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1,25(OH)₂D₃ and specific IgE levels in children with recurrent tonsillitis, and allergic rhinitis

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ABSTRACT

Objectives: We investigated 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] and specific immunoglobulin E (IgE) levels in children with recurrent tonsillitis (RT) plus allergic rhinitis (AR).

Methods: Thirty children with RT + AR were included in the study group, and 30 healthy children comprised the control group. AR-related symptoms were determined using a symptom scale. 1,25(OH)₂D₃ and specific IgE measurements were made in both groups.

Results: The 1,25(OH)₂D₃ value was significantly lower in the RT + AR group than in the control group. Specific IgE (mixed) panels were in normal limits in both groups; whereas specific IgE (mixed) grass pollen panel value of RT + AT group was significantly higher than that of the control group. Higher nasal itching, nasal obstruction, and concha edema scores were related to significantly higher specific IgE values for the (mixed) grass pollen panel, whereas higher sneeze scores were related to higher specific IgE values for the (mixed) pediatric panel.

Conclusions: Children with grass pollen allergy may not be exposed to sufficient sunlight. With reduced 1,25(OH)₂D₃, T helper cells may increase, and allergic response also increases. As allergic events increased, these children did not go outside and thus lacked sun exposure. This vicious cycle must be broken, and children with RT + AR should have sunlight exposure to increase 1,25(OH)₂D₃ levels.

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1. Introduction

Allergy, one of the most important host factors predisposing to the development of asthma, is caused by the production of abnormal amounts of immunoglobulin E (IgE) in response to environmental antigens, called allergens [1,2]. IgE also plays an essential role in type I hypersensitivity [3], which manifests as various allergic diseases, such as allergic asthma, allergic rhinitis (AR), food allergy, and some types of chronic urticaria and atopic dermatitis [4]. Based on the previously established 95% predictive decision points for egg, milk, peanut, and fish allergy, more than 95% of food allergies diagnosed in the present prospective study were correctly identified by quantifying serum food-specific IgE concentrations [5].

The hormonal form of vitamin D affects adaptive and innate immune functions involved in the development of allergies.

Certain genotypes have been found to alter the association between vitamin D deficiency (VDD) and the risk of food sensitization in children [6]. 1,25-Dihydroxyvitamin D₃ [1,25(OH)₂D₃] has been reported to potentiate the efficacy of immunotherapy and the regulatory cytokines interleukin (IL)-10 and transforming growth factor-beta have been found to play crucial roles in the effector phase of an experimental mouse model [7].

Vimalleswaran et al. [6] examined the associations of 27 functional single-nucleotide polymorphisms in or near selected candidate genes with total IgE level and effect modification by 1,25(OH)₂D₃ in a 1958 British birth cohort (aged 45 years, *n* = 4921). A cutoff value of 50 nmol/L was used to define VDD. They found that VDD was associated with higher total IgE level only in carriers of the 'C' (IL-4) allele, comprising 86% of Caucasian Europeans but only 26% of Chinese individuals and <20% of some African populations. The findings of their study in Caucasian European adults were consistent with those of a previous study in children from largely non-Caucasian ethnic groups, suggesting that IL-4 and MS4A2 genotypes modify the association between VDD and allergy risk. The risk allele in IL-4 is present in nearly 90% of Caucasian Europeans.

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In the present study, we investigated 1,25(OH)₂D₃ and specific IgE levels in children with recurrent tonsillitis (RT) plus AR.

2. Materials and methods

The present study was conducted in the ear, nose, and throat (ENT) Department of the Istanbul Medeniyet University, Göztepe Training and Research Hospital.

2.1. Subjects

The current study included 30 children [19 (57.6%) males and 11 (40.7%) females] with RT and AR symptoms, such as nasal discharge, nasal itching, nasal obstruction, and sneezing, for at least 1 year, as well as concha edema on ENT examination (RA + AR group). ENT examinations of these children revealed grade 3–4/>5 tonsil hypertrophy, according to Brodsky's classification [8]. RT was defined as three or more attacks per year using the criteria of the American Academy of Otolaryngology – Head and Neck Surgery [9]. Their age (median) was 5.00 (range, 2.00–11.00) years.

