A study to assess the relationship between vitamin D3 levels and the risk of acute exacerbation in patients with chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the top three causes of mortality worldwide. Vitamin D deficiency in COPD has been associated with poor lung function and decreased muscle power, which further increases the risk of exacerbations. The role of vitamin D in preventing acute exacerbations of COPD has conflicting results in the literature. Hence, we planned this study to assess the relationship between vitamin D3 levels and the risk of acute exacerbations among COPD patients in a tertiary care center in northern India. This was a prospective randomized controlled trial that was performed on 100 consecutive stable COPD patients attending the Department of Respiratory Medicine at Maharishi Markandeshwar Medical College and Hospital, Solan, India. The patients with subnormal vitamin D3 levels (*i.e.*, less than 30 ng/mL) were divided into the intervention and control groups. Baseline demographic profiles, lung function, COPD assessment test (CAT) score, modified Medical Research Council grade, and chest radiology were performed and repeated after 12 months in all these patients. All these parameters were recorded and compared with the baseline values obtained at the beginning of the study. Out of 100 subjects, 96 had vitamin D deficiency, of whom 48 were assigned to the intervention group and 48 to the control group. Among the 100 subjects, 74 (74%) were males and 26 (26%) were females, with a mean age of 66.9±9.4 years. The mean vitamin D level was 14.71±6.69 in these 96 patients. The vitamin D level improved after 3 months of supplementation to the mean level of 45.56±16.18 in the intervention group. Vitamin D supplementation was positively correlated with a decrease in the rate of acute exacerbations in the intervention group in terms of reduction in mean CAT score (4.17 in the intervention group and 1.43 in the non-interventional group, $p<0.001$), number of acute exacerbations (1.7 in the intervention group and -1.05 in the non-interventional group, $p<0.001$), and number of emergency visits ($p=0.0121$) during the 9-month period after attainment of a normal vitamin D level. Vitamin D supplementation plays a key role in COPD patients with D3 hypovitaminosis in decreasing COPD acute exacerbations, improving the CAT score, and reducing the number of emergency visits.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the top three causes of mortality worldwide [1]. More than 90% of these

deaths occur in low- and middle-income countries like India. The common respiratory symptoms of COPD include cough with or without sputum production and dyspnea. Exacerbations of these symptoms may be triggered by respiratory infections with bacteria and/or viruses, environmental pollutants, or other unknown factors, resulting in increased airway inflammation during such episodes. During exacerbations, there is an increase in gas trapping and hyperinflation, with decreased expiratory flow, leading to increased dyspnea. There may also be worsening of V/Q abnormalities resulting in hypoxia [2]. According to the World Health Organization report, nearly 65 million people are suffering from moderate to severe COPD globally, and nearly half a million people in India alone die due to COPD, which is four times the number of COPD deaths in the whole of Europe [3].

Osteoporosis is one of the important clinical manifestations among COPD patients, which adversely affects the quality of life. Many patients with COPD confine themselves at home, which is not only due to breathlessness or wheeze, but also due to severe bony pain, muscle wasting, and generalized weakness [4]. The skeletal manifestation occurs due to vitamin D deficiency following poor intake, limitation of physical activities, and prolonged use of corticosteroids. Many recent studies revealed that vitamin D plays a key role in various diseases like COPD, cancer, cardiovascular disease, autoimmune disease, systemic hypertension, diabetes mellitus *etc*. [5,6]. Many studies revealed that vitamin D deficiency is common in patients with COPD, and its prevalence among COPD varies from 31-77% [5,6]. The association of hypovitaminosis D with the prevalence, severity of COPD, and its exacerbations has been highlighted by a number of studies, but with inconclusive variable results. A previous randomized controlled trial (RCT) tried to study the role of vitamin D supplementation for the prevention of COPD exacerbation found the protective role of vitamin D3 supplementation in COPD patients with vitamin D3 levels less than 50 nmol/L in moderate or severe exacerbation, but not for upper respiratory infection [7]. However, another RCT conducted in 63 patients with COPD reported a significant role of vitamin D3 supplementation in terms of an increase in quality of life in patients with COPD, but there was no significant improvement in lung function and number of exacerbations in patients with COPD ($p>0.05$) [8]. There is a lack of consistent data regarding the role of vitamin D3 in COPD the previous studies, and there are only a few studies from our geographical area. Hence, we planned this RCT to assess the relationship between vitamin D3 levels and the risk of acute exacerbations among the COPD patients in a tertiary care center of northern India.

