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Impact of vitamin D status on CF and non-CF bronchiectasis outcomes

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Abstract

Background: Vitamin D deficiency occurs frequently in cystic fibrosis (CF) and non-CF bronchiectasis patients. Yet, few studies have assessed the impact of vitamin D status on the clinical outcomes in pediatric bronchiectasis. This study is designed to assess vitamin D level and determine its effect on exacerbations, bacterial colonization, and lung function in pediatric patients with CF and non-CF bronchiectasis.

Results: This cross-sectional case-control study assessing vitamin D level was performed in a total of sixty cases under the age of 18 years—forty cases with CF and non-CF bronchiectasis and twenty age- and sex-matched healthy controls. Associations between serum vitamin D and clinical and laboratory parameters were assessed in the patient groups. Vitamin D deficiency was more prevalent among CF and non-CF bronchiectasis patients (75%, 45%) compared to controls (10%) ($P < 0.001$). In addition, vitamin D deficiency was associated with more frequent and severe pulmonary exacerbations (66.7%, 46.7%) (P=0.033, < 0.001), chronic *Pseudomonas* infection (80%) (P=0.060) among CF patients, and with lower FEV1 (66%) (P= 0.071) among non-CF bronchiectasis. Moreover, a cutoff value of vitamin D level equal or less than 22.5 ng/ml was accurate in differentiating moderate from mild pulmonary exacerbations in both patients' groups (AUC=0.809) (p=0.004).

Conclusions: Vitamin D deficiency is not uncommon in both CF and non-CF bronchiectasis. In this population, vitamin D deficiency is associated with more frequent pulmonary exacerbations, chronic *Pseudomonas* infection, and worse lung function.

Keywords: Cystic fibrosis, Non-CF bronchiectasis, Vitamin D deficiency, Colonization, Exacerbations

Background

Bronchiectasis is conventionally used as a descriptive term for an irreversible condition characterized by chronic suppurative airway disease manifested clinically by chronic productive cough and radiologically by bronchial dilation and thick-walled bronchi [1]. Bronchiectasis is classified into bronchiectasis secondary to cystic fibrosis (CF) and bronchiectasis not related to CF, which is called non-cystic fibrosis bronchiectasis [2].

Vitamin D deficiency occurs frequently in patients with CF [3] and non-CF bronchiectasis [4]. In these patients, vitamin D deficiency can arise from multiple causes as pancreatic exocrine insufficiency, absence of outdoor activity, and alterations of vitamin D metabolism [3].

Vitamin D is known to be involved in a wide spectrum of significant immunomodulatory effects as downregulation of pro-inflammatory cytokines and chemokines [2]. It also regulates the secretion of antimicrobial peptides like cathelicidin (LL-37) which has a potent antimicrobial activity against *Pseudomonas aeruginosa* [4].

Higher vitamin D is associated with better lung function [3]. The mechanism by which vitamin D improves lung function may be through its action on regulating inflammation, inducing antimicrobial peptides, or its action on muscle [5].

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We hypothesized that vitamin D deficiency may negatively affect bronchiectasis outcomes in both CF and non-CF bronchiectasis pediatric patients. For this reason, this study was conducted to evaluate the influence of vitamin D status on CF and non-CF bronchiectasis outcomes.

Methods

Patients and settings

This cross-sectional study assessed vitamin D level (25-OHD) in twenty CF and twenty non-CF bronchiectasis children under the age of 18 years during the period between 1 March 2019 and 1 September 2019; the patients were recruited from pediatric chest clinic and chest department, Children's Teaching Hospital. Also, the study included twenty age- and sex-matched healthy controls without any respiratory problems who were attending the outpatient clinics for routine care (either for vaccination or for following up their anthropometric measurements).

Patients were included if they had (1) confirmed CF diagnosis by positive sweat chloride test equal or above 80 mmol/L using the Nanoduct® Neonatal Sweat Analysis System (Wescor) [6] measured twice and / or had two known CF disease causing mutations [7] and (2) a documented diagnosis of non CF bronchiectasis by clinical history of chronic sputum production with confirmed radiological findings of bronchiectasis by high-resolution computed tomographic (HRCT) lung scanning with a negative sweat test [8, 9]. Control subjects and non-CF bronchetasis patients were not receiving vitamin D supplements before and during the period of the study. The CF patients were taking vitamin D supplement as a part of their multivitamins with a dose not exceeding 2000 IU daily.

