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Mini Review

Lower Respiratory Tract Infections and Vitamin D

Sezer RG* and Bozaykut A
Department of Pediatrics, Zeynep Kamil Maternity and Childrens' Diseases Training and Research Hospital, Turkey

***Corresponding author:** Rabia Gönül Sezer, Zeynep Kamil Maternity and Childrens' Diseases Training and Research Hospital, Department of Pediatrics, Istanbul, Turkey

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Abstract

The present review focuses on vitamin D deficiency in children and its' impact on lower respiratory tract infections. Low serum levels of 25-hydroxyvitamin D is proposed to be risk factor for lower respiratory tract infections, more severe disease progression, exacerbation of astma.

The associations between lower respiratory tract infections and vitamin D does not prove a causal association. Vitamin D supplementation for infants and childen is not routinely suggested for preventing lower respiratory tract infections if vitamin D deficiency is not demonstrated.

Keywords: Asthma; 25-OH-D; Vitamin D; Lower respiratory tract

Abbreviations

25-OH-D: 25-Hydroxyvitamin D; LRTI: Lower Respiratory Tract Infections

Introduction

Low serum levels of 25-hydroxyvitamin D (25-OH-D) is associated with higher risk of lower respiratory tract infections (LRTI) [1-5]. Association between subclinical 25-OH-D deficiency and LRTI in non-rachitic children was first reported by Wayne *et al.* [6] in 2004.

The optimum level of vitamin D intake from diet and sun exposure is still not clear [7]. Routine screening for vitamin D deficiency is not recommended in healthy children [8]. Serum 25-OH-D is a useful marker of vitamin D status [9]. American Academy of Pediatrics defines vitamin D deficiency with serum 25-OH-D levels<20 ng/mL (20 ng/mL=50 nmol/L, based on vitamin D correction); severe deficiency with levels<10 ng/mL [10]. These cut-off values and also recommended daily intake in children are under debate.

The present review focuses on vitamin D deficiency in children and its' impact on LRTI. This review does not include genetic studies and also studies about tuberculosis, atopic diseases other than asthma.

Vitamin D and Lower Respiratory Tract Infections

Wayse *et al.* [6]studied 150 children, aged 2-60 months; serum 25-OH-D>22.5 nmol/L significantly decreased the risk of severe LRTI. In a study of LRTI in children under 5 years old, mean 25-OH-D levels were lower in children who were admitted to intensive care unit than the children admitted to general pediatric ward [1]. Although, this difference was not statistically significant, 25-OH-D levels might influence the severity of infection [1]. These case-control studies suggest low 25-OH-D levels as a risk factor for LRTI and support supplementation to prevent LRTI [1,5,6]. In a hospital-based case study from Japan, 25-OH-D levels<15 ng/mL were correlated with supplementary oxygen need and ventilator management [11]. Oduwole *et al.* [4] proposed serum level of 25-OH-D<30 ng/mL to be an important risk factor for lower respiratory tract infections and pneumonia [4]. This study from Nigeria had a sample size of 24 children with pneumonia and 10 controls, also there was no significant differences in vitamin D status of children with LRTI and controls [4].

It is known that 25-OH-D levels of newborns are highly correlated with mothers' serum 25-OH-D concentrations [5]. Neonates with acute LRTI, admitted to neonatal intensive care unit had lower 25-OH-D levels than healthy control group [5]. Dinlen *et al.* [12] evaluated 60 mother-infant pair; 30 neonates with LRTI admitted to neonatal intensive care unit and 30 healthy controls both in the newborns and the mothers. Vitamin D deficiency in the neonates increased the risk of acute LRTI with an odds ratio of 5.3 (95% CI=1.3-21.1; p=0.01) [12]. The median 25-OH-D level was lower in the study group than in the control group [12]. Camargo *et al.* [2] studied the relationship between the cord 25-OH-D levels and risk of LRTI, wheezing, asthma in newborns. Lower cord levels were found to be associated with increased risk of respiratory infection and wheezing [2]. Belderbos *et al.* [3] followed 156 neonates prospectively; infants with low cord blood 25-OH-D levels at birth were associated with a sixfold increased risk of having RSV-associated LRTI during the first year of life [3].

