

Is vitamin D insufficiency to blame for recurrent wheezing?

Soner Demirel, MD, Sukru Nail Guner, MD, Mehmet Halil Celiksoy, MD and Recep Sancak, MD

Background: Vitamin D (VitD) and its metabolites play important roles in the regulation of the respiratory and immune systems. The aim of this study was to examine serum 25(OH) vitamin D [25(OH)D] levels and VitD deficiency on the development of wheezing and clinical features.

Methods: This study was a prospective cross-sectional survey that included a total of 70 infants being followed in the Pediatric Immunology and Allergy Unit at Ondokuz Mayıs University. Forty of these infants (patient group), ranging in age from 1 to 3 years, had been diagnosed as wheezy infants; 30 were age-and-gender matched healthy infants (control group). Prior to the study, blood samples were taken from both groups to determine their serum VitD, blood eosinophil, and serum immunoglobulin E (IgE) levels.

Results: The duration of breastfeeding was similar for both groups. The serum 25(OH)D levels of the patient group

were significantly lower than those of the control group. Although there was a negative relationship between 25(OH)D level and IgE_(log10) values for the wheezy infants with VitD deficiency, the control group had a negative relationship between VitD level and IgE_(log10).

Conclusion: Serum 25(OH)D levels must be evaluated when following wheezy infants, and those with deficiency must be treated with VitD. © 2014 ARS-AAOA, LLC.

Key Words:

asthma; allergens; therapeutics; vitamin D; 25(OH)D

How to Cite this Article:

Demirel S, Guner SN, Celiksoy MH, Sancak R. Is vitamin D insufficiency to blame for recurrent wheezing? *Int Forum Allergy Rhinol.* 2014;4:980-985.

Vitamin D (VitD) is a secosteroid obtained either through endogenous production in the skin with exposure to ultraviolet (UV) B radiation or from dietary sources. Vitamin D acts as a hormone and is well-known for its role in calcium and phosphorus homeostasis and skeletal health.

The frequency of asthma increases away from the equatorial region, which suggests that a relationship may exist between VitD and asthma.¹ Experimental and clinical studies have shown that VitD might have positive effects on the regulation of the immune system, lung development, and response to asthma treatment.²⁻⁶ Several studies have indicated that VitD deficiency might lead to an increase in the frequency of asthma and wheezing attacks, thus requiring more medications. At the same time, VitD deficiency

could protect children against viral infections and decrease asthma exacerbation.^{7,8} VitD taken during pregnancy was shown to enhance lung development in infants and have a protective effect on the development of wheezing and asthma.⁹⁻¹¹

Two contradictory hypotheses have been suggested on the relationship between VitD, asthma, and allergy. Wjst¹² suggested that VitD administration was responsible for the worldwide increase in allergic diseases, which was due to the fact that VitD caused T helper 2 (Th-2) response to the fore. VitD was associated with a dose-dependent reduction in the transcription of Th-1 cytokines, such as interleukin 2 (IL-2), granulocyte-macrophage colony-stimulating factor, and interferon gamma, as well as with an increased expression of the Th-2 cytokines IL-4, IL-5, and IL-10 in adult peripheral blood cell cultures.¹¹⁻¹³ On the other hand, Litonjua and Weiss¹ asserted that the increase in allergic diseases was associated with the prevalence of VitD deficiency in Western countries and the responsible mechanism might be related to the effect of VitD on T regulatory cells.^{14,15}

Children with asthma are expected to spend more time indoors than healthy children. Particularly, families of the children with frequent attacks in our patient group tended to keep their children indoors in order to protect them from outdoor stimuli. Sunlight is the most important source for

Division of Pediatric Allergy and Clinical Immunology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Correspondence to: Sukru Nail Guner, MD, Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Clinical Immunology, Beysehir Yolu, 42080, Konya, Turkey; e-mail: gunersukru@hotmail.com

Funding sources for the study: Project no. PYO.TIP.1904.10.047 from Ondokuz Mayıs University.
Potential conflict of interest: None provided.