The control group consisted of 30 healthy children [14 (42.4%) males and 16 (59.3%) females] who visited the hospital for reasons other than RT + AR. They had normotrophic tonsils, according to Brodsky's classification [8], and their age (median) was 6.00 (range, 2.00–10.00) years.

Children were enrolled in the RA + AR group year-round, including during the winter and summer months. Enrollment timing was the same for the RA + AR and control groups. All children in both groups were chosen from the Göztepe region of Istanbul to ensure the similarity of environmental conditions.

Parents of all children in both groups provided written informed consent to their children's participation in the study. Except for RT and AR in the RA + AR group, no child in either group had a chronic systemic disease (e.g., diabetes mellitus or hypertension) or asthma.

2.2. Methods

All patients' families provided detailed history of the patients, and ENT examinations were performed. During ENT examination, tonsillar hypertrophy and concha edema were also evaluated. AR-related symptoms were determined using a symptom scale. 1,25(OH)₂D₃ and specific IgE measurements were made in both groups.

2.3. Allergic rhinitis symptom scale

All participants were asked about symptoms of nasal discharge, nasal itching, nasal obstruction, and sneezing. Additionally, concha edema was evaluated during ENT examination. All items were scored as follows: 0, none; 1, low; 2, medium; and 3, high.

2.4. Instrumentation

Using radioimmunoassays, serum 1,25(OH)₂D₃ measurements were performed with the ICN ISO DATA Gamma Counter (Belgium) and DiaSource RIA-CT kit (Louvain-La-Neuve, Belgium). Using enzyme-linked immunosorbent assay (ELISA), specific IgE measurements were performed with the Pasteur ELISA reader (Belgium) and Bio-line ELISA kit (Belgium).

The normal values were as follows:

- **1,25(OH)₂D₃**: 19.6–65 pg/mL [10];
- **Specific IgE (mixed) wood panel** [birch (*Betula verrucosa*), birch (*Acer stachyophyllum*), beech, oak, and walnut]: negative, <0.7 RU/mL; positive, >0.7 RU/mL;
- **Specific IgE (mixed) pediatric panel** (eggs, milk, wheat, peanuts, and soybeans): negative, <0.7 RU/mL; positive, >0.7 RU/mL;
- **Specific IgE (mixed) HB2 panel** (house dust, mites, cockroaches): negative, <0.7 RU/mL; positive, >0.7 RU/mL; and
- **Specific IgE (mixed) grass pollen panel**: negative, <0.7 RU/mL; positive, >0.7 RU/mL.

Table 1
Allergic rhinitis symptoms and 1,25(OH)₂D₃ and specific IgE measurement results in the RT + AR and control groups.

Allergic symptoms and findings	Groups						z	p ^{**}
	RT + AR group			Control Group				
	Median	Min	Max	Median	Min	Max		
Nasal discharge	1.50	1.00	3.00	0.00	0.00	1.00	−6.485	0.000
Nasal itching	2.00	1.00	3.00	0.00	0.00	1.00	−6.776	0.000
Nasal obstruction	2.00	1.00	3.00	0.00	0.00	1.00	−6.955	0.000
Sneeze	2.00	1.00	3.00	0.00	0.00	0.00	−7.203	0.000
Concha edema	2.00	2.00	3.00	0.00	0.00	1.00	−7.012	0.000
	Groups						t	p ^{***}
	RT + AR group			Control group				
	Median	Min	Max	Median	Min	Max		
Age	5.00	2.00	11.00	6.00	2.00	10.00	0.050	0.960
Measurement results								
1,25(OH) ₂ D ₃	34.65	24.25	59.28	52.86	24.71	69.27	3.468	0.001
Specific IgE (mixed) wood panel ^a	0.22	0.10	19.00	0.22	0.10	0.62	0.318	0.751
Specific IgE (mixed) Pediatric panel ^a	0.37	0.16	1.80	0.25	0.04	0.51	1.888	0.069
	Groups						z	p ^{**}
	RT + AR group			Control group				
	Median	Min	Max	Median	Min	Max		
Measurement results								
Specific IgE (mixed) HB2 panel ^a	0.24	0.10	0.53	0.24	0.11	0.51	−0.422	0.673
Specific IgE (mixed) Grass pollen panel ^a	0.28	0.10	0.70	0.20	0.10	0.50	−2.486	0.013