Materials and Methods

The present study was conducted in the Department of Respiratory Medicine in collaboration with the Department of Biochemistry at M.M. Medical College and Hospital (MMM C&H), Kumarhatti, Solan, Himachal Pradesh, a tertiary care center of northern India. This study was approved by the Institutional Ethical Committee (MMMCH/IEC/21/433).

This was a prospective randomized controlled (1:1) trial conducted among the stable COPD patients who came to the Respiratory Medicine Outpatient Department of MMM C&H, Solan. The total duration of the study was 18 months from April 2021 to October 2022. The sample size for the study was calculated to be 100 (50 cases and 50 controls).

Inclusion criteria: patients meeting the "Global Initiative for Chronic Obstructive Lung Disease COPD guideline-2020" criteria for the diagnosis of COPD [9]. Participants willing to participate and having given written consent were included in the study.

Exclusion criteria: patients having association of any other lung disease, obstructive sleep apnea, ischaemic heart disease, pregnancy, hemodynamically unstable and having any other severe organ dysfunction were excluded from the study.

COPD is defined as a patient having symptoms of chronic cough, shortness of breath, and post post-bronchodilator forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) ratio <0.70 on spirometry test. Acute exacerbation of COPD is defined as a patient presenting with acute worsening of respiratory symptoms *viz*. increased dyspnea, sputum purulence and volume, together with increased cough and wheeze that results in the need for additional therapy.

Statistical analysis

Data obtained was entered into Microsoft Excel (Redmond, WA, USA), and data were analyzed by software (SPSS 25, IBM, Armonk, New York). Descriptive analysis was performed on the data. Quantitative data was expressed using measures of central tendency and variance. Qualitative data was expressed in counts and percentages. Statistical significance of the association between different parameters was analyzed by employing tests of significance such as the *t*-test and analysis of variance (ANOVA). A p-value of less than 0.05 was considered significant for disproving the null hypothesis.

Data collection and processing

After taking written informed consent from all the patients, baseline demographics, including detailed history, and clinical profile, were recorded. Patients were divided into the following groups: interventional case group, control group, and group of patients having normal vitamin D levels. Randomization was done based on odd and even numbers as decided by their number of sequential enrolments in the study. Patients whose enrolment number was odd were assigned to the intervention case group, while even number enrolment cases were assigned to the control group. Blood samples were taken from each participant to measure the levels of 25-hydroxyvitamin D (vitamin D) at the time of induction and after 3 months. One year of follow-up was done for each patient. The severity of the disease was assessed by spirometry parameters *viz*. FEV_1, FVC, ratio of FEV_1/FVC, COPD Assessment Test (CAT) Score, Modified Medical Research Council (mMRC) dyspnea grade, peripheral arterial blood oxygen saturation (Spo2), chest X-rays, routine blood investigations, number of acute exacerbations and intensive care unit (ICU) visits at 0 month and 12th month. In the intervention group, vitamin D supplementation was given to each patient with weekly oral doses of 60,000 IU of vitamin D3 for 8 weeks and a maintenance dose of 1500-2000 IU daily for 1 year. All patients were advised (or called telephonically) for visit to the hospital at the end of the 1-year period from the date of enrolment, thereupon a thorough history and clinical examination was done along with repeat spirometry, SpO2 level, mMRC grading, CAT score, chest X-rays, number of emergency and ICU visits in the 1-year period. All these parameters were recorded and compared with the baseline values obtained at the beginning of the study.

Results

A total of 100 stable COPD patients were enrolled in this study. Out of which 96 (96%) patients were having vitamin D deficiency

with a mean ± standard deviation (SD) of 14.71±6.69, which improved after 3 months of supplementation with a mean±SD of 45.56±16.18, and 4 patients were having normal vitamin D3 levels. The mean age of study participants was 66.9±9.4 years, with males being the majority [74 (74%)]. Baseline demographic profiles of participants are depicted in Table 1. The most common (49%) presenting complaint of the subjects was a wet cough. A total of 96 patients having vitamin D3 deficiency were randomized (1:1 ratio) to case (48) and control (48). Distribution of study variables among interventional and control groups is shown in Table 2, while the association of various variables at 0 and 12 months is shown in Table 3.