Subjects were excluded if (1) CF patients had liver disease based on Debray's criteria [10], or renal disease based on estimated creatinine clearance using the Schwartz formula [11], because these might affect the metabolism of vitamin D (details of these are available in the (supplementary data); (2) CF patients had pancreatic sufficiency; (3) the CF patients were receiving vitamin D supplements exceeding 2000 IU per day; (4) the studied patients were receiving steroid therapy in the last 6 weeks; (5) the studied patients had chronic lung diseases other than CF and non CF bronchiectasis; (6) the studied patients had any other systemic illness; or (7) non CF bronchiectasis patients and controls were taking any vitamin D supplements during the last three months prior to the study.

Ethics approval and consent to participate

The study was approved by the Research Ethical Committee, Faculty of Medicine, Institutional University, Children's Hospital. Informed written consents were obtained from the patients' guardians prior to the inclusion in the study.

Measurements

At enrollment, from each patient, a detailed history was undertaken, focusing on respiratory symptoms including type of cough, expectoration, dyspnea, respiratory distress, hemoptysis, and cyanosis, besides, symptoms suggestive of pulmonary exacerbations over the last 12 months. A full dietetic history with special emphasis on dietary vitamin D intake was calculated from the 24-h dietary recall for 3 days for both the patients and the controls. The amount of vitamin D obtained from each food focusing on foods with significant vitamin D content was calculated and was summed to obtain the mean of the total amount of dietary vitamin D intake per day, and its percentage of the recommended dietary allowances (RDAs) [12] for vitamin D per day was calculated in the studied patients and controls. In addition, history of vitamin D supplement and its dose as well as any additional supplements, total daily dose of pancreatic enzyme replacement therapy for CF patients, and history of sunlight exposure were obtained. Adequate sunlight exposure for infants and children was defined as sunshine exposure of extremities at morning 10 a.m. to 2 p.m. for 15–30 min at least three times per week [13, 14]. Socioeconomic status in all participants was also evaluated using El-Gilany score [15].

The forty studied bronchiectasis patients were also assessed by clinical parameters including age, sex, and body mass index (BMI) percentile [16]. Chest auscultation and pulse oximetry were also performed.

Furthermore, the studied bronchiectasis patients were subjected to lower respiratory tract samples cultures, colonization status assessment, and pulmonary function tests (PFTs) for cooperative patients older than 6 years. Serum vitamin D 25(OH) D measurement and serum laboratory inflammatory markers as complete blood count and C-reactive protein were also recorded. For controls, demographic data and anthropometric measures were obtained. Serum vitamin D 25(OH) D was recorded as well.

PFTs were done using standardized spirometry, which was performed and interpreted according to the American Thoracic Society Guidelines [17] for both CF and non-CF bronchiectasis patients.

A pulmonary exacerbation was defined based on Fuchs criteria [18] for the CF patients and British Thoracic Society bronchiectasis guidelines [19] for non-CF bronchiectasis patients which were applied on the studied patients, diagnosed and revised by at least two pulmonologists during examination.

Frequent exacerbations were defined as more than three exacerbations per year [20, 21].

A mild-to-moderate exacerbation was further defined as 1 to 2 signs or symptoms present or that the symptom severity is mild. A moderate-to-severe exacerbation was defined as more than 3 new findings or 1 to 2 severe findings (e.g., oxygen desaturation, new crackles) or a mild-to-moderate exacerbation unresponsive to oral or inhaled antibiotics [22].

Chronic lung colonization was defined by at least two out of the three cultures positive for the same organism with at least 1-month intervals in the absence of signs of infection within the last 6 months prior to the study [23]. Chronic lung infection by *Pseudomonas aeruginosa* was defined when *Pseudomonas* cultures were positive in more than 50% of months in a 12-month period prior to the study [24].

Organisms were detected in the lower respiratory tract samples (either induced, expectorated sputum, or bronchial lavage), using standard clinical microbiological protocols [25].

Assessment of serum vitamin D levels

At enrollment, 3 ml of venous blood were withdrawn from each child under aseptic conditions on gel vacutainers. Serum was separated by centrifugation at 3500 rpm for 15 min and stored at −20°C till used for assessment of the level of 25(OH)D. Levels of 25(OH)D were assessed using enzyme linked immunoassay Kit supplied by Calbiotech, USA, guided by the manufacturer's instructions [26]. Briefly, 10 µl of each standard, control, and sample was added to the corresponding wells; then, 200µl of biotinylated conjugate was added. The plate was then incubated for 90 min at room temperature followed by washing three times and the addition of 200 ul of Streptavidin-HRP. The plate was then incubated at room temperature for 30 min followed by washing of the wells 3 times. Then, 200 µl of TMB substrate were added to each well followed by incubation at room temperature for 30 min away from light, after which 50 µl of the stop solution were added and the optical density was read at 450nm. A standard curve was plotted using the standards' readings, and concentrations of the samples were deduced from the curve.

