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A STUDY OF CORRELATION OF VITAMIN D LEVELS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Respiratory Medicine

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KEYWORDS

INTRODUCTION

Chronic obstructive lung disease (also known as Chronic Obstructive Pulmonary Disease, or COPD) is attributed to persistent respiratory symptoms and airflow limitation that is the resulting of airway and/or alveolar abnormalities emanating from significant exposure to noxious gases or particles.[1] It is a fundamental cause of morbidity and mortality worldwide, projected to be the third leading cause of mortality by 2020. [2] WHO statistics suggest that 90% of COPD-related deaths occur in low and mediocre-income countries; moreover, India and China constitute 33% of the total human population and account for 66% of the global COPD mortality.[2]

COPD has a complex pathophysiology. There are countable factors influencing the course of the disease. These factors, in due course lead to an amplified inflammatory response, which is persistent and hence proving guilty behind the physiological abnormalities seen in the same. Narrowing of the peripheral airways causing a decrease in FEV1 is a feature of the disease.(1)

Risk factors for COPD include cigarette smoking - the most prevailing, and most widely studied one - biomass exposure, chronic fumes/dust exposure, and multiple genetic and developmental factors. Recurrent pulmonary infections, presenting as acute exacerbations, is a familiar risk factor for deteriorating lung function.[1]

Over the years, many genetic factors have come into the eminence, out of which the deficiency of alpha-1 antitrypsin[3] single-handedly stands out to be the most common but somehow, contributes to a very small percentage of the total cases of COPD. Smokers with matrix metalloproteinase 12 deficiency and glutathione--transferase enzyme defects have been found to have a greater propensity to develop COPD.[1]

Vitamin D is a hormone associated with bone mineral homeostasis in the body. Direct synthesis on exposure to sunlight or by incorporating into diet is the two ways vitamin D endures in our body. It is further metabolised in the body into active metabolites, which act on bone, kidneys, and the gut to increase serum calcium levels, amongst other actions.

Till recently, knowledge of the role of Vitamin D was restricted to calcium and bone homeostasis. However, the latest founding suggests that Vitamin D may have a role in various non-communicable diseases, e.g., obesity, autoimmune disorders, coronary artery disease, cancer, diabetes and COPD, among others.

Recent studies show that vitamin D has numerous actions in the human body, aside from calcium homeostasis. It has been proven to be an important regulator of both elements of the immune system. Vitamin D has been shown to affect dendritic cell maturation[4], T-cell activation and proliferation[5], and Th1 T-cell development.[6] Adding to it, vitamin D deficiency is associated with increased susceptibility to respiratory infections, which may in part be explained by the ability of $1,25(OH)_2D$ to increase the expression of antimicrobial peptides and to decrease the expression of pro-inflammatory cytokines and chemokines by airway epithelial cells.[7]

Apparently proven, vitamin D deficiency may lead to an increase in respiratory tract infections in patients with COPD, which present as exacerbations. Increased frequency of the same has been shown to contribute to long-term lung functional decline.[8]

MATERIALS AND METHODS

Study Setting:

The study was conducted in the Department of Respiratory Medicine, Career Institute Of Medical science and Hospital, Lucknow.

Study Design:

Comparative Cross-sectional study

Study Subjects:

COPD patients admitted as inpatients, and those presenting to the OPD were taken as study subjects.

Age gender, BMI (body mass index) matched controls were also taken.

Sample Size:

Total of 120 subjects, 60 cases and 60 controls with matched age, gender and BMI.

Consent and ethical clearance:

Written and informed consent was taken from all the subjects participating in the study. Ethical clearance was from the ethical committee before conducting the study.

Study Duration:

The study was conducted over a course of 18 months

Inclusion And Exclusion Criteria

Inclusion Criteria:

Patients aged 18-65 years meeting GOLD criteria for Chronic obstructive pulmonary disease were included in the study.

Exclusion Criteria:

- Co-existing chronic kidney disease
- Celiac disease, inflammatory bowel disease, or history suggestive of malabsorption History of small bowel resection
- Active cancer
- Granulomatous disorders
- History of anti-tubercular drug intake, anti-epileptic drug intake (phenytoin, phenobarbital, carbamazepine), weight lowering drug intake eg orlistat, cholesterol lowering agent cholestyramine, and glucocorticoids
- Any bony deformity

- Known case of psychiatric disorders like depression, psychosis
- Pregnancy
- Patients with pulmonary tuberculosis
- Patients who cannot undergo spirometry – have undergone recent abdominal surgery, myocardial infarction in last 3 months, pregnant patients, any respiratory infection leading to copious amounts of sputum production, known case of coronary artery disease
- Patients already on Vitamin D supplementation

METHODOLOGY

After taking written and informed consent form each patient (Annexure 3), brief history was taken and clinical examination of all patients was done.

