Clinical Study

The Impact of Serum 25-Hydroxyvitamin D3 Levels on Allergic Rhinitis

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Abstract

We aimed to clarify the relation between allergic rhinitis and the serum levels of 25-hydroxivitamin D in the adult population. The study group consisted of 86 patients with allergic rhinitis who were diagnosed with the help of history of allergy, positive signs for allergy, blood samples, and positive skin prick tests; while the control group included 43 age- and sex-matched healthy volunteers with negative skin prick tests. The demographic data, medical history, findings in the physical examinations, serum levels of total immunoglobulin E (IgE) and 25-hydroxyvitamin D, and skin prick test results of the groups were noted. A total of 129 patients fulfilling the necessary criteria were enrolled. The median serum 25-hydroxyvitamin D levels in the study group were significantly lower compared to the control group ($P = .014$). In the study group, median serum vitamin D levels were significantly higher in men, compared to women ($P = .03$). There was a significant negative correlation between IgE and vitamin D levels in the allergic rhinitis group ($P = .028$, $r = -0.246$). This study showed that patients with allergic rhinitis might be more vulnerable to have lower serum levels of vitamin D. Thus, vitamin D supplementation as an adjunctive therapy may be considered in those patients.

Introduction

Allergic rhinitis (AR) is a common allergic disorder with type 1 allergic reaction of the nasal mucosa distinguished by paroxysmal sneezing, itching, serous rhinorrhea, and nasal blockage. However, ocular symptoms, postnasal drip, itching of the palate, and chronic cough can associate the nasal symptoms. The incidence rate has been increasing worldwide.[1,2] According to Allergic rhinitis and its impact on asthma (ARIA) guidelines, the prevalence of self-reported AR is approximately 1% to greater than 40% in adult population.[1] The prevalence of confirmed AR in European adults was reported as between 17% and 28.5%.[1,3] Although the morbidity and mortality are relatively low, AR has remarkable burden and costs.

In patients with AR, the antigens inhaled through the nasal mucosa are binded to immunoglobulin E (IgE) antibodies on the mast cells, located in the entire nasal mucosa. This antigen–antibody complex provokes the synthesis of various chemical mediators, especially histamine and peptide leukotrienes from the mast cells. These chemicals stimulate the nerve endings and blood vessels, leading to sneezing, rhinorrhea, and nasal mucosal congestion. Nearly 6 to 10 hours after the antigen exposure, various cytokines, chemokines, and activated eosinophils are synthesized, which are responsible for the late-phase reactions.[2]

In addition to its role in skeletal development, vitamin D has various important roles in nonskeletal tissues. It has complex various immunoregulatory effects on both innate and adaptive immunities.[4,5] Vitamin D, via its nuclear receptors (vitamin D receptor) found in various immunologically active cells, such as macrophages, T cells, B cells, and dendritic cells, function both as an anti-inflammatory and an immunoprotective agent.[4,5,6]

Since the past 50 years, many studies have been conducted to investigate the relation between allergy and the serum levels of vitamin D; however, the results are inconsistent and most of them were performed on the pediatric population. We aimed to

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clarify the relation between AR and the serum levels of 25-hydroxivitamin D in the adult population.

Materials and Methods

The research was conducted at Başkent University Medical Faculty Otorhinolaryngology Department between September 2018 and February 2019. Following the sample size calculations for both groups, a total of 129 patients fulfilling the necessary criteria were enrolled. The study group consisted of 86 consecutive patients with AR, while the control group included 43 age- and sex-matched healthy volunteers, who had no history of allergy and had negative skin prick tests. Exclusion criteria were as follows:

1. Pediatric patients
2. Patients with comorbid systemic diseases
3. Gestation
4. Being diagnosed with musculoskeletal diseases such as osteoporosis
5. Presence of acute upper respiratory tract infections
6. Patients using drugs, such as phenobarbital, phenytoin, and cholestyramine
7. Patients diagnosed with non-AR
8. Patients using hormone replacement or oral contraceptive therapy
9. Smoking
10. Patients already using medical therapies for AR and/or vitamin D deficiency
11. Patients who have skin diseases or any condition that may have the possibility to interfere the skin prick test.

