Original Article

Vitamin D status and pulmonary exacerbations in children and adolescents with cystic fibrosis: Experience from a tertiary care center

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ABSTRACT

Background: The function of Vitamin D in preventing inflammation and infection has been studied previously for different pathologies in different populations globally. Relationships between serum Vitamin D levels and its effect on pulmonary exacerbations in the cystic fibrosis (CF) population are not well studied in our part of the world. Therefore, we aimed to ascertain the Vitamin D status in pediatric and adolescent CF patients and its association with pulmonary exacerbations. **Materials and Methods:** A retrospective study was conducted at The Aga Khan University Hospital from 2015 to 2018. Patients of CF with sweat chloride value >60 mmol/l and who had at least one measurement of 25 hydroxy Vitamin D (25 OHD) were included in the study. Annual serum Vitamin D levels were documented for enrolled patients and their past 1-year data were analyzed for pulmonary exacerbations, average length of stay, and tracheal/airway colonization with organisms. **Results:** 69 patients were included in the study. 28 patients (40.57%) were found to be Vitamin D deficient, 22 patients (31.88%) were Vitamin D insufficient and 19 patients (27.53%) were labeled as Vitamin D insufficient. The average number of exacerbations per year was significantly high in Vitamin D deficient group (3.71 ± 0.96) in comparison with insufficient (3.18 ± 1.09) and sufficient groups (2.26 ± 0.93) ($P < 0.001$). **Conclusion:** Vitamin D deficiency is related to an increased number of annual pulmonary exacerbations and pseudomonas infections.

KEY WORDS: 25-hydroxyvitamin D (25-OHD), cystic fibrosis, pseudomonas colonization, pulmonary exacerbations, Vitamin D Deficiency

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INTRODUCTION

The cystic fibrosis (CF) patient population suffers from Vitamin D deficiency due to inappropriate absorption of fat-soluble vitamins, reduced sunlight contact, and decreased intake of Vitamin D-enriched foods.[1] Recent literature suggests Vitamin D has a great impact on lung function and to combat pulmonary infections.[2] Additionally, to effects on bone health, there is mounting evidence that Vitamin D plays a vital role in controlling inflammation and maintaining balance in the immune system.[3] Certain evidence suggests that deficiency in Vitamin D results in an imbalance in pulmonary physiology

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and alters lung architecture.[4] Healthy infants and children with a deficiency of Vitamin D have been documented to have an increased risk of severe respiratory disease.[5] The role of Vitamin D in the CF population is now well recognized in literature and its deficiency is associated with an increased risk of pulmonary exacerbations.[2] Pulmonary functions and the lung's ability to combat infections are important predictors of mortality and morbidity in CF patients and Vitamin D status in patients influences these predictors.[6,7] Vitamin D deficiency prevalence is elevated amongst neonates and children in South Asia.[8] Children with CF in South Asia are usually diagnosed late and this leads to higher morbidity and mortality.[9]

Serum Vitamin D levels and its effect on pulmonary exacerbations are not well documented in our part of the world. The objective of our study was to establish the Vitamin D status in pediatric CF patients and determine its association with pulmonary exacerbations, length of stay (LOS) in hospital on average for each exacerbation, and bacterial growth in tracheal cultures especially in context to *Pseudomonas aeruginosa*. We hypothesize a higher rate of pulmonary exacerbations amongst patients with lower Vitamin D status.

MATERIALS AND METHODS

A retrospective study was conducted at The Aga Khan University Hospital, Karachi, Pakistan. The study duration was from January 2015 to December 2018. We selected children and adolescents aged 3–18 years with CF, diagnosed based on clinical features and sweat chloride value of >60 mmol/L and who had at least one serum measurement of 25 hydroxy Vitamin D (25 OHD) levels during the study period. Patients were categorized into three groups, Vitamin D sufficient, Vitamin D insufficient, and Vitamin D deficient groups. CF Patients with serum 25 OHD concentrations < y 20 ng/ml were labeled as Vitamin D deficient, and those with serum 25 OHD concentrations between 20 and 29.9 ng/ml were categorized as Vitamin D insufficient, and patient with serum 25 OHD concentrations ≥30 ng/ml were labeled as Vitamin D sufficient.[2] Annual serum Vitamin D levels were documented for every patient and their data for the past 1 year were analyzed for pulmonary exacerbations, average LOS per admission, and colonization of trachea/airway with bacteria specifically CF-related organisms like *P. aeruginosa* patients who had CF-related hepatitis or pancreatitis were excluded from the study.

