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RESEARCH ARTICLE

ASSOCIATION OF SERUM VITAMIN D LEVELS WITH SEVERITY OF ACUTE RESPIRATORY TRACT INFECTIONS IN CHILDREN FROM AN AREA WITH ABUNDANT SUNLIGHT

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ABSTRACT

This study is to find the association between serum vitamin D levels and severity of acute respiratory tract infections (ARTI) in children from an area with abundant sunlight. A one year cross sectional observational study conducted at a rural tertiary teaching hospital at Kolar, South India with a sample size of 82 clinically diagnosed ARTI and serum Vitamin D levels measured. Cases were classified into three sub groups as per Integrated management of childhood illnesses (IMNCI).Amongst, thirteen (15.8%) cases had no pneumonia, 38 (46.4%) had pneumonia and 31 (37.8%) had severe pneumonia. Vitamin D level was insufficient in 58.5%, deficient in 34.2% and sufficient in 7.3%. Pneumonia and its severity with deficient Vitamin D levels association were statistically significant ($p<0.001$). Significant association existed between Vitamin D levels with clinical pallor, socioeconomic status and sunlight exposure. The deficiency of vitamin D was found to be a modifiable risk factor in prevention of ARTI.

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INTRODUCTION

Vitamin D is a fat-soluble vitamin obtained either from diet or synthesized in skin tissues predominantly. Ultraviolet- B (UV-B) light induces the biosynthesis by converting 7-dehydrocholesterol present in skin to previtamin D3, which is then converted to vitamin D3, hydroxylated in the liver to 25-hydroxyvitamin D (25-OH D3) and finally in the kidney to an active metabolite 1, 25-dihydroxyvitamin D by hydroxylase action (Holick, 2013). The major role of vitamin D in bone mineralization and calcium metabolism is established by way of its endocrine like actions. In addition, recently Vitamin D is found to have several other functions in humans such as modulation of cell growth, immune function and reduction of inflammation (Holick, 2013). The immuno modulation role of vitamin D against infections is explained in terms of synthesis of antimicrobial peptide (AMP), cathelicidin antimicrobial peptide (CAMP) and defensin in the body (Prietl, 2013). Many gene encoding proteins that regulate cell proliferation, differentiation and apoptosis are shown to be modulated at least in part by vitamin D. The recent focus of Vitamin D is on its role in non-skeletal conditions including immunity (Deeb, 2004; Albanna *et al*., 2010). Low vitamin D status has also been associated with an increased risk of type - 1diabetes mellitus (Kostoglou-Athanassiou, 2013), cardiovascular disease (Danik, 2012), certain cancers (Garland, 2006), cognitive decline (Raina, 2016), depression (Spedding, 2014), autoimmunity (Arnson, 2007) and even frailty (Wilhelm-Leen, 2010). There has been increasing interest in the role of vitamin D in respiratory infections. In one Indian study, an association between low serum vitamin D levels and an increased incidence of respiratory tract infections has been reported (Wayse, 2004). Vitamin D deficiency is widely prevalent in a subclinical form in children and adults (Papandreou, 2010). There is evidence to suggest that subclinical vitamin D deficiency is common in India despite lying in low latitude and having plentiful sunshine. Modern day life styles have significantly reduced the total duration of sun exposure in children. UV B rays, having shorter wavelength, tend to scatter earlier or later in the day and hence cutaneous vitamin D synthesis is maximum between 10 AM and 3 PM. Generally, during this time most of the children are either in school or indoors. Exposure of only face, hands and arms due to clothing versus whole body is associated with marked differences in Vitamin D synthesis predisposing to decreased levels of Vitamin D (Rathi, 2011). Acute respiratory tract infection (ARTI) is a major public health problem worldwide. In young children, it is responsible for an estimated 3.9 million deaths worldwide. In developing countries, seven out of 10 deaths in children under 5 years of age occur due to ARTI (Park, 2013). In India, ARTI contributes to 15-30% of all under five deaths

