Comparison of Viral Agents and Vitamin D Levels in Children with Acute Bronchiolitis Infection

Akut Bronşiyolit Enfeksiyonu Olan Çocuklarda Viral Etkenler ile D Vitamin Düzeyinin Karşılaştırılması

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Abstract

Objective: The aim of this study was to determine the vitamin D level and prognostic relationship with viral agents causing acute bronchiolitis.

Material and Methods: Files of the patients who were hospitalized with the diagnosis of acute bronchiolitis in the pediatric service and intensive care unit of Ankara Training and Research Hospital were reviewed retrospectively. Patients were classified as mild, moderate or severe according to clinical evaluation. Serum 25 (OH) vitamin D levels were classified as < 20 ng/mL deficient, 20-30 ng/mL insufficient, and > 30 ng/mL normal.

Results: Median age of 130 patients was 8 months (1-108) and 60.8% were male. 69.2% of the patients were the citizens of the Republic of Turkey while 30.8% were refugees. 28.5% of the patients had mild, 30% had moderate, and 41.5% had severe scores. High flow oxygen therapy was applied to 56.9% of the patients and oseltamivir treatment was given to 50.8% of the patients. 26.9% of the patients were observed in intensive care and 3.8% were observed in mechanical ventilator. Respiratory syncytial virus was detected in 55.3% of nasopharyngeal swab specimens. Vitamin D deficiency was found in 36.9% and vitamin D insufficiency was found in 33.8% of the patients. Male patients who were citizens of the Republic of Turkey and who were given prophylactic vitamin D had significantly higher 25 (OH) vitamin D levels than other groups (p< 0.05). 25 (OH) vitamin D levels were found to be 21.9 ng/mL in patients with respiratory syncytial virus infection and 24.2 ng/mL in other viral swab samples (p= 0.058). Vitamin D levels were below normal in 70.3% of high-flow oxygen therapy patients and 71.2% of patients receiving oseltamivir treatment.

Öz

Giriş: Akut bronşiyolite neden olan viral etkenler ile D vitamini düzeyi ve prognostik ilişkinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada Ankara Eğitim ve Araştırma Hastanesi Çocuk Servisi ve Yoğun Bakımında akut bronşiyolit tanısı ile yatırılan hastaların dosyaları geriye dönük olarak incelendi. Hastalar klinik değerlendirilmesine göre hafif-orta ve ağır olarak sınıflandırıldı. Serum 25 (OH) D vitamin düzeyi < 20 ng/mL olan değerler D vitamini eksikliği, 20-30 ng/mL arasındaki değerler D vitamini yetersizliği, > 30 ng/mL olan değerler ise normal olarak değerlendirildi.

Bulgular: D vitamini düzeylerine bakılan 130 hastanın yaş ortancası 8 ay (1-108) ve %60.8'i erkek idi; hastaların %69.2'sinin Türkiye Cumhuriyeti vatandaşı, %30.8'inin mülteci olduğu saptandı. Hastaların %28.5'i hafif, %30'u orta, %415'i ağır şiddet skoruna sahipti. Hastaların %56.9 'una yüksek akımlı oksijen tedavisi uygulandı ve %50.8'ine oseltamivir tedavisi verildi. Hastaların %26.9'u yoğun bakımda, %3.8'i mekanik ventilatörde izlendi. Nazofarengeal sürüntü örneklerinden %55.3'ünde respiratuar sinsityal virüs (RSV) saptandı. Hastaların %36.9'unda D vitamini yetersizliği, %33.8'inde D vitamini eksikliği saptandı. Erkeklerde, Türkiye Cumhuriyeti vatandaşı olanlarda ve profilaktik D vitamini kullanmış olan hastalarda 25 (OH) D vitamini düzeyi diğer gruba göre istatistiksel olarak daha yüksek saptandı (p< 0.05). RSV enfeksiyonu olanların 25 (OH) D vitamin düzeyi 21.9 ng/mL, diğer viral sürüntü örneklerinde ise 24.2 ng/mL olarak saptandı (p= 0.058). Yüksek akımlı oksijen tedavisi uygulanan hastaların %70.3'ünde ve oseltamivir tedavisi alan hastaların %71.2'inde D vitamin düzeyleri normalin altında idi.

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Conclusion: Although there was no relationship between vitamin D levels and viral agents, 25 (OH) vitamin D levels of patients with severe bronchiolitis, intensive care unit patients, and high flow oxygen therapy patients were found to be below normal. We think that 25 (OH) D vitamin levels should be considered in children with acute bronchiolitis clinic and vitamin D treatment can be useful.

