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Serum vitamin D levels and its relationship with asthma control and severity among asthmatic children in Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria

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ABSTRACT

Background: Asthma is a heterogeneous disease characterized by chronic airway inflammation with a rising prevalence globally, and its aetiology has been linked to vitamin D (VD) deficiency. **Aim**: This study aimed to determine the serum VD levels and its relationship with asthma control and severity among asthmatic children in UDUTH, Sokoto, Nigeria. **Materials and methods:** This was a cross-sectional study among 60 asthmatic children selected by systematic sampling technique. Data were collected with a proforma; anthropometric measurements, estimation of serum VD levels, and assessment of lung function were done. **Results:** The median age of the asthmatic children was 9.47 years (IQR = 3.98) and majority of them (58.3%) were males. The median serum VD level was 16.25 ng/ml (IQR = 13.38), and about two-thirds of the participants (63.3%) were VD deficient. A half of the participants 30 (50.0%) had well-controlled asthma, 21 (35.0%) had partly-controlled asthma, while 9 (15.0%) had uncontrolled asthma. There was no relationship ($p > 0.05$) between the serum VD levels and asthma control. Almost all the participants (98.3%) had mild to moderate asthma, and majority of them (66.7%) had intermittent or mild persistent asthma. There was no relationship ($p > 0.05$) between the serum VD levels and asthma severity. **Conclusion:** Although VD deficiency was very prevalent among the participants, there was no relationship between the serum VD levels and asthma control and severity. There is need to prevent and control VD deficiency in the study population through VD supplementation, food fortification and promotion of adequate exposure of children to sunlight by mothers.

Keywords: Serum vitamin D levels, asthma control, asthma severity, children

INTRODUCTION

Asthma is a chronic inflammatory condition of airways which gives rise to episodic airflow obstruction.[1] It is the most common chronic obstructive respiratory problem worldwide contributing to a major public health issue.[2] Vitamin D (VD) is a micro element with immunomodulatory and anti- inflammatory functions, and evidence suggests that VD has a role in the aetiopathogenesis of asthma.[3-5] The major source of VD is synthesis of cholesterol in the skin by UV irradiation (dependent on sun exposure).[6] Other sources are by means of diet and supplements. Vitamin D (VD) has long been identified as important in bone and calcium metabolism.[6] The detrimental effects of VD deficiency in paediatrics have become increasingly apparent and extend beyond skeletal health.[7] Additional important role of VD in extra skeletal health, particularly childhood asthma has been found.[7] Vitamin D has basic regulatory roles in immune function (immunomodulatory properties) of almost all cells especially on the airways of asthmatic children.[8] It affects Th1 and Th2 cytokines which contribute to the development of atopy (including asthma).[9] Moreover, VD has effects on epithelial, T and B lymphocytes, and antigen presenting cell functions.[10] In addition, by induction of regulatory T (T reg) cells to produce interleukin (IL) – 10, VD modulates inflammatory processes and could help to control asthma severity.[11] It acts as a paracrine factor modulating foetal lung maturation and smooth muscle cell proliferation thereby promoting lung development.[12] Studies suggest that there is a probable relationship between VD status and asthma-related symptoms presumably via the immune modulatory effects of VD.[13-16] Freishtat *et al*[16] in 2010 observed that a great majority of urban children in U.S.A with persistent asthma had

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VD deficiency and / or insufficiency. Uysalol *et al*[15] in 2013 studied VD deficiency in Italian asthmatic children and observed a causal relationship between them. A higher frequency of asthma attacks, more severe asthmatic episodes and greater difficulty in asthma control were observed in asthmatic children with low VD levels.

Reduced VD levels in adult and paediatric patients with asthma are associated with impaired lung function, increased airway hyperreactivity, and reduced corticosteroid response.[17] Also, children experiencing mild to moderate asthma with low VD concentration had more exacerbations.[18] However, some studies have reported contrasting effects of VD on asthma.[19,20] Nevertheless, there are uncertainties in defining the appropriate VD cutoffs and threshold/critical values for respiratory diseases and variables that may affect the utilization of VD in different populations.[21] This study was conducted to determine the serum VD levels among asthmatic children, and to also determine the relationship between serum VD and asthma control, severity and frequency of asthma exacerbation.

MATERIALS AND METHODS

Study Design, Population, Sample Size Estimation and Sampling Technique

This was a cross-sectional study among asthmatic children in Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto, Nigeria, from October 2019 to February 2021.