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and most of these deaths are preventable (Sharma, 2013). A number of social and environmental factors are associated with ARTI morbidity and mortality in childhood. Various risk factors associated with ARTI are poverty, malnutrition, low birth weight, inadequate breast feeding, overcrowding, poor housing conditions, micronutrient deficiency, indoor and outdoor air pollution (Jackson, 2013). Various measures have been taken up for the prevention and control of ARTI all over the world, which include exclusive breast feeding up to six months of age, vaccinations, providing adequate nutrition, encouraging hand washing and intake of micronutrients (Roth, 2008). Nutritional Vitamin D deficiency in Indian children was observed and reported to be a significant risk factor for severe ARTI (Muhe, 1997 and Bergman, 2013). They are also at a greater risk of developing asthma with low levels of vitamin D[21]. Therefore, studies suggested that subclinical Vitamin D deficient levels predisposes to ARTI (Kostoglou-Athanassiou, 2013; Danik, 2012; Garland, 2006; Larkin, 2014). ARTI is commonly seen in children with rickets, but subclinical vitamin D insufficiency predisposes children to ARTI in spite of belonging to areas of geographical areas with plenty of sunshine. Thereby, evaluation of an association of Vitamin D levels with ARTI in a geographical area needs to be assessed; this forms the basis and need of our study.

MATERIALS AND METHODS

Study population

Children with ARTI aged between two months and five years attending the Department of Paediatrics at a rural tertiary level care teaching hospital of South India were clinically diagnosed and enrolled in the study after obtaining informed consent from the parents . Study was conducted between November 2014 and November 2015 after obtaining ethical clearance (No: DMC/KLR/ IEC-CER/254 / 2016-2017) from Institutional ethics committee. Study design was a cross sectional observational hospital based study. A sample size of 82 was estimated based on the prevalence of ARTI of 20% (Park, 2013).

Study tools: Children were evaluated with a detailed clinical history (nature and duration of symptoms) and background characteristics including feeding practices (breastfeeding history and age of introduction of complementary foods), immunization status and socio-demographic variables such as the parental education, occupation, family income, details of cooking fuel used in the household, family history of smoking, and history of ARTI in the past. Information was also collected regarding the practice of exposure of the child to sunlight. A semi-structured proforma was prepared. Based on severity of ARTI, patients were classified according to the IMCI criteria (WHO, 2012).

Sample collection: Two milliliters of venous blood sample was collected under aseptic condition using plain vacutainer, allowed to clot and the serum was separated by centrifugation. The clear sera were stored at -80^0 C until analysis. Vitamin D levels were classified as per the Endocrine Society recommendations in which vitamin D deficiency was defined as a 25(OH)D level of 20 ng/mL or less, 21 to 29 ng/mL as insufficient and 30 ng/mL or greater as sufficient[1]. All children with deficient Vitamin D levels (≤ 20ng/ml) received Vitamin D supplementation as per Stoss regimen (Holick, 2013). All other children received the recommended Vitamin D supplements of 400 IU/day.

Method: In vitro quantification of serum 25-hydroxy Vitamin D (25-OH D2& 25-OH D3) was estimated by Immuno enzymatic assay according to the procedure sheet of MicroVue 25-OH Vitamin D Enzyme Immunosorbent (EIA) Assay kit supplied by the QUIDEL Corporation USA. A calibration curve was plotted and the total 25OH Vitamin D (D2 and D 3) concentrations of the samples were determined by dose interpolation from the calibration curve (Product insert MicroVue).

Inclusion criteria

Children aged between two months and five years with ARTI. Based on Revised Classification and Treatment of Childhood Pneumonia under Integrated Management of Childhood Illnesses (IMCI) (WHO, 2012), ARTI was defined as follows: No Pneumonia- Cough or cold (by history) and no fast breathing; Pneumonia- Cough or difficulty breathing (by history) and chest in-drawing (fast breathing: number of breaths in one minute for 2-12 months as ≥ 50 breaths per minute; 12 months -5 years fast breathing ≥40 breaths per minute); Severe Pneumonia /Very Severe Disease - Cough or chest in drawing or stridor in a calm child or difficulty breathing and any general danger signs like inability to feed, lethargy, cyanosis.

Exclusion criteria

Children already on vitamin D supplementation and children with clinical rickets.

Statistical Analysis: Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions.

