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Association of Serum Vitamin D Levels in Acute Exacerbation of COPD

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ABSTRACT

Background: Chronic obstructive pulmonary disease represents a major health challenge worldwide, accounting for substantial illness and death. Episodes of acute deterioration accelerate the decline in respiratory capacity and are a leading cause of hospital admissions. Adequate vitamin D status is integral to immune regulation and pulmonary health, whereas deficiency has been consistently linked with heightened vulnerability to infections and more frequent disease flare-ups in individuals with chronic obstructive pulmonary disease. **Objective:** To determine the association of serum vitamin D concentrations in patients admitted with acute exacerbation of COPD. **Design of the Study:** Case-control study: **Study duration and settings:** The study was conducted in the Department of Pulmonology, Combined Military Hospital (CMH) Rawalakot, Azad Kashmir, from March to August 2024. **Methodology:** A total of 84 participants were included, comprising 42 patients aged 40 years and above with acute exacerbation of COPD and 42 healthy controls without chronic respiratory disease. Detailed clinical histories and physical examinations were conducted. Serum 25-hydroxy vitamin D concentrations were measured using chemiluminescence immunoassay. **Study Results:** In this study the mean serum vitamin D level in COPD patients was 26.32 ± 10.39 ng/mL, significantly lower than that of controls, which was 34.14 ± 11.09 ng/mL (p = 0.001). Vitamin D deficiency was more frequent among COPD patients (35.7%) compared with controls (14.3%). **Conclusion:** In this study COPD exhibited markedly reduced serum vitamin D concentrations in comparison with healthy control subjects.

INTRODUCTION

Chronic obstructive pulmonary disease is a progressive pulmonary condition marked by irreversible airflow obstruction and sustained inflammatory changes within the airways and parenchymal structures. Episodes of acute exacerbation are identified by an acute intensification of respiratory manifestations that mandate escalation of medical therapy.[1–2] These exacerbations represent a critical determinant of morbidity and mortality, accounting for frequent hospital admissions and hastening the decline in lung function. On a global scale, chronic obstructive pulmonary disease is recognized as the third leading cause of death, with a disproportionate disease burden observed in low- and middle-income regions.[3–4]

In India, chronic obstructive pulmonary disease affects an estimated 55 million individuals, resulting in considerable illness burden and heavy utilization of healthcare resources.[5] In Pakistan, reported prevalence among adults ranges between 2% and 6%, although true rates are likely higher due to inadequate application of spirometric testing and insufficient public and clinical awareness.[6–7] Widespread exposure to harmful agents, including biomass combustion products, tobacco smoke, occupational particulates, and urban air pollution, plays a central role in sustaining the disease load across both nations.[5,8]

Vitamin D is essential for skeletal integrity, mineral metabolism, and proper functioning of the immune system. It enhances innate immune defenses, regulates inflammatory mechanisms, and may reduce vulnerability to respiratory tract infections.[9–10] Evidence from several investigations has shown markedly lower circulating vitamin D concentrations in individuals with chronic obstructive pulmonary disease compared with those without the disease.[11–12] Insufficiency of vitamin D has been linked to reduced muscular strength, compromised lung performance, and heightened risk of disease progression. Observational data further indicate that deficiency is associated with increased frequency and severity of exacerbations, thereby aggravating clinical outcomes.[13–14]

Data on the association between vitamin D insufficiency and acute exacerbation of chronic obstructive pulmonary disease remains sparse in Azad Kashmir. Here, individuals are normally subjected to risk factors such as household biomass smoke, cigarette smoking, and low dietary intake that predispose to respiratory disease and low concentration of vitamin D. The mountain climate and low

level of sunshine all year round further enhance risk for vitamin D insufficiency.

METHODOLOGY

Following ethical clearance from the institutional review board, recruitment of study participants commenced. In total, 84 subjects were included, divided equally between the two study arms. Group A consisted of individuals diagnosed with chronic obstructive pulmonary disease experiencing acute exacerbation, whereas Group B comprised healthy volunteers matched for age and sex, serving as the control cohort.