All the patients involved in the study were informed and asked to sign the clinical research informed consent form. This study was approved by Başkent University institutional review board and ethics committee (project no.: KA19/98) and supported by Başkent University Research Fund.

The demographic data, medical history, findings in the physical examinations, serum levels of total IgE and 25-hydroxyvitamin D, and skin prick test results of the groups were noted. The diagnosis of AR was made clinically according to ARIA guidelines.[1]

The skin prick test was performed using standardized allergen extracts Dermatophagoides *pteronyssinus*, Dermatophagoides *farinea*, grass-mix pollens, grain-mix pollens, weed-mix pollens, *Blatella germanica* (cockroaches), cat dander, dog dander, latex, *Plantain plantago*, *Parietaria officinalis*, *Cladosporium*, *Alternaria alternata*, *Artemisia vulgaris*, *Penicillium mix*, *Olea europaea*, tomato, banana, and *Betula betulaceae* (Allergopharma D-21462 Reinbek, Germany), with the technique standardized by the European Academy of Allergy and Clinical Immunology.[7] Histamine and physiologic saline were used for positive and negative controls, respectively. The skin reactions on both forearms were recorded after 15 minutes and the wheal diameters were measured. Results 3 mm greater than the negative control were marked positive.

Table 1. Demographic Data, Vitamin D, and Total IgE Levels in Both Groups.

	Control, n = 43	AR, n = 86	P
Sex, n (%)			
Female	25 (58.1)	55 (63.9)	.567[a]
Male	18 (41.9)	31 (36.1)	
Vitamin D groups, n (%)			
I	27 (62.8)	67 (77.9)	.059[b]
II	8 (18.6)	14 (16.3)	
III	8 (18.6)	5 (5.8)	
Age, median (min/max)	38 (19/75)	39.5 (15/74)	.784[c]
Vitamin D, median (min/max)	17 (6/35)	12.7 (2.4/70.7)	.014[c]
Total IgE, median (min/max)	27.95 (4.31/79.3)	92.1 (1.72/2000)	.049[c]

Abbreviations: IgE, immunoglobulin E; max, maximum; min, minimum.
[a]Pearson χ^2 test (Exact).
[b]Fisher-Freeman-Halton test (Monte Carlo).
[c]Mann-Whitney *U* test (Monte Carlo).

Patients with positive skin test to at least one of the allergens were considered atopic.

Even though 1,25-dihydroxyvitamin D is an active form, serum 25-hydroxyvitamin D is the most abundant (100-fold higher serum levels than the active form) and stable form of vitamin D in human systemic circulation. Serum 25-hydroxyvitamin D is considered to reflect directly the serum vitamin D levels and preferred test to diagnose vitamin D insufficiency. Serum 25-hydroxyvitamin D concentrations were determined by a chemiluminescent microparticle immunoassay with Alinity analyzer (Abbott Diagnostics, Chicago, Illinois). The assay is standardized against National Institute of Standards and Technology Standard Reference Material 2972 (NIST SRM 2972). Levels <20 ng/mL, between 20 and 30 ng/mL, and ≥30 ng/mL were defined as group 1 (*deficient*), group 2 (*insufficient*), and group 3 (*normal*), respectively.[6,8,9]

SPSS version 25.0 (IBM Corporation, Armonk, New York) program was used to analyze the variables. The Shapiro-Wilk test was used to determine the normal distribution of the data. The Mann-Whitney *U* test was used along with Monte Carlo results for comparing the 2 independent groups to each other according to the quantitative data. Kruskal-Wallis *H* test and the Whitney *U* test were used to determine the correlations of the variables and Spearman ρ test was used to examine the correlations of the variables. In the comparison of categorical variables, Pearson χ^2 and Fisher exact tests were analyzed using exact results, while Fisher-Freeman-Holton test was tested with Monte Carlo Simulation technique. Quantitative variables were expressed as median (minimum/maximum) and categorical variables as n (%). The variables were examined at 95% confidence level and *P* value less than .05 was considered significant.

