Original Article

The Association between Serum Vitamin D Deficiency and Chronic Obstructive Pulmonary Disease Exacerbation

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by irreversible airway obstruction and impaired pulmonary function. Acute exacerbation is responsible for the majority of COPD mortality and morbidity. This study aimed to evaluate the association between serum Vitamin D deficiency and COPD exacerbation. **Materials and Methods:** This cross-sectional study was conducted on 80 COPD patients who were hospitalized for severe acute exacerbation in Imam Reza Hospital, Mashhad, Iran, in 2016–2017. Subjects were excluded if they were taking corticosteroid, calcium, phosphorus, or Vitamin D supplements. Immunocompromised patients and cases with underlying cardiovascular, liver, or renal diseases, metabolic syndrome, cancers, electrolyte imbalance, and any diseases related to Vitamin D metabolism and absorption were also excluded. A blood sample of 3 ml was taken from each participant to measure 25-hydroxyvitamin D (25OHD) level, up to 24 h after hospitalization. The severity of the disease was assessed by forced expiratory volume in 1 s obtained from spirometry tests, and hypoxemia level using O_2 saturation. **Results:** The lower levels of mean serum 25OHD were significantly associated with the increased number of exacerbations ($P = 0.01$). Hypoxemia levels and the mean serum 25OHD level were found to have a significant association as well ($P = 0.01$). However, no significant relationship was observed between the mean serum 25OHD level and the duration of hospitalization ($P = 0.1$). **Conclusions:** Serum Vitamin D deficiency was associated with increased COPD exacerbation and poor clinical outcomes. Therefore, Vitamin D supplementation should be considered to reduce the risk of COPD exacerbation.

Keywords: Chronic obstructive pulmonary disease, exacerbation, hypoxemia, Vitamin D

Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of death throughout the world,[1] is a progressive disease of irreversible airway obstruction with an impaired respiratory function.[2,3] In 2017, about 545 million people were diagnosed with COPD and over 3.9 million deaths were confirmed worldwide.[1] It is also reported that COPD is more common in males than in females.[4,5] Increased incidence of COPD in the past decade suggests that the world may face COPD as a global economic, social, and health burden in future.[6] Acute exacerbation, which manifests with a change in the patients' condition and worsening of symptoms (cough, sputum production, dyspnea, and airflow limitation),[7,8] is responsible for the majority of COPD mortality and morbidity.[9,10] Associated medical expenses of COPD exacerbation, as well as the suffering experience that it brings to the patients, emphasize the need for more attention.[11,12] Viral and bacterial respiratory infections are the most important known cause among all,[11] which can be prevented with an optimized serum level of 25-hydroxyvitamin D (25OHD) in adults.[13,14] The role of 25OHD deficiency in increasing the exacerbation frequency and duration of hospitalization has been shown in the literature.[15,16]

25OHD is a fat-soluble steroid (cholecalciferol, D3, and ergosterol, D2) which plays an important role in bone mineralization and calcium homeostasis.[17,18] The optimal

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Access this article online

Quick Response Code:

Website: www.ijrc.in

DOI: 10.4103/ijrc.ijrc_157_21

How to cite this article: Ebrahimzadeh F, Bahrami M, Rezaeetalab F, Asl FT, Mirvahabi MS, Kafa Z, *et al*. The association between serum Vitamin D deficiency and chronic obstructive pulmonary disease exacerbation. Indian J Respir Care 2022;11:140-4.

Received: 10-12-2021 **Revised:** 12-02-2022
Accepted: 12-02-2022 **Published:** 08-04-2022

serum level of 25OHD is higher than 32 ng/mg (80 nmol/L).[19] Lower levels can be associated with the incidence of chronic diseases such as cancers, infections, autoimmune diseases, and chronic lung diseases like COPD.[17,18] Vitamin D supplementation, in patients with its deficiency, decreases the risk of COPD exacerbation[20] as 25OHD plays a protective role by increasing the antimicrobial peptide production and inhibition of pro-inflammatory cytokine production.[21]

As COPD exacerbation and 25OHD deficiency are both becoming considerable global problems[3,22] and due to the debatable findings of previous studies, the relationship between these medical conditions needs to be further investigated. Therefore, we aimed to evaluate the association of serum levels of 25-hydroxyvitamin D with acute exacerbation of COPD.

