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Original Article

Serum vitamin D concentration in children with pneumonia and acute respiratory infections, risk factors for its low level

Gohar Ayvazyan[1], Nune Baghdasaryan[1], Lilit Avetisyan[2,3], Nane Mnatsakanyan[2,3], Lilit Aleksanyan[3]

[1] *Children Health Center, Yerevan, Armenia*
[2] *Yerevan State Medical University, after M. Heratsi, Yerevan, Armenia*
[3] *Ministry of Health of the Republic of Armenia, Yerevan, Armenia*

Abstract

Introduction: While there is extensive literature discussing the link between various respiratory infections and risk factors that contribute to low vitamin D levels, there is still no consensus on this relationship. The aim of this study was to test whether low vitamin D levels are associated with pneumonia and acute respiratory infections (ARI) and to identify risk factors for low vitamin D levels in children with these conditions.

Methodology: The study was conducted at the Muratsan Hospital in Yerevan from February to December 2017. It included 140 randomly selected children aged 1 to 5 years, half of whom had pneumonia and the other half had ARI. Based on serum vitamin D levels, the children were further divided into groups with low (52 patients with pneumonia and 38 patients with ARI) and normal vitamin D levels (18 patients with pneumonia and 32 patients with ARI). Factors such as feeding, age, gender, and mother's education were included as indicators of risk for low vitamin D.

Results: The difference between the mean values of vitamin D in groups of children with pneumonia and ARI was statistically significant ($p < 0.05$). Feeding was positively, and age was negatively associated with the level of vitamin D ($p < 0.05$).

Conclusions: We found that children with pneumonia had a lower vitamin D level. We also found that poor nutrition and the age of the child (1 to 5 years) were risk factors for low vitamin D levels with respiratory infections.

Key words: pneumonia; ARI; children; 25-hydroxyvitamin D; risk factors.

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Introduction

While there is extensive literature discussing the link between low vitamin D levels, various respiratory infections, and risk factors that contribute to low vitamin D levels, there is still no consensus on the link between various respiratory infections and low vitamin D levels. Acute respiratory infections (ARI) and pneumonia are the most common illnesses in children under 5 years of age, and the death rate from pneumonia is high, with approximately 1.8 million children dying of pneumonia every year. The World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) are developing a global plan for the prevention and control of pneumonia [1]. Various factors are believed to exacerbate the severity of acute lower respiratory tract infections and are also important determinants of mortality from severe respiratory infections. In this regard, the role of vitamin D is interesting. The problem of vitamin D deficiency is one of the most urgent since according to the results of numerous studies, its deficiency is recorded in half of the world's population [2,3]. It is known that the main functions of vitamin D in the human body are growth, bone mineralization and regulation of the immune system [4,5]. Vitamin D slows down the maturation of dendritic cells, promotes the differentiation of macrophages, affects the functioning of nonspecific defense mechanisms and adaptive immunity, and has anti-inflammatory properties, thereby helping to protect against bacterial and viral infections [6,7]. There have been numerous clinical studies and meta-analyses showing an association between vitamin D deficiency and ARI. However, there is currently no complete understanding of the role of vitamin D in the development of respiratory infections in children, which requires further clarification. Analysis of studies carried out in different countries has shown the presence of alternative views on this problem.

Some authors believe that the lack of vitamin D in children leads to the incidence of respiratory infections. Studies in Ethiopia, Jordan and India have shown that vitamin D deficiency can be considered a predisposing factor to pneumonia in children under 5 years of age, and that subclinical vitamin D deficiency is a significant risk factor for severe lower respiratory tract infections [8,9]. In the group of children with rickets, infections of the lower respiratory tract and a longer hospital stay were much more common [10].