Keywords: Acute bronchiolitis, viral infection, 25 (OH) vitamin D levels

Sonuç: D vitamini düzeyi ile viral etkenler arasında bir ilişki bulunmamasına rağmen ağır bronşiyolit kliniği olan, yoğun bakıma yatan ve yüksek akımlı oksijen tedavisi alan hastaların 25 (OH) D vitamin düzeyleri, normalin altında saptanmıştır. Akut bronşiyolit kliniği olan çocuklarda 25 (OH) D vitamin düzeyi bakılması ve gerekli hastalara D vitamini tedavisinin yapılmasının faydalı olabileceğini düşünmekteyiz.

Anahtar Terimler: Akut bronşiyolit, viral enfeksiyon, 25 (OH) D vitamin düzeyi

Introduction

Lower respiratory tract infections (LRTI) (i.e. acute bronchiolitis, pneumonia, bronchopneumonia) seen frequently in childhood can cause significant levels of diseases and morbidity (1). There are many causes leading to the development of LRTI in children. Most frequently encountered causes include age (< 1 year), preterm birth, low birth weight, chronic disease, nutrition disorders, not being breastfed, crowded life conditions, cigarette use in the family, and insufficient immunization (2).

The effect of vitamin D over calcium and bone metabolism is well known. In recent genetic and epidemiological studies, it has been put forth that vitamin D has a vital and complex role in the function and regulation of the immune system and in the defense of the host against respiratory tract infections (3-5). Lα-hydroxylase enzyme producing active vitamin D and released by air way epithelia, alveolar macrophages, dendritic cells and lymphocytes show that active vitamin D can be locally produced within the lungs (6). The effects of vitamin D within the lungs have been reported as follows: increasing antimicrobial peptides, particularly the production of cathelicidin in epithelial cells; rising the cytotoxic activity of natural killer cells and the formation of superoxide of monocytes; decreasing chemokine production; and the inhibition of dendritic cell activation (5,6). The hypothesis claiming that the decrease in vitamin D production due to the reduction in ultraviolet B rays during winter months leads to the increase in the frequency of LRTI has been put forth (6,7).

Viruses are the most common causes of respiratory tract infections in children. Although viral respiratory tract infections affect all age groups, they can cause recurrent infections seen within a year in early aged groups (1,2). Respiratory syncytial virus (RSV), rhinovirus, influenza virus, coronavirus, parainfluenza virus, human metapneumovirus, adenovirus are the most commonly observed viruses leading to respiratory tract disorders (8,9). RSV and influenza viruses responsible for hospital admittance in adult patients can lead to severe infections in children under the age of five (10,11).

The relation between vitamin D and RSV and LRTI have been shown in the literature (3,11). In this study, it was aimed to investigate the relation between vitamin D and viral agents (RSV and other agents) causing LRTI in patients with acute bronchiolitis and also the relation between the level of vitamin D with the severity of the disease and the treatment implemented.

Materials and Methods

In this study, the files of the patients admitted to the pediatric service and the intensive care unit of Ankara Training and Research Hospital with a diagnosis of acute bronchiolitis between October 2017 and March 2018 were retrospectively reviewed. Demographics of the patients, month of referral, clinical and laboratory findings, hospitalization duration, whether the patients received high flow oxygen therapy and oseltamivir therapy or not, and the results of the nasopharyngeal swabs were recorded. Out of the children diagnosed with lower respiratory tract infection, those with preterm birth, low birth weight and chronic diseases, those receiving antibiotics, and those in whom no agent was detected in the nasopharyngeal swab and those without vitamin D results were excluded from the study. By retrospectively reviewing general polyclinic files, the control group included children without an active infection and chronic disease in the same age group, whose vitamin D level was tested for any other reason.

Patients were classified as mild, moderate and severe according to their clinical evaluation (8). Serum 25 (OH) vitamin D levels of < 20 ng/mL were classified as Vitamin D deficient, 20-30 ng/mL as Vitamin D insufficient, and > 30 ng/mL as normal (12).

SPSS (Stastistical Package For Social Sciences) for Windows 20.0 was used for data analysis. Kolmogorov-Smirnov test was used to determine whether the distribution of continuous and discontinuous numerical variables was close to normal. Defining statistics were shown as median (minimum-maximum) for continuous and discontinuous numerical variables, and categorical variables were shown as case number and "%". The significance of the difference between the groups in terms of median values was investigated by Mann-Whitney U test. Categorical variables were evaluated by either Pearson`s Chi-square or Fisher`s Exact Chi= Square test.

Approval from our hospital's ethical board was received for the study under the number 0058-599.

