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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Dependence of the allergic status markers on the level of vitamin D in the serum

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SUMMARY

Introduction/Objective Recent researches show a link between low vitamin D serum levels and increased prevalence of allergic disease.

The objective of this study was to show whether there is any dependence of the allergic status markers: skin prick test (SPT), total immunoglobulin E IgE (tIgE), and allergen-specific IgE (sIgE ≥ 3 class) in serum from the serum 25(OH)D (vitDs) level in children with allergic disease/s.

Methods A total of 150 children with allergic disease/s were enrolled into this study. The vitDs, tIgE, SPT, and sIgE ≥ 3 class for aeroallergens and common food allergens were simultaneously assessed.

Results We found a negative correlation between vitDs level and age groups and a statistically significant positive correlation between vitDs level and tIgE, sIgE ≥ 3 class for hen's egg yolk and hen's egg white. A statistically significant positive correlation was determined between vitDs level and SPT on *Dermatophagoides pteronyssinus*, and a negative correlation between tIgE and SPT on *Dermatophagoides pteronyssinus*, as well as between vitDs level and sIgE ≥ 3 class for *Cladosporium* and *Alternaria* molds. We confirmed the dependence of nettle rash and comorbidity asthma from the vitamin D insufficiency and vitamin D deficiency. We did not find any dependence of serum tIgE on vitDs level for the sample.

Conclusion In order to get an adequate insight into the allergic status in children, we must take into account the pleotropic effects of vitamin D, according to which we suggest that, in the future, vitDs level should be determined synchronously with known markers of allergic status.

Keywords: immunoglobulin E; vitamin D; child; allergen

INTRODUCTION

An allergy is a disorder caused by an abnormal reaction to a harmless substance called an allergen. An allergy may manifest itself as a food allergy, atopic dermatitis, allergic asthma, allergic rhinitis, allergic conjunctivitis, and urticaria. The prevalence of allergic disease has increased considerably during the last decades. About 30% of the population in Europe is "attacked by allergies;" the situation with children is alarming – every third child suffers from at least one allergic disease.

Considering the pleiotropic effects of vitamin D (especially on the development of immune system tolerance and of the integrity of the epithelial barrier), recent studies have hypothesized a correlation between vitamin D and the rising incidence of allergic disease.

Markers of allergic status – skin prick test, total and specific immunoglobulin E

Allergy skin prick test (SPT) is the gold standard for confirmation of immunoglobulin E (IgE)-mediated allergic diseases. SPT is well reproducible, easy to perform, reliable, very safe, and more sensitive than allergen-specific IgE (sIgE) [1]. SPT imperfections are many: it is difficult to compare results from different countries because they use different extracts, training of staff and parents is required, it takes a long time to perform, and in some countries SPT is considered less safe than sIgE for certain allergens. Serum sIgE emerges as an alternative test in the field of allergy diagnosis. In some countries, for reasons of conformity, it is resorted to an estimate of the atopic state in young children solely by measuring the level of sIgE (circulating IgE) for certain allergens in the serum [2].

A link between vitamin D serum levels and an increased prevalence of allergic diseases has been proposed. Results of the National Health and Nutrition Examination Survey for 2005–2006 determined a consistent association between 25(OH)D deficiency and higher levels of IgE sensitization in children and adolescents [3].

However, there are not many studies that evaluate the correlation between serum 25(OH)D level (vitDs) and the markers of allergic status (SPT, tIgE, sIgE) in children with allergic disease/s. Since tIgE is considered a good predictor of allergy in children, and SPT and allergen sIgE are the most widely used diagnostic tests in allergy, we observe the association, correlation, and dependence between them (SPT, tIgE, sIgE) and vitDs level.

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Vitamin D and immunomodulation related to allergy

The potential role of vitamin D on the immune system is described after the discovery of VDR on macrophages, dendritic cells, activated B and T lymphocytes, as well as the ability of these cells to express 1-α-hydroxylase [4]. Up-regulation of 1-α- hydroxylase in DC is associated with the maturation process of these cells, suggesting that local production of 1,25(OH)D might serve as negative feedback to prevent inflammation. Vitamin D inhibits the expression of inflammatory cytokines and interferons in monocytes (IL-1, IL-6, IL-8, IL-12, TNF-α). Also, vitamin D affects the cells of the humoral immune response; it inhibits the proliferation and differentiation of B cells, thereby indirectly affecting the synthesis of immunoglobulins [5, 6, 7].

