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Original article

The relationship between vitamin D and moderate/severe persistent allergic rhinitis

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ABSTRACT

Background. – Vitamin D is a fat-soluble vitamin that plays an important role in regulation of the immune system. However, there is still a lack of consensus on the relationship between vitamin D and allergic rhinitis (AR). In this study, we explored the relationship between 25-hydroxyvitamin D [25(OH)D3] and moderate-to-severe persistent AR.

Patients and methods. – Thirty-nine adult patients with moderate-to-severe persistent AR and 20 healthy people serving as a control group were recruited at the affiliated Chengdu University Hospital of Traditional Chinese Medicine from June 2018 to January 2019. The subjects were selected at random and participated voluntarily in our research. Vitamin D3 levels were determined in the blood samples of all subjects. Levels of IFN- γ , IL-4, IL-10 and total immunoglobulin E (IgE) were measured in the AR group, and scores on a visual analogue scale (VAS) and on a nasal-ocular- conjunctival quality-of-life questionnaire (Rhinoconjunctivitis Quality of Life Questionnaire, RQLQ) were also recorded for the AR group.

Results. – There was a significant difference in 25(OH)D3 levels between the control group and the AR group ($P < 0.01$). In the correlation analysis, a positive correlation was observed between IFN- γ and 25(OH)D3, but a negative correlation was seen between total IgE, IL-4, VAS and RQLQ scores in the AR patient group. However, multiple linear regression analysis revealed no significant correlation between total IgE, IL-4 and 25(OH)D3.

Conclusion. – In the correlation analysis, we confirmed that serum 25(OH)D3 displays significant negative correlation with total IgE, IL-4, VAS and RQLQ scores, which indicates that the lower the 25(OH)D3 level, the higher the VAS and RQLQ scores, and thus the more severe the symptoms in AR patients.

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1. Introduction

AR is an inflammatory mucosal disease driven by Th2, which is mainly mediated by IgE and involved in a variety of vasoactive factors and cytokines following exposure of atopic individuals to allergens; it is characterized by nasal congestion, runny nose, sneezing and nasal itching [1]. Epidemiological studies have shown that the prevalence of AR is increasing year by year, and currently affects 40% of the world's population [2]. Despite the universal and long-term nature of AR and its burden on personal productivity, quality of life and society, patients' lack of systematic awareness of it coupled with irregular drug use mean that it remains

underestimated, with considerable impact on the entire health system [3].

Vitamin D (VitD) is a fat-soluble vitamin that depends on ultra-violet radiation to produce endogenous vitamins in the skin, and ultimately produces the active form of 1,25(OH)₂D3 under the action of the liver and kidneys. VitD plays an important role in maintaining normal bone metabolism and nerve function [4]. In recent years, studies on serum VitD levels and the prevalence of AR, the effects of VitD on the immune system, and the role of VitD receptors in regulating gene expression, provide evidence that further reveals the relationship between VitD and AR. Although most of the current literature suggests a certain correlation between VitD and AR, there are conflicting results in reports concerning the relationship between VitD levels and the prevalence of AR [5,6,7]. At the same time, there is some controversy about the effect of VitD on the immune system. On one hand, VitD can inhibit the maturation of DC and the proliferation and differentiation of lymphocytes to mediate immune tolerance and reduce allergy [8–10]. On the other,

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it can aggravate allergy by stimulating the expression of IL-4 and IL-10 and reducing secretion of IFN- γ and IL-12, thus skewing the Th1/Th2 axis towards Th2 [11,12]. This contradictory result raises the following questions: what is the specific correlation between VitD and AR? How strong or weak is the ability of VitD to mediate immune tolerance and bias towards Th2? This study provides further clinical evidence of the correlation between VitD and AR, and it further discusses the correlation between VitD and multiple indexes of AR.

