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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 north India. This was a prospective randomized control 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 which 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 intervention and 1.43 in non-interventional group, $p<0.001$), number of acute exacerbations (1.7 in intervention and -1.05 in 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.

Key words: COPD, CAT, vitamin D, mMRC grade, acute exacerbations, AE-COPD.

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 dyspnoea. Exacerbations of these symptoms may be triggered by respiratory infections with bacteria and/or viruses, environmental pollutants, or other unknown factors resulting in an increased airways inflammation during such episodes. During exacerbations there is increase in gas trapping and hyperinflation, with decreased expiratory flow, leading to increased dyspnoea. 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 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 whole of the Europe [3].

Osteoporosis is one of the important clinical manifestations among the 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 researches but with inconclusive variable results. Previous randomized control trial (RCT) tried to study the role of vitamin D supplementation for prevention of COPD exacerbation found 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 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 lack of consistent data regarding the role of vitamin D3 in COPD the previous studies and there are only few study from our geographical area. Hence we planned a RCT to assess the relationship between Vitamin D3 levels and the risk of acute exacerbations among the COPD patients in a tertiary care centre of north 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 centre of north India. This study was approved by the Institutional Ethical Committee (MMMCH/IEC/21/433).

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

Inclusion criteria: Patients meeting the "GOLD COPD guideline-2020" criteria for the diagnosis of COPD [9]. Participants willing for participation having given written consent were included in the study.

Exclusion criteria: Patients having association of any other lung disease, Obstructive Sleep Apnoea (OSA), Ischaemic Heart Disease (IHD), Pregnancy, Hemodynamically unstable and having any other severe organ dysfunction were excluded from the study.

COPD defined as patient having symptoms of chronic cough, shortness of breath and post bronchodilator FEV1/FVC ratio < 0.70 on spirometry test. Acute exacerbation COPD defined as patient presenting with acute worsening of respiratory symptoms viz. increased dyspnoea, sputum purulence and volume together with increased cough and wheeze that results in need of additional therapy.

Statistical analysis

Data obtained was entered into Microsoft Excel 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 association between different parameters was analysed by employing tests of significance such as t test and ANOVA. 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 was recorded. Patients were divided into following groups: Interventional case group, Control group and Group of patients having normal Vitamin D levels. Randomization was done on the basis of 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. Forced Expiratory Volume in first-second (FEV1), Forced Vital Capacity (FVC), ratio of FEV1/FVC, COPD Assessment Test (CAT) Score, Modified Medical Research Council (mMRC) dyspnoea grade, peripheral arterial blood oxygen saturation (Spo2), chest x-ray, routine blood investigations, number of acute exacerbations and Intensive Care Unit (ICU) visits at 0 month and 12^{th} month. In the intervention group, vitamin D supplementation was given to each patient with weekly oral doses of 60000 IU of Vitamin D3 for 8 weeks and a maintenance dose of 1500-2000 IU daily for a period of 1 year. All patients were advised (or called telephonically) for visit to the hospital at the end of one 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-ray, number of emergency and ICU visits in 1 year period. All these parameters were recorded and compared with the baseline values obtained at the beginning of the study.

Results

Total 100 stable COPD patients were enrolled in this study. Out of which 96 (96%) patients were having Vitamin D deficiency with a mean±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 the male majority 74 (74%). Baseline demographic profiles of participants are depicted in Table 1. Most common (49%) presenting complaint of the subjects was wet cough. Total 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 are shown in Table 2 while Association of various variables at 0 and 12 months are 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 CAT Score (P value<0.001). The CAT score calculated in the present study at 0 and 12 months was analysed using paired t tests for the patients receiving Vitamin D supplementation. Relationship between Vitamin D supplementation and 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 reduction in the number of acute exacerbations in 1 year (P value<0.001). Comparison of number of acute exacerbations among Interventional group, Control group and patients having normal Vitamin D level is shown in

Figure 1. Pearson's Correlation test was done to find the significance of association of Vitamin D serum levels with 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 reduction in the number of emergency visits in 1 year (P value=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 one year of study period. However, we did not find any statistically significant correlation between Vitamin D3 supplementation and in age, gender, BMI, smoking history, comorbidities, SpO2, FEV1, FEV1/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 characterised 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 lesser outdoor activity with reduced sun exposure leading on to 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 on 1:1 ratio to 48 cases and 48 control patients. Total 48 subjects in Intervention group were given 60000 IU Vitamin D 3 supplementation weekly for 8 weeks, followed by maintenance dose of 1500-2000 IU daily for a period of 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. Similar observation was observed in study by Persson LJP et al where mean age of COPD patients was 63.5±6.9 years [11]. 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 male population as compared to females. This result is similar to the study done by Janssens W et al which found that 82.06% of COPD cases were males and 17.94% were females. In the present study, deficiency of serum Vitamin D level is observed in 96% patients with a mean value of 14.71±6.69 ng/ml [8]. The later normalised to mean value 45.56±16.18 ng/ml after 3 months

