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RESEARCH ARTICLE/ARAŞTIRMA

The Relationship Between Vitamin D Deficiency and Wheezing in Young Children; A Randomized Study

Küçük Çocuklarda D Vitamini Eksikliği ile Vizing Arasındaki İlişki; Randomize Çalışma

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ABSTRACT

Objective: Vitamin D (VD) plays a critical role in immunological processes and studies have been conducted to investigate its role in the development of several allergic and infectious diseases. The aim of this study was to determine the factors that affect the 25(OH)D level in children, and also to assess the relationship between VD and wheezing, allergy, and infection.

Materials and Methods: Sixty-four children between 18-24 months of age were included in this study. At the beginning and at the end of the study, a physical examination was performed, blood samples were taken, and parents completed the questionnaire. Half of the children had been recommended at the first visit to take daily 400 units of VD. Follow-up visits were scheduled at the 3rd, 6th and 12th months of the study.

Results: The mean age of the infants participating in the study was 20.3±1.5 months. 46.9% (n=30) of the infants were female and 53.1% (n=34) were male. While the 25(OH)D level was 29.8±10.8 ng/ml at the beginning of the study, it was 26.5±10.3 ng/ml (p=0.017) at the end of the study. The percentage of patients with sufficient 25 (OH) D levels was 48.4% (n = 31) at the beginning of the study and 29.7% (n = 19) at the end of the study (p=0.010). A statistically significant relationship was determined between VD intake and serum 25(OH)D level. At the beginning and at the end of the study, the 25(OH)D level was statistically inversely correlated with wheezing. Low 25(OH)D levels were also found to be a risk factor for the development of wheezing. No statistically significant relationship was determined between the serum 25(OH)D level and allergic and respiratory outcomes.

Conclusion: When the factors which effect 25(OH)D level were examined, it was only associated with VD supplementation. VD deficiency showed a significant relationship with wheezing development, regardless of supplementation of VD.

ÖZ

Giriş: D vitamini (VD) immünolojik süreçlerde kritik bir rol oynamaktadır ve çeşitli allerjik ve enfeksiyöz hastalıkların gelişimindeki rolünü araştırmak için çalışmalar yürütülmektedir. Çalışmanın amacı, çocuklarda 25(OH)D düzeyini etkileyen faktörleri belirlemek ve VD ile vizing, allerji ve enfeksiyonlar arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Çalışmaya, 18-24 ay arasında 64 çocuk dahil edildi. Çalışmanın başında ve sonunda fizik muayene yapıldı, kan örnekleri alındı ve aileler bir anket doldurdu. İlk vizitte çocukların yarısına 400 ünite VD desteği önerildi. Çalışmanın 3., 6. ve 12. aylarında takip vizitleri planlandı.

Bulgular: Çalışmaya alınan çocukların ortalama yaşı 20.3±1.5 ay idi. %46.9'u (n=30) kız, %53.1'i (n=34) erkekti. Çalışmanın başlangıcında ortalama 25(OH)D düzeyi 29.8±10.8 ng/ml iken, çalışmanın sonunda ortalama 25(OH)D düzeyi 26.5±10.3ng/ml idi. Çalışmanın başlangıcında %48.4'ünün (n=31) 25(OH)D düzeyi yeterliyken, çalışmanın sonunda %29.7'sinin (n=19) 25(OH)D düzeyi yeterliydi. Vitamin D alımı ile 25(OH)D düzeyi arasında istatistiksel olarak anlamlı ilişki saptandı. Çalışmanın başında ve sonunda, 25(OH)D seviyesi ile vizing arasında istatistiksel ters ilişki tespit edildi. Düşük 25(OH)D seviyelerinin vizing gelişiminde bir risk faktörü olduğu da görüldü. Serum 25(OH)D seviyesi ile allerjik ve solunumsal bulgular arasında istatistiksel olarak anlamlı bir ilişki saptanmadı.

Sonuç: 25(OH)D düzeyini etkileyen faktörler incelendiğinde, sadece VD takviyesi ile ilişkili olduğu saptandı. VD eksikliğinin, VD desteği ile ilişkisiz olarak vizing gelişimiyle ilişkili olduğu gözlendi.