Chi-square test was used as test of significance for qualitative data. Yates correction was applied where ever applicable.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data. EPI Info (CDC Atlanta), Open Epi, Med calc and Medley's desktop were used to estimate sample size, odds ratio and reference management.

RESULTS

The present study results illustrates relationship between Vitamin D and ARTI, age, gender, religion, socio-economic status, feeding types, exposure to sunlight and clinical pallor.

Vitamin D with ARTI: Out of 82 children with ARTI, serum Vitamin D was significantly less in majority (92.7%) of subjects. Vitamin D insufficiency was present in 48 (58.5%) and deficiency in 28(34.2%). Pneumonia and severe pneumonia or very severe disease was present in 69(84.2%) of the study subjects collectively of whom 38(46.4%) had pneumonia and 31(37.8%) had severe pneumonia or very severe disease. This clearly indicates that majority (92.7%) of study subjects having insufficient or deficient serum Vitamin D levels had a higher incidence of pneumonia and severe pneumonia or very severe disease as shown in Table 1.

Table 1. Association of serum vitamin d with severity of pneumonia

Vitamin d levels	No pneumonia	Pneumonia	Severe pneumonia Orvery severe disease	Total	χ2 value	'p' value
SUFFICIENT ≥30ng/ml N=6	4(66.6%)	1(16.7%)	1(16.7%)	6	36.6	<0.001
IN SUFFICIENT 21-29ng/ml N=48	9(18.8%)	30(62.5%)	9(18.7%)	48		
DEFICIENT ≤20ng/ml N=28	-	7(25%)	21(75%)	28		
TOTAL	13	38	31	82		

Table 2. Association between age of arti cases and serum vitamin d levels

	Age in months					χ2 VALUE	'P' VALUE
	2-12	13-24	25-36	37-48	49-60		
SUFFICIENT ≥30ng/ml N=6	5(83.3%)	1(16.6%)	-	-	-	2.51	0.867
IN SUFFICIENT 21-29ng/ml N=48	27(56%)	9(18.7%)	6(12.5%)	3(6.4%)	3(6.4%)		
DEFICIENT ≤20ng/ml N=28	14(50%)	7(25%)	3(11%)	1(3.5%)	3(10.5%)		

Table 3. Association between gender of arti cases and serum vitamin d levels

Vitamin d	Gender		χ2 Value	'P' Value
	Male	Female		
SUFFICIENT ≥30ng/ml N=6	3(50%)	3(50%)	0.522	0.770
IN SUFFICIENT 21-29ng/ml N=48	31(64%)	17(36%)		
DEFICIENT ≤20ng/ml N=28	17(60%)	11(40%)		

Table 4. Association between socio economic status of arti cases and serum vitamin d levels

	Upper class	Upper middle Class	Middle Class	Lower Middle Class	Lower Class	χ2 value	'p' value
SUFFICIENT ≥30ng/ml N=6	1(16.66%)	3(50%)	1(16.66%)	1(16.66%)	-	23.8	0.002*
IN SUFFICIENT 21-29ng/ml N=48	1(2%)	15(31%)	10(20%)	16(33%)	6(14%)		
DEFICIENT ≤20ng/ml N=28	1(3%)	3(13%)	19(67%)	4(14%)	1(3%)		

Vitamin D levels and age: In the study, out of 63 study subjects below 24 months of age, only 6(9.5%) had sufficient Vitamin D levels while none of the subjects above 24 months of age had sufficient serum Vitamin D.

Vitamin D and gender: In the study, there was a male predominance (62.2%) among the subjects with ARTI. Out of 51 male children, only 3(5.8%) had sufficient Vitamin D levels. Likewise out of 31 female children only 3(9.7%) had sufficient Vitamin D levels as depicted in Tables 2.

Vitamin D and religion: In our study, out of 82 subjects only 8(9.7%) children were Muslims and 4(5.3%) were Christians. The remaining 70(85%) study subjects were Hindus. All the 6 children with sufficient Vitamin D levels were Hindus. We could not find any association between religion and Vitamin D levels as majority (85%) of study subjects were Hindus.

