Vitamin D Levels and Risk of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

A Prospective Cohort Study

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Rationale: Low blood levels of 25-hydroxyvitamin D (25[OH]D) have been associated with a higher risk of respiratory infections in general populations and higher risk of exacerbations of lung disease in people with asthma. We hypothesized that low blood levels of 25(OH)D in patients with chronic obstructive pulmonary disease (COPD) would be associated with an increased risk of acute exacerbations of COPD (AECOPD).

Objectives: To determine if baseline 25(OH)D levels relate to subsequent AECOPD in a cohort of patients at high risk for AECOPD.

Methods: Plasma 25(OH)D was measured at baseline in 973 participants on entry to a 1-year study designed to determine if daily azithromycin decreased the incidence of AECOPD. Relationships between baseline 25(OH)D and AECOPD over 1 year were analyzed with time to first AECOPD as the primary outcome and exacerbation rate as the secondary outcome.

Measurements and Main Results: In this largely white (85%) sample of North American patients with severe COPD (mean FEV₁ 1.12L; 40% of predicted), mean 25(OH)D was 25.7 ± 12.8 ng/ml. A total of 33.1% of participants were vitamin D insufficient (≥20 ng/ml but <30 ng/ml); 32% were vitamin D deficient (<20 ng/ml); and 8.4% had severe vitamin D deficiency (<10 ng/ml). Baseline 25(OH)D levels had no relationship to time to first AECOPD or AECOPD rates.

Conclusions: In patients with severe COPD, baseline 25(OH)D levels are not predictive of subsequent AECOPD.

Clinical trial registered with www.clinicaltrials.gov (NCT00119860).

Keywords: chronic obstructive pulmonary disease; vitamin D; exacerbations

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are associated with increased risk of short-term mortality (1, 2) and impaired respiratory health status (3). Exacerbations

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Low vitamin D levels are common in chronic obstructive pulmonary disease (COPD). Low vitamin D levels are associated with higher risk of respiratory infections in the general population, and higher risk of exacerbations in people with asthma. Studies examining relationships between vitamin D levels and acute exacerbations of COPD are lacking.

What This Study Adds to the Field

In this large cohort study of 973 exacerbation-prone patients with COPD, we found no association between baseline vitamin D levels and subsequent risk of acute exacerbations of COPD.

are also costly (4–7), making prevention of AECOPDs an important goal of COPD management. Proven therapies to reduce AECOPDs include long-acting inhaled bronchodilators, inhaled corticosteroids, and macrolide antibiotics, but they are only modestly effective, and additional interventions are needed.

Viral and bacterial respiratory infections are thought to trigger most COPD exacerbations (8). As such, therapies that reduce respiratory infection risk might reduce the frequency of AECOPDs. A growing body of evidence suggests an important role for vitamin D in mounting appropriate innate and adaptive immune responses to infections (9–11). Cross-sectional (12) and prospective cohort (13) studies show that lower 25-hydroxyvitamin D (25[OH]D) levels are associated with a higher frequency of respiratory infections in healthy adults and more frequent asthma exacerbations in children (14, 15). A randomized trial of 430 Japanese schoolchildren during influenza season showed that, compared with placebo, vitamin D supplementation lowered the frequency of influenza A, although a secondary outcome of influenza B infections showed a nonstatistically significant trend toward higher frequency in the children who received supplements (16).

Vitamin D insufficiency and deficiency are highly prevalent in patients with COPD, with the lowest vitamin D levels being associated with the most severe airflow obstruction (17). Because patients with the most severe COPD are also at highest risk for exacerbations (18) it is reasonable to posit that low levels of vitamin D might be an independent risk factor for AECOPDs. We therefore conducted a large observational cohort study to test this hypothesis in exacerbation-prone patients with COPD.

METHODS

This study was a secondary analysis of data collected in a randomized, controlled trial testing the hypothesis that daily azithromycin decreases the frequency of AECOPD (19).