Supplementation with vitamin D in patients having vitamin D deficiency (interventional group) has a statistically significant positive impact on COPD patients in the form of improvement of the CAT score ($p<0.001$). The CAT score calculated in the present study at 0 and 12 months was analyzed using paired t-tests for the patients receiving vitamin D supplementation. The relationship between vitamin D supplementation and the number of exacerbations of COPD in 1 year was compared using ANOVA. Vitamin D supplementation in patients having vitamin D deficiency (interventional group) has a statistically significant positive impact on COPD patients in the form of a reduction in the number of acute exacerbations in 1 year ($p<0.001$). The comparison of the number of acute exacerbations

Table 1. Baseline demographic profiles of participants.

Variables		n=100, n (%)
Age (years)	(Mean±SD)	66.9±9.4
Gender	Male	74 (74)
	Female	26 (26)
BMI (kg/m^2)	(Mean±SD)	24.12±4.19
Smoking status	Yes	85 (85)
	No	15 (15)
Biomass fuel exposure	Yes	55 (55)
	No	45 (45)
Alcohol intake	Yes	15 (15)
	No	85 (85)
Symptoms	Dry cough	19 (19)
	Wet cough	49 (49)
	Fever	19 (19)
	Diabetes mellitus	11 (11)
	Hypertension	9 (9)
	Cor-pulmonale	4 (4)
	Hypoalbuminemia	4 (4)
	PAH	1 (1)
	Secondary polycythemia	10 (10)

SD, standard deviation; BMI, body mass index; PAH, pulmonary arterial hypertension.

Table 2. Distribution of variables among interventional and control groups.

Variables		Interventional group n=48, n (%)		Control group n=48, n (%)	
		At 0 month	At 12 month	At 0 month	At 12 month
mMRC dyspnea grade	Grade 1	0 (0)	6 (12.5)	1 (2.1)	1 (2.1)
	Grade 2	22 (45.8)	19 (39.5)	23 (47.9)	25 (52.1)
	Grade 3	13 (27.1)	12 (25)	11 (22.9)	9 (18.7)
	Grade 4	13 (27.1)	11 (22.9)	13 (27)	13 (27)
Spirometry	FEV_1 (% predicted) (mean±SD)	53.54±13.75	57.29±14.50	51.91±13.75	50.33±14.50
	FEV_1/FVC (%) (mean±SD)	60.75±13.75	59.54±14.50	63.02±13.75	60.61±14.50
CAT score	(Mean±SD)	16.06±5.8	11.89±5.15	19.51±6.21	20.94±6.51
Spo2 (%)	(Mean±SD)	90.45±6.21)	91.89±6.51	94.45±6.21	92.81±6.51
No of acute exacerbations in 1 year	(Mean±SD)	2.98±0.92	1.28±0.74	2.24±1.2	3.29±1.7
No of emergency visits in 1 year	(Mean±SD)	2.04±1.14	1.69±1.02	1.98±2.31	1.69±2.13
No of ICU admissions in 1 year	(Mean±SD)	1.85±0.97	1.08±1.24	1.97±1.69	1.87±1.08

SD, standard deviation; CAT, COPD assessment test; Spo2, peripheral arterial blood oxygen saturation; ICU, intensive care unit; mMRC, modified Medical Research Council; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity.

Table 3. Association of various variables at 0 and 12 months among interventional and control groups.

Variables	Association of various variables at 0 and 12 months among interventional group p	Association of various variables at 0 and 12 months among control group p
Dyspnea grade (mMRC)	0.0644	0.1041
FEV_1 (% Predicted)	0.0847	0.0984
FEV_1/FVC (%)	0.0742	0.0985
CAT score	<0.001*	0.1821
Spo2 (%)	0.0647	0.1054
No of acute exacerbations in 1 year	<0.001*	0.851
No of emergency visits in 1 year	0.0121*	0.0654
No of ICU admissions in 1 year	0.0612	0.1847

*p<0.05; mMRC, modified Medical Research Council; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_1/FVC, the forced expiratory volume in the first second divided by the forced vital capacity; CAT, chronic obstructive pulmonary disease assessment test; Spo2, peripheral arterial blood oxygen saturation; ICU, intensive care unit.

among the interventional group, control group, and patients having normal Vitamin D levels is shown in Figure 1. Pearson's correlation test was done to find the significance of the association of vitamin D serum levels with the number of emergency and ICU visits in the 1 year. Vitamin D supplementation in patients having vitamin D deficiency (interventional group) had a positive impact on COPD patients in the form of a reduction in the number of emergency visits in 1 year (p=0.0121). We found that vitamin D supplementation caused an improvement in exacerbations in the intervention group of patients in terms of reduction in CAT score, number of acute exacerbations, and number of emergency visits during the 1-year study period. However, we did not find any statistically significant correlation between vitamin D3 supplementation and age, gender, body mass index (BMI), smoking history, comorbidities, SpO2, FEV_1, FEV_1/FVC, mMRC grade, number of ICU visits, and radiology findings.