Vitamin D and socioeconomic status: In the present study, it was observed that out of 6 children with sufficient serum Vitamin D levels, 3(50%) hailed from upper middle class families. In children with deficient Vitamin D levels, majority

(67%) belonged to middle class families while only 3% belonged to upper class families. Similarly, only 2% of subjects in the insufficient group hailed from upper class families as indicated in Table 3.

Vitamin D and type of feeding: Study results observed that majority (73.2%) of children were exclusively breast fed. Out of 6 children with sufficient vitamin D levels, 5 (83.3%) received exclusive breast feeding. Out of 48 children with insufficient vitamin D, majority (77%) were exclusively breast fed. Likewise, out of 28 children with deficient vitamin D levels, 64.2% were breast fed exclusively. However, there was no significant association between type of feeding and Vitamin D levels in our study (p value =2.40).

Vitamin D and duration of exposure to sunlight: In our study with sufficient vitamin D levels, 50% of children were exposed to 1-2 hours of sunlight per day. In the group with deficient serum vitamin D levels, 60% received 3-4 hours of exposure to sunlight per day while 18% and 11% received 5-6 hours and >6 hours of sunlight exposure per day respectively. The study shows that vitamin D deficiency was significantly more in children receiving less hours of sunlight exposure($p<0.008$).

Vitamin D and clinical pallor: In the group with sufficient vitamin D levels, clinical pallor was present in only 33.4% while in the insufficient group and deficient groups it was present in 66.6% and 92.8% respectively showing a significant association between serum Vitamin D deficiency and clinical pallor as presented in Table 4.

DISSCUSSION

Our study showed that majority (92.7%) of study subjects having insufficient or deficient serum Vitamin D levels had a higher incidence of pneumonia and severe pneumonia or very severe disease. Wayse *et al*. (Wayse *et al*., 2004) observed that sub clinical vitamin D deficiency was a significant risk factor for ALRI in children below 5 years of age which is in conformity with our study. Many increasing number of in vitro, ex vivo and animal studies have described the effects of Vitamin D on the innate immune response as well as on the B and T cell response with contradictory results (Khoo *et al*., 2012). And a study has summarised that Vitamin D seems to facilitate the direct antimicrobial effects of the innate immune system and to attenuate an (over-)whelming inflammatory response by modulating the crosslink between cells of the innate immune system and T cells (Pletzetal, 2014). Roth *et al*. (2010) reported similar results in children 1 to 18 months of age who were hospitalized with acute lower respiratory tract infections. These studies suggest that Vitamin D deficiency might increase the severity of a respiratory infection in children and that infants and children with vitamin D deficiency and ARTI might require higher levels of care than in children with sufficient Vitamin D levels. Overall serum Vitamin D levels were low in the subjects below 5 years of age however; there was no significant association between age and serum Vitamin D levels found in our study. High prevalence rates of Vitamin D deficiency are reported in otherwise healthy infants, children and adolescents from India and abroad (Holick *et al*., 2013). Roth *et al*. (2010) reported that 25(OH)D levels were significantly lower in children aged 1-18 months with ARTI than in control subjects which is in conformity with our study. In contrast, Wayse *et al*. (2004) observed a significant increase of serum Vitamin D levels with age in children below 5 years with ARTI which is not in conformity with our study. There was no significant association between Vitamin D status and gender in our study. Rabbani *et al*. (2009) however reported that low serum Vitamin D levels were five times more prevalent in girls than in boys among healthy school children in Teheran. This finding can possibly be explained by the prevailing cultural practices, skin pigmentation, more clothing of the body and lesser participation in outdoor activities leading to decreased cutaneous vitamin D synthesis. Our study showed a significant association between socio economic status and serum vitamin D levels. In a review article, it was reported that individuals with hypovitaminosis D were mostly of low socio economic status with low daily intake of calcium (Arabi *et al*., 2010) while another study by Vasudevan *et al*. (2014) found that children from the higher socio economic group were at greater risk of hypovitaminosis D probably due to less sun exposure. However, Wayse *et al*. (2004) found no relationship between Vitamin D levels and socio- economic status of the children with ARTI.

