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Effects of Vitamin D3 as Adjunct Therapy in Chronic Obstructive Pulmonary Disease: A Comparative Cross-Sectional Study

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ABSTRACT

Objective: To evaluate the effects of vitamin D3 supplementation on exacerbation rates, lung function, inflammation, and quality of life in COPD patients.

Methodology: A comparative cross-sectional was carried out at the Department of Pulmonology, Mayo Hospital, Lahore over a six-month duration. 92 diagnosed cases of COPD were randomly distributed into two groups. One group received monthly oral Vitamin D (cholecalciferol, 200,000 IU) with standard COPD management, while the other group received a placebo. Follow-up assessments were carried out at baseline, three months, and six months to measure the incidence of exacerbations, COPD Assessment Test (CAT) scores, levels of C-reactive protein (CRP), and pulmonary function (FEV1/FVC).

Results: The vitamin D-receiving group had experienced a significant reduction in exacerbation rates from 73.9% in the one month to 23.9% by the sixth month. Furthermore, the Vitamin D group showed a marked decrease in CRP levels (from 7.85 ± 5.44 to 4.04 ± 3.05), substantial improvements in CAT scores (from 27.52 ± 3.53 to 11.24 ± 3.45), and with rise in FEV1/FVC rising from 48.26 ± 3.85 to 63.69 ± 9.72. The placebo group experienced worsening inflammation and only minimal gains in scoring of CAT score and functioning of the lungs.

Conclusion: Vitamin D supplementation in COPD patients has been shown to markedly decrease exacerbations, and improve lung function tests highlighting the possible utility of Vitamin D in addition to the regular treatment of COPD.

Keywords: Chronic obstructive pulmonary disease (COPD), Lung Function Testing, Forced Vital Capacity (FVC), Vitamin D, Forced Expiratory Volume (FEV-1), COPD Assessment Test (CAT) Score

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth major cause of mortality and morbidity globally. In Pakistan, the estimated prevalence rate of COPD is as high as 2.1% in ages 40 years and above.[1] COPD is both a preventable and treatable condition and is defined by the obstruction in respiratory airflow. It progressively worsens over time and is linked to a chronic inflammatory response within the airways. COPD patients suffer from frequent exacerbations, reduced lung functions, reduced exercise capacity, and development of extra-pulmonary diseases leading to a rise in the disease morbidity.[2]

Patients suffering from COPD also have decreased serum cholecalciferol (D3) levels associated with higher susceptibility to exacerbation, poor lung functions, and

poor quality of life of patients. Hospitalization is often required during exacerbations and is a major contributor to mortality and morbidity rates. The treatment approach for exacerbations focuses on mitigating their detrimental effects and preventing subsequent incidents. Therefore, vitamin D3 supplementation might have a beneficial role when used with conventional COPD treatment. [3-5]

Vitamin D, a fat-soluble vitamin, plays a crucial role in supporting the health of bones and maintaining the levels of calcium and phosphorus. The genomic effects of vitamin D are through its interaction with the nuclear vitamin D receptor (VDR), which regulates gene transcription and impacts around 3% of the human genome. The regulation of genes involved in numerous biological processes, such as cell growth, differentiation, control, regulated cell death, and new blood vessel formation, is significantly influenced by vitamin D. Consequently, it is recognized as a pleiotropic prohormone, with its receptor found extensively across different tissues. [6] VDR is connected to the expression of the enzyme CYP27B1 in numerous immune cells, such as macrophages, neutrophils, T cells, B cells, and airway epithelial cells, in addition to immune cells found within the lungs. Vitamin D and VDR are considered to be vital in protecting against respiratory infections.[7, 8] Vitamin D exhibits immunomodulatory effects that can strengthen innate immune responses in the face of infection and also influence adaptive immune responses. There is an expectation that administering vitamin D could lower the frequency of exacerbations in individuals suffering from COPD. (9). Furthermore, vitamin D also improves COPD assessment test(CAT) scores in COPD patients. [10]