^a Specific IgE (mixed) wood panel, birch (*Betula verrucosa*), birch (*Acer stachyophyllum*), beech, oak, walnut; specific IgE (mixed) HB2 panel, house dust, mites, cockroaches; specific IgE (mixed) pediatric panel, eggs, milk, wheat, peanuts, soybeans; specific IgE (mixed) grass pollen panel.

^{**} p-Value shows the results of the Mann–Whitney U-test.

^{***} p-Value shows the results of the independent-samples t-test.

The current study was conducted in accordance with the Helsinki Declaration [11].

2.5. Statistical analysis

All study data were evaluated using the Statistical Package for the Social Sciences (SPSS) software (ver. 16.0; SPSS Inc., Chicago, IL, USA). The independent-samples *t*-test, Mann–Whitney *U*-test, chi-squared test, and Spearman's rank correlation (rho coefficient) test were used. A *p*-value < 0.05 was deemed to be statistically significant.

3. Results

The RT + AR group consisted of 19 (57.6%) males and 11 (40.7%) females; the control group comprised 14 (42.4%) males and 16 (59.3%) females. A chi-squared test revealed no significant sex difference between the groups (*p* = 0.299, χ^2 = 1.077). An independent-samples *t*-test showed no age difference between the groups (*p* = 0.960; Table 1).

Allergic rhinitis symptom scale (ARSS) scores and 1,25(OH)₂D₃ and specific IgE measurement results from the RT + AR and control groups are shown in Table 1 and Figs. 1 and 2. The Mann–Whitney *U*-test was used to analyze differences in ARSS scores between the RT + AR and control groups. The nasal discharge, itching and obstruction; sneezing, and concha edema values were significantly higher in the RT + AR group than in the control group (*p* < 0.05).

1,25(OH)₂D₃ values of the RT + AR and control groups are expressed as median, minimum and maximum values in Table 1. Additionally, results from individual subjects are expressed in pg/mL in Fig. 1. An independent samples *t*-test revealed that 1,25(OH)₂D₃ values were significantly lower in the RT + AR group (median, 34.65 pg/mL) than in the control group (median, 52.86 pg/mL; *p* = 0.001; Table 1).

Specific IgE measurement results for the RT+AR and control groups are expressed as median, minimum and maximum values in Table 1. Measurements were made for the four panels and none of them exceeded the normal limit of 0.7 RU/mL (negative). Although specific IgE (mixed) grass pollen panel value of RT + AT group was negative; it was significantly higher than that of the control group (*p* = 0.013) (Table 1 and Fig. 2).

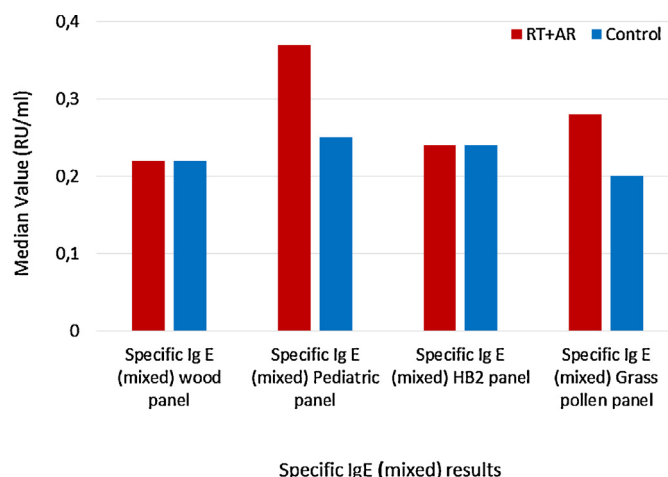


Fig. 2. Specific IgE (mixed) measurement results in the RT + AR and control groups.