2. Materials and methods

2.1. Subjects

This study was conducted at the Chengdu University Hospital of Traditional Chinese Medicine from June 2018 to January 2019. All 39 patients were diagnosed as having moderate-to-severe persistent AR. The inclusion criteria were as follows: patients had to meet the diagnostic criteria of moderate-to-severe persistent AR [13], to be aged between 18 and 65 years old, and regardless of gender, they must not have been using any drugs for treatment of atopic diseases in the 2 weeks before joining the study. All subjects took part in the study voluntarily and signed an informed consent form. The exclusion criteria were as follows: patients on long-term medication for other chronic diseases, patients with bronchial asthma or other atopic diseases, and patients with chronic sinusitis, nasal polyps or severe nasal septum deviation. Twenty healthy subjects were recruited to form the control group. All participants signed the completed informed consent form before the study. This trial was approved by the Sichuan Regional Ethics Review Committee for Traditional Chinese Medicine and the Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (Approval number: 2016KL-034-02).

2.2. Sample collection and measurement

The age, gender and serum 25(OH)D3 levels of all participants were recorded, as were levels of IFN- γ , IL-4, IL-10 and total immunoglobulin E (IgE), together with the VAS and RQLQ scores of patients with AR. In total, 3 mL of blood were withdrawn from the cubital vein of participants in the seated position, centrifuged at 3000 rpm/min for 5 minutes, and supernatant was separated after 30 minutes and stored at -80°C . The concentrations of 25(OH)D3, IFN- γ , IgE and IL-4 in the serum samples were determined using ELISA.

2.3. Statistical analysis

All study parameters were recorded, an index was created in an Excel database, and the statistical data were entered into SPSS22.0 for statistical analysis. Where there were no data less than 1 or fewer than 40 cases in the counting data, a Chi² test was used. If so, the exact probability method of a four-grid table was used. A Pearson or Spearman coefficient was used for the correlation analysis. A *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographics and serum 25-hydroxyvitamin D3

The gender data in the two groups were tested using Pearson's Chi² test ($\chi^2 = 0.103$, $P = 0.95 > 0.05$). The age data and serum VitD3 showed normal distribution; an independent-samples *t*-test was used to analyze this data and the results were as follows: age analysis ($t = -1.678$, $P = 0.099 > 0.05$), serum VitD3 ($t = 3.126$,

Table 1

Demographics and serum 25-hydroxyvitamin D3 for study subjects.

Variable	Healthy group	AR group	<i>t</i> / χ^2	<i>P</i>
Gender (male/female)	9/11	16/23	0.086	0.770
Age (years)	29.60 $\pm$ 7.30	33.33 $\pm$ 8.46	-1.678	0.099
25(OH)D3 (ng/mL)	31.82 $\pm$ 11.45	23.41 $\pm$ 8.84	3.126	0.003

$P = 0.003 < 0.05$). Table 1 shows that the baseline indexes of the two groups were the same, and that there was a significant difference in serum VitD3 between the healthy group and the moderate-to-severe persistent AR group.

3.2. Correlation with other parameters

As shown in Fig. 1, serum VitD3 was negatively correlated with VAS, RQLQ, IgE and IL-4, but positively correlated with IFN- γ , with highly correlation between RQLQ and IFN- γ .

3.3. Multiple linear regression analysis

25(OH)D3 (ng/mL) was taken as the dependent variable, with VAS score, RQLQ score, total IgE, IFN- γ and IL-4 taken as the independent variables. As shown in Table 2, in the case of normal distribution of residuals, the final model in multiple linear regression analysis shows that VAS score ($t = -2.230$, $P = 0.032$), RQLQ score ($t = -3.693$, $P = 0.001$), and IFN- γ ($t = 3.443$, $P = 0.002$) were significantly correlated, with degree as follows: RQLQ score $>$ IFN- γ $>$ VAS score. However, total IgE ($t = 0.073$, $P = 0.942$), IL-4 ($t = 0.102$, $P = 0.919$) were not significantly correlated.