The studied cases were classified into three groups according to the serum 25(OH)D status: vitamin D-deficient group which had a serum 25(OH)D < 20 ng/ml, vitamin D insufficient group with serum 25(OH)D 20–29.9 ng/ml, and vitamin D sufficient group with serum 25(OH)D ≥ 30 ng/ml [23].

Statistical analysis

Data were analyzed in the form of mean ± standard deviation (± SD), median, and interquartile range (IQR) or frequencies (number of cases) and percentages. One-way ANOVA was used to compare parametric quantitative data while Kruskal-Wallis test was used to compare non-parametric quantitative data and whenever significant a post hoc test was used. Chi-square test was using to compare categorical data and to study associations. *P* values less than 0.05 was considered statistically significant and *P* less than 0.01 was considered highly significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) [27].

Sample size was calculated using PASS 11.0. The total sample of 60 subjects achieves 83% power to detect differences among the serum vitamin D level means versus the alternative of equal means using an *F* test with a 0.01000 significance level. The size of the variation in the means is represented by their standard deviation which is 2.49. The common standard deviation within a group is assumed to be 4.70.

Results

The present study was conducted on sixty participants under the age of 18 years. The subjects were classified into to 3 groups: *group I* non-cystic fibrosis bronchiectasis patients (no=20), *group II* cystic fibrosis patients (*n*=20), and *group III* age- and sex-matched healthy controls without any respiratory problems (*n*= 20). Demographics, anthropometric data, and serum vitamin D concentrations were obtained from the three studied groups. The etiology of non-CF bronchiectasis in the patients of group I is summarized in (Table S3).

Demographic data (Table 1)

The mean age of CF patients (4.80±3.85) was significantly lower than the mean age of non-CF bronchiectasis patients (9.55±4.05) (*P*=0.002). Also, positive consanguinity and family history of bronchiectasis were significantly higher among CF patients (75%, 60%) than controls (35%, 0%) (*P*= 0.036) (< 0.001).

Comparison of vitamin D level in the studied cases

The mean serum vitamin D level was significantly lower among the CF group (20.15±11.66) and the non-CF bronchiectasis group (20.85±7.21) compared to the control group (35.15±12.84) (*P* < 0.001). Moreover, deficient vitamin D level was significantly more prevalent among CF patients (75%) and non-CF bronchiectasis patients (45%) compared to controls (10%), while

Table 1 Comparison between non-CF bronchiectasis, CF bronchiectasis, and controls as regards demographic data

Demographic data		Diagnosis			*P*-value	Post hoc test
		Non CF bronchiectasis	CF bronchiectasis	Controls		
Age (Y) (mean ± SD) **Range**		9.55±4.05 (1–17)	4.80±3.85 (1–17)	5.75±4.23 (1–17)	0.002●	(I vs II) **
Sex, *n* (%)	**Male**	10 (50.0%)	15 (75%)	10 (50%)	0.180#	
	Female	10 (50.0%)	5 (25%)	10 (50%)		
Body mass index (mean ± SD)		16.56±2.91	15.59±2.57	17.91±1.19	0.425●	
BMI *Z* score (mean ± SD)		−.59± 1.14	−.63±1.77	−.39±1.01	0.828●	
Residence	**Urban**	12 (60%)	13 (65%)	14 (70%)	0.803#	
	Rural	8 (40%)	7 (35%)	6 (30%)		
Socio-economic status	**Very low**	9 (45%)	8 (40%)	4 (20%)	0.384#	
	Low	9 (45%)	9 (45%)	10 (50%)		
	Middle	2 (10%)	3 (15%)	6 (30%)		
Consanguinity	**Positive**	12 (60%)	15 (75%)	7 (35%)	0.036#	(II vs III) *,
Family history of bronchiectasis	**Positive**	4 (20%)	12 (60%)	0 (0%)	< 0.001#	(II vs III) **, (I vs III) *

● ANOVA, #chi-square test, *significant, **highly significant

vitamin D insufficiency was more frequent among non-CF bronchiectasis (40%) compared to CF patients (20%) and controls (35%) ($p < 0.001$). In addition, daily dietary intake of vitamin D was significantly lower among the CF patients (313.80±65.66) than among the controls (357.25±40.54) (P=0.063). Meanwhile, the dietary intake of vitamin D in non-CF bronchiectasis patients was (338.50±62.17). Regarding sun exposure, it was adequate only in 15% of CF patients, 30.0% of non-CF bronchiectasis group, and 40% of the control group. Vitamin D concentrations among the studied groups are presented in Table 2.