Correlation analysis was performed using Spearman's correlation (rho coefficient) test. A correlation matrix was created using age; sex (1 = male, 2 = female); nasal discharge, nasal itching, nasal obstruction, sneezing, and concha edema (0 = none, 1 = low, 2 = medium, 3 = high); 1,25(OH)₂D₃ level (pg/mL); specific IgE (mixed) wood, HB2, pediatric, and grass pollen panel results (RU/mL); group (1 = RT + AR, 2 = control); and tonsil hypertrophy grade (1 = Brodsky grade 3–4 [8], hypertrophy present; 0 = Brodsky grade 3–4 [8], hypertrophy absent; Table 2).

1. **Age:** The specific IgE (mixed) HB2 panel was found to be significantly higher in older children (*p* < 0.05; Table 2).
2. **Nasal symptom scores:** In the RT + AR group, in children with higher scores for any nasal symptoms, all other nasal symptom scores were also significantly higher; and 1,25(OH)₂D₃ values were significantly lower (*p* < 0.05; Table 2).

In children with higher nasal itching, nasal obstruction, and concha edema scores, specific IgE (mixed) grass pollen panel values were significantly higher (*p* < 0.05). In children with higher sneeze scores, specific IgE (mixed) pediatric panel values were significantly higher (*p* < 0.05; Table 2).

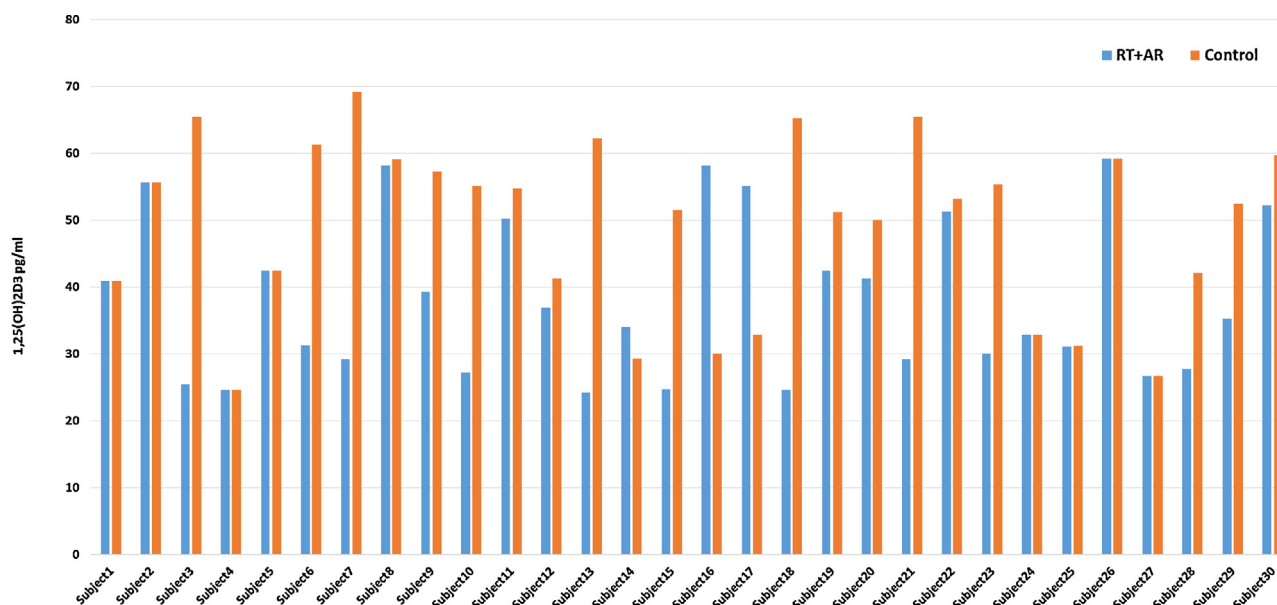


Fig. 1. 1,25(OH)₂D₃ measurement results for individual subjects in the RT + AR and control groups.

