Is There Any Link Between Vitamin D Deficiency and Lower Respiratory Tract Infections?

Z Cerit, B Şanlıdağ, C Dalkan

ABSTRACT

Objective: Lower respiratory tract infections (LRTIs) are an important public health problem leading to high mortality and morbidity rates in children. Vitamin D (vitD) deficiency has been found associated with rickets/osteomalacia, autoimmune diseases, cardiovascular system diseases and infectious diseases. Growing evidence demonstrated that vitD has a key role in cellular and humoral immunity and also pulmonary functions. Therefore, we aimed to assess the association between vitD deficiency and severity of LRITs in children.

Methods: Hundred and eighteen children aged between six months and five years with LRTIs were enrolled in this study. Wood-Downes scale (0–10 points; mild < 3, moderate 4–7, severe > 8) was used to define the severity of LRITs. Vitamin D deficiency was defined as serum levels of 25-(OH) vitamin D < 20 ng/mL.

Results: The prevalence of vitD deficiency was found 55.9% in our study population. Indoor smoking, inadequate breastfeeding, and the vitD deficiency was found independent predictors of severe LRTIs.

Conclusion: Vitamin D deficiency was found independent predictor of severe LRTIs. Vitamin D deficiency should be kept in mind one of the preventable causes of LRTIs.

Keywords: Breastfeeding, lower respiratory infections, indoor smoking, Vitamin D

From:Department of Pediatrics, Near East University Hospital, Nicosia, Cyprus.

Correspondence: Dr Z Cerit, Near East University Hospital, Department of Pediatrics, Near East Boulevard, Nicosia, Cyprus, Tel: 00903926751000; Fax: 00903926751000.
Email: drceritzeyno@gmail.com

INTRODUCTION

Lower respiratory tract infections (LRTIs) are the most important causes of the morbidity and mortality in the childhood. Lower respiratory tract infections are estimated to cause 75% of all acute illnesses and are the leading cause of hospitalization worldwide (1). Premature delivery, low birthweight, malnutrition, inadequate breastfeeding, lower socioeconomic level, crowded living conditions, maternal age, educational level of parents, indoor/outdoor air pollution (especially smoking) and inadequate immunization were defined as predisposing factors of LRTIs (2).

Vitamin D (vitD) is known to play a key role in calcium metabolism and bone health, stimulating intestinal absorption of calcium and phosphorus (3). Vitamin D deficiency is well-known to cause rickets and retard skeletal growth. Several studies demonstrated that correlation between rickets and LRTIs (4, 5). Additionally, Wayse *et al* (6) demonstrated an association of subclinical vitD deficiency and LRTIs in non-rachitic children. Growing evidence demonstrated that vitD is beneficial for cardiovascular health, preventing systemic diseases (diabetes mellitus, autoimmune disorders, various cancers), pulmonary functions and infectious diseases (7, 8).

There are inconsistent results about the association between vitD deficiency and severity of LRTIs in the literature (6, 9–13). Therefore, we aimed to assess the association between vitD deficiency and severity of LRITs.

SUBJECTS AND METHODS

A hospital-based case-control study was conducted in Near East University Hospital, Cyprus in January 2016 – January 2018. A total of 118 cases were children younger than five years of

age admitted to the outpatient clinic with LRTIs. Acute LRTIs defined as a temperature greater than 38 ˚C, consolidation on a chest radiograph, and tachypnea [respiratory rate more than 60 per minute in infants less than two months, more than 50 per minute in infants 3–12 months and more than 40 per minute in children 13–60 months] (14). The study was approved by the local ethics committee.

A structured questionnaire was used to obtain information concerning the age of the child, education of parents (primary education, secondary, graduate or postgraduate), smoking by any member in the family, breastfeeding history, immunization status, and prematurity.

Prematurity was defined as a gestational age under 36 weeks. Adequate breastfeeding was defined as having been breastfed for at least six months. An incomplete immunization was defined as none or partial vaccination schedule in children over two months of age.

Wood-Downes scale

Wood-Downes scale (0–10 points; mild < 3, moderate 4–7, severe >8) was used to define the severity of LRITs. Wheezing, retractions, respiratory rate, heart rate, inspiratory breath sounds and synaosis were used to calculate of Wood-Downes scores.