Received: 4 February 2014; Revised: 4 June 2014; Accepted: 8 July 2014
DOI: 10.1002/alr.21401
View this article online at wileyonlinelibrary.com.

VitD synthesis, and increased time indoors decreases exposure to sunlight, leading to deficient VitD synthesis. In light of these possibilities, the question “Does VitD deficiency lead to asthma attacks or does asthma lead to VitD deficiency?” needs to be considered. In this study, we examined VitD levels in infants who were brought to us because of wheezing, and we evaluated low VitD levels in relation to the severity of illness.

Patients and methods

Forty-five infants, ranging in age from 1 to 3 years, with 3 or more troublesome episodes of physician-diagnosed wheezing and at least one direct relative (parent or sibling) with physician-diagnosed asthma were recruited from our outpatient clinic in the division of Pediatric Immunology and Allergy, Faculty of Medicine, Ondokuz Mayıs University. Thirty-five age-and-gender matched healthy children were randomly selected as a control group from the Unit of Social Pediatrics. The diagnosis, severity, and control level of wheezing were assessed in compliance with The Global Initiative for Asthma (GINA) criteria.¹⁶ Approval was granted by the Ondokuz Mayıs University Ethics Committee of Medical Research (decision no. 2010/87 dated 26.08.2010).

The inclusion criteria for the patient group consisted of the following: living in Samsun; full term with birth weight appropriate for gestational age; no treatment regarding gastroesophageal reflux; no instance of attack in the last 1 month; no hospitalization due to a severe wheezing attack in the last 3 months; no instance of any infection that happened in the last 15 days; no infection that concerned any system during the study period (1 month); and percentiles 10 to 90 for stature-for-weight and body mass index (BMI) measurements. Infants in the control group were matched by age and gender; had no instance of chronic disease or chest deformity; no diagnosed asthma, allergic bronchitis, bronchial hyperactivity, atopic dermatitis, allergic rhinitis, or chronic urticaria; no food or drug allergy; no diagnosed liver disease; no instances of lower respiratory tract infection in the last 3 months; no instance of infection in the last 15 days; and no long-term supportive VitD treatment in the last 3 months.

A 49-item questionnaire was completed by the same doctor (S.D.) after face-to-face interviews with the patients. The questionnaire examined the patients' physical characteristics; address and birth details; the family's socioeconomic conditions; details about their living arrangements; presence of a smoking habit in the family; the presence of asthma, allergic rhinitis, and eczema; the frequency of coughing and wheezing, night coughing, coughing with exercise, hospitalization, emergency consultation, school absenteeism; and the medicines being used. All the data were recorded on the questionnaire form. Informed consent and written approvals were provided by their parents.

The diagnostic periods and clinical findings of the treatments that they received were recorded. Serum samples taken from the patient and control groups for determin-

ing 25(OH)D were stored at -20°C . The samples were processed within 5 days by an isocratic high-performance liquid chromatography (HPLC) system equipped with a UV detector at the biochemistry laboratory.

Study calendar

The patients suitable for the study were determined by examining the data in the record database of the Pediatric Immunology and Allergy Unit between December 2010 and November 2011 and then were randomly selected and telephoned to be informed about the study. The voluntary patients were given appointments and invited to the hospital during June 2011. Blood samples were taken from the groups for determining serum 25(OH)D, blood eosinophil, and serum immunoglobulin E (IgE) levels. Forty-five of the 90 children that were in conformity with the inclusion criteria were selected at random. Of these, 5 patients were excluded from the patient group: 3 were unwilling to undergo skin-prick testing and the remaining 2 developed respiratory tract infection during the study. Five infants were also omitted from the control group: 3 because they performed improperly on skin-prick testing and 2 because of a positive Dep 1 detected with the skin prick. One infant in the patient group and 2 infants in the control group were excluded from the study because they developed respiratory tract infection. Consequently, the study continued with 40 infants in the patient group and 30 in the control group.

All of the infants received a detailed physical examination during the first and second visits, and the findings were recorded. Any patients with infectious findings or with symptoms of active asthma were excluded from the study.

