СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

Katerina Dajić[1], Nebojša Stojković[2], Ljiljana Novković[3], Ana Vujić[1,4], Anđelka Stojković[1,4,†]

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

Зависност маркера алергијског статуса од концентрације витамина Д у серуму

[1]University in Kragujevac, Faculty of Medical Sciences, Department of Paediatrics, Kragujevac, Serbia;
[2]Paraćin General Hospital, Children's Department, Paraćin, Serbia;
[3]Clinical Centre of Kragujevac, Clinic for Pulmonology, Kragujevac, Serbia;
[4]Clinical Centre of Kragujevac, Pediatric Clinic, Kragujevac, Serbia

Received: August 22, 2018
Revised: January 9, 2019
Accepted: March 14, 2019
Online First: March 20, 2019
DOI: https://doi.org/10.2298/SARH180822025D

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

†**Correspondence to:**
Anđelka STOJKOVIĆ
Paediatric Clinic, Kragujevac Clinical Centre, Zmaj Jovina 30, 34000 Kragujevac, Serbia
E-mail: **andja410@mts.rs**

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

Зависност маркера алергијског статуса од концентрације витамина Д у серуму

SUMMARY

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

The aim of this study was to show is there any dependence the markers of allergic status: skin prick test(SPT), total 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 150 children with allergic disease/s were enrolled in this study. The vitDs, tIgE, SPT and sIgE≥3 class for aeroallergens and food common allergens were assessed, simultaneously.

Results We found negative correlation between vitDs level and age groups and statistically significant positive correlation between, vitDs level and on the other side, tIgE, sIgE≥3 class for Hen's egg yolk and Hen's egg white. Statistically significant positive correlation was determined between vitDs level and SPT on Dermatophagoides pteronyssinus and negative correlation between tIgE and SPT on Dermatophagoides pteronyssinus as between vitDs level and sIgE≥3 class on mold Cladosporium Alternaria. We confirmed the dependence of nettle rash and comorbidity asthma from the vitamin D insufficiency and vitamin D defficiency. We did not find dependence of serum tIgE from vitDs level for whole 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, the vitDs level would be determined synchronously with known markers of allergic status.

Keywords: immunoglobulin E; vitamin D; child; allergen

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: алерго Прик кожног теста (СПТ), концентрације укупног ИгЕ (уИгЕ) и концентрације алерген специфичног ИгЕ-а (сИгЕ≥3 класе) у серуму од серумске концентрације 25(*OH*)*D* (витДс) у деце оболеле од алергијске болести.

Методе 150 деце са алергијским болестима били су укључени у ову студију. Процењени су, истовремено, ВитДс, уИгЕ, СПТ 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 СПТ на кућну грињу и негативна корелација између уИгЕ и СПТ на кућну грињу као између витДс и сИгЕ≥3 класе на гљивицу *Cladosporium 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 витДs синхроно са познатим маркерима алергијског статуса.

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

INTRODUCTION

An allergy is a disorder caused by an abnormal reaction to a harmless substance called an allergen. The allergy may manifest as food allergy, atopic dermatitis, allergic asthma, allergic rhinitis, allergic conjuctivitis, and urticaria. The prevalence of allergic disease has increased considerably during the last decades. About 30% of the population in Europe are

"attacked by allergies," a 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 relationship 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, highly secure and more sensitive than allergen specific IgE(sIgE) [1]. SPT imperfections are many: difficult to compare results from different countries because they use different extracts, required training of staff and parents, performing a long time and in some countries SPT is considered less safe than sIgE for certain allergen. Serum sIgE emerges as an alternative test in the field of allergy diagnosis. In some countries, from the conformist reasons, it is resorting to an estimate of the atopic state in young child solely by measuring the level of sIgE (circulating IgE) for certain allergen in serum [2].

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

However, there are not many studies who evaluated the relationship 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 as a good predictor of allergy in children, and SPT and allergen sIgE are most widely used diagnostic test in allergy, we observe the association, correlation and dependence between them (SPT, tIgE, sIgE) and vitDs level.

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]. Upregulation 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 a 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. Inhibits the proliferation and differentiation of B cells, and thereby, indirectly affects the synthesis of immunoglobulins [5,6,7].

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

METHODS

A150 children with allergic disease were included in the study to investigated the association and dependence between, on the one side, vitDs level, and on the other side, the markers of allergic status (SPT, tIgE, sIgE). The study was conducted, with permission of the Ethics Committee (01-6917/23.05.2016), at the Clinic of Pediatrics (PC), Kragujevac Clinical Center (CC), Serbia, in the period from January 2014 to June 2016.