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INTRODUCTION

A significant increase in the frequency of allergic diseases throughout the whole world has been noticed in the last few decades (1). Although the strong genetic relationship in the development of allergic diseases is known, environmental factors (exposure to microbial organisms and air pollution) linked to the hygiene hypothesis and changes in life style are also influential in this increase (2). However, these notions cannot individually explain the increase in these diseases. Some studies have evaluated the significance of nutritional status in the development of allergic diseases (3).

Simultaneously with the allergy epidemic taking place during this period, the use of vitamin D (VD) all over the world brings up the question 'is there a connection between allergic diseases and VD supplements' (4,5). Various birth cohort studies have suggested that VD deficiency could be one of the reasons for this global allergic disease epidemic (6,7). Although it is generally believed that VD has a protective effect from allergic diseases, at the same time its effects as both increaser and inhibitor of Th2 cells, which play an important role in the pathogenesis of these diseases, are being reported (8,9).

While being a strong regulator of the adaptive immune system, it also plays a role in stimulating the innate immune response against infections (4). It is also reported that VD supplementation of children in the winter months decreases the frequency of respiratory tract infections (10).

Age, gender, dark colored skin, dressing style, and VD supplements in food are some of the factors that affect the serum 25-hydroxyvitamin D (25(OH)D) level. In our country, the most frequent reasons for VD deficiency are maternal VD deficiency and insufficient intake through food (unsupplemented breastfed babies) (11). Although our country is located in a warm climate zone, VD deficiency rates of up to 80% are reported, especially in adolescents (12,13).

The primary objective of this study was to evaluate whether 25(OH)D levels are associated with the risk of wheezing, allergy, and infectious diseases in early childhood. The secondary objective was to determine the factors that affect the 25(OH)D levels of these children.

MATERIALS and METHODS

Study Design and Participants

This prospective study included 78 patients who were admitted to the Pediatric Allergy and Immunology outpatient clinic of Çukurova University School of Medicine. Fourteen children were excluded from the study by investigators because of incorrect phone number, no response and moving of a family to another residence, leaving a total of sixty-four children to be evaluated. The study protocol was approved by the university's Human Research Ethics Committee (TF2013LTP5). Written informed consent was obtained from the parents of each infant that was enrolled.

Exclusion criteria were history of staying in the newborn intensive care unit due to respiratory distress syndrome, history of intubation or assisted ventilation during the neonatal period, congenital heart disease, immunodeficiency, neurologic or metabolic diseases, and malnutrition.

Multiple evaluations were done during follow-up (Figure 1). Two types of questionnaires related to the infants were administered during the study: baseline (completed by the mother at first visit) and follow-up (multiple time points; Figure 1). The baseline questionnaire provided information on birth data (gender, weight, gestational age at birth), the number of respiratory tract infections, how many wheezing attacks they had, the child's dietary intake of VD supplementation, mother's dressing style (covered/uncovered), other factors that may affect the 25(OH)D level (sun exposure, diarrhea, housing, skin pigmentation), physician-diagnosed wheezing and allergic diseases [allergic rhinitis (AR), atopic dermatitis (AD), food allergy (FA), drug allergy, urticaria in children and the family, and the family's demographic data. Follow-up visits were scheduled at the 3rd, 6th and 12th months of the study. 3rd and 6th month visits were performed as phone

interviews. At each visit, the mother completed a follow-up questionnaire. This instrument gathered data on the child's dietary as well as other VD supplements, respiratory tract infections, asthma medications, any signs and symptoms of allergic disease that the mother had observed in her child, wheezing, and doctor diagnosed allergic diseases. The infants' 25(OH)D level was examined from their peripheral blood and the atopic status was evaluated at the beginning and end of the study. Half of the infants were recommended to take 400 units VD daily at the first visit. In addition, the skin prick test (SPT) and food specific (s) immunoglobulin (Ig) E level measurements were carried out when there was any suspicion of allergic disease from the history and/or physical examination.

