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Regular paper

Vitamin D supplementation improves the therapeutic effect of mometasone on allergic rhinitis

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This study aimed to investigate the efficacy and safety of vitamin D supplementation in the treatment of allergic rhinitis (AR) using mometasone. A total of 140 patients with moderate and severe AR treated at our hospital between January 2017 and August 2020 were recruited as subjects for this study. The patients were randomly divided into control and experimental groups, with 70 patients in each group. Mometasone nasal spray was used in both groups, and vitamin D was administered to the experimental group for four weeks. The total nasal symptom scores (TNSS) and rhinoconjunctivitis quality of life questionnaire (RQLQ) were used to assess the efficacy of treatment. T lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD8^+$) and serum anti-inflammatory and proinflammatory cytokines such as interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) were analyzed. The incidence of adverse reactions was recorded. Serum vitamin D levels were lower in patients with AR. After 4 weeks of treatment, total TNSS scores, T lymphocyte subsets ($CD3^+$, $CD4^+$), $CD4^+/CD8^+$ ratio, TNF-α, and total RQLQ scores were significantly reduced compared to the initial testing ($P<0.05$) in the two groups; $CD8^+$, IFN-γ, and IL-10 levels as well as serum vitamin D were significantly increased compared to the initial test ($P<0.05$). The improvement in these parameters in the experimental group was significantly greater than that in the control group ($P<0.05$), except for sneezing and eye symptoms in the TNSS and RQLQ scores. It was concluded that vitamin D supplementation improves the therapeutic effect of mometasone nasal spray on AR and is thus recommended as an adjuvant therapy for moderate and severe AR.

Keywords: vitamin D, mometasone, allergic rhinitis, immunomodulation

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Abbreviations: AR, allergic rhinitis; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; TNF, tumor necrosis factor-α; IFN, interferon; RQLQ, rhino conjunctivitis quality of life questionnaire; S.D., standard derivation; TNSS, Total nasal symptom score

INTRODUCTION

Allergic rhinitis (AR), although a non-life-threatening disease, is a common disorder that frequently occurs in children and adolescents after exposure to allergens in a highly prevalent environment (Meng *et al.*, 2019). It is often associated with other allergic diseases such as asthma and has adverse effects on sleep, school performance, quality of life, and important short-term and long-term health consequences (Foresi, 2000; Schuler & Montejo, 2019). AR patients develop specific immunoglobulin E (IgE) antibody responses to allergens, resulting in repeated sneezing, rhinorrhea, nasal congestion, itching, ocular redness, tearing, and itching (Bernstein *et al.*, 2016). Epidemiological studies have shown that the prevalence of this disease among adults and children has increased in recent years (Kakli & Riley, 2016; Khan, 2014). The etiology of AR is complex and is affected by many factors, including heredity, environment, and immune function (Eifan & Durham, 2016; Khan, 2014). Several pharmacotherapy guidelines have been developed to treat the disease, and routine therapy options consist of the use of antihistamines, intranasal corticosteroids, and decongestant drugs such as cetirizine, montelukast, mometasone, and desloratadine (Bousquet *et al.*, 2020; Okubo *et al.*, 2020). Although these drugs have demonstrated efficacy in AR, they require a long treatment time and have poor patient compliance (Khare & Martin, 1995). Furthermore, despite recent epidemiologic data showing that the incidence of AR is increasing worldwide, less than 12% of AR patients seek medical recommendations, resulting in the disease being frequently under-recognized, misdiagnosed, and ineffectively treated (Berger, 2003; Dennis *et al.*, 2012).

