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Study of the Role of Vitamin (D) Deficiency in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Background: COPD is a variety of lung symptoms that are characterized by persistent, frequently worsening airflow restriction and chronic respiratory symptoms (dyspnea, cough, and formation of sputum) owing to diseases in the bronchial tree (bronchiolitis, bronchitis), or/and alveoli (emphysema).

Objectives: To research the impact of vitamin (D) deficiency in individuals with stable and acute exacerbation COPD.

Subjects and methods: This case-control study was carried out at Al-Azhar University Hospital-Assuit between February 2022 and December 2022 on (100) COPD patients and another (50) control group of individuals who looked to be in good health.

Result: Moreover, Levels of vitamin (D) were markedly high in controls compared to Stable COPD group and levels of vitamin D were relatively high in Stable COPD compared to the AECOPD group.

Conclusion: AECOPD patients were shown to have vitamin D insufficiency and vitamin D insufficiency was strongly related to the severity of COPD. Vitamin D insufficiency was also related to illness exacerbation.

Keywords: COPD exacerbation, Severity of COPD, Vitamin (D)

1. Introduction

Although the prevalence of COPD is frequently directly correlated with the rate of tobacco usage, in many countries, outdoor, occupational, and household air pollution (caused by the burning of wood and other biomass fuels) are significant COPD risk factors. COPD is a leading source of death and morbidity with a substantial and growing economic and social burden. Vitamin D influences calcium homeostasis, which contributes to its relationship with bone health. Several studies have also suggested a link between vitamin D and the pathogenesis of several autoimmune diseases, as well as the onset of cancer, asthma, and infections like respiratory infections and tuberculosis. In addition to playing a role in the etiology of COPD, vitamin D also lessens the incidence of respiratory infections, hinders the body's ability to respond to pathogens, and prevents the growth of airway smooth muscles. Studying the impacts of vitamin (D) insufficiency in individuals with acute COPD exacerbations and stable COPD was the goal of the work.

2. Patients and methods

This case-control study was carried out at Al-Azhar University Hospital-Assuit between February 2022 and December 2022, involving (100) COPD patients and (50) participants who appeared to be in good health.

2.1. Patients

One hundred COPD patients with or without acute exacerbation, were hospitalized to the department of chest diseases at Al-Azhar Assiut...
University Hospital. Additionally, (50) people who seemed to be in good health were involved in the research as a control group and Patients were Grouped into two groups: Group A: (50) patients with an acute exacerbation of COPD (AECOPD). Group B: (50) COPD patients without exacerbation. Group C: Above 50 apparently healthy individuals were enrolled as a control group.

2.2. Inclusion criteria

Age more than 40 years, confirmed COPD diagnosis in accordance with GOLD guidelines, (COPD was classified as having postbronchodilator FEV1/FVC ratios <0.70 and FEV1 levels <80% of expected levels, which correspond to GOLD (Global Initiative for Obstructive Lung Disease) stages 2–4)3 and above 40 age (50) apparently healthy individuals.

2.3. Exclusion criteria

Patients with interstitial lung diseases, bronchial asthma, or other pulmonary diseases that are clinically evident, patients who also have connective tissue abnormalities, sleep apnea syndrome, or other clinically evident causes of PH and age less than 40.

2.4. Methods

All patients were undergone to:

2.4.1. Complete history taking

Including demographic, clinical data and symptoms of vitamin D deficiency as bone ache, muscle fatigue.

2.4.2. Full clinical examination

Full Clinical Examination including assessment of general condition, vital signs (temperature, pulse, blood pressure, and respiration rate). Local chest evaluation was assessed; Height and weight were measured, while The body's mass index (BMI) is calculated by dividing weight in kilograms by the square of height in meters.

2.4.3. Laboratory investigations

ALT, AST, S. Albumin, total serum bilirubin, international normalised ratio (INR), RBS (Random Blood Sugar), complete Blood Picture, serum Creatinine and Urea and serum 25-hydroxy vitamin D (25(OH)D) concentrations.

