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SHORT REPORT

Vitamin D and responses to inhaled fluticasone in severe chronic obstructive pulmonary disease

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Background: Patients with chronic obstructive pulmonary disease (COPD) demonstrate variable responses to inhaled corticosteroids (ICS). The factors contributing to this variability are not well understood. Data from patients with asthma have suggested that low 25-hydroxyvitamin D [25(OH)D] levels contribute to a lack of ICS response in asthma. The objective of this study was to determine whether serum levels of 25(OH)D were related to ICS responses in patients with COPD.

Methods: A total of 60 exsmokers with severe COPD (mean forced expiratory volume in one second [FEV_1] 1.07 L, 36% of predicted) spent 4 weeks free of any ICS, followed by 4 weeks of ICS use (fluticasone propionate 500 µg twice daily). Spirometry was performed prior to and after 4 weeks of ICS use. Blood 25(OH)D levels were measured prior to ICS use and examined for relationships to changes in FEV_1 following the 4 weeks of ICS use.

Results: The mean 25(OH)D level was 23.3 ± 9.3 ng/mL. There was a high prevalence of vitamin D insufficiency (35%) and deficiency (40%). There was no relationship between baseline 25(OH)D and changes in FEV_1 following 4 weeks of ICS.

Conclusion: Baseline 25(OH)D does not contribute to the variation in short-term FEV_1 responses to ICS in patients with severe COPD.

Keywords: COPD, androstadienes, anti-inflammatory agents, spirometry

Introduction

Vitamin D has received increasing amounts of attention in recent years, particularly its potential nonskeletal effects in diseases such as cancer, cardiovascular disease, and infectious diseases. Although an optimal level of vitamin D has not been defined for nonskeletal outcomes, 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL are widely considered to reflect deficiency. Using this definition, patients with chronic obstructive pulmonary disease (COPD) have a high prevalence of vitamin D deficiency, ranging from approximately 30% in mild COPD to over 75% in severe COPD.[1–5] The clinical consequences of these low 25(OH)D levels in COPD patients have not been studied extensively. Among patients with asthma, low 25(OH)D levels have been associated with an increased risk of severe asthma exacerbations,[6] hospitalizations,[7] poor asthma control,[8] and steroid resistance.[9] We pursued the current study to investigate relationships between 25(OH)D and responses to inhaled corticosteroid (ICS) treatment in patients with COPD.

ICS are widely used in the treatment of COPD. However, the clinical response to ICS is variable, and some patients respond more favorably than others. The underlying causes of this variable response are not well understood. Recent data from patients

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with asthma suggest that low blood 25(OH)D levels might contribute to poor glucocorticoid responses.[10,11] We therefore examined the hypothesis that among patients with COPD, 25(OH)D levels were associated with the variation in responsiveness to ICS treatment.

Methods

This study was conducted using stored serum from a previous study designed to examine the ability of exhaled nitric oxide and blood markers of systemic inflammation to predict forced expiratory volume in one second (FEV_1) responses to ICS treatment in patients with COPD. Results have been previously published.[12]

Subjects

The institutional review board of the Minneapolis Veterans Affairs Medical Center approved the original study and this secondary analysis. All subjects provided written informed consent for the original study and for storage of blood samples for future research. The study did not meet trial registration criteria at the time of its conduct between 2005 and 2006.

Subjects were recruited from the Minneapolis Veterans Affairs Medical Center between May 2005 and February 2006. Inclusion criteria were: 1) a clinical diagnosis of COPD, with a FEV_1/forced vital capacity (FVC) ratio $<70\%$, and FEV_1 $<60\%$ of predicted; 2) age >45 years; 3) cigarette smoking history of >10 pack-years; 4) abstinence from cigarette smoking of at least 6 months; 5) stable clinical status, as evidenced by the lack of hospitalizations, urgent care visits, antibiotics, or changes in medications within 4 weeks prior to enrollment; and 6) ability to provide informed consent. Exclusion criteria were: 1) a clinical diagnosis of asthma; 2) leukotriene inhibitor use; 3) severe or uncompensated heart failure; 4) the presence of conditions known to elevate C-reactive protein (CRP) levels such as collagen vascular disease and chronic infection; 5) malignancy requiring active treatment with chemotherapy or radiation therapy, or any comorbidity making survival longer than 1 year unlikely; 6) women who were pregnant or lactating; 7) oral corticosteroid use within 4 weeks prior to enrollment; and 8) participation in another investigational trial within 4 weeks of enrollment and for the 8-week duration of this study.