Vitamin D is an important human nutrient and functions as an immunomodulatory hormone. In recent years, studies have shown that vitamin D has an immune regulatory effect and can be used as a supplement to treat asthma and other immune-related diseases, including AR, with satisfactory results (Charoenngam & Holick, 2020; Forno *et al.*, 2020; Yepes-Nunez *et al.*, 2018). Vitamin D plays an important role in regulating the immune system and has been demonstrated to have therapeutic benefits in the treatment of various diseases, such as melanoma, inflammatory bowel diseases, rheumatoid arthritis, tuberculosis, sepsis, and respiratory infection (Battistini *et al.*, 2020; Charoenngam & Holick, 2020; Sun *et al.*, 2021). It may alleviate AR symptoms by reducing IgE, cytokines, interleukin (IL)-4, IL-5, and interferon (IFN) to suppress inflammation (Cho *et al.*, 2019; Yu *et al.*, 2017). However, the therapeutic effect of vitamin D on AR remains controversial (Bhardwaj & Singh, 2021; Liu *et al.*, 2020; Luo *et al.*, 2022) and the effect of vitamin D on AR treated with corticosteroids has not been fully explored. In the present study, the impact of vitamin D supplementation was assessed in patients with moderate-to-severe seasonal pollen AR.

MATERIALS AND METHODS

Trial design and study population

We conducted a randomized, assessor/statistician-blinded, single-center trial with two parallel groups to investigate the effects of vitamin D on AR. Patients

treated at our hospital between January 2017 and January 2022 were enrolled in this study. Patients were included if they met the diagnostic criteria of the Guidelines for Diagnosis and Treatment of Allergic Rhinitis (Subspecialty Group of Rhinology *et al.*, 2016), confirmed by allergen tests, had moderate-to-severe AR (symptoms (nasal congestion, runny nose, itchy nose, or sneezing) occurring ≥4 days per week for consecutive 4 weeks and were severe enough to affect quality of life) according to the disease severity classification based on the above guidelines, did not receive any AR-related treatment within two weeks of diagnosis, were aged between 16 and 60 years, and had good drug compliance. Patients were excluded if they had non-allergic rhinitis, severe organ dysfunction, malignant tumor, other respiratory diseases, and nasal cavity abnormalities such as sinusitis and nasal polyps. Pregnant and lactating women were excluded from the study. The sample size was determined using the formula N (each group) = (r+1) $(Z\alpha/2 + Z1\text{-}\beta)^2\ \sigma^2/\ rd^2$ (Suresh & Chandrashekara, 2012). In a pilot study, the minimal detectable difference means (d) of the two group as 0.62 scores on the total nasal symptom scale (TNSS) and 1.21 the standard deviation (σ), respectively. Therefore, the minimum sample size for each group required to detect the mean difference between the two means was 37 persons/group. Considering a dropout rate of 10%, 45 patients were required for each treatment group. This study was approved by the Ethics Committee of the Huichang People's Hospital, Ganzhou, China. Informed consent was obtained from all the patients.

Randomization and blinding

After baseline evaluations and routine laboratory tests, the patients were randomly allocated 1:1 to the control and experimental groups. The assignment was made according to a computer-generated randomization table created by a biostatistician. The treatments were labelled A and B to ensure blinding of the biostatistician. A physician from another department was tasked with using a randomization list to allocate patients. All assessors were blinded to group allocation, treatment details, and patient information.

Treatment

Patients in both groups were administered 200 μg mometasone nasal spray (Xianju Pharmaceutical, Zhejiang, China) 2 puffs BD for four weeks. In addition, two oral vitamin D capsules (400 IU vitamin D per capsule, Shuangjing Pharmaceuticals, Qingdao, China) were given BD in the experimental group for 4 weeks.

Biochemical assessments

Peripheral venous blood samples were collected before and one month after treatment. Lymphocytes and T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$) were measured on a flow cytometer (Accuri C6 plus cell analyzer, BD, US) using monoclonal four-color antibody CD3/CD4/CD8/CD45 (cat. no. 561707), monoclonal antibodies to CD3 (cat. no. 30062), CD4 (cat. no. 100538), and CD8 (cat. no. 561644) (produced by BD, USA). The contents of interleukin-10 (IL-10, IL-10 Human ProcartaPlex™ Simplex Kit, cat. no. EPX01A-10215-90), tumor necrosis factor (TNF-α, TNF alpha Human ProQuantum Immunoassay Kit, cat. no. A35601), and interferon-γ (IFN-γ, IFN gamma Human ProQuantum Immunoassay Kit, cat. no. A35576) were assessed by enzyme-linked immunosorbent assay (ELISA) using kits purchased from Thermo Fisher Scientific, USA, according to the manufacturer's instructions. Vitamin D levels were assessed using ELISA kit (cat. no. EY-01H1295) was obtained from Yiyan Biotech (Shanghai, China). All assays were performed in triplicate.