The objective of this study was to show whether there is any dependence of the allergic status markers (SPT, tIgE, sIgE) on serum vitDs level in children with an allergic disease.

METHODS

A total of 150 children with allergic disease were included in the study to investigate the association and dependence between the vitDs level and the markers of allergic status (SPT, tIgE, sIgE). The study was conducted with permission of the institutional ethics committee (01-6917/23.05.2016), at the Clinic of Pediatrics (PC), Kragujevac Clinical Center, Serbia, from January 2014 to June 2016.

The main criteria for patients included in the study were as follows: 1) age: 0–18 years; 2) suffering from at least one of the following diseases: asthma, allergic rhinitis, atopic dermatitis, urticaria, food allergies; the diagnosis was made according to the criteria defined by the protocols of Global Initiative for Asthma and Allergic Rhinitis and its Impact on Asthma [9], and of the World Allergy Organization [8, 9, 10]; for the classification of children, we used the diagnosis with which the children were discharged; 3) tIgE; 4) vitDs; 5) SPT; 6) sIgE with cut-off class three (sIgE ≥ 3 class).

Allergy skin prick test

We used allergen extract solutions manufactured by Torlak (Belgrade, Serbia) for seven aeroallergens (animal hair – cat's and dog's hair, molds, mix of tree pollens, mix of ragweed pollens, house dust mites, cockroach) and six food allergens (hen's egg yolk, hen's egg white, cow's milk, wheat flour, soybean, peanut). The test was performed according to the European standard for SPT to inhaled and nutritive allergens and positive/negative control [histamine dihydrochloride (10 mg/ml) / physiological sodium chloride (9 mg/ml)] [11]. Positive SPT was defined as a wheal diameter ≥ 2 mm above the negative control for children aged 0–3 years, and wheal diameter ≥ 3 mm for the children aged four years or older.

Specific immunoglobulin E in serum

The sIgE level was determined by using the AlleisaScreen (Mediwiss Analytic GmbH, Moers, Germany) screening method that is an immunoblot quantitative assessment of circulating allergen-specific IgE in serum. Tests were performed for matched panel of 17 aeroallergens (cat and dog hair E1–E5, *Cladosporium* and *Alternaria* M2–M6, *Penicillium–Aspergillus* M1–M3, maple pollen T1–T11, poplar T14, alder T2, birch T3, beech T5, ash T15, ragweed pollen W1–W2, *Dermat. pteronyssinus* D1, and cockroach I6) and eight food allergens (hen's egg yolk F75, hen's egg white F1, wheat flour F4, soybean F14, peanuts F13, lactalbumin alpha F76, lactalbumin beta F77, casein F78). The sIgE level ≥ 3.5 IU/ml or ≥ 3 class for certain allergens was adopted as an indicator of convincing allergic sensitization.

Serum measurements of total IgE and vitamin D

Total serum IgE was determined by using the electrochemiluminescence immunoassay (Cobas E 411) and was constituted in IU/ml. Measurements of vitamin D level was performed using electro-chemiluminescence binding assay (ECLIA) for the in-vitro determination of total 25(OH)D on Cobas® e 601 analyzer (Roche Diagnostics, Mannheim, Germany). VitDs were categorized into three vitamin D statuses: sufficient (≥ 30 ng/ml), insufficient (20–30 ng/ml), and deficient (< 20 ng/ml) [12].

Statistical analysis

Statistical data processing was performed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). We used descriptive statistical methods for continuous variables: mean, standard deviation. The correlations were assessed by Spearman's rank correlation test. In order to test the hypothesis of the mean values, we used nonparametric tests, Mann–Whitney U test for comparisons between two groups, and Kruskal–Wallis test for comparing three or more groups, followed by Bonferroni post-hoc test for multiple comparisons between subgroups. P-values < 0.05 were considered statistically significant.