Study design

Subjects who met study criteria and agreed to participate entered a 4-week run-in period. During the run-in, subjects were treated with salmeterol, 50 μg inhalation twice daily (Serevent Diskus®; GlaxoSmithKline, Research Triangle Park, NC). The use of ICSs was not allowed during the run-in. Tiotropium use was not allowed for the duration of the study; however, tiotropium was not in wide use at the time of this study. Subjects were allowed to continue use of all other respiratory medications, including short-acting beta agonists and ipratropium.

After the run-in, subjects returned to the study center for baseline measurements of prebronchodilator spirometry and blood collection. All visits were in the morning and subjects were fasting. Before each study visit, subjects withheld use of short-acting bronchodilators for 6 hours and withheld use of salmeterol for 12 hours. For the next 4 weeks, subjects were treated twice daily with 500 μg of fluticasone propionate and 50 μg of salmeterol (Advair Diskus 500/50®; GlaxoSmithKline). After 4 weeks, subjects returned to the study center for repeat measurement of prebronchodilator spirometry and blood sample collection.

Protocols

Spirometry was performed in accordance with American Thoracic Society (ATS) standards[13] (MicroLab 3500, Micro-Medical, Kent, UK). Third National Health and Nutrition Examination Survey spirometric reference values were used as reference.[14]

Serum blood samples were allowed to clot at room temperature, centrifuged, and immediately frozen at –80°C in aliquots. Stored serum for 25(OH)D assay was available for all patients who completed the original study. For this study, 25(OH)D levels were measured from stored samples collected at the visit following the run-in ("baseline"), prior to ICS initiation. 25(OH)D was measured by liquid chromatography tandem mass spectroscopy (ThermoFisher Scientific, Franklin, MA; Applied Biosystems-MDS Sciex, Foster City, CA) at the Mayo Clinic Immunochemical Core Laboratory (Rochester, MN).

Statistical methods

The primary outcomes of interest in the original study were correlations between potential predictor variables (exhaled breath and blood inflammatory markers) and the outcome variable: prebronchodilator change in FEV_1 from baseline to after 4 weeks of ICS therapy. The study was powered (two-sided alpha of 0.05 and beta of 0.20) to detect a correlation coefficient of 0.35. This resulted in a sample size calculation of 62 patients. Seventy-eight subjects consented, which allowed for 20% of consented subjects to either fail spirometry screening or not complete the full protocol.

This secondary analysis of 25(OH)D levels as a predictor variable of ICS response was not planned at the time of the original study.

Because ICS responses were not normally distributed, analyses were conducted with nonparametric statistical tests. For the primary correlation analyses, Spearman's rank-correlation testing (reported as Spearman's rho) was used. For secondary analyses, we dichotomized subjects into responders and nonresponders to ICS therapy, using a FEV_1 improvement of ≥200 mL after 4 weeks of ICS therapy to define responders. There is no consensus on a meaningful FEV_1 response to ICS therapy in COPD. We thus extrapolated from ATS guidelines which require ≥200 mL improvement in FEV_1 as a component of defining a significant bronchodilator response.[13]

Distributions of 25(OH)D among responders and nonresponders were compared using the Wilcoxon rank-sum test. Receiver-operating characteristic (ROC) analyses were also conducted, using FEV_1 improvement of ≥200 mL after 4 weeks of ICS therapy as the outcome of interest. We also dichotomized subjects using conventional 25(OH)D cut points for vitamin D deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) and compared distributions of FEV_1 change using the Wilcoxon rank-sum test.

All statistical analyses were performed using Stata software (v. 9; StataCorp LP, College Station, TX).

Results

A total of 76 patients consented to study participation, and 16 (21%) did not complete the full protocol. Three failed to meet screening spirometry criteria, seven experienced COPD exacerbations during the study, and six withdrew consent during the study, chiefly for subjective dyspnea. Therefore, 60 patients provided complete data for analysis. Compared to participants who completed the study, participants who withdrew from the study had similar COPD severity, but were more likely to have been prescribed antibiotics and prednisone in the previous 12 months, and were more likely to have received more inhaled medications, including inhaled corticosteroids, before study participation (Table 1).