2.4.4. Pulmonary functions tests

PFT was performed using the device (Ultima CPX 790705-205, USA), spirometric examination was performed according to the European Respiratory Society (ERS) criteria, the FEV1 and FVC were also estimated as percentages of predicted values in accordance with the ERS's prediction equations, depending on postbronchodilator (post-BD) FEV1/forced vital capacities (FEV1/FVC) < 0.70, COPD was diagnosed using GOLD-2007 criteria.

2.4.5. Case definition

The guideline (GOLD) recommendations were used to make the diagnosis of COPD.3 The guidelines' definition of COPD is postbronchodilator FEV1/FVC ratio <0.70 and FEV1 <80% expected. The obstructive lung disease gold standard. (AECOPD) defined as sustained (48 h) worsening of the cough, production of sputum or dyspnea leading to frequent utilization of maintenance medicines and/or extra supplementing with additional medications, systemic steroids or antibiotics.4 The GOLD standard for control participants is postbronchodilator FEV1/FVC ≥0.7 and FEV1 ≥80% expected.3 According to the Institute of Medicine's recommendations, those with plasma 25(OH)D concentrations of 20 ng/ml or more were regarded to have appropriate amounts of vitamin D, while those with blood serum 25(OH)D concentrations below 20 ng/ml were deemed to have vitamin D deficiency.3

2.4.6. Ethical aspects

Patients who were clinically stable or the responsible family members of critically sick patients given their informed written consent. The procedure and outcomes remain secret, as was disclosed to all qualified patients.

Al-Azhar Assiut University Faculty of Medicine's local Ethics Committee gave approval for this study.

2.5. Statistical analysis

With the help of the statistical tool for special sciences SPSS version 22 (SPSS Inc. Chicago, IL, USA), all data were acquired, recorded, and statistically evaluated as follows: Coding and editing, data entry in computer, for parametric and non-parametric variables, the mean and SD (standard deviation) were utilized to describe quantitative data. Qualitative data were expressed as frequencies and relative percentage. The Shapiro-Wilk test was utilized to determine if the data had a normal dispersion. Data were managed with the use of suitable statistical significance tests such: The variance in quantitative
measures in two groups was determined using the independent $t$-test and the mann-whitney test. Using two dependent groups of variables that are distributed normally, do a paired $t$-test. The variance between qualitative data was assessed utilizing the chi square test ($\chi^2$) and fisher exact. $P$ values $\leq 0.05$ indicate substantial differences, $P$ values $< 0.001$ indicate extremely substantial differences, and $P$ values $> 0.05$ indicate no substantial differences in all statistical comparisons.

3. Results

Table 1.
Age, sex, and BMI varied significantly between the three groups that were examined (Table 2).

Regarding Hb, RBS, and albumin, there is a considerable variation between the three groups under study (Table 4).

Table 5.
The three groups under study varied significantly in terms of vitamin D values.

Additionally, vitamin D values were considerably greater in controls compared to the COPD group and in the COPD group compared to the AECOPD group (Table 6).

4. Discussion

These study is a case-control and was performed at Al- Azhar University Hospital-Assuit, chest department on (100) patients with COPD and another (50) apparently healthy individuals were joined in the study as a controls.

The duration of the research between February 2022 and December 2022.

BMI, Age and sex varied significantly between the three groups that were examined.

In contrary to our results the other study belonging Lokesh et al., their prospective case-control study was done on 60 patients diagnosed as COPD. The patients were randomly selected by the cross-over method (1 : 1). Also, a control group from 24 healthy participants of the same age and sex were participated in the study. There was no variation between the studied groups as regard BMI, Age and sex.

With the exception of renal insufficiency, the current investigation revealed a substantial variation in comorbidities across the study groups.

While, in the study of Shabana et al., there was no discernible variation in smoking index between present and former smokers in the patient group compared to the control group (24.66%), however there were fewer never smokers in the patient group.