The main criteria for patients included in the study were: 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 GINA [8], and ARIA [9], and the World organization allergy [10]. For the classification of children, we took the diagnosis with which the children were discharged to home; 3/tIgE; 4/vitDs; 5/SPT; 6/sIgE with cut-off class three (sIgE≥3 class).

Allergy skin prick test (SPT)

We used allergen extract solutions manufactured by Torlak (Belgrade, Serbia) for 7 aeroallergens (animal hair–cats and dog, molds, mix tree pollens, mix ragweed pollens, house dust mites, cockroach) and 6 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 year, and for the children aged 4 years or older wheal diameter ≥3 mm.

Specific immunoglobulin E in serum (sIgE)

The sIgE level was determined by using a screening method Alleisa screen (Mediwiss Analytic GmbH, Germany) that is immunoblot quantitative assessment of circulating allergen-specific IgE in serum. Tests were performed for matched panel of 17 aeroallergens (hair cat and dog E1_E5, Cladosporium Alternaria M2_M6, Penicillinum 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 8 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 allergen 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 analyser (Roche Diagnostics, Mannheim, Germany). VitDs were categorized into three vitamin D status: sufficient (≥30 ng/ml), insufficient (20-30 ng/m), and deficient (<20 ng/ml) [12].

Statistical analysis

Statistical data processing was performed using standard statistical software IBM SPSS statistic version 20. We used descriptive statistical methods for continuous variables: mean, standard deviation. The correlation were assessed by Spearman rank correlation. In order to test the hypothesis of the mean values, we used nonparametric tests, for comparison between two groups of Mann-Whitney-U tests and for comparing between three or more groups Kruskal-Wallis test followed by Bonferroni post hoc test for multiple comparison between subgroups.P-values <0.05 were considered statistically significant.

RESULTS

From 150 patients enrolled in this study 86 patients were boys (56.0%) and 66 (44.0%) were girls. The age groups range from 1 months to 17 years old, with the mean age of 7.11±3.8 years. A 47 (31.7%) patients had a positive history of allergic disease in the mother and 33 (22.0%) in the father. A 122 patients (81.3%) had positive SPT. A 86 (57.3%) patients had increased serum sIgE≥3 class 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 56.0% of the patients with mean value 14.46±3.5, then insufficiency (20-30 ng/ml) in 31.3% of the patients with mean value 24.88±2.9, and sufficiency (>30 ng/ml) in 12.7% of the patients with mean value 35.87±4.0.

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

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

Table 3 represents correlation between vitamin D status in patients with allergic disease and one of markers of allergic status. Here, we can see that there is 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 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 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 the 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 to food allergens, the most patients were highly sensitive to soybean and peanuts. Also, we can consider an increased expression of sIgE in the patients with allergic rhinitis (alone) as and in patients with, comorbidity asthma with allergic rhinitis, then comorbidity asthma with allergic rhinitis and atopic dermatitis, then 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±9.3ng/ml. Contrary to this, children with asthma comorbidity (with one or more allergic diseases) had lower mean serum 25(OH)D level 19.13±7.4ng/ml.

Table 6 gives the correlation analysis between serum tIgE(IU/ml) and sIgE≥3 class on certain aeroallergens as 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 next allergens: *derm. pteronyssinus* (p=0.004), mold *Penicillinum aspergilus* (p=0.001), three 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 mold Cladosporium Alternaria and (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 the significant positive correlation between vitDs level and serum sIgE≥3 class on hen's egg yolk (p=0.000), hen's egg white (0.050).

We found a significant negative correlation between serum tIgE and SPT on *derm. pteronyssinus* (p=0.000) and three pollen (p=0.001), which we shown in table 8. We did not find significant correlation between serum tIgE and SPT on food allergens. We represented this results in table 9. By analysis, we found positive correlation and dependence of, only, SPT to *derm. pteronyssinus* from vitDs level (p=0.050) and we didn't 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 of allergic disease. Park at al. in their study showed that the serum total IgE level is a good predictor of allergy in children [13]. Several papers indicated a problem of discrepancy between the results obtained to an SPT and allergen sIgE. Schoos at al. determined bad or moderate degree of agreement between the results obtained from SPT and sIgE for a certain allergen and shows that this ratio is deteriorates with age of the child [14]. According to this Norwegian authors suggested that is necessary to use complementary SPT and allergen sIgE, but not interchangeably, especially in young children (0-2 years) child [14]. Regarding to 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 the certain allergen. Studies conducted by Kolokotroni at al. indicated that serum level of vitamin D is positively associated with tIgE level and sIgE on Dematophagoides farina in

Cyprus children [15]. In our study, we found a negative correlation between vitDs level and on the other side, tIgE and sIgE≥3 class to aeroallergens, 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 as between each other dependence. Likewise, related to food allergens, we found a statistically significant positive correlation between vitDs level and on the other side, tIgE, and sIgE≥3 class on Hen's egg yolk and Hen's egg white (p=0.006), which we consider as between each other dependence.