The mean age was 71 years (98% males), with a mean FEV_1 of 1.07 L ± 0.36 L (36% of predicted). ICS compliance was excellent (93% of expected doses used) as assessed by device dose delivery counters. FEV_1 change after ICS treatment ranged from –0.49 to 0.64 L (median change of 0.07 L; interquartile range, –0.02–0.14 L). Mean 25(OH)D level was 23.3 ± 9.3 ng/mL. There was no correlation between baseline 25(OH)D levels and baseline FEV_1 (Spearman rho = –0.10; $P = 0.46$) (Figure 1). There was a high prevalence of vitamin D deficiency (n = 24; 40%) when using the standard definition of deficiency being a 25(OH)D level <20 ng/mL. Vitamin D insufficiency, defined as a 25(OH)D level ≥20 ng/mL but <30 ng/mL, was also prevalent (n = 21, 35%). Only 25% of study participants had a 25(OH)D level considered normal.

There was no correlation between baseline 25(OH)D and subsequent FEV_1 responses to ICS (Spearman rho = 0.01; $P = 0.93$) (Figure 2). When ICS responders were defined as experiencing ≥200 mL improvement in prebronchodilator FEV_1 between baseline and after ICS therapy, the median baseline 25(OH)D of ICS responders (n = 11) and nonresponders (n = 49) was equal (23 ng/mL and 23 ng/mL, respectively; Wilcoxon rank-sum, $P = 0.97$) (Figure 3). ROC analysis showed that 25(OH)D had no ability to discriminate ICS responders from nonresponders (ROC area under curve = 0.50; 95% confidence interval: 0.31–0.68). When patients were dichotomized as vitamin D deficient (25[OH]D <20 ng/mL) or not deficient, there was no difference in the median FEV_1 improvement with ICS in each group (75 mL and 50 mL, respectively; Wilcoxon rank-sum, $P = 0.64$) (Figure 4). Results did not change when the 25(OH)D cutoff was changed to <30 ng/mL to compare those with vitamin D insufficiency or deficiency to those with normal vitamin D levels (median FEV_1 improvement of 80 mL and 50 mL, respectively; Wilcoxon rank-sum, $P = 0.78$).

Discussion

This study utilized stored samples from a previous study examining predictors of ICS responses in patients with COPD. In the original study, exhaled nitric oxide was shown to have a modest relationship to ICS responses. In this secondary analysis of stored samples from that study, baseline 25(OH)D had no relationship to FEV_1 changes after 4 weeks of ICS use.

This secondary analysis was largely prompted by Sutherland and colleagues' findings.[10] In their sample of 54 adults with asthma, low 25(OH)D levels were associated with blunted corticosteroid responses. However, corticosteroid responses in their study were assessed by an in-vitro assay of dexamethasone-induced mitogen-activated protein kinase phosphatase (MKP)-1 expression by peripheral blood mononuclear cells (PBMCs), rather than spirometry. As such, the clinical extension of their in vitro finding remains to be validated. In a related study of 100 children with asthma, Searing and colleagues reported similar in vitro effects of vitamin D on dexamethasone-induced MKP-1 expression by PBMCs.[11] Relationships between vitamin D and steroid

Table 1 Characteristics of study sample at time of enrollment

Baseline characteristics at screening	Completed study (n = 60)	Withdrawn from study (n = 13)
Demographics and smoking history		
Male	59 (98%)	13 (100%)
Female	1 (2%)	0 (0%)
Age (years)	71 ± 7.3	70 ± 7.9
Smoking history (pack-years)	57 ± 30.6	53 ± 26.1
Duration of smoking abstinence (years)	13 ± 10	13 ± 9.4
Spirometry		
Prebronchodilator FEV_1 (L)	1.07 ± 0.36	1.09 ± 0.28
Prebronchodilator FEV_1 (% predicted)	35.6 ± 10.6	33.0 ± 8.5
Prebronchodilator FVC (L)	2.44 ± 0.72	2.54 ± 0.62
Prebronchodilator FVC (% predicted)	58.5 ± 14.6	56.8 ± 12.9
Medication use		
Prescribed one or more courses of antibiotics in the 12 months prior to enrollment	11 (18%)	6 (46%)
Prescribed one or more courses of prednisone in the 12 months prior to enrollment	7 (12%)	6 (46%)
Prescribed chronic oxygen	10 (16%)	3 (23%)
Prescribed albuterol	59 (98%)	12 (92%)
Prescribed ipratropium	35 (58%)	11 (84%)
Prescribed long-acting beta agonist	30 (50%)	9 (69%)
Prescribed long-acting anticholinergic	1 (2%)	0 (0%)
Prescribed inhaled corticosteroid	28 (47%)	9 (69%)
Prescribed theophylline	2 (3%)	0 (0%)
Comorbid conditions		
Coronary artery disease	16 (27%)	1 (8%)
Heart failure	6 (12%)	1 (8%)
Hypertension	36 (60%)	8 (62%)
Atrial fibrillation/flutter	5 (8%)	0 (0%)
Hyperlipidemia	37 (62%)	8 (62%)
Diabetes mellitus	14 (23%)	1 (8%)
Peripheral vascular disease	9 (15%)	1 (8%)
History of stroke	2 (3%)	0 (0%)
Chronic kidney disease	5 (8%)	0 (0%)
Obstructive sleep apnea	4 (7%)	0 (0%)
Gastroesophageal reflux disease	12 (20%)	1 (8%)
Chronic rhinosinusitis	5 (8%)	1 (8%)