25(OH)D Testing

Each sample was centrifuged at 5.000 rpm for 10 minutes, and the serum was separated and stored at -40°C until it was analyzed. EDTA-plasma samples were used for 25(OH)D determination with high-performance liquid chromatography at the Çukurova University Biochemistry Laboratory (Spectra System AS3000, Thermo Separation Products, Thermo). Three different cut off levels were used in the study to categorize 25(OH)D concentrations. A serum 25 (OH)D level <30 ng/ml was accepted as insufficient and ≥30 ng/ml as sufficient. 25(OH)D levels >150 ng/ml were considered as VD intoxication (14).

Food s-IgE Testing

Each infant's serum was screened for the six most common food allergens (fx5) using an ImmunoCAP® kit. If this test was positive, the serum was analyzed for s-IgE antibodies for cow's milk, hen's eggs, soy, wheat, fish, and peanuts. Values greater than 0.35 kU/L were accepted as positive.

Skin Prick Test

A SPT was performed using commercially available extracts of major inhalant allergens (Allergopharma, Germany): tree mixture (alder, hazel, poplar, elm, sallow), mold mixture (*Alternaria alternata, Cladosporium herparum, Fusarium moniliforme*), pollen mixture (grass,

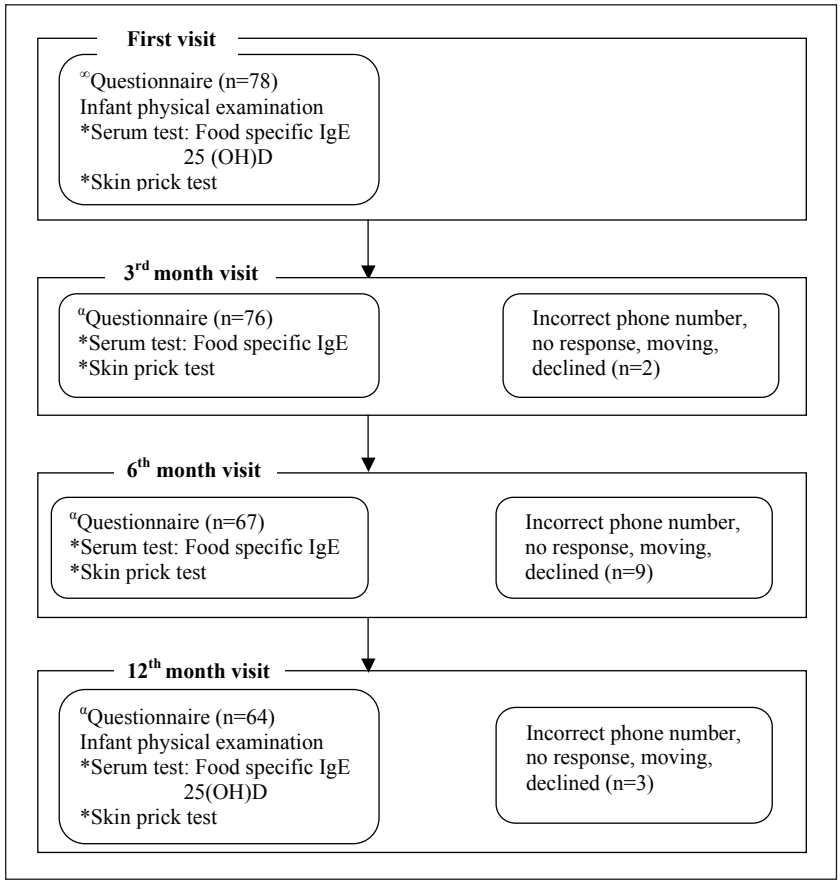

Figure 1. The scheduled follow-up assessments during the study.
IgE: Immunoglobulin E,
∞: Baseline questionnaire,
α: Follow-up questionnaire
* Physical examination, SPT and specific IgE level measurements were performed when there was any suspicion of allergic disease.

barley, oat, rye, wheat, velvet, orchard, rye, timothy, blue grass, and meadow fescue), *Dermatophagoides pteronyssinus* and *farinea*, and food allergens (milk, egg, wheat, peanut, and banana). In addition, when there was any suspicion of food allergen by fx5 (e.g. soy, fish) SPT was carried out with these allergens. The SPTs were performed using standard methods, and the result for each allergen was defined as positive if the mean wheal diameter was ≥3 mm (14).