of weekly supplementation of vitamin D3 and subsequent daily maintenance dosage in intervention group. These results were comparable to those obtained in studies done by Janssens W et al , Persson LJ 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 CAT Score (4.17 in Intervention and 1.43 in non-interventional group, p value<0.001) in our study. This finding was similar to that observed in a previous study conducted by Xiaoyan Li 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 number of exacerbations of COPD during 12 months period using ANOVA. Vitamin D supplementation in COPD patients having Vitamin D deficiency had shown a statistically significant positive impact in the form of reduction in the number of acute exacerbations during 12 months period (1.7 in Intervention and -1.05 in non-interventional group, p value<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, 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 intervention group [10]. Our findings were comparable to meta-analysis done by Xaoyan Li et al [13]. Another study conducted in Mysuru, India reported three times higher risk of COPD exacerbations among the 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 reduction in the number of emergency visits during 12 months period (P value=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 (NHANES), which was a large US population-based study involving over 14,000 people, demonstrated that Vitamin D supplementation improves the FEV1 and FVC independently [16]. However we did not find any statistically significant correlation between Vitamin D supplementation and FEV1, FEV1/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 FEV1 in COPD patients and concluded that Vitamin D improves the FEV1 after intervention however the same was not observed in their control subjects [6].

In an another study conducted on ninety seven COPD patients with the aim to assess the relationship of serum vitamin D levels with COPD severity and acute exacerbations of COPD (AECOPD) revealed that Vitamin D deficiency was independently associated with exacerbations and hospitalisation. No difference between patients with and without severe vitamin D deficiency was found in age, gender, BMI, smoking history, lung function, and comorbidities and FEV1 [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 IL-6 response, airway and/or systemic inflammation [19,20]. The study demonstrated the relationship between smoking induced vitamin D signalling, 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) in with COPD patients are also present in the literature.

Strengths of our study includes randomization of participants, longer follow-up duration of both the study groups for one 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 minimum 150 patients, which happen due to COVID-19 pandemic during the study period. Further it was a single centre study.

Conclusions

Our study demonstrates that Vitamin D supplementation plays a key role in COPD patients with hypovitaminosis D in reducing frequency of acute exacerbation in terms of reduction in CAT score, rate of acute exacerbations and number of emergency visits during 9 months after normalisation 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 size and longer follow up duration are required to establish the effect of Vitamin D supplementation in prevention of acute exacerbation of COPD.

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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 Polycythaemia	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	FEV1 (% Predicted) (Mean±SD)	53.54±13.75	57.29±14.50	51.91±13.75	50.33±14.50
	FEV1/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.

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	Association of various variables at 0 and 12 months among Control group
	p value	p value
Dyspnea grade (mMRC)	0.0644	0.1041
FEV1 (% Predicted)	0.0847	0.0984
FEV1/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; FEV1, forced expiratory volume in the first second; FEV1/FVC, the forced expiratory volume in 1 second divided by the forced vital capacity; CAT, COPD assessment test; Spo2, peripheral arterial blood oxygen saturation; ICU, intensive care unit.

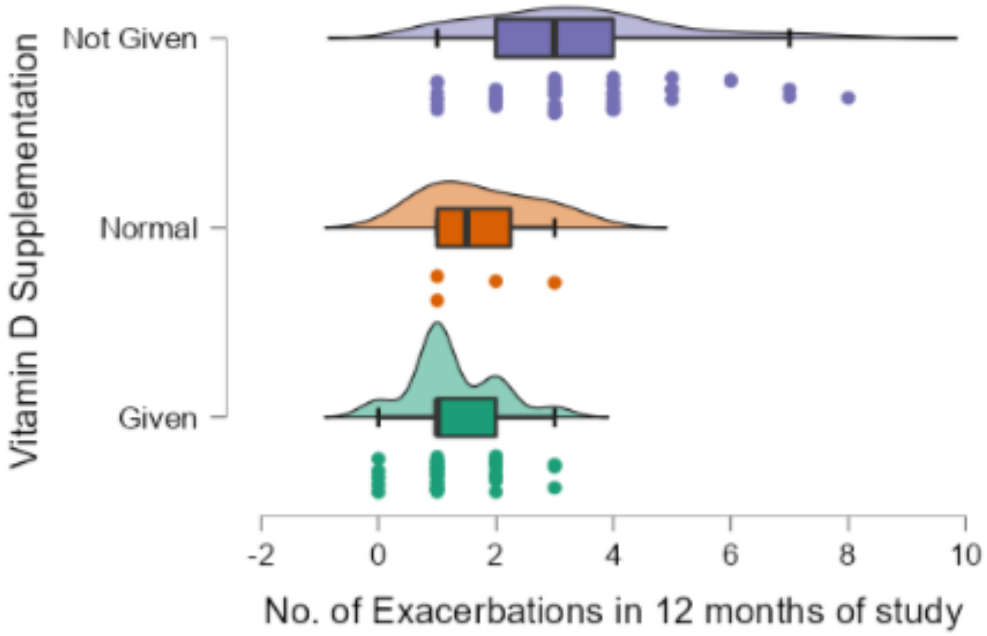

Figure 1. Comparison of number of acute exacerbations among Interventional group, Control group and patients having normal Vitamin D level.