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ORIGINAL ARTICLE

Clinical Efficacy of Vitamin D3 Adjuvant Therapy in Allergic Rhinitis: A Randomized Controlled Trial

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ABSTRACT

Background: Vitamin D supplementation has been proven to have efficacy in the treatment of allergic rhinitis (AR). **Objective:** We conducted the present study to explore the role and efficacy of vitamin D adjuvant therapy in the inflammation in the patients with AR. **Methods:** Out of the 127 patients with potential eligible AR, 60 were randomly assigned into two groups and were finally included for analysis (n=30 for each intervention). The patients with potential eligible AR were randomly allocated to intervention with desloratadine citrate disodium (DCD, 8.8 mg/day) without and with vitamin D3 nasal drops (1.5x106 IU, once/week) for four weeks. Thirty healthy control subjects were included in our study. We assessed the changes in the serum 25(OH)D, peripheral blood eosinophils, interleukin (IL)-4 levels, and nasal symptoms. Serum 25(OH)D, peripheral blood eosinophils, and IL-4 levels were detected respectively with liquid chromatography-tandem mass spectrometry (LC-MS/MS), a blood detector, and enzyme-linked immunosorbent assay. **Results:** Our patients who received vitamin D3 adjuvant therapy had a higher serum 25(OH)D level (47.57 ± 2.83 vs. 31.51 ± 2.95 ng/ml) and lower AR symptoms score (2.07 ± 1.89 vs. 3.37 ± 1.50), serum IL-4 (10.38 ± 3.41 vs. 12.79 ± 5.40 pg/ml), and peripheral blood eosinophils (0.34 ± 0.09 vs. 0.41 ± 0.10 109/l) compared with DCD single treatment. The effective rate of DCD with and without vitamin D3 in AR was 97% and 84%, respectively. **Conclusion:** Nasal vitamin D3 combined with DCD could improve the clinical symptoms of AR. Vitamin D3 adjunct therapy showed impressive effects on inhibiting inflammation in patients with AR. We concluded that vitamin D3 supplementation into routine therapy could be an effective adjuvant therapy in AR patients by inhibiting inflammation.

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Keywords: Allergic Rhinitis, Interleukin-4, Peripheral Blood Eosinophils, Vitamin D3

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INTRODUCTION

Allergic rhinitis (AR), a type of chronic inflammatory disease that affects the nasal membrane, occurs once the immune system overreacts to the allergens in the air. It is mainly mediated employing immunoglobulin E (IgE) (1-3). The prevalence rate of AR is 4%–38% in the cities of China and is 10% to 40% worldwide (4-6). AR has a significant influence on a patients' mental and behavioral consciousness, and serious interference in their daily life. The routine therapies for AR include nasal hormones and oral antihistamines or antileukotriene drugs, such as cetirizine, montelukast, and desloratadine citrate disodium (7-9). Desloratadine citrate disodium possesses antihistaminic, anti-allergic, and anti-inflammatory properties. It is often used to treat allergic rhinitis. However, it is involved with certain complications, for instance taking medicine for a long time and being easy to relapse. These drugs have demonstrated impressive effects on AR, yet issues such as the length of treatment and poor patient compliance remain. Nowadays, the supplementations of vitamin D into routine therapies have shown remarkable results in AR treatment (10-12). Vitamin D could regulate multiple bioactivities in the body, and the decreased level of it increases susceptibility to diseases like AR and asthma (10-12). Vitamin D alleviates AR symptoms via reducing IgE and cytokines (13,14). Cho *et al.* reported that the supplementation of vitamin D significantly reduced the serum interleukin (IL)-4, IL-5, and interferon (IFN)-γ in BALB/c AR mice (14). Wu *et al.* indicated that vitamin D was inversely associated with blood eosinophils in patients with persistent AR (15). These studies suggested the strong effects of vitamin D on AR and the mechanism of it. However, there is less information on the effect of vitamin D on both eosinophil and IL-4 in patients with AR. Herein, we explored a novel adjuvant therapy (vitamin D supplementation via intranasal way) based on a recommended treatment in order to provide a novel direction for AR prevention and treatment. To explore the efficacy of vitamin D supplementation via intranasal way, individuals with AR were assigned into two groups and then treated with desloratadine with and without vitamin D. The serum vitamin D level, IL-4 level, and peripheral blood eosinophil level as well as the AR clinical symptoms were detected and compared in order to determine the role and efficacy of vitamin D in the treatment of AR.