Results

The age, sex distribution, the number of patients in each subgroup, median serum vitamin D, and total IgE levels in both

Table 2. Age and Serum Total IgE Levels Reached Statistical Significance.

| | AR | | | | | | |
| | I | II | III | | | | |
Vitamin D Groups	(n = 67)	(n = 14)	(n = 5)	P			
Sex, n (%)					P Values Comparison of Pairs of Subgroups		
Female	41 (61.2)	11 (78.6)	3 (60)	.535[a]	I-II	I-III	II-II
Male	26 (38.8)	3 (21.4)	2 (40)				
Age, median (min/max)	37 (15/74)	50.5 (18/74)	46 (43/54)	.023[b]	.028	.058	.658
Total IgE, median (min/max)	108 (5.51/2000)	50.85 (1.72/1563)	19.4 (2.87/39.2)	.007[b]	.184	.003	.058

Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E; max, maximum; min, minimum.
[a]Fisher-Freeman-Halton test (Monte Carlo).
[b]Kruskal-Wallis H test (Monte Carlo).
[c]Post Hoc test: Dun Test.

Table 3. Comparison of Vitamin D Subgroup 1 Among the Study and Control Groups for Sex, Age, and Serum Vitamin D Levels.

| | Vitamin D Group 1 | | |
	Control, n = 27	AR, n = 67	P
Sex, n (%)			
Female	19 (70.4)	41 (61.2)	.481[a]
Male	8 (29.6)	26 (38.8)	
Age, median (min/max)	36 (19/56)	37 (15/74)	.394[b]
Vitamin D, median (min/max)	13.2 (6/24)	11 (2.4/19.9)	.193[b]

Abbreviations: AR, allergic rhinitis; max, maximum; min, minimum.
[a]Pearson χ^2 test (Exact).
[b]Mann-Whitney U test (Monte Carlo).

Table 4. Comparison of Vitamin D Subgroup 2 Among the Study and Control Groups for Sex, Age, and Serum Vitamin D Levels.

| | Vitamin D Group 2 | | |
	Control, n = 8	AR, n = 14	P
Sex, n (%)			
Female	3 (37.5)	11 (78.6)	.081[a]
Male	5 (62.5)	3 (21.4)	
Age, median (min/max)	47.5 (26/75)	50.5 (18/74)	.774[b]
Vitamin D, median (min/max)	22 (19.5/27.3)	24.15 (19.6/29.4)	.501[b]

Abbreviations: AR, allergic rhinitis; max, maximum; min, minimum.
[a]Fisher exact test (Exact).
[b]Mann-Whitney U test (Monte Carlo).

Table 5. Comparison of Vitamin D Subgroup 3 Among the Study and Control Groups for Sex, Age, and Serum Vitamin D Levels.

| | Vitamin D Group 3 | | |
	Control, n = 8	AR, n = 5	P
Sex, n (%)			
Female	3 (37.5)	3 (60)	.592[a]
Male	5 (62.5)	2 (40)	
Age, median (min/max)	49.5 (21/75)	46 (43/54)	.999[b]
Vitamin D, median (min/max)	31.4 (29.5/35)	32.5 (29.8/70.7)	.401[b]

Abbreviations: AR, allergic rhinitis; max, maximum; min, minimum.
[a]Fisher exact test (Exact).
[b]Mann-Whitney U test (Monte Carlo).