Vitamin D deficiency and pulmonary exacerbations

Frequent pulmonary exacerbations were significantly higher among vitamin D deficient group (66.7%) than the sufficient (0.0%) and insufficient (0.0%) vitamin D groups in CF bronchiectasis patients (P=0.033). Furthermore, moderate to severe pulmonary exacerbations were more prevalent among vitamin D-deficient patients (93.4%) compared to the other groups (P <0.001) (Table 3). Also, more frequent (66.7%) and moderate to severe pulmonary exacerbations (88.9%) were presented among vitamin D deficient non-CF bronchiectasis patients, although it was statistically non-significant (P= 0.166 and 0.232 respectively) (Table 4).

Vitamin D and colonization status

Among CF patients, bacterial colonization was prevalent among 83% of vitamin D-deficient group, 17% of vitamin D insufficient group, and 0% of the sufficient group, where the most frequently isolated organism was *Pseudomonas aeruginosa* which was significantly higher among vitamin D-deficient group (80%) than vitamin D

Table 2 Vitamin D levels, status, and intake among studied groups

		Non-CF bronchiectasis (group I)	CF bronchiectasis (group II)	Controls (group III)	*P* value	Post hoc
Serum vitamin D level, mean ± SD		20.85±7.21	20.15±11.66	35.15±12.84	<0.001●	(I vs III) ** (II vs III)**
Vitamin D level status, *n* (%)	**Deficient**	9(45.0%)	15(75.0%)	2(10.0%)	<0.001#	(II vs III)** (I vs III)*
	Insufficient	8(40.0%)	4(20.0%)	7(35.0%)		
	Sufficient	3(15.0%)	1(5.0%)	11(55.0%)		
Daily dietary intake of vitamin D (IU) (mean ± SD)		338.50±62.17	313.80±65.66	357.25±40.54	0.063●	(II vs III) *
Vitamin D dietary intake % of RDA (mean ± SD)		56.42±10.36	56.85±6.90	60.39±9.75	0.467●	
Sun exposure, *N* (%)	**Adequate**	6 (30.0%)	3 (15.0%)	8 (40.0%)	0.552#	
	Inadequate	14 (70.0%)	17 (85.0%)	12 (60.0%)		

RDA recommended daily allowance. *Significant, **highly significant, ●ANOVA, #chi-square test

Table 3 Relationship between vitamin D status and both frequency and severity of exacerbations in the last year in CF bronchiectasis patients

Pulmonary exacerbations in the last year		Vitamin D group			*P*-value	Post hoc
		Deficient (< 20 ng/mL)	Insufficient (20–29 ng/mL)	Sufficient (≥30 ng/mL)		
Frequency	**Infrequent (< 3 times)**	5(33.3%)	4(100.0%)	1(100.0%)	0.033[#]	(I vs II) *, (I vs III) *
	Frequent (≥3 times)	10(66.7%)	0(0.0%)	0(0.0%)		
Severity	**Mild**	1(6.7%)	4(100.0%)	1(100.0%)	<0.001[#]	(I vs II) *, (I vs III) *
	Moderate	7(46.7%)	0(0.0%)	0(0.0%)		
	Severe	7(46.7%)	0(0.0%)	0(0.0%)		

*Significant, **highly significant, [#]chi-square test

Table 4 Relationship between vitamin D level and both frequency and severity of exacerbations in the last year in non-CF bronchiectasis patients

Pulmonary exacerbations in the last year		Vitamin D group			*P*-value
		Deficient (< 20 ng/mL)	Insufficient (20–29 ng/mL)	Sufficient (≥30 ng/mL)	
Frequency	**Infrequent (< 3 times)**	3(33.3%)	5(62.5%)	3(100.0%)	0.166[#]
	Frequent (≥3 times)	6(66.7%)	3(37.5%)	0(0.0%)	
Severity	**Mild**	1(11.1%)	3(37.5%)	2(66.7%)	0.232[#]
	Moderate	6(66.7%)	5(62.5%)	1(33.3%)	
	Severe	2(22.2%)	0(0.0%)	0(0.0%)	

[#] Chi-square test

insufficient group (20%) and vitamin D sufficient group (0%) (P=0.060) followed by *Staphylococcus aureus* and MRSA colonization (Table 5).

Among non CF bronchiectasis patients, bacterial colonization was found among 53.3% of vitamin D-deficient group, 26.7% of vitamin D insufficient group, and 20.0% of the sufficient group, where the most predominant organism was *Staphylococcus aureus*, which was presented among 57.1% of the vitamin D-deficient group, 28.6% of vitamin D insufficient group, and 14.3% of vitamin D sufficient group followed by *Pseudomonas aeruginosa* and *Klebsiella*, although the difference was statistically non-significant (p=0.818) (Table 6).