RESULTS

Out of 150 patients enrolled in this study, 86 were male (56%) and 66 (44%) were female. The age groups ranged from one month to 17 years, with the mean age being 7.11 ± 3.8 years. Forty-seven (31.7%) patients had medical history positive for allergic disease in the mother and 33 (22%) in the father; 122 patients (81.3%) had positive SPT; 86 (57.3%) patients had increased serum sIgE ≥3 class for at least one of the tested allergens. The mean value of total serum IgE was 327.42 ± 533.56 IU/ml. The mean level of vitDs was 20.44 ± 8.26ng/ml. Established vitamin D statuses were deficiency (< 20 ng/ml) in 56% of the patients with the mean value of 14.46 ± 3.5, followed by insufficiency (20–30 ng/ml) in 31.3% of the patients with the mean value

being 24.88 ± 2.9, and sufficiency (> 30 ng/ml) in 12.7% of the patients, with the mean value being 35.87 ± 4.

Table 1 represents the mean value of tIgE and vitDs according to the age groups. We found a statistically significant difference in vitDs level between the age groups (p = 0.009). Also, there was a statistically significant difference in tIgE between the age groups (p = 0.004).

Table 1. Mean value of total immunoglobulin E (IgE) and vitamin D according to age groups

Age group (years)	Total IgE (IU/ml)	Vitamin D (ng/ml)
0–12 months (n = 7; 4.7%)	71.09 ± 96.8	35.38 ± 10.3
13–24 months (n = 18; 12%)	131.89 ± 314.6	23.24 ± 10.5
3–5 years (n = 26; 17.3%)	199.64 ± 263.2	20.10 ± 8.1
6–11 years (n = 79; 52.7%)	399.64 ± 64	18.94 ± 6.7
12–18 years (n = 20; 13.3%)	473.97 ± 520.2	19.02 ± 5.6

Table 2 shows the correlation between the age groups, tIgE, and vitDs level. We found significant positive correlation between the age groups of the participants and tIgE (p = 0.000). Also, we found a negative correlation between the vitDs level and age groups of the participants (p = 0.030).

Table 3 represents the correlation between vitamin D status in patients with allergic disease and one of the markers of allergic status. There we can see that there is a significant positive correlation between vitamin D status and SPT to aeroallergens (p = 0.016). Also, we found significant positive correlation between vitamin D status and sIgE ≥ 3 class to aeroallergens (p = 0.004).

In consideration of immunomodulatory effects of vitamin D in allergic disease, we observed the correlation between tIgE and vitDs level in patients with allergic disease. In our study we found a significant negative correlation between tIgE and vitDs level in patients with nettle rash (p = 0.000) and in patients with comorbidity asthma with atopic dermatitis (p = 0.000). Results of correlation between vitDs level and tIgE level in allergic diseases are shown in Table 4.

Table 2. Correlation between age groups (years), total immunoglobulin E (IgE) and serum 25(OH)D level

Parameter	total IgE (IU/ml)	Correlation between age in years and total IgE		Vitamin D (ng/ml)	Correlation between age in years and vitamin D	
		*rho	p		*rho	p
Age, years	327.42 ± 533.56	0.314**	0.000	20.44 ± 8.2	-0.178*	0.030

*p < 0.05;
**p < 0.001

Table 3. Correlation between vitamin D status and one of allergy screening tests

Allergy screening tests	Vitamin D status			Statistical correlation	
	Deficiency (n = 84)	Insufficiency (n = 47)	Sufficiency (n = 19)	*rho	p
Positive skin test to food allergens (n = 71)	45 (53.6%)	18 (38.3%)	8 (42.15%)	0.130	0.112
Negative skin test to food allergens (n = 79)	39 (46.4%)	29 (61.7%)	11 (57.9%)		
Positive skin test to aeroallergens (n = 106)	65 (77.4%)	32 (68.1%)	9 (47.4%)	0.196*	0.016
Negative skin test to aeroallergens (n = 44)	19 (22.6%)	15 (31.9%)	10 (52.6%)		
Positive sIgE to food allergens (n = 30)	17 (20.2%)	11 (23.4%)	2 (10.5%)	0.031	0.703
Negative sIgE to food allergens (n = 120)	67 (79.8%)	36 (76.6%)	17 (89.5%)		
Positive sIgE to aeroallergens (n = 79)	50 (59.5%)	28 (59.6%)	1 (5.3%)	0.234**	0.004
Negative sIgE to aeroallergens (n = 71)	34 (40.5%)	19 (40.4%)	18 (94.7%)		

Vitamin D statuses: sufficient (≥ 30 ng/ml), insufficient (20–30 ng/m), and deficient (< 20 ng/ml);
sIgE – allergen-specific IgE;
*p < 0.05;
**p < 0.001