Laboratory methods

A blood sample was obtained by venipuncture in the participating subjects for serum acquirement during admission. Samples were kept at 48 ˚C for up to 24 hours before being stored at -80 ˚C. Serum 25-(OH) vitD levels were measured by chemiluminescence immunoassay using a Lıaıson analyser (DiaSorin Inc). Vitamin D deficiency was defined as serum levels of 25-(OH) vitD < 20 ng/mL.

Statistical analysis

Statistical analysis was performed using the SPSS, version 20.0 (SPSS, IBM Inc., Armonk, NY, USA) software package. Continuous variables were expressed as the mean ± standard deviation (mean ± SD), and categorical variables were expressed as a percentage (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student's *t*-test was used to evaluate continuous variables showing normal distribution and Mann-Whitney U-test was used to evaluate variables that did not show normal distribution. A *p*-value < 0.05 was considered statistically significant. To identify predictors of severe LRTIs, the following variables were initially assessed in a univariate model: indoor smoking, inadequate breastfeeding, prematurity, incomplete immunization and vitD deficiency. Significant variables in univariate analysis were then entered into a multivariate logistic-regression analysis using backward stepwise selection.

RESULTS

The mean age was found to be 36.7 ± 23.4 months in the severe LRTIs group and 37.1 ± 22.9 months in the non-severe LRTIs group. There was no statistical significant difference between the severe and non-severe LRTIs groups in terms of mean age [$p = 0.743$] (Table 1).

The mean vitD level was found to be 14.1 ± 8.3 ng/mL in the severe LRTIs group and 26.7 ± 11.4 ng/mL in the non-severe LRTIs group. There was significant difference found between the two groups in terms of mean vitD levels ($p < 0.001$). Vitamin D deficiency was found at a rate of 55.9% in all children included in the study. Vitamin D deficiency was found with a rate of 67.1% and 42.5 in severe LRTIs and non-severe LRTIs group, respectively.

There was significant difference found between the two groups in terms of vitD deficiency [$p < 0.001$] (Table1). There was no significant difference between two groups in terms of educational level of parents (Table1).

Table 1: General characteristics of patients.

Patient characteristics		**Severe LRTIs**		***p***
		+	**-**	
		(n = 64)	**(n = 54)**	
Age (months)		36.7 ± 23.4 (46.9)	37.1 ± 22.9 (48.1)	0.726
Educational level of parents	Primary school, n(%)	26 (40.6)	23 (42.5)	0.471
	Secondary school, n(%)	12 (18.7)	10 (18.5)	0.863
	Graduate, n(%)	19 (29.6)	15 (27.7)	0.397
	Postgraduate, n(%)	7 (10.9)	6 (11.1)	0.789
Indoor smoking, n(%)		46 (71.8)	11 (20.3)	< **0.001**
Inadequate breastfeeding, n(%)		39 (60.9)	14 (25.9)	< **0.001**
Incomplete immunization, n(%)		12 (18.7)	3 (5.5)	< **0.001**
Prematurity, n(%)		21 (32.8)	7 (12.9)	< **0.001**
Vitamin D level (ng/ml)		10.7 (14.1±8.3)	28.1 (26.7±11.4)	< **0.001**
Vitamin D deficiency, n(%)		43 (67.1)	23 (42.5)	< **0.001**

LRTIs: Lower respiratory tract infections

Table 1. General characteristics of patients.

There were significant difference between two groups in terms of indoor smoking, inadequate breastfeeding, incomplete immunization, prematurity and mean Wood-Downes scores [71.8% *vs* 20.3% $p < 0.001$, 60.9% *vs* 25.9% $p < 0.001$, 18.7% *vs* 5.5% $p < 0.001$, 32.8% *vs* 12.9% $p < 0.001$, 12.7 ± 3.1 *vs* 4.1 ± 2.8 $p < 0.001$; respectively] (Table1).

The results of univariate analyses are presented in Table 2. On univariate analysis, indoor smoking, inadequate breastfeeding, incomplete immunization, prematurity and vitD deficiency were associated with severe LRTIs (Table2).

Table 2: Univariate analysis of predictors for severe LRTIs.

Predictor variables	**OR (95% CI)**	***p***
Indoor smoking, n(%)	2,842 (1.861 – 4.937)	< **0.001**
Inadequate breastfeeding, n(%)	1.634 (1.276 – 2.058)	< **0.001**
Incomplete immunization, n(%)	1.417 (1.149 – 1.938)	< **0.001**
Prematurity, n(%)	2.627 (2.053 – 5.861)	< **0.001**
Vitamin D deficiency, n(%)	2.382 (1.867 – 4.381)	< **0.001**

LRTIs: Lower respiratory tract infections,

Table 2. Univariate Analysis of Predictors for Severe LRTIs.