Vitamin D deficiency and its relation to lung function

Among the non-CF bronchiectasis patients, the median FEV1% of predicted was significantly lower among the vitamin D deficient group (66%) with IQR of 56–73% and insufficient group (67%) with IQR of 40–79% than among the vitamin D sufficient group (80.0%) with IQR of 75–88% (P=0.071). Similarly, among CF patients, the median FEV1 was lower among the vitamin D deficient

Table 5 Relationship of vitamin D status and bacterial colonization in CF bronchiectasis

Bacterial colonization	Vitamin D group			*P*-value[●]
	Deficient (< 20 ng/mL)	Insufficient (20–29 ng/mL)	Sufficient (≥30 ng/mL)	
Negative bacterial colonization	1(33.3%)	1(33.3%)	1(33.3%)	0.278
Positive bacterial colonization	14 (83%)	3(17%)	0(0.0%)	
***Pseudomonas aeruginosa* (*n*=10)**	8(80%)	2(20%)	0(0.0%)	0.060*
***Staphylococcus aureus* (*n*=5)**	4(80.0%)	1(20.0%)	0(0.0%)	0.999
MRSA (*n*=3)	2(66.7%)	1(33.3%)	0(0.0%)	0.601
***Klebsiella* (*n*=0)**	0(0.0%)	0(0.0%)	0(0.0%)	
***Streptococcus pyogens* (*n*=0)**	0(0.0%)	0(0.0%)	0(0.0%)	

*Significant, [●]Kruskal-Wallis test

Table 6 Relationship of vitamin D status and bacterial colonization in non-CF bronchiectasis

Bacterial colonization	Vitamin D group			*P*-value●
	Deficient (< 20 ng/mL)	Insufficient (20–29 ng/mL)	Sufficient (> 30 ng/mL)	
Negative bacterial colonization	1 (20%)	4(80%)	0(0.0%)	0.126
Positive bacterial colonization	8(53.3%)	4(26.7%)	3(20.0%)	
***Staphylococcus aureus* (*n*=7)**	4(57.1%)	2(28.6%)	1(14.3%)	0.818
***Pseudomonas aeruginosa* (*n*=4)**	3(75%)	0(0.0%	1(25.0%)	0.215
***Klebsiella* (*n*=3)**	1(33.3%)	1(33.3%)	1(33.3%)	0.526
MRSA (*n*=2)	0(0.0%)	2(100.0) %	0(0.0%)	0.432
***Streptococcus pyogens* (*n*=1)**	1(100.0%)	0(0.0%)	0(0.0%	1.000

● Kruskal-Wallis test

group (69%) with IQR of (60 -70%) and insufficient group (71%) with IQR of (65-75%) than among vitamin D sufficient group (80%), although the difference was not statistically significant (P=0.423). All these data are summarized in Table 7.

Finally, ROC curves of serum vitamin D for diagnosis of CF and non-CF pulmonary exacerbations severity showed that serum vitamin D was 95% accurate in determining exacerbations severity (AUC=0.809, p=0.004). At a cutoff value equal or less than 22.5 ng/ml, serum vitamin D level has shown 79% sensitivity and 75% specificity for differentiating moderate from mild pulmonary exacerbations while at a cutoff value equal or less than 16.5 ng/ml, serum vitamin D level has shown 77% sensitivity and 58% specificity for differentiating severe from moderate pulmonary exacerbations (AUC=0.764, p=0.168) as presented in (Figs. 1 and 2).

Discussion

To our knowledge, this is the one of the fewest pediatric studies that evaluated the serum vitamin D level in both CF and non-CF bronchiectasis patients and determined its relation to the disease outcomes.

The present study showed that the studied subjects' mean age was 4.80±3.85 in CF patients, 9.55±4.05 in non-CF bronchiectasis, and 5.75±4.23 in controls which was ranged from 1 to 17 years.

Males were predominant in CF bronchiectasis patients (75%), while represented (50.0%) in both non-CF bronchiectasis patients and controls.

The current study showed that vitamin D deficiency and insufficiency were significantly prevalent among CF and non-CF bronchiectasis patients (95%, 85%) respectively and surprisingly among 45% of the healthy control group with the lowest vitamin D levels were among the CF patients' group (p< 0.001) (Table 2).

Our findings could be explained by low dietary intake of vitamin D especially among the CF patients (313.80±65.66), which presented less 61% of the RDA even in the control group. Also, inadequate sun exposure was prevalent among the studied patients especially among the CF patients (85%).

