Original Article

Vitamin D and Acute Respiratory Infections in Children

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Abstract

Background: This study sought to evaluate the association between serum vitamin D levels and acute respiratory infection (ARI) in under-five children in Nnamdi Azikiwe University Teaching Hospital (NAUTH) in Nigeria.

Methodology: This study was conducted in NAUTH, Nigeria, in 2017, in 250 children with ARI, classified into those with acute upper respiratory infection (AURI) and those with acute lower respiratory infection (ALRI). and 250 children without ARI, matched for age and gender. Sociodemographic data and serum vitamin D were obtained. The data were compared between the study and the control groups. The data were compared between those with AURI and those with ALRI.

Results: The mean serum 25(OH)D of (52.2±25.6 ng/ml) in the study subjects was lower than the (57.0±23.9 ng/ml in the control group (t=2.20, p=0.03).The mean serum 25(OH)D levels in children with ALRI [39.8±23.8 ng/ml] was lower than in those with AURI [56.0±24.9ng/ml] (t= 14.83, p <0.001). In addition, the association between low levels of serum 25(OH)D and severity of ALRI was significant (x^2 = 9.45, p = 0.002).

Conclusion: In under-five children, serum vitamin D levels were low, and these low levels were associated more with ALRIs than AURIs in this study.

Keywords: Vitamin D; Vitamin D Deficiency; Under-Five Children; Acute Upper Respiratory Infection; Acute Lower Respiratory Infection.

Introduction

The past decades have witnessed a heightened interest in vitamin D studies and research. This extraordinary renaissance stems largely from a re-evaluation of Vitamin D's potential benefits to human health. Aside from its effect on calcium and phosphorus homeostasis, the discovery that most cells in the human body are endowed with a vitamin D receptor (VDR) and that up to 3% of the human genome may be influenced by vitamin D has provided new insights into the functions of this important vitamin.[1] Vitamin D, traditionally known for its role in calcium homeostasis and bone health also possesses many non–calcemic

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properties one of which is its effects on immunity and respiratory health.[2] It regulates the immune system and as a result influences the susceptibility of children to infections like acute respiratory infection (ARI). As a potent immune system modulator, it acts through its receptor, the Vitamin D Receptor (VDR), which is expressed by most tissues in the body including the cells of the immune system and respiratory system. It enhances chemotaxis and phagocytic properties of cells of the immune system; boosts the function of the innate and adaptive immune system as well as activates the transcription of antimicrobial peptides.[3] These peptides are protective against bacteria, viruses and fungi.

In 2016, the World Health Organization (WHO) estimated that 16% of the 5.6 million under-five deaths were due to ARIs principally pneumonia.[4,5]The majority of these deaths occurred in Africa and South-East Asia. Acute respiratory infections are a significant cause of morbidity and mortality in children, especially in developing countries. Pneumonia alone is the single largest infectious cause of death in children worldwide.[4]Although robust epidemiological data on the burden of ARI in Nigerian children are not available, a study done in Ibadan documented an incidence rate of 6.1 - 8.1 episodes per child per year for ARIs in under-five children.[6]

Studies have shown that the risk factors for ARIs in children include low birth weight, lack of exclusive breastfeeding for six months, overcrowding, incomplete immunization, malnutrition, attendance at day-care centres, exposure to indoor air pollutants from domestic biomass fuel and presence of coughing siblings.[7-9] Low levels of Vitamin D have been linked to increased susceptibility to, and severity of, ARI.[10,11] There are considerable variations in studies comparing serum vitamin D concentration between children with respiratory infections and This association has shown divergent results. People with the lowest blood vitamin D levels reported having significantly more recent colds or cases of flu.[12]Children who took vitamin D_3 supplements daily during winter were 42% less likely to get infected with seasonal flu than those who had placebo.[13]