4. Discussion

AR is a disease commonly encountered in otorhinolaryngology that is more detrimental to efficiency in the workplace than other chronic diseases such as diabetes and hypertension [14]. In addition, AR is often closely related to a variety of diseases. Statistical data shows that 10% to 40% of AR patients are simultaneously presenting asthma; there is growing evidence that AR precedes the emergence of asthma symptoms and that its severity affects asthma control [15]. At the same time, the incidence of sinusitis, conjunctivitis and secretory otitis media in patients with a history of AR is significantly higher and the symptoms more severe [16]. In children, the incidence of AR is associated with sleep disorders, characterized by an increased risk of snoring, sleep apnea disorder and sleep apnea syndrome, and it constitutes a risk factor for long-term deterioration of quality of life after adenoidectomy [17]. As well as being detrimental to the physical functioning of individuals, AR also imposes a huge financial burden on society.

The main circulating form of VitD is 25(OH)D3, which is also the main form measured using standard laboratory methods, and it is used to evaluate the status of VitD levels in the body [18]. An article in Iran reported a negative correlation between serum VitD levels and AR [19]. A report from the annual National Health and Nutrition Inspection Survey in Korea found potential correlation between low VitD levels and prevalence of AR in Korean adults. Another study evaluating children with AR and normal subjects

Table 2

Multiple regression analysis of the effects of variable factors on 25(OH)D3.

Variable	<i>t</i>	<i>P</i>
VAS score	-2.230	0.032
RQLQ score	-3.693	0.001
total IgE	0.073	0.942
IL-4	0.102	0.919
IFN- γ	3.443	0.002

