Research Article / Araştırma Makalesi

Comparison of Vitamin A and Vitamin D Levels of 0-36 Months Old Children, Who were Admitted to Pediatric Inpatient Clinic with Lower Respiratory Tract Infection and Healthy Children within the Same Age Group

Çocuk Servisinde Yatırılarak Tedavi Edilen Alt Solunum Yolu Enfeksiyonu Tanılı 0 – 36 Ay Arası Çocukların Vitamin A Ve Vitamin D Düzeylerinin Aynı Yaş Grubu Sağlıklı Çocuklar Ile Karşılaştırılması

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Abstract

Background: Lower respiratory system infections are highly common in young children and may require inpatient treatment. Studies have shown that patients treated and followed up for lower respiratory system infections have low levels of vitamin A and Vitamin D. In our study, we aimed to determine whether the deficiencies of these vitamins are risk factors for the development of lower respiratory system infections by comparing the serum vitamin A and vitamin D levels of 0-36 months old patients with lower respiratory tract infection and healthy children.
Materials and Methods: The study included 82 children who applied to pediatric outpatient clinic between February 1st 2020 and June 30th 2020 with lower respiratory tract infection between the age 0-36 months. Blood samples were obtained after getting written consent from the families for determination of serum vitamin A and vitamin D levels. 58 healthy children who applied to the outpatient clinic for routine check-up were determined as the control group. Age, sex, height and weight of all children were recorded.
Results: The average vitamin D level of the lower respiratory tract infection group was 15.96±7.49ng/ml and those in the healthy group had average vitamin D levels of 32.19±14.27ng/ml, showing that the patient group had statistically significantly lower levels of vitamin D (p=0.0001). The median vitamin A level of those in the patient group was found to be 172 ng/ml (128-249), whereas those in the control group had median vitamin A levels of 263 ng/ml (222-312,5), which showed that patient group had statistically significantly low levels of vitamin A (p=0.0001). Our study showed that there is a positive statistically significant correlation between the vitamin D variable and the vitamin A variable (r=0.432, p=0.0001).
Conclusions: Our study is the first study in the literature in which vitamin A and vitamin D levels were compared together in children with Lower Respiratory Tract Infection (LRTI). Vitamin A and vitamin D levels are lower in children with LRTI than in healthy children and vitamin levels should be checked in such children.

Key Words: Lower Respiratory System Infection, Vitamin D, Vitamin A

Öz

Amaç: Alt solunum yolu enfeksiyonları özellikle küçük çocuklarda sık görülmekte olup aynı zamanda hastaneye yatırılarak tedaviyi gerektirmektedir. Çalışmalarda alt solunum yolu enfeksiyonu nedeniyle takip ve tedavi edilen hastalarda vitamin A ve D düzeylerinin düşükolduğu bildirilmiştir. Çalışmamızda 0-36 ay grubu alt solunum yolu enfeksiyonu tanısıyla takip edilen çocuklarda serum vitamin A ve serum vitamin D düzeylerinin saptanarak, aynı yaş grubundaki sağlıklı çocuklarla karşılaştırılması ve bu vitamin eksikliklerinin alt solunum yolu enfeksiyonu gelişiminde bir risk faktörü olup olmadığının saptanması amaçlanmıştır.
Materyal ve Metod: Çalışmamızda 01 Şubat 2020-30 Haziran 2020 tarihleri arasında Bağcılar Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Polikliniğine başvuran 0-36 ay arası alt solunum yolu enfeksiyonu tanısı ile izlenen ve serum A ve D vitamin saptanması için kan alınan 82 çocuk çalışmaya alındı. Polikliniğe rutin kontrol için başvuran ve serum A ve D vitamin düzeyleri bakılan 58 sağlıklı çocuk kontrol grubu olarak alındı. Çocukların yaş, cinsiyet, boy ve kilo değerleri kaydedildi.
Bulgular: Çalışmamıza katılan hasta grubunun vitamin D ortalaması 15,96±7,49ng/ml, kontrol grubunun vitamin D ortalaması 32,19±14,27 ng/ml olup istatistiksel olarak hasta grubunun vitamin D düzeyi anlamlı derecede düşük bulunmuştur (p=0,0001). Çalışmamıza katılan hasta grubunun vitamin A median değeri 172 ng/ml (128-249 IQR), kontrol grubunun vitamin A median değeri 263 ng/ml (222-312.5 IQR) olup istatistiksel olarak hasta grubunun vitamin A düzeyi anlamlı derecede düşük bulunmuştur (p=0,0001). Çalışmamızda vitamin D değişkeni ile vitamin A değişkeni arasında pozitif yönde istatistiksel olarak anlamlı korelasyon gözlenmiştir (r=0,432 p=0,0001).
Sonuç: Çalışmamız alt solunum yolu enfeksiyonu olan çocuklarda vitamin A ve vitamin D düzeylerinin beraber karşılaştırıldığı literatürdeki tek çalışmadır. Alt solunum yolu enfeksiyonu geçiren çocuklarda vitamin A ve vitamin D düzeyleri sağlıklı çocuklara gore daha düşük görülmekte olup bu çocukların vitamin değerlerinin kontrol edilmesi gereklidir.