Clinical efficacy evaluation

The TNSS and rhinoconjunctivitis quality of life questionnaire (RQLQ) were used to assess the efficacy. The TNSS is a subjective evaluation tool used to measure the severity of the main symptoms of patients with AR (Downie *et al.*, 2004). Four symptoms, runny nose, itchy nose, nasal congestion, and sneezing, were assessed in all patients using a score of 4 (0 = no symptoms and 3 = severe symptoms), with lower scores indicating less severe symptoms.

Patients were also assessed for improvement in their quality of life after treatment using the RQLQ. The

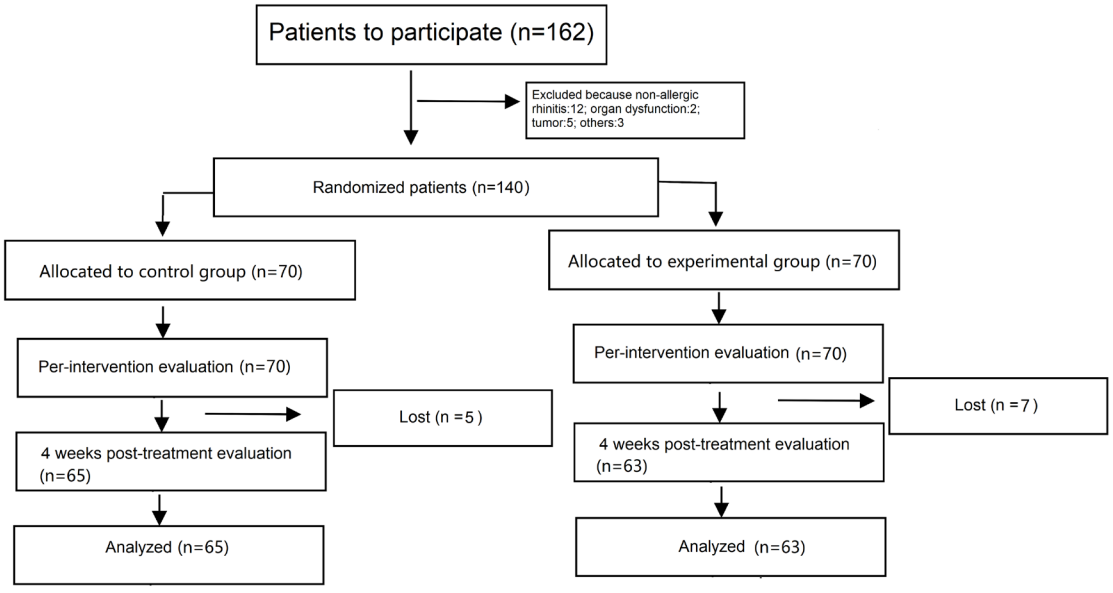

Figure 1. Diagram of patient selection, treatment and analysis

Table 1. Baseline characteristics of patients

Variable	Control group (n=65)	Experimental group (n=63)	*P*-value*
Female, n (%)	19 (29.2)	20 (31.7)	0.725[c]
Age; yrs., mean (S.D.)	32.1 (11.1)	32.8 (10.2)	0.159[a]
Severity of disease			
Moderate, n (%)	45 (69.2)	42 (66.7)	0.237[c]
Severe, n (%)	20 (30.8)	21 (33.3)	0.531[c]
Mean course of disease; yrs., mean (S.D.)	4.3 (1.6)	4.1 (1.2)	0.164[a]