On multivariate analysis Indoor smoking, inadequate breastfeeding, and the vitD deficiency were found the independent predictors of severe LRTIs [OR 2.137; 95% CI: 1.439–3.185; $p < 0.001$, OR 2.429; 95% CI: 1.716-4.384; $p < 0.001$, OR 1.967; 95% CI: 1.429-3.065; $p < 0.001$, respectively] (Table3).

Table 3: Multivariate analysis of predictors for severe LRTIs.

Predictor variables	**OR (95% CI)**	***p***
Indoor smoking, n(%)	2.137 (1.439 – 3.185)	< **0.001**
Inadequate breastfeeding (n%)	2.429 (1.716 – 4.384)	< **0.001**
Vitamin D deficiency, (n%)	1.967 (1.429 – 3.065)	< **0.001**

LRTIs: Lower respiratory tract infections,

Table 3. Multivariate Analysis of Predictors for Severe LRTIs.

DISCUSSION

Our study demonstrated that indoor smoking, inadequate breastfeeding and vitD deficiency were found the independent predictors of severe LRTIs. Growing evidence demonstrated that vitD plays a key role in cardiovascular outcomes, antimicrobial activity, inflammation, lung functions along with calcium and phosphorous homeostasis (15–24).

Vitamin D plays an important role in the maintenance of calcium and phosphate metabolism and bone homeostasis. Serum vitD levels were inversely associated with serum parathormone and phosphorus. Previous studies revealed that a close association between vitD and immune functions, insulin resistance, cardiovascular diseases, autoimmune diseases, and various cancer. Adequate sun exposure, milk products, and other food products (salmon, sun-dried mushrooms and egg yolk) are rich in vitD.

Lack of exposure to sunlight and low physical activity were main risk factors for vitD deficiency (25, 26). Vitamin D modulates the activity of the Toll-like receptor (TLR)-4, responsible for initiating the immune response through pathogen-associated molecular

patterns (27). Human antimicrobial peptides synthesized and expressed by neutrophils, macrophages, and respiratory epithelium have activity against bacteria and respiratory viruses [influenza and respiratory syncytial virus] (28).

Previous studies demonstrated that vitD deficiency has a negative effect on the prevalence of LRTIs and disease severity and increases intensive care and oxygen requirements in patients with LRTIs (6, 10, 29, 30). Belderbos *et al* (31) have found a strong inverse association between cord blood vitD levels of newborns and acute respiratory infections (ARIs). Additionally, Camargo *et al* (32) have shown an inverse association between supplementation of vitD and the risk of ARIs. Protective effects of vitD on LRTIs are associated with not only immune modulatory functions but also better lung functions (33). Karatekin *et al* (11) reported that newborns with subclinical vitD deficiency might have an increased risk of suffering from ARIs. Cebey-López *et al* (12) revealed that lower levels of vitD were found to be correlated with severity of the LRTIs. Conversely, several studies reported that there was no found correlation between vitD levels and LRTIs (9, 10, 13). In our study, the vitD deficiency was found independent predictor of the severity of LRTIs.

Environmental tobacco smoke (ETS) exposure is a well-known risk factor for acute and chronic lower respiratory illness (34). Tobacco use is the leading global cause of preventable death (35). Despite worldwide initiatives to reduce tobacco smoking, it is estimated that up to 40% of children are still exposed to tobacco smoke (36). Environmental tobacco smoke exposure often begins in utero with maternal smoking or exposure. Potential mechanisms for ETS induced damage include impaired *in utero* lung growth from suppression of fetal breathing or direct genotoxicity (37). Tobacco smoke comprises a large number of chemicals and carcinogens, all of which may affect the developing respiratory system (38). Further, there is evidence linking the effects of tobacco smoke exposure to

impaired early-life immune function resulting in an imbalance in Th1 and Th2 responses increasing the susceptibility to allergic diseases and childhood respiratory infections (38, 39).

Previous studies demonstrated that indoor smoking is an independent predictor of severe LRTIs (10, 34). Consistent with previous studies we found that indoor smoking is an independent predictor of severe LRTIs.

Exclusive breastfeeding for the first six months of life with breastfeeding along with complementary feeding after that is recommended by the World Health Organization (WHO) (2). Beneficial effects of breastfeeding including against a wide range of infections and illnesses are well-known (40, 41). Breast milk contains various antimicrobial/anti-inflammatory components and factors that promote immune development (41, 42).