Similar to our results, recent studies [28, 29] demonstrated that the prevalence of vitamin D insufficiency in the CF population is up to 90% [3]. Also, large CF centers observed that >90% of patients had vitamin D levels <30 ng/mL [30]. In addition, Brodlie and colleagues [31] found that 90% of their pediatric CF population was vitamin D insufficient, and after increasing the supplementation dose, 49% remained insufficient.

Our results also go parallel with the findings of a case control study conducted on 402 adults with non-CF bronchiectasis by Chalmers et al. [4] which showed that the median serum 25-OHD was 24.7 nmol/l and 50% of

Table 7 FEV1% of predicted among different vitamin D status in non-CF bronchiectasis and CF patients

	Vitamin D status						*P*-value	Post hoc
	Deficient (< 20 ng/mL)		Insufficient (20–29 ng/mL)		Sufficient (> 30 ng/mL)			
FEV1%	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**		
Non-CF bronchiectasis	66.00	56–73	67.00	40–79	80.00	75–88	0.071●	(I vs III)*, (II vs III)*
CF	69.00	60–70	71.00	65–75	80.00	0.00	0.423●	

● Kruskal-Wallis test, *significant

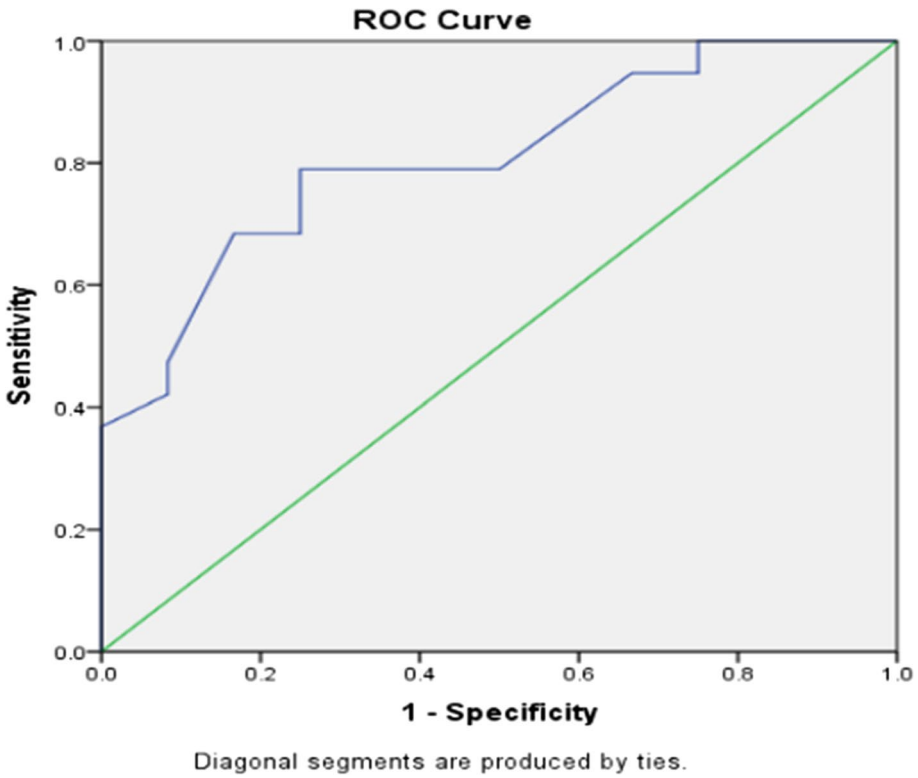

Fig. 1 ROC Curve denoting diagnostic accuracy of vitamin D to differentiate between mild and moderate pulmonary exacerbations in both CF and non-CF bronchiectasis

patients with bronchiectasis were vitamin D deficient and 43% insufficient, only 7% sufficient and these percentages were significantly higher in comparison with only 12% in control group.

The higher level of vitamin D deficiency in our study may be explained by poor nutritional status with lower mean BMI (P=0.062), lower socioeconomic status with bad housing among vitamin D deficient non CF bronchiectasis patients (P= 0.040) (Table S1) and the prevalence of pancreatic insufficiency (72.2%) and severe CFTR mutations (53.2%) among vitamin D-deficient CF patients (Table S2) and the absence of routine screening of vitamin D level among the studied CF patients, inadequate sun exposure and inadequate dietary intake of vitamin D among the study participants (Table 2).

The higher prevalence of vitamin D deficiency and insufficiency among the normal healthy controls (45%) compared to previous studies [32, 33] conducted on vitamin D level among the healthy subjects should raise the awareness about the importance of adequate sun exposure and routine screening of vitamin D deficiency among the Egyptian children.

