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Original Article

Vitamin D deficiency is associated with pulmonary dysfunction in cystic fibrosis ☆

William P. Sexauer [a,*,1], Anas Hadeh [b,c], Pamela A. Ohman-Strickland [d], Robert L. Zanni [e], Laurie Varlotta [f,g], Douglas Holsclaw [h], Stanley Fiel [i], Gavin R. Graff [j], Arthur Atlas [k], Dorothy Bisberg [l], Denis Hadjiliadis [h], Suzanne H. Michel [m,2], Daria Mintz [n], Rebanta Chakraborty [b], Bridget Marra [e], Paula Lomas [i], Tara Ward [o], Meagen Sassman [p], Giovanna C. Imbesi [h], Diane M. Kitch [j], Allison M. Mallowe [q]

[a] *Pulmonary and Critical Care Division, Department of Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA*
[b] *Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Drexel University College of Medicine, Philadelphia, PA, USA*
[c] *Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Florida, Weston, FL, USA*
[d] *Rutgers School of Public Health, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA*
[e] *Pulmonary Division, Department of Pediatrics, Monmouth Medical Center, Long Branch, NJ, USA*
[f] *Department of Pediatrics, Drexel University College of Medicine, Philadelphia, PA, USA*
[g] *Section of Pediatric Pulmonology, St. Christopher's Hospital for Children, Philadelphia, PA, USA*
[h] *Division of Pulmonary, Allergy and Critical Care Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[i] *Adult Cystic Fibrosis Center, Morristown Medical Center, Morristown, NJ, USA*
[j] *Pulmonary Division, Department of Pediatrics, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA*
[k] *Pulmonary Division, Department of Pediatrics, Goryeb Children's Hospital, Morristown Medical Center, Morristown, NJ, USA*
[l] *Barnabas Health, West Orange, NJ, USA*
[m] *Pulmonary Division, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA*
[n] *Pulmonary Division, Department of Pediatrics, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, USA*
[o] *Department of Medicine, Morristown Medical Center, Morristown, NJ, USA*
[p] *Cystic Fibrosis Center, St. Christopher's Hospital for Children, Philadelphia, PA, USA*
[q] *Department of Clinical Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA*

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Abstract

Background: Vitamin D deficiency is common in CF. Whether vitamin D affects pulmonary function in CF is unknown.
Methods: Data were abstracted from clinically stable CF patients who had pulmonary function studies and serum 25-hydroxyvitamin D [25(OH)D, ng/ml] levels drawn within 2 months of each other. Findings were adjusted for multiple variables known to affect pulmonary function in CF.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; COPD, chronic obstructive pulmonary disease; DEXA, dual-energy X-ray absorptiometry; FEF_{25-75}, forced expiratory flow at 25%–75% of forced vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NHANES III, Third National Health and Nutrition Survey; 25(OH)D, 25-hydroxyvitamin D; ΔF508, delta F 508 cystic fibrosis mutation; iu, international units; LC–MS/MS, liquid chromatography–tandem mass spectrometry

☆ Partial results of this study were presented in abstract and poster form, as follows: Sexauer W, Hadeh A, Zanni R, et al. Relationship between vitamin D and pulmonary function in cystic fibrosis. Pediatr Pulmonol Suppl 2009; Suppl 32:410. Presented at the Twenty-Third Annual North American Cystic Fibrosis Conference, October 2009, Minneapolis, MN.

* Corresponding author at: Division of Pulmonary and Critical Care Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, 834 Walnut Street, Suite 650, Philadelphia, PA 19107, USA. Tel.: +1 215 952 1383; fax: +1 215 955 0830.
E-mail address: william.sexauer@jefferson.edu (W.P. Sexauer).

[1] Performed work while in Division of Pulmonary and Critical Care Medicine, Department of Medicine, Robert Wood Johnson Medical School, New Brunswick, NJ.
[2] Performed work while in the Nutrition Department and the Cystic Fibrosis Center, The Children's Hospital of Philadelphia, Philadelphia, PA.

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Results: Enrollees totaled 597. Overall mean 25(OH)D level was 29.6 ± 12.8 ng/ml (SD). Serum 25(OH)D levels showed a significant correlation with forced expiratory volume in 1 s (FEV_1) % predicted ($r = 0.20$, $p < 0.0001$) and forced vital capacity % predicted ($r = 0.13$, $p = 0.0019$). Multivariate analysis revealed that serum 25(OH)D remained an independent predictor of FEV_1 % predicted even after controlling for multiple other factors known to affect CF lung function.
Conclusions: Serum 25(OH)D levels are significantly associated with pulmonary function in CF. Further study is required to determine whether this association is causal.