Table 2
Correlation matrix for the RT+AR and control groups.[†]

		Age	Gender	Nasal discharge	Nasal itching	Nasal obstruction	Sneeze	Concha edema	1,25(OH) ₂ D ₃	Specific IgE (mixed) wood panel*	Specific IgE (mixed) HB2 panel*	Specific IgE (mixed) Pediatric panel*	Specific IgE (mixed) Grass pollen panel*	Group	Tonsil hypertrophy (Brodsky Grade 3–4) (8)
Age	<i>r</i>														
	<i>p</i>														
Gender	<i>r</i>	0.024													
	<i>p</i>	0.853													
Nasal discharge	<i>r</i>	0.040	–0.135												
	<i>p</i>	0.764	0.305												
Nasal itching	<i>r</i>	–0.142	–0.144	0.775											
	<i>p</i>	0.280	0.274	0.000*											
Nasal obstruction	<i>r</i>	–0.007	–0.109	0.795	0.781										
	<i>p</i>	0.960	0.405	0.000*	0.000*										
Sneeze	<i>r</i>	0.004	–0.165	0.811	0.851	0.876									
	<i>p</i>	0.978	0.206	0.000*	0.000*	0.000*									
Concha edema	<i>r</i>	0.000	–0.141	0.830	0.815	0.862	0.895								
	<i>p</i>	0.996	0.284	0.000*	0.000*	0.000*	0.000*								
1,25(OH) ₂ D ₃	<i>r</i>	–0.099	–0.060	–0.357	–0.437	–0.412	–0.342	–0.409							
	<i>p</i>	0.450	0.649	0.005*	0.000*	0.001*	0.007*	0.001*							
Specific IgE (mixed) wood panel [△]	<i>r</i>	0.224	–0.020	0.088	0.106	0.115	0.148	0.107	0.018						
	<i>p</i>	0.085	0.877	0.504	0.420	0.383	0.260	0.417	0.889						
Specific IgE (mixed) HB2 panel [△]	<i>r</i>	0.291	–0.091	0.041	0.073	0.102	0.097	–0.023	0.054	0.317					
	<i>p</i>	0.024*	0.489	0.756	0.579	0.437	0.460	0.859	0.682	0.014*					
Specific IgE (mixed) Pediatric panel [△]	<i>r</i>	–0.045	–0.100	0.240	0.326	0.340	0.355	0.329	–0.079	0.540	0.272				
	<i>p</i>	0.808	0.592	0.193	0.074	0.061	0.050*	0.071	0.673	0.002*	0.138				
Specific IgE (mixed) Grass pollen panel [△]	<i>r</i>	–0.031	–0.088	0.217	0.332	0.316	0.339	0.360	–0.040	0.453	0.369	0.471			
	<i>p</i>	0.812	0.503	0.095	0.010*	0.014*	0.008*	0.005*	0.759	0.000*	0.004*	0.008*			
Group	<i>r</i>	0.027	0.168	–0.844	–0.882	–0.906	–0.938	–0.913	0.407	–0.103	–0.055	–0.341	–0.324		
	<i>p</i>	0.837	0.201	0.000*	0.000*	0.000*	0.000*	0.000*	0.001*	0.433	0.677	0.061	0.012*		
Tonsil hypertrophy (Brodsky Grade 3–4) (8)	<i>r</i>	–0.027	–0.168	0.844	0.882	0.906	0.938	0.913	–0.407	0.103	0.055	0.341	0.324	–1.000	
	<i>p</i>	0.837	0.201	0.000*	0.000*	0.000*	0.000*	0.000*	0.001*	0.433	0.677	0.061	0.012*		

[△]Specific IgE (mixed) wood panel, birch (*Betula verrucosa*), birch (*Acer stachyophyllum*), beech, oak, walnut; specific IgE (mixed) HB2 panel, house dust, mites, cockroaches; specific IgE (mixed) pediatric panel, eggs, milk, wheat, peanuts, soybeans; specific IgE (mixed) grass pollen panel.

[†]*p*-Value shows the results of Spearman's correlation (rho coefficient) test.

*Statistically significant difference was present (*p* < 0.05); and demonstrated by bold appearance.