Patients in Group A were recruited through the Departments of Medicine and Pulmonology when they presented with worsening breathlessness, cough, and/or sputum production requiring additional treatment. Sample size was calculated using OpenEpi software, which estimated 84 participants (42 per group) at a 95% confidence level and 80% power, based on mean serum vitamin D levels reported in COPD patients (25.82 ± 10.62 ng/mL) and healthy controls (32.57 ± 11.32 ng/mL).[15]

Inclusion criteria for Group A were age ≥40 years, previously diagnosed COPD confirmed on spirometry (post-bronchodilator FEV_1/FVC ratio <0.70), and current presentation with acute exacerbation. Exclusion criteria included bronchial asthma, tuberculosis, lung cancer, interstitial lung disease, chronic kidney disease, chronic liver disease, or vitamin D supplementation within the preceding three months. Group B consisted of healthy controls without chronic respiratory disease, recent respiratory infection, systemic inflammatory conditions, or vitamin D supplementation in the last three months. Controls were selected from hospital staff, attendants, and outpatient visitors after informed written consent, applying the same exclusion criteria.

A detailed history was recorded for all participants, including age, sex, smoking status, duration of illness (for COPD patients), number of previous exacerbations, and comorbidities. Clinical examination assessed vital signs, oxygen saturation, and respiratory findings in COPD patients.

For biochemical analysis, 5 mL of venous blood was collected under aseptic conditions and analyzed using chemiluminescence immunoassay to measure serum 25-hydroxy vitamin D concentrations. Levels <20 ng/mL were considered deficient, 20–29 ng/mL insufficient, and ≥30 ng/mL sufficient. All demographic, clinical, and laboratory data were documented on a predesigned proforma and stored securely to ensure confidentiality.

Statistical evaluation was conducted using SPSS version 27. Continuous data were presented as mean values accompanied by standard deviations, while categorical data were described in terms of absolute numbers and corresponding percentages. Comparisons of continuous data were carried out using the independent samples t-test. Differences in the frequency of vitamin D deficiency between study groups were assessed using the chi-square test or Fisher's exact test. Additional stratified analyses were performed according to demographic and clinical characteristics, with value of p≤ 0.05 was taken as statistical significance.

RESULTS

In this study, male participants comprised 59.5% of the COPD group and 61.9% of controls, while females represented 40.5% and 38.1% respectively. Age distribution was comparable with 50.0% vs 52.4% in the 40-60 years category and 50.0% vs 47.6% in the 61-80 years category for COPD and control groups respectively, with mean ages of 59.74±11.38 years and 59.36±11.59 years. Body mass index was slightly lower in COPD patients (25.56±3.55 kg/m^2) compared to controls (26.98±3.85 kg/m^2). Smoking prevalence was similar between groups (42.9% vs 45.2%), as were diabetes mellitus rates (33.3% vs 31.0%) and hypertension rates (38.1% vs 35.7%) (as shown in Table 1).

Table 1

Comparison of Distribution of Different Variables between Groups

Variables		Groups	
		COPD (n=42)	Control (n=42)
Gender	Male	25(59.5%)	26(61.9%)
	Female	17(40.5%)	16(38.1%)
Age groups	40-60 years	21(50.0%)	22(52.4%)
	61-80 years	21(50.0%)	20(47.6%)
	Mean±SD	59.74±11.38	59.36±11.59
BMI (kg/m^2)	Mean±SD	25.56±3.55	26.98±3.85
Smoking	Yes	18(42.9%)	19(45.2%)
	No	24(57.1%)	23(54.8%)
Diabetes mellitus	Yes	14(33.3%)	13(31.0%)
	No	28(66.7%)	29(69.0%)
Hypertension	Yes	16(38.1%)	15(35.7%)
	No	26(61.9%)	27(64.3%)

The primary outcomes revealed significantly lower mean vitamin D levels in COPD patients compared to controls (26.32±10.39 ng/mL vs 34.14±11.09 ng/mL, p=0.001). Vitamin D deficiency was significantly more prevalent in the COPD group (35.7%) than in controls (14.3%, p=0.023) (as shown in Table 2).

Table 2

Comparison of Outcomes between Groups

Outcomes		Groups		p-value
		COPD	Control	
Mean vit. D levels (ng/mL)		26.32±10.39	34.14±11.09	0.001
Vit. D deficiency	Yes	15(35.7%)	6(14.3%)	0.023
	No	27(64.3%)	36(85.7%)	