Examination of blood samples

Serum IgE levels were measured in IU/mL with a Siemens BN II nephelometerTM and an N Latex IgE Mono kit, Erlangen, Germany. An Agilent 1100 series (UV detector 265 nm) HPLC, Waldbronn, Germany was used for determining the VitD serum levels. Blood samples were taken into 2.5 cc anticoagulant-containing tubes for a complete blood count (CBC), which was performed with a Coulter LH 750 in the Pediatric Hematology Laboratory of Ondokuz Mayıs University. VitD deficiency was defined as 25(OH)D ≤ 20 ng/mL, VitD insufficiency as 25(OH)D 20–30 ng/mL, and normal (VitD sufficiency) as 25(OH)D > 30 ng/mL.

Skin-prick testing

Skin-prick testing was performed on all infants whose families had given approval. The testing was conducted by Laboratoire des Stallergenes (Fresnes Cedex, France) with food allergens (milk, hen's egg, soy, wheat, peanut, fish, and hazelnut), *Dermatophagoides farinea* (DF), *D. pteronyssinus* (DP), grass-pollen mixture (*Chenopodium*, *Artemisia*, *Plantago*, *Salsola kali*), tree-pollen mixture (*Ulmus*, *Quercus*, *Populus*, *Salix*), weed mixture (poa mix, *C. dactylon*, *P. pratensis*, *D. glomerata*, *A. sativa*, *Festuca*, *Aspergillus fumigatus*,

Alternaria alternata), cat and dog hair, and cockroaches. If the weal diameter was 3 mm or more in the presence of negative control, the testing was accepted as positive.

Examination of the data and statistical analysis

The NCSS PASS (Power Analysis and Sample Size) 2008 package program was used to detect the power of the study. With 40 and 30 infants in the patient and control groups, respectively, the infants' prior data indicated that the failure rate among controls was 0.4. If the true failure rate for the patient group was 0.72, the null hypothesis that the failure rates for the study and control groups were equal with a probability (power) of 0.79 was rejected. The type I error probability associated with this null hypothesis test was 0.05. An uncorrected chi-square statistic was used to evaluate this null hypothesis.

The Statistical Package for the Social Sciences (SPSS) for Windows version 15.0 was used for examining the data. The Shapiro-Wilk test for normality was performed for comparing the general characteristics of the study and control groups by the test of Fisher's exact tests were used to compare the difference between the frequency rates of the categorical data. Numeric data that complied with normal distribution were given as mean $\pm$ standard deviation (SD), whereas those that did not comply with normal distribution were given as median (minimum–maximum). The Student *t* test or The Mann-Whitney *U* test was used to compare the difference of the continuous variables. For all results, a *p* value of less than 0.05 was accepted as significant, and the 95% confidence interval (CI) was determined.

Results

The patient group of 40 infants comprised 14 girls (35%) and 26 boys (65%), whereas the control group of infants comprised 10 girls (33.3%) and 20 boys (66.7%). Tables 1 and 2 show the demographic features of the patient and control groups. The duration of breastfeeding in the control group was longer than that in the patient group ($p = 0.004$). No statistical differences between the study and control groups were determined for gender, the family's educational level, the family's income level, presence of allergy among siblings, type of delivery, house structure and heating, smoking, number of people in the household, contact with pets, and sunlight in the child's room. There was no significant confounding factor linked to outdoor exposure habits for either group.