(Received in original form September 12, 2011; accepted in final form October 19, 2011)

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Supported by the Minnesota Veterans Medical Research and Education Foundation (to K.M.K.), UL1 RR024150 (to Mayo Clinic) and to COPD Clinical Research Network sites: U10 HL074407, U10 HL074408, U10 HL074409, U10 HL074416, U10 HL074418, U10 HL074422, U10 HL074424, U10 HL074428, U10 HL074431, U10 HL074439, and U10 HL074441.

Author Contributions: K.M.K. drafted the protocol, obtained the funding, directed several of the statistical analyses, wrote the manuscript, and provided approval of the final manuscript. D.E.N. revised the protocol for critical intellectual content, directed several of the statistical analyses, and reviewed and approved the final manuscript. J.E.C. revised the protocol for critical intellectual content, performed the statistical analyses, and reviewed and approved the final manuscript.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 185, Iss. 3, pp 286–290, Feb 1, 2012

Published 2012 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201109-1644OC on November 10, 2011
Internet address: www.atsjournals.org

Study Participants

Inclusion criteria included a ratio of FEV₁/FVC less than 70%; FEV₁ less than 80% of predicted; greater than or equal to 10 pack-year smoking history; and an increased risk of AECOPD in the subsequent year (requiring oxygen, using systemic corticosteroids, or having an emergency department visit or hospitalization for COPD within 1 yr of study entry). Exclusion criteria included a diagnosis of asthma or a disease resulting in the patient being either medically unstable or having a predicted life expectancy less than 3 years; macrolide hypersensitivity; taking medications with azithromycin interactions; electrocardiographic QTc interval greater than 450 milliseconds; resting heart rate greater than 100 beats per minute; hepatic or renal insufficiency (creatinine >1.5 mg/dl and estimated creatinine clearance <20 ml/min); bronchiectasis; or hearing impairment. Participants were required to be free of AECOPD for greater than or equal to 4 weeks before enrollment.

Participants were randomly assigned in a 1:1 ratio to either daily azithromycin or placebo for 1 year given in addition to their usual treatment. Participants were seen in clinic or contacted by telephone on alternate months and detailed exacerbation information was collected over 1 year. AECOPDs were defined as a complex of respiratory symptoms (increased or new-onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with duration of at least 3 days and requiring treatment with an antibiotic or systemic corticosteroid.

All participants provided written informed consent to study participation and to storage of blood specimens for future research, such as this secondary analysis of vitamin D levels. Each participating institution's institutional review board approved the protocol.

Plasma was collected at baseline, centrifuged, frozen at -80°C , and shipped to the data coordinating center (University of Minnesota, Minneapolis, MN). Plasma was subsequently delivered to the Mayo Clinic Immunochemical Core Laboratory (Mayo Clinic, Rochester, MN) for determination of 25(OH)D concentrations using liquid chromatography tandem mass spectroscopy. 25(OH)D has been shown to be stable in stored blood samples (20, 21). 25(OH)D measurement was not a preplanned analysis before initiation of the trial.

Statistical Methods

The prespecified primary outcome of this study was the relationship between baseline 25(OH)D and time to first AECOPD as determined by multivariate Cox proportional hazards analysis. Covariates included characteristics potentially associated with both 25(OH)D status and AECOPD risk, such as age, sex, ethnicity, FEV₁ % predicted, baseline smoking status, season (Winter = January–March; Spring = April–June; Summer = July–September; and Winter = October–December) and clinical center. Treatment assignment in the trial was also included as a covariate to account for the differential AECOPD risk among patients randomized to the two arms of the original trial.

A prespecified alternate analysis using annualized rates of AECOPDs was also conducted. Rates of AECOPDs were determined by dividing the number of AECOPDs by person-years of follow-up and allowed for use of data from patients with multiple exacerbations over the 1 year of follow-up time. Although the optimal analytic method of such data is not fully agreed on (22, 23) we analyzed the relationship between baseline 25(OH)D and AECOPD rates using Poisson and negative binomial analyses.

We also explored relationships among five 25(OH)D strata and AECOPD data, analyzing both time to first AECOPD using log-rank testing and annualized rates of AECOPDs using analysis of variance (ANOVA).

