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Evaluation of Vitamin D, IL6 and Hs-CRP in Different Stages of Chronic Obstructive Pulmonary Disease and Their Correlation with Severity of Disease and Frequency of Exacerbations

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Abstract

Background: The role of systemic inflammation in COPD has been proved in recent studies. It is associated with increased level of inflammatory cytokines such as IL-6 (Interleukin 6) & inflammatory mediators such as hs-CRP (high sensitivity C Reactive Protein). There is also extensive evidence supporting the action of vitamin D in immunity & inflammation. Low blood levels of 25-hydroxyvitamin D have been associated with a higher risk of respiratory infections in general populations and higher risk of exacerbations of lung disease in people with asthma. Low levels of vitamin D have been shown in COPD. We evaluated levels of vitamin D, hs-CRP, IL-6 in different stages of COPD and its correlation with severity of disease & frequency of AECOPD.

Methods: 182 subjects of COPD and 20 controls were recruited. After clinical history & examination, Spirometry was performed. 6 Minute Walk Test (6MWT) was done & BODE index was calculated. Clinical COPD questionnaire (CCQ) and mMRC were used to assess functional status. Levels of vitamin D, IL-6 & hs-CRP were estimated by ELISA & correlated with disease severity and frequency of exacerbation during 6 month follow up.

Results: IL-6 & hs-CRP were higher in study group than the normal controls & the difference was statistically significant with 'p' value of 0.024 & < 0.01 respectively whereas vitamin D was significantly lower in study group ($p < 0.01$). Levels of Vit D were found to be lower in severe COPD as compared to mild COPD. Levels of IL6 and hs-CRP were also seen to increase with the increasing severity of the disease. Vitamin D levels were lower in COPD and show moderate correlation to severity & frequency of AECOPD. hs-CRP levels were higher in COPD and showed weak correlation to disease severity & frequency of AECOPD. IL-6 levels were higher in study group but did not correlate with disease severity & frequency of AECOPD.

Keywords

Chronic obstructive pulmonary disease (COPD), Cytokines, vitamin D, Dyspnea

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity & mortality worldwide & results in an economic & social burden that is both substantial & increasing [1]. According to WHO estimates, 80 million people have moderate to severe COPD. About 3 million people die due to COPD every year, which corresponds to 5% of all deaths globally, making it the 4th largest cause of mortality in the world [2-4]. It has been estimated that by the year 2030, COPD will become the third biggest cause of death globally. It is known that 90% of COPD deaths occur in low & middle income countries [2-4]. In India median prevalence of COPD is 5% in men & 2.7% in women [5]. About half a million people die due to COPD in India, this is over 4 times the number of people who die due to COPD in Europe & USA.

In the past, COPD was regarded solely as a lung disease. However, it is now accepted as a multi-component disease characterized by extra-pulmonary effects that contribute to disease severity [6]. The characteristic pathological changes of COPD are due to inflammatory cells & inflammatory mediators, oxidative stress & proteases & anti-proteases imbalance [7].

An exacerbation is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD [7]. It is the major cause of deterioration of functional capacity of a COPD subject causing debilitation and death.

Recent studies have shown association of COPD with systemic inflammation [8]. This is associated with activation of circulating inflammatory cells & increased level of pro-inflammatory cytokines such as IL-6 & inflammatory mediators such as CRP. Studies show that reduced lung function is associated with elevated systemic inflammatory factors that increase during exacerbations & these factors may contribute to the co-morbidities associated with COPD [8].

There is now extensive evidence supporting the action of vitamin D in immunity & inflammation [8,9]. Low blood levels of 25-hydroxyvitamin D have been associated with a higher risk of respiratory infections in general populations [10] & higher risk of exacerbations of lung disease in people with asthma. Low levels of

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vitamin D have been shown in COPD [11,12]. However, Current studies have failed to prove that low vitamin D levels predispose to increased exacerbations in COPD [13,14]. Based on the data from the previous studies we hypothesized that baseline 25(OH)D, hs-CRP & IL-6 levels should correlate to the severity of disease & frequency of acute exacerbations in COPD.