Pourrashid et.al found that raising the levels of vitamin D from 10.59 ± 3.39 ng/ml to 36.85 ± 11.80 ng/ml demonstrated a statistically significant improvement in health-related quality of life (HRQOL) for a time duration of 120 days, in contrast to the placebo group ($p = 0.001$). Moreover, there were no statistically significant differences identified in terms of length of stay (LOS), rehospitalization, or mortality rates.[11] Sami et.al reported in Khyber Pakhtunkhwa, Pakistan, a statistically significant correlation was observed between reduced levels of vitamin D and advance level of COPD. The average serum concentration of vitamin D in COPD patients was recorded at 16.01 ng/ml, whereas healthy controls exhibited a mean concentration of 35.98 ng/ml ($p<0.0001$). It is suggested that severity of COPD has inverse association with serum levels of vitamin D.[12]

The literature about the impact of level of vitamin D on the improvement of COPD regarding the events of exacerbations of the disease, pulmonary function tests as FEV1, assessment of COPD severity through the CAT score, and evaluation of the inflammation in the body as through the C-reactive protein is lacking for the population of Lahore, Pakistan. A thorough investigation is crucial to determine the impact of vitamin D on patients suffering from COPD. This study aims to assess the effects of vitamin D supplementation on the frequency of acute COPD exacerbations, CAT scores, pulmonary function test outcomes (FEV1), and levels of inflammatory biomarkers.

Methodology

A comparative cross-sectional study was conducted at the Department of Pulmonology, Mayo Hospital, Lahore from (01-03-2024) to (02-09-2024). The patients of both genders aged between 40-70 years with a history of exacerbations of COPD in the previous 2 years with FEV1 <80% predicted and FEV1/FVC <0.70 (Post bronchodilator value) were included. Pregnant or breast-feeding females, pulmonary diseases other than COPD as pulmonary fibrosis, lung cancer, active tuberculosis, hypercalcemia>10mg/dl or hypervitaminosis D >100 ng/ml were excluded.

The estimated sample size was 92, divided equally into two groups of 46 participants each. This estimation was based on a significance level of 5% and a power of 90%. The expected mean for the placebo group was 0.35 ± 1.02, and for the Vitamin D group, it is -1.25 ± 1.63. [11]

Informed consent was acquired from all the participants before inclusion in the study after a detailed explanation of the purpose of the study along with the benefits and side effects of vitamin D supplementation. The participants could withdraw at any moment before the completion of the study and no personal information was recorded to keep the data anonymous. The Institutional Review Board of King Edward Medical University, Lahore approved the study with IRB no. 159/RC/KEMU Dated 08-06-2023

A predesigned proforma was used for the collection of the data. The demographic information of the participants as age and gender was recorded. The patients were randomized via the lottery method into two groups i.e. Group A and Group B. The participants in group A were given monthly oral Vitamin D injection vials of cholecalciferol (200,000 units, 5mg/ml) for six months, and participants in group B were given placebo (saline

vials) and regular treatment of COPD with same schedule. A series of follow-up evaluations took place at 1st, 3rd, and 6th month. During these visits, patients were assessed through their medical history and the number of exacerbations. The effectiveness of the treatment on the patient's overall well-being and daily life was determined using the CAT scoring method. As part of the follow-up process, a CRP test was conducted. Furthermore, spirometry was utilized to measure the FEV1/FVC ratio and the FEV1.

Data analysis was done by using Statistical Package for Social Sciences (SPSS) version 26.0. Qualitative variables such as gender and number of exacerbations were documented as frequency and percentage. Quantitative variables such as age, and the values of CRP, CAT, FEV1/FVC, and FEV1 at 1st, 3rd, and 6th month were presented as mean along with standard deviation. Variables in two groups placebo and vitamin D were compared by independent sample t-test. The *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 92 participants were include with 46 in each group, with a mean age of 57.09 ± 6.61 years and 85.9% of the participants were male. The overall rate of exacerbations decreased from 64.1% in 1st month to 27.2% by the 3rd month, and raises to 42.4% by the 6th month. The CAT scores had a significant reduction from 25.07 ± 6.47 in the 1st month to 16.42 ± 7.05 in the 6th month. (Table I)

The mean age of participants in Group A and B was 56.93 ± 6.97 years and 57.24 ± 6.31, respectively. Majority of the participants in both groups were male. The acute exacerbations of COPD at 1st, 3rd, and 6th months in Group A were 73.9%, 13.0% and 23.9%, while in Group B were 54.3%, 41.3% and 60.9%, respectively. CRP levels exhibited a consistent decline from 7.85 ± 5.44 in the 1st month to 4.04 ± 3.05 by the 6th month in Group A and a consistent rise from 4.70 ± 3.06 in the 1st month to 11.07 ± 4.40 by the 6th month in Group B. The FEV1/FVC ratio raises from 48.26 ± 3.85 in the first month to 63.69 ± 9.72 by the sixth month, and FEV1 increased from 1.26 ± 0.35 to 2.16 ± 0.58 in Group A. FEV1/FVC increased slightly from 58.18 ± 8.09 at the first month to 59.09 ± 8.01 at the sixth month, while FEV1 experienced a marginal rise from 1.66 ± 0.56 to 1.71 ± 0.58 in group B. (Table I & II)

Table I: Demographics of Group A & Group B.