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Results

One hundred and thirty patients admitted to the pediatric service and intensive care unit of our hospital with the diagnosis of acute bronchiolitis and whose vitamin D levels were screened were included into the study. Sixty children were included into the control group. Median age of the patients was 8 months (1-108) and 60.8% (n= 79) were male. Median age of the control group was 11 months (5-101) and 55% were male. No significant difference was detected in terms of age and sex between the patient and control groups (p> 0.05). While 69.2% of the patients were citizens of the Republic of Turkey and 30.8% were refugees, 56.7% of the controls were citizens of the Republic of Turkey and 43.3% were refugees (p= 0.091) (Table 1).

Table 1. Demographics of the patients included into the study

	n	%
Sex		
Female	51	39.2
Male	79	60.8
Nationality		
Republic of Turkey	90	69.2
Refugee	40	30.8
Date of referral (month)		
October	12	9.2
November	4	3.1
December	0	0
January	46	35.4
February	46	35.4
March	22	16.9
Disease severity		
Mild	37	28.5
Moderate	39	30
Severe	54	41.5
Number of attacks		
First	90	69.2
Second	18	13.8
≥ Third	22	16.9
History of prophylactic vitamin D use		
Yes	113	86.9
No	17	13.1
Viral swab results		
RSV	72	55.3
Rhinovirus	14	10.8
Metapneumovirus	13	10
Multiple reproduction	9	7
Coronavirus	8	6.1
Parainfluenza virus	5	3.9
Bocavirus	4	3.1
Adenovirus	3	2.3
Influenzavirus	2	1.5
25 (OH) vitamin D level (ng/mL)		
< 20	48	36.9
20-30	44	33.8
> 30	38	29.2

RSV: Respiratory syncytial virus.

28.5% of the patients had mild, 41.5% had moderate, and 41.5% had severe severity score. 86.9% of the patients (n= 113) had used prophylactic vitamin D under the age of 1. Median hospitalization duration was 7 days (3-54). High flow oxygen therapy was given to 56.9% (n= 74) of the patients and oseltamivir treatment to 50.8% (n= 66). 26.9% of the patients (n= 35) were followed in the intensive care unit and 3.8% in mechanical ventilation. RSV was seen in 55.3% of the nasopharyngeal swab specimens, rhinovirus in 10.7%, multiple reproduction in 6.92% and influenza virus in 1.5% (Table 2).

While serum 25 (OH) vitamin D median of the patients was found as 22.5 ng/mL (3-58.7), serum 25 (OH) vitamin D median of the control group was 22.2 ng/mL (10-39.8). No significant difference in terms of 25 (OH) Vitamin D levels between the patient and control groups was detected (p= 0.746). 36.9% of the patients (n= 48) had vitamin D deficiency, 33.8% (n= 44) had vitamin D insufficiency and only 29.2% (n= 38) had vitamin D sufficiency. In 70.7% of all patients (n= 92), 25 (OH) vitamin D level was < 30 ng/mL.

When factors affecting 25 (OH) vitamin D levels in males, Turkish citizens and in patients who had used prophylactic vitamin D, 25 (OH) vitamin D level was detected statistically higher as regards the other group (p< 0.05) (Table 2). A significant relation between the severity of the disease and 25 (OH) vitamin D level was not determined (p= 0.418).

Although a statistical relation was not found between the severity of the disease and vitamin D levels being < 20 ng/mL, 20-30 ng/mL and > 30 ng/mL, vitamin D level was detected as < 30 ng/mL in 74% of the patients with severe (n= 40) and in 68.4% of the patients with mild-moderate disease severity scores (p= 0.438) (Table 3). Even though 25 (OH) vitamin D level in 77.1% of the patients requiring intensive care (n= 27) and in 68.4% of the patients not requiring intensive care (n= 65) was, < 30 ng/mL, a statistical difference was not found (p= 0.332).

While 25 (OH) vitamin D levels of the patients in the intensive care unit was 21.2 ng/mL (3.1-57.9), 25 (OH) vitamin D levels of the patients followed in the service was 23 ng/mL (3-58.7) (p= 0.071) (Table 2). A relation was not determined between low vitamin D levels and number of attacks, hospitalization duration and high flow oxygen therapy (p> 0.05).

25 (OH) D vitamin D level of the patients with RSV infection was 21.9 ng/mL (3.09-58.7) and it was 24.2 ng/mL (3-57.9) in other viral swab specimens, and a statistical difference was not present (p= 0.058). Vitamin D deficiency was detected in 40.3% of the patients with RSV infection and vitamin D insufficiency in 36.1% of the patients (p= 0.289).