The sample size of 973 patients (of whom 63% experienced an AECOPD) provided 84% power with a two-tailed α error rate of 0.05 to detect a hazard ratio of 1.10 for a 10-unit change in 25(OH)D and time to first AECOPD.

Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Among 1,142 participants in the trial, 25 (2.2%) had no follow-up after the baseline visit and were not included in this analysis. AECOPD data were therefore available for 1,117 participants. Of these participants, 973 (87%) had viable plasma samples

available for this secondary analysis of the relationship between baseline 25(OH)D and subsequent AECOPDs.

The demographic data of the trial participants are provided in Table 1, for those with and without plasma samples available for 25(OH)D analysis.

Mean 25(OH)D was 25.7 ± 12.8 ng/ml. A total of 33.1% were vitamin D insufficient (defined as ≥ 20 ng/ml but < 30 ng/ml by widely used criteria [24]); 32% of participants were vitamin D deficient (< 20 ng/ml); and 8.4% of participants had severe vitamin D deficiency (< 10 ng/ml). 25(OH)D levels were related to the season of the year in which the blood was drawn (ANOVA; $P = 0.009$), with summer levels averaging the highest (27.3 ± 10.7 ng/ml) and winter levels the lowest (24.1 ± 15.7 ng/ml) (Figure 1). There was a significant ethnic difference in 25(OH)D levels, with lower mean levels in African-Americans (17.6 ± 10.2) and Hispanics (19.1 ± 9.7), compared with whites (27.2 ± 12.6) and other ethnicity patients (25.1 ± 14.7) (ANOVA; $P < 0.001$) (Figure 1). There was no significant association between clinical center and 25(OH)D levels (ANOVA; $P = 0.254$) (Figure 1). Low 25(OH)D levels were associated with worse baseline health status as assessed by both Medical Outcomes Study 36-item Short Form and St. George's Respiratory Questionnaire data (see online supplement).

These 973 participants experienced 1,415 AECOPDs over 1 year. A total of 360 (37%) remained AECOPD-free over 1 year; 278 (29%) had one AECOPD; 133 (14%) had two AECOPDs; and 202 (21%) had three or more AECOPDs.

In the primary analysis, 25(OH)D had no relationship to time to first AECOPD; for a 10 ng/ml increment in 25(OH)D, the estimated hazard ratio was 1.04 (95% confidence interval, 0.97–1.12). In the secondary statistical analyses, 25(OH)D had no relationship to annualized rates of AECOPDs in either Poisson ($P = 0.82$) or negative binomial analyses ($P = 0.87$).

An analysis of AECOPD rates stratified by 25(OH)D levels showed that participants with severe vitamin D deficiency (< 10 ng/ml) had a higher mean rate of AECOPDs, but this difference was not statistically significant (Table 2). When using time-to-event analysis, patients with severe vitamin D deficiency did not exhibit any faster time to first AECOPD. In fact, patients in the highest 25(OH)D stratum had the shortest time to first AECOPD, but this difference did not reach statistical significance.

There was no evidence in the data of interactions between the randomized treatment assignment (azithromycin vs. placebo) and baseline 25(OH)D levels as predictors of time to first exacerbation or rates exacerbations per person-year (P values for interaction > 0.50 for time to first exacerbation and rates of exacerbations; analyses not shown).

DISCUSSION

Although some data suggest that low 25(OH)D levels are associated with an increased risk of respiratory infections, we found no relationship between baseline 25(OH)D levels and time to first AECOPD. The primary outcome used in this analysis was time to first AECOPD, but when the data were analyzed using exacerbation rates, the consistent result was that baseline 25(OH)D had no relationship to AECOPD.

Based on these main results, we sought to explore a secondary hypothesis that the subgroup with severe vitamin D deficiency (25[OH]D < 10 ng/ml) might be particularly vulnerable to AECOPD. In this *post hoc* analysis, there was no statistically significant difference across the strata. Mean AECOPD rate was highest in the low 25(OH)D group, but median time to AECOPD was shortest in the high 25(OH)D group. Neither of these differences was statistically significant, and we stress the *post hoc* nature of these stratified analyses.