Anahtar Kelimeler: Alt Solunum Yolu Enfeksiyonları, vitamin D, vitamin A

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Received / Geliş tarihi: 21.07.2023

Accepted / Kabul tarihi: 13.11.2023

DOI: 10.35440/hutfd.1327349

Introduction

Lower respiratory tract infections (LRTI) are common under the age of 5, and seen in approximately 120 million children worldwide, causing 1.8 million deaths per year (1). In developing countries, lower respiratory tract infections are the most common cause of death in children under five years of age. Respiratory syncytial virus (RSV) (15-20%) is the most common cause of pneumonia in patients under the age of five, whilst Mycoplasma pneumoniae (M. pneumoniae) (4-39%) is the leading cause in patients older than 5 years old. Other common causes of pneumoniae include parainfluenza virus (PIV), *Streptococcus pneumoniae* (S. pneumoniae), *Staphylococcus aureus* (S. aureus), *Chlamydia trachomatis* (C. trachomatis), *Chlamydia pneumoniae* (C. pneumoniae), influenza virus and adenoviruses (2,3).

Vitamin D plays an important part in the bone metabolism. Beside being a hormone, it also has key roles in immunomodulation. Its most important effect is on calcium, phosphorus metabolism and bone mineralization. Moreover, in recent years, it has been found that vitamin D deficiency has impacts on common cancer types, cardiovascular diseases, metabolic syndrome, infectious and autoimmune disease (4). Vitamin D is important for cellular and humoral immunity as well as lung function. Its relevance in severe lower respirotary system infections has been shown in the most recent studies (5,6).

Vitamin A deficiency is a major public health problem, affecting 190 million children under the age of 5 in low and middle income countries. Vitamin A deficiency predisposes children to many diseases, including respiratory diseases, diarrhea, measles and vision problems, and can lead to death. A review of forty-three randomized studies reported that giving vitamin A capsules to children aged 6 months to 5 years reduced the overall risk of death by 24%. Vitamins A and D are good antioxidants and they stabilize the structure of the cell membrane as well as provide resistance against lipid peroxidation (7). It is known that there is an imbalance between oxidant and antioxidant mechanisms in pneumonia. It is also important in defense against diarrhea and lower respiratory tract infections (8,9).

In our study, we aimed to determine the serum vitamin A and D levels in patients treated for lower respiratory tract infections between the ages of 0-36 months.

Materials and Methods

82 patients diagnosed with lower respiratory tract infection between the ages 0-36 months who were treated as inpatient between February and June 2020 at xxxxxxxxxx Hospital and 53 healthy children who had routine check-ups at the outpatient clinic were included. Ethical board approval was received from xxxxxxxxxx Hospital (February 2nd 2020, number: 2020.02.05.023). At the inpatient clinic, 3 ml blood sample was obtained from children who were being treated for lower respiratory tract infection with no history of chronic disease, between 08:30-10:00 a.m. Blood samples were then kept at -40^{0}C. All of our patients were being treated for their first lower respiratory tract infection and had no history of recurrence. Our patients were diagnosed with lower respiratory tract infection according to clinical findings, and bronchiolitis, viral, bacterial pneumonia were not differentiated. Vitamin A levels of the taken samples were measured using high-performance liquid chromatography colon Schimadzu 1c20 hplc device. Vitamin D levels were measured using chemiluminescence immunoassay method using Beckman Access 25(OH) Vitamin D total kit.

