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IMPACT OF VITAMIN D DEFICIENCY ON ACUTE EXACERBATION OF COPD PATIENTS

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Abstract:

Objective: *This study was performed to evaluate vitamin D status among chronic obstructive pulmonary disease (COPD) patients and determine the role of vitamin D deficiency in COPD exacerbations.*

Methods: *This study included 70 patients diagnosed to have COPD following the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria. Serum 25-hydroxyvitamin D levels were measured. Clinical characteristics and demographic data were recorded for all participants.*

Results: *A total of 71.4% (50) of patients were classified as GOLD stage II and 28.6% (20) of patients were GOLD stage III. Vitamin D levels for stage II and III patients were 14.56 ± 4.03 ng/mL and 14.40 ± 5.40 ng/ml, respectively. Mean number of acute exacerbations of COPD (AECOPD) for all patients was 3.4 ± 0.79 over the last year. Regression analysis model showed that low vitamin D levels were significantly associated with the mean number of AECOPD (R2 0.468, SE 0.58, p < 0.001). Interestingly, vitamin D deficient patients develop frequent AECOPD (3.58 ± 0.62) compared to vitamin D insufficient patients (2.40 ± 0.97) (F 5.700, 95% CI 1.64-0.72, P 0.020).*

Conclusions*: Vitamin D deficiency was prevalent among Saudi COPD patients and hypo-vitaminosis D was significantly associated with acute exacerbation of COPD.*

Key words: *Vitamin D, Vitamin D Deficiency, COPD, Acute Exacerbation.*

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INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) represents a major burden of chronic morbidity and mortality in developing and developed countries.[1] COPD is characterized by slowly progressive airflow limitation in response to an enhanced chronic inflammatory process.[2] Acute exacerbation of COPD (AECOPD) is an inevitable event during the clinical course demanding an urgent interference and it is associated with significant mortality.[3] The coexistence of comorbidities with AECOPD represent a major challenge for disease management and may have an adverse impact on survival.[2] These acute exacerbations are frequently encountered and affect the phenotypic presentation of COPD patients.[4] The average of acute exacerbations among COPD patients was estimated to be one to four attacks per year.[3] The degree of severity and frequency of AECOPD are major determinants of management and outcome of COPD.[2] Frequent exacerbation has an impact on the quality of life and accelerates lung function decline.[5] It has been reported that acute exacerbation in COPD course is an overwhelming event with comparable consequences and effects to that produced by acute myocardial infarction in patients with coronary heart disease.[3] Respiratory infections (bacterial or viral) and environmental triggers such as air pollution are common predisposing factors for acute exacerbations.[3] About 50% of exacerbation attacks occur due to respiratory infections and 10% due to environmental pollutants, while 30 - 40% are of unknown cause.[6,7] Recently, the spotlight has been directed toward the potential role of vitamin D in developing immune response to infections and determining the pathogenesis of COPD extra-pulmonary effects.[8,9] Specifically, many studies showed that lower 25-hydroxyvitamin D were associated with higher frequencies of respiratory infections and asthma exacerbations.[10,11] Moreover, publications showed a considerable interest in whether vitamin D deficiency may have an impact on developing frequent exacerbation of COPD.[10,12] The aim of the current study was to evaluate vitamin D status among Saudi COPD patients and determine the role of vitamin D insufficiency/deficiency on disease exacerbations and severity.

SUBJECTS AND METHODS:

We conducted a cross sectional survey of patient diagnosed to have COPD according to the American Thoracic Society's criteria [13] and COPD was rated at four stages by the forced expiratory volume in one second (FEV_1) according to The Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines.[2] Exclusion criteria included a diagnosis of asthma, bronchiectasis, lung cancer, disease that may lead to instability of the patient's medical condition and patients who have a documented deficiency/insufficiency of vitamin D or suffer from osteopenia/osteoporosis and receive vitamin D supplements prior to the time of blood sample withdrawal. All patients were stable during the last month and were randomly selected from all diagnosed COPD patients seen in the outpatient clinics of King Fahd governmental hospital for regular monitoring. Detailed information about each exacerbation attack was collected over 1 year and AECOPD were defined following the GOLD guidelines.[2] A venous blood sample withdrawn from all participants to determine 25-hydroxyvitamin D level using the same chemiluminescent assay and an arterial blood sample was used for arterial blood gas analysis (ABG) for all cases. All patients provided written informed consent. The study protocol was approved by the Institutional Review Boards of Al Maddinah Directorate for health Affairs and King Fahd Hospital.

