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RESEARCH ARTICLE

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Low serum 25-hydroxyvitamin D levels are associated with perennial allergic rhinitis but not disease severity

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Abstract

Background: Vitamin D deficiency plays an essential role in allergic rhinitis(AR), but the role of vitamin D deficiency in perennial allergic rhinitis (pAR) remains unclear. Therefore, our study explored 25(OH)D levels in patients with pAR and healthy individuals in a single center in China for three years.

Methods: A total of 655 patients with pAR and 682 healthy controls were enrolled in this study from 2015 to 2017. Patients' clinical history and symptoms were recorded. sIgE tests were performed using the allergen detection system (UniCAP), and the ADVIA centaur XP system (SIEMENS) was used to measure serum 25(OH)D levels.

Results: Serum 25(OH)D levels were significantly different between the pAR group and control group over the three-year study period(all $P < .05$). Specifically, 25(OH)D levels were decreased in the pAR groups over three years. Serum25(OH)D deficiency, insufficiency, and sufficiency were noted in 66.9% ~71.9%, 22.5% ~29.4%, and 2.5%~5.6%, respectively, of patients in the pAR group and 53.2%~60.7%, 31.4%~36.6%, and 7.9% ~11.4%, respectively, of participants in the control group. We did not identify significant associations between serum 25(OH)D levels and clinical characteristics of patients with pAR over the three-year period (all $P > .05$) after adjusting for sex, age, duration of disease, total nasal symptom score (TNSS), sIgE levels, number of positive allergens, and family history.

Conclusion: pAR patients exhibited lower serum 25(OH)D levels compared with healthy people with a high prevalence of 25(OH)D deficiency or insufficiency. We did not identify a significant correlation between 25(OH)D and pAR associated factors.

KEYWORDS

25-hydroxyvitamin D, Allergic rhinitis, Deficiency, Vitamin D

1 | INTRODUCTION

Allergic rhinitis (AR) is noninfectious rhinitis, and its common symptoms include rhinorrhea, sneezing, nasal blockage, and itching of nose. The epidemic prevalence of AR is a significant public health problem. The estimated incidence rate in China is 8 ~ 21.4%, and AR has impacted the quality of life of approximately 300 million Chinese people.[1]

Many studies have shown that vitamin D deficiency is intimately related to allergic diseases, including adult asthma, childhood asthma, eczema, atopic dermatitis, chronic urticaria, and AR.[2,3] Vitamin D is a critical factor that bridges the gap between innate and adaptive

TABLE 1 General characteristics of the total subjects

Variable	2015			2016			2017		
	AR groups (N = 160)	Control groups (N = 158)	*P*-value	AR groups (N = 136)	Control groups (N = 142)	*P*-value	AR groups (N = 359)	Control groups (N = 382)	*P*-value
Male (N, (%))	74 (46.3)	68 (43.0)	0.57	77 (56.6)	85 (59.9)	0.58	182 (50.7)	173 (45.3)	0.14
Age	24.44 ± 12.87	25.34 ± 16.29	0.75	22.59 ± 14.39	21.98 ± 13.72	0.36	23.66 ± 13.91	24.04 ± 16.76	0.35
BMI	19.69 ± 1.78	19.78 ± 2.02	0.97	19.69 ± 1.82	19.90 ± 1.91	0.47	19.63 ± 1.95	19.46 ± 1.43	0.95
Season of blood sampling (N)									
Spring	26	36	0.21	34	42	0.41	72	95	0.58
Summer	49	36		39	37		101	91	
Autumn	47	41		42	35		125	131	
Winter	38	45		21	30		61	65	

immunity. For example, increased serum 25(OH)D levels were associated with reductions in the quantity and percentage of Treg cells. Treg cell reductions can alleviate Th2-mediated allergic inflammation.[4,5] Furthermore, this inhibition of Treg cells has synergistic effects on control drugs.[6] Vitamin D plays a vital role in the protection against allergic diseases.[7,8] However, data from some studies did not support the inhibitive effects of vitamin D in AR while presenting an increased risk between high 25(OH)D concentrations and allergic diseases. Therefore, the relationship between vitamin D and AR remains controversial. In this study, we aim explored vitamin D levels in patients with pAR and healthy people in central China for three years.

2 | MATERIALS AND METHODS

2.1 | Participants

The current study was conducted at the Departments of Otorhinolaryngology, Allergy, and Pediatrics, and the Health Examination Center in the First Affiliated Hospital of Anhui Medical University. 655 patients were diagnosed as pAR according to the Allergic Rhinitis and its Impact on Asthma guidelines[9] and 682 healthy people were recruited from January 2015 to December 2017 in this study. Patients with pAR had signs and symptoms of perennial AR without other nasal disorders, asthma, atopic dermatitis, chronic renal insufficiency, and malignant diseases. The sIgE of patients with pAR was positive for common aeroallergens, including Dermatophagoides farinae with or without other allergens. The control group was composed of healthy people who did not present any allergic symptoms. All subjects did not receive vitamin D supplementation within three months before blood testing. Our institutional review board approved this study. Informed written consent was obtained from all participating subjects or their guardians.