Table 4. Correlation between serum 25(OH)D level and total immunoglobulin E (IgE) in allergic disease

Allergic disease	Parameters			
	Total IgE (IU/ml)	Vitamin D (ng/ml)	Spearman's correlation	p
Asthma	27.95 ± 14.2	26.17 ± 10.7	0.700	0.188
Allergic rhinitis	127.99 ± 305.2	22.16 ± 8.6	-0.277	0.251
Atopic dermatitis	45.53 ± 75.1	31.16 ± 11.6	0.607	0.148
Nettle-rash	181.37 ± 279.7	20.0 ± 3.6	-1.000**	0.000
Food allergy	55.85 ± 78.2	22.06 ± 6.7	0.100	0.873
Asthma + comorbidities				
Allergic rhinitis	253.99 ± 461.4	18.70 ± 6.7	-0.009	0.951
Atopic dermatitis	267.76 ± 333.4	21.55 ± 14.1	-1.000**	0.000
Allergic rhinitis + atopic dermatitis	466.16 ± 560.9	21.10 ± 10.3	0.273	0.446
Rhinitis allergic + food allergy	538.0 ± 665.1	19.05 ± 7.3	-0.067	0.643

**p < 0.001

Table 5. Features and findings in children suffering from allergic disease/s

Allergic disease/s	Sex M/F	Total IgE (IU/ml)	Vitamin D (ng/ml)	Specific IgE (IU/ml)													
				Aeroallergens					Food allergens							Skin Prick Test	
				D1	E1–E5	M2–M6, M1–M3	TP	I6	F2	F75	F1	F4	F14	F13	Aeroallergens P/N	Food allergens P/N
Asthma	4/1	27.95 ± 14.2	26.17 ± 10.7	0.03 ± 0.06	0.00	0.00	0.00	0.00	0.01 ± 0.0	0.00	0.00	0.00	0.00	0.00	3/2	3/2
Allergic rhinitis	11/8	127.99 ± 305.2	22.16 ± 8.6	1.74 ± 5.9	0.43 ± 1.5	0.87 ± 3.2	2.49 ± 10.4	0.52 ± 2.0	0.15 ± 0.2	0.02 ± 0.0	0.05 ± 0.1	0.79 ± 3.2	0.27 ± 1.0	0.62 ± 2.2	10/9	3/16
Atopic dermatitis	3/4	45.53 ± 75.1	31.16 ± 11.6	0.00	0.03 ± 0.0	0.05 ± 0.1	0.02 ± 0.06	0.00	0.10 ± 0.1	0.00	0.16 ± 0.4	0.42 ± 0.9	0.00	0.09 ± 0.2	4/3	4/3
Nettle rash	2/1	181.37 ± 279.7	20.0 ± 3.6	0.05 ± 0.0	0.09 ± 0.1	0.15 ± 0.2	0.06 ± 0.1	0.00	0.37 ± 0.6	0.01 ± 0.0	0.95 ± 1.5	0.03 ± 0.0	4.5 ± 7.9	0.62 ± 1.0	0/3	0/3
Food allergy	1/4	55.85 ± 78.2	22.06 ± 6.7	0.43 ± 0.6	0.11 ± 0.2	0.23 ± 0.2	0.04 ± 0.0	0.00	0.11 ± 0.2	0.02 ± 0.0	0.28 ± 0.6	0.58 ± 1.3	1.97 ± 4.3	0.38 ± 0.5	4/1	3/2
Asthma + comorbidities																
Allergic rhinitis	25/21	253.99 ± 461.4	18.70 ± 6.7	6.39 ± 14.0	0.15 ± 0.7	0.99 ± 4.3	1.04 ± 4.4	0.26 ± 1.0	0.26 ± 0.4	0.41 ± 2.6	0.17 ± 0.4	0.49 ± 1.9	0.39 ± 1.9	4.43 ± 20.6	33/13	21/25
Atopic dermatitis	1/1	267.76 ± 333.4	21.55 ± 14.1	7.85 ± 11.1	0.00	0.00	0.00	0.00	0.10 ± 0.1	0.00	0.50 ± 0.7	0.00	0.07 ± 0.0	0.70 ± 0.0	2/0	1/1
Allergic rhinitis + atopic dermatitis	6/4	466.16 ± 560.9	21.10 ± 10.3	5.90 ± 7.4	2.12 ± 6.0	1.34 ± 3.3	0.08 ± 0.2	0.00	0.27 ± 0.4	0.01 ± 0.0	10.02 ± 31.6	0.02 ± 0.0	0.00	0.74 ± 2.3	6/4	5/5
Allergic rhinitis + food allergy	31/22	538.0 ± 665.1	19.05 ± 7.3	11.65 ± 20.9	0.48 ± 1.9	1.19 ± 3.9	1.05 ± 2.9	0.16 ± 0.4	0.31 ± 1.0	0.44 ± 2.5	0.63 ± 2.7	0.42 ± 1.2	0.14 ± 0.3	2.43 ± 8.4	44/9	31/22