STATISTICAL ANALYSIS:

Descriptive statistics were reported as frequencies and percentages for qualitative variables and means ± standard deviation for quantitative variables. Correlation analysis using Pearson's correlation coefficient to evaluate the strength of association between vitamin D levels, age, sex, body mass index (BMI), smoking and associated comorbidities. Relationship of vitamin D levels with pulmonary functions and arterial blood gases variables was assessed by simple linear regression analysis. Disease severity was determined based on % predicted of airflow obstruction (Forced expiratory volume in one second). Differences between vitamin D deficiency and insufficiency in relation to pulmonary functions testing were compared by independent samples t-test. The analysis was performed in 95% confidence interval using Statistical Package for Social Science (SPSS), version 20 (IBM, Armonk, NY, USA). Statistical methods were applied assuming a significant level of $p < 0.05$ and a highly significant level of < 0.001

RESULTS:

A total 70 patients with COPD (Mean age 69.3 ± 10.1 years; 50 males and 20 females) were included in this study. Of these patients, 34.3% were current smokers, 42.9% were ex-smokers and 22.9% were non-smokers. Associated comorbidity was found in 62.9% of patients. The most prevalent comorbidity was diabetes mellitus either alone (10.0%) or in

combination with hypertension (25.7%) and/or ischemic heart disease (1.4%). Mean BMI of all patients was 22.72 ± 3.66. Detail demographic and clinical characteristics were mentioned in Table 1. During the last year, mean number of AECOPD was 3.4 ± 0.79 for all patients. A total of 63 patients experienced three or more AECOPD; 5 patients had two AECOPD; 2 patients had one AECOPD over one-year period. According to the GOLD classification criteria for COPD most patients were diagnosed with GOLD stage II (50 patients; 71.4%) and stage III (20 patients; 28.6%). Mean vitamin D level among all COPD patients was 14.51 ± 4.43 ng/mL. A total of 85.7% were vitamin D deficient (< 20 ng/ml) and 14.3% of patients were vitamin D insufficient (defined as >20 ng/ml but <30 ng/ml). The mean ± SD of vitamin D levels for stage II and III COPD patients were 14.56 ± 4.03 ng/mL and 14.40 ± 5.40 ng/ml, respectively. There was no statistical significant difference between vitamin D levels among stage II and III COPD patients (95% CI 2.513-2.193, p 0.220). We examined whether vitamin D deficiency was influenced by any factor. There was no significant correlation between vitamin D levels and age (*p-value* 0.279), sex (*p-value* 0.065), smoking (*p-value* 0.327) and associated comorbidity (*p-value* 0.162) Table 1. The mean values ± SD for pulmonary function tests were as follow (FEV1) 56.57 ± 8.38; (FVC) 7.74 ± 7.04; (FEV1/ FVC) 62.43 ± 4.53; (PEF) 67.86 ± 5.54, 65.61 ± 4.69, while mean value ± SD for ABG results were (PH) 7.35 ± 0.03; (PO_2) 75.90 ± 5.19; (PCO_2) 68.41 ± 4.78 and (HCO_3) 30.90 ± 5.22. Simple linear regression analysis model showed that low vitamin D levels were significantly associated with arterial blood gas components PH (R2 0.178, SE 0.03, $p < 0.001$), PCO_2 (R2 0.186, SE 4.34, $p < 0.001$) and number of AECOPD in last year (R2 0.468, SE 0.58, $p < 0.001$). However, there was no statistically significant relationship found between vitamin D level and other pulmonary function and ABG variables (Table 2). In an attempt to evaluate the effect of severity of low vitamin D levels (Deficiency vs insufficiency) on clinical course of COPD patients, we found that vitamin D deficient patients develop frequent AECOPD (Mean ± SD: 3.58 ± 0.62) compared to vitamin D insufficient COPD patients (Mean ± SD: 2.40 ± 0.97) (F 5.700, 95% CI 1.64-0.72, *P* 0.020), otherwise there was no statistically significant difference between vitamin D deficient and vitamin D insufficiency COPD patients with regards to pulmonary function test and ABG components (Table 3).

DISCUSSION:

In this study, we found that low vitamin D level was prevalent and represent a health problem among Saudi COPD patients. The mean vitamin D level among all COPD patients was 14.51 ± 4.43 ng/mL with 85.7% of COPD patients were vitamin D deficient and 14.3% of them were vitamin D insufficient. We investigated the non-supplemented COPD patients (Not receiving vitamin D supplements for any cause prior to the time of blood sample withdrawal) and this procedure could explain the relatively highest proportion of cases with low vitamin D levels in our study. Regression analysis model showed that low vitamin D level was significantly associated with the mean number of acute exacerbation of COPD in last year in addition to the ABG components PH and PCO2 levels. Interestingly, we found that vitamin D deficient COPD patients develop frequent acute exacerbations compared to vitamin D insufficient COPD patients. In agreement with our results, it was reported that vitamin D insufficiency/deficiency have been found to be prevalent in patients with COPD [10] and low 25-hydroxyvitamin D levels were associated with a higher rate of asthma exacerbation.[11,15] On the other hand, data obtained from research on COPD patients or population based studies investigating the effect of low 25-hydroxyvitamin D levels on disease exacerbations are conflicting. Kunisaki and colleagues reported that in severe COPD patients 25-hydroxyvitamin D levels did not predict subsequent acute exacerbations,[12] while Lehouck et al. showed an evidence that vitamin D supplementation may reduce the incidence of COPD exacerbations in severely deficient patient.[16] Recently, it has been reported that genetic polymorphism in vitamin D receptor and vitamin D-binding-protein in conjunction with vitamin D deficiency potentiate the risk of developing tuberculosis.[17,18] Given the complex nature of COPD and the interplay of vitamin D in disease exacerbations it would be helpful to study the effect of genetic susceptibility in combination with low vitamin D status as potential risks of COPD exacerbation to delineate a possible mechanism. In this report, low vitamin D levels were significantly associated with ABG components PH and PCO_2, but there was no statistically significant relationship found between vitamin D levels and pulmonary functions. Similar findings were reported by Shaheen et al in 2011.[19] Nevertheless, Black and coworkers reported in a population based national survey a positive association between serum 25-hydroxyvitamin D and FEV_1 and FVC.[20] In conclusion, vitamin D deficiency was common among Saudi COPD patients and hypo-vitaminosis D was significantly associated with AECOPD. Further investigations are required to define the role of genetic susceptibility and base line vitamin D status

