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Vitamin D Deficiency in Children with and without Cystic Fibrosis: A Cross-Sectional Study

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ABSTRACT

Objective: To compare the vitamin D deficiency in children with and without cystic fibrosis.

Methods: This case-control study was conducted at National Institute of Child Health (NICH) Karachi, Pakistan from October 2018 to April 2019. All children of age ranged 10 months to 15 years of either gender were consecutively enrolled. Cases were defined as children diagnosed with cystic fibrosis irrespective of duration of symptoms whereas controls were apparently healthy children attended outpatient department with no severe disease and had recent vitamin D level report in medical record. Cystic fibrosis was confirmed based on sweat chloride test at the time of presentation. A sweat chloride test result of ≥60 mmol/L along with clinical features suggests cystic fibrosis. Serum 25-OHD <20 ng/ml was classified as vitamin D deficiency.

Results: Of total 93 patients (31 with cystic fibrosis and 62 without cystic fibrosis), the overall median age of the patients was 10 (5-11) years. There were 29 (31.2%) males and 64 (68.8%) females. The median vitamin D level was significantly lower in patients with cystic fibrosis as compared to the patients without cystic fibrosis, i.e. (15 (12-25) ng/ml and 29 (22-32) ng/ml respectively, p-value <0.001. Vitamin D deficiency showed that of 93 patients, 37 (39.8%) patients had vitamin D deficiency. Moreover, Vitamin D deficiency was significantly higher in cystic fibrosis patients as compared to without cystic fibrosis patients, i.e. 23 (74.2%) and 14 (22.6%) respectively (p-value <0.001).

Conclusion: A considerably higher number of patients with cystic fibrosis had low level of vitamin D.

Keywords: Vitamin D status, children, cystic fibrosis.

INTRODUCTION

Vitamin D is a fat soluble vitamin, most commonly recognized for its importance in regulating serum electrolyte levels, particularly calcium and phosphate, along with its role in muscle development and bone growth in children, specifically.[1] Its insufficiency has emerged as common problem across many age groups.[2] Multiple sources in literature have shown that Vitamin D deficiency has a high prevalence in the pediatric population.[3,4]

Vitamin D insufficiency remains a stringent cause of concern in pediatric patients diagnosed with Cystic Fibrosis. Exocrine pancreatic insufficiency is well known for causing malabsorption of fat soluble. It is commonly seen in cystic fibrosis patients, therefore putting this patient population at risk of developing deficiencies of fat soluble vitamins including Vitamin D.[5,6] Vitamin D deficiency has been seen to be proportional to an increase in morbidity and mortality, due to a higher risk of decline in pulmonary function, increased occurrences of fractures and kyphosis, all of which can affect the quality of a patient's life severly.[7] In addition, Wani et al[8] also found that Vitamin D insufficiency was significantly associated with higher rates of pulmonary exacerbations and higher incidences of pulmonary bacterial colonization as well as decresed lung compliance in younger patients.

Multiple risk factors for developing Vitamin D deficiency have been identified and investigated in children, including associations with rickets, respiratory tract infections, tuberculosis and growing pain.[8,9] However, there is scarcity of current literature exploring the prevalence of Vitamin D insufficiency in pediatric cystic fibrosis patients in Pakistan as well as a lack of evaluation of risk factors as they pertain to our local and regional climate.[10] We have planned this study to compare the vitamin D deficiency in children with and without cystic fibrosis. This will allow us to reasonably devise policy frameworks to screen and supplement vitamin D to minimize the morbidity associated with vitamin D insufficiency / deficiency.

METHODS

This case-control study was conducted at National Institute of Child Health (NICH) Karachi, Pakistan from October 2018 to April 2019. Institutional approval was obtained prior conducting of the study.

All children of age ranged 10 months to 15 years of either gender were consecutively enrolled. Cases were defined as children diagnosed with cystic fibrosis irrespective of duration of symptoms whereas controls were apparently healthy children attended outpatient department with no severe disease and had recent vitamin D level report in medical record. Children already on vitamin D treatment and bowel pathologies like celiac disease and abdominal tuberculosis were excluded. Cystic fibrosis was defined on the basis of sweat chloride test at the time of presentation. A sweat chloride test result of ≥60 mmol/L along with clinical features suggests cystic fibrosis.

Open Epi sample size calculator is used for the estimation of sample size taking two-sided significant level as 99%, power as 95%, ratio of unexposed to exposed 2, percentage of vitamin D deficiency in cystic fibrosis as 96.3%[10] and percentage of vitamin D deficiency in controls 55.6%. The estimated sample size came out to be 31 for exposed and 62 for unexposed.

Vitamin D status was classified as following: Vitamin D sufficiency: serum level of 25-OHD >30 ng/ml, vitamin D insufficiency: serum 25-OHD 30-20 ng/ml, vitamin D deficiency: serum 25-OHD <20-10 ng/ml, and severe vitamin D deficiency: serum 25-OHD <10 ng/ml. This information along with patient's demographics like age, gender, weight (in kg), height (in cm), BMI (in kg/m^2), and duration of symptoms was recorded.