3. 1,25(OH)₂D₃ values: In children with higher nasal symptom scores and Brodsky grade 3–4 tonsillar hypertrophy [8], 1,25(OH)₂D₃ values were significantly lower ($p < 0.05$). Compared with the control group, 1,25(OH)₂D₃ values were significantly lower in the RT + AR group ($p < 0.05$; Table 2).

4. Specific IgE (mixed) panel results

There were positive significant correlations between specific IgE (mixed) panel results ($p < 0.05$; Table 2). In older children, specific IgE (mixed) HB2 panel values were also found to be higher ($p < 0.05$; Table 2). In children with higher sneezing scores, specific IgE (mixed) pediatric panel values were found to be significantly higher ($p < 0.05$). In children in the RT + AR group with Brodsky grade 3–4 tonsillar hypertrophy [8]; and in children with higher nasal symptom scores, specific IgE (mixed) grass pollen values were found to be significantly higher ($p < 0.05$; Table 2).

4. Discussion

Using two experimental systems in mice with the allergens ovalbumin and papain, respectively, ultraviolet irradiation of the skin prior to allergen sensitization reduced the expression of allergic airway disease, particularly the late phase response [12]. The prevalence of patients with specific IgE to microbial antigens increased in relation to VDD and atopic dermatitis severity [13].

Environmental factors, such as tobacco exposure, indoor climate, and diet, are known to be involved in the development of allergy-related diseases, such as asthma, atopic eczema, and AR [14,15]. The development and phenotypic expression of atopic diseases depend on a complex interaction among genetic factors, environmental exposure to allergens, and nonspecific adjuvant factors, such as tobacco smoke, air pollution, and infections. Preventive measures may include exposure to allergens and adjuvant risk/protective factors and pharmacological treatment [16].

1,25(OH)₂D₃ suppressed neutrophil activation, which is impaired in newborns; and decreased lipopolysaccharide (LPS)-induced expression of macrophage inflammatory protein-1 β and vascular endothelial growth factor in adult neutrophils. It also suppressed expression of cyclooxygenase-2 and induced expression of 5-lipoxygenase in LPS-exposed adult neutrophils, whereas neonatal cells were not affected. The anti-inflammatory activity of vitamin D is impaired in neonatal neutrophils, possibly due to decreased expression of vitamin D receptor (VDR) and 1 α -hydroxylase. Insensitivity to 1,25(OH)₂D₃ may contribute to chronic inflammation in neonates [17]. Reid et al. [18] reported that low 1,25(OH)₂D₃ levels were related to darker skin, increased body mass index, and larger assessed tonsil size.

In the present study, ARSS scores were significantly higher and 1,25(OH)₂D₃ values were significantly lower in the RT + AT group than in the control group. Specific IgE (mixed) panels were in normal limits in both groups; whereas specific IgE (mixed) grass pollen panel value of RT+AT group was significantly higher than that of the control group. In older children, the specific IgE (mixed) HB2 panel value was found to be higher. Increased nasal symptom scores were related to lower 1,25(OH)₂D₃ levels and higher specific IgE (mixed) grass pollen values. Nasal itching and obstruction and concha edema scores were related to higher specific IgE (mixed) grass pollen panel values, whereas higher sneezing scores were related to higher specific IgE (mixed) pediatric panel values. Yildiz et al. [19], they reported that serum 1,25(OH)₂D₃ levels were lower in the RT group than in healthy children similar to our study. Whereas, Aydin et al. [20] found no difference in serum 1,25(OH)₂D₃ level or VDR gene polymorphism between children with RT and healthy children. VDD was more prevalent in children with RT (18%).

A major source of vitamin D is its manufacture through a photolysis reaction in the skin. Sunlight exposure provides significantly less vitamin D in northern climates, and concentrations are especially low during the winter [10,11]. Vitamin D is a selective regulator of the immune system, and the outcome of 1,25(OH)₂D₃ treatment, VDD, or VDR deficiency depends on the nature of the immune response (e.g., infectious disease, asthma, or autoimmune disease) [21]. In the present study, lower 1,25(OH)₂D₃ values were detected in the RT + AR group. Because the symptoms of subjects with grass pollen allergy are more pronounced during exposure to grass pollens, such children may be cared for at home to prevent allergic reactions and may not be given permission to play in gardens with grasses and trees. Because they have no chance of exposure to the sun and ultraviolet rays, vitamin D synthesis may not be sufficient, leading to lower vitamin D levels.