Our study has found that vitamin D deficiency among CF patients was significantly linked with more frequent and mostly moderate to severe pulmonary exacerbations compared to vitamin D sufficient and insufficient groups (P=0.033, < 0.001). Similar findings were reported among vitamin D deficient non-CF bronchiectasis patients, although it was statistically non-significant (P= 0.166, 0.232) (Tables 3 and 4).

These finding may indicate a relation between vitamin D deficiency and the bronchiectasis severity as reported by several studies that frequent pulmonary exacerbations are associated with a higher risk of future exacerbations [20] and higher mortality rates [21].

Our results were also in agreement with previous retrospective studies [30, 34, 35] which have indicated that low vitamin D status in children was associated with increased number of pulmonary exacerbations of CF [36].

Similarly, McCauley et al. [34] reported that serum vitamin D level less than or equal to 20 mg/L in CF children is associated with a three times higher rate of pulmonary exacerbations than those with vitamin D levels greater than or equal to 30 mg/L(sufficient). Furthermore, having a higher serum 25-hydroxyvitamin D in children was protective of having a pulmonary exacerbation during adolescence [36].

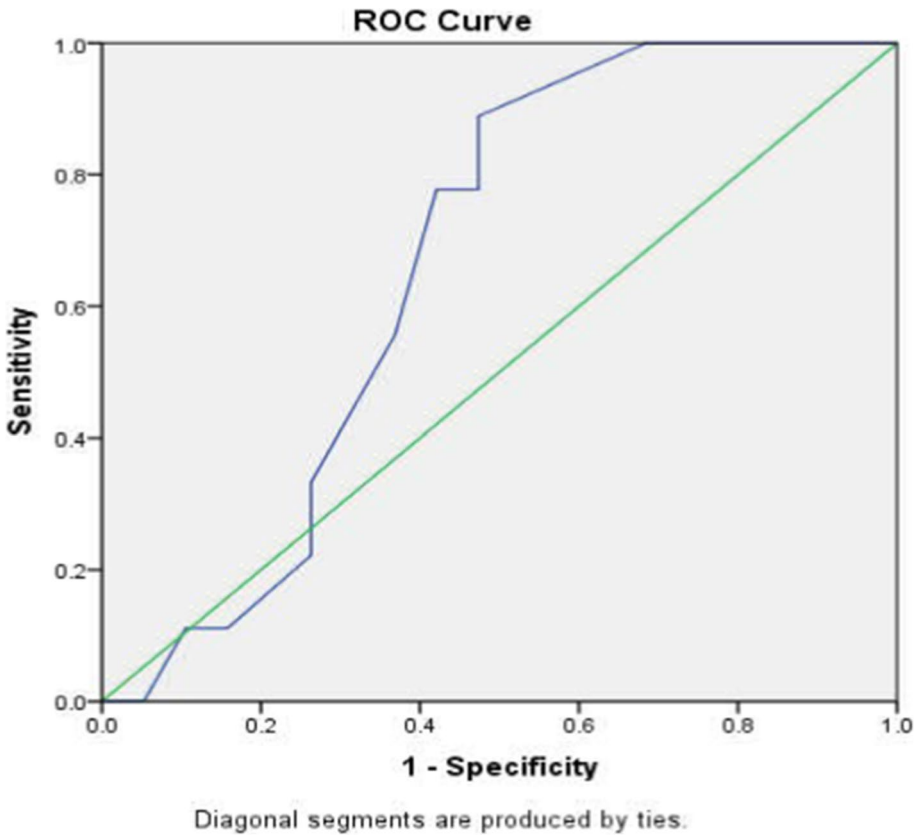

Fig. 2 ROC Curve denoting diagnostic accuracy of vitamin D to differentiate between moderate and severe pulmonary exacerbations in both CF and non-CF bronchiectasis

On the same hand, Chalmers et al. [4] highlighted that vitamin D deficient non-CF bronchiectasis patients have more frequent pulmonary exacerbations and 27.4% of deficient patients had an unscheduled hospitalization for a severe exacerbation compared to 19.7% of insufficient patients and 7.1% of sufficient patients.

The previous findings may raise the possibility of the use of vitamin D therapy as a therapeutic tool for prevention and treatment of pulmonary exacerbations in bronchiectasis patients.

The current study found that a higher percentage of bacterial colonization was found among vitamin D-deficient CF group than vitamin D insufficient and sufficient groups where chronic *Pseudomonas* infection was significantly higher among vitamin D deficient group (80%) than the other two groups (20%, 0%) (P=0.060) (Table 5). Similar findings were found among non-CF bronchiectasis patients where 75% of chronic pseudomonas infection and 57.1% of *Staphylococcus aureus* colonization were more prevalent among vitamin D-deficient group (P=0.215, 0.818) (Table 6).