The minimum sample size required (n) was calculated as follows:[22]

$$n = \frac{Z_{1-\alpha/2}^2 \delta^2}{D^2}$$

Where:

$Z_{1-\alpha/2}$ = percentage point of the normal distribution corresponding to the required (two-sided) significance level (α) of 0.05 = 1.96.

δ= standard deviation of variable under study = 7.2 ng/mL (from a previous study).[23]

D = margin of error = 2 ng/mL

$$n = \frac{1.96^2 * 7.2^2}{2^2} = 50$$

The final sample size (n_f) after correcting for an anticipated 85% response rate =

$$n_f = \frac{n}{0.85} = \frac{50}{0.85} = 60$$

A total of 60 asthmatic children aged 5-15 years were enrolled by systematic sampling technique. Participants were enrolled from the Paediatric Pulmonology and Allergy Clinic, and the Emergency Paediatric Unit of the Department of Paediatric, UDUTH, Sokoto, Nigeria, with diagnosis made according to the GINA guideline.[24] Patients with chronic respiratory or cardiac diseases like pulmonary tuberculosis, congenital heart diseases, and those on VD supplement intake were excluded.

Data Collection

A proforma was used to obtain information on the participants' bio-data, disease history and results of anthropometric measurements, serum vitamin D estimation, and lung function assessment. Socio – economic class was classified as high-, middle- and lower-class based on the Oyedeji social class scheme.[25] Weight was measured to the nearest 0.1kg using a seca digital weighing machine, height was measured to the nearest 0.1cm using a seca stadiometer, and body mass index (BMI) was computed as = weight (kg) / height^2 (m^2).

Detailed spirometry was performed on all the participants to assess their lung function (LF) according to the American Thoracic Society guideline[26] using a BTL- 08 Spiro Pro portable spirometer under aseptic procedure which is an important part of the assessment of future risk exacerbation (asthma control). The spirometer was calibrated daily, and the procedure was done under ambient temperature, pressure and humidity. The procedure was explained and demonstrated to all the study participants. An incentive spirometer was used to encourage the participants while the subjects' seat on a chair and instructions were given. The subjects were allowed two to three practice trial blows and three test blows for 4 -6 seconds, and the personal best FVC, FEV_1, FEV_1/ FVC, PEFR- peak expiratory flow rates were recorded. Asthma severity was assessed using the NAEPP and GINA classifications.[27,24]

Based on the NAEPP classification, asthma severity was graded as intermittent, mild persistent, moderate persistent, and severe persistent, while it was graded based on the GINA classification as mild, moderate and severe. Asthma control was assessed using the GINA asthma control assessment as follows:

a. Asthma symptoms control: Well-controlled, partly-controlled, and poorly-controlled asthma.
b. b. Risk factors for poor asthma outcome: low FEV_1 (<60% predicted), ≥1 exacerbation in the previous year, socioeconomic problems, incorrect inhaler use, and co-morbidities.

Two milliliters of blood was collected from all the study participants in an aseptic procedure and analyzed for serum VD levels. The blood was centrifuged; serum was stored at -20^{0}C until the time for assay (i.e., 2 weeks). Serum levels of VD were quantified by ELISA kit immunodiagnostic systems. A 25-OH Vitamin D ELISA Assay kit, catalogue number: VID31-K1, was used for this study, it contains 96 wells and was meant for research use only (RUO), v.2.1 08.28.17 (packaged and produced by Eagle Biosciences, Inc, U.S.A). The VD ELISA kit is a complete kit for quantitative determination of serum levels of VD with sensitivity of 1.6ng/mL and uses newly monoclonal antibody which is specific for VD2 and VD3 at 100% specificity.

The values obtained and recorded for serum VD levels were categorized into four as follows:[28]

- VD levels < 20ng/mL were considered as deficient; VD levels from 20-30ng/mL were considered as insufficient; VD levels from >30-150ng/mL were considered as sufficient, and values greater than 150ng/mL were considered as hyper-vitaminosis D

Data Analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 20.0. (Armonk, NK: IBM Corp, USA). Non- parametric tests were used after testing for normality with Shapiro-Wilk test. Descriptive statistical analysis such as median and inter-quartile range (IQR) were done for quantitative variables, Wilcoxon rank sum test and Kruskal Wallis H test were used to compare if differences exist in serum VD levels and asthma control, severity and frequency of asthma exacerbation between 2 or >2 groups respectively, while the Chi square test was used to determine if there is any relationship between categorized serum VD levels and childhood asthma control and severity. Spearman rho correlation was used to determine if there is any relationship between serum VD levels and frequency of exacerbation of asthma. All levels of statistical significance were set at $p < 0.05$.

