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ORIGINAL ARTICLE

# Serum Vitamin D Levels in Children with Recurrent Respiratory Infections and Chronic Cough

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**Abstract**
*Objectives* To evaluate serum vitamin D levels in cases of recurrent respiratory infections and chronic cough and to investigate the effect of vitamin D therapy on recurrence of the diseases.
*Methods* This prospective observational study was performed by comparing serum vitamin D levels in children with recurrent respiratory infections, chronic cough and healthy children. One-hundred-one children with chronic cough, ninety-eight children with recurrent respiratory infections and one-hundred-twenty-four healthy children were enrolled in the study. A structured questionnaire was completed to collect data on demography, diet, duration of breastfeeding, vitamin D supplementation and family history for allergic diseases. In patients with low serum vitamin D levels (<20 ng/ml), vitamin D therapy was administered in addition to conventional treatment for the diseases. Patients were followed up for 6 mo and their complaints were evaluated.
*Results* Mean serum 25(OH) vitamin D level in the recurrent respiratory infections group was 11.97 ± 4.04 ng/ml, chronic cough group was 13.76 ± 4.81 ng/ml and control group was 31.91 ± 18.79 ng/ml. Comparison of serum 25(OH) vitamin D levels between the study groups revealed a statistically significant difference ($p < 0.05$). 25(OH)D deficiency in children was associated with increased frequency of recurrent respiratory infections and chronic cough.
*Conclusions* To conclude, administration of supplementary vitamin D may be useful in the treatment and preventation of recurrent respiratory infections and chronic cough.

**Keywords** 25-hydroxyvitamin D · Child · Cough · Recurrent infections

## Introduction

Vitamin D receptors are found in most cells and tissues in the body, including osteoblasts, immune cells, β-islet cells, brain, heart, skin, gonads, prostate, colon and breast. Vitamin D regulates the activity of various immune cells, including monocytes, dendritic cells, T and B lymphocytes and immune functions of epithelial cells [1]. Vitamin D increases the conversion of immature monocytes to mature macrophages and causes an increase in other macrophage functions. The antimicrobial activity of vitamin D starts with recognition of bacterial products by toll-like receptors [1]. Vitamin D deficiency can lead to inflammation [2]. Recurrent respiratory infections (RRI) and chronic cough in childhood are widespread diseases and some of the most common reasons for consultation in routine pediatric practice [3]. The prevention and treatment of these diseases is important.

A previous study demonstrated that vitamin D metabolites up-regulate the synthesis of intercellular antimicrobial peptide (cathelicidin) which is capable of killing micro-organisms and viruses [4]. Vitamin D levels above the threshold of 20 ng/ml (50 nmol/L) are necessary to optimize bone density and

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immunological health in children [5]. Studies have demonstrated the role of vitamin D in decreasing the risk of pediatric infections [6] and acute lower respiratory tract infections [7] and also linked vitamin D deficiency with severe lower tract respiratory infections requiring hospitalisation [8, 9]. The severity of allergic diseases tend to increase in children who have lower levels of vitamin D. In addition, a recent clinical study suggests a therapeutic role for vitamin D supplementation in the treatment of allergic diseases [10].

Chronic cough is usually descibed as the cough lasting more than 4 wk [11] and is associated with high morbidity in children and their families. The prevalance of chronic cough is 22 % in children [11]. The causes of chronic cough in children vary depending on age. In preschoolers with chronic cough, the most common cause was persistent bacterial bronchitis (40 %). The next most common cause was prolonged upper respiratory tract infection (URTI), while only 10 % of cases were caused by asthma, upper airway cough syndrome or gastroesophageal reflux disease. In school children, the most common causes of chronic cough were asthma (25 %), persistent bacterial bronchitis (23 %), upper airways syndrome (20 %) and gastroesophageal reflux disease (5 %) [11]. Inflammatory processes of the respiratory tract are associated with up regulation of both cough hyperactivity and bronchial hyperactivity and may lead to asthma or are associated with chronic cough. In recent decades, the prevalence of recurrent infections and chronic cough have been steadily increasing [12]. However, quite a few data are available on the effect of vitamin D therapy in recurrent infections and chronic cough cases with low serum vitamin D levels [6, 7].

The aims of this study were to compare the association between serum 25 hydroxy vitamin D [25(OH)D] levels and RRI and chronic cough in children and investigate the effect of vitamin D therapy on the recurrence of these diseases.