T helper (Th) cells are central to all antigen-specific immune responses. The microenvironment in which naive Th cells develop determines which of two subtypes predominates (Th1 or Th2). The Th1 and Th2 cell responses regulate each other and, during “normal” immune responses, the host responds with a balance of the two subtypes. Th1 cells secrete interferon (IFN), IL-2, and tumor necrosis factor. Th1 cell activation is essential for strong cell-mediated immune responses, including host responses to tumors and intracellular pathogens (e.g. viruses). In autoimmune diseases, Th1 cells are misdirected against self proteins, resulting in pathologic conditions. Allergies and asthma are diseases driven by Th2 cells, occurring when the immune system responds to different environmental antigens. The balance in Th cell responses dictates the outcome of any given challenge to the immune system. Some outcomes are beneficial (clearance of infections), and some are detrimental (autoimmunity and asthma). Th1 and Th2 cells are direct targets of 1,25(OH)₂D₃, which has been found to decrease the proliferation of purified Th cells and the production of IFN, IL-2, and IL-5 [22]. In the present study, as children with grass pollen allergy were not exposed to sufficient sunlight, 1,25(OH)₂D₃ levels were reduced, and Th cells and the allergic response increased. Due to concern about allergic events, these children did not go outside for sun exposure, and the vicious cycle persisted.

Little knowledge exists concerning the effect of vitamin D status on the ability of the host to fight infections. An interesting but mechanistically unsubstantiated link between VDD and cases of tuberculosis has been described [23]. Experimentally, VDD and host resistance to infectious diseases have not been studied extensively [21]. Little is known regarding the role of vitamin D and 1,25(OH)₂D₃ in regulating immune responses to infectious diseases [9]. Our results showed that 1,25(OH)₂D₃ levels reduced in children with RT.

Goleva et al. [24] reported that deficient serum vitamin D levels (<20 ng/mL) were found in 47.6% of asthmatic patients and 56.8% of healthy control subjects. Vitamin D was also related to IgE levels in children. Sharief et al. [25] found that allergic sensitization to 11 of 17 allergens was more common in children and adolescents with 1,25(OH)₂D₃ deficiency. 1,25(OH)₂D₃ levels <15 ng/mL were associated with peanut, ragweed, and oak allergies. They concluded that VDD is associated with higher levels of IgE sensitization in children and adolescents.

The serum 1,25(OH)₂D₃ concentration in children with cow's milk allergy (CMA) in the spring–summer and autumn–winter seasons has been reported to indicate the optimal vitamin D status. Constant medical and nutritional care is a condition for appropriate vitamin D supply in children with CMA. In our study, infections (RT) may have led to an increase in AR symptoms; therefore, we suggest the provision of vitamin D as a supplement to children with VDD and RT + AR [26].

In the present study, a combination of allergy and chronic infection (RT) was found in the RT + AR group. A comorbidity of allergic reactions and chronic infections may also exist. In this matter, VDD, detected in the RT + AR group, also contributed to the disease. A comorbidity or VDD caused an increase in the symptoms. The association between allergy and recurrent infections is well known, and allergy is a predisposing factor for RT and tonsillar hypertrophy.

Vitamin D may be important for immune function. Studies to date have shown an inconsistent association between vitamin D and infection regarding respiratory viruses. Science et al. [27] reported that younger age and lower serum 1,25(OH)₂D₃ level were associated with an increased risk of viral respiratory tract infection. 1,25(OH)₂D₃ levels were associated with an increased risk of laboratory-confirmed viral respiratory tract infection in children. They concluded that intervention studies evaluating the role of vitamin D supplementation to reduce the burden of viral respiratory tract infection are warranted.

In conclusion, VDD may exist in children with RT + AR, particularly those with higher specific IgE (mixed) grass pollen values. Gorman et al. [28] suggested that VDD modulates the capacity of lymphocytes to respond to allergens. Thus, these children should be exposed to sunlight as much as possible.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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