obstruction							
Control	40	3.20	1.159	35	2.44	1.133	0.205
Study	40	3.13	1.305	33	2.12	0.893	
Hyposmia							
Control	40	2.87	1.260	35	2.32	1.147	0.205
Study	40	3.10	1.057	33	2.00	0.901	
PND							
Control	40	3.70	1.203	35	3.06	1.278	0.006
Study	40	3.38	1.254	33	2.21	1.139	
Eye pruritus							
Control	40	2.75	1.235	35	2.12	1.149	0.185
Study	40	2.63	1.213	33	1.77	0.884	
Eye redness							
Control	40	2.18	1.279	35	1.97	1.114	0.139
Study	40	2.30	1.203	33	1.61	0.761	
Eyelid edema							
Control	40	2.03	1.271	35	1.85	1.132	0.06
Study	40	1.93	1.095	33	1.42	0.620	

Table 3 The correlation between total symptoms score after 4 and 8 weeks of study initiation in the control group (cetirizine alone) and intervention group (vitamin D in addition to cetirizine) at the end of the study

Group statistics				
Group	*N*	Mean	Std. deviation	Sig. (two-tailed)
Score at 4 weeks				
Control	38	26.08	9.107	0.073
Intervention	36	22.39	8.285	
Score at 8 weeks				
Control	35	24.51	9.040	0.007
Intervention	33	18.70	8.160	

in the volume of studies evaluating the effect of vitamin D on immune system diseases in general and allergic diseases in particular.

To date, the association between vitamin D and a wide range of allergic diseases such as asthma, eczema, atopic dermatitis, and allergic rhinitis has been studied, but most research has been focused on asthma [16, 17]. In the present study, we studied the effect of vitamin D on allergic rhinitis.

Most similar studies in the literature have an observational setting and have only examined the relationship between vitamin D level and the incidence as well as the severity of allergic rhinitis [5-7, 18]. These studies frequently reported an inverse relationship between vitamin D level and the occurrence of AR [5-7]. However, contrary results have been mentioned by a few other studies [18].

Modh et al. performed the first study comparing vitamin D level before and after supplementation therapy in AR patients. This study was conducted on 21 patients in a prospective setting. Cholecalciferol with a dosage of 1000 IU was prescribed for 21 days along with routine allergy treatment. The results showed an improvement in vitamin D levels ($P=0.01$) and total nasal symptoms score ($P<0.05$) in the post-treatment phase [19].

To the authors' knowledge, a limited number of studies have had an interventional approach and aimed to assess the effect of vitamin D as a preventive supplement for AR during pregnancy, lactation, and infancy [5, 11, 20] and as a therapeutic supplement in childhood and adolescence [19, 21].

In this double-blind controlled clinical trial, the effect of vitamin D was investigated on AR patients. Since the significant effect of gender and age was confirmed on vitamin D and AR in previous studies, these variables were kept homogenous for the two groups in the present study. Moreover, there was no significant difference between the two groups regarding the vitamin D level at baseline ($P=0.189$).

After an 8-week treatment course, a remarkable increase was observed in vitamin D level; in addition, there was a significant decrease in the allergic symptoms in the intervention group ($P=0.007$). This can be justified by the fact that vitamin D can reduce the risk of inflammatory events leading to AR, including T-cell proliferation, facilitated induction of Foxp3+ cells, and Th17 cells differentiation, as well as bioactivity and transcription inhibition [8, 9].

In a randomized controlled trial (RCT) conducted by Jerzynska et al., the immunologic effect of vitamin D supplementation was investigated on children aged 5–12 years who were sensitive to grass in the pollination season. In addition to reduced clinical scores in the vitamin D group, an increase was observed in the percentage of CD4 + CD25 + Foxp3 + cells [21]. These cells have a remarkable role in inhibiting allergic disorders in humans [22].

However, another hypothesis has been suggested due to the different results reported by other studies. In a cohort study conducted by Hypoppen et al. in Finland during 1996, a significantly higher rate of atopy, AR, and asthma at 31 years of age was observed in a group which had regularly consumed vitamin D supplements in their 1st year of life [11]. This can be attributed to the role of vitamin D in inducing a cellular shift from Th1 to Th2 resulting in the production of Th2-related cytokines which influence the secretion of allergic substances [23].

Based on these findings, the dual role of vitamin D in the immunologic process is further clarified. Although it is difficult to achieve a coherent conclusion based on the current findings, it can be hypothesized that the timing of vitamin D supplementation (1st year of life vs. childhood or adulthood) determines the role of vitamin D in ceasing or initiating immunologic procedures.

Nevertheless, in comparison to other studies on vitamin D and AR in children and adults, the current study had the largest study population among the RCTs. Totally, 40 cases were enrolled in each group in this study; however, 35 and 33 patients in the intervention and control groups completed the study, respectively. All participants had vitamin D deficiency and the treatment duration and dosage were determined by the Endocrine Society Clinical Practice Guideline [13].

According to the results, no significant difference was observed between the two groups regarding the mean score of symptom severity after 4 weeks of treatment ($P=0.073$). This could be due to the lack of time for vitamin D to induce its immunological effects. However, at the end of the 8-week treatment course, a significant decrease was observed in the intervention group in terms of the mean score of symptom severity ($P=0.007$).

One of the main limitations of the present study includes the lack of simultaneous assessment of immunologic cells and inflammatory cytokines at the mentioned time points. It could have helped us with a better understanding of the immunologic effects of vitamin D alongside the clinical changes. This was performed in a study by Jerzynska et al.

[21] with a smaller study population. Despite the changes in the CD4 + CD25 + Foxp3+ cell percentage, compared to baseline, they found no significant difference in terms of the level of inflammatory cytokines in the above-mentioned study.

Conclusion

It seems that vitamin D supplementation along with antihistamines can result in the improvement of relative symptoms in AR patients with vitamin D deficiency.

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Compliance with ethical standards

Conflict of interest None of the authors have a conflict of interest to declare.

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