Data were entered and analyzed on SPSS version 20. Median and interquartile range was calculated for age, duration of symptoms, weight, height, and BMI of the children. Frequency and percentages were calculated for variables including gender and vitamin D deficiency. Inferential statistics were explored using Mann-Whitney U test for median difference in between groups and chi square/fisher exact test for qualitative variables comparison with respect to group. p value ≤0.05 was taken as significant.

RESULTS

Of total 93 patients (31 with cystic fibrosis and 62 without cystic fibrosis), the overall median age of the patients was 10 (5-11) years. There were 29 (31.2%) males and 64 (68.8%) females. The median weight, height, and BMI was 32 (18-36) kg, 138 (109-144) cm, and 18 (13-21) kg/m^2 respectively.

An insignificant median difference of age (p-value 0.135), weight (p-value 0.184), height (p-value 0.322), and BMI (p-value 0.091) was observed in between groups. (Table 1) Of 31 patients with cystic fibrosis, the median duration of symptoms was 14 (4-22) months.

The median vitamin D level was 26 (15-32) ng/ml. The median vitamin D level was significantly lower in patients with cystic fibrosis as compared to the patients without cystic fibrosis, i.e. (15 (12-25) ng/ml and 29 (22-32) ng/ml respectively, p-value <0.001. (Figure 1)

Vitamin D deficiency showed that of total 93 patients, 37 (39.8%) patients had vitamin d deficiency. Moreover, Vitamin D deficiency was significantly higher in patients with cystic fibrosis as compared to the patients without cystic fibrosis, i.e. 23 (74.2%) and 14 (22.6%) respectively (p-value <0.001). (Figure 2)

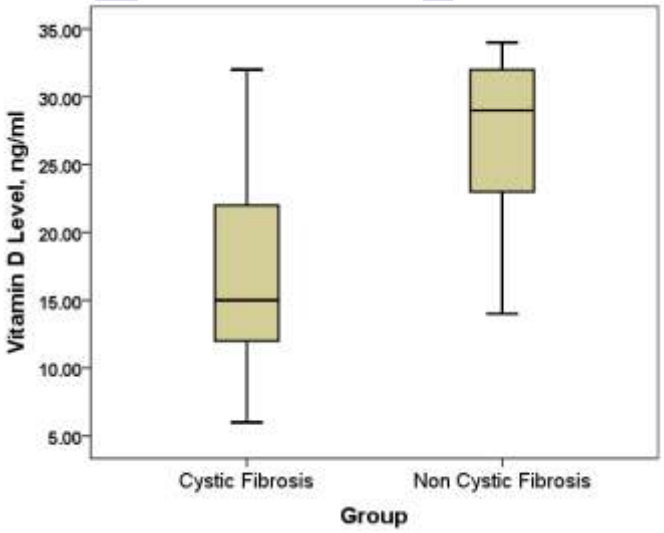

Figure 1: Box-plot showing median values of vitamin d level with cystic and non-cystic fibrosis patients

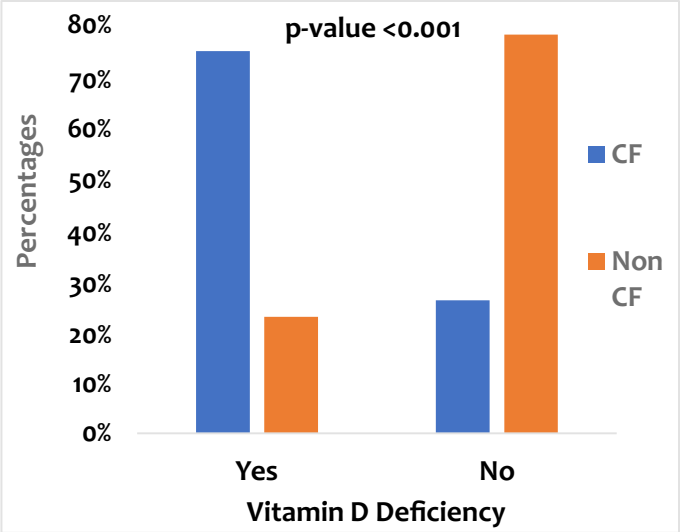

Figure 2: Vitamin D deficiency with and without cystic fibrosis

Table 1: Comparative analysis of demographic characteristics with respect to group (n=93)

Variables	Cystic Fibrosis (n=31)	Non-Cystic Fibrosis (n=62)	
	median (IQR)	median (IQR)	p-value
Age, years	6 (2-10)	10 (5-11)	0.135
Weight, kg	18 (12-32)	32 (18-39)	0.184
Height, cm	109 (86-138)	138 (110-149)	0.322
BMI, kg/m2	13 (11-18)	18 (13-210	0.091
Duration of symptoms, months	14 (4-22)	-	-
	n (%)	n (%)	p-value
Age, years			
≤7	16 (51.6)	24 (38.7)	0.236
>7	15 (48.4)	38 (61.3)	
Gender			
Male	12 (38.7)	17 (27.4)	0.268
Female	19 (61.3)	45 (72.6)	
BMI, kg/m2			
≤16	21 (67.7)	27 (43.5)	0.028
>16	10 (32.3)	35 (56.5)	
Duration of symptoms, months			
≤12	8 (25.8)	-	-
>12	23 (74.2)	-	

