ORIGINAL RESEARCH

A study of serum ferritin levels in copd patients and its correlation with severity and grading of copd

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ABSTRACT

Aim and objectives: The aim of the study was to analyse serum ferritin levels in COPD patients and its correlation with severity and grading of COPD. **Materials and method:** The present cross sectional study was conducted among 100 COPD patients of both genders in the department of medicine, CSS Hospital, Subharti Medical College, Meerut from December 2020 to August 2022. **Results:** According to GOLD criteria; Gold stage I+II, III and IV was reported among 44%, 30% and 26% of the subjects respectively. Maximum subjects were from the age group of >60 years (57%) followed by 51-60 years (39%). Males were comparatively more ascompared to females. COPD severity also increases along with the increase in smoking pack-years consumption. Serum ferritin was found to be raised among 24% of the COPD patients. Maximum raised ferritin level was found among subjects with GOLD IV (34.62%) followedby Gold III (26.67%). Hence raised serum ferritin was associated with severity of COPD. According to Pearson correlation analysis, significant positive correlation (r=0.29, p=0.038)was found between ferritin level and severity of COPD.

Conclusion: Hyperferritinemia was associated with severity of COPD because of inflammatory mechanisms independent of iron stores.

Keywords: COPD, Gold stage, Hyperferritinemia

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is primarily characterised by the presence of airflow limitation resulting from airways inflammation and remodeling often associated with parenchymal destruction and the development of emphysema. However, in many patients the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-relatedquality of life and increased mortality. The best recognized manifestations include the presence of concomitant cardiovascular compromise, malnutrition involving primarily the loss and dysfunction of skeletal muscles, osteoporosis, anaemia, increased gastroesophageal reflux and clinical depression and anxiety. Importantly, the presence of airflow limitation greatly increases the likelihood that patients may develop lung cancer over time.[1]

It is a leading cause of death globally and accounts for about half a million deaths in India annually.[2] In the natural history of COPD, comorbidities greatly influence the morbidity, economic burden, and mortality. COPD is associated with various comorbidities such as cardiovascular disease, diabetes, pneumonia, weight loss, anemia, etc., all of which have a deleterious effect on the disease.[3] Screening of the comorbidities should be an important component in the management of a COPD patient.

Smoking and biomass exposure, along with genetic predisposition, are the major risk factors for developing COPD. Anemia is seen to be present as comorbidity in various chronic disease states and therefore understanding its pathogenesis is important. In recent years, anemia is also seen as a common comorbidity in COPD patients and associated with reduced

functional capacity, impaired quality of life, greater likelihood of hospitalization, and early mortality.[4] Thus, developing new tools for its treatment should be our priority.

Iron is essential for multiple metabolic processes, but it is hazardous in excess amounts because its ability to catalyze the generation of reactive oxygen species can cause oxidative stress and damage cellular membranes. Ferritin is a specialized iron storage protein that regulates body iron homeostasis and reflects iron stores in the body. Ferritin also can become elevated in the presence of oxidative stress and inflammation irrespective of iron status and can contribute to various clinical diseases, especially pulmonary and cardio-metabolic diseases.[5,6]

This suggests that decreased lung function could be associated with elevated serum ferritin level in pathological conditions. Even in healthy subjects, airway epithelial cells could be exposed to oxidative stress and inflammation because of ambient air pollution aerosols, which recently have increased rapidly as a consequence of regional urbanization and industrialization.[7]

Air pollution particulate matter (PM) contains transition metals such as iron (usually most abundant), which can be mobilized from the PM to lung epithelial cells and disrupt iron homeostasis both in the lung and systemically.[8,9] Iron overabundance relative to metabolic needs inside lung epithelial cells can result in ferritin release from damaged cells, which could result in elevated serum ferritin concentration and loss of lung function under normal physiological conditions.[7-9] Nevertheless, epidemiological evidence to support that hypothesis is scarce.

Serum ferritin is supposed to be a cellular means of storing iron,[10] not of transporting it, yet serum ferritin levels are widely measured as indicators of iron status. This is because serum ferritin levels can be raised significantly in response to inflammation and/or a variety of diseases. "Serum ferritin" thus presents something of a paradox.[11]

To date, potential association between ferritin and COPD, has been rarely investigated. Hence this study is conducted to analyse serum ferritin levels in COPD patients and its correlation with severity and grading of COPD.