History included asking the patient for -

- Shortness of breath – onset, duration, severity according to Modified Medical Research Council scale
- Cough – onset and duration, whether associated with expectoration or not
- Fever
- Past hospitalisations for the same complaints
- History of smoking, passive smoking, chronic exposure to fuel emissions, pollution
- History of occupational exposures
- Co-existing co-morbidities e.g., diabetes mellitus, hypertension, coronary artery disease, metabolic syndrome
- Severity of disease was measured by COPD Assessment Test questionnaire [Hindi version] (Annexure 4), and mMRC grading. Patients were instructed that there are no right or wrong answers, and all patients underwent testing. Patients were classified according to GOLD as having less symptoms (CAT <10) and breathlessness (mMRC grade 0–1) and more symptoms (CAT ≥10) and breathlessness (mMRC grade ≥2).
- For serum Vitamin D (25, OH-D) level, 3 ml of serum samples were collected in plain vials and processed in biochemistry lab at CIMS & HOSPITAL by ELISA method. Patients were then classified based on their vitamin D levels into deficient, insufficient and sufficient when Vitamin D levels were <20 ng/ml, 20-30 ng/ml, >30 ng/ml, respectively.
- All cases underwent spirometry, by Medisoft Spiroair Model Body Box 5500 spirometer, which was performed in the Department of Respiratory Medicine, CIMS & HOSPITAL. Patients were instructed to withdraw short-acting β2-agonists at least 6 hours, long-acting β2-agonist at least 12 hours, long acting muscarinic antagonist 24 hours and short acting muscarinic antagonist 12 hours before undergoing spirometry. Spirometry was done after administration of 400 mcg of salbutamol, according to ERS/ATS recommendations. [88] The following parameters were recorded:

FEV_1(Forced expiratory volume in 1st second)
FVC (Forced Vital Capacity)
FEV_1/FVC
Patients were then classified on the basis of results for severity of COPD by GOLD classification.

Table 1- Gold Classification:

	COPD Grade	FEV1/FVC	FEV1
GOLD 1	Mild	< 0.7	> 80% of predicted value
GOLD 2	Moderate	<0.7	>=50 to <80% of predicted value
GOLD 3	Severe	<0.7	>=30 to <50% of predicted value
GOLD 4	Very Severe	<0.7	<30% of predicted value

ABE classification was further done by considering exacerbation history and current symptoms.

Table 2- Gold Abe Assessment Tool:

	Symptoms:	
Exacerbation history	CAT < 10 mMRC 0-1	CAT >= 10 mMRC >=2
>=2 moderate exacerbation or >=1 leading to hospitalisation	E	
0 or 1 moderate exacerbation (not leading to hospitalisation)	A	B

Severity of disease was measured by mMRC grading and CAT questionnaire.[1]

As the study was based in Luckonw, where patients are predominantly Hindi speakers, the Hindi version of the CAT questionnaire (Annexure 4) was used. Permission for the same was obtained from GlaxoSmithKline (Annexure 5).

Table 3- mMRC Grading:

Grade 0	No dyspnea	Not troubled by breathlessness except with strenuous exercise.
Grade 1	Slight dyspnea	Troubled by shortness of breath when hurrying on a level surface or walking up a slight hill.
Grade 2	Moderate dyspnea	Walks slower than normal based on age on a level surface due to breathlessness or has to stop for breath when walking on level surface at own pace.
Grade 3	Severe dyspnea	Stops for breath after walking 100 yards or after a few minutes on a level surface.
Grade 4	Very severe dyspnea	Too breathless to leave the house or becomes breathless while dressing or undressing.