MATERIALS AND METHODS

Subjects. The individuals with mild seasonal pollen AR, who referred to the Department of Otorhinolaryngology in our hospital between September 2015 and September 2016, were included. AR was diagnosed according to the guidelines published by Tianjin in 2015 (16). The exclusion criteria included the patients with vascular motility rhinitis, non-allergic rhinitis along with eosinophilia, infectious nasal sinusitis, asthma, vitamin D deficiency, other severe and immunity diseases, and a medical history of the disease within the month before the study treatment. In addition, the patients were excluded from the study if they suffered an asthma exacerbation or a drug allergy during the treatment. Thirty healthy controls without detected diseases were enrolled in our study after health examination. The present study was approved by the Committees of Medical Ethics Inner Mongolia People's Hospital and written informed consents were obtained from all the participants before our trials.

Grouping and Treatments. The eligible individuals with AR were assigned into two groups according to the following intervention strategies: 1- those treated with oral desloratadine citrate disodium (DCD, 8.8 mg/day; Guangzhou Hairui Pharmaceutical Co. Ltd., Guangzhou, China) plus vitamin D_3 nasal drops (13,17) (1.5×10^6 IU, once/week, Shanghai General Pharmaceutical Co., Ltd., Shanghai, China; Combination, Com for short) for 4 consecutive weeks, 2- those only treated with DCD (8.8 mg/day, oral) for 4 consecutive weeks. The healthy controls received no medication.

Evaluation Standards for AR Symptoms. The severity of the nasal symptom and physical signs of AR patients before and after the interventions were assessed in a blinded way according to the guidelines published in *Otorhinolaryngology Head and Neck Surgery* a Chinese journal on 2008 (18). The scoring system was a 6-point scale (Table 1). Improvements were considered to be significant if the nasal symptoms and physical signs of AR decreased by ≥ 51% after the treatment. They were considered to be effective if alleviation in nasal symptoms and physical signs of AR were moderated following the treatment (score decrement 21% ~50%). Ineffective improvement was defined if there were no alleviation (decrement ≤20%) in nasal symptoms and physical signs.

Table 1. The scoring systems for nasal symptoms and physical signs of Allergic Rhinitis patients.

	Nasal symptoms			
Scores	Sneeze (times/day)	Rhinorrhea (times/day)	Nasal congestion	Nasal itching
1	3~5	≤ 4	Occasional	Occasional
2	6~10	5~9	Moderate	Moderate
3	≥11	≥10	Breathe through mouth almost all day	Unbearable
	Physical signs			
	Inferior turbinate, septum/nasal floor		Middle turbinate	
1	The inferior turbinate is slightly swollen; the septum is visible.		Visible	
2	The inferior turbinate is close to the septum/bottom of the nose; gap is visible.		Moderate	
3	The septum is not visible; without gap.		Not visible; or polyps.	

Serum 25(OH)D, IL-4 and Peripheral Blood Eosinophils. Two to three milliliters of fasting venous blood were collected from the AR patients (before and after treatment) and the controls. The samples were centrifuged at 3000 r/min for 15 min. The serum 25(OH)D was measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS; Shimadzu, Kyoto, Japan). Standard 25(OH)D was purchased from Thermo Fisher Scientific, Inc., (Waltham, USA). The serum IL-4 level was analyzed using the enzyme-linked immunosorbent assay (ELISA) method with a human ELISA assay kit

(Abcam, Cambridge, UK). Routine examination of the blood eosinophil level in the peripheral blood was performed utilizing a blood detector (Acon, Shanghai, China).

Statistical Analysis. We aimed to recruit 26 patients per arm with sample size calculation using 80% power and 5% significance. However, we included 30 patients in each arm after estimating a 15% attrition rate during the intervention. All the data were statistically analyzed employing SPSS version 20.0. Continuous data were presented as the means ± standard deviations. The *t*-tests, χ^2 tests, and one-way ANOVA were used to compare the obtained data. We utilized Mann-Whitney U test for comparing the efficacy between the two groups. $p<0.05$ was considered significant.

RESULTS

Patient Characteristics. A total of 127 patients with potential eligible AR were admitted in our hospital during September 2015 to September 2016. Among them, 52 were ineligible patients and were excluded according to the inclusion criteria (Figure 1). The remaining 75 patients with AR were randomly assigned into two groups, and a total of 69 patients received allocated interventions, out of whom 7 were lost during the intervention and 2 were excluded from analysis.