TABLE 1. BASELINE CHARACTERISTICS OF TRIAL STUDY PARTICIPANTS, FOR PATIENTS INCLUDED AND NOT INCLUDED IN THIS ANALYSIS OF 25(OH)D

	Included in 25(OH)D Analysis (n = 973)	Not Included in 25(OH)D Analysis (n = 144)	P Value*
Age, yr (mean ± SD)	65.4 ± 8.6	63.6 ± 8.6	0.02
Female sex, %	40	46.5	0.14
Race or ethnicity, %			
White	85.2	72.2	<0.01
African-American	13.8	27.1	<0.01
Hispanic	2.5	0.7	0.18
Asian	1	0.7	0.71
Native American	3.1	4.2	0.49
More than one	3	4.2	
Post-bronchodilator FEV ₁ , L (mean ± SD)	1.12 ± 0.51	1.08 ± 0.49	0.45
Post-bronchodilator FEV ₁ , % predicted (mean ± SD)	39.6 ± 15.6	39.3 ± 15.8	0.80
FEV ₁ /FVC, % (mean ± SD)	42.7 ± 12.8	41.7 ± 12.5	0.41
GOLD category, %			
1	0.1	0	1.00
2	26	27.8	0.65
3	41.9	31.3	0.02
4	32.1	41	0.03
Smoking history, pack-years (mean ± SD)	58.1 ± 31.7	60.6 ± 34.7	0.39
Current smokers, %	20.8	30.6	0.01
Medication use, %			
Inhaled corticosteroids only	5.2	4.2	0.58
Long-acting muscarinic antagonists only	6.7	7.6	0.71
Long-acting β ₂ -agonists only	1.6	3.5	0.13
Inhaled corticosteroids + long-acting β ₂ -agonists	20.8	18.8	0.58
Inhaled corticosteroids + long-acting muscarinic antagonists	4.9	2.1	0.13
Long-acting β ₂ -agonists + long-acting muscarinic antagonists	4.5	6.3	0.36
Inhaled corticosteroids + long-acting β ₂ -agonists + long-acting muscarinic antagonists	47.3	47.2	0.99
None	8.8	10.4	0.54

Definition of abbreviations: 25(OH)D = 25 hydroxyvitamin D; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

* P values derived from *t* test for continuous data or chi-square test for categorical data; not adjusted for multiple comparisons.

The main strengths of our study include its large sample size (the largest to date regarding 25[OH]D levels in a COPD-specific cohort); use of an experienced laboratory to perform the 25(OH)D assays; a wide distribution of 25(OH)D levels; and the standardized, prospective collection of AECOPD data in the context of a clinical trial using AECOPD as its primary outcome. However, there are certain limitations to the data.

Our study was restricted to a single baseline assessment of 25(OH)D levels. Therefore, we cannot exclude the possibility that 25(OH)D levels may have changed after the baseline measures. Although it is unlikely that many patients began vitamin D supplementation during the trial, one certainly cannot exclude such a possibility, especially in light of the popular media's recent attention on vitamin D.

25(OH)D levels are also known to vary by season, so we cannot exclude the possibility that individual subjects experienced subsequent seasonal changes in 25(OH)D levels after the baseline measurement. Although the analysis showed a statistically significant difference between mean 25(OH)D levels drawn in summer versus winter, the magnitude of the summer versus winter seasonal difference was only 4.1 ng/ml. This difference is much smaller than the 14.2 ng/ml seasonal difference reported in a sample of 24 United Kingdom patients with COPD (25) and the 13.4 ng/ml seasonal difference we reported in a sample of 198 Lung Health Study 3 (LHS 3) participants (26). We used the same laboratory and the same liquid chromatography tandem mass spectroscopy methodology for 25(OH)D assays in both the previous LHS 3 study and the current study, so differences in analytic techniques do not explain the difference in seasonal effects. One potential explanation is that the previous LHS 3 sample was a group of patients with relatively mild COPD (mean FEV₁ of 72% of predicted), whereas patients in this current study had much more severe COPD (mean FEV₁ of