Aeroallergens: *Derm. pteronyssinus* – D1, animal hair (dog, cat) – E1–E5, mold (*Cladosporium–Alternaria* – M2–M6, *Penicillium–Aspergillus* – M1–M3), tree pollen – TP; insect (cockroach) – I6; food allergens: milk – F2 (F76, F77, F78), hen's egg yolk – F75, hen's egg white – F1, wheat flour – F4, soybean – F14, peanuts – F13;
IgE – immunoglobulin E

Table 5 represents the frequency of different allergic diseases in our patients with vitDs level, tIgE level, sIgE ≥ 3 class on different allergens and SPT on different allergens. Also, we did not find significant difference in the incidence of some allergic disease between boys and girls (p = 0.953). There is significant difference of tIgE level in different allergic diseases (p = 0.000). When it comes to aeroallergens, we observed that most of the patients were highly sensitive (sIgE ≥ 3 class) to dust mite, mold, and tree pollens. The analysis of the children's sensitivity to mold from the air (*Cladosporium–Alternaria* – M2–M6, *Penicillinum–Aspergilus* – M1–M3) is shown as the common result.

As regards food allergens, most of the patients were highly sensitive to soybean and peanuts. Also, we can consider an increased expression of sIgE in patients with allergic rhinitis (alone) as well as in patients with comorbidity asthma with allergic rhinitis, followed by comorbidity asthma with allergic rhinitis and atopic dermatitis, and comorbidity asthma with allergic rhinitis and food allergy. Also, we observed that the patients who had asthma with the associated allergic disease manifested highly sensitivity confirmed by SPT. There was no significant difference in vitDs level in different allergic diseases (p = 0.149). At the same time, there was a significant difference in vitDs level among children who had only one allergic disease and those with asthma comorbidity (p = 0.005). The mean serum 25(OH)D level in children who had only one allergic disease was 24.15 ± 9.3 ng/ml. Contrary to this, children with asthma comorbidity (with one or more allergic diseases) had lower mean serum 25(OH)D level of 19.13 ± 7.4 ng/ml.

Table 6 provides the correlation analysis between serum tIgE(IU/ml) and sIgE ≥ 3 class on certain aeroallergens and between sIgE ≥ 3 class on certain aeroallergens and vitDs level. We found a significant positive correlation between serum tIgE(IU/ml) and sIgE ≥ 3 class on the following allergens: *Derm. pteronyssinus* (p = 0.004), mold *Penicillinum–Aspergilus* (p = 0.001), tree pollens – ash tree (p = 0.001), and cockroach (p = 0.041), as between serum sIgE ≥ 3 class on animal hair (cat and dog) and vitDs level (p = 0.008). The negative correlation determined between vitDs level and serum sIgE ≥ 3 class on *Cladosporium–Alternaria* mold (p = 0.001).

Table 7 represents the correlation analysis between serum tIgE and sIgE ≥ 3 class on food allergen as between serum sIgE ≥ 3 class on food allergen and vitDs level. Here, we found the statistical positive correlation between serum tIgE and sIgE ≥ 3 class on certain food allergen for hypersensitivity on: alfa-lactoglobulin (p = 0.007), hen's egg yolk (p = 0.000), hen's egg white (0.048). Likewise, we found a significant positive correlation between vitDs level and serum sIgE ≥ 3 class on hen's egg yolk (p = 0.000) and hen's egg white (0.050).