2.2 | Demographic and clinical assessment

Demographic information, body mass index (kg/m^2), nasal symptom score, ocular symptoms, asthma symptoms, eczema symptoms, food allergy, medicine allergy, and family history of allergic disease were documented for all subjects. Total nasal symptom score(TNSS) was assessed based on the severity of nose symptoms(rhinorrhea, sneezing, nasal blockage, and itching). The severity degree of each symptom was graded as follows: 0 = no symptom; 1 = mild, unobtrusive symptoms; 2 = moderate, disturbing but tolerable symptoms; and 3 = severe, disturbing and difficult to tolerate.

2.3 | Allergy test

Skin prick tests(SPTs) with10 different aeroallergens, including Dermatophagoides farinae, fungi(Alternaria alternate, Penicillium

TABLE 2 skin prick test results and sIgE levels

		2015			2016			2017		
		dermatophagoides	fungi	pollen	dermatophagoides	fungi	pollen	dermatophagoides	fungi	pollen
SPT	(+)	16	47	54	27	19	40	32	67	78
	(++)	43	27	31	20	8	16	45	11	18
	(+++)	51	2	6	18	5	21	55	6	30
	(++++)	48	4	2	78	5	8	209	7	24
sIgE levels	1	22	2	13	14	11	11	35	4	8
	2	26	1	12	14	9	4	36	10	22
	3	68	12	4	16	3	5	85	8	5
	4	34	10	0	17	1	0	84	3	1
	5	4	0	0	16	1	0	56	0	0
	6	6	0	0	59	0	1	63	0	1

chrysogenum, and Cladosporium herbarum), pollens(maple leaf sycamore, rape, and Chinese scholar tree), and weeds(ragweed, Artemisia sieversiana, and Chenopodium album), were performed. Histamine hydrochloride and normal saline were used as positive and negative controls, respectively. A mean wheal diameter of 3 mm was considered a positive result. Serum-specific IgE tests were performed using an allergen detection system (UniCAP, Thermo Fisher Scientific). Different sIgE tests were chosen according to skin prick tests or a standard panel, including d2(Dermatophagoides farinae), tx4(maple leaf sycamore, willow, oak, elm, and cottonwood), wx1(ragweed, Chenopodium album, Artemisia vulgaris, and Plantagoasiatica) and mx2(Alternaria alternate, Penicillium chrysogenum, Aspergillus fumigates, Cladosporium herbarum, Candida albicans, and Setomelanomma rostrata). sIgE was classified into 6 levels: level 0, <0.35 U/mL; level 1, (0.35 ~ 0.7) U/mL; level 2, (0.7 ~ 3.5)U/mL; level 3, (3.5 ~ 17.5) U/mL; level 4, (17.5 ~ 50) U/mL; level 5, (50 ~ 100) U/mL; and level 6, >100 U/mL. The positive cut-off value of sIgE was 0.35 U/mL.

2.4 | 25(OH) vitamin D concentration

A three-ml blood sample was obtained and centrifuged. The samples were stored at 4°C for 24 hours until analysis. The ADVIA Centaur XP(SIEMENS) was used to measure serum 25 (OH) D levels. Serum 25 (OH) D levels less than or equal to 20 ng/mL, between 20 and 30 ng/mL, and greater than or equal to 30 ng/mL were considered to represent vitamin D deficiency, insufficiency, and sufficiency, respectively.[9]The seasons of blood sampling were defined as follows: spring (March-May); summer (June-August); autumn (September-November); and winter (December-February).

2.5 | Statistical analyses

Statistical analysis was performed using SPSS 17 software. Differences between groups were assessed by chi-square tests for categorical variables and by independent and nonparametric tests for continuous variables with non-normal distribution. Independent and nonparametric tests include Mann-Whitney *U* and Kruskal-Wallis H. Statistical significance was fixed at $P < .05$.