40% of predicted). FEV₁ % predicted was not provided for the 24 patients in the United Kingdom study, but a mean FEV₁ of approximately 1.2 L suggests they also had severe COPD. One important note is that participants in the current study were selected for particularly high risk of AECOPDs (>80% experienced an AECOPD in the year before enrollment and there were 1,415 exacerbations during follow-up in these 973 patients), so they represent the most severely ill patients with COPD. As such, these participants may have had more ambulatory limitation than the participants in the LHS 3 or United Kingdom studies. Ambulatory limitation can limit sunlight exposure, leading to blunting of typical seasonal effects on 25(OH)D levels.

Study participants had a wide distribution of 25(OH)D levels across the spectrum of "normal," "insufficient," and "deficient," but these definitions have largely been defined on the basis of bone disease and suppression of parathyroid hormone levels (24). For nonskeletal effects of 25(OH)D, such as prevention of respiratory infections or AECOPDs, the threshold levels for benefits are unknown. Hypothetically, if the threshold 25(OH)D level to prevent AECOPDs is greater than 50 ng/ml, we only had 23 patients in this supranormal range so our study was not powered to address relationships between supranormal 25(OH)D and AECOPDs. Because of the rare finding of naturally occurring supranormal 25(OH)D levels, observational studies to explore this question would require very large cohorts to achieve adequate power. Patients with levels this high also tend to achieve such levels through vitamin D supplementation, thus also introducing confounders, such as health behaviors associated with vitamin use. Therefore, randomized, controlled trials would likely be the only way to test the hypothesis that supranormal 25(OH)D levels reduce AECOPD risk.

Our primary results contrast with similar studies conducted in patients with asthma, another obstructive lung disease associated

Figure 1. Distribution of vitamin D levels by season and ethnicity (upper panel) and clinical center (lower panel). 25(OH)D = 25 hydroxyvitamin D; A. Arbor = Ann Arbor, MI; Balt = Baltimore, MD; Birm = Birmingham, AL; Bost = Boston, MA; Denv = Denver, CO; Minn = Minnesota; Phil = Philadelphia, PA; Pitt = Pittsburgh, PA; UCLA = University of California, Los Angeles; UCSF = University of California, San Francisco.

with episodic exacerbations. A cross-sectional study of 616 children with asthma in Costa Rica showed that low 25(OH)D levels were associated with a higher number of self-reported asthma hospitalizations in the previous year (14). A larger study of 1,024 children with asthma used similar methodology to our study by measuring a single baseline 25(OH)D level and then assessing relationships between baseline 25(OH)D and subsequent severe asthma exacerbation data collected as part of a large randomized trial (15). In that study, lower baseline 25(OH)D was related to a higher hazard of time to first severe asthma exacerbation and higher odds of ever having a severe exacerbation over the course of the study. A threshold 25(OH)D level of greater than 30 ng/ml also seemed to be associated with a reduction in the observed risk of exacerbations, suggesting that at least in those with asthma, supranormal 25(OH)D levels may not be necessary to potentially reduce exacerbation risk.

Although 25(OH)D may have an effect on respiratory exacerbation risk in patients with asthma, complex effects in COPD, such as bacterial colonization, airway inflammation, systemic inflammation, oxidative stress, and impaired mucociliary clearance, may have stronger effects on AECOPD risk than any effects of 25(OH)D. It must

be stressed that our data remain observational in nature and only a randomized controlled trial can definitively answer the question of whether or not modification of 25(OH)D levels (easily achievable through vitamin D supplementation) can alter the risk of AECOPD.

Published results from randomized trials of vitamin D supplementation in patients with COPD are currently lacking, but recent randomized controlled trial data in healthy individuals (27, 28) together with our current observational data suggest such trials are not likely to show an effect of vitamin D supplementation on AECOPD prevention. We also note that the current data are consistent with our previous findings that 25(OH)D levels in COPD are not related to either longitudinal lung function decline or FEV₁ responses to inhaled corticosteroids (26, 29).