Definitions

In our prospective study, a history of wheezing was considered to have occurred when receiving a positive reply to the question: "has your child previously had physician-diagnosed wheezing (general pediatricians and pediatric allergists) (15). The asthma medication question was "has your child used any inhaled medicines such as an inhaler or nebulizer for breathing problems?". Upper and lower respiratory symptoms were questioned and evaluated according to the modified Johnston scoring method (16). Wheezing developing without these symptoms and the need to take asthma medication were considered as bronchospasm that developed due to non-infectious reasons. Information on AD outcomes was obtained from the questionnaires completed by the parents and confirmed by the clinician in our clinic and/or another pediatrician/dermatologist. Atopic dermatitis was diagnosed using the simplified criteria established by Williams (17). Infants with history of skin reaction or respiratory and/or gastrointestinal system reaction after a specific food intake, those with food s-IgE ≥0.35 kU/L, and those with a positive SPT were further evaluated with an elimination diet and were then offered a food challenge. Food allergy was defined as a positive food challenge test (18). Presence of sneezing, or a runny or blocked nose when the child did not have a cold or the flu, was considered AR (19). Drug allergy was defined as the adverse effects that clinically resemble allergic reactions (20).

The VD supplementation of the infant was evaluated with the question: "has your child taken any multivitamins or single VD product until today?" In Turkey, both infants' multivitamins and single product VD supplements generally contain a VD dose of 400 IU. Mothers' covered dressing style was defined as completely covering head, legs and arms, but not hands and face. However uncovered dressing style was defined as head, arms and legs uncovered. Mothers were asked whether their infant was exposed to the sun, or had outdoor activity between 10:00 AM and 4:00 PM and whether they used sun protection during this time. The duration of daily exposure to the sun was considered without the use of sun protection, and counted as an hour per day on most days of the previous month.

Statistical Analysis

Statistical analysis was performed using the statistical package *SPSS software* (Version 17.0, SPSS Inc., Chicago, IL, USA). If the continuous variables were normal, they were described as the mean ± standard deviation in Kolmogorov-Smirnov test or Shapiro-Wilk (n<30)), and as the median if the continuous variables were not normal. Comparisons between groups were applied using the Chi-square test. A multiple regression analysis was used to find out associations between VD and other measurements. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Study Population

Of the 78 potential participants, 64 infants (30 females, 34 males) were ultimately enrolled. The main reasons for declining to participate were incorrect phone numbers, family moving, serious illness and poor parental understanding. The age average of the infants who were studied was 20.3±1.5 months.

Factors Affecting the Serum 25(OH)D Levels at the Beginning of the Study

At the baseline of the study, 56.2% (n=36) of the infants had taken VD (400 U/day) for 6 months or less, 43.8% (n=28) of the infants had taken VD (400 U/day) for more than 6 months. It was seen in our study that the gender, birth weight, natal specifications such as feeding conditions, housing conditions of the infant, the VD supplementation and mother's factors did not affect the serum 25(OH)D level statistically.

It was determined that infant's sun exposure was related to the serum 25(OH)D level (Table I).

The 25(OH)D Level and Wheezing, Allergic Diseases and Infection Relation at the Beginning of the Study

At the baseline of the study the 25(OH)D level was: insufficient in 51.6% (n=33) and sufficient in 48.4% (n=31) of the infants. The average of the infants' 25(OH)D level was 29.8 ±10.8 ng/ml. No VD intoxication was determined in any of the infants.