Variables	Group A N (%)	Group B N (%)
Gender		
Male	40 (87.0%)	39 (84.8%)
Female	6 (13.0%)	7 (15.2%)
Exacerbation at 1st Month		
Yes	34 (73.9%)	25 (54.3%)
No	12 (26.1%)	21 (45.7%)
Exacerbation at 3rd Month		
Yes	6 (13.0%)	19 (41.3%)
No	40 (87.0%)	27 (58.7%)
Exacerbation at 6th Month		
Yes	11 (23.9%)	28 (60.9%)
No	35 (76.1%)	18 (39.1%)
Mean ± S.D.		
Age	56.93 ± 6.97	57.24 ± 6.31
CRP at 1st Month	7.85 ± 5.44	4.70 ± 3.06
CRP at 3rd Month	5.50 ± 2.81	7.22 ± 3.54
CRP at 6th Month	4.04 ± 3.05	11.07 ± 4.40
CAT at 1st Month	27.52 ± 3.53	22.61 ± 7.74
CAT at 3rd Month	18.70 ± 4.35	22.41 ± 5.79
CAT at 6th Month	11.24 ± 3.45	21.61 ± 5.81
FEV 1/ FVC at 1st Month	48.26 ± 3.85	58.18 ± 8.09
FEV 1/ FVC at 3rd Month	55.55 ± 9.43	58.38 ± 7.72
FEV 1/ FVC at 6th Month	63.69 ± 9.72	59.09 ± 8.01
FEV 1 at 1st Month	1.26 ± 0.35	1.66 ± 0.56
FEV 1 at 3rd Month	1.74 ± 0.43	1.69 ± 0.54
FEV 1 at 6th Month	2.16 ± 0.58	1.71 ± 0.58

The variance in acute exacerbations of COPD in Group A and Group B at 1st, 3rd, and 6th months remained statistically significant as $p < 0.001$, $p = 0.002$ and $p < 0.001$, respectively. CRP level and CAT score in Group A was lower at 6th month than the Group B ($p < 0.001$). FEV_1/ FVC and FEV_1 at 6th month was lower in Group A than the Group B ($p < 0.001$). (Table IIII)

Discussion

COPD is a widespread health issue that can be prevented and effectively treated. It is marked by a sustained limitation of airflow, which tends to worsen over time. The condition is connected to an increased chronic inflammatory response in the airways and lungs, resulting from exposure to detrimental particles or gases. Additionally, exacerbations and comorbidities are crucial factors to assess the overall severity experienced by individual patients.[13] Vitamin D deficiency is common in COPD patients and tends to occur more frequently with rise in severity. [14]

The incidence of exacerbation in study group was 13.0% and 23.9% in comparison to the control group with

Table II: Demographics of Group B.

Variables	N(%)
Gender	
Male	39 (84.8%)
Female	7 (15.2%)
Exacerbation at 1st Month	
Yes	25 (54.3%)
No	21 (45.7%)
Exacerbation at 3rd Month	
Yes	19 (41.3%)
No	27 (58.7%)
Exacerbation at 6th Month	
Yes	28 (60.9%)
No	18 (39.1%)
Mean ± S.D.	
Age	57.24 ± 6.31
CRP at 1st Month	4.70 ± 3.06
CRP at 3rd Month	7.22 ± 3.54
CRP at 6th Month	11.07 ± 4.40
CAT at 1st Month	22.61 ± 7.74
CAT at 3rd Month	22.41 ± 5.79
CAT at 6th Month	21.61 ± 5.81
FEV 1/ FVC at 1st Month	58.18 ± 8.09
FEV 1/ FVC at 3rd Month	58.38 ± 7.72
FEV 1/ FVC at 6th Month	59.09 ± 8.01
FEV 1 at 1st Month	1.66 ± 0.56
FEV 1 at 3rd Month	1.69 ± 0.54
FEV 1 at 6th Month	1.71 ± 0.58

Table III: Independent Sample t-test for comparison of Group A and Group B.