BMI in the AECOPD group was $32.3 \pm 8.4$ against $33.8 \pm 7.3$ ($P = 0.18$) in the control group. When one or two comorbidities are present, there is no statistical substantial variation between the patient group and control groups. However, the COPD group exhibited a larger proportion of 0 comorbidities [62 (30.24%)] compared with the control group [41 (27.3%)] ($P < 0.05$). With a $P < 0.05$, the control group had a larger number of patients with three comorbidities [41 (27.3%)] than the COPD group [42 (20.48%)].

Whereas in the study belonging Abdel Ghany et al., their prospective case-control study was done on 60 patients diagnosed as COPD. The patients were randomly selected by the cross-over method (1 : 1). Also, a control group from 24 healthy participants of the same age and sex were participated in the study. There was no variation between the studied groups as regard BMI, Age and sex.

In the Malinovschi et al., heart disease (HD) and hypertension were the most prevalent comorbidities, affecting nearly (2/3)of the individuals.

According to our current study, there is no obvious variation between the two case study groups regarding GOLD classification.

Our findings were consistent with Lokesh et al., which found no discernible differences between the

Table 1. Data about the researched groups' demography.

<table>
<thead>
<tr>
<th></th>
<th>AECOPD (n = 50)</th>
<th>COPD (n = 50)</th>
<th>Control (n = 50)</th>
<th>$F/\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year and Mean ± SD</td>
<td>65.34 ± 8.77</td>
<td>63.51 ± 9.16</td>
<td>60.28 ± 6.93</td>
<td>4.71</td>
<td>0.010</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (94%)</td>
<td>40 (80%)</td>
<td>32 (64%)</td>
<td>6.14</td>
<td>0.046</td>
</tr>
<tr>
<td>Female</td>
<td>3 (6%)</td>
<td>10 (20%)</td>
<td>18 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI as kg/m$^2$ and Mean ± SD</td>
<td>28.87 ± 4.85</td>
<td>28.71 ± 4.92</td>
<td>26.14 ± 3.4</td>
<td>5.93</td>
<td>0.003</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>30 (60%)</td>
<td>32 (64%)</td>
<td>27 (54%)</td>
<td>1.1</td>
<td>0.592</td>
</tr>
<tr>
<td>Urban</td>
<td>20 (40%)</td>
<td>18 (36%)</td>
<td>23 (46%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. GOLD classification among the groups under study.

<table>
<thead>
<tr>
<th></th>
<th>AECOPD (N = 50)</th>
<th>COPD (N = 50)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD A</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
<td>1.79</td>
<td>0.618</td>
</tr>
<tr>
<td>GOLD B</td>
<td>13 (26%)</td>
<td>13 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD C</td>
<td>16 (32%)</td>
<td>17 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD D</td>
<td>19 (38%)</td>
<td>15 (30%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
examined case groups in terms of GOLD classification.

More than (1/2) of the subjects (57%) in Malinovschi et al.,8 55% of whom were frequent exacerbators, were in the moderate GOLD class, and 52% had spent at least one night in the hospital the year prior.

A pathological inflammatory response of the airways to the intake of gases or noxious particles, such as cigarette smoke, is a feature of (COPD). Patients experience systemic effects and become more vulnerable to viral exacerbations as the disease progresses, as indicated by a reduction in FEV1 Bulut et al.9

The three analysed subjects in our current study varied significantly in terms of Hb, RBS, and albumin.

Regarding FVC%, FEV1%, and FEV1/FVC, the three people under study vary substantially from one another.

Our findings were in line with research of Lokesh et al.,5 revealed that there was substantial variation between their studied groups regarding FVC%, FEV1% and FEV1/FVC.