Among males, COPD patients had significantly lower levels (26.14±10.64 ng/mL vs 34.17±10.64 ng/mL, p=0.010), while the difference in females approached significance (26.58±10.33 ng/mL vs 34.10±12.35 ng/mL, p=0.054). Age-stratified analysis showed significant differences in both 40-60 years (28.29±10.75 ng/mL vs 32.15±12.13 ng/mL, p=0.027) and 61-80 years groups (24.36±9.89 ng/mL vs 36.33±9.64 ng/mL, p=0.001). Smoking status revealed significant differences in both smokers (25.19±10.03 ng/mL vs 34.43±11.01 ng/mL, p=0.012) and non-smokers (27.17±10.79 ng/mL vs 33.91±11.39 ng/mL, p=0.043). Diabetes mellitus stratification showed lower vitamin D levels in COPD patients regardless of diabetes status: diabetics (25.93±8.80 ng/mL vs 36.03±9.07 ng/mL, p=0.007) and non-diabetics (26.52±11.25 ng/mL vs 33.31±11.93 ng/mL, p=0.032). Similarly, hypertensive COPD patients had significantly lower levels (27.71±10.64 ng/mL vs 39.14±11.70 ng/mL, p=0.001), as did normotensive patients (25.47±10.36 ng/mL vs 36.92±9.88

ng/mL, p=0.001) (as shown in Table 3).

Table 3

Stratification of Mean vit. D Levels between Groups with Respect to Different Variables

Variables		Groups		p-value
		COPD	Control	
Gender	Male	26.14±10.64	34.17±10.64	0.010
	Female	26.58±10.33	34.10±12.35	0.054
Age groups	40-60 years	28.29±10.75	32.15±12.13	0.027
	61-80 years	24.36±9.89	36.33±9.64	0.001
Smoking	Yes	25.19±10.03	34.43±11.01	0.012
	No	27.17±10.79	33.91±11.39	0.043
Diabetes mellitus	Yes	25.93±8.80	36.03±9.07	0.007
	No	26.52±11.25	33.31±11.93	0.032
Hypertension	Yes	27.71±10.64	39.14±11.70	0.001
	No	25.47±10.36	36.92±9.88	0.001

Vitamin D deficiency stratification revealed significant differences in several subgroups. Among males, deficiency rates were higher in COPD patients (36.0% vs 11.5%, p=0.040), while female differences were non-significant (35.3% vs 18.8%, p=0.286). Age stratification showed no significant difference in the 40-60 years group (28.6% vs 22.7%, p=0.661), but a marked difference in the 61-80 years group (42.9% vs 5.0%, p=0.005). Smoking stratification revealed significant differences among smokers (38.9% vs 10.5%, p=0.044) but not non-smokers (33.3% vs 17.4%, p=0.210). Diabetes mellitus stratification showed non-significant trends in both diabetics (35.7% vs 7.7%, p=0.080) and non-diabetics (35.7% vs 17.2%, p=0.113). Hypertension stratification demonstrated no difference among hypertensive patients (31.3% vs 33.3%, p=0.901) but significant differences among normotensive individuals (38.5% vs 3.7%, p=0.002) (as shown in Table-IV).

Table 4

Stratification of Vit. D Deficiency between Groups with Respect to Different Variables

Variables		Vit. D deficiency	Groups		p-value
			COPD	Control	
Gender	Male	Yes	9(36.0%)	3(11.5%)	0.040
		No	16(64.0%)	23(88.5%)	
	Female	Yes	6(35.3%)	3(18.8%)	0.286
		No	11(64.7%)	13(81.2%)	
Age groups	40-60 years	Yes	6(28.6%)	5(22.7%)	0.661
		No	15(71.4%)	17(77.3%)	
	61-80 years	Yes	9(42.9%)	1(5.0%)	0.005
		No	12(57.1%)	19(95.0%)	
Smoking	Yes	Yes	7(38.9%)	2(10.5%)	0.044
		No	11(61.1%)	17(89.5%)	
	No	Yes	8(33.3%)	4(17.4%)	0.210
		No	16(66.7%)	19(82.6%)	
Diabetes mellitus	Yes	Yes	5(35.7%)	1(7.7%)	0.080
		No	9(64.3%)	12(92.3%)	
	No	Yes	10(35.7%)	5(17.2%)	0.113
		No	18(64.3%)	24(82.8%)	
Hypertension	Yes	Yes	5(31.3%)	5(33.3%)	0.901
		No	11(68.8%)	10(66.7%)	
	No	Yes	10(38.5%)	1(3.7%)	0.002
		No	16(61.5%)	26(96.3%)	

DISCUSSION

The present study reveals a significant association between vitamin D deficiency and COPD, with COPD being defined by significantly lower mean levels of vitamin D and a larger proportion of deficiency than healthy controls. Results of mean vitamin D levels of 26.32±10.39 ng/mL for COPD cases and 34.14±11.09 ng/mL for controls, and proportions of deficiency of 35.7% and 14.3% accordingly, suggest an association with scientific implications.