Several studies investigated the relationship between vitamin D deficiency and allergic diseases. The conclusions of this studies were that low level of vitamin D is associated with increased incidence of allergies and asthma [16, 17, 18]. Poole and al. in their study conducted on infants, showed that vitamin D insufficiency is associated with an increased risk of challenge proven peanut/egg allergy [19]. Quirk at al. suggest that vitamin D deficiency increases the risk of sensitization to food allergens particularly to milk and wheat [20]. 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), what we consider as between each other dependence.

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 25(OH)D level 23.34±9.2 ng/ml in serum. 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 defficiency which leads us to conclude that there is dependence between these two variables.

In our study we did not find correlation between serum tIgE and vitDs level (rho=-0.126, p=0.126). But, 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 did separately correlations between serum tIgE and vitDs in the individually allergic disease, 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 differences 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 was 5.1±3.1 years. Also, we found a statistically significant difference between child's age and increased sIgE≥3 class (p=0.004) (7.8±3.3 vs 6.0±4.2 years).

CONCLUSION

We found the significant dependence of positive SPT and high serum sIgE≥3 class to certain allergens from the low serum 25(OH)D level (insufficiency or defficiency) which means that vitD contributes to reactivity to a certain allergen. We remarked the increased tendence to allergies and, simultaneously, low level of vitamin D with 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 have presented a more pronounced tendency to one or more allergic diseases.

Our findings suggest that the vitDs level would 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. How we should be able to get full insight into the allergic status of children, in the future, we need to manage more investigation into the relationship between serum 25(OH)D level, tIgE level, sIgE≥3 class and SPT.

Conflict of interest: None declared

REFERENCES

1. BogomolovAE.Disagreement between skin prick test and specific IgE levels in paties with respiratory aller gy (literature review and our own research data). Астма та алергія, 2015;3:51–5.
2. Chauveau A, Dalphin ML, Kaulek V, Roduit C, Pugin A, von Mutius E ,et al. Disagreement between Skin Prick Tests and Specific IgE in Early Childhood. International Archives of Allergy and Immunology 2016;170(2):69–74. doi: 10.1159/000446776.
3. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: Results from NHANES 2005–2006. The Journal of allergy and clinical immunology. 2011;127(5):1195-1202. doi:10.1016/j.jaci.2011.01.017.
4. Radović J, Marković D, Veličkov A, Đorđević B, Stojnev S. Imunomodulatorno dejstvo vitamina D. Acta Medica Medianae. 2012; 51(4) doi:10.5633/amm.2012.0409s
5. Ando, E., Morisaki, N., Asakura, K., Sasaki, S., Fujiwara, T., & Horikawa, R. (2018). Serum 25-hydroxyvitamin D levels showed strong seasonality but lacked association with vitamin D intake in 3-year-old Japanese children. British Journal of Nutrition. 2018;120(9):1034-1044. doi:10.1017/S0007114518002258.
6. Wu S, Zhang Y, Lu R, et al. Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. Gut 2015;64:1082-1094. dx.doi.org/10.1136/gutjnl-2014-307436.
7. Brett NR, Lavery P, Agellon S, et al. Vitamin D Status and Immune Health Outcomes in a Cross-Sectional Study and a Randomized Trial of Healthy Young Children. Nutrients. 2018;10(6):680. doi:10.3390/nu10060680.
8. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. Available from www.ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/
9. Brozek LJ, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy clin immunol. 2017; 140(4):951–8. dx.doi.org/10.1016/j.jaci.2017.03.050.
10. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organization Journal 2015; 8:32. doi:10.1186/s40413-015-0080-1
11. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test – European standards. Clinical and Translational Allergy. 2013;3:3. doi:10.1186/2045-7022-3-3.
12. Pludowski P, Holick FH, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A,et al. Vitamin D supplementation guidelines. J Steroid BiochemMol Biol. 2018; 175:125–35. doi: 10.1016/j.jsbmb.2017.01.021.
13. Park HJ, Kim EJ, Yoon D, Lee JK, Chang WS, Lim YM, Park JW, Lee JS. Prevalence of Self-reported Allergic Diseases and IgE Levels: A 2010 KNHANES Analysis. Allergy Asthma Immunol Res. 2017 Jul;9(4):329-339. doi.org/10.4168/aair.2017.9.4.329.
14. Schoos AM, Chawes BL, Følsgaard NV, Samandari N, Bønnelykke K, Bisgaard H. Disagreement between skin prick test and specific IgE in young children. Allergy. 2015; 70(1):41–8. doi: 10.1111/all.12523
15. Kolokotroni O, Middleton N, Kouta C, Raftopoulos V, Yiallouros PK. Association of serum vitamin D with asthma and atopy in childhood: review of epidemiological observational studies. Mini Rev Med Chem. 2015;15:881–99. doi: 10.2174/1389557515666150519105541.
16. Igde M, Baran P, Oksuz B G, Topcuoglu S, Karatekin G. Association between the oxidative status, Vitamin D levels and respiratory function in asthmatic children.Niger J Clin Pract 2018;21:63-68. DOI: 10.4103/njcp.njcp_373_16.
17. Hibbs AM, Ross K, Kerns LA, et al. Effect of Vitamin D Supplementation on Recurrent Wheezing in Black Infants Who Were Born Preterm: The D-Wheeze Randomized Clinical Trial. JAMA. 2018;319(20):2086–2094. doi:10.1001/jama.2018.5729.
18. Chen Y, Xu T. Association of vitamin D receptor expression with inflammatory changes and prognosis of asthma. Exp Ther Med. 2018;16(6):5096-5102. doi: 10.3892/etm.2018.6867.
19. Poole A, Song Y, Brown H, Hart PH, Zhang GB. Cellular and molecular mechanisms of vitamin D in food allergy. J Cell Mol Med. 2018;22(7):3270-3277. doi: 10.1111/jcmm.13607.
20. Quirk SK, Rainwater E, Shure AK, Agrawal DK. Vitamin D in atopic dermatitis, chronic urticaria and allergic contact dermatitis. Expert Rev Clin Immunol. 2016;12(8):839-47. doi:10.1586/1744666X.2016.1171143.