Serum IgE distribution was not normal, and so a logarithmic correction was made. No relationship was found between $\text{IgE}_{(\log_{10})}$ and 25(OH)D for the control group ($r = 0.14$; $p = 0.46$), but there was a negative relationship for the patient group ($r = -0.31$; $p = 0.04$) (Fig. 1). $\text{IgE}_{(\log_{10})}$ level in the patient group was significantly higher than that in the control group ($p < 0.001$) (Fig. 2), whereas serum 25(OH)D levels in the control group were significantly higher than those in the patient group ($p = 0.008$) (Table 2). In the control group, the ratio of 25(OH)D-

TABLE 1. Demographic characteristics of the patient and control groups

	Patient (n = 40)	Control (n = 30)	Total (n = 70)	<i>p</i> ^a
Gender, n (%)				1.0
Female	14 (35)	10 (33.3)	24 (34.3)	
Male	26 (65)	20 (66.7)	46 (65.7)	
Income level, n (%)				0.54
U.S.\$500–1000 p/m	8 (20)	7 (23.3)	15 (21.7)	
U.S.\$1000–1500 p/m	25 (62.5)	15 (50.0)	40 (56.6)	
>U.S.\$1500 p/m	7 (17.5)	8 (26.7)	15 (21.7)	
History of allergy, n (%)				
Parental	14 (35)	2 (6.2)	16 (22.8)	0.01
Siblings	12 (30)	2 (6.7)	14 (20)	0.03
Delivery, n (%)				0.58
Vaginal	15 (37.5)	17 (56.6)	32 (45.7)	
Cesarean	25 (62.5)	13 (43.4)	38 (54.3)	
Passive smoking, n (%)	22 (57.9)	14 (58.3)	8 (57.1)	1.0
Smoking in pregnancy, n (%)	1 (1.4)	1 (2.5)	0 (0)	1.0
Home heating, n (%)				1.0
Stove	31 (81.6)	20 (83.3)	11 (78.6)	
Radiator	7 (18.4)	4 (16.7)	3 (21.4)	
Pet contact, n (%)	10 (14.3)	10 (25.0)	0 (0)	1.0
Age, months, mean $\pm$ SD	23.3 $\pm$ 7.0	24.4 $\pm$ 5.9	24.9 $\pm$ 6.5	0.56
Weight, kg, mean $\pm$ SD	18.6 $\pm$ 4.4	16.6 $\pm$ 2.9	17.5 $\pm$ 3.6	0.11
Height, cm, mean $\pm$ SD	88.2 $\pm$ 8.2	86.4 $\pm$ 6.6	87.5 $\pm$ 7.5	0.42
BMI, %, mean $\pm$ SD	23.1 $\pm$ 3.5	22 $\pm$ 2.8	22.7 $\pm$ 3.2	0.20
Birth weight, g, mean $\pm$ SD	3250 $\pm$ 390	3150 $\pm$ 450	3200 $\pm$ 420	0.33
Breastfeeding, months, mean $\pm$ SD	5.7 $\pm$ 3.9	8.9 $\pm$ 6.9	9.4 $\pm$ 3.6	0.004
Persons in the household, n, mean $\pm$ SD	4.9 $\pm$ 0.9	4.9 $\pm$ 1.1	4.9 $\pm$ 1.0	0.92

^aBold *p* values are significant.

BMI = body mass index [weight (kg)/height (m)²]; SD = standard deviation.

deficient and 25(OH)D-insufficient infants was significantly lower than that of the patient group ($p = 0.002$) (Table 3). The rate of VitD insufficiency was statistically higher in the patient group ($p = 0.008$; odds ratio [OR] 4.6; 95% CI, 1.5 to 14.1) after multinomial logistic regression was used to eliminate the impact of parental, siblings allergy, and the duration of breastfeeding. Positive skin-prick test results were detected for 15 (37.5%) infants in the patient group and 2 (6.7%) infants in the control group ($p = 0.004$). In

TABLE 2. Comparison of the differences for serum vitamin D level and IgE levels of the patient and control groups*