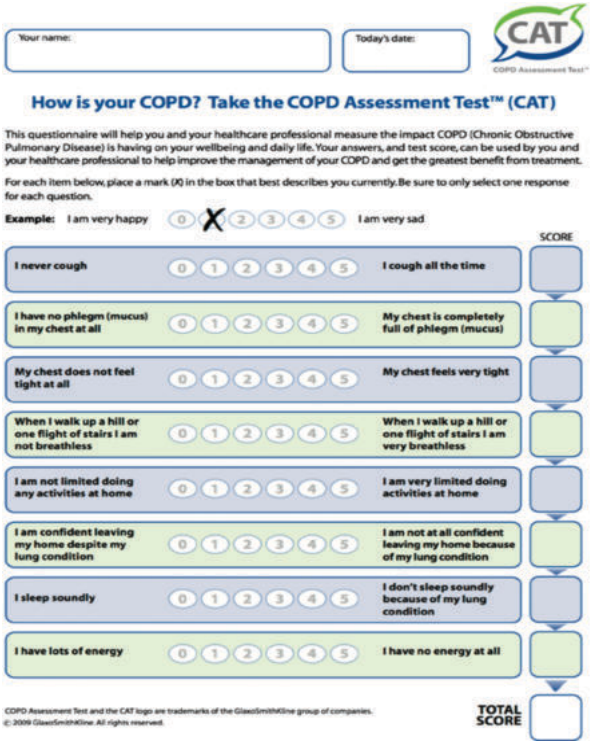

Figure 1- COPD Assessment Test (CAT)

RESULT

Table 4: Comparison of the 3 Subgroups of the Variable COPD Class in Terms of S. Vitamin D (ng/mL) (n = 60)

S. Vitamin D (ng/mL)	COPD Class			Kruskal Wallis Test	
	A	B	E	χ2	p value
Mean (SD)	17.25 (3.89)	25.09 (17.49)	15.85 (13.63)	11.813	0.008
Median	17.25	16.7	12.35		
Range	14.5 – 20	8.7 - 66.6	2.2 - 70.4		

The variable S. Vitamin D (ng/mL) was not normally distributed in the 3 subgroups of the variable COPD Class. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons. There was a significant difference between the 3 groups in terms of S. Vitamin D (ng/mL) ($\chi2 = 11.813$, $p = 0.008$), with the median S. Vitamin D (ng/mL) being highest in patients of COPD class A.Strength of Association (Kendall's Tau) was 0.33 (Medium Effect Size).

Table 5: Association Between S. Vitamin D deficiency, insufficiency, and sufficiency and COPD Class (n = 60)

COPD Class	S. Vitamin D				Fisher's Exact Test	
	<20 ng/mL	20-30 ng/mL	>30 ng/mL	Total	χ2	P Value
A	1 (2.4%)	1(11.1%)	0(0.0%)	2(3.3%)	9.722	0.165

B	11 (26.2%)	3 (33.3%)	6 (66.7%)	20 (33.3%)		
E	30 (71.4%)	5 (55.6%)	3 (33.3%)	30 (50.0%)		
Total	42 (100.0%)	9(100.0%)	9(100.0%)	60 (100.0%)		

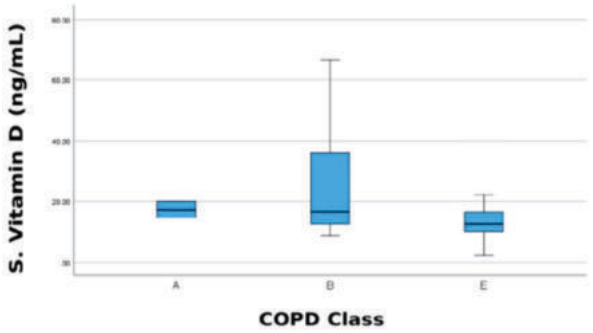

Figure 2- Box and whisker plot: Association between S. Vitamin D and COPD Class of Cases

Fisher's exact test was used to explore the association between 'S. Vitamin D' and 'COPD Class' as more than 20% of the total number of cells had an expected count of less than 5.There was no significant difference between the various groups in terms of distribution of COPD Class ($\chi 2 = 9.722$, $p = 0.165$).

DISCUSSION

COPD spared no gender, race, or sex. COPD is highly wide spread worldwide, and with increasing air pollution, tobacco use (even in women), and economic enevenness, making the poor even more vulnerable to these risk factors, the burden of this disease is becoming substantial.[1]

It has now become obligatory to acquainted of putting a stop to prevent this disease, as the number of people living with it getting bigger. While taking the course of action against control the most well known risk factors of COPD, like smoking cessation programmes, pollution control programmes, etc, are absolutely necessary to implement, it is uniformly important to identify factors which can be easily measured and if not avert, either restrict its progression, or indicate risk of progression so that early interventions can be done.

Vitamin D, a fat-soluble vitamin, which is derived from metabolism of 7-dehydrocholesterol in the skin via UV rays, or from the diet, is to a great extent associated with bone mineral homeostasis, but its pleotropic effects are increasingly being recognised.[9] Vitamin D deficiency, defined as serum 25, OH D levels < 20ng/mL, and deficits, defined as levels between 20-30 ng/mL, are increasing worldwide, with unchecked sunscreen use, avoidance of sunlight exposure, and lessening in milk consumption in both Western countries[10] and India[11].