Variables	Group A	Group B	*p*-value
Exacerbation at 1st Month			
Yes	34 (73.9%)	25 (54.3%)	< 0.001
No	12 (26.1%)	21 (45.7%)	
Exacerbation at 3rd Month			
Yes	6 (13.0%)	19 (41.3%)	0.002
No	40 (87.0%)	27 (58.7%)	
Exacerbation at 6th Month			
Yes	11 (23.9%)	28 (60.9%)	< 0.001
No	35 (76.1%)	18 (39.1%)	
Mean ± SD.			
CRP at 1st Month	7.85 ± 5.44	4.70 ± 3.06	< 0.001
CRP at 3rd Month	5.50 ± 2.81	7.22 ± 3.54	0.12
CRP at 6th Month	4.04 ± 3.05	11.07 ± 4.40	< 0.001
CAT at 1st Month	27.52 ± 3.53	22.61 ± 7.74	< 0.001
CAT at 3rd Month	18.70 ± 4.35	22.41 ± 5.79	< 0.001
CAT at 6th Month	11.24 ± 3.45	21.61 ± 5.81	< 0.001
FEV 1/ FVC at 1st Month	48.26 ± 3.85	58.18 ± 8.09	< 0.001
FEV 1/ FVC at 3rd Month	55.55 ± 9.43	58.38 ± 7.72	0.120
FEV 1/ FVC at 6th Month	63.69 ± 9.72	59.09 ± 8.01	0.015
FEV 1 at 1st Month	1.26 ± 0.35	1.66 ± 0.56	< 0.001
FEV 1 at 3rd Month	1.74 ± 0.43	1.69 ± 0.54	0.620
FEV 1 at 6th Month	2.16 ± 0.58	1.71 ± 0.58	< 0.001

40.3% and 60.9% at 3rd and 6th month, respectively, with a *p*-value of < 0.001. It indicated that vitamin D reduces the incidence of exacerbation events in the COPD patient. Bellocchia et. al reported that supplementation with vitamin D in COPD patients decreases the number of exacerbations of COPD from 1.98±0.144 to 0.75±0.118, having a statistical significance as *p*-value <0.001 and also the incidence of hospitalization from 0.39±0.093 to 0.160±0.072, having a statistical significance with a *p*-value = 0.006 (15). Similarly, Malinovschi reported acute exacerbations of COPD and severe deficiency of vitamin D had a strong correlation with an adjusted odds ratios (aOR) of 30.5 (95% CI 5.55, 168) having a statistical significance as *p*-value < 0.001.[16]

The CRP level at 1st month was 7.85 ± 5.44 and 4.70 ± 3.06 in study and control group, respectively, with a *p*-value < 0.001. The CRP level was later on reduced at 6 months to 4.04 ± 3.05 in study group and was increased to 11.07 ± 4.40 in the control group, having a statistical significance *p*-value < 0.001. The decrease in the level of CRP in the study group receiving vitamin D supplementation elaborates anti-inflammatory activity of vitamin D. Kruit and Zanen reported that serum levels of vitamin D had significant relation with the level of CRP having a statistical significance (p < 0.001), with a regression coefficient of -0.879. This indicates higher levels of 25(OH) vitamin D are inversely related to CRP levels. However, in the non-inflammatory group, regression coefficient for relation between the level of vitamin D and serum level of CRP was calculated as -0.499, while in group suffering from inflammatory disease, it remained at -0.879. These negative regression coefficients suggested the elevation in levels of vitamin D correspond to reduced levels of CRP, with a more pronounced effect observed in group with the inflammatory disease in comparison to the group without inflammatory disease.[17] Rezk et.al reported that supplementation with vitamin D in COPD patients leads to the decrease in level of mean CRP from 23.67 ± 18.91 to 13.00 ± 14.59 over a time period of 1 year with a *p*-value < 0.001 being statistically significant .[18]