## Material and Methods

This prospective observational study included 323 children who aged 6–86 mo and visited outpatient clinic of the Department of Pediatrics, Baskent University Hospital, from June 2014 through May 2015. Ninety-eight children with RRI, one-hundred-one children with chronic cough and one-hundred-twenty-four children with no symptoms or signs of RRI and chronic cough as controls were enrolled. The study conformed to the principles outlined in the Declaration of Helsinki. Informed written was obtained from the parents. The study was approved by Baskent University Institutional Review Board (Project no: KA15/215) and supported by Baskent University Research Fund.

Cough lasting more than 4 wk was described as chronic cough [11]. Type of cough, diurnal pattern, aggravating factors, quality of the cough (dry or productive) and associated symptoms were evaluated from the clinical records. A child with URTI at least 6 times or lower respiratory tract infection (LRTI) at least 2 times per year was defined as a patient with RRI [13]. The interval between every two infections should be at least 7 d. Infants under 11 mo with LTRI at least 2 times per year were accepted as RRI. Diagnosis of rhinitis, nasopharyngitis, oropharyngitis, tonsillitis, laryngitis or otitis media were evaluated as URTI. Tracheitis, bronchitis, bronchiolitis and pneumonia were assessed as LRTI. The admitting physicians diagnosed LRTI on the basis of the modified WHO criteria which include a history of fever, cough, rapid breathing, abnormal auscultatory findings (crackles, crepitations, bronchial breath sounds) and radiological evidence of abnormal pulmonary parenchymal disease [14].

Otherwise healthy subjects with no history of RRI and chronic cough were accepted as control group. Controls were age-matched and had similar demographic characteristics with cases and had no active infection. Children having a history of congenital disease, hereditary disease, tumor, surgery, gastroesophageal reflux and foreign body aspiration were excluded from this study. Baseline demographic data including age and gender were collected for all participants in the study. Each parent completed a structured questionnaire to collect data regarding breastfeeding history, vitamin D supplementation, type of outdoor clothing, duration of exposure to sunlight in a week and family history of allergic diseases. Cases in the study and control groups were enrolled during the same seasonal period. Systemic physical examination was performed in the study and control groups; calcium, phosphorus, hemoglobin, white blood cell count, eosinophil (%), mean platelet volume (MPV), 25(OH)D levels were measured in each case. Blood samples were taken when the patients had no active infection. Serum hemoglobin and ferritin levels were measured to rule out iron deficiency anemia.

Serum 25(OH) D levels above 20 ng/ml were regarded as normal, 15–20 ng/ml as vitamin D insufficiency, <15 ng/ml as vitamin D deficiency, and <5 ng/ml as severe vitamin D deficiency [15, 16]. Patients with low serum vitamin D levels (<15 ng/ml) were administered vitamin D3 (cholecalciferol) 5000 IU/day for 3 mo in addition to conventional treatment for diseases. Vitamin D3 therapy of 400 IU/day was administered to patients with serum 25(OH)D levels >15 ng/ml. All cases were followed up for number of RRI attacks within 6 mo after treatment being recorded.

Venous blood samples were drawn and sera were stored at –20 °C after centrifugation until testing. All assays were carried out at the same time. The levels of 25(OH)D were assayed using chemiluminescent microparticle immunoassay (Abbott Architect I2000 analyser). The Architect 25-OH Vitamin D assay is designed to have a Limit of Detection (LoD) of≤10.0 ng/ml. Serum leukocyte, platelet, hemoglobin, calcium, phosphorus, eosinophils and MPV (blood samples anticoagulated with $K_3$EDTA) were measured in blood cell

counter using an Abbott Cell-Dyn Ruby System (Abbott Diagnostics, Santa Clara, CA, USA).