Statistical analysis: a. independent two-sample Student's *t*-test, b. Mann Whitney U Test and c. chi-square test

Table 2. The scores of total nasal symptoms scores in the two groups

Items assessed	Assessment date (weeks)	Treatment		*t*-value	*P*-value
		Control	Experimental		
Total TNSS score	0	14.60±2.25	14.63±2.26	0.224	0.327
	4	4.40±0.29*	1.62±0.27*	4.201	<0.01
Runny nose	0	3.11±0.76	3.42±0.87	0.529	0.782
	4	1.14±0.27*	0.31±0.11*	2.115	<0.01
Itchy nose	0	4.73±1.02	4.21±0.89	0.162	0.744
	4	1.53±0.16*	0.30±0.17*	8.665	<0.01
Nasal congestion	0	4.21±0.11	4.42±0.11	0.313	0.541
	4	0.92±0.11*	0.25±0.07*	3.771	<0.01
Sneezing	0	2.55±0.67	2.58±0.62	0.326	0.667
	4	0.81±0.11*	0.76±0.12*	0.310	0.451

Statistical analysis: repeated measured ANOVA, *denotes significant difference from before treatment within group ($P<0.05$), *t* value of independent two-sample Student's *t*-test.

RQLQ has 28 questions in 7 sections (activity limitation, sleep disturbances, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function). Patients responded to the questions on a 7-point scale (0 = not impaired at all, 6 = severely impaired), with higher scores indicating worse quality-of-life (Juniper & Guyatt, 1991).

Safety evaluation

Adverse reactions, including nausea, diarrhea, nasal dryness and bleeding, and throat irritation in the two groups were recorded to assess the safety of the treatment.

Statistical analysis

All statistical analyses were performed using the SPSS19.0 statistical software. Quantitative data were described as mean ± standard deviation (S.D.), and the independent t-test or Mann Whitney U test was used to compare the mean values between the two groups. Qualitative data are described as [n (%)], and compared using the χ 2 test or Fisher's exact test. A *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics

A total of 140 patients were enrolled and randomized to two groups, and 128 patients completed the study after 5 and 7 patients were lost during the treatments. There were 46 males and 19 females with an average age of 31.4±12.7 years in the control group and 43 males and 20 females with an average age of 30.9±10.7 years in the experimental group (Fig. 1). The numbers of patients with moderate and severe AR were 45 and 20 in the control group and 42 and 21 in the experimental group, respectively. The mean courses of disease were 4.2 and 4.0 years, respectively, in the two group. Statistical analysis showed that there was no difference in sex, age, disease severity, or course of disease between the two groups (Table 1; $P>0.05$).

Vitamin D improves AR symptoms and quality-of-life

After 4-week treatment, the TNSS scores in both groups were assessed and compared (Table 2). The results showed that the total TNSS scores were significantly reduced compared with those before treatment in both groups for all four main symptoms assessed: itching, runny nose, nasal congestion, and sneezing ($P<0.05$). The improvements with vitamin D supplementation were significantly greater than those of the control group in the symptoms assessed, except for sneezing (Table 2, $P<0.05$).

At the end of the 4-week treatment, we assessed the quality-of-life of the participating AR patients using the RQLQ. The results showed that the scores in both groups were significantly lower after the therapy than before the therapy in all aspects ($P<0.05$), and the improvements with vitamin D supplementation were significantly greater than those in the control group, except for eye symptoms, which were improved, but the differ-