Ethical Consideration

The study was approved by the Research Ethics Committee of UDUTH, Sokoto, Nigeria (UDUTH/HREC/2020/995/V1). All patients' parents/caregivers were required to sign a written informed consent form; parents/caregivers who could not sign made their thumbprints on the consent form. Assent was also obtained from children aged 7 years and above.

RESULTS

Socio-demographic characteristics of participants

Majority, 35 (58.3%) of the 60 participants were males, with a male to female ratio of 1.4: 1. The median age of the participants was 9.47 years (IQR = 3.98 years). Thirty-three (55.0%) were aged less than 10 years, and most of the participants (91.7%) reside in urban communities (Table 1).

Table 1: Socio-demographic characteristics of participants

Variables	Frequency (%) n = 60
Age group (years)	
5 - <10	33 (55.0)
10 – 15	27 (45.0)
Gender	
Male	35 (58.3)
Female	25 (41.7)
Domicile	
Urban	55 (91.7)
Rural	5 (8.3)

Anthropometric characteristics of participants

The median weight of the participants was 24.25 ± 14.25kg, majority of them (56.6%) had normal weight, about a third (36.7%) were underweight, while only a few of them were overweight (1.7%) and obese (5.0%) [Table 2].

Table 2: Anthropometric characteristics of participants

Variables	Frequency (%) n = 60
Nutritional status	
Underweight	22 (36.7)
Normal weight	34 (56.6)
Overweight	1 (1.7)
Obese	3 (5.0)
Anthropometric parameters	
Weight (kg): Median = 24.25; IQR = 14.25	
Height (m): Median = 131.00; IQR = 26.05	
BMI (kg/m^5): Median = 14.68; IQR = 2.60	

Participants' median serum VD levels

The median serum VD level among the study participants was 16.25 ± 13.38 ng/mL. There was no significant difference in the median serum VD levels of the male and female participants (w = - 0.712, p = 0.476). Likewise, there was no significant difference in the median VD levels of those that were aged < 10 years, and those that were aged 10-15 years (w = -0. 512, p = 0.572) [Table 3].

Table 3: Participants' median serum VD levels

Variables	VD levels (ng/mL)		Test of significance
	Median	IQR	
Sex			
Male	15.90	13.50	w = -0.712,
Female	16.00	14.05	p = 0.476
Age group (years)			
5 - <10	16.60	10.75	w = -0.512,
10 - 15	15.90	15.50	p = 0.572

IQR- Inter-quartile range; w – Wilcoxon rank sum test

Pattern of asthma symptoms control among the participants

A half of the participants 30 (50.0%) had well-controlled asthma, 21 (35.0%) had partly-controlled asthma, while 9 (15.0%) had uncontrolled asthma. Although, the proportion of participants with well-controlled asthma was higher among males (31.7%) as compared to females (18.3%), and among those that were aged < 10 years as compared to those that were aged 10-15 years, there was no significant difference ($p > 0.05$) in the distribution of asthma control by sex and age (Table 4).

Relationship between the serum VD levels and asthma symptoms control among the participants

Nineteen (63.3%), 13 (61.9%) and 6 (66.7%) of participants with well-controlled, partly-controlled and uncontrolled asthma respectively were VD deficient. There was no significant difference in the median VD levels of the asthma symptom control types ($r_s = 0.023$, $p = 0.702$). There was no relationship between the serum VD status and asthma symptoms control ($\chi^2 = 2.026$, $p = 0.731$) [Table 5].

Relationship between the serum VD levels and asthma severity among the participants

Almost all, 59 (98.3%) of the 60 participants had mild to moderate asthma by the GINA classification. There was no relationship between the serum VD levels and asthma severity ($H = 4.666$, $p = 0.097$). Also, majority of participants, 40 (66.7%) had either intermittent or mild persistent asthma by the NAEPP classification, and there was no relationship between the serum VD levels and asthma severity ($H = 7.110$, $p = 0.068$) [Table 6].

Relationship between the serum VD levels and frequency of asthma exacerbations among the participants

The median VD levels were not significantly different across the categories of the frequency of asthma exacerbations ($H = 0.665$, $p = 0.881$). There was no relationship between the frequency of asthma exacerbations and the serum VD levels ($r_s = -0.022$, $p = 0.867$) [Table 7].