The required sample size by power analysis results in three groups with atleast 97 individuals in each; in total, including atleast 291 individuals, were determined. With this, 80.04 % of the power test is expected to be obtained. The results of tests were expressed as the number of observations (n), mean ± standard deviation, median and min-max values. The results of the homogenity (Levene's test) and normality tests (Shapiro Wilk) were used to decide which statistical method to apply in comparison of the study groups. Normally distributed and homogeneous variances groups were compared, two groups by Student's *t* test and three or more groups by Analysis of Variance. According to the test results, parametric test assumptions were not available for some variables, so the comparisons of two independent groups were performed by Mann–Whitney *U* test, comparisons of three independent groups were performed by Kruskal Wallis test. For multiple comparison tests, adjusted Bonferroni test was used. Categorical data was analysed with Fischer's Exact Test and Chi-square test. Exact Test provides two additional methods for calculating significance levels for the statistics available through the Crosstabs and Nonparametric Tests procedures. These methods, the exact and Monte Carlo methods, provide a means for obtaining accurate results when the data fails to meet any of the underlying assumptions necessary for reliable results using the standard asymptotic method. All statistical analyses were performed with the SPSS software (SPSS Ver. 17.0; SPSS Inc., Chicago IL, USA). *p* value of < .05 was considered statistically significant.

## Results

Ninety eight children with RRI, one hundred and one children with chronic cough and one hundred and twenty four children as controls were enrolled. The clinical characteristics of the study subjects are shown in Table 1. Mean age was 45.9 ± 16.2 mo in RRI group, 47.9 ± 15.5 mo in chronic cough group and 30.1 ± 19.4 mo in control group. There were no significant differences in baseline variables (age, gender, diet) between the groups. Duration of exclusive breastfeeding was similar between cases and controls. Duration of vitamin D supplementation was lower in RRI group compared to control group (Table 1) ($p < 0.001$).

The levels of 25(OH)D, ferritin, eosinophil (%), mean platelet volume (MPV), hemoglobin, white blood cell (WBC) and platelet counts were compared between the RRI, chronic cough and control groups (Table 2). Mean serum 25(OH)D level was 11.9 ± 4.04 ng/ml in RRI group, 13.7 ± 4.8 ng/ml in chronic cough group and 31.9 ± 18.7 ng/ml in control group. Serum 25(OH) D levels were lower in RRI and chronic cough groups than control group ($p < 0.05$) (Table 2). There was no significant difference in serum 25(OH) D levels between RRI group and chronic cough group. In RRI group, 85.7 % ($n = 84$) of infections were URTI and 14.3 % ($n = 14$) were LRTI.

Allergy history and family history of allergic diseases (bronchiolitis, asthma, allergic rhinitis and wheezing) showed statistically significant difference between the groups ($p < 0.05$) (Table 1). In chronic cough group, children with allergy history (12.7 ± 4.4) had lower serum 25(OH)D levels than children without allergy history (14.6 ± 5.0) ($p < 0.05$). In RRI group, there was no difference in 25(OH)D levels between allergy history positive and negative children.

**Table 1** Clinical characteristics of the study subjects

| Characteristic | RRI group ($n = 98$) | Chronic cough group ($n = 101$) | Control group ($n = 124$) | *p* value |
|---|---|---|---|---|
| Age (mo) | | | | |
| Mean ± SD | 45.94 ± 16.21 | 47.95 ± 15.57 | 30.19 ± 19.42 | 0.24 |
| (min-max) | (6–84) | (6–86) | (6–79) | |
| Male/female | | | | |
| No. | 43/55 | 54/47 | 67/5 | 0.26 |
| (%) | (43.9/56.1) | (53.5/46.5) | (54/46) | |
| Vitamin D supplementation (mo) | | | | |
| Mean ± SD | 10.16 ± 2.28* | 10.34 ± 2.21 | 10.62 ± 3.2* | 0.43 |
| (min-max) | (4–18) | (4–12) | (4–24) | |
| Duration of breastfeeding (mo) | | ($n = 95$) | ($n = 120$) | |
| Mean ± SD | 8.25 ± 3.2 | 8 ± 2.75 | 8.3 ± 2.9 | 0.81 |
| (min-max) | (3–24) | (2–12) | (3–24) | |
| Allergy history (%) | $n = 56$ (57.1) | $n = 55$ (54.5) | $n = 52$ (41.9) | <0.05 |
| Family history of allergic diseases (%) | $n = 60$ (61.2) | $n = 66$ (65.3) | $n = 60$ (48.4) | <0.05 |

*$p < 0.001$

*n* Number of patients; *SD* Standard deviation; *RRI* Recurrent respiratory infections