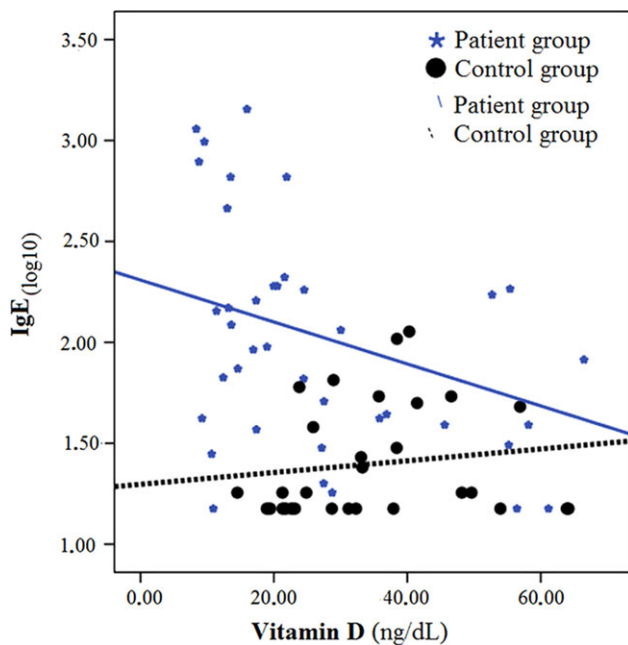
	Patient	Control	p
25(OH)D ^a (ng/mL)	27.16 ± 17.43	34.68 ± 13.55	0.008
	21.10 (8.35–66.48)	32.68 (14.51–64.15)	
IgE ^b	54.5 ± 374.7	31.7 ± 26.3	<0.001
	93.3 (15–1480)	18 (15–113)	
IgE _(log10)	2.03 ± 0.57	1.40 ± 0.28	<0.001
Eosinophils (/mm ³)	378.8 ± 251.5	222.3 ± 166.6	<0.001

*Values are mean ± SD and/or median (minimum–maximum). Bold values of p are significant.

^aSerum 25(OH) vitamin D level (ng/mL).

^bSerum IgE levels (IU/mL).

25(OH)D = 25(OH) vitamin D; IgE = immunoglobulin E; SD = standard deviation.

**FIGURE 1.** The correlation between serum 25(OH)D and IgE_(log10) levels in the patient and control groups. IgE = immunoglobulin E.

the patient group, 14 (48.3%) of the 29 VitD insufficiency patients had a positive skin-prick test, whereas this test was positive only for 1 (9.1%) of 11 normal VitD patients ($p = 0.03$).

Discussion

About 20% of infants experience at least 1 wheezing attack in the first year of life. This proportion may increase up to 40% in the first 3 years. In Turkey, wheezing was found to affect 15.1% of 46,813 infants surveyed.¹⁷ However, the relationship between major risk factors, such as viral infections, and allergic inflammation in airways that contribute to these attacks has not yet been clarified. The control of en-

vironmental factors that trigger asthma and the treatment of asthma-accompanying diseases will improve quality of life and contribute to the national economy. Asthma and VitD deficiency are common in many societies, and recent studies have shown that VitD deficiency may lead to an increase in the frequency of asthma and wheezing attacks and necessitate more medication.³

The experimental models that have discussed the VitD–asthma hypothesis have shown that the addition of VitD to mice with eosinophil inflammation decreases eosinophil recruitment and IL-5 level.¹⁸ Zosky et al.¹⁸ found that VitD deficiency in mice was significantly associated with decreased lung and tissue volumes and increased airway resistance. They proposed that VitD deficiency could increase the risk of reduced lung volume through the effects on lung tissue growth. Searing et al.² found that 47% of patients with asthma were deficient in serum VitD levels; they showed that there was an inverse relationship between VitD level and the consumed total steroid dose and IgE, and a positive relationship between forced expiratory volume in 1 second (FEV1) and the ratio of FEV1 to forced vital capacity [FVC] (FEV1/FVC). With the addition of dexamethasone (10 or 100 nmol/L) and 1,25(OH)₂D (10 nmol/L) to the culture media prepared from the patients' peripheral blood cells, the increase was more significant than mitogen-activated protein kinase phosphatase 1 and the administration of single-dose dexamethasone at IL-10 messenger RNA (mRNA).