Table 4: Pattern of asthma symptoms control among the participants

Variables	Asthma symptoms control status			Total	Test of significance
	Well-controlled Frequency (%)	Partly-controlled Frequency (%)	Uncontrolled Frequency (%)	Frequency (%)	
Sex					
Male	19 (31.7)	10 (16.7)	6 (10.0)	35 (58.3)	$\chi^2 = 3.451$,
Female	11 (18.3)	11 (18.3)	3 (5.0)	25 (41.7)	p = 0.457
Age group (years)					
5 - <10	19 (31.7)	10 (16.7)	4 (6.6)	33 (55.0)	$\chi^2 = 3.123$,
10 - 15	11 (18.3)	11 (18.3)	5 (8.3)	27 (45.0)	p = 0.425
Total	30 (50.0)	21 (35.0)	9 (15.0)	60 (100.0)	

χ^2 – Pearson's Chi-square test

Table 5: Relationship between the serum VD levels and asthma symptoms control among the participants

Asthma symptoms control status	Serum VD status			Median serum VD levels (ng/mL)
	Deficient Frequency (%)	Insufficient Frequency (%)	Sufficient Frequency (%)	
Well-controlled (n = 30)	19 (63.3)	9 (30.0)	2 (6.7)	14.50
Partly-controlled (n = 21)	13 (61.9)	5 (23.8)	3 (14.3)	18.61
Uncontrolled (n = 9)	6 (66.7)	3 (33.3)	0(0)	15.80
Test of significance	$\chi^2 = 2.026$, p = 0.731			$r_s = 0.023$, p = 0.702

χ^2 – Pearson's Chi-square test; r_s – Spearman rho correlation

Table 6: Relationship between the serum VD levels and asthma severity among the participants

Asthma severity status	Frequency (%)	Serum VD levels (ng/mL)		Test of significance
		Median	Inter-quartile range (IQR)	
GINA classification				
Mild asthma	45 (75.0)	18.60	13.30	H = 4.666, p = 0.097
Moderate asthma	14 (23.3)	11.25	9.61	
Severe asthma	1 (1.67)	9.60		
Total	**60 (100)**			
NAEPP classification				
Intermittent	16 (26.7)	20.50	13.68	H = 7.110, p = 0.068
Mild persistent	24 (40.0)	16.25	13.18	
Moderate persistent	11 (18.3)	18.61	2.50	
Severe persistent	9 (15.0)	9.90	5.90	
Total	**60 (100)**			

H - Kruskal Wallis test

Table 7: Relationship between the serum VD levels and frequency of asthma exacerbations in the previous year among the participants

Number of asthma attacks	Frequency (%)	Serum VD levels (ng/mL)		Test of significance
		Median	Inter-quartile range (IQR)	
0-3	43 (71.7)	16.25	13.30	r_s = -0.022, p = 0.867
4-7	13 (21.7)	14.50	13.80	
8-13	4 (6.7)	15.00	13.95	H = 0.665, p = 0.881
Total	**60 (100)**			

r_s – Spearman rho correlation; H - Kruskal Wallis test

DISCUSSION

This study assessed the serum VD levels among asthmatic children and also determined the relationship between the serum VD levels and asthma control, severity and frequency of asthma exacerbations. The median serum VD level among the participants in this study was 16.25ng/mL. Uysalol *et al*[15] and Freishtal *et al*[16] reported similar findings among Turkish and American children with serum VD levels of 16.6ng/mL and 18.5ng/mL respectively. The prevalence of VD deficiency among the participants in this study was 63.3%. Bener *et al*[29] in Qatar, made a similar observation with a VD deficiency prevalence of 68.0% among asthmatic children. This observation is also consistent with the findings in previous studies.[30-32]

Considering the fact that the study area is a tropical area with abundant sunshine, VD deficiency should supposedly be an uncommon finding in this study. The observed high prevalence of VD deficiency in this study despite availability of adequate sunshine in the study area could be due to the dark skin (melanin) complexion of the study participants which acts as a natural sunscreen, thus inhibiting absorption of VD from the sunlight. Furthermore, majority of the study participants were from a Muslim background who are known to cover their body due to their religious and cultural beliefs,[33,34] this style of dressing prevents the absorption of cutaneous VD from its main source; which is the sun. Moreover, this was a cross-sectional study that was done during the harmattan period in which there is usually little or no sunshine, and people tend to stay indoors to protect themselves against the dusty and cold weather;[34] and these in turn reduce the availability of VD for absorption. More than 90% of the participants live in urban areas, and urbanization comes with changes in lifestyle including spending more time indoors[35] which could prevent them from getting adequate exposure to sunlight for VD absorption.