We found a significant negative correlation between serum tIgE and SPT on *Derm. pteronyssinus* (p = 0.000) and tree pollen (p = 0.001), as shown in Table 8. We did not find significant correlations between serum tIgE and SPT on food allergens. We presented these results in Table 9. By analysis, we found positive correlation and

Table 6. Correlation between total and allergen-specific immunoglobulin E (IgE) > 3 class on certain aeroallergens, as well as sIgE > 3 class on certain aeroallergens and serum 25(OH)D level

Aeroallergens	sIgE (IU/ml) > 3 class	Serum total IgE (IU/ml) level	Correlation total IgE *vs.* sIgE		Vitamin D (ng/ml)	Correlation vitamin D *vs.* sIgE > 3 class	
			*rho	p		*rho	p-value
Dermatophagoides pteronyssinus (n = 38)	24.91 ± 20.8	674.40 ± 765.48	0.813**	0.004	18.33 ± 6.8	-0.104	0.527
Animal (n = 6)	9.03 ± 5.7	948.45 ± 631.62	0.353	0.493	16.57 ± 5.1	0.884**	0.008
Cladosporium–Alternaria (n = 14)	16.01 ± 15.5	618.31 ± 690.7	-0.103	0.725	18.39 ± 8.8	-0.699**	0.001
Penicillinum–Aspergilus (n = 2)	8.65 ± 6.3	581.07 ± 807.6	1.000**	0.001	24.85 ± 3.8	-1.000	/
Tree pollen							
Maple (n = 8)	22.23 ± 27	629.48 ± 470.6	-0.253	0.545	19.39 ± 6.5	0.157	0.711
Poplar (n = 3)	8.23 ± 5.7	529.09 ± 514.5	1.000	/	16.89 ± 4.9	0.500	0.667
Alder (n = 9)	14.82 ± 11	644.54 ± 463.16	-0.193	0.618	21.23 ± 8.2	0.059	0.881
Birch (n = 11)	11.46 ± 7.1	571.90 ± 445.9	0.78	0.821	19.52 ± 8.3	0.196	0.563
Hazel bush (n = 12)	7.20 ± 10	760.52 ± 487.6	-0.310	0.327	21.41 ± 10	0.014	0.965
Beech (n = 11)	25.79 ± 28	608.14 ± 434.2	0.132	0.689	17.25 ± 6.6	0.562	0.072
Mix of ragweed (n = 7)	32.41 ± 23.4	681.98 ± 538	0.429	0.337	19.40 ± 6.3	-0.714	0.071
Ash tree (n = 2)	5.95 ± 2.7	601.41 ± 705.8	1.000**	0.001	19.57 ± 2.5	-1.000	
Cockroach (n = 3)	6.53 ± 2.2	529.09 ± 514.58	0.727*	0.041	16.89 ± 4.9	0.500	0.667

sIgE – allergen-specific IgE;
*p < 0.05;
**p < 0.001

Table 7. Correlation between total total and allergen-specific immunoglobulin E (IgE) > 3 class on certain food allergen, allergen-specific immunoglobulin > 3 class on certain food allergen and serum 25(OH)D level

Food allergens	sIgE (IU/ml) > 3 class	Serum total IgE (IU/ml) level	Correlation total IgE *vs.* sIgE		Vitamin D (ng/ml)	Correlation vitamin D *vs.* sIgE > 3 class	
			*rho	p		*rho	p
Milk (n = 0)	/	/	/	/	/	/	/
Alfa-lactoglobulin (n = 6)	5.35 ± 5.6	275.87 ± 343.6	0.993**	0.007	18.76 ± 5.6	0.029	0.957
Beta-lactoglobulin (n = 0)	/	/	/	/	/	/	/
Casein (n = 2)	10.12 ± 9	579.41 ± 809.9	/	/	18.50 ± 5	/	/
Hen's egg yolk (n = 2)	18.20 ± 0.5	579.41 ± 809.9	1.000**	0.000	15.50 ± 5	1.000**	0.000
Hen's egg white (n = 4)	32.50 ± 45.4	869.55 ± 552	0.949*	0.048	24.94 ± 10.7	0.949*	0.050
Wheat flour (n = 5)	9.28 ± 3.3	552.83 ± 365.31	0.053	0.933	20.50 ± 6	-0.684	0.203
Soybean (n = 4)	10.33 ± 4.1	344.91 ± 512.8	-0.800	0.200	20.24 ± 3	0.400	0.600
Peanuts (n = 9)	36.07 ± 39.3	923.99 ± 896.9	-0.33	0.932	20.91 ± 8.4	-0.435	0.242

sIgE – allergen-specific IgE;
*p < 0.05
**p < 0.001

dependence of only SPT to *Derm. pteronyssinus* from vitDs level (p = 0.050) and we did not find the correlation and dependence of other SPT to aero- and food allergens from vitDs level.