A Turkish study showed that newborns with subclinical vitamin D deficiency have an increased risk of developing lower respiratory tract diseases [11]. The National Institute of Health found a strong correlation between vitamin D deficiency and the incidence of ARI in the first 3 months of life, as well as a high risk of developing respiratory syncytial virus (RSV) in the first year of life [12]. There have also been studies that support the premise that the severity of lower respiratory tract infections in children depends on the level of vitamin D [13,14]. Inamo *et al.* conducted a study in Japan from November 2008 to May 2009 and showed that children with pneumonia and bronchiolitis treated in the intensive care unit have low vitamin D levels [14]. Ginde *et al.* showed that there is a season-independent inverse relationship between serum 25(OH)D and upper respiratory tract infection [15]. The authors found an inverse association between serum 25(OH)D levels and recent upper respiratory tract infection. Children with vitamin D deficiency have also been shown to have a higher risk of developing community-acquired pneumonia [16]. Zhou *et al.* argued that vitamin D status can be used as a new biomarker for the early detection of children with recurrent wheezing, especially in children at risk of severe acute respiratory viral infections. Feketea *et al.* argued that it can also be used to control different wheezing phenotypes. The authors showed that children born in Indonesia with ARI and pneumonia may be deficient in vitamin D [17]. Another study by Oktaria *et al.* argued that vitamin D supplements and sun exposure can increase vitamin D levels and reduce the incidence of these infections [18]. The study found that children under the age of five years with pneumonia were deficient in vitamin D, but did not find a link between the levels of vitamin D and the severity of pneumonia. Comparing children with bronchiolitis with those with non-respiratory infection with a febrile illness, Golan-Tripto *et al.* found that vitamin D levels were significantly lower in the bronchiolitis group, but that the level of vitamin D did not affect the severity of bronchiolitis. While the authors concluded that vitamin D deficiency may be a risk factor for the development of acute bronchiolitis, they suggested that more research on the topic is needed [19].

The meta-analysis by Salamah *et al.* examined the association between vitamin D and ear disease and found that children under 5 years of age with acute otitis media had lower levels of vitamin D, compared with children over 5 years of age. Besides, they found a statistically significant association between otitis and vitamin D deficiency in young children [20].

However, other studies have failed to establish a reliable relationship between vitamin D status and the risk of hospitalization for lower respiratory tract infections. For instance, viral bronchiolitis was not found to be associated with the status of vitamin D among children aged 1-25 months in Canada [21]. Similarly, in Nigeria, the development of lower respiratory tract infection in children was not associated with vitamin D status [22]. Omand *et al.* did not find statistically significant associations between 25-hydroxyvitamin D levels and supplementation vitamin D in the treatment of upper respiratory tract infections [23]. There was also no correlation found between vitamin D levels and lower respiratory tract infections in the study by Işmanlar *et al*., although nearly half of the children included in the study had low vitamin D levels [24].

Among the studies on the role of vitamin D status and the use of vitamin D supplements for the prevention of ARI, the meta-analysis by Cho *et al.* found no statistically significant association between vitamin D supplementation and the prevention of ARI [25]. However, the authors argued that vitamin D deficiency contributes to a high risk of bacterial and viral infections, because it suppresses natural immunity. Another study by Taghivand *et al*. suggested that vitamin D supplementation affects maternal and cord blood vitamin D status in newborns, but does not affect the incidence of pneumococcal disease in infants. Specifically, their results showed that maternal vitamin D intake did not affect the development of pneumococcal infection in infants under 6 months of age, although in vitro vitamin D supplementation had a positive effect on the immune system [26]. Balan *et al*. focused on the link between the levels of vitamin D deficiency among children under 5 years of age and high risk of morbidity and mortality of viral and bacterial pneumonia, both associated with high morbidity and mortality rates among these children. The authors also emphasized the importance of further investigating this problem [27]. All in all, while prior research has extended our understanding of the role of

vitamin D in respiratory infections, further research on the topic is required to make practical recommendations about the association of vitamin D with the more severe types of infections [28].

Objectives

The aim of this study was to test whether low 25-hydroxyvitamin D levels are associated with respiratory infections, with varying severity levels, such as pneumonia and ARIs, and to identify risk factors for low vitamin D levels in children with these diseases.