However, on the contrary, Omole *et al*,[23] obtained high serum VD levels (with a mean of 47.2ng/mL) in a study among asthmatic children in Ile-Ife, Nigeria. The disparity between the latter study and this study could be

due to the good nutritional status of their study participants which gave them a better chance of having adequate/high serum VD levels. Whereas, more than a third (36.7%) of the participants in this study were underweight (which is in consonance with their low serum VD levels, and it also highlights VD deficiency as a common micronutrient deficiency in the study area),[36] only 7.8% of the participants in the latter study were underweight. Also, undernutrition causes a decrease in the VD binding protein in the blood, which decreases the ability of the body to conserve and store 25-hydroxyvitamin D.[36] In addition, differences in the methods of assay of serum VD (high performance liquid chromatogram UV method was used in the latter study[23] while ELISA kit was used in this study) could account for the discrepancy, due to their varied sensitivity and specificity to serum VD.[37] Complete body coverage was not a common finding in the culture of the Omole *et al* study population (i.e., South-western Nigeria), hence the study population had adequate exposure to sunlight with better absorption of cutaneous VD. In addition, the Omole *et al*[23] study area was semi-urban with fewer effects of urbanization, and with more time being spent outdoor (these expose their study population to adequate sunlight and increase availability of VD)[33,35] in contrast to the index study area which is urban.

This study reported no relationship between serum VD levels and asthma symptoms control, severity, and frequency of asthma exacerbations. This was previously reported by Omole *et al*[23] and Menon *et al*.[38] On the contrary, some studies[15,29] found direct relationship between the serum VD levels and asthma severity, control and frequency of exacerbations. With the finding of a high prevalence of VD deficiency in this study (which could also be a reflection of the global epidemic of VD deficiency),[39] one would expect to find a deterioration in asthma control, severity and worsening in the frequency of asthma exacerbations among the asthmatic children, but in fact the reverse is true as majority of them had well controlled asthma (50%), mild asthma severity (67%), and fewer episodes of asthma symptoms exacerbation (72%). Thus, despite the high prevalence of VD deficiency among study participants, asthma control, severity and frequency of asthma exacerbations were not affected by the low serum VD levels. Based on the absence of any relationship between low serum VD levels and asthma control among the participants in this study one may infer that serum VD does not play a significant role in the aetio-pathogenesis of asthma or/and even if it does, the serum VD level that may be detrimental enough to affect asthma may be lower than the median value reported in this study. Perhaps VD may have a threshold dose for effect, and in populations with generally low serum VD levels, the micronutrient may not be an important modifier of asthma disease. Interestingly Elnady *et al* [40] reported an inverse relationship between serum VD levels and asthma severity among Egyptian children. Also, the effects of VD supplementation on asthma severity and control have yielded conflicting results[19,20,] in which there were reports of either a direct relationship between serum VD levels and asthma control and severity, or no relationship. These observations call for a more careful review of the relationship between asthma and serum VD levels among children, and definition of the role of VD in asthma. Also, there is need to identify the optimal dose of serum VD in different groups based on cultural/religious practices, skin pigmentation, seasonality, nutritional status and asthmatic phenotypes, as all of these factors affect VD absorption and availability. If these issues are addressed, the results to be obtained in future reviews would be more conclusive and objective enough to provide a better insight as to whether serum VD is indeed the "light at the end of the tunnel" for asthmatic children.

CONCLUSION

Although VD deficiency was very prevalent among the participants, there was no relationship between serum VD levels and asthma control, severity and frequency of asthma exacerbations. There is need to prevent and control VD deficiency in the study population through VD supplementation, food fortification and promotion of adequate exposure to sunlight by mothers. Longitudinal studies on serum VD levels are recommended such that they span all seasons (heat, rainy and harmattan), and with a standard method of assay for a better interpretation and inference on serum VD levels among asthmatic children.

Limitation of the study

A cross-sectional study design which is not ideal for establishing temporal relationship / causality between the serum VD levels and asthma control, severity and frequency of asthma exacerbations was employed in this study.

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Conflict of interest

None declared.

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