Table I. Factors affecting the 25(OH)D level at the beginning of the study

Characteristics	25(OH)D level (ng/ml)		*p*
	<30	≥30	
Gender			
Male	17 (51.5)	13 (41.9)	0.465
Female	16 (48.5)	18 (58.1)	
Gestational age			
≥ 38	28 (84.8)	23 (69.7)	0.359
<38	5 (15.2)	8 (30.3)	
Birth weight (gram)			
≥ 2500	28 (84.8)	26 (83.8)	0.999
<2500	5 (15.2)	5 (16.2)	
Sun exposure during pregnancy (hour/day)			
Did not sunbathe	5 (15.1)	1 (3.2)	0.551
0-1	22 (66.6)	22 (71)	
≥2	6 (18.3)	8 (25.8)	
Mother's skin type			
Fair	15 (45.5)	16 (51.5)	0.671
Medium fair	11 (33.3)	11 (35.5)	
Dark	7 (21.2)	4 (13)	
Mother's dressing style			
Covered	21 (63.6)	19 (61.3)	0.999
Uncovered	12 (36.4)	12 (38.7)	
Consumption of milk during pregnancy (ml/day)			
Yes	23 (69.7)	26 (83.8)	0.241
No	10 (30.3)	5 (16.2)	
The location of the house			
Gets sunlight	29 (87.8)	27 (87)	0.776
Does not get sunlight	4 (12.2)	4 (13)	
Infant's sun exposure (hour/day)			
0-1	14 (42.4)	11 (35.5)	**0.049**
1-2	17 (51.5)	11 (35.5)	
>2	2 (6.1)	9 (29)	
Total duration of breastfeeding			
>12 months	25 (75.7)	23 (74.2)	0.982
6-12 months	6 (18.1)	5 (16.1)	
<6 months	2 (6.2)	3 (9.7)	
Consumption of fish (serving/month)			
<1	23 (69.7)	20 (64.5)	0.791
≥1	10 (30.3)	11 (35.5)	
Infants skin type			
Fair	19 (57.5)	15 (48.3)	0.447
Medium fair	8 (24.2)	12 (38.7)	
Dark	6 (18.3)	4 (13)	
Number of diarrhea (/year)			
None	18 (54.6)	19 (61.3)	0.841
1	12 (36.4)	10 (32.2)	
≥2	3 (9)	2 (6.5)	

At the baseline of the study, statistical relationship was determined between the 25(OH)D level, wheezing and asthma medication use (Table II).

The infants' 25(OH)D, Wheezing, Allergy and Infection Data at the End of the Study

At the end of the study, the serum 25(OH)D level was sufficient in 29.7% (n=19) of the infants and insufficient in 70.3% (n=45). The average serum 25(OH)D level was 26.5±10.3. No VD intoxication was determined in any of the infants.

Throughout the study 51.6% (n=33) of the infants complied with the VD (400 unit/day) supplement suggestion for 6 months and/or shorter period, and 48.4% (n=31) complied with it for longer than 6 months. At the end of the study, while the serum 25(OH)D level of 48.4% (n=15) of the infants that took VD (400 unit/day) for longer than 6 months was sufficient, the serum 25(OH)D level of only 12.1% (n:4) of the infants that took VD (400 unit/day) for less than 6 months was sufficient (p=0.002).

At the end of the study, no statistically significant relationship was determined between VD intake and wheezing, allergic diseases, URTI, LRTI and asthma medication use (data not shown).

The Relationship Between Serum 25(OH)D Level and Wheezing, Allergic Diseases and Infection at the End of the Study

No statistically significant relationship was determined between serum 25(OH)D level and allergic and respiratory outcomes (URTI, LRTI, bronchospasm symptom during non-infectious period, asthma medication history) (Table III). However, wheezing occurrence was detected as statistically significantly higher in the group with insufficient 25 (OH)D level (Table IV). Furthermore, the low 25(OH)D vitamin level was detected as a risk factor for wheezing occurrence when evaluated with regression analysis (p=0.027) (data not shown).