Table 3. The scores of quality of life of AR patients the two groups

Items assessed	Assessment date (weeks)	Treatment		*t*-value	*P*-value
		Control	Experimental		
Total RQLQ score	0	17.4±2.01	16.98±2.14	0.112	0.327
	4	7.29 ±1.11*	3.68±0.86*	5.661	<0.01
Activity limitation	0	3.25±0.56	3.29±0.77	0.439	0.862
	4	1.11±0.67*	0.52±0.10*	2.825	0.002
Sleep problems	0	3.44±0.84	3.47±0.91	0.223	0.708
	4	1.44±0.11*	0.55±0.10*	5.675	<0.01
Non-nose/eye symptoms	0	2.71±0.14	2.77±0.10	0.323	0.241
	4	0.92±0.12*	0.41±0.06*	2.751	0.014
Practical problems	0	2.55±0.62	2.64±0.60	0.316	0.510
	4	0.88±0.10*	0.42±0.13*	1.380	0.034
Nose symptoms	0	3.58±0.45	3.49±0.52	0.376	0.310
	4	1.07±0.12*	0.42±0.13*	2.931	0.023
Eye symptoms	0	2.44±0.24	2.47±0.36	0.336	0.455
	4	0.88±0.11*	0.79±0.10*	1.251	0.087
Emotion	0	2.18±0.34	2.22±0.23	0.397	0.450
	4	0.99±0.15*	0.53±0.12*	3.651	0.018

Statistical analysis: *T*-test for paired samples. *denotes significant difference from before treatment within group ($P<0.05$), *t* value of independent two-sample Student's *t*-test.

Table 4. Compositions of T lymphocyte subsets between the two groups

Assessment date (weeks)	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$ ratio	
	0	4	0	4	0	4	0	4
Control	64.72±5.14	63.72±4.16	41.2±3.14	35.11 ±3.27*	22.40±2.58	29.15±3.46*	1.82±0.12	1.20±0.11*
Experimental	63.74±5.21	62.65±4.08	42.52±3.37	30.81 ±2.44*	22.34±2.67	36.17±4.19*	1.90±0.12	0.92±0.08*
T value	0.029	1.199	0.165	3.718	0.342	7.229	0.260	6.855
P-value	0.435	0.315	0.826	<0.01	0.562	<0.01	0.775	<0.01

Statistical analysis: *T*-test for paired samples. *denotes significant difference from before treatment within group ($P<0.05$), *t* value of independent two-sample Student's *t*-test.

ence was not statistically significant as compared to the control ($P<0.05$, Table 3).

Vitamin D alters T lymphocyte subsets

We also compared the levels of T lymphocyte subsets before and after the therapy. The results showed that while the percentage of $CD3^+$ in the lymphocytes remained unchanged, the percentages of $CD4^+$ and $CD4^+/CD8^+$ ratios were reduced, and the percentages of $CD8^+$ were increased in the two groups after the therapy compared to before the therapy ($P<0.05$). Furthermore, compared to the control group, vitamin D supplementation resulted in greater changes in the subsets (Table 4).

Vitamin D changes serum levels of pro-inflammatory anti-inflammatory cytokines

To further assess the impact of vitamin D on AR-associated inflammation, we profiled the serum levels of pro-inflammatory and anti-inflammatory cytokines before and after therapy. The data showed that TNF-α levels were significantly decreased, and IFN-γ and IL-10 levels were significantly increased in the two groups after the therapy compared to before the therapy ($P<0.05$, Table 5). These changes were significantly greater in the experimental group than in the control group ($P<0.01$, Table 5).

Vitamin D is reduced in patients with AR and increased after treatment

To elucidate the role of vitamin D in AR, we analyzed serum vitamin D levels in patients with AR before and after treatment. The results showed that compared to healthy participants, patients with AR had significantly lower serum vitamin D levels, which were significantly increased after vitamin D supplementation (Table 6).

Adverse reactions

No serious adverse reactions were observed in either of the groups. In the experimental group, one patient

Table 5. Comparison of serum pro-inflammatory anti-inflammatory cytokine levels between the two groups

Group	IL-10 (pg/mL)		TNF-α (pg/mL)		IFN-γ (pg/mL)	
	Before	After	Before	After	Before	After
Control (*n*=45)	5.93±0.82	7.79±1.21*	6.24±0.71	5.06±0.42*	4.68±0.57	6.62±1.02*
Experimental (*n*=45)	5.96±0.71	9.52±1.69*	6.19±0.72	4.56±0.44*	4.79±0.48	7.64±1.19*
t	0.439	4.622	0.435	4.331	0.114	3.603
P	0.673	<0.01	0.541	<0.01	0.763	0.01

Statistical analysis: *T*-test for paired samples. *denotes significant difference from before treatment within group ($P<0.05$), *t* value of independent two-sample Student's *t*-test.