In light of the studies on maternal and neonatal 25(OH)D levels, a low 25(OH)D level can be expected to enhance the frequency and effects of respiratory tract infection.¹⁰ While planning our study, we considered questioning the mothers on their nutritional habits during maternity. Taking the duration of breastfeeding and baby food use into consideration, we found that the duration of breastfeeding in the patient group was shorter than that in the control group, whereas the duration of baby food use was longer in the patient group. Breast milk is known to have a protective effect against asthma.¹⁹ However, what this protective effect derives from remains unclear. It reduces the frequency of viral bronchiolitis and pneumonia caused by asthma-related viruses, such as human respiratory syncytial virus (RSV) and the influenza virus,^{20–22} and builds a barrier against pathogenic microorganisms in intestinal flora due to its probiotic effect.¹⁹ Oddy et al.²³ showed that infants who were breastfed for less than 4 months were more vulnerable to asthma development. Although some studies suggest that breastfeeding for more than 6 months is protective against temporary early wheezing, it is also accepted as a risk factor for late-starting wheezing. In our study, we found that the duration of breastfeeding in the patient group was 8 months shorter than the control group.

Various studies have suggested that nutritional habits during infancy may affect the future asthma frequency in infants. Whether VitD taken during infancy will lead to or protect against asthma is an unanswered question. A significant inverse relationship between antenatal dietary

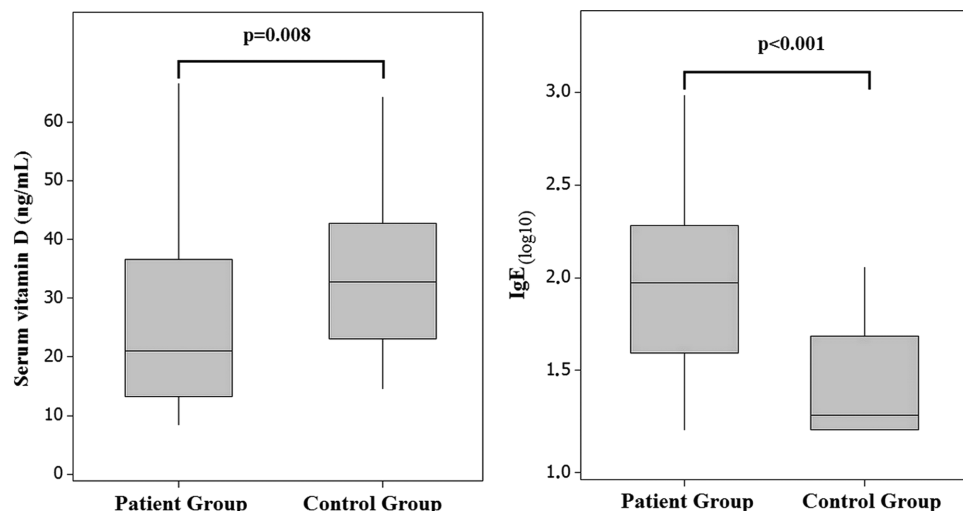


FIGURE 2. IgE_(log10) and serum 25(OH)D in the patient and control groups. (A logarithmic correction was made for IgE). IgE = immunoglobulin E.

TABLE 3. Comparison of the ratio for serum 25(OH)D status of the patient and control groups

	Patient (n = 40)	Control (n = 30)	p ^a
25(OH)D, n (%) ^b			0.002
≤20 ng/mL	19 (47.5)	3 (10.0)	
20–30 ng/mL	10 (25.0)	9 (30.0)	
≥30 mg/mL	11 (27.5)	18 (60.0)	

^aBold p values are significant.

^bSerum 25(OH) vitamin D level.

25(OH)D = 25(OH) vitamin D.

and supplemental VitD intake and the risk of wheeze symptoms has been reported. For each 100 IU/day incremental increase in VitD intake, there is a 10% decreased risk of wheezing and 13% decreased risk of recurrent wheezing at 2 years.^{9,24,25} Adequate VitD levels at birth might prevent early life viral infections; however, VitD status on subsequent wheezing episodes remains unclear.²⁶ Camargo et al.²⁷ reported a linear relationship between 25(OH)D with wheezing at 15 months of age through 5 years and respiratory tract infection at 3 months; no relationship was noted between 25(OH)D and asthma or sensitization. In Turkey, despite supplementation with 400 IU of VitD daily, the rate of VitD deficiency was high (56%) in 4-month-old breastfed infants.²⁸ Direct sun exposure is the most important source for VitD synthesis; therefore, remaining indoors may decrease direct sun exposure and this will cause deficient VitD synthesis.