CONCLUSIONS

Among patients with COPD at high risk of AECOPD, baseline blood 25(OH)D levels are not related to the risk of subsequent AECOPDs. The notion that vitamin D supplementation might reduce AECOPD risk is not supported by our data.

TABLE 2. COMPARISON OF AECOPD EVENT DATA, STRATIFIED BY BASELINE 25(OH)D STATUS

AECOPD metric	25(OH)D category					P Value
	0–9.99 ng/ml (n = 82)	10–19.99 ng/ml (n = 229)	20–29.99 ng/ml (n = 322)	30–39.99 ng/ml (n = 233)	≥40 ng/ml (n = 107)	
Mean exacerbation rate, exacerbations per year ± SD	2.20 ± 5.27	1.57 ± 2.02	1.57 ± 1.93	1.47 ± 1.80	1.79 ± 1.96	0.17
Median time to first exacerbation, d (95% CI)	215 (145,361)	235 (196,298)	225 (188,269)	242 (188,294)	166 (124,299)	0.47

Definition of abbreviations: 25(OH)D = 25 hydroxyvitamin D; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CI = confidence interval. P value for AECOPD rate derived from analysis of variance testing; P value for time to first exacerbation derived from log-rank statistic.

Author disclosures are available with the text of this article at www.atsjournals.org.

Members of the COPD Clinical Research Network: J.J. Reilly, Jr (PI), G.R. Washko (co-PI), R. Rosiello, M.L. Moy (investigators), Brigham and Women's Hospital (affiliated sites Fallon Clinic and West Roxbury Veterans Hospital; grant HL074428); R.K. Albert (PI), B. Make (co-PI), M. Schwarz, C. Welch (investigators), Denver Health Medical Center (affiliated sites National Jewish Medical & Research Center and University of Colorado; grant HL074409); R. Casaburi (PI), J. Porszasz (investigator), Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (grant HL074407); D.E. Niewoehner (PI), C. McEvoy, K.R. Rice, P.D. Scanlon (co-PIs), Minnesota Veterans Research Institute, Minneapolis (affiliated sites HealthPartners Research Foundation and Mayo Clinic; grant HL074416); G.J. Criner (PI), W. Chatila, N. Marchetti, V. Kim, G. D'Alonzo, S. Krachman, F. Cordova, K. Brennan, N. Patel, J. Mamary (investigators), Temple University (grant HL074408); W.C. Bailey, J.A.D. Cooper (co-PIs), M.T. Dransfield, L.B. Gerald, P. O'Reilly (investigators), University of Alabama at Birmingham (grant HL074418); S.C. Lazarus (PI), H.A. Boushey, P.G. Woodruff (investigators), University of California, San Francisco (grant HL074431); S.M. Scharf (PI), M. Alattar, P. Amelung, M. Cowan, J. Hanson, J. Hasday, A. Iacono, C. Shanholtz, N. Todd, A. Verceles (investigators), University of Maryland, Baltimore (grant HL074441); F.J. Martinez (PI), J.L. Curtis, M.K. Han, K.R. Flaherty, S.E. Gay, T.E. Sisson (investigators), University of Michigan, Ann Arbor (grant HL074422); F. Sciruba (PI), J. Bon (investigator), University of Pittsburgh (grant HL074439); and J.E. Connett (PI), N.R. Anthonisen (Steering Committee Chair), C. Wendt (co-PI), University of Minnesota (Data Coordinating Center; grant HL074424).

Acknowledgment: The authors thank R. Singh and H. Blair (Immunochemical Core Laboratory, Mayo Clinic, Rochester, MN) for critical assistance in performing 25 (OH)D laboratory analysis, and A. Boggess (University of Minnesota, Minneapolis, MN), A. Fabbri, and D. Stuber (Minneapolis VA Medical Center, Minneapolis, MN) for assistance with plasma sample identification and preparation. The COPD Clinical Research Network is supported by a Cooperative Agreement from the Division of Lung Diseases of the National Heart, Lung, and Blood Institute. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, the National Institutes of Health, the U.S. Government, or the authors' affiliated academic institutions.

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