There was not a difference between the level of 25 (OH) vitamin D and the patients` use of oseltamivir (p= 0.263) and high flow oxygen therapy intake (p= 0.272) (Table 2). Howev-

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Table 2. 25 (OH) vitamin D levels according to the demographics of the study group *

	Median	Minimum-Maximum	p
Sex			
Female	20.0	3.0-50.4	0.028
Male	24.0	3.9-58.7	
Natinality			
Reoublic of Turkey	24.2	3.0-58.7	0.001
Refugee	17.4	3.1-57.9	
Disease severity			
Mild	23.0	3.0-39.2	0.418
Moderate	24.0	3.8-50.4	
Severe	22.0	3.0-58.7	
Prophylactic vitamin D use			
Yes	23.0	3.1-58.7	0.001
No	16.0	3.0-31.0	
High flow oxygen therapy			
Yes	23.0	3.1-58.7	0.272
No	24.0	3.0-50.4	
Intensive care stay			
Yes	21.2	3.1-57.9	0.071
No	23.0	3.0-58.7	
Viral swab result			
RSV	21.9	3.1-58.7	0.058
Other	24.2	3.0-57.9	
RSV: Respiratory syncytial virus.			

Table 3. Evaluation of the demographics of the study group in terms of vitamin D level

	< 30 n (%)	> 30 n (%)	p	Odds ratio
Disease severity (n)				
Mild-moderate (76)	52 (68.4)	24 (31.6)	0.438	0.591-3.364
Severe (54)	40 (74)	14 (26)		
High flow oxygen therapy (n)				
Present (74)	52 (70.3)	22 (29.7)	0.886	0.472-2.272
Absent (56)	40 (71.5)	16 (28.5)		
Oseltamivir treatment (n)				
Present (66)	47 (71.2)	19 (28.8)	0.910	0.450-2.039
Absent (64)	45 (70.3)	19 (29.7)		
Intensive care necessity (n)				
Present (35)	27 (77.1)	8 (22.9)	0.332	0.261-1.579
Absent (95)	65 (68.4)	30 (31.6)		
Viral swab(n)				
RSV (72)	55 (76.4)	17 (23.6)	0.117	0.856-3.939
Other (58)	37 (63.8)	21 (36.2)		
RSV: Respiratory syncytial virus.				

er, vitamin D levels were below normal range in 70.3% of the patients receiving high flow oxygen therapy and in 71.2% of the patients using oseltamivir (Table 3).

Discussion

Viruses are the most common causes of respiratory tract infections in children. These viruses can lead to a clinical picture without any symptoms or to severe infections necessitating intensive care (13). RSV, which leads to both upper and lower respiratory tract infections, is the most common cause of respiratory tract infections in children worldwide (9,10,13).

In recent studies, vitamin D deficiency, which also plays part in the development of immunity, has been reported to be of outmost importance in bronchiolitis that develop with RSV (11,14). There are various studies in the literature investigating the relation between vitamin D and LRTI in children: however, studies on the subject matter discussed are very scarce in our country (11,15-17).

Various studies have shown that epithelial cells of the respiratory system can synthesize active vitamin D and that this vitamin D plays an important role in the production of antimicrobial peptides (cathelicidin/defensin) (18,19). Cathelicidin

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aids in preventing the production of infections originating from bacteria and viruses (*Mycobacterium tuberculosis*, RSV) (19,20). Therefore, it has been put forward that LRTI sensitivity and production show an increase in patients with low serum vitamin D (17,20).

In our study, median 25 (OH) vitamin D was 22.5 ng/mL (3-58.7), and vitamin D insufficiency and vitamin D deficiency were observed in 36.9% and 33.8% of the patients, respectively. In a study by Şişmanlar et al., it has been reported that in 19% and 31% of the patients between the ages of 6 months-5 years receiving LRTI diagnosis for the first time had vitamin D insufficiency and vitamin D deficiency, respectively. In our study, a higher-level vitamin D insufficiency and deficiency was detected (16). Vitamin D is affected by many factors including age, sex, season, ethnic origin, socioeconomic level, exposure to sun light, prophylactic vitamin use, and diet (15,17). 30.8% of the patients in our study were refugees. While 25 (OH) vitamin D level of Turkish citizens was 24.2 ng/mL (3-58.7), that of the refugees was 17.4 ng/mL (3.1-57,9), and hence it was seen that vitamin D level was lower in the refugees. It was speculated that nutrition deficiency and a more conservative clothing style that does not permit for exposure to sun light may have led to higher vitamin D deficiency and insufficiency. In addition, 13.1% of the patients under the age of 1 stated that they had not used prophylactic vitamin D. As expected, patients who had used prophylactic vitamin D were determined to have higher 25 (OH) vitamin D level in comparison to the ones who had not.