Several case-control studies conducted in Bangladesh and India reported significant differences in vitamin D status between children with ARI and their controls.[14-17]Conversely, some studies conducted in Canada, India and Egypt showed no differences in the mean vitamin D concentration of subjects with ARI and their controls.[18,19,20] Roth et al[18] and McNally et al[19] noted that the vitamin D status between acute lower respiratory infection (ALRI) subjects and controls were comparable. Jat et al in his study of Indian children aged 1-12 years found no difference between subjects with pneumonia and controls without pneumonia.[20] In Nigeria, a prospective study of 50 children matched for age and gender, by Ahmed et al[21], reported no difference in the mean concentration of 25(OH)D between subjects and controls. Several other studies also showed disparities in their findings.[10,22-5]

There is a paucity of studies on the influence of vitamin D in under-five children in Southeast Nigeria. This has prompted us to undertake this study to determine the association between vitamin D and ARI and its severity in the under-five children with a view to early identification of those at risk and initiating preventive vitamin D supplementation measures to reduce morbidity and mortality in this group of subjects.

Materials and Method

Study Area

The study was conducted February to October 2017 in the children out- patient clinic and children's Emergency room of Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, Nigeria. NAUTH is a tertiary health institution. The hospital maintains a paediatric clinic, which runs Monday to Friday every week from 8 a.m. to 4 p.m. and 24-hour emergency room headed by two consultant paediatricians.

Study Design

This study was a cross-sectional, comparative and hospital-based. The study subjects and control group were matched for age and gender.

Study Participant/ Recruitment

The Subjects were 250 under-five children who presented at the Children's Outpatient Clinics

(CHOP) and Children Emergency Room (CHER) of NAUTH, Nnewi, Nigeria, diagnosed for respiratory tract infections. The Controls were 250 children without respiratory symptoms enrolled from immunization, Outpatient clinics and those being booked for elective surgery in NAUTH. The study subjects and the control group were matched for age and gender. Those participants whose parents/ caregivers gave consent were recruited consecutively as they presented. (Convenient sampling method.)

Sampling Method

All eligible participants who met the inclusion criteria and whose parents/caregivers gave consent were recruited consecutively as they presented to CHER and CHOP until the required sample size was attained. Each subject was assigned a study identification number which was used to label the specimen bottles. The ratio of Subjects to Controls was 1:1 and matched for both age and gender. Children with chronic diseases or malnourishment and those on anticonvulsants were excluded from the study.

Data Collection

Data were collected using a pretested questionnaire administered by the researchers and their research assistants. The research assistants were 3 house officers trained on how to administer the questionnaire to the Parent/Caregiver and the techniques of blood sample collection and they assisted in that capacity.

All cases of ARI were classified into AURI and ALRI. Acute upper respiratory infectionin this study was defined as syndromes involving the upper airways such as rhinitis, pharyngitis, sinusitis, otitis media, epiglottitis, and tonsillitis typically lasting not more than 2 weeks.[26]

ALRI was further classified into pneumonia and bronchiolitis. Pneumonia was classified based on severity as detailed in the Paediatric Association of Nigeria (PAN) guidelines[27]which classifies pneumonia as non-severe if there are mild chest in-drawing and chest auscultatory signs comprising decreased breath sounds, bronchial breath sounds, crackles or crepitations. Severe pneumonia is when a patient has at least one or more of the following features outlined below in addition to the signs of non-severe pneumonia.

- Central cyanosis or oxygen saturation 90% or less on pulse oximetry in room air
- Severe respiratory distress (e.g. grunting, very severe chest in-drawing)
- Chest auscultatory signs: decreased/absent breath sounds or vocal resonance
- Signs of pneumonia with a general danger sign: Inability to breastfeed or drink, lethargy or unconscious, convulsions

Severity of bronchiolitis was assessed using a scoring tool[28]

Tachypnoea was defined as respiratory rate ≥ 60 cycles/minute for children less than 2 months, ≥ 50 cycle/minute for children 2–12 months and ≥ 40cycles/minutes for children aged 12–59 months.[29]

Sample Collection/storage

2ml of venous blood was collected from each participant for vitamin D assay under aseptic technique. The serum of each blood sample was separated and labelled with a study identification number. Separated samples were stored in refrigerators at a temperature -20° c28 and monitored with Fisher brand thermometer and Eurolab ST9269B multi-thermometer until analysis. Analysis was done using ELISA with the assistance of a laboratory scientist.