Contrary to those findings, there are also studies showing no relationship between 25-OH-D levels and LRTI. Ahmed *et al.* [13] studied 50 children with acute LRTI and 50 age and gender matched controls, aged 2-60 months, serum 25-OH-D levels were not different between groups. Mean serum 25-OH-D level was 50> nmol/L in this study [13]. Only the percentage of body surface area exposed to sunlight increased the odds ratio of acquiring acute LRTI [13]. A study from Canada did not find any association between vitamin D status and the risk of hospitalization for acute bronchiolitis [14]. A prospective birth cohort of 777 mother-infant pairs were evaluated for cord blood 25-OH-D levels and the risk of LRTI in the first year of life [15]. The association between decreased cord 25-OH-D levels and LRTI disappeared after stratification for season. Only for children born in fall, the risk for LRTI was associated with low 25-OH-D status [15]. An observational study of children from USA included 38 cases admitted to hospital with acute LRTI, stated that there were no association between vitamin D status and illness severity, length of stay in hospital or the need for pediatric intensive care [16].

The studies with high prevalence of vitamin D deficiencies

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(25-OH-D<50nmol/L) and low mean serum levels (range = 22.8-40.8 nmol/L) found an association between LRTI and vitamin D [5,6]. Studies with lower prevalence of vitamin D deficiency and higher mean serum 25-OH-D levels (range=61.5-130 nmol/L) did not find any association between LRTI and vitamin D status [4,13,14].

Vitamin D and Asthma

Several mechanisms are suggested about the relationship between vitamin D and asthma. Vitamin D decreases alveolar smooth muscle proliferation and airway inflammation, reverses steroid resistance and modulates respiratory infections. Vitamin D and the vitamin D reseptor are both needed in the lung, to induce Th2 cell response and inflammation. Many asthmatic children are vitamin D insufficient, the severity of asthma correlates with the degree of deficiency [17]. Lower vitamin D levels correlated with higher eosinophil counts, increased IgE levels and hyperreactivity [17]. Also, risk of severe athma exacerbations increases with vitamin D deficiency [18]. Mean FEV1 were low in children with vitamin D insufficiency [18]. After correcting for the possible confounder effect of race, the association between asthma and vitamin D deficiency was still significant [18]. No association was found with lower cord levels of 25-OH-D and asthma [2].

On the other hand, there are studies suggesting that vitamin D can be a risk factor for asthma and atopic diseases. Infants, given 200 IU/day vitamin D supplement in the first year of life, had higher risk of allergic rhinitis, asthma, atopy at 31 years old than unsupplemented control group in Finland [19]. A study from Sweden reported daily vitamin D intake >400 IU correlated with the risk of egzema at 6 years of age [20].

Supplementation

The effect of vitamin D supplementation is studied in some double-blind randomised controlled trials. Urashima *et al. [21]* from Japan supplement 1200 IU/day oral vitamin D; risk of influenza A and asthma attacks reduced significantly [21]. A single bolus dose of 100000 IU vitamin D is given to children with pneumonia, the risk of repeat episode decreased within 90 days [22]. When the authors applied 100000 IU vitamin D every 3 months for 18 months to 3046 Afghani children, but increased incidence of radiologically confirmed pneumonia is detected [23]. In these trials, it is not reported if the children had vitamin D deficiency or not [21-23]. Majak *et al.* [24] provided 500 IU/day vitamin D for 6 months and risk of asthma exacerbations decreased [24]. Supplementation of 300 IU/day vitamin D for 7 weeks revealed significant decrease in parent reported acute respiatory infections [25]. Grant *et al.* [26] followed 260 healthy pregnant women from 27 weeks'gestation and their infants from birth to 6 months. Mother-infant pairs received randomly, placebo/placebo, 1000 /400 IU or 2000/800 IU vitamin D/day [26]. Infants in the higher vitamin D group had reduced primary care respiratory infections up to 18 months compared to placebo group [26].

Conclusion

The associations between LTI and vitamin D does not prove a causal association [9,27]. Vitamin D supplementation for infants and childen is not routinely suggested for preventing LRTI if vitamin D deficiency is not demonstrated [27]. Currently recommended doses for vitamin D for children younger than one year are 400 IU/day; older than one year old are 600 IU/day from the Institute of Medicine [8,9].

Future studies should focus on populations at particular high-risk of vitamin D insufficiency, such as infants and pre-school children. The design and interpretation of studies should take into account skin pigmentation/race, latitude, physical activities, sun related variations, obesity, season, nutritional status [7,9]. There is a need for consensus on vitamin D levels appropriate for global health, doses for supplementation, cutoff values for deficiency and/or insufficiency.

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