Table 6. Comparison of Vitamin D levels Among Females and Males in the Control Group.

| | Control | | |
	Female, n = 25	Male, n = 18	P
Vitamin D, n (%)			
I	19 (76.0)	8 (44.4)	.105[a]
II	3 (12.0)	5 (27.8)	
III	3 (12.0)	5 (27.8)	
Vitamin D, median (min/max)	16.7 (6/33.1)	20.25 (6.4/35)	.093[b]

Abbreviations: max, maximum; min, minimum.
[a]Fisher-Freeman-Halton test (Monte Carlo).
[b]Mann-Whitney U test (Monte Carlo).

groups were presented in Table 1. The median serum 25-hydroxyvitamin D levels in the study group were significantly lower in the study group compared to the controls ($P = .014$; Table 1).

In the AR group, there was no statistical difference of sex among subgroups, but in group 1 and group 2, there was statistically significant difference of age ($P = .028$). Total IgE levels were significantly different in group 1 and group 3 in AR group ($P = .003$; Table 2). In the control group, there was no difference for the parameters mentioned above ($P > .05$).

When all the 3 subgroups were compared for age, sex, and vitamin D levels, there was no statistically significant difference among the study and control groups ($P > .005$; Tables 3-5).

In the control group, serum vitamin D levels showed no statistically significant difference among females and males ($P > .05$; Table 6). In the study group, median serum vitamin D levels were significantly higher in men, compared to women ($P = .03$; Table 7).

Table 7. Comparison of Vitamin D Levels Among Females and Males in the Study Group.

		AR		
		Female, n = 55	Male, n = 31	*P*
Vitamin D, n (%)				
	I	41 (74.5)	26 (83.9)	.533[a]
	II	11 (20.0)	3 (9.7)	
	III	3 (5.5)	2 (6.5)	
Vitamin D, median (min/max)		11 (2.4/70.7)	15 (7.2/32.5)	.030[b]

Abbreviations: AR, allergic rhinitis; max, maximum; min, minimum.
[a]Fisher-Freeman-Halton test (Monte Carlo).
[b]Mann-Whitney *U* test (Monte Carlo).

There was a significant negative correlation between IgE and vitamin D levels in the AR group ($P = .028$, $r = -0.246$).

Discussion

The majority of the daily vitamin D requirement is by exposure to sunlight. However, intensity of the sunlight, amount of skin exposed, duration of exposure, the zenith angle of the sun, thickness of the skin, and the skin color differ the amount of vitamin D generation among individuals.[10]

Apart from its skeletal effects, vitamin D has various non-skeletal benefits, including improved immunity, decreased diabetes mellitus, prevention of cancer, decreased all-cause mortality, decreased pulmonary morbidities, and decreased cardiovascular diseases.[10]

Considering the importance of vitamin D in regulating the immune system, the relation between AR and the levels of vitamin D has attracted interest in recent years.

It has been known for nearly 30 years that vitamin D has immunoregulatory effects on T cells, B cells, dendritic cells, monocytes, and macrophages.[6] 1,25-Dihydroxyvitamin D inhibits the proliferation of T cells, induces a shift from Th1 to Th2, and provokes the synthesis of T regulatory cells that are important immune reactions in the course of AR.[11-13] Additionally, vitamin D activates apoptosis of activated B cells and inhibits plasma cell differentiation and immunoglobulin secretion, including IgE.[14,15]

Vitamin D increases the antimicrobial activity in monocytes; however in later stages, it provokes them to secrete anti-inflammatory agents and decreases macrophage inflammation and T-cell proliferation.[16,17] Additionally, it induces up and down regulations of various specific cytokines.[11]

Various studies suggested that higher levels of vitamin D are associated with reduced risk of asthma attacks.[18,19,20] However, the studies searching the relationship between AR and vitamin D are contradictory. A survey study from Germany[21] reported that patients with high serum levels of vitamin D are at high risk for AR. The authors defined AR by the question "Did a doctor ever tell you had hay fever?." Mai et al[22] conducted the HUNT survey and found opposite results. Aryan et al[23] found a negative correlation between

AR and levels of vitamin D in pediatric population. Keleş et al[5] reported similar results in their study, in which they searched serum 1,25-dihydroxyvitamin D levels in adults. Lee et al[4] found that serum levels of vitamin D were lower in AR compared to vasomotor rhinitis and control groups in Korean children. They also noted an inverse correlation between IgE levels and vitamin D. We also detected a negative correlation between serum IgE levels and vitamin D.