Discussion

The present study was undertaken in the Department of Respiratory Medicine in collaboration with the Department of Biochemistry at MMM C&H, Solan, to study the relationship between vitamin D3 levels and the risk of acute exacerbations in COPD patients.

COPD is characterized by progressive, not fully reversible airway obstruction and lung parenchymal damage. There is multisystem involvement in COPD patients, including skeletal muscle impairment, systemic inflammation, and an increased prevalence of osteoporosis, cardiovascular disease, and lung cancer. Patients with COPD have reduced vitamin D as they spend less time doing outdoor activities, leading to reduced sun exposure and lower levels of vitamin D than subjects without COPD. The pathological mechanisms implicated in COPD are complex, including evidence for alteration of the protease/antiprotease balance mediated by an increase in neutrophils and macrophages, autoimmune dysfunction, increased oxidative stress, and dysregulation of pathways of lung development [10].

In the present study, a total of 96 patients were randomized in 1:1 ratio to 48 cases and 48 control patients. A total of 48 subjects in the intervention group were given 60,000 IU vitamin D3 supplementation weekly for 8 weeks, followed by a maintenance dose of 1500-2000 IU daily for 1 year. In our study, the mean age of the patients was 66.9±9.4 years, with a majority of patients in the age group of 60-70 years. A similar observation was reported in the study by Persson *et al.*, where the mean age of COPD patients was 63.5±6.9 years [11]. The male-to-female ratio in our study was 2.84:1, with 74% male and 26% female, respectively, suggesting that COPD is more common in males. This may be due to the higher rate of smoking in the male population as compared to females. This result is similar to the study done by Janssens *et al.*, which found that 82.06% of COPD cases were males and 17.94% were females. In the present study, a deficiency of serum vitamin D level is observed in 96% of patients with a mean value of 14.71±6.69 ng/mL [8]. The latter normalized to the mean value 45.56±16.18 ng/mL after 3 months of weekly supplementation of vitamin D3 and subsequent daily maintenance dosage in the intervention group. These results were comparable to those obtained in studies done by Janssens *et al*., Persson *et al*., and Monadi *et al.* [6,11,12].

Supplementation with vitamin D in COPD patients having vitamin D deficiency (interventional group) has a statistically significant positive impact in the form of improvement of the CAT score (4.17 in the intervention group and 1.43 in the non-interventional group, p<0.001) in our study. This finding was similar to that observed in a previous study conducted by Xiaoyan *et al*., in the department of respiratory and critical care medicine at the First Affiliated Hospital of Chengdu Medical College, Chengdu, China [13].

We compared the relationship between vitamin D supplementation and the number of exacerbations of COPD during a 12-month period using ANOVA. Vitamin D supplementation in COPD patients having vitamin D deficiency showed a statistically significant positive impact in the form of s reduction in the number of acute exacerbations during a 12-month period (1.7 in the intervention and -1.05 in the non-interventional group, p<0.001). In contrast to our study, a randomized, double-blinded clinical trial conducted in 63 patients with COPD reported no significant difference among FEV_1,