In the study of Khan et al.,10 The median FEV1 was 67.54 ± 5.50 at baseline, 71.07 ± 5.68 at 2 months, 74.18 ± 6.81 at 5 months, and 78.97 ± 6.94 at 6 months. After 6 months, patients’ FEV1 significantly improved. The study’s findings revealed that the median FVC at baseline was 77.83 ± 5.49, the mean at 2 months was 89.75 ± 7.77, the mean at 4 months was 89.75 ± 7.77, and the median at 6 months was 91.34 ± 5.52. The variation was substantial.

Globally, Chronic Pulmonary Obstruction Disease [COPD] frequently causes morbidity and mortality. Exacerbations of COPD are linked to high rates of morbidity, death, reduced quality of life, and financial burden. Protective variables with the ability to reduce the severity and frequency of COPD exacerbations are of interest. Vitamin D is of particular interest because of its numerous lung-related effects, tissue remodeling, reduced of pro-inflammatory cytokines, helpful modulation of both innate and adaptive immune systems, regulation of more than 1000 genes, and significance for regular human physiology outside of the skeletal system.8

Due to a number of factors, including inadequate diet, excessive outdoor activity, enhanced vitamin D catabolism by drugs, and decreased storage capacity, COPD patients are at a very high risk of vitamin D deficiency. COPD and Vitamin D are correlated, according to indirect evidence. Vitamin D is essential for the formation and correct operation of both innate and adaptive immunity, including the maturation of dendritic cells, the inhibition of pro-
inflammatory cytokines and chemokines, and the maturation and development of T cells. Immune cells have the ability to lessen the pathogenic burden of microorganisms because they express the Vitamin D receptor (VDR) and the hydroxylase enzyme. Pathogens are killed by vitamin D in the airway epithelium through TLR and CD14 dependent pathways. Low vitamin D levels may enhance vulnerability to repeated infections, and increase the microbial colonization of the Airways. A lack of vitamin D has been linked to greater airway smooth muscle, structural changes in the lungs, including airway remodeling brought on by higher MMPs and enhanced collagen deposition. Lungs affected by COPD are shown to have less VDR. Animal experiments that have knocked out the crucial nuclear hormone receptor VDR have shown lung alterations like those of COPD, including enhanced inflammation, up-regulation of many MMPs, early-onset emphysema, and a loss in lung function. It has been shown that VDR polymorphisms influence susceptibility to COPD acute exacerbations. Clinical studies have demonstrated that taking more vitamin D lowers the incidence of mild to moderate acute COPD exacerbations.\(^5\)

According to the current study, vitamin D levels were both considerably higher in controls when compared to the COPD group and in the COPD group when compared to the AECOPD group. In both the AECOPD and COPD groups, there is a strong positive connection between vitamin D and FVC, FEV1, and FEV1/FVC.

The study by Islam et al.\(^11\) which indicated that the means vitamin D (25-OHD) levels of COPD subjects was reported to be considerably lower than control subjects (32.57±11.32 ng/mL), is in line with our findings. The severity of COPD was revealed to be substantially correlated with vitamin D insufficiency by the Pearson correlation test. Age (by years), FEV1 (predicted percentage), numerous exacerbators (2 in the preceding year), and smokers (>40 pack year) were all substantially linked to vitamin D deficiency, according to multivariate analysis. Vitamin D insufficiency was discovered in individuals with acute exacerbations of COPD, and this was found to be substantially correlated with the severity of COPD.

Similar to this, Lokesh et al.\(^5\) discovered that even with daily exposure to the sunlight, 64.50% (95.0% CI 57.7–70.80) of subjects also had vitamin D insufficiency. In comparison to controls, subjects with COPD exhibited a higher possibility of vitamin D insufficiency (modified OR: 5.05; 95% confidence interval 1.40–17.80). Subjects with Vitamin D insufficiency were 3 times more likely to have had exacerbations in the previous year compared to COPD individuals without the condition. For COPD and AECOPD, the greatest specificity and sensitivity levels were linked to levels of vitamin D of 20.81 ng/mL and 18.45 ng/mL, respectively.