3 | RESULTS

3.1 | General characteristics

The general characteristics of the subjects are described in Table 1. The pAR group comprised 655 subjects: 160 patients in 2015, 136 patients in 2016, and 359 patients in 2017. The control group comprised 682 subjects: 158 patients in 2015, 142 patients in 2016, and 382 patients in 2017. The proportion of males over the 3-year period was 46.3%~56.6% in the pAR groups and 43.0%~59.9% in the control groups. No statistically significant differences were detected in sex, age, BMI, and the season of blood sampling between the two groups ($P > .05$ for all). Skin prick test results and sIgE levels were described in Table 2. Due to skin problems, 2, 17, and 18 patients did not undergo skin prick tests in 2015, 2016, and 2017, respectively. sIgE test results revealed that 17, 24, and 21 patients with pAR were allergic to Dermatophagoides farinae and fungi in 2015, 2016, and 2017, respectively. In addition, 21, 20, and 33 patients with pAR were allergic to Dermatophagoides farinae and pollens in 2015, 2016, and 2017, respectively. Moreover, 8, 1, and 4 patients with pAR were allergic to Dermatophagoides farinae, fungi, and pollens in 2015, 2016, and 2017, respectively.

3.2 | Serum 25(OH)D levels and status for 3 years

The differences in serum 25(OH)D levels between pAR groups and control groups were statistically significant for all 3 years (all $P < .05$) (Table 3).These differences revealed statistically decreased 25(OH) D levels in the pAR groups for all 3 years. Serum 25(OH)D statuses in the pAR groups and control groups are described in Table 4. Serum

TABLE 3 Serum 25(OH)D levels in patients with pAR groups and control groups

	AR groups		Control groups			
year	N	25(OH)D levels	N	25(OH)D levels	Z-value	*P*-value
2015	160	17.50 ± 6.47	158	19.40 ± 7.82	−2.056	.040
2016	136	16.64 ± 6.68	142	19.28 ± 8.91	−2.40	.016
2017	359	16.89 ± 6.38	382	18.47 ± 8.03	−2.20	.028

TABLE 4 Serum 25(OH)D status in patients with pAR groups and control groups

	2015			2016			2017		
25 (OH) D status (ng/ml)	AR groups	Control groups	*P*-value	AR groups	Control groups	*P*-value	AR groups	Control groups	*P*-value
deficiency (≤20)	115 (71.9)	84 (53.2)	.002	91 (66.9)	76 (53.5)	.029	247 (68.8)	232 (60.7)	.002
insufficiency (20-30)	36 (22.5)	56 (35.4)		40 (29.4)	52 (36.6)		103 (28.7)	120 (31.4)	
Sufficiency (≥30)	9 (5.6)	18 (11.4)		5 (3.7)	14 (9.9)		9 (2.5)	30 (7.9)	

TABLE 5 The relation between serum 25(OH)D levels and Clinical characteristics of patients with pAR

	2015			2016			2017		
Variables	N	25(OH)D levels	*P*-value	N	25(OH)D levels	*P*-value	N	25(OH)D levels	*P*-value
Sex									
Male	74	17.98 ± 5.62	.16	77	17.06 ± 6.44	.31	182	17.13 ± 6.46	.65
female	86	17.17 ± 7.06		59	16.09 ± 6.99		177	16.65 ± 6.29	
Age(years)									
≤16	46	18.00 ± 7.52	.99	65	17.02 ± 6.76	.59	140	16.83 ± 6.22	.94
>16	114	17.36 ± 5.79		71	16.28 ± 6.63		219	16.94 ± 6.49	
Course of disease (years)									
≤3	72	17.39 ± 6.93	.85	62	16.93 ± 6.67	.61	191	17.29 ± 6.29	.11
>3	88	17.67 ± 6.03		74	16.40 ± 6.72		168	16.45 ± 6.47	
TNSS									
4 ~ 6	74	16.97 ± 7.14	.17	34	16.20 ± 5.92	.56	96	16.65 ± 6.42	.86
7 ~ 9	60	17.89 ± 5.29		65	16.93 ± 6.04		177	17.01 ± 6.16	
10 ~ 12	26	18.38 ± 6.78		37	16.52 ± 7.59		86	16.95 ± 6.82	
sIgE levels									
≤2	48	17.08 ± 5.27	.70	28	16.24 ± 5.84	.90	71	17.50 ± 6.96	.47
≥3	112	17.74 ± 6.88		108	16.74 ± 6.90		288	16.75 ± 6.23	
Positive allergens									
Dermatophagoides	114	16.82 ± 5.55	.10	91	16.89 ± 7.13	.64	301	17.06 ± 6.46	.69
Dermatophagoides + fungi	17	19.73 ± 9.49		21	17.10 ± 6.16		21	15.51 ± 5.19	
Dermatophagoides + pollen/fungi	29	19.42 ± 7.37		24	15.28 ± 5.26		37	16.49 ± 6.12	
Family history									
Negative	111	17.18 ± 6.58	0.08	92	16.93 ± 7.20	.70	230	16.89 ± 6.59	.82
Positive	49	18.37 ± 6.07		44	16.02 ± 5.44		129	16.91 ± 6.00	

25(OH)D status was classified as deficiency, insufficiency, and sufficiency in 66.9%~71.9%, 22.5% ~29.4%, 2.5% ~ 5.6% of patients, respectively, in pAR groups and 53.2%~60.7%, 31.4%~36.6%, and 7.9% ~11.4%, respectively, in control groups. The differences in serum 25(OH)D statuses between the pAR groups and control groups were statistically significant for 3 years (all $P < .05$).