Wu et al[24] found lower serum levels of vitamin D in persistent AR when compared to the controls; however, their results did not reach statistical significance. Bunjavanich et al[25] reported that each 100 IU/d of vitamin D intake during the first and second trimesters of gestation was decreasing the incidence of AR at school age. Dogru and Suleyman[26] compared serum 25-hydroxyvitamin D levels in children with AR and non-ARs and found that the mean serum levels of vitamin D in patients with AR and non-AR were lower than the controls. Jung et al[27] investigated the role of vitamin D in Korean adults and found a significant relation between vitamin D and AR. The determination of AR was achieved by having an answer "yes" to a question "Are you diagnosed AR by a doctor?", history of rhinitis symptoms, and patients' rhinological findings.

Another study found a significant correlation between AR in males and levels of vitamin D.[23] On contrary, in a study by Lee et al,[4] no gender differences of vitamin D status among groups were observed. In our study, the serum levels of vitamin D are significantly lower in AR group. Males had significantly higher serum vitamin D levels compared to females in our study group. Women may spend more time indoors compared to men due to sociocultural, socioeconomic causes, and child care. Therefore, the amount of sun exposure and its duration may be shortened, causing lower serum vitamin D levels.

In order to maintain a normal immunological activity, the required minimum level of 25-hydroxyvitamin was determined as 30 ng/mL.[10] For respiratory system infections and asthma attacks, levels at least between 30 and 40 ng/mL are recommended. We grouped the individuals as group 1, group 2, and group 3 according to the serum levels of vitamin D as aforementioned. We considered the levels ≥30 ng/mL as *normal*, which is consistent with the literature.[8,10,28]

We observed significantly lower levels of 25-hydroxyvitamin D in AR group when compared to the healthy volunteers. To our knowledge, this current study has the widest patient series among the studies searching the relation between 25-hydroxyvitamin D levels and AR, which was confirmed by history of allergy, endoscopic examination, skin prick, and allergy-specific laboratory tests.

However, how vitamin D affects the development and/or exacerbations of AR is still unknown. The effects of vitamin D supplementation therapies and the optimal serum levels of vitamin D to suppress AR are still unclarified. Further prospective studies including larger patient series are necessary.

We performed our study between September and February, a time period in which exposure to sunlight is relatively low. Vitamin D levels alter in different seasons. Therefore, further

studies investigating the correlation between AR and vitamin D levels in different seasons are required.

As Kim et al [29] suggested, lower vitamin D levels may co-occur with AR, instead of causing it. People with AR may refrain outdoor activities to avoid exacerbations of AR. They also suggested that use of oral steroids for atopic dermatitis and asthma may cause lower levels of vitamin D. It seems that the relationship between AR and vitamin D status is versatile and complex.

Conclusion

As the prevalence of AR is increasing, an increasing amount of studies are being conducted in order to highlight the immunological pathogenesis of the disease. Vitamin D, which is an immunomodulating agent, seems to have a role in the pathogenesis of AR. This study suggested that serum levels of 25-hydroxyvitamin D may have an impact on AR. However, there is much to clarify with further studies, regarding this topic.

Authors' Note

Informed consent was obtained from all individuals included in the study.

Declaration of Conflicting Interests

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References

1. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466-476.

2. Okubo K, Kurono Y, Fujieda S, et al. Japanese guideline for allergic rhinitis 2014. *Allergol Int*. 2014;63(3):357-375.

3. Tian HQ, Cheng L. The role of vitamin D in allergic rhinitis. *Asia Pac Allergy*. 2017;7(2):65-73.

4. Lee SJ, Kang BH, Choi BS. Vitamin D serum levels in children with allergic and vasomotor rhinitis. *Korean J Pediatr*. 2015; 58(9):325-329.