Materials and Methods

Study population

We conducted our research with a cross-sectional design on 80 COPD patients who were hospitalized for severe acute exacerbation in Imam Reza Hospital, Mashhad, Iran, in 2016–2017. The diagnosis of COPD exacerbation was established based on the criteria of the American Thoracic Society guideline, and patients were graded for the severity of exacerbation accordingly.[23] To ensure the validity of findings, we carefully excluded patients who were taking medicines that could have affected serum Vitamin D concentration (such as corticosteroid, calcium, phosphorus, or Vitamin D supplements) and avoided immunocompromised patients or cases with underlying cardiovascular, liver, or renal diseases, metabolic syndrome, cancers, electrolyte imbalance, and any diseases related to Vitamin D metabolism and absorption. Ethical considerations such as voluntary participation, documentation of written informed consent prior to study entrance, anonymity, confidentiality, and procedure's potential harm were taken into account during the conduction of the study. All procedures of the present study were reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences (registered number IR.MUMS.fm REC.1395.11) and were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Measurements

The demographic characteristics of patients including age, sex, body mass index (BMI), history of smoking, baking bread, and opium and hookah use were collected at reference using an author-made checklist. Clinical presentation, chief complaints, respiratory rate, heart rate, systemic blood pressure, and body temperature of all patients were also recorded. The severity of COPD was assessed by forced expiratory volume in 1 s obtained from spirometry tests, and hypoxemia level by O_2 saturation (O_2Sat). Acute exacerbation of COPD was defined as a sudden increase in dyspnea and exacerbation of cough and sputum disposal that leads to hospitalization and intensive unit care. Up to 24 h after hospitalization, patients were tested for serum Vitamin D concentration and blood potential of hydrogen (pH). A blood sample of 3 ml was taken from each participant to measure the serum concentration of 25OHD using ELIZA technique (kit manufactured by Padtan Gostar, Iran) and blood pH by venous blood gas (VBG) analysis. The patients were deemed fit to discharge after they had achieved a sufficient improvement in dyspnea and oxygen saturation status, had a clinically stable condition, and no longer needed continuous oxygen therapy.

Statistical analysis

Data analysis was performed by SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). Quantitative data were described using mean ± standard deviation (SD), and qualitative data using tables and charts. Frequency and percentage of demographic characteristics was calculated. To determine the normality of data distribution, the KolmogorovSmirnov test was performed, which resulted in normal data distribution. Consequently, independent *t*-test was used for comparison of the outcomes with gender and one-way analysis of variant for comparison of the outcomes with the rest of the parameters. Chi-squared or equivalent nonparametric tests were used if needed. $P < 0.05$ was considered statistically significant. Our sample size consisted of all patients who were hospitalized for COPD exacerbation at the time of the study and agreed to cooperate. Therefore, any potential selection bias was ruled out.

Results

After assessment for eligibility, 80 patients were enrolled in the study, of which 52 were males (65.0%). The mean age of the participants was 58.02 ± 9.86 years, and the study population was mostly comprised of subjects with 51–60 years of age (38.8%). Furthermore, the average BMI of the subjects was 23.88 ± 1.4 kg/m^2 for the entire population. All baseline characteristics of participants are summarized in Table 1. Among subjects, 42 had a history of smoking (including 39 men [92.9%]), 12 had a history of baking bread (including 2 men [16.7%]), and 35 had a history of opium and hookah use (including 19 men [54.3%]).