Sweat was stimulated by means of pilocarpine iontophoresis and sweat collection was done with Wescor® macroduct sweat collection system as per hospital protocol. Total patients with positive sweat chloride >60 mmol/L were analyzed for Delta F-508 genetic mutation. The measurement of 25 hydroxy Vitamin D was done in the hospital laboratory with a radioimmunoassay kit. These data were retrieved from online patient records and pharmacy profile.

The fecal elastase test was not available for all patients enrolled in the study; therefore, we included all patients in our cohort irrespective of their pancreatic sufficiency or insufficiency status. Pulmonary exacerbations in CF patient was defined as "any hospitalization due to respiratory function deterioration clinically observed as increased cough frequency, increased sputum production, increase work of breathing, and/or new crackles on auscultation."[10] Weight, height, sweat chloride value, and Delta F-508 mutation analysis were documented for selected cases. Failure to thrive was defined as weight for age below −2 SD on Z score. Short stature was defined height or length less than two standard deviations for age and gender (height for age <−2 *Z*-score.).

Statistical analysis

Qualitative data were presented as frequencies and percentages, whereas quantitative data were presented as mean and standard deviation. The normality of the data was checked using histograms and Kolmogorov–Smirnov test and data were essentially normally distributed. One-way ANOVA was used to assess the difference in mean values amongst the groups and Chi-square test was used for categorical data. The data were analyzed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 97 CF patients were screened out of which 69 CF patients fulfilled the eligibility criteria within the study duration. Male: female ratio was 1.47:1. 28 patients (40.57%) were found to be Vitamin D deficient, 22 patients (31.88%) were labeled as Vitamin D insufficient whereas 19 patients (27.53%) were Vitamin D sufficient. Frequencies of patients with failure to thrive and short stature were similar between the three groups of patients and not related to their Vitamin D status. Demographic details of CF patients stratified on Vitamin D levels are presented in Table 1.

Mean pulmonary exacerbations per year was significantly high (3.71 ± 0.96) in Vitamin D deficient groups in comparison with insufficient (3.18 ± 1.09) and sufficient group (2.26 ± 0.93) $P < 0.001$. Figure 1 shows the comparison of CF patients divided into three groups according to the number of exacerbations/years with Vitamin D status. Four age categories of patients were defined from 3 years to 6 years, 7 years to 10 years, 11 years to 14 years, and 15 years to18 years. It was noticed that the age of the patients had no linear relationship with the average number of exacerbations/year and patients in different age groups showed varied frequencies of exacerbations/year Average LOS per hospital admission did not show a significant difference between the three groups ($P = 0.16$) [Table 2]. The frequency of pseudomonas infections showed a

Table 1: Demographic details and laboratory features of cystic fibrosis population (*n*=69)

	Vitamin D sufficient	Vitamin D insufficient	Vitamin D deficient	*P*
Patients, *n* (%)	19 (27.53)	22 (31.88)	28 (40.57)	
Age (months)	10.53±4.53	9.45±4.57	11.51±4.41	
Male: Female	1.50	1.450	1.8	
Failure to thrive (weight for age−2SD), *n* (%)	13 (68.42)	16 (72.72)	22 (78.57)	0.36
Short stature (height less than−2SD), *n* (%)	11 (57.89)	13 (59.09)	21 (75)	0.14
Mean sweat chloride value (mmol/L)	68.07±6.61	77.15±6.92	72.62±6.88	0.69
Delta F-508 mutation, *n* (%)	3 (15.78)	4 (18.18)	4 (14.28)	0.53
Mean serum 25-OH Vitamin D value (ng/ml)	52.78±9.63	25.04±3.07	11.11±4.13	<0.05

SD: Standard deviation

Table 2: Average number of exacerbations, length of stay, and pseudomonas infection per year

	Vitamin D sufficient (*n*=19)	Vitamin D insufficient (*n*=22)	Vitamin D deficient (*n*=28)	*P*
Mean pulmonary exacerbations/year	2.26±0.93	3.18±1.09	3.71±0.968	<0.001
Average length of stay/admission (days)	5.92±1.91	6.35±2.04	6.79±2.14	0.16
Pseudomonas infection, *n* (%)	9 (47.36)	15 (68.18)	23 (82.14)	0.043

