Serum Vitamin D Levels Among Recurrently Wheezy Infants

Tekrarlayan Hışıltılı Solunumu Olan Bebeklerde Serum Vitamin D Düzeyleri

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ABSTRACT Objective: Epidemiologic studies have shown that low serum 25-hydroxyvitamin D (25(OH)D) levels are associated with increased risk of lower respiratory tract infections in young children. Almost all viral respiratory tract infections occur between November and March, months that also are associated with vitamin D deficiency. Vitamin D recently has been shown to have an important role in the immune regulation especially in innate immunity as well as production of antimicrobial peptides. In this study, we evaluated the relationship between serum 25(OH)D levels and recurrent respiratory tract infections with wheezing in young children. **Material and Methods:** Serum 25(OH)D levels were analysed in 60 wheezy infants, aged 6-36 months, with three or more viral wheezing episodes and 40 healthy controls at the same age. The study was done between November 2009 and March 2010, months that viral infection-associated wheezing episodes were common. Vitamin D levels were categorized into deficient (≤20 ng/mL), insufficient (21-29 ng/mL) and sufficient (≥30 ng/mL), based on previous recommendations. **Results:** The mean serum 25(OH)D concentration of wheezy infants (30.1±7.6 ng/mL) was lower than the healthy controls (33.9±9.8 ng/mL) (p=0.049). Vitamin D deficiency was found in 7/60 (12%) of wheezy infants and 2/40 (5%) of healthy controls.Vitamin D insufficiency frequency was 21/60 (35%) in wheezy infants and 13/40 (32%) in healthy controls. The differences between wheezy infants and controls were insignificant. Serum vitamin D level was significantly associated with age, duration of breastfeeding and maternal clothing in wheezy infants. **Conclusion:** Vitamin D insufficiency is prevalent among young children in our region. According to the previous studies supporting the role of vitamin D in innate immunity and antiviral defence, we suggest that it might be particularly important in wheezy children. Future investiagtions will demonstrate the exact role of vitamin D on respiratory tract infections and wheezing illnesses in young children.

Key Words: Vitamin D; respiratory tract infections; respiratory sounds

ÖZET Amaç: Epidemiyolojik çalışmalar, düşük serum 25(OH)D düzeylerinin küçük çocuklarda artmış alt solunum yolu enfeksiyonu riski ile ilişkili olduğunu göstermektedir. Viral solunum yolu enfeksiyonlarının sık görüldüğü Kasım-Mart ayları, aynı zamanda vitamin D eksikliğinin sık görüldüğü dönemdir. Vitamin D'nin immün regülasyondaki önemi, özellikle doğal immünite ve antimikrobiyal peptid üretimine etkisi, son yıllarda yapılan çalışmalarda gösterilmiştir. Çalışmamızda tekrarlayan hışıltı atakları ile başvuran hastalarımızın serum 25(OH)D düzeyleri değerlendirilerek hışıltı ile seyreden solunum yolu enfeksiyonları ile ilişkisi araştırıldı. **Gereç ve Yöntemler:** Çalışmaya, 6-36 ay arasında, üç veya daha fazla viral enfeksiyonla tetiklenen hışıltısı olan 60 çocuk hasta grubu olarak, aynı yaş grubundan 40 sağlam çocuk da kontrol grubu olarak alındı. Çalışmamız viral hışıltının sık görüldüğü Kasım-Mart ayları arasında yapıldı. Serum 25(OH)D düzeyi ≤20 ng/mL vitamin D eksikliği, 21-29 ng/mL vitamin D yetersizliği, ≥30 ng/mL vitamin D yeterli düzey olarak kabul edildi. **Bulgular:** Serum 25(OH)D düzeyi hasta grubunda 30,1±7,6 ng/mL, kontrol grubunda ise 33,9±9,8 ng/mL olup, her iki grup arasında anlamlı farklılık saptandı (p=0,049). Vitamin D eksikliği hasta grubunun 7 (%12)'sinde, kontrol grubunun 2 (%5)'sinde, vitamin D yetersizliği ise hasta grubunun 21 (%35)'inde, kontrol grubunun 13 (%32)'ünde saptandı. Hasta ve kontrol grupları arasındaki fark anlamlı değildi. Hasta grubunun serum 25(OH)D düzeyleri ile yaş, anne sütü alım süresi ve anne giyim tarzı arasında anlamlı ilişki bulundu (p<0,05). **Sonuç:** Ülkemizde çocukluk yaş grubunda serum vitamin D düzeyleri genel olarak düşüktür. Vitamin D'nin immün sistem ve antiviral savunma üzerine etkisi göz önüne alınırsa, tekrarlayan hışıltı gelişiminde önemli bir faktör olabileceği düşünülebilir. Çocuklarda vitamin D'nin solunum yolu enfeksiyonları ve hışıltılı hastalıklar ile ilişkisini ortaya koyacak, ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Vitamin D; solunum yolu enfeksiyonları; hışıltılı çocuk