Decreased levels of vitamin D in COPD can be accounted for by several related pathophysiological processes. Enhanced intake of vitamin D owing to its use as an anti-inflammatory molecule and modulator of immunity owing to chronic inflammation that is characteristic for COPD can result in low levels of systemic vitamin D. Decreased outdoor activity and sun exposure in COPD owing to exercise intolerance and shortness of breath further result in low cutaneous production of vitamin D. The disease pathological process can also interfere with vitamin D metabolism owing to alterations of renal and liver functions, as these are primary sites of action for activation of vitamin D. Further, majority of COPD patients also suffer from malnutrition and malabsorptive syndromes, thus decreasing dietary ingestion and absorption of vitamin D.

Age-stratified studies showing increased vitamin D deficiency in older COPD cases (61-80 years) reflect natural age-dependent loss of skin capacity to synthesize vitamin D for its exacerbation by disease burden. The comparable vitamin D deficiency across all smoking status subgroups suggests that while smoking is a leading risk agent for developing COPD, the vitamin D deficiency presumably would be more connected to disease pathophysiology than to smoking per se. Finding in normotensive COPD cases with significant differences of vitamin D deficiency from controls again asserts that such association persists irrespective of comorbid cardiovascular disease and validates direct association of COPD with dysfunction of vitamin D metabolism.

Janssens et al. previously reported a high prevalence of vitamin D insufficiency in COPD, with an inverse relationship to disease severity, possibly mediated through impaired lung function, heightened inflammation, and reduced innate immunity.[16] Camargo et al. similarly found lower vitamin D levels in COPD patients and demonstrated that supplementation reduced exacerbation rates, aligning with our findings.[17] Kunisaki et al. conducted a large randomized controlled trial (RCT) that identified prevalent vitamin D deficiency in COPD, but high-dose supplementation benefited only severely deficient individuals, underscoring the importance of defining deficiency thresholds, as 35.7% of our cohort were deficient.[18]

Li et al., in a meta-analysis, confirmed lower vitamin D levels in COPD compared to controls (weighted mean difference: −6.3 ng/mL), consistent with our observed difference of 8 ng/mL.[19] Persson et al. associated vitamin D deficiency with higher risks of exacerbations and hospitalizations.[20] Regional studies support these trends: in Pakistan, mean vitamin D levels were 20.25 ± 7.34 ng/mL in COPD patients versus 28.34 ± 9.13 ng/mL in controls,[21] while in India, Mishra et al. reported 23.2 ± 8.5 ng/mL versus 31.4 ± 10.2 ng/mL, respectively.[22] Agarwal et al. found a higher deficiency rate of 67% in COPD patients,[23] compared to our 35.7%, potentially explained by differences in disease severity, season, and nutrition. Hashim et al. reported a prevalence of 49% in Saudi Arabia,[24] further indicating regional variability but a consistent link.

Findings from interventional research on vitamin D in

chronic obstructive pulmonary disease have been inconsistent. Lehouck et al. reported that supplementation did not significantly reduce exacerbation frequency overall, although secondary analysis indicated a protective effect in patients with profound deficiency (<10 ng/mL).[25] In contrast, Mete et al. documented markedly lower vitamin D concentrations in affected patients (14.5 ± 6.2 ng/mL) compared with controls (21.2 ± 8.4 ng/mL), with deficiency correlating with diminished pulmonary performance and reduced quality of life.[26] Similarly, Zhou et al. identified vitamin D deficiency as an independent predictor of recurrent exacerbations,[27] while Rafiq et al. observed that supplementation was associated with fewer severe episodes and hospital admissions.[28] Moreover, Martineau et al., through an individual patient data meta-analysis of randomized controlled trials, concluded that vitamin D administration significantly decreased the incidence of acute respiratory infections, particularly in deficient populations, lending biological plausibility to the associations demonstrated in our study.[29]

Our research shows that screening for and correcting vitamin D insufficiency in COPD patients can improve clinical effectiveness, reduce exacerbation frequency, and prevent hospitalization. Future interventional studies need to define best-optimized supplemental doses for deficient COPD subgroups to confirm vitamin D correction as a routine part of COPD management.

There were limitations to this study. The sample was modest in size, and that might limit generalizability. There was no measurement of seasonal variation of vitamin D levels. In addition, disease severity and lung function parameters were not separated by vitamin D status, and that might impact outcomes.

CONCLUSION

Our studies have shown that patients with acute exacerbation of Chronic Obstructive Pulmonary Disease have significantly low serum concentrations of vitamin D compared to normal controls.

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