Materials and Methods

This was a prospective study conducted at the Clinical Research Centre, Vallabhbhai Patel Chest Institute (VPCI), University of Delhi over a period of one year. A total of 182 consecutive patients with the diagnosis of COPD as per GOLD guidelines attending the outpatient department of pulmonary medicine were recruited. The diagnosis of COPD was based on clinical history consistent with COPD and Pulmonary function test showing irreversible bronchial obstruction. Patients having acute respiratory infection during the past 4 weeks or those treated with antibiotics, steroids or vitamin D during the past 4 weeks were excluded. Subjects with other systemic illness were also excluded.

These patients were subjected to detailed history & clinical examination. All subjects were then subjected to baseline investigations to rule out any associated co-morbidity. Once patients were recruited in the study, a written informed consent was taken. And baseline initial assessment was done that includes Spirometry with reversibility. hs-CRP, IL-6 & 25-hydroxy vitamin D levels were performed on patient serum samples on TECAN automated ELISA reader using respective ELISA kits based on Quantitative sandwich immunoassay.

All subjects were classified as per GOLD stages I, II, III, IV based on PFT & as grade A, B, C, D based on history & spirometry was done as per GOLD guidelines. 6 min walk test was done & BODE index was calculated. All subjects were asked to fill CCQ at initial presentation & then at weekly intervals that was recorded & assessed at monthly follow-ups. All subjects then received standard inhalational therapy as per the GOLD guidelines. Subjects were followed up at monthly intervals for 6 months. Subjects also reported if exacerbations occurred.

The data was examined for distribution and homogeneity of variance. Multiple groups were compared using analysis of variance and Kruskal Wallis test. Groups were compared using student's t test, Wilcoxon sign rank test and Mann Whitney U test. For comparing proportions of patients, chi square test were used. Correlations were computed using Pearson/Spearman's test. Multivariate analysis (logistic/linear) were used to identify factors determining outcomes after adjustment for cofactors. A conventional value of $p < 0.05$ was used for statistical clinical significance of the study. 20 healthy disease free volunteers were also recruited to establish normal values of test parameters.

Results

Study population

Study group included 158 (87%) males & 24 (13%) females with age ranged between 45 to 77 years with a mean age of 57.42 ± 7.37 years. Mean BMI of subjects was 24.26 ± 5.17 kg/m^2. Out of 182 subjects, 37 were current smokers, 129 were former smokers. 33 had history of significant exposure to biomass fuel smoke while 12 had history of both smoking as well as biomass fuel smoke exposure. Mean smoking index amongst the smokers was 739.81 ± 427.39.

Table 1: Mean value of vitamin D, hs-CRP & IL-6.

	IL-6 (pg/ml)	hs-CRP (mg/l)	25-OH D3 (ng/ml)
Cases (n = 182)	3.97 + 1.02	3.89 + 1.97	22.28 + 14.64
Control (n = 20)	0.91 + 0.62	0.28 + 0.13	36.15 + 11.57
p value	0.024	0.001	0.001

Duration of disease ranged from 1 year to 17 years with mean of 7.614 ± 8.33 years. History of persistent cough & sputum along with progressive dyspnea & wheezing was present in all the subjects. Chest tightness was present as presenting symptoms in 87 (47.80%) cases. Nasal symptoms were present in 70 (38.46%) cases. Family history suggestive of COPD was present in 51 (28.02%) cases.

Baseline scores and investigations

Out of 182 cases, 70 had no activity limitation with mMRC score of 0 to 1 whereas 29 cases had grade 2 dyspnea, 52 had grade 3 dyspnea, & 31 cases had dyspnea on routine daily activities with mMRC grade being 4. CAT score was > 10 in 121 (67%) cases. History of frequent exacerbations (≥ 2/year) was present in 107 (59%) cases whereas 88 (48%) cases had ≥ 1 exacerbation during follow up.

Mean distance in six minute walk test was 328.42 ± 101.73 meter with 18 cases failed to walk more than 150 m in 6 minutes. Mean value of BODE index calculated in the study group was 3.47 ± 1.54. The mean value of baseline CCQ score in study group was 1.98 ± 0.73 with mean & standard deviation of mental, symptom, & functional score being 0.46 ± 0.22, 0.69 ± 0.32 & 0.87 ± 0.57 respectively.