Table 6. Serum vitamin D contents in healthy and AR patients before and after treatment.

Group	n	Vitamin D (nmol/L)
Healthy participants	25	42.12±4.07
Patients not supplemented with vitamin D	45	
Before treatment		36.40±3.01[a]
After treatment		36.11±3.01[a]
Patients not supplemented with vitamin D	51	
Before treatment		36.61±3.58[a]
After treatment		39.41±3.21[b]

[a]$P<0.05$ compared with healthy participants; [b]$P<0.05$ compared with patients not supplemented with vitamin D

reported a mild dry nasal membrane that was relieved without medical treatment.

DISCUSSION

In this study, we investigated the effect of vitamin D as a supplementary therapeutic to mometasone in moderate-to-severe AR. Our results showed that vitamin D effectively improved the therapeutic efficacy of mometasone. It moderates T lymphocyte subsets and pro-inflammatory and anti-inflammatory cytokine levels, leading to significantly better quality-of-life with AR.

As a common disease that seriously affects the physical and mental health and quality of life of patients. Currently, there is no cure for RA, but active treatment can effectively control the pathological symptoms of patients to reduce pain and stop or slow further damage (Bullock *et al.*, 2018). Therefore, it is important to develop better treatment plans with fewer complications, better patient compliance, and lower costs. Nasal glucocorticoids and antihistamines are the first-line clinical drugs for AR with excellent efficacy for persistent moderate-to-severe AR, and the combination of intranasal antihistamines and corticosteroids is conducive to the rapid control of symptoms and reduction of TNSS (Wheatley & Togias, 2015), there are various adverse effects, including osteoporosis, dyslipidemia, body fat redistribution, insulin resistance, glucose intolerance, and even diabetes associated with glucocorticoid drugs (Sundahl *et al.*, 2015). Recent studies have shown that vitamin D deficiency is common in AR patients whose serum contains less vitamin D than in healthy individuals (Chen *et al.*, 2016). Vitamin D, as an important human nutrient, does not cause any adverse reactions if taken at the dose recommended by the physician. Vitamin D has been demonstrated to have various immunomodulatory effects and to protect against a number of autoimmune diseases, including multiple sclerosis and inflammatory bowel disease (Christakos *et al.*, 2016; Holick, 2007). However, the benefits of vitamin D in AR treatment with corticosteroids have not yet been fully explored.

The corticosteroid drug mometasone has been demonstrated to be effective and safe for treating inflammatory diseases of the nose and paranasal sinuses including AR (Yarom *et al.*, 1982). As expected, treatment with nasal spray for one month, resulted in significant control of all AR-related symptoms as well as better quality of life in our cohort with moderate-to-severe AR, as assessed using the TNSS and RQLQ, both of which are well-recognized tools that assess the primary outcome in clinical trials on AR. Furthermore, the assessments showed that Vitamin D supplementation further improved the control of AR and quality-of-life of AR patients in all assessed items except sneezing and eye symptoms. These data demonstrate that vitamin D supplementation improves the overall therapeutic effect of corticosteroid drugs, to a certain extent.

In the present study, the vitamin D dose prescribed were 1600 IU per day based on the manufacture's recommendation to minimize potential adverse effect. Previously, various doses have been used from 100 IU per day for patients with refractory allergic rhinitis (Chen *et al.*, 2016), 2000 IU over 2 months in children (Tiazhka & Selska, 2020) to 42000 IU per day via nasal dropping (Liu *et al.*, 2018) and 50000 IU/week of vitamin D for 8 weeks along with antihistamines (Bakhshaee *et al.*, 2019). It is likely that the optimal dose is depending on the formulations (chew pill, soft gel and capsule) and patient populations and need to be defined further.