No significance was found in our study between type of feeding and serum Vitamin D levels .Exclusive breast feeding in the first 4 months of life was significantly associated with decreased risk of severe ALRI in the study conducted by Wayse *et al*. (2004) and Leis *et al*. (2012). On the other hand, Abdul Razzak *et al*. (2011) reported that, Infants who were exclusively breast fed had a higher risk of Vitamin d deficiency and insufficiency than those who were bottle fed. The vitamin D stores of the newborn depend entirely on the vitamin D stores of the mother. Hence, if the mother is vitamin D-deficient, the infant will be deficient because of decreased materno-foetal transfer of vitamin D (Salle *et al*., 2000). The risk factors associated with low maternal 25-OHD include low educational level, insufficient intake of vitamin D in diet and dressing habits (Balasubramanian and Ganesh, 2008). Hence exclusively breast fed infants may be predisposed to hypovitaminosis D secondary to decreased vitamin D levels in mothers which may in turn predispose the infants to ARTI. We also found that duration of sun exposure and serum levels of vitamin D had a significant association as cultural and health practices can contribute to vitamin D insufficiency preventing infants from acquiring vitamin D from sun exposure. In some cultures infants are swaddled when outdoors, minimizing their sun exposure. Application of sunscreen lotions and creams to limit the sun's damage to skin can suppress cutaneous synthesis of vitaminD3 by blocking the absorption of UV B radiation[7]. In addition, atmospheric pollution may decrease the UV rays reaching the children exposed to sunlight in spite of belonging to area with plenty of sunshine as explained in study by Agarwal *et al*. (2002).

Our study findings showed a significant association between serum Vitamin D deficiency and clinical pallor. Similarly, in a study done in South Korea on children aged $\leq$ 2 years, the authors showed a significant association between coexisting iron deficiency and vitamin D deficiency (Grindulis *et al*., 1986). Several mechanisms have been proposed to explain the association of vitamin D deficiency and anemia. Erythroid precursors are believed to be directly stimulated by vitamin d suggesting the latter's role in erythropoiesis. Another explanation offered is that absorption of vitamin D may be impaired due to iron deficiency. However there is a controversy as to which deficiency causes the other (Dastidar and Halder, 2015). Study of risk factors for ARTI in our study showed presence of anaemia as a significant risk factor for developing

ARTI. The proposed pathophysiologic basis for increased risk of infection is that neutrophils have a decreased capacity to kill organisms due to decreased myelo peroxidase activity. It was also proposed that both the proportion and absolute number of circulating 'T' cells are also reduced and also have defective DNA synthesis. It is known that partially immunized children are more prone to pneumonia. A significant association was found between immunization status and ARTI in a study done by Broor *et al*. (2001) but no such association was demonstrated in our study. In our study, Murray *et al*. (2012) in their study found significant association between type of fuel used as a risk factor for pneumonia but no such association was found in the present study. A significant association between type of feeding in first six months and severity of pneumonia was observed in the present study. It was found that those children receiving top milk were associated with pneumonia. Colostrum is known to possess antibodies against various pathogens, higher concentration of C3, Ig A and lactoferrin which protect the breast fed children against infection (Savitha *et al*., 2007). In the present study it was also found that there was an association between the passive smoking and severity of pneumonia which was similar to another study by Broor *et al*. (2001). In the present study, the significant risk factors for ARTI were presence of clinical pallor, passive smoking and inadequate breastfeeding in first six months of life.

Conclusion

Variables from this study showed statistically significant associations between severity of ARTI and serum vitamin D levels. Results from this study concludes that deficiency of vitamin D is a modifiable risk factor in prevention of ARTI. There is a significant association between levels of serum Vitamin D and presence of clinical pallor and hence it can be concluded that decreased levels of serum vitamin D levels can also predispose children to anaemia. A significance association ($p<0.002$) between serum vitamin D levels socioeconomic status and duration of exposure to sunlight in our study. Vitamin D deficiency was significantly more in children receiving less hours of sunlight exposure even though subjects are from area receives good sun light. And hence necessary measures needs to be taken for corrections of vitamin d deficiency.

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Limitation of Study: Small sample size -No comparison done with healthy subjects.

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