**Table 2** Comparison of laboratory parameters between recurrent respiratory infection, chronic cough and control cases

| | RRI group ($n=98$) | Chronic cough group ($n=101$) | Control group ($n=124$) | $p$ value |
|---|---|---|---|---|
| 25(OH)D (ng/ml) | | | | |
| Mean ± SD | 11.97 ± 4.04 [a] | 13.76 ± 4.81 [b] | 31.91 ± 18.79 [a,b] | <0.001 |
| (min-max) | (3.6–19.9) | (3.1–37.6) | (19.7–160) | |
| Ferritin (ng/ml) | | | | |
| Mean ± SD | 43.13 ± 36.42 | 39.79 ± 30.05 | 43.45 ± 33.71 | 0.69 |
| (min-max) | (4.1–237) | (1.5–154) | (3.17–215) | |
| Eosinophil (%) | | | | |
| Mean ± SD | 1.82 ± 1.65 | 2.31 ± 2.07 | | 0.11 |
| (min-max) | (0–6.58) | (0–11.2) | | |
| Mean platelet volume (fL) | | | | |
| Mean ± SD | 7.58 ± 1.36 | 7.62 ± 1.56 | 7.42 ± 1.42 | 0.53 |
| (min-max) | (4.5 ± 11.2) | (0.5 ± 11.8) | (4.6 ± 11.68) | |
| Hemoglobin (g/dl) | | | | |
| Mean ± SD | 12.83 ± 1.28 | 13.09 ± 1.4 | 12.56 ± 1 | <0.01 |
| (min-max) | (10.8–21.7) | (9.7–21.7) | (9.4–16.2) | |
| WBC ($\times 10^3$ /ml) | | | | |
| Mean ± SD | 9.32 ± 3.83 | 9.09 ± 3.15 | 10.25 ± 4.2 | <0.05 |
| (min-max) | 3.67–24.6 | 3.4–20.8 | 3.4–28.9 | |
| Platelets ($\times 10^3$ /ml) | | | | |
| Mean ± SD | 290.8 ± 71.3 | 313.54 ± 75.16 | 342.33 ± 93.54 | <0.001 |
| (min-max) | 128–461 | 164–553 | 151–658 | |

[a,b] $p < 0.05$

*n* Number of patients; *SD* Standard deviation; *25(OH)D* 25-hydroxyvitamin D; *RRI* Recurrent respiratory infections; *WBC* White blood cell

When allergy history negative children in RRI ($n=55$) and chronic cough groups ($n=53$) were compared with control group, lower 25(OH)D levels were found in RRI (11.9 ± 3.6) and chronic cough group (14.6 ± 5.0) than in control group (31.9 ± 18.7).

The mean serum ferritin and MPV levels were similar between the groups. There was no significant difference in serum eosinophil (%) between RRI group and chronic cough group.

Treatment was initiated in cases diagnosed with 25(OH)D deficiency and patients were followed up with regular visits to the hospital. In 6-mo follow-up of RRI and chronic cough group, frequency of diseases and symptoms were found to be decreased with the vitamin D supplementation in 66 (67.3 %) and 59 (58.4 %) of patients, respectively.

## Discussion

Vitamin D is known to play a role in the regulation of immune responses [1]. Studies indicate that vitamin D deficiency may contribute to increased risk of respiratory infections [7, 9]. The aim of the index study was to determine whether 25(OH)D levels were related with RRI and chronic cough. This is the first study evaluating the association between serum 25(OH)D levels and chronic cough. Additionally, the authors investigated the frequency of infections after 25(OH)D treatment. In this study, 25(OH)D levels were found to be lower in RRI and chronic cough groups compared to the control group. The authors also found an association between 25(OH)D levels and RRI. This finding is consistent with other reported studies on the relationship between vitamin D and pediatric infections [7, 17, 18].

Immune response is disturbed, pro-inflammatory cytokines as well as tendency to infections increase in vitamin D deficiency [19]. Vitamin D deficiency predisposes to infection due to effects on cathelicidin, an antimicrobial peptide [4]. Observational studies indicate that vitamin D deficiency is a predisposing factor for infections and may contribute to increased risk of LRTI and URTI [7, 9, 18, 20]. One study reported that vitamin D status is associated with early childhood LRTI and interventions to improve vitamin D status can reduce the burden of LRTI in early childhood [18]. Similarly, the authors found that serum vitamin D levels in patients with RRI were lower than those in the control group. Magnus et al. showed that higher maternal mid-pregnancy 25(OH)D level was associated with a modestly reduced risk of recurrent LRTI by 36 mo, but was not associated with current asthma at 36 mo

[15]. Camargo et al. also suggested that cord-blood levels of 25(OH)D are inversely associated with the risk of respiratory infection and childhood wheezing, but not with incident asthma [16]. In a recent study, vitamin D deficiency also was reported to be common in sick children admitted to pediatric intensive care units [8, 21, 22]. Treatment and preventation of RRI are important since RRI causes morbidity in childhood. These studies together with the index study show a possible contribution of vitamin D deficiency as a risk factor for recurrent infections and support the theory that vitamin D supplementation could be a part of strategies to prevent early childhood infections.