To better understand the mechanisms underlying the improved therapeutic effect of vitamin D supplementation, we compared the changes in T lymphocyte subsets following the therapies. The results showed that the levels of $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ in the experimental groups were changed compared to those in the control group, suggesting that vitamin D might modulate cellular immune function by lowering the levels of $CD4^+$ and increasing the level of $CD8^+$. Vitamin D receptor (VDR) is produced in respiratory epithelial cells, where Vitamin D binds to vitamin D receptor (VDR) to enhance both innate and acquired immunity *via* various immune cells, including dendritic cells, monocytes, megaphagocytes, T lymphocytes, and B lymphocytes (Bakdash *et al.*, 2014; Mailhot & White, 2020). It inhibits the proliferation of T lymphocytes and promotes the differentiation of $Foxp3^+$ regulatory T cells (Barragan *et al.*, 2015; Hewison, 2011). Therefore, at least part of the enhanced therapeutic effect of vitamin D is likely due to the modulation of immune function in patients with AP.

Vitamin D also exerts regulatory effects on many cytokines involved in inflammation. For example, it downregulates the production of IL-12, TNF-α, and IL-2 and upregulates the synthesis of IL-4 and IL-10 (Barragan *et al.*, 2015; Hewison, 2011), which are secreted by immune cells to regulate their proliferation and differentiation of immune cells. Our data showed that pro-inflammatory cytokine TNF-α levels were significantly reduced and anti-inflammatory cytokine IFN-γ and IL-10 levels were significantly increased after vitamin D supplementation, suggesting that vitamin D may improve the therapeutic effect by modulating cytokine production to inhibit inflammation. IL-10 and IFN-γ can not only inhibit the T cell response but also inhibit the production of immunoglobulin E, which plays a negative role in regulating AR pathological symptoms. TNF-α mediates various inflammatory reactions, and a reduction in TNF-α levels may lead to the inhibition of AR-related inflammation.

In addition, vitamin D supplementation may attenuate vitamin D deficiency in patients with AR and modulate immune function to strengthen its anti-inflammatory effect. In this study, the serum level of vitamin D was found to be lower in AR patients, and this vitamin D deficiency was partially alleviated after vitamin D supplementation. These results are consistent with those of previous studies on children and women (Aryan *et al.*, 2017; Srimani *et al.*, 2017).

This study had several limitations. Although this trial was blinded to the assessors, the patients were aware of their treatment because of the absence of placebo indistinguishable from patients, resulting in potential bias in treatment outcomes. In addition, physiologic measures, including peak nasal inspiratory flow and nasal airflow, were not used to measure the outcomes, yielding potential bias in the results. A single dose of vitamin D was applied in the therapy; patients were not classified based on the AR etiologies, such as seasonal allergic rhinitis or perennial allergic rhinitis, for better treatment and explanation of the therapeutic outcome. For example, patients with seasonal allergic rhinitis pass the onset season and recover spontaneously. Since this was a single-center, short-term, and small-scale study, more extensive multicenter work is needed to address the limitations and to validate our conclusion.

CONCLUSIONS

Vitamin D supplementation of mometasone nasal spray is effective and safe for improving AR symptoms and quality of life. These improvements were partially due to the modulation of cellular immunity and inhibition of inflammation. Therefore, vitamin D adjuvant therapy is highly recommended for patients with moderate or severe seasonal AR.

Declarations

Ethics approval and consent to participate: The Ethics Committee of Huichang People's Hospital, Ganzhou, China, obtained written informed consent from all participants.

Consent for publication: N/A.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: None.

Funding: None.

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Authors' contributions: MG designed the study, performed the research, analyzed the data, wrote the manuscript, confirmed the authenticity of all raw data, and read and approved the final manuscript.

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