Data Analysis

Data collected were entered in excel and analysed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM SPSS statistics 21).Subjects and Controls were stratified and matched for age and gender. The relevant means and standard deviation were calculated for normally distributed continuous variables such as age and serum vitamin D level. Categorical variables were presented as percentages for gender, place of residence, social class. Test of statistical significance for the relationship between serum vitamin D status and type and severity of acute respiratory infection was done using chi-square test.

Differences in mean serum level of vitamin D between Subjects and Controls, type and severity of

ARI were assessed using student t-test. A p value of < 0.05 was deemed statistically significant. Findings were presented using appropriate frequency tables and charts.

Socio-economic class was assigned to each participant using Oyedeji's classification.[30]

Definition of terms

Socio-economic class (SEC) defined as the sum of father's occupation and education scores plus mother's occupation and education scores divided by four. Oyedeji's classification has a total of ten points. Five points each for both occupation and educational status. It is the social standing or class of an individual or group.

Low SEC = 4 -5
Middle SEC = 3
High SEC = 1 -2

Vitamin D

Vitamin D status in relation to serum 25-hydroxy vitamin D level was documented based on the America Academy of Paediatrics (AAP)[31] and Institute of Medicine(IOM)[32] reports as follows: Severe deficiency as <5ng/ml (0-12.5nmol/L), Deficiency as 5-<15ng/mL (12.5-37.5nmol/L), Insufficiency as 15-<20ng/mL (37.5-50nmol/L), Sufficiency as 20-100ng/mL (50-<250nmol/L) and Excess as 100-150ng/ml(250-372.5nmol/L). These cut off points were used because of the IOM report that at ≥ 20ng/ml(50nmol/L) the vitamin D needs of majority of the population is met.[32]

Insufficiency = 16 -20ng/dl

Ethical Consideration

Ethical clearance for the study was obtained from the Ethics Committee of NAUTH Nnewi NAUTH/CS/66/VOL.8/91. Permission to conduct the study was also obtained from the Head of Department of Paediatrics, NAUTH Nnewi. Written informed consent was obtained from each participant's parent/caregiver before enrolling the selected subjects into the study after educating them on the overall nature and possible benefits of the study and the role the result of the study may play in improving the management of the patients. Participation in the study was voluntary. No penalty was borne by those who declined inclusion. Every information obtained from the subjects and the controls were treated confidentially as all information was coded. The researcher bore the financial costs for the laboratory tests and no incentives were provided for them.

Results

A total of 500 children aged 1-59 months who met the inclusion criteria were enrolled - 250 Subjects and 250 controls stratified according to age.

There was a slight preponderance of males among the Subjects (57.2%). The number of Subjects and Controls in each age strata were (1-12 months) 90 (36.0%), (12-23 months) 60 (24%), (24-35months) 40(16%), (36-47 months) 30 (12%) and (48-59 months) 30 (12%). There was a significant difference between place of residence of the Subjects and Controls as most children with ARIs resided in the urban areas (56.8%), while those without ARIs were found to reside in the rural areas (53.6%). The flat was the predominant accommodation of the Controls (49.6%), while flat (36.8%) and tenement (poor housing) (36.4%) were the most common accommodation types for the Subjects. Majority of the Subjects (48.0%) and Controls (51.6%) belonged to low socio-economic class (Table 1). Most of the Subjects and Controls had sufficient vitamin D levels greater than 20ng/dl (85.6% and 90.0%) respectively. However, a higher proportion of the Subjects had low vitamin D levels compared to Controls (10.8% versus 3.2%), indicating a prevalence of vitamin D deficiency of 10.8% in the study subjects and 3.2% in the control group in this study. Furthermore, comparison of the means showed that mean serum vitamin D levels of the Subjects - 52.2±25.6 ng/ml was significantly lower than the mean values obtained in the Controls - 57.0±23.9 ng/ml (t=2.20, p=0.03) (Table 2).