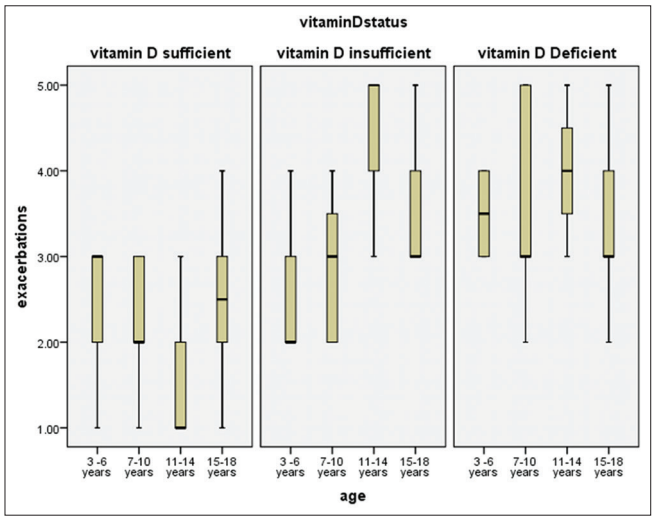

Figure 1: Comparison of Vitamin D status and exacerbations/year in different age categories

statistically significant difference between the three groups ($P = 0.043$).

DISCUSSION

Our study highlights a significant association between the status of Vitamin D in CF patients and pulmonary exacerbations. 40.57% of patients were Vitamin D deficient and 31.88% patients were Vitamin D insufficient. The average number of exacerbations per year was significantly high in Vitamin D deficient group (3.71 ± 0.968) compared to insufficient and sufficient groups ($P < 0.001$). Average LOS per admission for CF patients showed no major differences between the groups ($P = 0.16$) and pseudomonas growth in tracheal swab/sputum cultures showed significant differences ($P = 0.043$).

In our study, CF patients have Vitamin D levels <30 ng/ml. Yadav *et al*. showed that majority of patients in their cohort had Vitamin D deficiency with almost all patients who had pulmonary exacerbations were deficient in Vitamin D.[9] Similarly, Vanstone *et al*. established depleted Vitamin D status as a significant cause of developing pulmonary exacerbations.[10] Regardless of patients receiving oral supplementation of Vitamin D, the levels remained low. Moreover, pulmonary bacterial colonization and exacerbations were more prevalent in Vitamin D deficient population.[11] 73% of children in our population failed to thrive and approximately 60% of children had short stature. There was no difference for these features among the three categories according to Vitamin D status. This indicates that nutritional status may not be an important factor in defining Vitamin D statuses in children and adolescents with CF.

Pulmonary exacerbations in CF children have a negative impact on pulmonary functions resulting in the poor quality of life and higher mortality.[12-14] In our study, it is evident that the average events of pulmonary exacerbations in the group with Vitamin D deficiency were significantly high in comparison with Vitamin D insufficient and Vitamin D sufficient groups. Our results concur with previously published reports, which showed a substantial increase in the number of exacerbations in patients with Vitamin D deficiency and insufficiency.[2,6,15] Protection from viral infections is stated in most studies as a major mechanism of Vitamin D in pulmonary protection.[16] There are strong data suggesting Vitamin D supplementation during inflammation resulting in the reduction of inflammatory marker interleukin-8 and improved forced vital capacity, suggesting an anti-inflammatory role.[17]

Pseudomonas airway colonization has a great impact on lung function, and it is one of the important factors that determine the morbidity and mortality in such patients.[18] Previously it has been shown that children with Vitamin D insufficiency have a higher tendency to be colonized with *P. aeruginosa*. This explains facilitating role of Vitamin D in preventing airway infections and long-standing lung function in CF.[18] Similarly, studies show that Vitamin D plays a role in controlling influential antimicrobial peptide

LL-37. LL-37 has a strong action against *P. aeruginosa* and it was hypothesized that the surplus of bacterial colonization predominantly *P. aeruginosa* in Vitamin-D deficient subjects may be the cause of decreased production of LL-37, Vitamin D increases levels LL-37 promoting the innate immunity.[19] In our study, we found that Vitamin D deficient group has an increased number of patients with pseudomonas colonization in comparison with insufficient and sufficient groups ($P = 0.043$).

The limitation of our study includes the inability to determine the exocrine pancreatic status of the patients due to limited excess for all patients for fecal elastase test during the study period. Pancreatic enzymes help in the absorption of fat-soluble vitamins including Vitamin D and have a strong link with the respiratory health and nutrition of these patients.[20] We also did not determine pulmonary function tests at the time of exacerbations in these patients due to the nonavailability of the facility.

CONCLUSION

Our study supports the current recommendation for annual screening of fat-soluble vitamin levels especially levels of Vitamin D in all patients with CF. Additionally, the association between Vitamin D deficiency with pulmonary exacerbation and *P. aeruginosa* colonization deserves further prospective design research in order to determine more definitively the influence of Vitamin D deficiency on inflammation, infection, and clinical outcomes.

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Conflicts of interest
There are no conflicts of interest.

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