Some researchers have suggested that enriching food with VitD may provoke an increase in asthma prevalence.¹⁰ Sears et al.²⁹ reported that breast milk had no protective effect against asthma and atopy and that it could even increase the risk. Serum 25(OH)D levels of breastfeeding mothers in Turkish society are generally low.³⁰ In our country, infants are given 400 IU VitD prophylaxis from birth.

VitD intake in infants is more or less 80% to 90% during the first month; however, it decreases to 60% after the sixth month.³¹

The duration of breastfeeding in the patient group was 8 months shorter than that in the control group. However, the duration of baby food use was 4 months longer in the patient group, although the difference was statistically insignificant. Baby foods in the Turkish market are enriched with VitD. When a short duration of breastfeeding and VitD-enriched baby food are taken into account, the patient group could have received more VitD in infancy, leading to a data bias and the possibility that high VitD intake could lead to increased wheezing frequency in infancy. However, without the ability to study retrospective feeding habits and the mothers' VitD levels, this remains speculative. In addition, we did not encounter any published study on the relationship between breast milk, VitD, and asthma. Future surveys of birth cohorts should examine this relationship.

There was a positive linear relationship between 25(OH)D and IgE in the patient group. Brehm et al.³² found a negative linear relationship between 25(OH)D and IgE and eosinophil levels and reported that each 10-ng/mL increase in 25(OH)D resulted in a 25-IU/mL decrease in IgE levels for asthmatic infants. On the other hand, Hyppönen et al.³³ reported a nonlinear (U-shaped association) relationship between 25(OH)D and IgE levels in adults and increasing IgE values at levels of 25(OH)D below 25 nmol/L and above 135 nmol/L. Matheu et al.³⁴ speculated that VitD could influence the development of a sustained T cell helper 2 (TH2) response, and this immune dysregulation may encourage metabolism to respond toward Th-2, leading to an allergic disease tendency in a murine model. On the other hand, Taher et al.³⁵ demonstrated the presence of 1,25(OH)D by its reduction of IL-5 and IL-13 in bronchoalveolar lavage fluid, inhibition of serum ovalbumine (OVA)-specific IgE levels, and augmentation of IL-10 in lung tissue in a mouse model. Particularly, as the regulatory effect of VitD on the immune system in healthy individuals

does decrease, there will be an increase in IgE synthesis. We found a negative linear relationship between 25(OH)D and $\text{IgE}_{(\log 10)}$ in the control group although this was statistically insignificant. This statistical insignificance might be due to the insufficient number of controls. Hyppönen et al.³³ noticed an increase in IgE synthesis at both low and high levels of 25(OH)D, which implies that especially abnormal VitD may lead to immune dysregulation. Our results that VitD and IgE in the patient group have a positive correlation whereas the relationship is negative in the control group demonstrates that VitD and IgE have a strict interaction with each other. Studies with larger control groups with

similar features should comprehensively examine IgE and VitD interactions.

Conclusion

We found that VitD is lower in wheezy infants than in healthy controls. All infants with recurrent wheezing should be scanned for VitD insufficiency. The duration of VitD supplementation could be extended, especially for infants who had been diagnosed with wheezing during the first year of their life. Further randomized controlled trials should be carried out to confirm our findings. 