A higher proportion of children with acute lower respiratory tract infections were more likely to have severe deficiency (3.4%), deficiency (8.5%) and insufficiency (11.9%) of vitamin D, compared to those with acute upper respiratory tract infection. The mean serum vitamin D level of those with ALRI was significantly lower than that of children with AURI; 39.8±23.8 ng/ml and 56.0±24.9 ng/ml respectively (t=14.83, p<0.001) (Table 3 and 4).

A significantly higher proportion of children with severe ALRI had vitamin D deficiency (20%) and insufficiency (20%) compared to those with non-severe forms of ALRI ($\chi2=9.45$, $p=0.002$) (Tables 4,5 and figure 1). Mean serum vitamin D level was also significantly lower among those with severe ALRI 25.1±15.9ng/ml than in those with non-severe ALRI- 47.4±23.7ng/ml ($t=3.79$, $p<0.001$) (Tables 5 and 6).

Table 1: Sociodemographic Characteristics of the Subjects and Controls

Characteristic	Subjects n (%)	Controls n (%)
Gender		
Male	143 (57.2)	143 (57.2)
Female	107 (42.8)	107 (42.8)
Age (months)		
<12	90 (36.0)	90 (36.0)
12-23	60 (24.0)	60 (24.0)
24-35	40 (16.0)	40 (16.0)
36-47	30 (12.0)	30 (12.0)
48-59	30 (12.0)	30 (12.0)
Mean±SD	**19.4±14.8**	**20.1±13.7**
Mode	<12mths	<12mths
Residence		
Urban	142 (56.8)	116 (46.4)
Rural	108 (43.2)	134 (53.6)
Type of accommodation		
Tenement	91 (36.4)	61 (24.4)
Flat	92 (36.8)	124 (49.6)
Bungalow	49 (19.6)	46 (18.4)
Semi-detached	18 (7.2)	19 (7.6)
Social Class		
High	23 (9.2)	28 (11.2)
Middle	104 (41.6)	93(37.2)
Low	123 (49.2)	129 (51.6)

Mnths=months

Table 2: Serum Vitamin D Level among the Subjects and Controls

Subjects			Controls			
Vitamin D category	n (%)	mean±SD	n (%)	mean±SD	χ	P value
Severe Deficiency	2 (0.8)	4.8±0.2	0 (0.0)			
Deficiency	9 (3.6)	11.9±1.6	4 (1.6)	12.9±1.6		
Insufficiency	16 (6.4)	17.9±1.6	4 (1.6)	18.5±1.8	13.20	*0.004
Sufficiency	214 (85.6)	54.6±20.0	225(90.0)	54.4±18.7		
Excess	9 (3.6)	116.8±11.	17 (6.8)	110.6±7.0		
Total	250(100)	**52.2±25.6**	250(100)	**57.0±23.9**		

SD- Standard deviation, * statistically significant

Table 3: Comparison of the Mean Serum Vitamin D Levels of Under-Five Children with ARIs and those without ARIs

Serum vit. D category	Mean ± SD		t-test (p-value)
	Cases	Controls	
Severe deficiency	2.9 ± 1.5	3.3 ± 2.3	
Deficiency	11.9 ± 1.6	11.6 ± 0.1	
Insufficiency	17.3 ± 0	-	
Sufficiency	53.8 ± 19.6	57.7 ± 19.4	
Excess	126.0 ± 21.3	126.0 ± 19.8	
			-2.397 (0.017*)
Total	60.8 ± 35.5	68.3 ± 33.0	