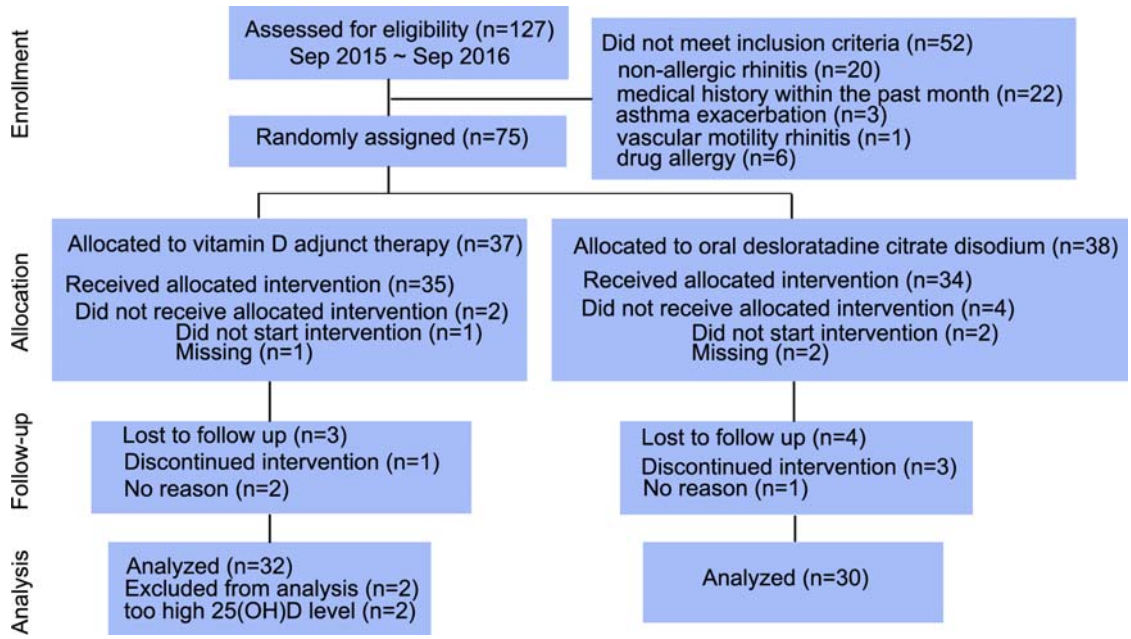

Figure 1. CONSORT diagram.

The analyzed 60 individuals with mild seasonal pollen AR included 29 males and 31 females, with an average age of 27.3 ± 7.9 years (13~53 years). There were no differences in the gender ratio and age among the intervention and control groups ($p>0.05$). The scores of AR patients (4.30 ± 1.49 vs. 4.43 ± 1.54) and the levels of serum IL-4 (14.58 ± 4.47 vs. 15.19 ± 5.14 pg/ml) and peripheral blood eosinophils (0.71 ± 0.14 vs. 0.67 ± 0.12 10^9/l) were comparable between the two groups ($p>0.05$, Table 2). Comparing the AR patients with the healthy controls, the serum 25(OH)D levels significantly decreased (Table 2).

Table 2. General characteristics of the patients and controls included in this study.

Variable	Patients		Control	p-value
	Com	DCD		
Gender (Male:Female)	15:15	14:16	12:18	0.731[a]
Age (years)	27.2 ± 8.8	27.3 ± 7.1	31.2 ± 10.6	0.149[b]
Scores	4.30 ± 1.49	4.43 ± 1.54		0.450[c]
IL-4 (pg/ml)	14.58 ± 4.47	15.19 ± 5.14		0.626 [c]
Eosinophils (10^9/l)	0.71 ± 0.14	0.67 ± 0.12		0.240 [c]
25(OH)D (ng/mL)	23.67 ± 4.47	23.42 ± 3.83	36.66 ± 4.74	<0.0001[b]

a, χ^2 test; b, one-way ANOVA; c, *t*-test.