MATERIALS AND METHOD

The present cross sectional study evaluated the COPD patients. The study was conducted in the department of medicine, CSS Hospital, Subharti Medical College, Meerut from December 2020 to August 2022.

STUDY POPULATION

The study sample comprised of 100 COPD patients who were sequentially allocated into study based on their criteria for fulfilling eligibility criteria. The study included Patients with symptoms suggestive of COPD (visiting internal medicine and pulmonary medicine OPD), Stable COPD patients had been receiving inhaled bronchodilator therapy in the form of long-acting β2-agonists and/or anticholinergic agents and Severe/very severe COPD patients were on inhaled corticosteroids as well.

The study excluded subjects with Spirometry proved Bronchial Asthma defined as an increase in the FEV1 of more than 15 percent above the baseline value or of 200 ml after the administration of a bronchodilator, Recent Myocardial infarction<4 months, Unstable angina, Congestive heart failure, Inability to perform spirometry or 6-minute walk test, Liver disease and Patients with acute exacerbation.

STUDY METHOD

The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, socioeconomic status, medical history and previous history of taking any medications and supplements.

The Diagnostic criteria (according to the GOLD guidelines)[11] were taken for the selection of COPD patients. Anthropometric, body composition, exercise capacity and dyspnea assessments were done during the clinical visit, the information about demographics and a detailed medical history was obtained from the patients. BMI was calculated as weight (in kilograms)/height2 (in meters). Functional exercise capacity was measured with the 6MWT in accordance with the ATS recommendations. The 6MWT was performed in a level, covered hospital corridor of approximately 50 m in length. Three tests were performed and the test with the maximum 6-minute walking distance (6MWD) was considered for analysis. Each patient received standard instructions and encouragement during the test.

The magnitude of dyspnea was assessed using the modified scale of Medical Research Council (mMRC). Patients were asked about their perceived breathlessness and was then classified into the mMRC five dyspnea grades (0 minimum to 4 maximum).

SERUM FERRITIN LEVEL MEASUREMENT

Serum ferritin was measured by immunoradiometric assay using a 1470 Wizard Gamma Counter (PerkinElmer Inc., Waltham, MA, USA). The reference range for serum ferritin is usually from 30 to 300 ng/mL in men and from 15 to 200 ng/mL in women 77.

STATISTICAL ANALYSIS

SPSS version 25.0 analyzed the Excel data when it was loaded. Quantitative (numerical variables) data was given as mean and standard deviation, whereas qualitative (categorical variables) data was provided as frequency and percentage. The student t-test was used to compare the two groups' mean values, while the chi-square test analyzed their frequency

differences. If p0.05, it was statistically significant.

RESULTS

Table 1 showing the basic information about the study population

		Number	%
Age Group (inyears)	31-50	4	4.0%
	51-60	39	39.0%
	>60	57	57.0%
Gender	Male	59	59.0%
	Female	41	41.0%
Stage	Gold I+Ill	44	44.0%
	Gold III	30	30.0%
	Gold IV	26	26.0%
Smoking Status	Smoker	63	63.0%
	Nonsmoker	37	37.0%
Biomass Exposure	Yes	16	16.0%
	No	84	84.0%

Out of 100 subjects, 59% were males and 41% were females. Maximum subjects were from the age group of >60 years (57%) followed by 51-60 years (39%). Only 4% of the subjects were from 31-50 year age group in the present study. According to GOLD criteria; Gold stageII, III and IV was reported among 44%, 30% and 26% of the subjects respectively. Smoking was found in 63% of the subjects. Biomass exposure was reported among 16% of thesubjects.