It enhances the immature immune system of the infant and strengthens defense mechanisms against infectious and other agents during the breastfeeding period (41–44). Mc Nally *et al* (10) reported that there was no significant association between inadequate breastfeeding and LRTIs. In our study, inadequate breastfeeding was found an independent predictor of severe LRTIs.

Our study has some limitations. First, a small sample size of the present study. Second, there is no data about treatment strategies of this population and response to treatment with regard vitD status.

CONCLUSION

In our study, the vitD deficiency was found independent predictor of severe LRTIs. Vitamin D deficiency should be kept in mind one of the preventable causes of LRTIs especially in patients with recurrent LRTIs. Further studies with a larger number of patients are required for the evaluation of the association between serum vitD level and severity of LRTIs.

Author contributions

ZC conceived paper, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. BŞ participated in study design, data analysis and interpretation, critically revised manuscript and approved final version. CD participated in study design, data analysis, and interpretation of data and revision of manuscript and approved final version. The authors declare that they have no conflicts of interest.

REFERENCES

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997; **349**: 1436–42

2. WHO. The World Health Report 2005: Redesigning child care: Survival, growth and development. Geneva: World Health Organization 2005; **127**-43.

3. Pettifor JM, Prentice A. The role of vitamin D in paediatric bone health. Best Pract Res Clin Endocrinol Metab 2011; **25**: 573–84

4. Muhe L, Lulseged S, Mason KE, Simoes EAF (1997). Case control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. Lancet 1997; **349:** 1801–4.

5. Najada AS, Habashneh MS, Khader M (2004). The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. J Trop Pediatr 2004; **50**: 364–8.

6. Wayse V, Yousafzai A, Mogale K, Filteau S.. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. Eur J Clin Nutr 2004; **58**: 563–7.

7. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006; **81**: 353-73.

8. Pichler J, Gerstmayr M, Szepfalusi Z, Urbanek R, Peterlik M, Willheim M. 1a,25(OH)2D3 inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. Pediatr. Res. 2002; **52**: 12–8.

9. Haugen J, Chandyo RK, Ulak M, Mathisen M, Basnet S, Brokstad KA, et al. 25-Hydroxy-Vitamin D Concentration Is Not Affected by Severe or Non-Severe Pneumonia, or Inflammation, in Young Children. Nutrients. 2017; **9**. pii: E52. doi: 10.3390/nu9010052.

10. McNally JD, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol. 2009; **44**: 981-8. doi: 10.1002/ppul.21089.

11. Karatekin G, Kaya A, Salihoğlu O, Balci H, Nuhoğlu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. Eur J Clin Nutr. 2009: **63**: 473-7.

12. Cebey-López M, Pardo-Seco J, Gómez-Carballa A, Martinón-Torres N, Rivero-Calle I, Justicia A, et al. Role of Vitamin D in Hospitalized Children With Lower Tract Acute Respiratory Infections. J Pediatr Gastroenterol Nutr. 2016 ; **62**: 479-85

13. Şişmanlar T, Aslan AT, Gülbahar Ö, Özkan S. The effect of vitamin D on lower respiratory tract infections in children. Turk Pediatri Ars. 2016; **51**: 94-9.

14. World Health Organization (1995): The Management of Acute Respiratory Infection in Children: Practical Guidelines for Outpatient Care. Geneva: WHO.)

15. Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). J Cyst Fibros 2007; **6**: 403–10.

16. Cerit L. Vitamin D as a Modifiable Risk Factor for Incident Heart Failure in Atrial Fibrillation. JACC Heart Fail. 2018; **6**: 85-6.

17. Cerit L. Cardiac Syndrome X, Vitamin D, and Lipoprotein(a). Heart Lung Circ. 2017; **26**: e104

18. Cerit L. Bermuda triangle; heart failure, atrial fibrillation, and vitamin D deficiency. J Cardiovasc Med (Hagerstown). 2017; **18**: 121.

19. Cerit L. Prediction of thromboembolic events for patients with non-valvular atrial fibrillation; CHA2DS2-VASc-UA2-VitD. Int J Cardiol. 2017; **229**: 13.

20. Cerit L. Heart failure and vitamin D receptor gene. Clin Nutr. 2017; **36:** 313.

21. Cerit L, Kemal H, Gulsen K, Ozcem B, Cerit Z, Duygu H. Relationship between Vitamin D and the development of atrial fibrillation after on-pump coronary artery bypass graft surgery. Cardiovasc J Afr. 2017; **28**: 104-7.