Vitamin D_3 Supplementation Has Impressive Efficacy on Improving Allergic Rhinitis Symptoms. We confirmed that the supplementation of vitamin D_3 nasal drops once per week for 4 weeks significantly improved the serum 25(OH)D level in the AR patients (47.57 ± 2.83 vs. 31.51 ± 2.95 ng/ml, p=0.000) and alleviated nasal symptoms (2.07 ± 1.89 vs. 3.37 ± 1.50, p=0.005) compared with DCD single treatment (Figure 2). We observed that the supplementation of vitamin D_3 had a higher efficacy in alleviating nasal symptoms in the AR patients compared with DCD single treatment (p=0.023, Table 3).

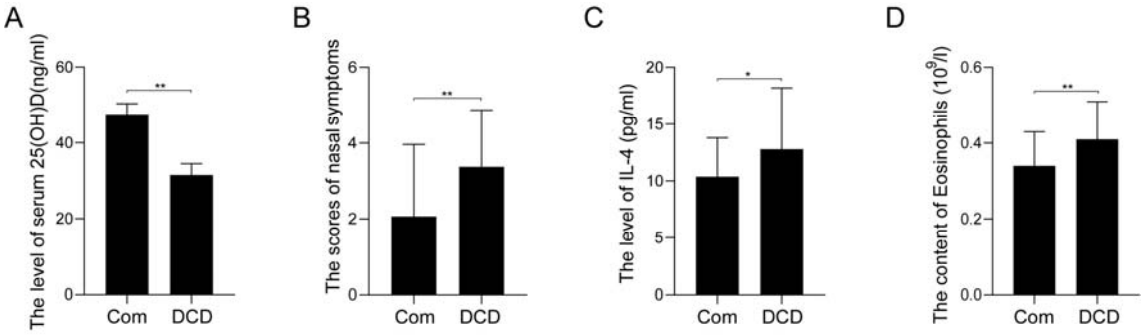

Figure 2. Effect of vitamin D on Allergic Rhinitis serum. (A) The serum 25(OH)D level of Com group (treatment with oral desloratadine citrate disodium plus vitamin D3 nasal drops) and DCD group (only treated with DCD). (B) The nasal symptoms scores of Com group and DCD group. (C) The IL-4 level of Com group and DCD group. (D) The content of peripheral blood eosinophils in Com group and DCD group. At least three repeats were carried out, and the mean ± SD is presented, *, P < 0.05, **, P < 0.01.

Furthermore, vitamin D3 nasal drops also significantly decreased IL-4 (10.38 ± 3.41 vs. 12.79 ± 5.40 pg/ml, p=0.043), peripheral blood eosinophils (0.34 ± 0.09 vs. 0.41 ± 0.10 10^9/l, p=0.003) and alleviated nasal scores (2.07 ± 1.89 vs. 3.37 ± 1.50, p=0.005) compared with DCD single treatment (Figure 2). These data proposed that vitamin D3 adjuvant therapy could significantly alleviate the AR symptoms via regulating the immune levels in patients.

DISCUSSION

Vitamin D, a fat-soluble hormone, is believed to be one of the essential nutrients for the human body. Considering the recent extensive researches on vitamin D, its relationship with AR has become a hot spot in the medical field (10,11,13,19). Certain scholars studied the correlation between the prevalence of AR and vitamin D level and found that vitamin D deficiency was more common in the patients with AR (10,11,20).

Table 3. Efficacy of the vitamin D3 supplementation on Allergic Rhinitis.

Group	Patient	Significant	Effective	Useless	*p-value*
Com	30	19 (63.33%)	10 (33.33%)	1 (3.33%)	0.023
DCD	30	11 (36.67%)	14 (46.67%)	5 (16.67%)	