In this present study, vitamin D levels of lower than 20ng/mL were accepted as vitamin D deficiency (10). For vitamin A levels, lower than 200ng/mL were accepted as vitamin A deficiency (11). All of our patients had used or were currently using vitamin D at the prophylaxis dose (400 IU). Children with chronic diseases, cardiovascular diseases and neurodevelopmental delay and patients who received vitamin D at therapeutic doses or who received other multi-vitamin therapy were not included in our study.

All of the data were analyzed with using the Statistical Package for the Social Sciences (SPSS 13.0 Statistical Software, SPSS Inc., Chicago, IL, USA). Descriptive statistics, including the means and ranges, were calculated for numeric variables. The Kolmogorov–Smirnov test was used to identify deviations from normal distribution and appropriate tests were selected accordingly. Additionally, the Student's t-test was used to the compare numeric data with normal distribution. The Mann-Whitney U test was used to compare the numeric data without normal distribution. In the data, height, weight and vitamin D levels show normal distributions, whereas vitamin A value do not. Therefore, the median (25-75 IQR) value of vitamin A was used. Additionally, chi-squared tests were used to compare the categorical variables. and Pearson correlation test was used in order to determine the relation amongst the variables. A p value of less than 0.05 was considered to indicate a significant difference.

Results

The age of the patients were between 1 month and 35 months with an average of 7.66±7.69 months. The age of those in the control group were between 3 months and 34 months with an average of 9.93±6.47 months. The sex, height and weight percentile data are shown in table 1. There was no significant difference in age, sex, height and weight percentile between the study and the control groups.

In our study, we found the mean serum Vitamin D levels of the study group was 15.96±7.49ng/ml, while the mean of the control group was 32.19±14.27ng/ml. The vitamin D levels of the study group were found to be meaningfully low (p=0.0001).

The median Vitamin A level of the study group was 172 ng/ml (128-249 IQR), the median of the control group was 263 ng/ml (222-312.5 IQR). The vitamin A levels of the study group were found to be meaningfully low (p=0.0001) (Table 2).

In our study, we found a statistically significant positive correlation between the vitamin D and vitamin A levels (r=0.432, p=0.0001). There were no significant correlations found between age, weight percentile, height percentile and Vitamin D levels (p>0.05). There was statistically significant positive correlation between vitamin A levels and age (months) (r=0.355, p=0.0001) while no such correlation was found between vitamin A levels and weight and height percentiles (p>0.05). (Table 3).

Table 1. Age, Sex and Percentile Data of the Study and Control Groups

Control Group				Study Group		p
Age (months)		9.93±6.47		7.66±7.69		0,069‡
Sex	**Male**	28	%52.83	54	%65.85	
	Female	25	%47.17	28	%34.15	0.130+
Weight Percentile		49.15±26.34		56.45±26.72		0.121*
Height Percentile		59.83±26.5		62.05±17.86		0.561*

**Independent t test ‡Mann Whitney U test +Chi-Squared test*

Table 2. Comparison of the serum Vitamin A and Vitamin D Levels of the Study and Control Groups

	Control Group	Study Group	p‡
Vitamin D (ng/ml)	32.19±14.27	15.96±7.49	**0,0001**
Vitamin A (ng/ml)	263 (222-312.5 IQR)	172 (128-249 IQR)	**0,0001**

‡Mann Whitney U test

Table 3. Correlation between variables and Vitamin A and Vitamin D of the study group

		Vitamin D (ng/ml)	Vitamin A (ng/ml)
Vitamin D (ng/ml)	**r**		**0.432**
	p		**0.0001**
Vitamin A (ng/ml)	**r**	**0.432**	
	p	**0.0001**	
Age (months)	**r**	0.068	**0.355**
	p	0.431	**0.0001**
Weight Percentile	**r**	-0.113	-0.057
	p	0.189	0.507
Height Percentile	**r**	-0.070	0.152
	p	0.418	0.077
CRP	**r**	-0.078	**-0.250**
	p	0.485	**0.024**