Vitamin D, IL6 and hs-CRP

IL-6 & hs-CRP were higher in study group than the normal controls and the difference was statistically significant with 'p' value of 0.024 & < 0.01 respectively whereas vitamin D was significantly lower in study group ($p < 0.01$) (Table 1).

Levels of vitamin D were found to be lower in severe COPD as compared to mild COPD. Levels of IL6 and hs-CRP were also seen to increase with the increasing severity of the disease. Vitamin D deficiency was present in 37.5%, 41.27%, 74.29%, and 81.82% of patients with GOLD stage I, II, III & IV respectively with a lower mean value in stage III & IV than other stages (Table 2). The differences in values were found to be significant. Vitamin D deficiency was present in 33.33%, 39.13%, 47.62%, & 84.37% of patients with GOLD group A, B, C & D respectively with group C & D having lower mean values than A & B (Table 2). Mean values of vitamin D, IL6 & hs-CRP are shown in relation to PFT staging in table 3, GOLD grouping in table 4 and to exacerbation during follow-up in table 5. The differences in values were found to be significant.

Table 3: Mean value of vitamin D, hs-CRP & IL-6 in relation to PFT stage.

GOLD stage (PFT)	IL-6 (pg/ml)	hs-CRP (mg/l)	25-OH D3 (ng/ml)
I (n = 16)	2.34 + 1.11	2.51 + 1.62	35.86 + 21.73
II (n = 63)	3.24 + 1.84	3.48 + 2.03	29.38 + 19.12
III (n = 70)	4.82 + 2.91	4.84 + 3.15	18.95 + 11.67
IV (n = 33)	5.57 + 3.78	4.96 + 3.24	15.14 + 7.35
Total (n = 182)	3.97 + 1.02	3.89 + 1.97	22.28 + 14.64

Table 4: Mean value of vitamin D, hs-CRP & IL-6 in relation to GOLD group.

GOLD group	IL-6 (pg/ml)	hs-CRP (mg/l)	25-OH D3 (ng/ml)
A (n = 42)	1.62 + 1.04	2.41 + 1.74	31.49 + 22.04
B (n = 23)	3.05 + 2.02	2.93 + 1.90	25.43 + 17.46
C (n = 21)	3.96 + 2.77	3.68 + 2.14	19.97 + 9.83
D (n = 96)	5.18 + 3.12	4.57 + 3.16	17.68 + 7.21
Total (n = 182)	3.97 +1.02	3.89 + 1.97	22.28 + 14.64

Table 5: Mean value of vitamin D, hs-CRP & IL-6 in relation to exacerbations during follow-up.

Exacerbations	IL-6 (pg/ml)	hs-CRP (mg/l)	25-OH D3 (ng/ml)
No (n = 98)	2.87 + 1.51	3.52 + 2.08	32.14 + 18.45
Yes (n = 84)	5.74 + 3.16	4.39 + 2.91	13.87 + 9.52
Total (n = 182)	3.97 +1.02	3.89 + 1.97	22.28 + 14.64

Table 2: Vitamin D deficiency in relation to stage of COPD.

PFT stage	Total no. of patients	vitamin D (< 20 ng/ml)	Percentage	GOLD group	Total no. of patients	vitamin D (< 20 ng/ml)	Percentage
I	16	6	37.50%	**A**	42	14	33.33%
II	63	26	41.27%	**B**	23	9	39.13%
III	70	52	74.29%	**C**	21	10	47.62%
IV	33	27	81.82%	**D**	96	81	84.37%

There was a modest correlation of vitamin D levels with severity of COPD as assessed by mMRC (-0.3831, p = 0.0021), 6MWD (0.4065, p = 0.0011), FEV1% (0.3918, p = 0.0016), PFT stage (-0.3687, p = 0.0031), GOLD group (-0.4064, p = 0.0011), BODE index (-0.4084, p = 0.0010), CCQ scores (-0.4954, p = 0.0003) and exacerbation risk i.e. frequency of exacerbations in the past & exacerbation during follow up (-0.5520, p = 0.0001).