Table 2 showing the association of COPD with different factors

		Stage			
		Gold I+II	**Gold III**	**Gold IV**	**p value**
Mean Age (in years)		53.89±6.89	56.73±7.04	60.29±7.24	0.003*
Smoking	Yes	20	20	23	< 0.001*
		45.45%	66.67%	88.46%	
	No	24	10	3	
		54.55%	33.33%	11.54%	
Mean pack years of smoking		8.04±6.94	16.56±7.01	24.77±7.67	< 0.001*
Mean BMI		23.09±2.41	21.18±2.19	19.97±2.36	0.002*

Mean age in Gold I, Gold II and Gold IV was 53.89±6.89, 56.73±7.04 and 60.29±7.24 years respectively with statistically significant difference as p<0.05. Smoking was found among 63% of the subjects with significantly higher subjects among Gold IV category (88.46%) compared to Gold I+II (45.45%). Mean smoking pack-years in Gold I+II, Gold III and Gold IV was 8.04±6.94, 16.56±7.01 and 24.77±7.67 respectively with statistically significant difference as p < 0.05. Mean BMI in Gold I+II, Gold III and Gold IV was 23.09±2.41, 21.18±2.19 and 19.97±2.36 respectively with statistically significant difference as p < 0.05.

Table 3 showing

	Stage			**p value**
	Gold I+II	**Gold III**	**Gold IV**	
Mean FEV1 (%)	59.91±9.67	46.79±10.56	37.98±9.03	< 0.001*

Mean Hb (gm/dL)	14.96±1.27	12.91±1.63	11.82±1.44	< 0.001*
Raise Ferritin Level	7 (15.91%)	8 (26.67%)	9 (34.62%)	0.041*

In our study, COPD severity increases along with the decrease in FEV1 (%). Mean FEV1 (%) in Gold I+II, Gold III and Gold IV was 59.91±9.67, 46.79±10.56 and 37.98±9.03
respectively. Mean Hb (gm/dL) level in Gold IV, Gold III and Gold I+II was 11.82±1.44, 12.91±1.63 and 14.96±1.27 respectively. Maximum raised ferritin level was found among subjects with GOLD IV (34.62%) followed by Gold III (26.67%). Hence raised serum ferritin was associated with severity of COPD. When raised serum ferritin was compared statistically according to severity of CO PD.

DISCUSSION

The systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators. As in other chronic inflammatory conditions, weight loss, muscle wasting, hypo-proteinemia and tissue depletion are commonly seen in COPD patients. The severity of COPD is usually assessed as respiratory and systemic expressions of COPD.

Iron is essential for multiple metabolic processes, but it is hazardous in excess amounts because its ability to catalyze the generation of reactive oxygen species that can cause oxidative stress and damage cellular membranes.[12] Ferritin is a specialized iron storage protein that regulates body iron homeostasis and reflects iron stores in the body. Ferritin also can become elevated in the presence of oxidative stress and inflammation irrespective of iron status and can contribute to various clinical diseases, especially pulmonary and cardio-metabolic diseases.[13,14]

Recent studies have suggested that inclusion of patients with clinical disease could distort the magnitude of association between lung function and ferritin. Thus, the exact nature of the relationship between ferritin and lung function, if one exists, remains unclear.[15]

According to GOLD criteria; Gold stage I+II, III and IV was reported among 44%,30% and 26% of the subjects respectively in this study. Khan NA et al.[16] reported that one hundred and forty-seven COPD patients were in GOLD II stage, 104 in GOLD III stage, and 39 were in GOLD IV stage.

Maximum subjects were from the age group of >60 years (57%) followed by 51-60 years (39%). Only 4% of the subjects were from 31-50 year age group in the present study. Severity of COPD increases with increase in age. Mean age in Gold I+II, Gold III and Gold IV was 53.89±6.89, 56.73±7.04 and 60.29±7.24 years respectively with statistically significant difference as p<0.05.

Chung KF et al.[17] and *Celli et al.*[18] has shown in their respective studies that severity of COPD increases with age. Similarly *Shivakumar BG et al.*[19] also showed that age significant increase in the severe and moderately severe COPD group compared to controls. *Sowmya et al.*[20] study reported that BODE index was found to increase with age with the mild group having a mean age of 53.47 years, moderate group 55.00 years and the severe group with
59.93 years as the mean age. *Chambellan et al.*[21] stated that there was a correlation between COPD severity and age.