Note: Data are presented as mean ± standard deviation for continuous variables or as number (%) for categorical variables.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

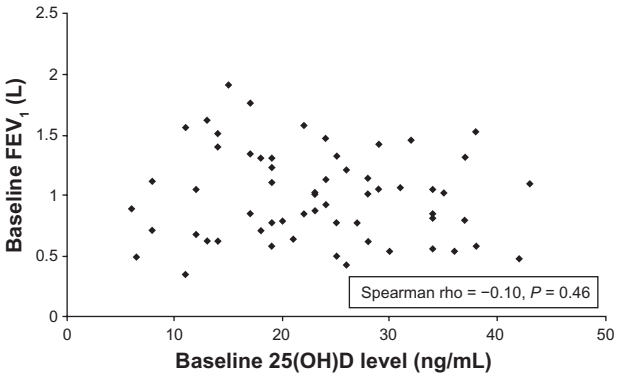

Figure 1 Scatterplot of baseline (pre-ICS) 25(OH)D and baseline pre-bronchodilator FEV_1. Spearman's rank-correlation test used for calculation of Spearman rho and corresponding *P* value.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

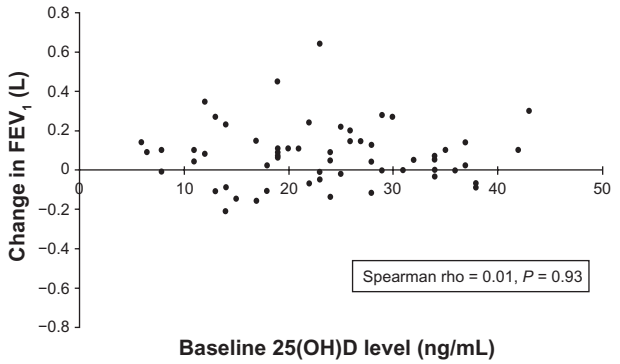

Figure 2 Scatterplot of baseline (pre-ICS) 25(OH)D and change in prebronchodilator FEV_1 following 4 weeks of ICS. Spearman's rank-correlation test used for calculation of Spearman rho and corresponding *P* value.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

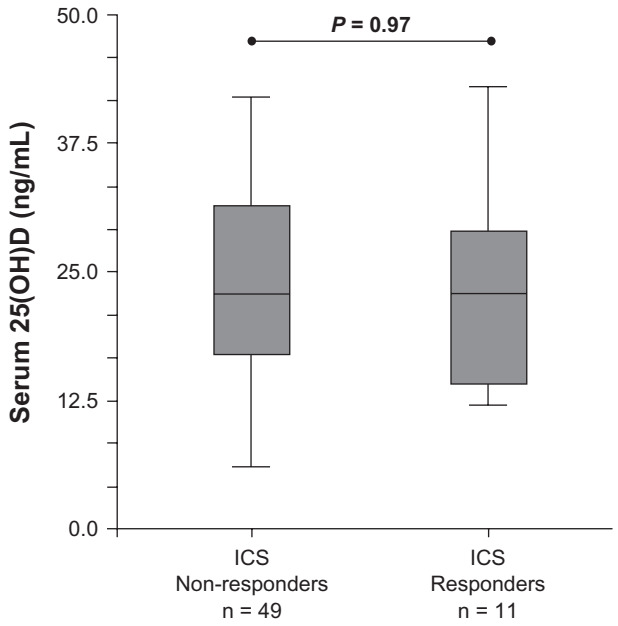

Figure 3 Boxplots of baseline (pre-ICS) 25(OH)D distributions among ICS nonresponders and ICS responders. ICS responders were defined as experiencing ≥200 mL FEV_1 improvement following 4 weeks of ICS. Wilcoxon rank-sum test used for calculation of *P* value.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