DISCUSSION

An increasing incidence of allergic disease during the past 30 years sets the need to seek laboratory parameters that are useful in diagnosing allergic disease. Park et al. [13] in their study showed that the serum total IgE level is a good predictor of allergy in children. Several papers indicated a problem of discrepancy between the results obtained with an SPT and allergen sIgE. Schoos et al. [14] determined poor or moderate degree of agreement between the results obtained from SPT and sIgE for a certain allergen, which shows that this ratio deteriorates with age of the child. According to these Norwegian authors, it is necessary to use complementary SPT and allergen sIgE, but not interchangeably, especially in young children (0–2 years) [14]. Regarding the role of vitamin D in the regulation of the immune system, vitamin D status can be one of the effective factors in the reactivity of a certain allergen. Studies conducted by Kolokotroni et al. indicated that serum level of vitamin D is positively associated with tIgE level and sIgE on *Dermatophagoides farinae* in Cyprus children [15]. In our study, we found a negative correlation between vitDs level and tIgE and sIgE ≥ 3 class to aeroallergens, as well as between vitDs level and sIgE ≥ 3 class on mold *Cladosporium–Alternaria*, and, finally, a statistically significant positive correlation between vitDs level and sIgE ≥ 3 class to animal hair (cat and dog), which we consider to be interdependence.

Likewise, related to food allergens, we found a statistically significant positive correlation between vitDs level and tIgE, and sIgE ≥ 3 class on hen's egg yolk and hen's egg white (p = 0.006), which we consider to be interdependence.

Table 8. Correlation between skin prick test (SPT) on aeroallergen and total immunoglobulin E (IgE), as well as that of SPT on aeroallergens and serum 25(OH)D level

SPT for aeroallergens	Total IgE *vs*. SPT		Vitamin D *vs*. prick test	
	*rho	p	*rho	p
Derm. pteronyssinus (n = 58)	-0.359**	0.000	0.157*	0.050
Mold (n = 19)	-0.059	0.477	-0.071	0.386
Animal (n = 9)	0.065	0.433	-0.091	0.270
Tree pollen (n = 46)	-0.273**	0.001	-0.015	0.852
Cockroach (n = 8)	0.082	0.317	0.095	0.246

*p < 0.05;
**p < 0.001

Table 9. Correlation between skin prick test (SPT) on food allergen and total IgE, as well as that of SPT on food allergens and 25(OH)D level

SPT for food allergens	Total IgE vs. SPT		Vitamin D vs. SPT	
	*rho	p	*rho	p
Milk (n = 12)	0.122	0.137	0.091	0.271
Hen's egg yolk (n = 12)	-0.083	0.313	-0.094	0.253
Hen's egg white (n = 14)	-0.065	0.432	0.001	0.995
Wheat flour (n = 11)	0.062	0.453	0.097	0.237
Soybean (n = 4)	0.072	0.383	-0.079	0.335
Peanuts (n = 19)	-0.013	0.877	0.026	0.751

*p < 0.05
**p < 0.001

Several studies investigated the relationship between vitamin D deficiency and allergic diseases and concluded that low level of vitamin D is associated with increased incidence of allergies and asthma [16, 17, 18]. Poole et al. [19] in their study conducted on infants showed that vitamin D insufficiency is associated with an increased risk of a challenge-proven peanut/egg allergy. Quirk et al. [20] suggest that vitamin D deficiency increases the risk of sensitization to food allergens, particularly to milk and wheat. In our study, we found a statistically significant correlation between nettle rash and comorbidity asthma (with one or more allergic diseases) and lower mean vitDs level (p = 0.005), which we consider to be interdependence.

We found a statistically significant difference in serum vitD level according to SPT in children with allergic disease (p = 0.050). The mean value of 25(OH)D level in children with positive SPT was 19.77 ± 7.91 ng/ml in serum. The children with negative SPT had a mean value of 23.34 ± 9.2 ng/ml in serum 25(OH)D. From this result, we can remark that the high frequency of positive SPT (81.3%) in children with allergic disease means high frequency of vitamin D insufficiency and vitamin D deficiency, which leads us to conclude that there is a dependence between these two variables.