Mean value of IL6 was higher in stage IV and group D but failed to reach statistical significance in relation to GOLD group. Also, Patients with higher mean value of IL6 had more exacerbations during follow-up (p = 0.047). Mean IL-6 could be correlated only to BODE index (0.2684, p = 0.0348), exacerbation during follow up (0.2112, p = 0.0993), FEV1% (-0.2653, p = 0.0371) and PFT stage (0.3226, p = 0.0105). This was a weak correlation. It failed to achieve correlation with other markers of severity.

BODE index & baseline CCQ scores were modestly correlated to hs-CRP and rest all other parameters had a weak correlation with hs-CRP. Mean hs-CRP levels could be correlated to mMRC (0.3152, p = 0.0126), 6MWD (-0.3183, p = 0.0117), FEV1% (-0.3103, p = 0.0141), PFT stage (0.3206, p = 0.0111), GOLD group (0.3272, p = 0.0094), BODE index (0.3677, p = 0.0033), CCQ scores (0.3780, p = 0.0025) & frequency of exacerbations (0.2714, p = 0.0328).

Discussion

COPD is a systemic illness associated with enhanced chronic inflammatory response in airways & is a leading cause of morbidity and mortality worldwide. Despite the best treatment, to date none of the existing medications for COPD has been conclusively shown to modify the long term decline in lung function in clinical trials [7].

Vitamin D deficiency has been linked to respiratory diseases like asthma [15], tuberculosis [16], and influenza [17]. Also, low levels of vitamin D have been seen in patients of COPD in recent studies [18-20]. IL6 [21,22] & hs-CRP [23-25] have also been linked as an inflammatory marker in COPD. CRP has been shown to be increased in COPD in stable condition and during exacerbations. IL6 has been linked as an inflammatory marker in COPD and acute exacerbations of COPD have been shown to be accompanied by elevation of IL-6 levels.

Vitamin D was considered deficient at levels < 20 ng/ml and insufficient when between 20-29 ng/ml. If vitamin D levels are found to be low, supplementation may be required. However, it is still not clear if the deficiency of vitamin D levels is the cause of severe COPD or a result of it. Further studies with supplementation of vitamin D along with pharmacologic therapy are required to further validate the benefit of supplementing vitamin D in poorly controlled cases of COPD having vitamin D deficiency. Till further results are available such deficiency should be treated in accordance to endocrine society guidelines for vitamin D deficiency due to multiple ill effects of vitamin D deficiency independent of COPD.

This study indicates that patients with COPD has lower mean value of vitamin D and there is a modest correlation of vitamin D with severity of COPD as assessed by functional scores like mMRC and 6MWD, lung function test scores i.e. FEV1% & stage on PFT, composite assessment scores like GOLD group and BODE index, health related quality of life scores i.e. CCQ scores and exacerbation risk i.e. frequency of exacerbations in the past & exacerbation during 6 month follow up.

In contrast to previous studies, our study has shown lower vitamin D levels in patients with frequent exacerbations. Also vitamin D deficiency was more prevalent in severe stages of COPD with mean value of vitamin D being lower in severe stages COPD than less severe stages as assessed by PFT & GOLD group. Mean IL-6 levels were higher in patients of COPD than normal subjects & could be correlated only to BODE index, exacerbation during follow up, FEV1% & PFT stage. This was a weak correlation. It failed to achieve correlation with other markers of severity. This is in contrast to our previous hypothesis where correlation of IL-6 with severity of disease & frequency of exacerbations in COPD was proposed.

Mean hs-CRP levels were higher in patients of COPD than normal subjects & could be correlated to all parameters except exacerbations during follow up. BODE index & baseline CCQ were modestly correlated to hs-CRP & rest all other parameters had a weak correlation with hs-CRP.

Conclusion

We therefore suggest that vitamin D levels be estimated in poorly controlled COPD cases especially those who are having severe disease, more functional limitation or having frequent exacerbations.

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