in the pathogenesis of COPD exacerbations.

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Table 1. Clinical characteristics, pulmonary function and arterial blood gas analysis of COPD Patients

	Vitamin D level (ng/mL)	
Demographic and clinical Characteristics	Mean ± SD	P value*
- Age (Years)	69.30 ± 10.12	0.279
- Sex (F/M), n. %	20/50, (28.6/71.4)	0.065
- BMI(Kg/ m2)	22.72 ± 3.66	
- Smoking (Smoker/Ex-smoker/non-smoker),n. (%)	24/30/16,(34.3/42.8/22.9)	0.327
- Comorbidities (Yes), n. (%)	44, (62.9%)	0.162
- Number of exacerbation in last year	3.41 ± 0.79	0.001
- Serum 25(OH)D (ng/mL)	14.51 ± 4.43	
- Vitamin D Insufficiency, n. (%)	10, (14.3)	
- Vitamin D deficiency, n. (%)	60, (85.7)	
Pulmonary function test		
- FEV1	56.57 ± 8.38	0.673
- FVC	73.74 ± 7.04	0.240
- FEV1/FVC	62.43 ± 4.53	0.792
- PEF	67.86 ± 5.54	0.397
- FEF 25	65.61 ± 4.69	0.066
- FEF 50	65.97 ± 4.53	0.094
- FEF 75	66.33 ± 4.50	0.089
Arterial blood gas analysis		
- PH	7.35 ± 0.03	0.001
- PO2	75.90 ± 5.19	0.778
- PCO2	68.41 ± 4.78	0.001
- HCO3	30.90 ± 5.22	0.459

All values are presented as mean ± SD unless otherwise stated; n, number; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; Vitamin D insufficiency defined as ≥ 20 ng/ml but < 30 ng/ml; Vitamin D deficiency defined as < 20 ng/ml. * P values derived from *t* test for continuous data or chi-square test for categorical data

Table 2. Pulmonary function, arterial blood gas components and number of acute exacerbation in relation to vitamin D level among COPD patients

	Vitamin D level (ng/mL)		
	R square	SE	P- value
Pulmonary function tests			
FEV1	0.003	8.43	0.673
FVC	0.020	7.02	0.240
FEV1/ FVC	0.001	4.56	0.792
PEF	0.004	4.56	0.397
FEF25	0.049	4.61	0.066
FEF50	0.027	4.47	0.094
FEF75	0.042	4.44	0.089
Arterial blood gas parameters			
PH	0.178	0.03	< 0.001
PO2	0.001	5.23	0.778
PCO2	0.186	4.34	< 0.001
HCO3	0.008	5.24	0.459
No. of acute exacerbation in last year	0.468	0.58	< 0.001

Table 3. Pulmonary function, arterial blood gas components and number of acute exacerbation associated with vitamin D deficient and insufficient COPD patients

	Vitamin-D deficiency	Vitamin-D insufficiency	F	95% CI	P value*
No. of exacerbation over 1 year	3.58 ± 0.62	2.40 ± 0.97	5.700	1.64-0.72	0.020
Pulmonary function test					
- FEV1	56.98±8.53	54.10±7.29	0.233	8.59-2.83	0.631
- FVC	73.85±7.13	73.10±6.82	0.010	5.58-4.08	0.919
- FEV1/FVC	62.30±4.50	63.20±4.87	0.084	2.20-4.01	0.773
- PEF	67.95±4.94	67.30±8.64	1.253	4.45-3.15	0.267
- FEF 25	66.07±4.95	62.90±4.31	1.573	6.29-0.04	0.214
- FEF 50	66.27±4.64	64.20±3.46	3.812	5.13-1.00	0.055
- FEF 75	66.68±4.56	64.20±3.46	2.069	5351-0.55	0.155
Arterial blood gas analysis					
- PH	7.34±0.03	7.37±0.03	0.001	0.00-0.04	0.982
- PO2	75.89±4.88	76.00±7.12	2.345	3.45-3.68	0.130
- PCO2	68.95±4.64	65.20±4.52	0.124	6.90-0.59	0.726
- HCO3	31.08±5.62	29.80±0.79	0.470	4.85-2.29	0.495

All values are presented as mean ± SD unless otherwise stated; Vitamin D insufficiency defined as ≥ 20 ng/ml but < 30 ng/ml; Vitamin D deficiency defined as < 20 ng/ml.