Table II. Relation between 25(OH)D and wheezing, allergy and infection at the beginning of the study

	25(OH)D level (ng/ml)		*p*
	<30	≥30	
Wheezing			
None	8 (24.2)	11 (35.5)	**0.021**
1-3	9 (27.4)	15 (48.4)	
>3	16 (48.4)	5 (16.1)	
Bronchospasm (non-infectious period)			
No	30 (90.9)	31 (100)	0.238
Yes	3 (9.1)	0 (0)	
URTI			
None	1 (3)	2 (6.5)	0.316
1-3	7 (21.3)	11 (35.5)	
>3	25 (75.7)	18 (58)	
LRTI			
None	17 (51.5)	18 (58)	0.235
1-3	16 (48.5)	11 (35.5)	
>3	0	2 (6.5)	
Hospitalization due to infection			
No	22 (66.6)	22 (71)	0.790
Yes	11 (34.4)	9 (29)	
Asthma medication use			
None	18 (54.5)	24 (77.4)	**0.046**
1-3	11 (33.3)	6 (19.3)	
>3	4 (12.2)	1 (3.3)	
Allergic diseases			
No	23 (69.7)	27 (87)	0.132
Yes	10 (30.3)	4 (13)	

URTI: Upper respiratory tract infection, **LRTI:** Lower respiratory tract infection.

Table III. Relation between 25(OH)D level and wheezing, allergy and infection at the end of the study

	25(OH)D level (ng/ml)		*p*
	<30	≥30	
Wheezing			
None	15 (33.3)	12 (63.1)	0.081
1-3	20 (44.4)	4 (21)	
>3	10 (22.3)	3 (15.9)	
Bronchospasm (non-infectious period)			
No	43 (95.5)	18 (96.7)	0.613
Yes	2 (4.5)	1 (3.3)	
URTI			
None	7 (15.5)	3 (15.8)	0.742
1-3	21 (46.7)	7 (36.8)	
>3	17 (37.8)	9 (47.4)	
LRTI			
None	29 (64.4)	14 (73.7)	0.572
1-3	14 (31.1)	5 (26.3)	
>3	2 (4.5)	0 (0)	
Hospitalization due to infection			
No	41 (91.1)	19 (100)	0.437
Yes	4 (8.9)	0 (0)	
Asthma medication use			
None	28 (62.2)	13 (68.4)	0.652
1-3	9 (20)	2 (4.4)	
>3	8 (17.8)	4 (27.2)	
Allergic diseases			
No	30 (66.6)	17 (95.6)	0.070
Yes	15 (33.4)	2 (4.4)	

URTI: Upper respiratory tract infection, **LRTI:** Lower respiratory tract infection.

Table IV. Relation between 25(OH)D level and wheezing at the end of the study

	25(OH)D level (ng/ml)		*p*
	<30	≥30	
Wheezing			
No	15 (33.4)	12 (63.1)	**0.02**
Yes	30 (66.6)	7 (26.9)	

DISCUSSION

Vitamin D deficiency is a condition that is still being reported at quite high rates all over the world, including developed countries, and it can lead to serious health problems (21). In our study, it was detected that while duration of VD intake is the only factor affecting the serum VD level, insufficient serum VD level is a risk factor related to wheezing. At the same time, a statistically significant relationship was found between low VD level and wheezing.

The main two sources of VD are sunlight and the diet (22). Other factors that cause VD deficiency are obesity, dressing style, usage of sun blocks with high protection factor, and insufficient UVB rays during September - April in northern regions above 35 ° latitude (23). However, the most frequent reason for VD deficiency in our country is maternal VD deficiency and its insufficient intake through food (11).

At the beginning of our study, the 25(OH)D levels in 48.4% of the infants (n=31) were sufficient. Furthermore, 25(OH)D level was associated with infant's sun exposure (Table I). Although almost half of the infants took VD regularly for more than 6 months during the study, at the end of the study the rate of infants with sufficient 25(OH) D level decreased to 29.7%. Even though we detected at the end of our study that the serum 25(OH)D level is merely associated with VD intake, this result indicated that solely 400 U per day VD supplementation is not effective in providing a sufficient serum 25(OH)D level. This result suggests that exposure to sun and VD-rich diet are also

important in addition to VD supplementation in order to provide sufficient serum 25(OH)D levels during infancy.