Methodology

The randomized study was conducted in the pediatric and laboratory diagnostics departments of the Muratsan Hospital in Armenia from February to December 2017. The study included 140 children aged 12 to 60 months; 70 children were diagnosed with pneumonia and 70 children with ARIs. All cases of pneumonia were confirmed by x-ray. Children under the age of 12 months and over 60 months, patients with chronic bronchopulmonary diseases, malabsorption syndrome, cardiovascular pathology, hereditary diseases, and children receiving anticonvulsants were excluded from the study. The two groups were similar in terms of gestational age at birth (all children were full-term), age and gender, and all children received a prophylactic dose of vitamin D during their first year of life. An individual card was filled out for each patient, and parents provided informed consent for their children to participate in the current study.

This study assessed clinical, laboratory, and visual indicators, as well as risk factors for vitamin D deficiency in the development of pneumonia and ARI. Risk factors included the child's age, nutrition, gender, mother's education, length of stay at home, number of hospitalizations, child attendance at kindergarten, having another child at home, sweating, time of birth, and place of residence of the child. In both groups (pneumonia and ARI), children were divided by gender, age (12-30 months and 30-60 months), and the level of vitamin D (deficiency, insufficiency, and sufficiency). The level of 25(OH)D (calcidiol) in the blood serum was determined using an immunological analyzer Cobas e 411 from ROCH (Warsaw, Poland) by the electrochemiluminescence method. The standard indicators of vitamin D in blood serum were adopted, taking into account the recommendation of the International Endocrinological Society in 2011, which defines deficiency of 25(OH)D as a level of < 20 ng/ml. According to the International Endocrinological Society, the deficiency, insufficiency, and normal levels of vitamin D are considered < 20 ng/ml, 20-30 ng/ml, and 30-100 ng/ml, respectively.

In the next section, we present the descriptive statistics as well as the results from ordinary least squares (OLS) regressions. The study was approved by the Ethics Committee of the Yerevan State Medical University, and it complies with the Declaration of Helsinki.

Table 1. Research groups.

Groups	Pneumonia n = 70	Acute respiratory infections n = 70
Gender		
Boys	37 (53%)	40 (57%)
Girls	33 (47%)	30 (43%)
Age		
12-30 months	30 (43%)	44 (63%)
31-60 month	40 (57%)	26 (37%)
Vitamin D level		
< 20 ng/mL	23 (33%)	18 (26%)
20-30 ng/mL	29 (41%)	20 (28%)
> 30 ng/mL	18 (26%)	32 (46%)

Results

In the group of children with pneumonia, 37 (53%) were boys and 33 (47%) were girls, while in the group with ARI, there were 40 (57%) boys and 30 (43%) girls. There were 30 children with pneumonia and 44 children with ARI, aged 12 to 30 months, and 40 children with pneumonia and 26 children with ARI, aged 31 to 60 months. Vitamin D deficiency was in 23 (33%) children with pneumonia and in 18 (26%) children with ARI. Vitamin D insufficiency was in 29 (41%) children with pneumonia and in 20 (28%) children with ARI. The normal level (sufficiency) of vitamin D was in 18 (26%) children with pneumonia and in 32 (46%) children with ARI. The groups for this study are presented in Table 1.

Figure 1. Comparison groups.

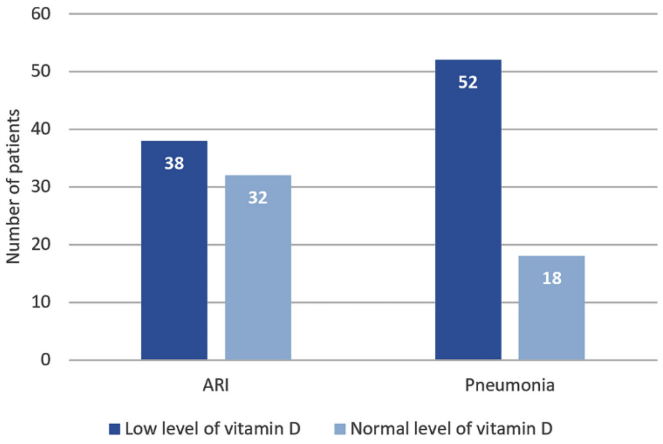


Table 2. Test of difference between groups with pneumonia and with acute respiratory infections.