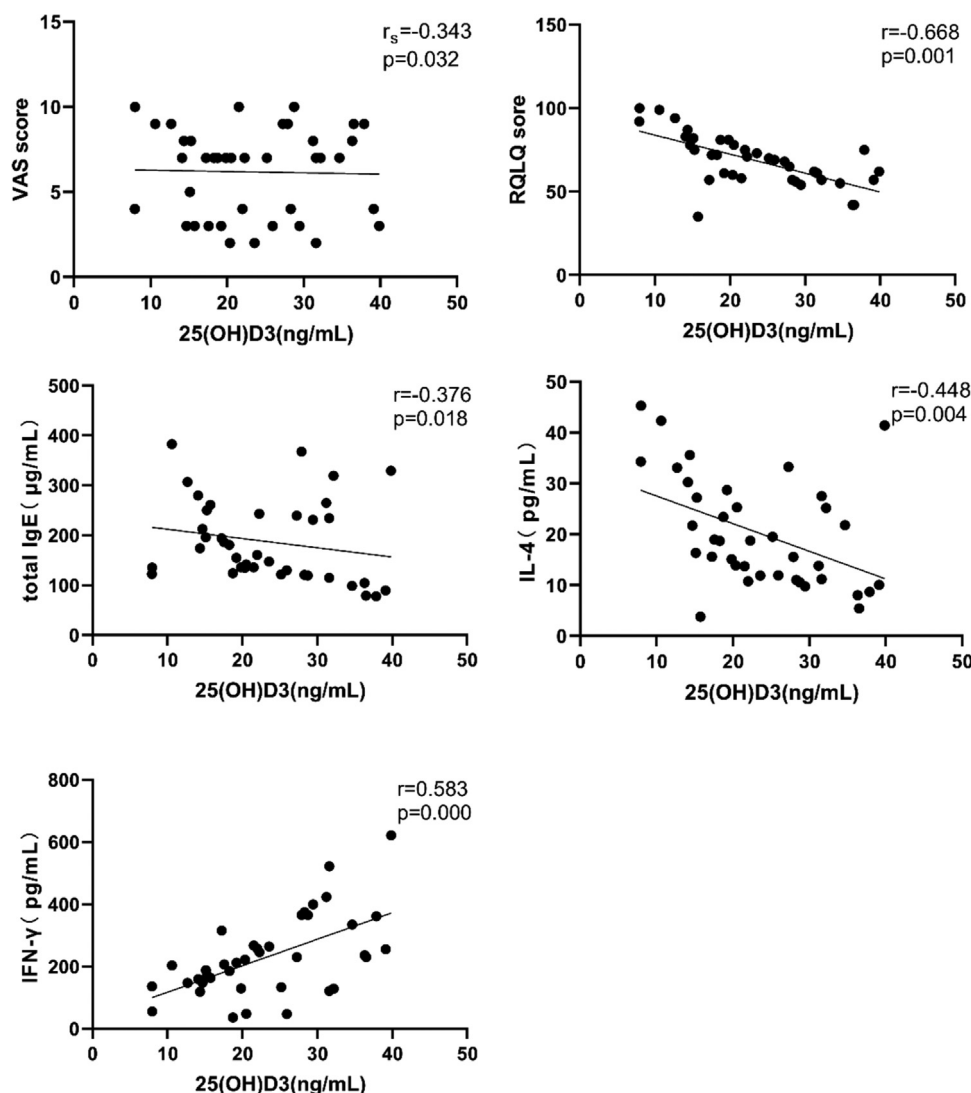


Fig. 1. Correlation between VAS, RQLQ, IgE, IL-4 and IFN- γ . The VAS scores were not normally distributed, and Spearman's rank correlation coefficient was used; the other data were normally distributed using Pearson's linear correlation coefficient.

showed the average level of serum VitD3 in children with AR to be significantly lower than that in the control group, while no significant difference in serum VitD3 was noted between children with mild AR and moderate-to-severe AR. It was concluded that serum Vitamin D levels in children with AR were significantly lower than in the control group [20,21]. In contrast, another study in Korea exploring the relationship between CD levels and allergy found a low level of serum VitD to be associated with atopic dermatitis but not with AR or asthma [22]. Interestingly, a Norwegian survey showed that a serum 25(OH)D3 level of less than 50 nM was associated with increased risk of AR in males (adjusted Odds ratios [AOR]: 2.55; 95%CI: 1.01–6.49). Each 25 nM reduction in 25(OH)D level was associated with an AOR of 1.84 (95% CI: 1.18–2.87). However, correlation in females was completely the opposite, with an AOR of 0.83 for every 25-nM decrease in serum 25(OH)D3, suggesting that VitD plays a different role in the development of AR in males and females [23]. At the cellular level, VitD may inhibit proliferation and differentiation of Th1 cells and regulate the production of relative cytokines, which is manifested through the expression of IL-2 and γ -IFN. 1,25(OH)2D3 also stimulates the formation of Th2 cells by upregulating specific transcription factors and Th2 cytokines such as IL-4 and IL-10, causing Th1/Th2 balance to shift to Th2 cells [24]. It can also reduce IL-17 secretion by inhibiting

Th17 [25]. A national health and nutrition survey data show that serum VitD level is inversely proportional to total IgE. Other studies have shown that active VitD can significantly inhibit B cells from producing IgE, which may be related to inhibition of the B cell cycle and to the promotion of B cell apoptosis by VitD [26,27].

VitD plays an important role in immune response. Most studies have shown a correlation between VitD level and AR, although certain other studies do not support this view, which may be associated with contradictory finding that on one hand, VitD mediates immune tolerance by inhibiting the maturation and antigen presentation ability of DC cells, as well as proliferation and differentiation of lymphocytes and stabilizing mast cells, and on the other hand, VitD shifts the Th1/Th2 axis to Th2 cells by reducing or increasing the secretion of certain cytokines [28,29]. This contradiction requires further clinical investigation to validate the specific roles played by VitD in the pathogenesis of AR.

5. Conclusion

In the correlation analysis, we confirmed that serum 25(OH)D3 displays significant negative correlation with total IgE, IL-4, VAS and RQLQ scores, which indicates that the lower the 25(OH)D3

level, the higher the VAS and RQLQ scores, and thus the more severe the symptoms in AR patients.

Disclosure of interest

The authors declare that they have no competing interest.

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