* = Significant at p-value < 0.05

Table 4: Comparison of Serum Vitamin D Levels Among the Subjects and Controls

CHARACTERISTICS – Serum vit D level	N (%) SUBJECTS N = 244	CONTROLS N = 233	TOTAL N = 477	χ² (p-value)
Severe deficiency: <5	12 (2.5)	2 (0.4)	14 (2.9)	
Deficiency: 5 - <15	6 (1.3)	2 (0.4)	8 (1.7)	
Insufficiency: 15 - <20	1 (0.2)	-	1 (0.2)	
Sufficiency: 20 -100	189 (39.6)	190 (39.8)	379 (79.5)	
Excess: > 100	36 (7.5)	39 (8.2)	75 (15.7)	
				10.002 (0.026*)

* = Significant at p-value < 0.05

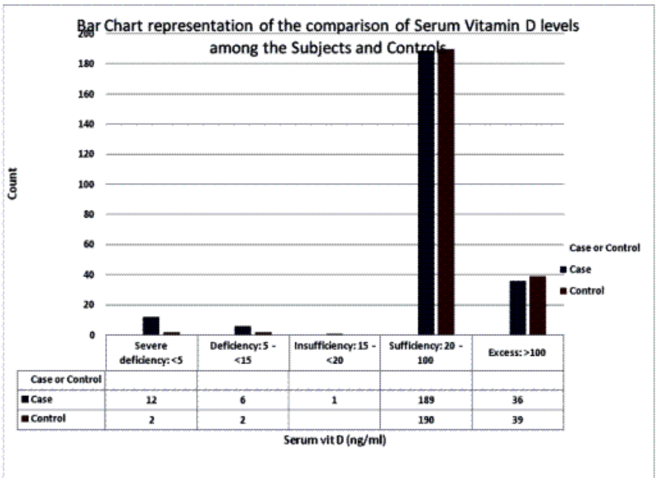

Figure 1:

Table 5: Relationship between Type of ARI and Serum Vitamin D categories among the Subjects

Vitamin D Category	ng/ml	AURI n=191 (%)	ALRI n=59 (%)	t-test	P value
Severe Deficiency	<5	0 (0.0)	2 (3.4)		
Deficiency	5-15	4 (2.1)	5 (8.5)		
Insufficiency	16-20	9 (4.7)	7 (11.9)	14.83	*<0.001
Sufficiency	21-100	170 (89.0)	44 (74.5)		
Excess	101-150	8 (4.2)	1 (1.7)		

****statistically significant***

Table 6: Relationship between Severity of ALRI and Serum Vitamin D status among the Subjects

Vitamin D Status	Mean (ng/ml)	Non-Severe LRTI n=39 (%)	Mean (ng/ml)	Severe LRTI n=20 (%)	χ^2	P value
Severe Deficiency		0 (0.0)	4.8±0.2	2 (10.0)		
Deficiency	10.6	1 (2.6)	11.5±1.6	4 (20.0)		
Insufficiency	19.2±1.0	3 (7.7)	17.6±2.1	4 (20.0)	9.45	*0.002
Sufficiency	48.5±17.9	34 (87.1)	37.7±12.6	10 (50.0)		
Excess	130.9	1 (2.6)		0 (0.0)		
Mean±SD	**47.4±23.7**		**25.1±15.9**			

**statistically significant*

Discussion

This study showed that 10.8% of the study subjects and 3.2% of the control group had serum vitamin D levels <20ng/ml which is the target level recommended by the American Academy of Paediatrics.[31] This finding in this study is much lower than that reported by Ahmed et al[21]and Oduwole and associates.[21,33] Ahmed et al reported 25% of the participants in their study had levels <20ng/ml. However, Oduwole et al documented a prevalence of 20% for vitamin deficiency among the participants, using a cut of value of 27.5nmol/l of vitamin D to define those with deficiency. This cut off value is about 11ng/ml higher than the value used in our study. the disparity in the cut off values of vitamin D might account for the difference in the prevalence of vitamin D deficiency between the Oduwole et al study and ours.