In the present study, smoking was found in 63% of the subjects. Biomass exposure was reported among 16% of the subjects. Out of 26 subjects in Gold IV category, 23 (88.46%) were having smoking habit while in Gold I+II, out of 44 subjects, 20 (45.45%) were having smoking habit. When smoking habit was compared according to severity of COPD, it was found to be statistically significant as p<0.05. COPD severity also increases along with the increase in smoking pack-years consumption. Mean smoking pack-years in Gold I+II, Gold
III and Gold IV was 8.04±6.94, 16.56±7.01 and 24.77±7.67 respectively with statistically significant difference as p<0.05.

Khan NA et al.[16] found that increase in smoking pack-years is associated with worsened COPD disease severity as assessed by BODE index scores. Studies by *Chung KF et al.*[17] and *Celli et al.*[18] have all proven beyond doubt that higher duration of smoking is associated with severity of COPD. *Sowmya et al.*[20] reported that severity of COPD was significantly associated with the number of pack years of smoking,7.42 pack yrs in mild cases, 15.07 in moderate and 26.90 in severe cases.

Shivakumar BG et al.[19] revealed that there was significant increase in COPD severity inpatients with a higher duration of smoking. The difference was not statistically significant among the control group and those in the mild COPD group. This probably means that the disease could still be reversed with the cessation of smoking.

COPD severity increases along with the decrease in BMI. Mean BMI in Gold I+II, Gold III and Gold IV was 23.09±2.41, 21.18±2.19 and 19.97±2.36 respectively with statistically significant difference as p<0.05.

In a study by *Shivakumar BG et al.*,[19] it was found that the BMI progressively declines with severity among the patients with COPD. *Celli et al.*[18] showed that BMI and BODE index are inversely related. Similar results were observed in a study by *Khan NA et al.*[16] which showed a significant decrease in BMI as the BODE index score increased. *Chambellan et al.*,[21] found a correlation between

COPD severity and BMI, which is similar to our study.

Mean Hb (gm/dL) level in Gold IV, Gold III and Gold I+II was 11.82±1.44, 12.91±1.63 and 14.96±1.27 respectively. When COPD severity was compared according to Hb (gm/dL) level, it was found to be statistically significant as $p<0.01$ in this study.

Anemia in patients with COPD is likely due to a combination of several factors i.e. elevated cytokines levels, especially Tumor Necrosis Factor alpha (TNF α) and interleukin-6 (IL-6).[22,23] Moreover, persistent inflammation may be associated with poor clinical outcome for COPD patients.[24] The elevation of cytokines can lead to reduced production of erythropoietin (EPO), reduced erythropoietic response of the bone marrow to EPO (i.e. resistance to EPO), hepcidin-induced failure of iron absorption from the gut, and hepcidin- induced trapping of iron in iron stores in the macrophages and hepatocytes.[25]

Serum ferritin was found to be raised among 24% of the COPD patients. Maximum raised ferritin level was found among subjects with GOLD IV (34.62%) followed by Gold III (26.67%). Hence raised serum ferritin was associated with severity of COPD. When raised serum ferritin was compared statistically according to severity of COPD, significant difference was found as $p<0.05$. According to Pearson correlation analysis, significant positive correlation ($r=0.29$, $p=0.038$) was found between ferritin level and severity of COPDin this study.

Chan Ho Lee et al.[26] in their study showed positive correlation between serum ferritin levels and lung function parallel the findings of studies that explored iron status in other respiratory diseases. *Sharkey et al*.[27] have demonstrated that the initial serum ferritin levels measured among patients with acute respiratory distress syndrome predicts the development of this syndrome and multiple organ failure. In a study by Jonghoo Lee et al.,[15] hyperferritinemia is significantly associated with decreased FVC% and FEV1%.

The potential limitations of our study were: our study being based in a tertiary care hospital most of our patients were moderate to severe category of COPD and thus might not be reflective of the general population. We did not have a control arm (non-COPD), so we could not comment whether increased ferritin in COPD patients was more common than in general population.

Not-withstanding the limitations, the current study made an earnest attempt to address issues of potential interest in patients with COPD and brought to light a significant relation between serum ferritin in COPD pattern.

CONCLUSION

Hyperferritinemia was associated with severity of COPD because of inflammatory mechanisms independent of iron stores. Future prospective studies will be needed to relation the causality between serum ferritin and lung functions and their role in COPD morbidity.

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