Groups	Pneumonia (n = 70)	Acute respiratory infections (n = 70)	t-test
Level of vitamin D	24.98 (1.295)	29.40 (1.599)	2.144**

** $p < 0.05$.

Since the vitamin D deficiency and insufficiency groups were small, they were included in the main group with a low vitamin D content for comparison with the control group with a normal vitamin D content. The main group included 52 children with pneumonia and 38 children with ARI. The control group included 18 children with pneumonia and 32 children with ARI. The comparison groups for this study are shown in Figure 1.

The average age of children with low calcidiol levels was 32.94 months. The number of children before and after 30 months was the same. The average age of children with normal calcidiol levels was 29.87 months. Children under 30 months predominated. There were 49 patients (36 with a low level of vitamin D and 13 with a normal level of vitamin D) with pneumonia and 45 (25 with a low level of vitamin D and 20 with a normal level of vitamin D) with ARI, admitted to the clinic that were from Yerevan. In addition, 21 (16 with low vitamin D and 5 with normal vitamin D) with pneumonia and 25 (12 with low vitamin D and 13 with normal vitamin D) with ARI, were from regions. The average gestational age of the examined children was 37.9 ± 2.7 in the main group and 38.6 ± 0.84 in the control group. Of the 140 children, 69 attended kindergartens, 46 (66.7%) in the main group and 23 (33.3%) in the control group, and 101 (72%) had other children in the family. Based on the anamnesis, 83 children (51 in the main group and 32 in the control group) received vitamin D for prophylaxis in the first year of life. All the patients were vaccinated. As a result, identical groups were obtained in terms of gestational age, growth rates, age, gender, and place of residence. We compared the main and control groups of children with pneumonia and ARI, using a t-test and obtained the results presented in Table 2.

We examined the risk factors for low vitamin D levels in the general group (140 children), using an OLS regression. These results are presented in Table 3. Feeding and age (in months) appear to have a significant effect on vitamin D levels. Although feeding has a positive effect on vitamin D levels ($p < 0.05$), the effect of age is negative ($p < 0.05$), which means that the older (30-60 months) the baby, the more likely it is to have lower vitamin D levels.

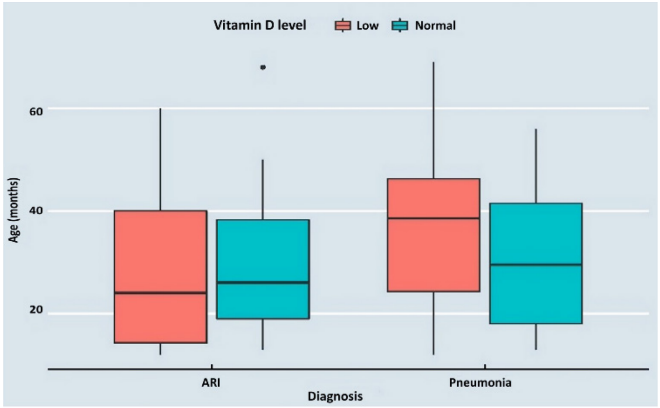
Figure 2 presents the results from comparing the risk factors between the groups of children with pneumonia and ARI. t-test results imply that the difference in means for Vitamin D levels for received status is statistically significant in ARI and pneumonia groups (p value = 0.007). Figure 3 presents the differences in the average level of vitamin D in the two groups of children, according to their intake of the

Table 3. Factors related to the level of vitamin D.