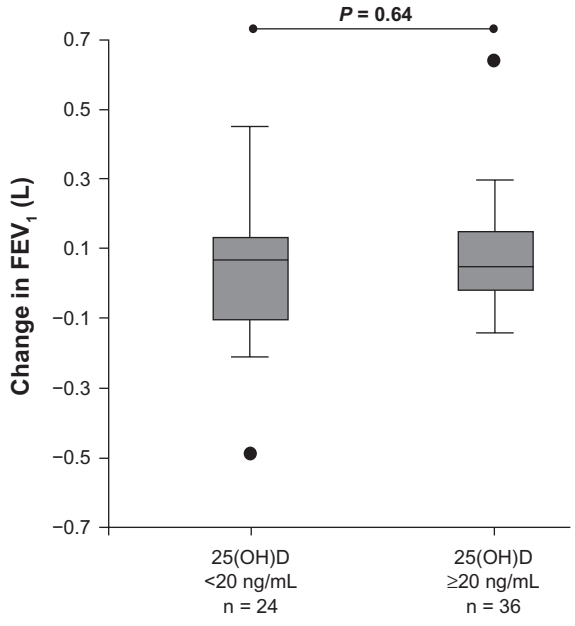

Figure 4 Boxplots of distributions in FEV_1 responses to ICS among study participants with vitamin D deficiency [25(OH)D <20 ng/mL] versus no deficiency. Wilcoxon rank-sum test used for calculation of *P* value.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

responses may be different in asthma and COPD, but there are currently no published reports regarding this topic among patients with COPD.

This is the first study to analyze 25(OH)D levels in relation to ICS responses in COPD. This study has several limitations. The study sample was essentially limited to elderly Caucasian males and was a single-center study. Our study was also relatively small in size, but all of our point estimates for differences clustered around the null hypothesis of no difference. As such, a larger sample size would not likely alter the conclusions. In addition, FEV_1 responses were only assessed over a relatively brief 4-week ICS intervention; longer-term outcome data were not collected. The rationale for this brief intervention was that the majority of ICS effects on FEV_1 have occurred within 2–4 weeks in previous large COPD clinical trials.[15–17]

The need for an ICS wash-out period may have also affected our results. Patients with previous good clinical responses to ICS therapy may have been either less likely to enroll in this study or more likely to withdraw during the study, as was suggested by the higher percent of previous ICS users in the group that did not complete the study. Thus, our sample may have been biased towards ICS nonresponders. A 4-week period for ICS wash-out could also limit ICS responses following re-introduction of ICS therapy. A study of ICS-naive patients would have eliminated the need for a wash-out, but such a study was felt to be unfeasible for a single-center study, due to a high rate of use of ICS in patients with COPD (nearly 50% in our recruited sample).

Another limitation of our study is that nonspirometric outcomes were not assessed, so an analysis of 25(OH)D relationships to outcomes such as acute exacerbations or respiratory health status could not be performed. Compared with patients without COPD, patients with COPD are also at increased risk of diseases such as cardiovascular disease, osteoporosis, and skeletal muscle dysfunction, which are all diseases which have been associated with low 25(OH)D levels.[18] As such, these are areas that require further investigation.

Our data confirm previous observations regarding a high prevalence of what is traditionally considered a suboptimal 25(OH)D level of <30 ng/mL. We were not able to explain the reasons for low 25(OH)D levels, as we did not collect information on common factors affecting vitamin D status, such as dietary supplement use, sunlight exposure, and skin pigmentation. We also note that while we found a high prevalence of 25(OH)D levels <30 ng/mL in our sample of patients with COPD, general population samples have also demonstrated a high prevalence of low 25(OH)D levels. Among 13,369 US participants in the National Health and Nutrition Examination Survey (NHANES) between 2001–2004, 77% had levels <30 ng/mL.[19]

In summary, there was a high prevalence of low blood 25(OH)D levels in a sample of patients with severe COPD, and these 25(OH)D levels were not associated with short-term FEV_1 responses to ICS therapy.

Disclosure

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