Though > 30 ng/mL is considered normal for 25 (OH) vitamin D level, it is still debatable which serum vitamin D level is effective in protecting the body against infections (15,21). Various studies have indicated that > 30 ng/mL level is sufficient for the extra-osseous beneficial functions of vitamin D (17,21). In our study, 70.7% of the patients had < 30 ng/mL 25 (OH) vitamin D level. Low vitamin D levels were high.

There are few studies reporting that clinical severity scores of patients with acute bronchiolitis and recurrent attacks are associated with vitamin D deficiency and that patients with vitamin D deficiency require intensive care and oxygen therapy more (15,17,22). In a study by Inamo et al. where they have retrospectively assessed 28 patients aged 1-4 years, it has been claimed that low vitamin D level and clinical severity of LRTI can be associated (22). Similarly, Moreno-Solis et al. have reported in a study including 48 infants that low vitamin D levels in patients under the age of 1 is associated with the clinical severity of LRTD (17). On the other hand, in two studies conducted in Canada, a relation has not been found between vitamin D levels and the clinical severity of LRTD (23,24). In a similar study carried out by Iqbal et al., a relation between low 25 (OH) vitamin D levels and the clinical severity of LRTD has not been found

in 38 patients with viral LRTD aged between 6 months and 12 years (25). In our study, a significant relation was not confirmed between the clinical severity of the infection and number of attacks and vitamin D deficiency. However, in 40.7% and 33.3% of the patients with severe clinical picture, vitamin D deficiency and vitamin D insufficiency were confirmed, respectively. In 74% of the children with severe acute bronchiolitis, vitamin D level was below the normal range.

In a study by McNally et al. consisting children under the age of five, it has been reported that vitamin D deficiency is not associated with the clinical severity of LRTI; however, patients with vitamin D deficiency require pediatric intensive care much more (23). In our study, 26.9% of the patients was followed in intensive care and 3.8% in mechanical ventilation.

Vitamin D deficiency and insufficiency were detected in 45.7% and 31.4% of the patients requiring intensive care, respectively. So, 25 (OH) vitamin D level was below normal range in 77.1% of the patients monitored in intensive care. Although there was no statistically significant difference between the 25 (OH) vitamin D levels of patients monitored and not monitored in intensive care, it was considered that there was a distinct lowness.

In a limited number of studies in the literature, vitamin D deficiency has been reported to be a risk factor in LRTI development associated with RSV (14,19,26). On the other hand, Mansbach et al. have not determined a relation between RSV and vitamin D in their study including 82 patients with 62 RSV infections (27). In another study, a relation has not been found between vitamin D and RSV bronchiolitis in 145 patients with RSV bronchiolitis under the age of 1 (11). In our study, RSV infection was confirmed in 55.3% of our patients, but a significant relation was not found between RSV and other viral agents and vitamin D levels. Vitamin D deficiency and insufficiency were found in 40.3 and 36.1% of the patients with RSV, respectively.

High flow oxygen therapy used in treatment was implemented on 56.9% of the patients. In 70.3% of the patients receiving high flow oxygen therapy, 25 9 (OH) vitamin D level was below the normal range. Despite not having found a statistically significant difference, it was observed that intense therapy was required by patients with low vitamin D levels.

In a study by Avenell et al. conducted in adults, it has been reported that daily 800U vitamin D supplement decreases infection frequency by 10-15% (28). It has been indicated by Leis et al. in a study conducted with 197 children aged under 5 years that children taking 800 U vitamin D develop four times less LRTI when compared to those taking vitamin D below 800 U (29). Larkin et al. have recommended vitamin D support to children aged 5 years and under who are at risk of developing LRTI (30).

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Along with a limited number of studies investigating the relation between vitamin D and LRTI in our country, any other study exploring the relation between high flow oxygen therapy and vitamin D and viral agents (RSV and others) was not found in the literature (15,16).

In spite of the fact that there was no relation between vitamin D level and RSV and other agents in our study, 25 (OH) vitamin D level of patients with severe bronchiolitis, patients who were monitored in intensive care and those who received high flow oxygen therapy was detected below the normal range. Since the effect of vitamin D on infections, pulmonary function and immunity development is taken into consideration, we are of the opinion that prophylactic vitamin D use should be well followed, 25 (OH) vitamin D level should be tested in children with LRTI and that vitamin D treatment would be beneficial to patients in need. Moreover, further studies are needed to determine the ideal vitamin D dosage that could prevent the infection to have a severe course clinically.

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