In the study of Bulut et al.\(^9\) The median reference level of 25 hydroxyvitamin D in serum for COPD patients was 12.5 ng/dl. Patients with mild deficiencies, insufficient levels, and severe deficiencies, of 25-hydroxyvitamin D showed a distinct risk of aggravation. The risk was decreased but not statistically substantial in individuals with acceptable levels. Low vitamin D levels are negatively

| Table 4. Pulmonary functions tests among the groups under study. |
|-------------------|-------------------|-------------------|----|----|----|
|                   | AECOPD (N = 50)   | COPD (N = 50)     | Control (N = 50) | F  | P   | LSD |
| FVC (%) Mean ± SD | 59.24 ± 11.4      | 66.56 ± 10.74     | 81.76 ± 6.85     | 67 | 0.000 | I*III P = 0.001 *IIIP = 0.000 II*III P = 0.000 |
| FEV1 (%) Mean ± SD | 41.52 ± 11.28     | 45.24 ± 15.14     | 75.96 ± 12.01    | 107| 0.000 | *IIIP = 0.167 II*III P = 0.000 II*III P = 0.000 |
| FEV1/FVC Mean ± SD| 70.72 ± 15.38     | 69.53 ± 23.66     | 80.34 ± 15.09    | 5.15| 0.007 | *IIIP = 0.765 II*III P = 0.002 II*III P = 0.008 |

| Table 5. Vitamin D Levels among the groups under study. |
|-------------------|-------------------|-------------------|----|----|----|
|                   | AECOPD (N = 50)   | COPD (N = 50)     | Control (N = 50) | F  | P   | LSD |
| Vitamin D (ng/ml) | 12.47 ± 4.26      | 15.38 ± 4.85      | 26.53 ± 6.92     | 391| 0.000 | I*III P = 0.000 II*III P = 0.000 II*III P = 0.000 |
| Mean ± SD         | 6.1–18.9          | 7.6–19.4          | 22–34            |    |      |     |

| Table 6. Relationship between other indicators in the groups under study and vitamin D. |
|-------------------|-------------------|-------------------|----|----|----|
|                   | AECOPD (N = 50)   | COPD (N = 50)     |    |    |    |
| Age               | 0.095             | 0.653             | −0.221| 0.289|
| BMI               | 0.029             | 0.892             | 0.024| 0.909|
| FVC %             | 0.342             | 0.014             | 0.263| 0.023|
| FEV1%             | 0.369             | 0.007             | 0.322| 0.016|
| FEV1/FVC          | 0.432             | 0.002             | 0.357| 0.009|
| Creatinine        | 0.001             | 0.095             | −0.366| 0.072|
| AST               | 0.305             | 0.054             | 0.076| 0.719|
| ALT               | 0.238             | 0.252             | 0.386| 0.057|
| Albumin           | 0.236             | 0.256             | 0.214| 0.304|
linked with FEV1 in COPD patients \( (r = 0.187, P = 0.0013) \).

In addition, metaanalysis conducted by Zhu et al.,\(^2\) There were 4818 COPD patients and 7175 controls in a total of 21 trials that came to an end. With regards to severe COPD patients and COPD exacerbation, meta-analysis revealed that blood vitamin D levels were lower in COPD patients than in controls. Deficit of vitamin D was not associated with COPD exacerbation, but it was associated with higher likelihood of developing COPD and COPD severity. The test techniques had a substantial impact on the variability of vitamin D deficiency and the risk of COPD.

Additionally, Li et al.,\(^1\) noted that serum values of vitamin D in COPD patients were less than those of smoking individuals. When the percentage of projected the forced expiratory volume - 1 s (FEV1\% pred) was more than or equal to 80% in COPD patients, the level of vitamin D was 39.43 nmol/l results of Vitamin D were 35.32 nmol/l, 32.21 nmol/l, and 26.25 nmol/l in the groups with FEV1\%pred 50%—80%, 30%—50%, and <30%, respectively \( (P = 0.01) \). Additionally, both COPD patients and healthy smokers showed a substantial correlation between 25-OHD levels and FEV1\%pred \( (r (2) = 1.911; P = 0.0001) \) Stages of the GOLD had a negative connection with the mean 25-OHD concentration. The 25-OHD levels and susceptibility to COPD were both independently correlated with homozygous carriers of the gene of vitamin D-binding protein rs7041 T allele.