There are many studies that focus on the relationship between VD, asthma and wheezing (23, 24-27). In a study where children with moderate to severe asthma were evaluated, the VD level was detected to be insufficient in 35% of the patients, and the ones with low level were found to have a higher frequency of applying to the Emergency Services due to asthma attacks during the four-year monitoring period (28). Vitamin D's role in innate immunity can explain the predisposition to asthma attacks and infections in susceptible individuals. Thus, it is suggested that VD can be effective on both asthma development and asthma attacks by causing a decrease in respiratory tract infection frequency (25). In the mice study by Zosky et al. (29) to indicate whether VD deficiency effects the lung structure and functions or not, the somatic development (weight, height), lung functions and lung structures of the pups of the mice in which VD deficiency was developed with dietary arrangements were studied. It was found that while vitamin D does not affect somatic development, it does decrease lung volume. The results of this study suggested that VD deficiency primarily causes function loss due to lung volume changes and it has been argued that it can explain the relationship between VD and obstructive lung diseases.

In our study, a statistically significant inverse relationship was detected between the 25(OH)D level, which was observed while the infants were taken into follow-up, together with wheezing occurrence and frequent asthma medication need. At the end of the study, no statistically significant relationship was found between the 25(OH)D level and respiratory outcomes. However, the wheezing occurrence in the group with insufficient 25(OH)D level was detected to have a statistically significantly higher rate. Furthermore, when evaluated with linear regression analysis, low 25(OH)D levels were detected as a risk factor for wheezing occurrence (data not shown).

Although contradictory results are being reported about the allergic diseases and VD relationship, it has been indicated that VD is effective on cytokine release of immune system cells. Although it is known that VD suppresses the proliferation of Th1 lymphocytes by suppressing the IL-12 production in the adaptive immune system, its effect on the Th2 lymphocytes is controversial. There are also studies that indicate VD increases Th2 lymphocytes by increasing IL-4, IL-5 and IL-13, or plays an inhibitor role (4). There are studies in the literature supporting either hypothesis. It has been indicated in the Finland Birth Cohort study that VD use in the first year (≥ 2000 IU/day) causes an increase in allergic rhinitis and atopy at the age of 31 (8). It was determined in the England Birth Cohort study that there was an increase in eczema at the 9th month and an increase in the asthma diagnosis at the 9th year of children of mothers with maternal VD level >30 ng/mL (10). However, there is no data about the 25 (OH)D level of the children in these studies. In our study, no relationship was detected between the serum 25 (OH) D level or VD intake and allergic diseases.

Studies that support VD's relation with respiratory tract infections are being reported. The relationship between VD deficiency and respiratory infections has gained speed with the frequent occurrence of respiratory infections in children with rickets (30-32). Epidemiologic studies indicate that there is a relationship between low VD level and frequency of upper and lower respiratory tract infections in children (10). In the prospective study of Camargo et al (25), it has been shown with 922 children who were followed for 5 years starting from birth that there is an inverse relationship between cord blood VD level with respiratory infection and childhood wheezing. Moreover, according to the results in this study it has been thought that the VD taken during pregnancy could help the immune system to develop during the in utero period and the first couple of months after birth. Nonetheless, in our study no statistically significant relationship was determined between serum 25(OH)D level and URTI, LRTI and hospitalization due to infection. All these variable results have suggested that allergic diseases, wheezing and asthma development could all be related to VD intake, the basal VD level, and in which period of life it was taken.

Some limitations should be considered while evaluating our study's results. The number of patients who participated in the study was low, and although there was close monitoring, compliance with the suggested VD intake was not at the required level. Conditions which could affect the VD level (dietary content, gestational and housing conditions) were evaluated with the subjective answers the families gave to the questionnaire. Furthermore, our results were not supported with molecular studies such as the genetic variants of the VD receptor which has an effect on 25(OH)D's function. However, with our study being a prospective study and due to frequent monitoring ranges,

we think that the negative effects of the memory factor on the questionnaires were very little.

CONCLUSIONS

In this study, a relationship between 25(OH)D and wheezing was detected. Still, to be able to find out vitamin D's effect on allergy and wheezing, advanced studies supported by genetic investigations and more patients are needed. It is thought that with these future studies, the period of life in which VD should be taken in order to prevent and control asthma and allergic diseases and its dosage and duration will be clarified.

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