22. Cerit L. Postoperative atrial fibrillation and vitamin D. J Geriatr Cardiol. 2016; **13**: 643-4.

23. Cerit L. Vitamin D3 supplementation: Response and predictors of vitamin D3 metabolites - A randomized controlled trial. Clin Nutr. 2016; **35**: 1583.

24. Cerit L. Genetic variation in vitamin D receptor gene (Fok1:rs2228570) is associated with risk of coronary artery disease. Biomarkers. 2017; **22**: 387.

25. Bener A, Al-Ali M, Hoffmann GF. VitaminDdeficiency in healthy children in a sunny country: associated factors. Int J Food Sci Nutr. 2009; **60**: 60-70. doi: 10.1080/09637480802400487.

26. Abu Shady MM, Youssef MM, Salah El-Din EM, Abdel Samie OM, Megahed HS, Salem SM, et al. Predictors of Serum 25-Hydroxyvitamin D Concentrations among a Sample of Egyptian Schoolchildren. ScientificWorldJournal. 2016; **2016**: 8175768.

27. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; **311**: 1770–3.

28. Kota S, Sabbah A, Chang TH, Harnack R, Xiang Y, Meng X, et al. Role of human beta-defensin-2 during tumor necrosis factoralpha/NF-kappaB-mediated innate antiviral response against human respiratory syncytial virus. J Biol Chem 2008; **283**: 22417–429.

29. Banajeh SM. Nutritional Rickets and Vitamin D Deficiency Association With the Outcomes of Childhood Very Severe Pneumonia: A Prospective Cohort Study. Pediatr Pulmonol 2009; **44**: 1207-15.

30. Inamo Y, Hasegawa M, Saito K, Hayashi R, Ishikawa T, Yoshino Y, et al. Serum vitamin D concentrations and associated severity of acute lower respiratory tract infections in Japanese hospitalized children. Pediatr Int 2011; **53**: 199-201.

31. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 2011; **127**: e1513–20.

32. Camargo CA Jr, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics 2012; **130**: e561–7.

33. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. Chest 2005; **128**: 3792–8.

34. Cheraghi M, Salvi S. Environmental tobacco smoke (ETS) and respiratory health in children. European Journal of Pediatrics. 2009; **168**: 897-905

35. World Health Organisation. WHO report on the global tobacco epidemic. Mpower. Luxemborg: WHO press; 2013.

36. Öberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. The Lancet. 2011; **377**: 139-46

37. Grant SG. Tobacco smoke exposure and somatic mutation in newborns. Open Pediatric Med J. 2010; **4**: 10-3.

38. Gibbs K, Collaco JM, McGrath-Morrow SA. Impact of Tobacco Smoke and Nicotine Exposure on Lung Development. Chest. 2016; **149**: 552-61.

39. Singh SP, Gundavarapu S, Pena-Philippides JC, Rir-Sima-ah J, Mishra NC, Wilder JA, et al. Prenatal secondhand cigarette smoke promotes Th2 polarization and impairs goblet cell differentiation and airway mucus formation. Journal of immunology (Baltimore, Md : 1950). 2011; **187**: 4542-52. Epub 2011/09/21.

40. Hörnell A, Lagström H, Lande B, Thorsdottir I. Breastfeeding, introduction of other foods and effects on health: a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nutr Res. 2013; **12**; 57.

41. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, et al. Breast-feeding: A commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2009; **49**: 112–25. doi: 10.1097/MPG.0b013e31819f1e05 PMID: 19502997

42. Hanson LA. Session 1: Feeding and infant development breast-feeding and immune function. Proc Nutr Soc. 2007; **66**: 384–96. doi: 10.1017/S0029665107005654 PMID: 17637091

43. Hanson LA, Korotkova M, Lundin S, Håversen L, Silfverdal SA, Mattsby-Baltzer I, et al. The transfer of immunity from mother to child. Ann N Y Acad Sci. 2003; **987**: 199–206.

44. Jansen MA, van den Heuvel D, van Zelm MC, Jaddoe VW, Hofman A, de Jongste JC, et al. Decreased Memory B Cells and Increased CD8 Memory T Cells in Blood of Breastfed Children: The Generation R Study. PLoS One. 2015; **10**: e0126019. doi: 10.1371/journal.pone.0126019.