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Wheezing illnesses are frequent among preschool children. In nearly 15% of children who wheeze before the third year of life, wheezing persists through the age of six years in association with some genetic and viral factors.[1] Most children wheeze only when they have upper respiratory tract infections, are usually nonatopic, and outgrow symptoms by 6 years of age.[2]

Epidemiologic studies have shown that low serum 25(OH)D levels are associated with increased risk of lower respiratory tract infections in young children.[3,4] Almost all viral respiratory tract infections occur between November and March, months that also are associated with vitamin D deficiency. Recently, vitamin D has been shown to have an important role in immune regulation, especially in innate immunity as well as production of antimicrobial peptides.[5,6] Vitamin D insufficiency may contribute to the seasonal nature of the wheezy respiratory tract infection in infants. In addition, early viral respiratory tract infections in a genetically susceptible host may induce subsequent asthma development and vitamin D may also have a role in this progress.[7]

Serum 25(OH)D is the major circulating form of vitamin D, and its serum levels reflect an individual's vitamin D status. In this study, we evaluated the relationship between serum 25(OH)D levels and recurrent respiratory tract infections with wheezing in young children.

MATERIAL AND METHODS

Participants were recruited at the Başkent University Adana Training and Research Hospital between November 2009 and March 2010. Adana is a city in Southern region of Turkey, at 37° parallel. The parents of each participant provided a written informed consent. The study was approved by the Research Ethics Board of the Başkent University Faculty of Medicine (Project number: KA09/410).

A total of 100 children including 60 patients and 40 controls, aged 6-36 months, were enrolled. Patients were selected among infants admitted to the Department of Pediatric Allergy with recurrent wheezing episodes. The controls were healthy children at the same age group, lived in the same region, they never had wheezing before and attended the pediatric outpatient clinics for vaccination during the study period.

Inclusion criteria were i) being 6 to-36 months of age, ii) had at least 3 wheezing episodes related to viral infections, first of which began before 12 months, iii) neither wheezing, nor asthmatic symptoms between episodes, and iv) exclusion of other causes of wheezing disorders.

Exclusion criteria were prematurity, wheezing history during the neonatal period, severe wheezing attacks requiring intensive care unit admission, growth retardation, cystic fibrosis, bronchopulmonary dysplasia, tuberculosis, congenital respiratory disorders, foreign body aspiration, immune deficiency, cardiac defects, clinical signs of rickets, systemic glucocorticoid treatment within last four weeks and anticonvulsant drug use.

Demographic and clinical data and risk factors included age during first wheezing episode, number of wheezing episodes, vitamin D supplementation and feeding practices in the first year of life, passive smoking and clothing style of the mother (if wear long-sleeved clothing and head cover).

Venous blood specimens were collected for serum calcium, phosphorus, alkaline phosphatase, 25(OH)D and total IgE from patients, and serum calcium, phosphorus and 25(OH)D from controls. Peripheral blood eosinophil count was measured by Coulter counter techniques.

Serum levels of 25(OH)D are considered the best circulating biomarker of vitamin D metabolic status. A single measurement of vitamin D was obtained for 60 patients and 40 healthy controls by using ECLIA (Electrochemiluminescence immunologic test) method. Vitamin D levels have been shown to be relatively stable when specimens had been -20° stored properly. We categorized vitamin D levels into deficient (≤20 ng/mL), insufficient (21-29 ng/mL), sufficient (≥30 ng/mL) and optimal level (>40 ng/mL), based on previous recommendations.