There is no scarcity of research on the subject matter of peculiar actions of Vitamin D, owing to the fact that, 1) the prevalence of Vitamin D short fall and deficiency are increasing, and 2) more and more recently developed knowledge of the nonhormonal, intracrine and paracrine actions of Vitamin D is becoming apparent.[12] Adverse effects on bone and mineral health are usually seen when Vitamin D levels fall down to deficient levels in an individual, but it has now been narrated that even inadequate levels may have hazardous effects on cardiovascular health, cause prone to infections, and are related with diabetes, obesity, and cancers.[13]

Hence, the interest in the correlation of Vitamin D levels in COPD become apparent. While Indian research on this topic is bounded, a number of international studies have been conducted on the same In this study, we aim to find, a correlation, if any, between Vitamin D levels and COPD, and its severity. This study was conducted in Career Hospital, Lucknow. Grounded on the inclusion and exclusion criteria, 60 COPD patients were enrolled in the study, both in-patients and out-patients. All were assessed with detailed history including demographics, duration of disease, extent of respiratory symptoms, number of exacerbations, smoking history and clinical examination (as per annexure 1). Sixty healthy controls were taken, who were age, sex and BMI matched. All patients underwent investigations, including serum Vitamin D levels, and COPD patients also underwent spirometry.

Our study showed that the major part of COPD patients were middle aged, with a mean age of 52.38 ± 6.81 years. The number of male patients was more than female patients, i.e., 44 (73.33%) males and 16 (26.67%) females. This is in acquiescence to preceding studies which appeared that COPD prevalence in males is far more than that in females.

The total number of patients in our study were, 60, distributed amongst various COPD classes (by the ABE assessment tool). Two (3.3%) patients fell under COPD class A, 20 (33.3%) fell into class B, 38 (63.3%) fell into class E.

In our study, a total of 70% of COPD patients were found to be deficient in Vitamin D, while a further 15% were found to have insufficiency.

It was also found in our research that COPD patients were more likely to fall under the deficient group, as compared with controls, which were in much larger numbers in the insufficient and sufficient groups, and that this difference was statistically significant (p value = 0.001) with moderate strength of association.

In summary compared to age, sex, and BMI matched controls, and that lower levels were associated with more severe disease. However, this only signifies a correlation, and not causality. The multipronged action of vitamin D and its consequences have been well elaborated above – it prevents infections hence decreases exacerbations, it improves musculoskeletal strength, and in general lower vitamin D levels are associated with higher morbidity and mortality in the general population. More studies are required to assess if a Vitamin D deficiency may be causal factor for COPD.

Between patients and controls, there was a significant difference in the levels of blood vitamin D (p 0.001). Serum vitamin D levels averaged 18.98 15.31 ng/mL in cases and 24.86 12.00 ng/mL in controls. Even after dividing vitamin D levels into several 81 subgroups, there was still a substantial difference between the two groups (deficient, insufficient, and sufficient) (0.01 p value)

CONCLUSION

Chronic Obstructive Pulmonary Disease is one of the highest contributors to morbidity and mortality, not just in India, but all over the world.[2] It is a disease characterised by persistent airflow obstruction due to significant exposure to noxious particles, which leads to respiratory symptoms.[1] The most common risk factors of COPD, i.e., tobacco smoking, air pollution, etc are factors which can only be controlled these factors as the burden of COPD increases, the identification of biological factors which may have a role in the pathogenesis of COPD, or may be useful in treatment of COPD, is equally important.

Vitamin D is one such factor, the role of which is being increasingly recognised in cancers, cardiovascular diseases, autoimmune diseases, etc. Thanks to the VDP, vitamin D has a myriad of actions on multiple organs in the body, and novel functions are being discovered every day. The role of Vitamin D in COPD is being increasingly recognised.

Our study aimed to find a correlation between vitamin D levels and COPD. We found that yes, COPD patients were more deficient in Vitamin D than their healthy counterparts, and that this deficiency positively correlated with the severity of the disease. As this was a cross sectional study, any causality between Vitamin D and COPD and its severity could not be established. But the multipronged action of Vitamin D at various levels, on various parts of body, as has been repeatedly proven in literature, indicates that there may be a causal role of its deficiency in COPD.

Serum Vitamin D levels may thus prove to be an important tool in assessing the severity of COPD and may prove to be a marker of severity of COPD, in conjunction with already existing ones.

Dietary supplementation of Vitamin D in these patients may improve the disease status and decrease the morbidity and mortality due to COPD. More studies are required to assess whether Vitamin D supplementation improves outcomes in COPD.

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