Table 1. Mean value of total 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; 12.0%)	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. Correlation between age groups (years), total IgE and serum 25(OH)D level

	total IgE (IU/ml)	**Correlation between age years and total IgE**		**Vitamin D (ng/ml)**	**Correlation between age years and vitamin D**	
		***rho**	**p value**		***rho**	**p value**
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

	Vitamin D status			Statistical correlation	
Allergy screening Tests	**Deficiency (n=84)**	**Insufficiency (n=47)**	**Sufficiency (n=19)**	***rho**	**p value**
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)

*p<0.05;
**p<0.001

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

Allergic disease	Parameters			
	Total IgE (IU/ml)	**Vitamin D (ng/ml)**	**Spearman's correlation**	**p value**
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 suffer 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 alle. 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
Rhinitis allergic + 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

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

		Serum total IgE (IU/ml) level	**Correlation total IgE vs sIgE**			**Correlation vitamin D vs. sIgE>3class**	
Aeroallergens	**sIgE (IU/ml)>3class**		***rho**	**p value**	**Vitamin D (ng/ml)**	***rho**	**p value**
Dermatophagoidespteronyssinus (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±27.0	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±11.0	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±10.0	760.52±487.6	-0.310	0.327	21.41±10	0.014	0.965
Beech (n=11)	25.79±28.0	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	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

*p<0.05;
**p<0.001

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

		Serum total IgE (IU/ml) level	**Correlation total IgE vs sIgE**			**Correlation Vitamin D vs. sIgE>3class**	
Food allergens	**sIgE (IU/ml)>3class**		***rho**	**p value**	**Vitamin D (ng/ml)**	***rho**	**p value**
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±9.0	579.41±809.9	/	/	18.50±5.0	/	/
Hen's egg yolk (n=2)	18.20±0.5	579.41±809.9	1.000**	0.000	15.50±5.0	1.000**	0.000
Hen's egg white (n=4)	32.50±45.4	869.55±552.0	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	-0.684	0.203
Soybean (n=4)	10.33±4.1	344.91±512.8	-0.800	0.200	20.24±3.0	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

*p<0.05
**p<0.00

Table 8. Correlation between SPT on aeroallergen and total IgE, as and SPT on aeroallergenand serum 25(OH)D level

SPT for aeroallergens	**Total IgE vs SPT**		**Vitamin D vs Prick test**	
	***rho**	**p value**	***rho**	**p value**
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<0.00

Table 9. Correlation between SPT on food allergen and total IgE, as and SPT on food allergen and 25(OH)D level

SPT for food allergens	Total IgE vs SPT		Vitamin D vs SPT	
	*rho	p value	*rho	p value
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