The mean serum level of 25OHD was found to have a significant association with the exacerbation frequency of COPD in patients. The serum 25OHD levels in patients with ≤2 acute exacerbations over the past year were lower than those who experienced <2 attacks during the same time period (17.15 ± 9.56 ng/mL vs. 34.82 ± 11.19 ng/mL; $P = 0.01$) [Figure 1]. Furthermore, a significant relationship between the mean serum level of 25OHD and hypoxemia level was observed. The mean ± SD serum level of 25OHD in patients with 60%–70%, 70%–80%, 80%–90%, and >90% of O_2Sat was reported 9.00 ± 6.35, 18.25 ± 12.32, 24.31 ± 10.76, and 23.38 ± 14.44 ng/mL, respectively. The patients with O_2 Sat of 60%–70% had the lowest serum level of 25OHD ($P = 0.01$) [Figure 2].

We also assessed the relationship between the mean serum level of 25OHD and the duration of patients' hospitalization

and found no statistical significance (P = 0.1). However, a considerable association was observed between the blood pH and the mean serum 25OHD level (P = 0.03). It was shown that patients with <7.25 blood pH had the lowest serum level of 25OHD (10.66 ± 7.50 ng/mL). We also evaluated the relationship between mean serum 25OHD level and demographic characteristics. Data analysis showed that the mean serum level of 25OHD was significantly higher in males compared to females (23.26 ± 12.34 ng/mL vs. 16.53 ± 10.96 ng/mL; P = 0.01). However, no significant association between the mean serum level of 25OHD and the age of patients was recorded (P = 0.3) [Table 2].

Table 1: Demographic and clinical characteristics of the study population

Variables	Frequency (n=80), n (%)	P*
Age (years)		
<40	1 (1.2)	NS
40–50	14 (17.5)	NS
51–60	31 (38.8)	NS
61–70	29 (36.3)	NS
>70	5 (6.2)	NS
Gender		
Male	52 (65.0)	NS
Female	28 (35.0)	NS
BMI (kg/m^2)		
<18.5 (underweight)	0	NS
18.5–24.99 (normal)	63 (78.7)	NS
25–29.99 (overweight)	17 (21.2)	NS
>30 (obese)	0	NS
Smoking history		
Male	39 (92.9)	NS
Female	3 (7.1)	NS
Total	42 (100.0)	NS
Baking bread history**		
Male	2 (16.7)	NS
Female	10 (83.3)	NS
Total	12 (100.0)	NS
Opium and hookah history		
Male	19 (54.3)	NS
Female	16 (45.7)	NS
Total	35 (100.0)	NS

*NS, **Two patients missed. NS: Not significant

Table 3 presents the common complaints of hospitalized patients including dyspnea (93.8%), cough (91.3%), sputum production (85.0%), fever (57.0%), hemoptysis (2.6%), consciousness disturbance (2.6%), and right-sided heart failure (39.7%). The duration of COPD in most cases (46.8%) was 6–10 years, and 14 subjects (17.5%) received continuous oxygen therapy at home. No COPD-attributable death occurred during the study.

Discussion

Acute exacerbation of COPD attributes to most of COPD morbidity and mortality.[9,10] Beside the economic expenses for the government, having to live with this unbearable condition adds up to the importance of implementation of evidence-based interventions to prevent or reduce the number of exacerbation attacks for the sufferer.[11,12] Investigations of thousands of COPD patients have shown that these cases have a lower level of Vitamin D profile.[15,24] These findings put forward the hypothesis of existence of a relationship between COPD exacerbation and lower levels of serum Vitamin D.[4] The proposed mechanism by which Vitamin D reduces the risk of COPD exacerbation is through exerting protective effects against the respiratory viral and bacterial infections that increase airway inflammation and trigger COPD exacerbation.[20] Accordingly, various researchers have pursued this issue and conducted studies to further investigate this relationship.[25,26] However, to this date, no consensus was made on this matter and it is not yet clear whether COPD exacerbation and Vitamin D deficiency are related.