Regarding comparison of CAT score in study and control group, CAT score was 27.52 ± 3.53 and 22.61 ± 7.74 at 1st month, 18.70 ± 4.35 and 22.41 ± 5.79 at 2nd month, and 11.24 ± 3.45 and 21.61 ± 5.81 at 6th month in study and control group, respectively, having the statistical significance with *p*-value < 0.001. Soeroto et.al reported that a significant inverse relationship was found among levels of vitamin D and symptoms measured by CAT

scores in patients with diagnosis of stable COPD, yielding a correlation coefficient of r=−0.802 and a p-value below 0.01.[19] Lee et.al reported that mean CAT score for individuals with deficiency of vitamin D was found to be more than the patients having sufficient levels of vitamin D, measuring 17.14 ± 8.57 against 13.31 ± 8.08, with a *p*-value of 0.004, having a statistical significance. Moreover, percentage of patients scoring 10 or more on the CAT was elevated in the group suffering from deficiency of vitamin D, at 80.4%, compared to 64.6% in the group with sufficient levels of vitamin D, with a p-value of 0.014.[20]

The FEV1/FVC in the study group at 1st month was 48.26 ± 3.85 and was lower than the control group with 58.18 ± 8.09 having a statistical significance < 0.001. The FEV1/FVC in vitamin D supplementation group was increased to 63.69 ± 9.72 at 6 months being higher than the group without vitamin D supplementation as 59.09 ± 8.01 with a *p*-value = 0.015. Bai and Dai reported that FEV1/FVC level in the asthma patients with severe deficiency of serum vitamin D was lower as 70.08±3.36 than the control group as 87.52±5.52 with a statistical significance as < 0.001.[21] Flexeder et.al reported concentrations of vitamin D exhibited significant correlation with FVC, FEV1, and the FEV1/FVC ratio, as measured prior to dilation of bronchioles, after controlling the confounding variables. Specifically, an increase of 10 mL in FEV1(95% CI 2–17), increased of 20 mL in FVC (95% CI 12–28), and decreased of 0.177% in FEV1/FVC ratio (95% CI −0.286 to −0.067) for every 10 nmol·L−1 rise in vitamin D concentration was found.[22]

The FEV1 in the study group was lower at 1st month 1.26 ± 0.35 than the control group 1.66 ± 0.56, with a *p*-vale < 0.001. The FEV1 in the study group after vitamin D supplementation was increased to 2.16 ± 0.58 in comparison to the control group 1.71 ± 0.58 having a statistical significance as *p*-value < 0.001. Babar et. al reported that after 3 months treatment with vitamin D supplementation FEV1 was higher as 75.15±2.04 in comparison to the placebo intake as 66.13±2.75 having a statistical significance with $p = 0.001$. [23] Zendedel et.al reported that supplementation with the vitamin D in COPD patients raises the mean FEV1 in the study group from 34.6±8.5 to 51.6±9.4 (*p*-value < 0.001) as to compare the control group the change in the FEV1 was from 34.4±9.2 to 31.9±7.6 (*p*-value = 0.53).[24]

It is recommended to further explore the influence of vitamin D supplementation in a larger and more heterogeneous cohort of COPD patients to substantiate the findings of this study. Long-term investigations should be performed for assessment of enduring effects of vitamin D on functioning of lungs, inflammatory markers, and the overall progression of the disease. Researchers should also focus on determining the ideal dosing and duration of vitamin D supplementation, as well as its effectiveness in preventing exacerbations in patients with different severities of COPD. Additionally, future studies could investigate the interaction between vitamin D and other therapeutic modalities to enhance comprehension of its potential as a standard adjunct therapy in the management of COPD. Furthermore, understanding the factors as genetic, environmental, and lifestyle affecting the response to vitamin D supplementation would be instrumental in refining treatment strategies.

Several limitations are associated with this study that must be acknowledged. Firstly, the relatively small sample size could affect the generalization to wider range of population. Secondly, the short duration of the study presents challenges in assessing the long-term effects of supplementation of vitamin D on both progression of disease and lung function. Additionally, the research did not account for potential confounding factors, including the participants' initial nutritional status, their levels of physical activity, or other comorbidities that could influence the results. Finally, inconsistencies in patient adherence to the supplementation could have impacted the study's findings.

Conclusion

To conclude, this study revealed the benefits of supplementation of vitamin D in enhancing functioning of lungs, minimizing the episodes of exacerbations, and improving overall quality of life for patients suffering from COPD. While the findings suggest a positive link between increased vitamin D levels and better health outcomes. The study also highlights the critical need to address vitamin D deficiency in this patient population, as it may lead to improved clinical outcomes and more effective disease management.

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