STATISTICAL ANALYSIS

Data were analyzed by using SPSS version 11.5. Descriptive statistics for variables were presented as ''means±standard deviations''. Categorical variables were compared by using Pearson'sChi-square and Fisher's exact tests. For comparison of groups, parametric data were assessed by using student's t-test and nonparametric data by Mann Whitney-U test. $p<0.05$ was considered as statistically significant.

RESULTS

In total, 60 (46 boys, 14 girls) wheezy infants (cases) and 40 (25 boys, 15 girls) healthy infants (controls) were enrolled. The mean age±standard deviation (SD) of the cases was 18.2±7.4 months and of controls was 19.5±9.6 months. The demographic characteristics and risk factors related to wheezing and vitamin D status among patients and controls are shown in Table 1.

There were no significant differences between the cases and the controls in terms of age, gender, in feeding practices, regular daily use of vitamin D supplementation, smoking at home, duration of breastfeeding, introduction of solids and cow's milk ($p>0.05$) (Table 2). Religious clothing style with long-sleeved clothing and head cover was more common among mothers of cases compared to that of controls ($p=0.006$).

Of 60 cases who had wheezing episodes triggered by a viral respiratory tract infection, 70% had five or more wheezing episodes, and 35% had at least one hospitalization history because of a wheezing attack. The mean age at first wheezing episode was 5.1±3.2 months. The median of eosinophil count was 250/mm^3 (10-880) and serum IgE level was 31.5 IU/L (1-1000) among the cases.

Serum calcium, phosphorus and alkaline phosphatase levels were in normal ranges in the cases and the controls, but serum calcium levels were lower in the cases compared to the controls ($p=0.009$).

TABLE 1: Demographic characteristics of the patients and the controls.

	Cases n=60	Controls n= 40	p
Age (months)	18.2±7.4	19.5±9.6	0.68
Gender			
Boys (%)	46 (76)	25 (63)	0.19
Girls (%)	14 (24)	15 (37)	
Weight (kg)	11.2±2.1	10.9±2.5	0.36
Height (cm)	80.4±7.4	81.1±9.2	0.75

TABLE 2: Distribution of the risk factors among wheezy infants and the controls.

	Cases n=60	Controls n= 40	p
Duration of breastfeeding (months)	11.6±6.1	10.4±6.8	0.36
Introduction of cow's milk (months)	8.7±5.6	10.1±4.4	0.23
Introduction of solids (months)	5.0±1.1	5.1±1.2	0.91
Nutritional status			
Breastfeeding +solids	24 (40%)	17 (42%)	0.96
Cow's milk+formula+solids	36 (60%)	23 (58%)	
Vitamin D supplementation			
Regular	41 (68%)	22 (55%)	0.25
Not-regular	19 (32%)	18 (45%)	
Smoking at home			
Yes	23 (38%)	8 (20%)	0.08
No	37 (62%)	32 (80%)	
Clothing style of mother			
Head cover	36 (60%)	12 (30%)	0.006
No head cover	24 (40%)	28 (70%)	

The mean serum 25(OH)D concentration in wheezy infants (30.1±7.6 ng/mL) was lower than the healthy controls (33.9±9.8 ng/mL), (p=0.049). The frequency of vitamin D deficiency was 7/60 (12%) among wheezy infants and 2/40 (5%) among the healthy controls, and the frequency of vitamin D insufficiency was 21/60 (35%) among wheezy infants and 13/40 (32%) among the healthy controls. Serum vitamin D statuses of the cases and the controls are shown in Table 3. Thirty two (53%) of the cases and 25 (63%) of the controls had a serum 25(OH)D level ≥30 ng/mL. There were no significant differences between the cases and the controls for vitamin D deficient, insufficient or sufficient levels (p>0.05).

Serum 25(OH)D level decreased significantly with age (Figure 1). The mean serum 25(OH)D level was significantly lower in cases <12 months age compared to cases >12 months age (p=0.028). Children whose mothers wore head covers had lower serum 25(OH)D levels (28.1±7.1 ng/mL) compared to children whose mother did not (32.8±7.5 ng/mL), (p=0.02).

Correlations between serum 25(OH)D levels and the risk factors for vitamin D deficiency are shown in Table 4. Among wheezy infants, there were negative correlations between serum vitamin D level and age, duration of breastfeeding and maternal clothing style (r=-0.24, r=-0.31, r=0.29, p=0.03, p=0.01, p=0.02, respectively). There was no significant correlation between serum 25(OH)D level and total eosinophil count or serum IgE (r=-0.13, r=-0.12, p=0.30, p=0.33, respectively).