With this in mind, we performed our study on severe cases of COPD exacerbation and made an effort to keep the confounders effects as minimized as possible. The results turned out to be promising. According to our findings, exacerbation frequency of COPD had a positive relationship with serum level of 25OHD. In other words, patients with lower levels of Vitamin D experienced more exacerbation attacks over the previous year. Furthermore, hypoxemia level significantly correlated with the

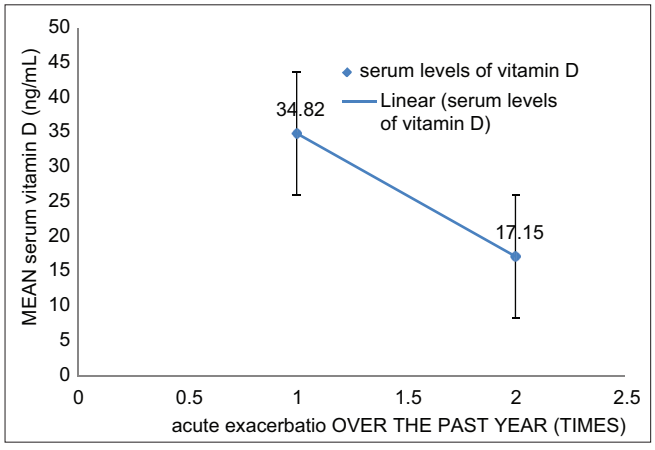

Figure 1: Serum level of Vitamin D according to exacerbation times

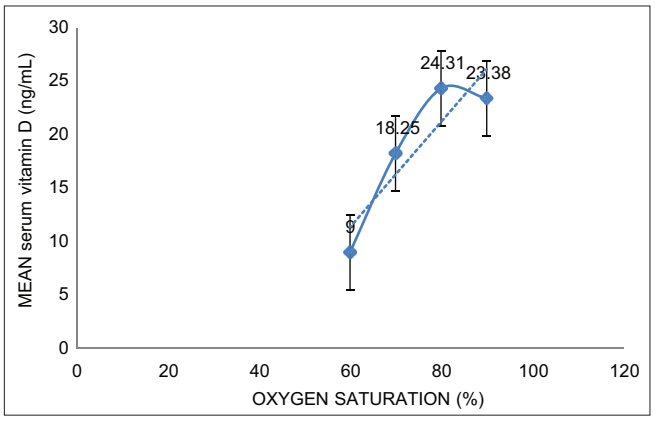

Figure 2: Serum level of Vitamin D according to hypoxemia level

Table 2: The association of participants' serum Vitamin D level with age, gender, blood pH, and duration of hospitalization

Variables	Frequency (*n*=80), *n* (%)	Vitamin D (ng/mL), mean ± SD	*P*
Age (years)			
<40	1 (1.2)	36.00±*	0.3
40–50	14 (17.5)	24.21 ± 12.16	
51–60	31 (38.8)	20.51 ± 13.18	
61–70	29 (36.3)	20.41 ± 11.92	
>70	5 (6.2)	14.00 ± 4.89	
Total	80 (100.0)	20.91 ± 12.24	
Gender			
Male	52 (65.0)	23.26 ± 12.34	0.01
Female	28 (35.0)	16.53 ± 10.96	
Blood pH			
>7.4	4 (5.0)	19.25 ± 10.21	0.03
7.35–7.40	24 (30.0)	9.75±*	
7.30–7.35	36 (45.0)	22.75 ± 13.41	
7.20–7.25	13 (16.2)	13.00 ± 10.98	
<7.25	3 (3.7)	10.66 ± 7.50	
Total	80 (100.0)	20.91 ± 12.24	
Duration of hospitalization (days)			
1–5	47 (58.7)	22.48 ± 12.14	0.1
6–10	23 (28.7)	20.00 ± 12.49	
11–15	7 (8.7)	13.71 ± 8.55	
16–20	2 (2.5)	10.50 ± 12.02	
>20	1 (1.2)	39.00±*	
Total	80 (100.0)	20.91 ± 12.24	

*Missed, Data are described as mean±SD for continuous data and frequency for categorical data, The number of cases is presented with percentages. SD: Standard deviation

Table 3: Patients' common complaints, duration of chronic obstructive pulmonary disease, and use of continuous O_2 therapy at home