References

1. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol*. 2007;120:1031–1035.
2. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol*. 2010;125:995–1000.
3. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med*. 2010;181:699–704.
4. Brehm JM, Acosta-Pérez E, Klei L, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. *Am J Respir Crit Care Med*. 2012;186:140–146.
5. Brehm JM, Schuemann B, Fuhlbrigge AL, et al.; Childhood Asthma Management Program Research Group. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126:52–58.
6. Paul G, Brehm JM, Alcorn JF, Holguín F, Aujla SJ, Celedón JC. Vitamin D and asthma. *Am J Respir Crit Care Med*. 2012;185:124–132.
7. Mansbach JM, Ginde AA, Camargo CA Jr. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: do children need more vitamin D? *Pediatrics*. 2009;124:1404–1410.
8. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol*. 2011;127:1294–1296.
9. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr*. 2007;85:788–795.
10. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007;85:853–859.
11. Pichler J, Gerstmayr M, Szépfalusi Z, Urbanek R, Peterlik M, Willheim M. 1 α ,25(OH) $_2$ D $_3$ inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. *Pediatr Res*. 2002;52:12–18.
12. Wjst M. Introduction of oral vitamin D supplementation and the rise of the allergy pandemic. *Allergy Asthma Clin Immunol*. 2009;5:8.
13. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol Nutr Food Res*. 2011;55:96–108.
14. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Curr Opin Allergy Clin Immunol*. 2009;9:202–207.
15. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II: Lower respiratory tract illnesses in the first year of life. *Am Epidemiol*. 1989;129:1232–1246.
16. van Weel C, Bateman ED, Bousquet J, et al. Asthma management pocket reference 2008. *Allergy*. 2008;63:997–1004.
17. Türktaş I, Selçuk ZT, Kalyoncu AF. Prevalence of asthma-associated symptoms in Turkish children. *Türk J Pediatr*. 2001;43:1–11.
18. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. *Am J Respir Crit Care Med*. 2011;183:1336–1343.
19. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol*. 2005;115:1238–1248.
20. Bozzetto S, Carraro S, Giordano G, Boner A, Baraldi E. Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy*. 2012;67:10–17.
21. Kieninger E, Regamey N. Rhinoviruses: markers of, or causative for, recurrent wheeze and asthma? *Eur Respir J*. 2012;39:238–239.
22. Jartti T, Kuusipalo H, Vuorinen T, et al. Allergic sensitization is associated with rhinovirus-, but not other virus-, induced wheezing in children. *Pediatr Allergy Immunol*. 2010;21:1008–1014.
23. Odby WH, Peat JK, Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol*. 2002;110:65–67.
24. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Prospective study of maternal intake of vitamin D during pregnancy and risk of wheezing illness in children at age 2 years. *J Allergy Clin Immunol*. 2006;117:721–722.
25. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J*. 2010;35:1228–1234.
26. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Curr Opin Allergy Clin Immunol*. 2013;13:211–216.
27. Camargo CA Jr, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics*. 2011;127:e180–e187.
28. Halicioglu O, Sutcuoglu S, Koc F, Yildiz O, Akman SA, Aksit S. Vitamin D status of exclusively breast-fed 4-month-old infants supplemented during different seasons. *Pediatrics*. 2012;130:e921–e927.
29. Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet*. 2002;360:901–907.
30. Andiran N, Yordam N, Özön A. Risk factors for vitamin D deficiency in breast-fed newborns and their mothers. *Nutrition*. 2002;18:47–50.
31. Tıraş Ü, Dilli D, Dallar Y. Evaluation of children followed-up at the Well-Child Unit of Ankara Training and Research Hospital. *Erciyes Med J*. 2007;29:444–450.
32. Brehm JM, Celedón JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179:765–771.
33. Hyppönen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE- a significant but nonlinear relationship. *Allergy*. 2009;63:613–620.
34. Matheu V, Bäck O, Mondoc E, Issazadeh-Navikas S. Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J Allergy Clin Immunol*. 2003;112:585–592.
35. Taher YA, van Esch BC, Hofman GA, Henricks PA, van Oosterhout AJ. 1 α ,25-dihydroxyvitamin D $_3$ potentiates the beneficial effects of allergen immunotherapy in a mouse model of allergic asthma: role for IL-10 and TGF- β . *J Immunol*. 2008;180:5211–5221.