Variables	Level of vitamin D
Feeding	3.215**
	(1.410)
Age (month)	- 0.197**
	(0.0781)
Gender	0.700
	(2.318)
Region	3.126
	(2.261)
Mother's education	0.179
	(1.191)
Kindergarten	1.590
	(2.558)
Another child at home	- 3.104
	(2.809)
Hospitalization type	0.475
	(0.627)
Home duration	- 0.328
	(0.220)
Sweat	1.070
	(2.164)
Birth season	0.0907
	(0.991)
Vitamin D dose	0.130
	(2.150)
Constant	31.71***
	(4.520)
Observations	140
R-squared	0.116

Robust standard errors in parentheses. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$.

Figure 2. Age of children and vitamin D levels, acute respiratory infection (ARI) and pneumonia groups.



prevention dose of vitamin D. The figure does not provide evidence for differences in the level of vitamin D between children, who were given the dose and those, who were not. Besides, in the group with pneumonia, the level of vitamin D seems to be even lower for children receiving the prophylactic dose versus those, who did not receive that dose.

Figure 4 presents the relationship between vitamin D levels and feeding in the ARI and pneumonia groups. We did not find a statistical difference in the mean vitamin D levels for the irrational and breasts categories for the ARI and pneumonia groups. There seems to be a difference in the two groups, based on formula feeding (p value = 0.029), however, the sample sizes (8 and 9 observations in the ARI and pneumonia groups, respectively) are too small to achieve good statistical power. Overall, the figure shows that vitamin D levels were low in children who received inappropriate feeding and did not depend on the diagnosis.

Discussion

Our research examined the link between vitamin D levels and respiratory diseases. Many articles have pointed to a high incidence of respiratory infections, both in adults and among young children with vitamin D deficiency [29]. In the context of COVID-19, a prior study by Puca *et al*. suggested a possible relationship between vitamin D deficiency and the severity of the viral disease [30]. Vitamin D is recognized for its vital role in various physiological processes within the body, particularly in its influence on the immune system. Vitamin D modulates the effect of both innate and adaptive immunity, regulates the function of the inflammatory cascade [29], reduces the maturation of dendritic cells and the release of cytokines, while increasing the differentiation of macrophages and

Figure 4. Feeding and vitamin D levels, acute respiratory infection (ARI) and pneumonia groups.

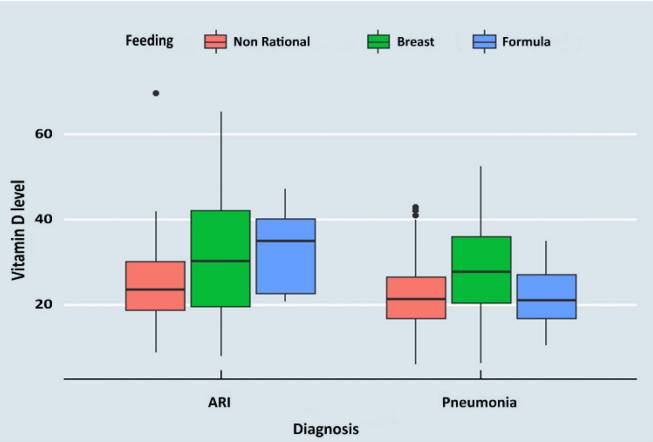
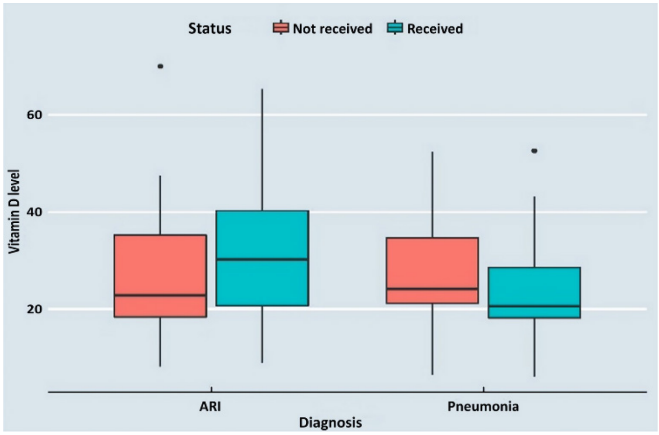