3.3 | Relationship between serum 25(OH)D levels and Clinical characteristics of patients with pAR over a 3-year period

No significant differences were noted between serum 25(OH)D levels and clinical characteristics of patients with pAR for all 3 years($P > .05$ for all) when adjusting for sex, age, course of disease, TNSS, sIgE levels, positive allergens, and family history(Table 5).

4 | DISCUSSION

Serum 25-hydroxyvitamin D (25(OH)D) is the most stable and major circulating form of vitamin D; thus, it is usually used to monitor serum vitamin D levels. Serum 25(OH)D levels are affected by season, dietary, age, latitude, and other factors.[10] In this study, there were no significant differences in sex, age, BMI, and season between 655 patients with pAR and 682 controls from 2015 to 2017. All subjects were recruited to this study from Anhui Province(central China), and diet and latitude were similar between pAR and control groups. No differences in factors affecting serum 25(OH)D levels were noted between pAR groups and control groups.

In the current study, significantly decreased serum 25(OH)D levels were noted in pAR groups for all 3 years compared with control groups (all $P < .05$). A few studies reported similar findings that lower serum 25(OH)D levels were associated with adults and/or childhood with pAR.[11,12] However, some studies[13] failed to confirm this result. In a study of 263 children with a history of hay fever, asthma, or eczema, 25(OH)D levels were tracked from birth to age 10 years and demonstrated that 25(OH)D deficiency in early childhood was associated with increased risk for persistent asthma if 25(OH)D status was monitored longitudinally and prospectively.[14] This finding suggested one reason for the lack of an association.

Our present findings from 2015 to 2017 reveal that 2.5%~5.6% of patients in the pAR groups over 3 years exhibited serum 25(OH)D sufficiency, and a significant difference was noted compared with control groups (7.9%~11.4%). The high proportion (88.6% ~92.1%) of serum 25(OH)D deficiency and insufficiency in healthy individuals over the 3-year period in this study was correlated with diet and the duration of sunshine in Central China. Previous study revealed serum 25(OH)D deficiency in healthy people.[15] Our study suggests that vitamin D should be supplemented in both patients with pAR and healthy people, that is, more sunshine, fatty fish, egg yolks, liver, milk, and vitamin D supplements.

In this study, there was no significant association between serum 25(OH)D levels and clinical characteristics of patients with pAR over 3 years(all P-values $> .05$) when adjusting for sex, age, course of disease, sIgE levels, positive allergens, and family history. Similar to our research results, one study reported no relationship between 25(OH)D levels and the severity, allergen sensitivities, and duration of allergic rhinitis.[12] In this study, no significant differences in different allergens were noted. The sIgE of patients with pAR was positive for Dermatophagoides farinae with or without other allergens, including fungi and pollens. It is possible that perennial AR and seasonal AR occurred in combination in this study and not as a single seasonal allergic rhinitis. However, some studies failed to confirm this result.[16] A study of 15 patients with AR identified a negative correlation for serum vitamin D levels with AR and TNSS. Research showed that vitamin D inhibits the proliferation of T lymphocytes and increase the transformation from Th1 to Th2 by stimulating the development of Th2 cells. In addition, vitamin D [16]◦ regulates the development, transcription, and biological activity of Th17 cells.[17,18] This mechanism may explain the negative correlation between vitamin D and AR. In our study, significantly decreased serum 25(OH)D levels were noted in pAR, but no significant association with TNSS was noted. This lack of an association may be related to the number of samples and degree of TNSS. For example, the number of samples was larger in this study, but there were fewer patients with high TNSS scores was less.

In summary, our study demonstrated a high prevalence of 25(OH)D deficiency and insufficiency in healthy people in central China. However, serum 25(OH)D levels in pAR patients were lower and more stable than serum 25(OH)D levels in healthy people. No association was noted between 25(OH)D level and sex, age, course of disease, TNSS, sIgE levels, number of positive allergens, and family history in the patients with pAR. Our study has some limitations. First, we did not prescribe vitamin D supplementation to pAR patients, and the effect of vitamin D supplementation was not clear. Second, the relationship between 25(OH)D levels and dendritic cells (CD80, CD83, CD86, and CD40), T cells (CD8 + T, CD4 + T, andTh17), and cytokines (IL-2, IL-4, IL-10, IFN-γ, and TNF-β) was not detected. Future studies should focus on these factors.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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