TABLE 3: Serum vitamin D status of wheezy infants and the controls.*

	Cases n (%)	Controls n (%)
Vitamin D deficient	7 (12)	2 (5)
Vitamin D insufficient	21 (35)	13 (32)
Vitamin D sufficient	27 (45)	17 (43)
Optimal level	5 (8)	8 (20)
	60 (100)	40 (100)

*The differences were insignificant.

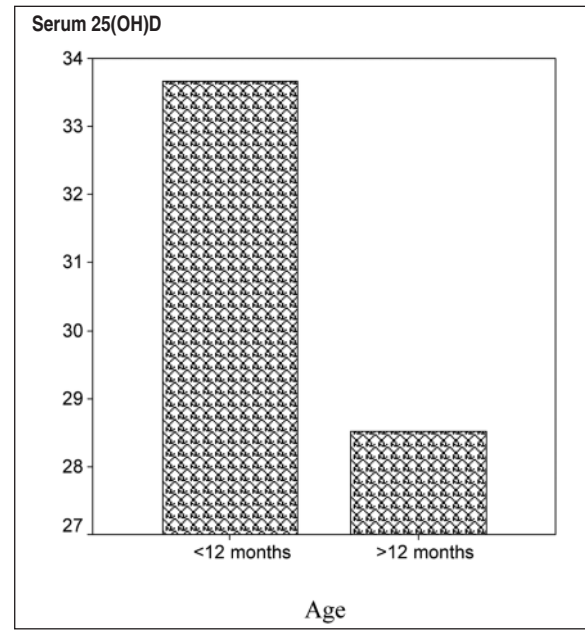

FIGURE 1: The alteration of serum 25(OH)D levels with age.

TABLE 4: Correlations between serum 25(OH)D levels and the risk factors for vitamin D deficiency.

	p value	Correlation
Age	0.03*	-0.24*
Weight	0.57	
Duration of breastfeeding	0.01*	-0.31*
Nutritional status	0.53	-
Vitamin D supplementation	0.80	-
Clothing style of mother	0.02*	0.29*

*Serum 25(OH)D levels have negative correlations with age, duration of breastfeeding and clothing style of the mother.

DISCUSSION

In this study, we found that the mean serum 25(OH)D concentration in wheezy infants was lower than the healthy controls. In addition, we detected the rate of vitamin D deficiency as %12 and vitamin D insufficiency as %35 in wheezy infants in our study.

Wheezing is a common problem in infancy and we believe that determining the risk factors is important in recurrent wheezing. Recent vitamin D studies suggest that low levels of 25(OH)D are associated with increased risk of lower respiratory tract infections, wheezing illnesses and asthma in young children.[8,9] In addition, some observational

studies reported that increased vitamin D in maternal diet may reduce the risk of recurrent wheezing.[10,11]

Upper respiratory tract infections account for more than 80% of wheezing episodes in children.[2] The incidence of viral infections, particularly in the pediatric population, typically peaks in the winter months when cutaneous vitamin D synthesis is naturally impaired. Our study was done between November and March, months that viral wheezing was common. Of 60 cases in our study, all had wheezing that triggered by a viral respiratory tract infection.

Immunomodulatory effect of vitamin D has been mentioned in recent studies.[12] Emerging evidence indicates that vitamin D-mediated innate immunity, particularly through enhanced expression of human cathelicidin antimicrobial peptide, is important in host defenses against respiratory tract pathogens.[13-16] Vitamin D insufficiency is associated with increased risk of respiratory tract infections, and may increase the frequency of wheezing.

We detected vitamin D deficiency in 12% of wheezy infants and 5% of healthy controls, and vitamin D insufficiency in 35% of wheezy infants and 32% of healthy controls in our study, but the differences between two groups were insignificant. However, the mean serum 25(OH)D concentration in wheezy infants was lower than healthy controls, which pointed a more deficient state that might predispose to wheezy disease. These findings may support the role of vitamin D in antiviral defense, and particular importance of vitamin D in wheezy infants. However, causality cannot be assessed by this cross-sectional analysis. In addition, our study has limitation due to its small sample size. Randomized controlled trials are needed to determine the association of vitamin D with wheezing.