These findings came different with what was reported in the literature that the most commonly isolated organisms in non-CF bronchiectasis children are non-type-able *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and to a lesser extent *Staphylococcus aureus* and *Pseudomonas aeruginosa* [2]. This observation highlights the role of vitamin D deficiency in enhancing the growth of *Pseudomonas aeruginosa* and *Staphylococcus aureus* by probably influencing the innate immunity, decreasing the induction of cathelicidin [37].

Our results were consistent with the findings of Simoneau et al. [23] who found *that Pseudomonas aeruginosa* was a frequent pathogen in the CF patients who were vitamin D-insufficient/deficient as compared to patients with sufficient vitamin D status (29% prevalence compared with 13% prevalence in the vitamin D-sufficient group).

On the same side, Chalmers et al. [4] reported that non-CF bronchiectasis patients with vitamin D deficiency (25[OH]D less than 25 n mol/L) had more bacterial colonization and 21.4% of colonized patients

had *Pseudomonas aeruginosa* colonization compared to 10.4% of insufficient patients and 3.6% of sufficient patients.

Our study also revealed that median (FEV1) % of predicted was significantly lower among vitamin D-deficient (66%) and insufficient (67%) non-CF bronchiectasis groups than among the sufficient group (80%) (p=0.071). The same findings were found among the CF patients, although the difference was not statistically significant (P=0.423) (Table 7)

Similar studies [2, 5, 30, 38] showed that higher vitamin D status in children and adults with CF has been associated with better lung function assessed by (FEV1).

On the same hand, Chalmers et al. [4] highlighted that vitamin-D-deficient patients had lower FEV1 % predicted (p=0.002); the median FEV1 was 68.0% (IQR 45.3–84.9%) in the vitamin D-deficient group. The study also demonstrated a more rapid decline of lung function over a 3-year follow-up period among vitamin D-deficient non-CF bronchiectasis patients.

On the contrary, previous studies [29, 39], have studied the prevalence of vitamin D deficiency in CF and examined its association with FEV1 but have found no association between vitamin D deficiency and FEV1.

Our results also showed the sensitivity of serum vitamin D for diagnosis of CF and non-CF bronchiectasis pulmonary exacerbations severity, where at a cutoff value equal or less than 22.5 ng/ml, serum vitamin D level has significantly differentiated moderate from mild pulmonary exacerbations (P= 0.004) (Fig. 1). While at a cutoff value equal or less than 16.5 ng/dl, serum vitamin D level has differentiated severe from moderate bronchiectasis pulmonary exacerbations (Fig. 2).

These findings suggest that serum vitamin D is playing an important role in determining the severity of pulmonary exacerbations which is the most contributing factor of bronchiectasis severity.

Conclusions

Vitamin D deficiency is prevalent among both CF and non-CF bronchiectasis pediatric patients (despite daily supplementation of the vitamin D in CF patients). In this population, vitamin D deficiency is associated with more severe and frequent pulmonary exacerbations, higher rates of chronic *Pseudomonas* infection, and lower lung function as measured by FEV1.

From these data, routine screening for vitamin D level is better to be done in both CF and non-CF bronchiectasis children. Additionally, further, large, prospective, multi-center randomized clinical trials should be conducted to justify the application of vitamin D supplementation as one of the therapeutic guidelines in all cases of bronchiectasis, not only in CF but also in non-CF bronchiectasis children.

Study limitation

The current study has some limitations. First, the sample size was relatively small. Second, the design was cross-sectional and only diseased cases were registered. Third, only pancreatic insufficient CF patients were included in the study. However, this study is one of the fewest studies that examined and compared the relation between vitamin D status and CF and non-CF bronchiectasis outcomes in pediatric patients

Abbreviations

CF: Cystic fibrosis; HRCT: High resolution computed tomography; RDA: Recommended daily allowance; BMI: Body mass index; PFTs: Pulmonary function tests; IQR: Interquartile range; AUC: Area under the curve.

Supplementary Information

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Additional file 1. Supplementary data. Tables S1–S3.

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Authors' contributions

HA performed the study design and wrote the manuscript. TD shared in the study design and approved the manuscript. DM did the laboratory work, data interpretation, and paper drafting. MM did the patients' enrollment and collection of data. All authors revised and approved the manuscript and agree to publish it in the *Egyptian Pediatric Association Gazette* (EPAG).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The Research Ethics Committee of the Faculty of Medicine, Ain Shams University, approved the protocol. Written consent was obtained from the patients' guardians. The reference number is not available at the time being.

Consent for publication

Nothing to declare

Competing interests

The authors declare that they have no competing interests.

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