In our study we did not find any correlation between serum tIgE and vitDs level (rho = -0.126, p = 0.126). However, there is a trend that the mean value of vitDs level decreased with age, while the serum concentration of total IgE increased with age. When we investigated separate correlations between serum tIgE and vitDs in individual allergic diseases, we noticed a significant negative correlation between them in children who had nettle rash (p = 0.000) and asthma comorbidity with atopic dermatitis (p = 0.000).

We found statistically significant differences in serum tIgE between boys and girls (p = 0.004). The mean total serum IgE in boys was higher (383.35 ± 519.91 IU/ml) than in girls (256.23 ± 546.11 IU/ml). Simultaneously, there is a statistically significant difference in serum 25(OH)D level between boys and girls (p = 0.020) so they maintain the same parity (21.98 ± 8.9 *vs*. 18.47 ± 6.9 ng/ml).

There was a statistically significant difference between child's age and positive/negative SPT (p = 0.004). The mean age of children who had positive SPT was 7.5 ± 3.8 years and of children who had negative SPT it was 5.1 ± 3.1 years. Also, we found a statistically significant difference between a child's age and increased sIgE ≥ 3 class (p = 0.004) (7.8 ± 3.3 *vs*. 6 ± 4.2 years).

CONCLUSION

We found a significant dependence of positive SPT and high serum sIgE ≥ 3 class to certain allergens from the low serum 25(OH)D level (insufficiency or deficiency), which means that vitD contributes to reactivity to a certain allergen. We noted the correlation of increased tendency to allergies and, simultaneously, low level of vitamin D with a child's age. Also, we confirmed the dependence of comorbidity asthma from hypovitaminosis D. We noticed a significant dependence of serum tIgE from the vitDs in children who had nettle rash or with comorbidity of asthma and atopic dermatitis. We did not find the correlation between serum tIgE level and vitD level for the whole group of participants. Children with hypovitaminosis D exhibited a more pronounced tendency to one or more allergic diseases.

Our findings suggest that the vitDs level could be determined synchronously with known markers of allergic status with the goal of precisely determining the child's allergic status. Perhaps correction of hypovitaminosis D would affect the decrease in the prevalence of allergic diseases. In order to gain full insight into the allergic status of children in the future, we need to conduct further investigations of the relationship between serum 25(OH)D level, tIgE level, sIgE ≥ 3 class, and SPT.

Conflict of interest: None declared.

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Зависност маркера алергијског статуса од концентрације витамина Д у серуму

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САЖЕТАК

Увод/Циљ Недавне студије су доказале везу између ниске серумске концентрације витамина Д и пораста преваленце алергијских болести.

Циљ овог рада је да покаже да ли постоји зависност маркера алергијског статуса: кожног (*prick*) алерготеста (КАТ), концентрације укупног имуноглобулина Е (уИгЕ) и концентрације ИгЕ специфичног за алерген (класа сИгЕ ≥ 3) у серуму од серумске концентрације 25(*OH*)*D* (витДс) код деце оболеле од алергијске болести.

Методе У ову студију је било укључено 150 деце са алергијским болестима. Процењени су, истовремено, ВитДс, уИгЕ, КАТ и сИгЕ ≥ 3 класе на инхалаторне и нутритивне алергене.

Резултати Утврдили смо негативну корелацију између нивоа витД и старосних група и статистички значајну позитивну корелацију између витДс и, с друге стране, уИгЕ, сИгЕ ≥ 3 класе на кокошје жуманце и беланце. Статистички значајна позитивна корелација утврђена је између витДс и КАТ на кућну грињу и негативна корелација између уИгЕ и КАТ на кућну грињу, као и између витДс и сИгЕ ≥ 3 класе на гљивице *Cladosporium* и *Alternaria*. Потврдили смо зависност копривњаче и коморбидитетне астме од инсуфицијенције витамина Д и дефицијенције витамина Д. Нисмо нашли зависност уИгЕ од витДс за цео узорак.

Закључак Да би смо добили адекватан увид у алергијски статус деце, морамо уважити плеотропне ефекте витамина Д, сходно чему предлажемо да се, убудуће, одређује витДс синхроно са познатим маркерима алергијског статуса.

Кључне речи: имуноглобулин Е; витамин Д; деца; алерген