5. Keleş E, Özkara Ş, İlhan N, Güngör H, Karlıdağ T, Yalçın Ş. The relationship between Th1/Th2 balance and 1α, 25-dihydroxyvitamin D_3 in patients with allergic rhinitis. *Turk Arch Otorhinolaryngol*. 2015;53(4):139-143.

6. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. *BMC Infect Dis*. 2015;15:487.

7. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Skin tests used in type I allergy testing position paper. *Allergy*. 1989;44(suppl 10): 1-59.

8. Pludowski P, Holick MF, Grant WB, et al. Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol*. 2018;175: 125-135.

9. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.

10. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol*. 2018;175:60-81.

11. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-dihydroxyvitamin D3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol*. 2001;167(9): 4974-4980.

12. Vasiliou JE, Lui S, Walker SA, et al. Vitamin D deficiency induces Th2 skewing and eosinophilia in neonatal allergic airways disease. *Allergy*. 2014;69(10):1380-1389.

13. Urry Z, Chambers ES, Xystrakis E, et al. The role of 1α,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct Foxp3+ and IL-10+ CD4+ T cells. *Eur J Immunol*. 2012;42(10): 2697-2708.

14. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol*. 2007;179(3):1634-1647.

15. Heine G, Anton K, Henz BM, Worm M. 1alpha,25-dihydroxyvitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. *Eur J Immunol*. 2002;32(12): 3395-3404.

16. Di Rosa M1, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immuno-modulator. *Immunology*. 2011; 134(2):123-139.

17. Korf H, Wenes M, Stijlemans B, et al. 25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. *Immunobiology*. 2012;217(12):1292-1300.

18. Uysalol M, Mutlu LC, Saracoglu GV, et al. Childhood asthma and vitamin D deficiency in Turkey: is there cause and effect relationship between them? *Ital J Pediatr*. 2013; 39:78.

19. Aldubi HM, Alissa EM, Kamfar HZ, Gaber O, Marzouki ZM. Bronchial asthma and hypovitaminosis D in Saudi children. *Asia Pac Allergy*. 2015;5(2):103-113.

20. Cassim R, Russell MA, Lodge CJ, Lowe AJ, Koplin JJ, Dharmage SC. The role of circulating 25 hydroxyvitamin D in asthma: a systematic review. *Allergy*. 2015;70(4):339-354.

21. Wjst M, Hyppönen E. Vitamin D serum levels and allergic rhinitis. *Allergy*. 2007;62(9):1085-1086.

22. Mai XM, Chen Y, Camargo CA Jr, Langhammer A. Serum 25-hydroxyvitamin D levels and self-reported allergic rhinitis in Norwegian adults—the HUNT study. *Allergy*. 2014;69(4): 488-493.

23. Aryan Z, Rezaei N, Camargo CA Jr. Vitamin D status, aeroallergen sensitization, and allergic rhinitis: a systematic review and meta-analysis. *Int Rev Immunol*. 2017;36(1):41-53.

24. Wu HY, Chen JX, Tian HQ, Zhang XL, Bian HY, Cheng L. Serum 25-hydroxyvitamin D inversely associated with blood eosinophils in patients with persistent allergic rhinitis. *Asia Pac Allergy*. 2017;7(4):213-220.

25. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization. *J Allergy Clin Immunol*. 2016;137(4):1063-1070.e2.

26. Dogru M, Suleyman A. Serum 25-hydroxyvitamin D3 levels in children with allergic or nonallergic rhinitis. *Int J Pediatr Otorhinolaryngol*. 2016;80:39-42.

27. Jung JW, Kim JY, Cho SH, Choi BW, Min KU, Kang HR. Allergic rhinitis and serum 25-hydroxyvitamin D level in Korean adults. *Ann Allergy Asthma Immunol*. 2013;111(5):352-357.

28. Li-Ng M, Aloia JF, Pollack S, et al. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect*. 2009;137(10):1396-1404.

29. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2016;27(6):580-590.