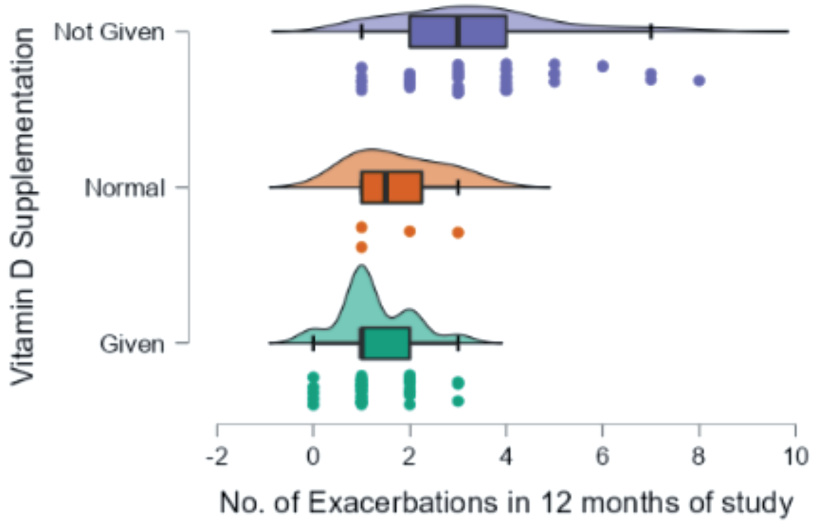

Figure 1. Comparison of the number of acute exacerbations among the interventional group, the control group, and patients having normal vitamin D levels.

FEV_1/FVC, and number of exacerbations in patients with COPD ($p>0.05$) but, a significant difference was observed in quality of life at 2 months ($p<0.001$) and 6 months ($p<0.001$) in the intervention group [10]. Our findings were comparable to the meta-analysis done by Xaoyan *et al*., [13]. Another study conducted in Mysuru, India, reported a three times higher risk of COPD exacerbations among patients with vitamin D deficiency as compared to COPD subjects without vitamin D deficiency [14]. Also, we found that vitamin D supplementation in patients having vitamin D deficiency had a positive impact in the form of a reduction in the number of emergency visits during 12 12-month period ($p=0.0121$). A systematic review and meta-analysis of four RCTs, including 560 concluded that vitamin D3 supplementation can be safely given to reduce the rate of moderate/severe COPD exacerbations in vitamin D3-deficient (<25 nmol/L) COPD patients [15].

Findings from the 3rd National Health and Nutrition Survey, which was a large US population-based study involving over 14,000 people, demonstrated that vitamin D supplementation improves the FEV_1 and FVC independently [16]. However, we did not find any statistically significant correlation between vitamin D supplementation and FEV_1, FEV_1/FVC, and improvement in mMRC grade of breathlessness. Other studies had demonstrated a precise relationship between vitamin D levels and lung function in normal subjects; however, the evidence in COPD patients is less studied so far [16,17]. The study by Janssens *et al.* observed a positive correlation between serum vitamin D supplementation and FEV_1 in COPD patients and concluded that vitamin D improves the FEV_1 after intervention; however, the same was not observed in their control subjects [6].

In another study conducted on 97 COPD patients to assess the relationship of serum vitamin D levels with COPD severity and acute exacerbations of COPD revealed that vitamin D deficiency was independently associated with exacerbations and hospitalization. No difference between patients with and without severe vitamin D deficiency was found in age, gender, BMI, smoking history, lung function, comorbidities, and FEV_1 [18]. There are multiple postulated mechanisms by which vitamin D3 may reduce the number of acute exacerbations and CAT score in COPD patients, including decreasing the oxidative stress, particulate matter-induced interleukin-6 response, airway and/or systemic inflammation [19,20]. The study demonstrated the role of smoking-induced vitamin D signaling, which causes deficiency in controlling pro-inflammatory processes in the airways of COPD patients [19, 20]. Similar to our study, the association of various antioxidants (zinc, vitamins A and D) with COPD patients is also present in the literature.

Strengths of our study includes randomization of participants, longer follow-up duration of both the study groups for 1 year and head-to-head comparisons of both the groups in terms of multiple parameters (CAT score, lung function, number of acute exacerbations and emergency/ICU admission) to demonstrates the role of vitamin D supplementation in COPD patients with hypovitaminosis D.

The major limitation of our study was the small sample size of 100 patients against the initially calculated sample size of a minimum of 150 patients, which happened due to the COVID-19 pandemic during the study period. Further, it was a single-center study.

Conclusions

Our study demonstrates that vitamin D supplementation plays a key role in COPD patients with hypovitaminosis D in reducing the frequency of acute exacerbations in terms of reduction in CAT score, rate of acute exacerbations, and number of emergency visits during 9 months after normalization of vitamin D level. Hence, it is suggested that COPD patients be investigated for vitamin D deficiency, and if found, may be treated with vitamin D supplementation. However, further multicentric studies with larger sample sizes and longer follow-up duration are required to establish the effect of vitamin D supplementation in the prevention of acute exacerbation of COPD.

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