Pearson Correlation Test

Discussion

Lower respiratory tract infections are commonly seen in pediatric patients under 5 years old and it is one of the main reasons for hospitalization and mortality in developing countries. It is estimated that 15.5% of child deaths worldwide are due to LRTIs. (12). Factors causing lower respiratory tract infections include young age (<1 years), low birth weight, prematurity, insufficient feeding, underlying diseases, no history of breastfeeding, low socioeconomic status, crowded living situations (large family, daycare etc.), no healthcare, age of the mother and the education of the mother, air pollution inside the house, smoking, insufficient immunization and vitamin D deficiency (13).

There are multiple studies in literature about the correlation between lower respiratory tract infections and vitamin D. (14-16). However, in our country, such research is low in number (17). Both pneumonia and vitamin D deficiency are common in children. Until recently, it was thought that vitamin D is mainly related to calcium and bone metabolism, but in recent years, there are many studies investigating the effects of vitamin D outside of bone metabolism. It is known that vitamin D modulates the body's natural immune system and has a protective role against many diseases, including pneumonia. More respiratory infections have been reported during the winter months, when vitamin D production is lowest. (15). Certain studies show that epithelial cells of the respiratory system can synthesize active vitamin D and this vitamin D play an important part in the production of antimicrobial peptides (cathelicidin and defensin) (18-20). Cathelicidin helps preventing infections caused by bacteria and viruses (Mycobacterium tuberculosis, RSV) (20). Early vitamin D treatment increases the production of allergen related proliferation of T cells thus Th2 cytokines (IL-4 and IL-13) and IgE (21). Therefore, lower respiratory tract infections are more common in patients with low serum vitamin D levels.

Our study found that the vitamin D levels of pediatric patients (0-36 months) treated in the pediatric ward were lower than that of healthy children of same age group. In a review of 12 studies evaluating the relationship between vitamin D deficiency and lower respiratory tract infections in

children, it was observed that children with lower respiratory tract infections had significantly lower vitamin D levels than the control group. A correlation was also found between Vitamin D levels and the severity of the disease compared to controls (15). In studies conducted in Kuwait, Egypt and Jordan, it has been reported that pneumonia is more common in children with rickets, and this prolongs the hospitalization period due to pneumonia. (22-24). A study conducted in Bangladesh on 50 children about the correlation between vitamin D levels and lower respiratory tract infections showed that when compared to the control group, children diagnosed with lower respiratory tract infections have lower serum vitamin D levels, reporting that vitamin D deficiency is in relation with lower respiratory tract infections in pediatric population (25). Sutcu et al (26) also showed that children younger than 5 years old treated at inpatient clinic who are diagnosed with lower respiratory tract infections have low vitamin D levels. Our results were similar to these studies.

Vitamin A, works in keeping the integrity of the respiratory tract epithelia, helping lower the frequency of lower respiratory tract infection in children younger than 5 years old (27,28). Moreover, vitamin A, increases the synthesis of immunoglobulins, thus effecting humoral and cellular immunity. Vitamin A deficiency is found to be in relation with dysfunction of humoral and cellular immunity, keratinization of respiratory epithelia and decrease in mucus secretion (29).

The study by Zhang X et al (30) showed that there is a meaningful relation between lower respiratory tract infections and vitamin A deficiency. Multiple studies show that following a vitamin A treatment, the hospitalization time due to lower respiratory tract infections decrease significantly (31,32). There are few studies in the literature showing the relation between vitamin A deficiency and lower respiratory tract infection. Studies about this subject are mostly on supplementation of vitamin A in order to decrease the symptoms of lower respiratory tract infection and the results are conflicting (31,33-35).