Chronic cough lasts more than 4 wk in children [11]. Chronic cough is associated with high morbidity in children and their families. Postinfectious cough, protracted bacterial bronchitis and asthma are the main causes of chronic cough in children [23]. Chronic cough is frequent in childhood and should be treated based on etiology. This is the first study evaluating the relationship between serum 25(OH)D levels and chronic cough in children. The authors propose that duration of cough in children may be prolonged due to vitamin D deficiency. They found that serum vitamin D levels in patients with chronic cough were lower than those in the control group. There was also no significant difference in serum 25(OH)D levels between RRI group and chronic cough group.

Inflammatory processes of the respiratory tract are associated with up regulation of both cough hyperactivity and bronchial hyperactivity and may lead to asthma or be associated with chronic cough. In nutritional rickets, Vitamin D has been shown to influence allergy-mediating immune cells such as T cells suggesting that vitamin D plays a role in allergy development. In children, lower 25(OH)D serum levels are associated with increased risks for allergic diseases [24, 25]. Zitterman et al. demonstrated an association between vitamin D deficiency and allergic diseases [26]. Vitamin D deficiency was found to increase the risk of allergic diseases in children such as asthma [27]. In the present study authors found an association between allergy history, family history of allergic diseases and serum vitamin D levels. Allergy history and family history of allergic diseases were found higher in RRI and chronic cough group than control group. Vitamin D deficiency may be common in children with allergic diseases. Supporting this notion, authors also found that serum 25(OH)D levels in children having chronic cough with positive allergy history were lower than children having chronic cough without allergy history. It is important to follow up children with history of chronic cough for developing allergic diseases.

The study also evaluated the risk factors for vitamin D deficiency in all subjects. In the index study, there was no significant difference between the duration of breastfeeding and serum 25(OH)D levels and vitamin D supplementation was lower in RRI group than control group. Vitamin D may also be important for improving infections. There was no significant difference in serum eosinophil (%) between RRI and chronic cough groups.

There was no association between serum ferritin levels and serum 25(OH)D levels. Vitamin D deficiency increases the release of pro-inflammatory cytokines such as IL-6 and TNF-α that may lead to a high MPV [28] and vitamin D restores immune function and decreases cytokines levels. However, in the index study authors could not find significant association between serum vitamin D levels and MPV.

Vitamin D has been shown to be an effective adjunctive therapy in the treatment of infections [29]. In the index study, low serum 25(OH)D levels were determined in patients with RRI and vitamin D supplementation was given in vitamin D deficient cases and complaints of patients were evaluated after vitamin D treatment. Since no attacks have been determined in majority of cases with RRI during a six-month-period suggests that vitamin D therapy is effective in children with RRI. Airway inflammation caused by infections, may be decreased by vitamin D replacement. Urashimo et al. showed that vitamin D supplementation in children during the winter months reduced the rate of influenza A infections and the frequency of asthma attacks [30]. With increasing rate of vitamin D deficiency and ease of supplementation in case of deficiency, vitamin D supplementation is likely to become a highly effective intervention in reducing child morbidity and mortality.

In conclusion, in the index study, significantly low serum 25(OH)D levels were found in children with RRI and chronic cough. Co-administration of supplementary 5000 IU/day vitamin D for 3 mo together with conventional treatments may be appropriate in the prophylaxis of RRI and chronic cough. The simple intervention of vitamin D supplementation appears promising in helping to prevent infections and chronic cough in children.

**Contributions** BO: Planning and writing of the paper; BTK: Collection and analysis of the data; NMK: Collection and follow up of the patients; MAT: Statistical analysis; ÖYÖ: Supervisor of the study and will act as guarantor for this paper.

**Compliance with Ethical Standards**

**Conflict of Interest** None.

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