Keywords: Cystic fibrosis; Pulmonary function; Lung function; Vitamin D

1. Introduction

Cystic fibrosis (CF) is a genetic, multisystem condition manifested primarily by progressive pulmonary disease and exocrine pancreatic insufficiency. Pulmonary dysfunction and malnutrition are major determinants of prognosis in CF and appear interrelated. There are many determinants of pulmonary function in CF including the underlying genetic defect(s), bacterial pathogens present, medication adherence, psychosocial factors, and nutritional status. Pancreatic insufficiency and resultant fat malabsorption place CF patients at risk for deficiency of the fat-soluble vitamins, including vitamin D.

Vitamin D deficiency in CF is common [1]. Deficiency of vitamin D is most commonly associated with poor bone health and is thought to contribute to the premature onset of osteopenia and osteoporosis commonly seen in CF [2,3]. Recently, vitamin D depletion has been associated with multiple other disease states in the general population, including hypertension, diabetes mellitus, cardiovascular disease, and cancer [4]. Pulmonary disorders, including asthma [5] and chronic obstructive pulmonary disease (COPD) [6], have also been associated with low serum 25-hydroxyvitamin D levels. That vitamin D may be integral to optimal pulmonary functioning is suggested by data from the Third National Health and Nutrition Survey (NHANES III), which showed a strong association between serum 25-hydroxyvitamin D levels and pulmonary function in the general population [7].

In light of these findings, it is possible that vitamin D deficiency contributes to pulmonary dysfunction in CF. This study examined the relationship between serum 25-hydroxyvitamin D levels and pulmonary function in patients with CF. The Cystic Fibrosis Foundation currently recommends that all patients with CF have their serum 25-hydroxyvitamin D level checked at least annually, with a recommended target level ≥ 30 ng/ml (≥75 nmol/l) [1]. Pulmonary function is checked often, usually every visit. We hypothesize that vitamin D deficiency contributes to pulmonary dysfunction in CF, and examine the impact of vitamin D on lung function after adjustment for multiple other clinical variables.

2. Methods

We abstracted data from the charts of patients attending the CF centers constituting the Mid-Atlantic Research Study Group (see Appendix 1 for participating institutions). We included subjects if they met the following criteria: diagnosis of CF confirmed by sweat test and/or genetic testing; age ≥ 6 years; serum 25(OH)D levels drawn with the patient's clinical state at or near baseline (non-exacerbated), as judged by their CF clinician; able to perform spirometry to American Thoracic Society standards; and spirometry performed within 2 months of 25(OH)D level being drawn, also with the clinical state at or near baseline. We excluded subjects who had a history of organ transplant and subjects who had spirometry performed only during an exacerbation. For patients with multiple 25(OH)D levels on the chart, we chose the most recent value that met all of the above criteria for analysis. This study was approved by the Institutional Review Board at each participating center.

All patients had the following data abstracted from their charts: 25(OH)D level (ng/ml), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, forced expiratory flow at 25%–75% of FVC ($FEF_{25–75}$), height (cm), and weight (kg). Body mass index (BMI, in kg/m^2), height, weight, BMI percentiles (the latter only for patients aged < 20 years), FVC and FEV_1 % predicted (Wang et al. [8] and Hankinson et al. [9]) were all abstracted from the North American CF Foundation's Registry access site by each center's data collectors to ensure standardization across centers.

Blood samples for 25(OH)D levels were run at a variety of commercial and hospital laboratories.

Most were performed by Quest diagnostics (Chantilly, Virginia) or Labcorp (Burlington, North Carolina). During the time period of the study, Quest performed 25(OH)D assays via liquid chromatography–tandem mass spectrometry (LC–MS/MS) technology. Labcorp performed assays using the DiaSorin 25-OHD radioimmunoassay kit. One center had studies performed at Mayo Medical Reference Laboratories (Rochester, Minnesota) using LC–MS/MS technology.

Additional data collected from charts included sex, age at diagnosis, age at 25(OH)D collection, month and day of 25(OH)D collection, pancreatic sufficiency status (defined by whether the patient was taking pancreatic enzyme supplementation), genotype, and bacterial pathogens present in the airways. We recorded the following co-morbidities: cystic fibrosis-related diabetes mellitus (CFRD) (defined for purposes of this study as on therapy with either insulin or an oral hypoglycemic agent), allergic bronchopulmonary aspergillosis, liver disease (defined here as either known/proven cirrhosis or portal hypertension or on therapy with ursodiol—the latter used as a surrogate for clinician's suspicion of clinically significant liver disease), and history of meconium ileus with bowel resection. For those patients in whom bone disease had been