In our study, it is shown that children hospitalized due to lower respiratory tract infection have low levels of vitamin A. There was no significant correlation between vitamin A levels and weight and height percentiles. It has been reported in the literature that low vitamin A level is a factor contributing to pneumonia in children and that vitamin A level is associated with the severity of pneumonia and the subsequent development of recurrent lower respiratory tract infections (36). Vitamin A, a micronutrient, is defined as a class of compounds that exert a multifunctional effect on human health. These molecules can act as regulators in biological functions such as development, vision, and intestinal barriers. It has been confirmed that vitamin A deficiency inhibits normal regeneration of the mucosal barrier disrupted by infection and impairs innate immunity by weakening the function of neutrophils, macrophages, and natural killer (NK) cells (37). Additionally, Vitamin A is indispensable for the adaptive immune system. In this present study, we detected that both vitamin A and vitamin D levels were low in children with lower respiratory tract infection.

Vitamin A and vitamin D are both lipid soluble vitamins and play key roles in the development, maturity and the strengthening of the immune system in pediatric population (37). The study by Zhang J et al. (37), examined the vitamin A, D and E levels in 422 children with lower respiratory tract infection and 100 healthy children. Four hundred and twenty two children were then divided into two groups: active and stable. Vitamin A levels of the children in both active and stable groups were found to be meaningfully lower than those of the control group. Similar results were found for vitamin D levels. Moreover, both vitamin A and vitamin D levels were lower in the active group when compared to those in the stable group. The study also concluded that there is a meaningful correlation between the active group and the vitamin A and D levels. Our study showed that patients with lower respiratory tract infection had lower vitamin A and vitamin D levels as well as a positive meaningful correlation between the vitamin A and vitamin D levels.

Lipid soluble vitamins are necessary micro nutrients and different vitamins play different roles in development of children. Several studies show that changes in the levels of lipid soluble vitamins A, D and E have impacts on the immune system. Low levels of vitamins A, D and E, reduce the immune response, causing severe cases of lower respiratory tract infections (38). Vitamin A deficiency cause contagious diseases and long term deficiency increase the death rates. Vitamin D, regulates hematopoietic system, inhibit the growth of tumor cells and have endocrine functions. Supplementation of vitamin D, impacts the clinical course in respiratory tract infections (38). Martineau et al., explained that Vitamin E, which has a similar physiologic function as vitamins A and D, is a good antioxidant and stabilizes the structure of the cell membrane as well as the resistance against lipid peroxidation. Therefore, the supplementation of vitamin E, helps support cellular immunity. Moreover, Martineau et al., showed that there is a positive correlation between vitamins A, D and E levels in children with active lower respiratory tract infections (7). Bergman et al. determined that low levels of vitamin D have positive correlation with the severity of lower respiratory tract infections (39). Studies show that serum calcium levels effect the cell membrane permeability of capillaries and this increases the risk of developing respiratory tract infections. Serum calcium levels are in a positive correlation with serum vitamin D levels, therefore, the possibility of having lower respiratory tract infection is lower in populations with normal levels of vitamin D. Sufficient vitamin levels, decrease the harm caused by lipid peroxide, increase immunity and lower the rate of respiratory tract infections (39).

The positive correlation between vitamins A and D, as well as low levels of vitamins A and D in patients with lower respiratory tract infections shown in our study is supportive of the data in the literature.

The limitation of our study is that the relation of vitamin levels and the severity of the illness have not been evaluated. The strength of our study is that there aren't many studies on the evaluation of serum vitamin A and D levels of children with lower respiratory tract infections, therefore our study contributes to the present literature.

In conclusion, lower respiratory tract infections are still a major cause of death in children 0-5 years in developing countries. Therefore, we believe that determination of vitamin A and vitamin D levels in children with lower respiratory tract infections and providing supplementation if needed is important..

Ethical Approval: *Ethical board approval was received from Bağcılar Education and Research Hospital (February 2nd 2020, number: 2020.02.05.023)*

Author Contributions:
Concept: HC, AÖ, ÖB, ME, ÖBG
Literature Review: HC, AÖ
Design : HC, ÖB, ME
Data acquisition: HC, AÖ, ÖB
Analysis and interpretation: HC, ÖB, ME
Writing manuscript: HC, AÖ, ÖB, ME
Critical revision of manuscript: HC, ME, ÖBG

Conflict of Interest: *The authors have no conflicts of interest to declare.*

Financial Disclosure: *Authors declared no financial support*

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