This present study has shown that the mean serum 25(OH)D levels in children with ARI were significantly lower than that of the controls (52.2±25.6 ng/ml versus57.0±23.9 ng/ml). This is similar to the findings of some previously recorded case-control studies.[14,15,23]Wayse et al in India found that subclinical vitamin D deficiency was significantly higher in patients 2 months to 5 years of age with severe pneumonia compared to apparently healthy Controls.[14]In Bangladesh, Roth et al in their study of 25 case-control pairs involving children 1-18 months, an age group that was observed to be dominant in our study, also reported that those who were admitted for ALRI had lower serum vitamin D levels than apparently healthy age and gender matched controls.[15] Furthermore, a study conducted in China amongst children with community acquired pneumonia (CAP) and apparently healthy controls revealed lower serum concentrations of 25(OH)D in Subjects with CAP than in Controls.[23] In addition, Jat[34] in a systematic review and meta-analysis of observational studies documented that children with acute respiratory infections had significantly lower mean serum 25(OH)D when compared with Controls. Conversely, not all researchers found a difference in vitamin D status between the subjects and their controls. In a study involving 50 case-control pairs aged 2-60 months in Nigeria, there was no significant difference in serum vitamin D concentration between the subjects and their controls.[21] In addition, Oduwole and associates also in Nigeria, compared children hospitalized with pneumonia to controls without respiratory symptoms and found no difference in mean 25(OH)D concentration between the two groups.[33] The difference between this present study and the previous studies conducted in Nigeria may be explained by the smaller sample size used by Ahmed and Oduwole. Ahmed used a sample size of fifty while Oduwole used a sample size of twenty four as against a sample size of 250 used in this study.

This study also showed a significant relationship between low serum 25(OH)D levels and presence of ARI similar to the observation made by Liu et al[28]. However, it contrasts with the findings of Iqbal et al[35]who did not find any relationship between serum vitamin D levels and the presence of respiratory illness. The reason for this could be explained by the difference in the methodology and participant characteristics, cut-off values for low vitamin D and inter- assay technique. The present study used a cut-off value of 20ng/ml to define low vitamin D as recommended by AAP as against 30ng/ml used by Iqbal et al and also studied children with different forms of respiratory illness and a wider age group of 6 months to 12years and also higher sample size of 250. Iqbal et also used a small sample size of 40 and vitamin D was assayed among children between the age of 1 month to 1 year. These might have affected the vitamin status of the participants. Age has been reported to affect vitamin D status of individuals.[12,23,36]

This study noted a significant difference in serum vitamin D concentrations between Subjects with AURI and those with ALRI, with the prevalence of low vitamin D observed to be higher in children with ALRI than in those with AURI. The reason for this is uncertain, though ALRI may be considered to run a more severe course than AURI.

Among the Subjects with ALRI, severity of presentation is significantly related to low vitamin D status (p=0.002),in agreement with that reported by Kulkarni and Chougule from India in which they demonstrated an association between hypo vitaminosis D and severity of illness.[37] McNally et al in a study of Canadian children reported an association between low vitamin D levels and severe ALRI requiring admission to a paediatric intensive care unit.[19] However, our study results contrast with the reports of Narang et al who found no association between serum levels of vitamin D and severity of ALRI.[17] Similarly, two Nigerian studies, previously mentioned, observed no significant relationship between serum 25(OH)D and severity of ARI.[21,33] Though as started earlier, the small sample sizes used in the two previous studies may have been accountable for this difference.

Overall, in this study, vitamin D status is significantly associated with the presence of ARI with subjects having significantly low levels compared to their controls. It also showed an association between low levels of vitamin D and severity of ARI. The association of severe ALRI with low vitamin D levels in the present study supports the finding that vitamin D may play an important role in immunity and respiratory health.
Conclusion: In under-five children, serum vitamin D levels were low, and these low levels were associated more with ALRIs than AURIs in this study. Further studies however, should explore a probable role for vitamin D supplementation in children with ARI.

Limitation

Analysis of vitamin D was done using ELISA which is not as sensitive as Liquid chromatography-tandem mass spectrometry which is the gold standard of vitamin D assay.

Conflict of Interest

The authors declare that there is no conflict of interest.

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