Moreover, in the study of Kunisaki et al.,\(^3\) in their mostly white (85%) group of severely ill COPD patients from North America (the mean of FEV1: 1.12 L; 40% of predicted) and mean 25(OH)D was 25.7 ± 12.8 ng/ml and a percent of 33.1% of subjects had inadequate vitamin D levels (≥20 ng/ml but <30 ng/ml); 32% of subjects had low vitamin D levels (less than 20 ng/ml); and 8.4% had extreme vitamin D insufficiency (less than 10 ng/ml). and the Baseline of 25(OH) vitamin D results there were no connection to time of first AECOPD or AECOPD rates. Differences in analytical procedures do not account for the variation in seasonal effects, which may be explained by the fact that they employed various labs and liquid chromatography tandem mass spectroscopy approach for 25(OH)D tests in their investigation. One reason for this difference is because patients in the present research had substantially more severe COPD than those in the prior sample, which contained patients with relatively moderate COPD (72% of anticipated by median FEV1). The 24 patients in the United Kingdom study’s FEV1% predicted were not given, however, given that their mean FEV1 was around 1.2 L, it is likely that they too had severe COPD. It’s crucial to emphasize that participants in the current research were chosen because they had a high risk of AECOPDs (1415 exacerbations occurred during follow-up in these 973 individuals, and >80% had an AECOPD in the year before to recruitment). As a result, they represent the sickest COPD patients. So, compared to individuals in the LHS 3 or United Kingdom trials, these patients may have had higher ambulatory restriction. Ambulatory limiting may reduce exposure to sunshine, which will soften the impact of the seasons on 25(OH)D levels.

The majority of patients (96%) were found to have vitamin D insufficiency, and this was severe in 35 participants (36%), according to Malinovschi et al.,\(^4\) however, Vit D and FEV1 or the annual reduction in FEV1 did not show any connection that was meaningful. Except for the recorded osteoporosis percent (60.9% with severe deficiency versus 22.7%, \( P = 0.001 \)), there was not any difference among participants who had or had not severely vitamin D deficient in terms of sex, age, smoking history, BMI, pulmonary function, or comorbidities. Patients with severe vit D deficiency were linked to increased risk of frequent exacerbations and hospitalization in many logistic regression models. The odds ratio for frequent exacerbation was 18.1 while patients with severe deficiency of vit D had the highest risk of death from all causes \( (P = 0.001) \). This might just be the result of the fact that a larger population would have been required to establish such a minor effect.

In addition, over 90% of COPD patients in the research by Abdel Ghany et al.,\(^6\) exhibited vitamin D deficiency. Although there was no statistically substantial variation between COPD with or without coexisting conditions \( (P > 0.05) \), blood vitamin D values in COPD with and without comorbidities were statistically significantly lower than in healthy controls \( (P = 0.001) \). Values of serum 25-hydroxyvitamin D did not seem to be connected to survival, length of admission, or need for mechanical ventilation. The findings of the modified Medical Research Council, St. George Respiratory Questionnaire, or forced expiratory volume in one second were not associated with vitamin D, either. The lifestyle differences between patients in various research may help to explain this (including sunlight exposure, outdoor activities, vitamin D fortifications in drinks and foods).

4.1. Conclusion

AECOPD patients were shown to have vitamin D insufficiency, and COPD severity was closely connected to vitamin D deficiency. Exacerbation of the
illness was also connected to vitamin D insufficiency.

Disclosure

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Conflicts of interest

The authors declared that there were NO conflicts of Interest.

References