Variables	Frequency (*n*=80), *n* (%)
Complaints	
Dyspnea	75 (93.8)
Cough	73 (91.3)
Sputum disposal	68 (85.0)
Fever	45 (57.0)
Hemoptysis	2 (2.6)
Disorientation	2 (2.6)
Right-sided heart failure*	31 (39.7)
Duration of COPD (years)**	
1–5	18 (22.8)
6–10	37 (46.8)
11–15	21 (26.6)
>15	3 (3.8)
Continuous O_2 therapy at home	14 (17.5)

*Two patients missed, **One patient missed, COPD: Chronic obstructive pulmonary disease

serum concentration of 25OHD. This could be interpreted that patients with lower level of serum 25OHD are more likely to be at increased risk for COPD exacerbation. These findings are in accordance with the findings of a study conducted by Burkes *et al.* who investigated 1609 patients with COPD exacerbation and identified 25OHD level as a helpful marker representing detrimental outcomes of COPD.[27] Several other studies also reported the same results.[4,20] On the contrary, in a study by Jung *et al.,* no significant relationship was found between 25OHD level and the frequency of exacerbations.[28] Mekov *et al*. stated the same findings as well.[29] These contradictory findings could have been caused by various factors. In both studies, patients were not screened for the use of Vitamin D supplements or any other medicine that can affect the serum Vitamin D levels.[28,29] Another reason could be the lower number of current smokers included in the Mekov E study in comparison to the nonsmokers and the ex-smokers (26.3%, 15.8%, and 57.9%, respectively). Smoking cessation could have prevented more COPD exacerbations.[30]

Duration of hospitalization and its relationship with the level of serum 25OHD was also assessed in our study. Previous studies have shown that 25OHD deficiency increases the need for longer hospitalizations.[16,31] However, we did not find any significant association. Further investigations are needed as the relationship is debatable. Our findings also demonstrated a significant association between Vitamin D deficiency and lower blood pH. The VBG analysis revealed that respiratory acidosis, the state of hypoventilation of lungs which leads to accumulation of carbon dioxide in blood, can be consequently related to Vitamin D deficiency. To the best of our knowledge, only a handful of studies have addressed the effect of Vitamin D deficiency on blood pH among COPD patients with acute exacerbation. Inconsistent with our findings, Gawron *et al*. reported no significant association between Vitamin D concentrations and blood pH according to the data obtained from 61 COPD patients with acute exacerbation.[32] More studies are needed to precisely assay this correlation.

We also found a significant relationship between the mean serum level of 25OHD and the gender of patients. A recent study showed a lower 25OHD level in females than males in patients with COPD[29] which was consistent with our study findings. However, in Baneen and Naseem study on COPD patients, it was shown that the serum level of 25OHD was independent of gender.[33] These different results might be due to the different associated factors such as geographical locations, types of clothing, skin colors, and diets.[34] Therefore, the lack of 25OHD in females of the present study might be related to less exposure to the sunlight, known as the main source of Vitamin D,[35] due to their types of clothing.

Although well designed, our study came across several limitations. First of all, some patients did not cooperate with examinations during the study; therefore, a part of their data was missed. Furthermore, since the investigations were carried out in a single health-care center, we had a relatively small sample size which limited the generalizability of the findings. Another limitation of our study was the use of pulse oximetry instead of arterial blood gas (ABG) analysis which is a more accurate technique. We also used VBG analysis to measure the patients' blood pH. Deteriorating condition of our patients and aggressive

nature of ABG was the major reason for the use of pulse oximetry and VBG which are less invasive measurement methods.

Conclusions

Vitamin D deficiency is a common finding in patients suffering from COPD exacerbations. Therefore, early detection of low levels of serum Vitamin D and supplementation can reduce adverse clinical outcomes efficiently. These findings are valuable in treatment procedures and future surveys. Well-established clinical trials with large sample size are suggested to further assay this issue.

Financial support and sponsorship

The study was funded by the Mashhad University of Medical Sciences (Grant No. 941215).

Conflicts of interest

There are no conflicts of interest.

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