Modh *et al.* confirmed that treating AR with vitamin D could significantly improve nasal symptoms and proposed vitamin D as an effective adjuvant therapy for AR (21). Kumar et al. confirmed that the severity of AR was closely correlated with vitamin D deficiency (serum 25(OH)D < 20 ng/ml) (22). In this study, we found that the serum 25(OH)D concentration in individuals with AR was significantly lower than that in the control (23.67 ± 4.47 and 23.42 ± 3.83 ng/ml vs. 36.66 ± 4.74 ng/ml). However, the supplementation of vitamin D_3 adjuvant therapy significantly increased it to 47.57 ± 2.83 ng/ml, which was higher than that in the control group and the patients who only received desloratadine citrate disodium. The reasons associated with low vitamin D levels include geographical location differences, indoor sports habits (such as gym sports), outdoor protection use (such as sunscreen), and inadequate supplementation (23). Furthermore, we believe that individuals with AR limit their activities to avoid being exposed to pollen and other allergens, and sun light, which results in the deficiency of vitamin D. However, the factors could be ignored in our study due to the comparable ages, gender ratio, and geographical location of the patients with AR. A Th1/Th2 imbalance is considered as the main immunological mechanism involved in AR pathogenesis (24-27). IL-4, a representative of the Th2 cytokine, has become the main diagnostic index of AR serum immunology (28,29). Pang *et al.* (29) performed an animal experiment in 2013 and confirmed that the AR animals had a higher IL-4 level compared with the normal group. The same trend was observed in the AR rat model established by Zhang and Tang (30). Vitamin D could alleviate the inflammation symptoms by reducing cytokines via conversing to its active form $1,25(OH)_2$ in immune system cells like monocytes and monocyte-derived macrophages (13,31,32). $1,25(OH)_2$ has an anti-inflammatory effect via downregulating the production of several pro-inflammatory cytokines, for instance IL-6, IL-1β, and TNF-α (32). In contrast, Cho *et al.* indicated that the supplementation of vitamin D into BALB/c AR mice significantly reduced the serum IL-4, IL-5, and IFN-γ (14), suggesting the alleviation of the inflammatory status in mice. In human beings, studies on the vitamin D adjuvant therapy have obtained remarkable results in AR treatment (10-12). Our present study demonstrated that the vitamin D adjuvant therapy significantly reduced the inflammation in the AR patients and the production of anti-inflammatory IL-4 in serum

blood. All these data revealed the efficacy of vitamin D on alleviating AR. The main manifestation of respiratory allergic diseases is EOS infiltration (33-36). EOS is also the main inflammatory cells reported to be related to AR (33,34). Lu *et al.* reported that vitamin D deficiency was an inducing factor for the spontaneous activation of eosinophils (33). Vitamin D was inversely associated with blood eosinophils in the patients with persistent AR (15). Eosinophilic esophagitis was IL-5 inducible (37) and associated with Th2-type allergic inflammatory response, and most patients with allergic disorders were reported with eosinophilic esophagitis (38). The main symptoms of AR are concentrated in the nose with obvious local pathological responses. The correlation between the eosinophil count in nasal mucosal secretions and AR has been studied (39,40). Ram et al. confirmed that almost all the patients with eosinophilic esophagitis have history of AR (39). Ellis et al. suggested that toxic protein substances in the eosinophils are the key to inducing non-AR (41). After recording the EOS counts of nasal secretion smears, researchers proposed that the eosinophil count could be used clinically to diagnose AR (42). These researchers stated that eosinophils in the bone marrow are stimulated and released into the blood system, eventually gathering at the site of inflammation (43). They also confirmed that the peripheral blood eosinophils level could be employed as an index of treatment efficacy for AR (44). Therefore, we selected the eosinophil level in the peripheral blood as one of the experimental indicators. Fortunately, we identified that the blood eosinophil level in AR patients significantly reduced with vitamin D_3 adjuvant therapy, just as the serum IL-4 level. The results indicated that vitamin D_3 combined with desloratadine citrate disodium was more effective on reducing eosinophil compared to desloratadine citrate disodium alone. Sultan *et al.* (45) proposed that the topical use of vitamin D via nasal administration increased the drug's availability and effectiveness. There are several reasons for the application of local nasal administration, including: 1- nasal mucosal drug specificity, the use of vitamin D_3 nasal drops avoids the digestive tract enzymes and liver metabolism which significantly improves its bioavailability owing to its small molecular weight (<4000 g/mol) (46); 2- the nasal mucosa has a high affinity for fat-soluble substances like vitamin D_3. This randomized trial had three key limitations. Primarily, it was conducted at a single center and the number of patients was small although it met the calculated minimum sample size. We believe that larger cohort from multiple centers could increase the credibility of our conclusion. Secondly, the subjective feelings of patients influenced the AR symptoms scores. Therefore, the accuracy of this study needs further support and demonstration in future experiments with a larger number of samples. In conclusion, the results presented in our study revealed that vitamin D_3 as an adjuvant therapy could significantly decrease serum IL-4 and blood eosinophil count as well as alleviating the nasal symptoms in patients with AR. We concluded that vitamin D_3 supplementation into routine therapy could be an effective adjuvant therapy in AR patients by inhibiting inflammation.

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