Figure 3. Differences in vitamin D levels associated with prophylactic vitamin D intake in groups with acute respiratory infection (ARI) and pneumonia.



bacterial killing. Vitamin D contributes to the suppression of the inflammatory process, due to a decrease in the production of TH1 cytokines and an increase in TH2 cytokines, as well as an increase in the suppression of T helpers [5,6]. Vitamin D enhances the production of endogenous cathelicidin peptide, which has antimicrobial activity [7]. Therefore, with a deficiency of vitamin D, the body's defense against respiratory infections is reduced.

In our study, the level of vitamin D in the group of children with pneumonia was significantly different from that in the group of children with ARI. Children with pneumonia had lower vitamin D levels. Our results were similar to those of some clinical trials. For example, studies have confirmed the role of vitamin D deficiency in the risk of tuberculosis in children, recurrent acute otitis media, and severe bronchiolitis, while further research is needed to confirm the association in children with recurrent pharyngotonsillitis, acute rhinosinusitis, and community-acquired pneumonia [16,29,31]. Li *et al*. found a significant difference in vitamin D levels in groups of children with pneumonia and sepsis, with lower serum vitamin D levels being associated with more serious medical conditions, such as sepsis [32]. The meta-analysis by Pham *et al.* [33] showed that there is a relationship between vitamin D concentration and ARI, and that vitamin D may play an important role in preventing the risk and severity of ARI, especially in patients with low 25(OH)D concentration.

Based on our study, feeding and age (in months) appear to significantly affect vitamin D levels in 140 children (children with pneumonia and ARI). Our results suggest that, especially in children with pneumonia, the older the child is, the more likely s/he

is to have lower vitamin D levels. In addition, we found that taking a prophylactic dose of vitamin D in the first year of life does not contribute to normal serum 25(OH)D levels in children with pneumonia. The other risk factors that we included in the study were also statistically insignificant. These factors include gender, maternal education, the presence of another child at home, region of residence, kindergarten attendance, amount of hospitalization, sweating, and season of the child's birth.

A prior study showed that subclinical vitamin D deficiency and non-exclusive breastfeeding in the first 4 months of life were significant risk factors for severe acute respiratory infections in children under 5 years of age [9]. Another study by Hashemian and Heidarzadeh found a significant link between vitamin D levels and the development of pneumonia [34]. In particular, the authors showed that low vitamin D levels were prevalent only in children with pneumonia aged 24-60 months, but that low levels of vitamin D were also observed in healthy children of the same age, although to a lesser extent.

Conclusions

In this study, we found that there is a link between vitamin D and respiratory diseases in young children. Vitamin D levels were found to be significantly lower in pneumonia, a more severe disease, compared to ARI. We also showed that age is a risk factor for low vitamin D levels in pneumonia. Among children aged 36 to 60 months, vitamin D levels were significantly lower in children with pneumonia than in children with ARI of the same age. A prophylactic dose of vitamin D in the first year of life did not affect serum 25(OH)D levels in children with pneumonia in this age group. Therefore, this difference in serum vitamin D levels emphasizes the need for preventive measures to address vitamin D deficiency in children after 36 months of age with more serious illnesses, like pneumonia. Our study also suggests that proper nutrition can contribute to a better vitamin D status in children. Finally, although our study revealed a positive correlation between vitamin D levels and pneumonia and ARI, it is limited by a small sample size. Hence, examining the association between vitamin D and respiratory infections in larger samples in multicenter facilities and with different ethnicities can be a fruitful avenue for future research.

Authors' contributions

All authors contributed equally to the creation of this manuscript.

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Corresponding author
Gohar Ayvazyan, MD, PhD.
Associate Professor, Children Health Center, Pediatrics Clinic, 11/4 Argishti Str., Yerevan 0015, Armenia.
Tel: +37499092950
Email: ayvgohar@gmail.com

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