Mann-Whitney U test applied, Chi-square test/Fisher-Exact test applied, p-value ≤0.05 considered as significant

DISCUSSION

In this study, deficiency of serum level of 25-OHD (Vitamin D) was found in almost forty percent children overall. However, in cystic fibrosis children, vitamin D deficiency was observed in seventy four percent children. A recent study done under similar parameters, found that among children with diagnosed cystic fibrosis only 37.2% had sufficient Vitamin D levels, with 47.1% and 15.7% deficient and insufficient respectively. Existing literature on this topic provides variable figures from across the world.[11] A study done in the United Kingdom found a prevalence rate of 87% (deficiency defined as 25(OH)D < 30 ng/ml) and a similar setup in Australia found a prevalence of 3% (deficiency defined as 25(OH)D < 20 ng/ml).[12,13] Another study done among children of various age groups found that among patients between the ages of 6 and 10 years, less than 5% of the study sample were found deficient (25(OH)D < 20 ng/ml) and 10 to 20% were insufficient (25(OH)D < 30 ng/ml); and between ages of 15 to 18 , about 10% were found deficient and 30% were insufficient.[14] Our results fall within this range.

Although, according to the current study findings, non-significant association of gender was observed with presence of cystic fibrosis. However, proportion of female patients were higher, and they were at risk for low vitamin D levels. A 2018 study done in Kuwait also came to the conclusion that this deficiency was more prevalent in adolescent girls, despite them having similar sun exposure to their male cohorts.[15] Additionally, a detailed review of literature concerning vitamin D levels in children and adolescent found that female gender had a higher chance of developing a Vitamin D deficiency as compared to the males.[16]

Another variable frequently discussed in literature is the nutrition status of children. Studies suggest that BMI, that measures weight for height of a patient, can be used as one marker of nutrition status. However, the effect of BMI or nutrition status on the prevalence and severity of this particular vitamin deficiency in children is not fully settled. A study done in Kenya found that vitamin D deficiency was associated with malnutrition and children with a poor nutrition status and lower BMI were more likely to develop diseases such as rickets due to vitamin D deficiency.[17] On the other hand a study published in the Global Pediatric Journal found that obesity was heavily associated with vitamin D deficiency and increased risk to cardiovascular disease in children.[18] Another study that looked at females from

various age groups suggested an inverse relation between BMI and serum 25-OHD levels; that is the more obese a patient is the higher their chance of deficiency.[8] However, it is important to note that these studies were conducted in normal pediatric population that did not suffer from cystic fibrosis. Our study did not find a significant association between BMI and vitamin D status. Similarly, a study published by the American Thoracic Society came to the conclusion, that they could not find any significant association between BMI percentile and vitamin D status in patients with cystic fibrosis.[19] However, the association between nutrition status, Vitamin D deficiency and their combined effects on the health of children with cystic fibrosis needs to be further explored.

The demographics of cystic fibrosis patients of the current study were similar to those present in papers across literature.[20-22] Moreover, a recent study done in a sample of 51 patients also showed similar baseline characteristics for cystic fibrosis patients.[7]

vitamin D has long been assumed important for good health and comfortable welfare of patients with cystic fibrosis. It is also suspected that vitamin D deficiency could be of importance in the pathogenesis of cystic fibrosis related bronchiectasis[5]. While exact mechanisms are not clearly recognized right now, it is suspected that suboptimal levels of this vitamin may have a serious impact on innate immunity which may be involved in the non-skeletal complications.

The limitations of this study include a small sample size, due to being limited to one healthcare center. Additionally, a more detailed look into variables explored in other studies such as patient blood glucose control could have shed light onto suspected associations such as Cystic fibrosis related diabetes. Further inquiry and detailed prospective studies appear to be necessary for verification and to probe the suspected connection between vitamin D and inflammation and bacterial colonization.

CONCLUSION

The findings of this showed that a considerably higher number of patients with cystic fibrosis had low level of vitamin D. Patients diagnosed with cystic fibrosis are known to suffer from a myriad of complications across many organ systems. Vitamin D deficiency can further deteriorate their quality of life and therefore must be monitored regularly.

AUTHORS' CONTRIBUTION:

RB: Study conception and design, acquisition of data. AA: Analysis and interpretation of data, drafting of manuscript.

MA & BN: Study conception and design, analysis and interpretation of data.

WH: Acquisition of data, drafting of manuscript.

ETHICAL APPROVAL: Ethics approval was obtained from the Institutional Ethical Review Board, National Institute of Child Health, Rafique Shaheed Road Karachi, Pakistan (IERB#EX-12/2020).

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