Jartti et al. demonstrated that low serum 25(OH)D levels were associated with increased risk of viral co-infections in wheezing children.[17] The mean 25(OH)D concentration was 68 nmol/L (27 ng/mL) in this study, and %31 had a serum 25(OH)D level <25 ng/mL, %6 had <10 ng/mL. In our study, mean serum 25(OH)D level was 30.1 ng/mL similar to aforementioned study, but vitamin D deficiency was less common. This may be due to several factors including the geographical area of living.

The major source of vitamin D has always been exposure to sunlight for most humans. Dietary intake (including supplementation) is an alternative source of vitamin D.[6,7] Maternal vitamin D status during pregnancy and lactation also affect the serum vitamin D level of the infant.[18] Risk factors for vitamin D deficiency include living in Northern latitudes, failing to get enough sun exposure, being dark-skinned, elderly or obese.[19] Less time spent outdoors, using sunscreens, and clothing styles as head cover for cultural reasons reduce the cutaneous synthesis of vitamin D.

There was no significant difference between the cases and the controls for age, gender, weight or height means, ethnicity, nutritional status, regular use of vitamin D supplementation, duration of breastfeeding, introduction of solids and cow's milk in our study, but the clothing style of the mothers, i.e. wearing long-sleeved cloths and head cover, was more common in the cases compared to the controls.

Several previous studies showed that adequate vitamin D concentrations played a potential role in protection against upper and lower respiratory tract infections. In these studies, it has been pointed that inadequate concentrations of vitamin D seem to clinically impact children more severely, and often before the manifestations of rickets.[5] The wheezy infants in our study had no physical signs of rickets and their serum calcium, phosphorus, alkaline phosphatase levels were normal.

In Turkey, national recommendations suggest administration of vitamin D supplementation of 400 IU/day to all young children before the age one year in order to prevent vitamin D deficiency and rickets. In our study, serum vitamin D levels decreased significantly with increasing age. The mean serum 25(OH)D was significantly lower in cases >12 months of age compared to cases <12 of months age. This may be due to several factors including discontinuation of vitamin D supplementation after

12 months of age. For this reason, vitamin D supplementation should be continued after 12 months, particularly in the winter season, when the sun exposure decreases.

Other factors that affect serum vitamin D levels are maternal vitamin D status during pregnancy and lactation, and dietary intake and supplementation of the infant.[16] In our study, serum 25(OH)D level was inversely associated with duration of breastfeeding. We know that infants who are exclusively breastfed but do not receive supplemental vitamin D or adequate sunlight exposure are at increased risk of developing vitamin D deficiency and/or rickets. Therefore, vitamin D supplementation should also be recommended to infants who breastfed for prolonged periods.

Another factor that affects serum 25(OH)D level in our study was the mothers' clothing style. Children whose mothers wore head covers had lower serum 25(OH)D levels compared to children whose mothers did not. Skin coverage (i.e.clothing or sunblock use) reduces the cutaneous synthesis of vitamin D, and may affect mothers' vitamin D status during pregnancy and lactation. It is known that pregnant and lactating women, infants and growing children are at higher risk for vitamin D deficiency. A number of studies have shown that vitamin D status of the baby is correlated with vitamin D status of the mother.[4,20] In addition, several studies have reported an inverse relationship between maternal vitamin D intake and wheezing diseases in children.[10,11,21] With these data taken into account, we also thought that vitamin D supplementation to mother during pregnancy might prevent future wheezing diseases.

Although severe vitamin D deficiency is rare, vitamin D insufficiency is common worldwide. Although Turkey is in a geographical location with abundant sunlight, vitamin D deficiency affecting pregnant women, infants and adolescents continues to be a major problem.[22] We found vitamin D insufficiency as % 35 in wheezy infants and as %32 in healthy children in the control group. These results support that vitamin D levels are generally insufficient in our region. Irrespective of any effects of vitamin D on respiratory illness, vitamin D insufficiency is clearly a public health problem in this country.

In summary, we found lower serum vitamin D levels in wheezy infants compared to controls, but vitamin D insufficiency was common in all children. Future investigations will demonstrate the exact dose and duration of vitamin D supplementation for prevention or control of wheezy respiratory tract infections, asthma and other allergic diseases in young children.[23] In addition, new guidelines for adequate sun exposure and supplemental vitamin D are needed in children.

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