

Anemia as Co-Morbidity in COPD: Comparative Study of Oxidant Anti-Oxidant Imbalance in Anemic and Non Anemic COPD Patients

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ABSTRACT

Introduction: COPD is slowly progressing chronic airway disease. It is known to be associated with co morbidities. Anemia is associated with chronic illnesses. Inflammation, oxidative stress and physical inactivity in COPD may contribute to anemia. The aim of the present study was to compare oxidant antioxidant imbalance in anemia and non anemic COPD patients.

Material and Methods: 336 COPD patients were enrolled in the present study. They were divided into anemic (n=168) and non anemic (n=168) groups on the basis of hematological parameters namely MCV (femtolitres), MCHC (%) and Hb (gm/dl) using automated analyzer.

Results: Overall the mean age of anemic and non anemic COPD group was 46.63±14.26 and 40.89±13.38 yrs respectively (p<0.001). Significant difference was found between mean Hb, MCV and MCHC between two groups. On the basis of severity of disease in anemic COPD group there was significant difference in Hb in mild, moderate and severe/very severe COPD group. Non significant differences were found in MCV, MCHC in same group. Similar results were found in non anemic mild, moderate, severe/very severe COPD groups. In both anemic and non anemic COPD groups significant difference was found in Hb and MCHC in both males and females.

Conclusion: There is oxidant antioxidant imbalance which is more in anemic COPD patients. Anemia is present as co morbidity in COPD and it is likely to influence the therapeutic outcome of the disease. Presence of anemia negatively influences the quality of life of patients. Thus it is important to identify anemia in COPD patients.

Keywords: Chronic Airway Disease, Anemia of Chronic Disease, Extrapulmonary Manifestations of COPD, Co Morbidity in COPD

INTRODUCTION

COPD is slowly progressing irreversible airflow limitation. The Airflow Dysfunction is usually progressive, associated with an abnormal inflammatory response of the lungs to noxious particles or gases.¹ Anemia is known to be associated with chronic illnesses. Around 10-30% of COPD patients are anemic.² Mechanism of anemia in COPD is not very well understood. Systemic inflammation, tissue hypoxia, oxidative stress and physical inactivity may be the contributory factors.³ Mediators of inflammatory response like Tumor Necrosis Factor α (TNF α), IL-6 and Interferon γ (IFN γ) play an important role in anemia as systemic manifestation in COPD.⁴

The prognosis and treatment outcome of COPD may depend upon the associated co morbidities. Usually the prognosis of COPD is poor in patients having low levels of Hemoglobin.⁵⁻⁷ Similarly, readmission rates of COPD patients with anemia are higher.⁸ In COPD there is inflammation and Oxidant Antioxidant imbalance is known to be associated with COPD.⁹ Oxidative stress leads to inflammation which also have potential

role in causing anemia. Anemia in COPD may lead to impaired exchange of gases, reduced availability and supply of oxygen to the muscle. These all are detrimental to the health of patients suffering from COPD.

The aim of the present study was to compare oxidant antioxidant imbalance in anemia and non anemic COPD patients. To the best of our knowledge very few studies of this kind are available.

MATERIAL AND METHODS

The present study was case control study. It was conducted in the Departments of Physiology and TB and Chest Diseases, IIMS&R, Integral University, Lucknow. The period of study was from April 2016-May 2017. Three hundred and thirty six subjects (both Anemia and Non Anemic COPD Cases) were enrolled in the present study. Diagnosed cases of COPD were taken from OPD of TB and Chest Diseases IIMS & R, Integral University, Lucknow. The study was approved by Institutional Ethics Committee.

Inclusion criteria

- COPD patients attending TB and Chest Diseases OPD. Patients (18-70 years of age) from various OPDs of IIMS&R.
- Patients with dyspnea, chronic cough/sputum for at least three months for two consecutive years.
- Patients with FEV1 less than 70 per cent of the predicted.
- Patients with FEV1/FVC ratio less than seventy per cent
- Patients with history of exposure to risk factors of COPD like smoking, exposure to biomass fuel.
- Subjects diagnosed with COPD were grouped into Anemic and Non Anemic group as per hematological profile: Hemoglobin (gm/dl), MCV(fl) and MCHC(%). The grading of anemia was done as per the WHO criterion.¹⁰

Exclusion criteria

The following subjects were excluded from the study:

- Subjects not giving consent
- Non COPD subjects, pregnant female, liver cirrhosis patients, renal failure patients
- Subjects with history of Diabetes Mellitus, Bronchial Asthma, Subjects having any chronic disease other than

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How to cite this article: Shah Mohammad Abbas Waseem, V K Srivastava, Rubeena Bano, Seema Singh, Homnath Dhunagana. Anemia as co-morbidity in COPD: comparative study of oxidant anti-oxidant imbalance in anemic and non anemic COPD patients. International Journal of Contemporary Medical Research 2017;4(6):1223-1227.

COPD, Subjects having undergone any recent surgery or blood loss.

Under aseptic precautions and prior consent of the subjects, venous blood was collected in anticoagulant vials from the peripheral veins. Hb (gm/dl), MCV (fl) and MCHC(%) were analyzed using automated analyzer. The serum was subjected to estimation of MDA(Malondialdehyde nmol/ml) using method of Philpot.¹¹ Antioxidant enzymes namely Catalase(units/mgm of serum proteins) was estimated by the method of Aebi¹², Glutathione Peroxidase (nmol NADPH oxidized/min/mgm of serum proteins) by the method of Paglia and Valentine¹³, Superoxide Dismutase (units/mgm of Serum Proteins) by method of McCord and Fridovich¹⁴ respectively.

STATISTICAL ANALYSIS

Data was analyzed using SPSS 21.0(Statistical package for social sciences 21.0). The data was expressed as Mean \pm S.D. Data was analyzed by applying chi square, unpaired t test and ANOVA. Pearson Correlation was used to find the correlation of MDA with Antioxidant Enzymes, Hb, MCV and MCHC. Correlation of BMI with Hb was also analyzed using pearson correlation. P value less than 0.05 will be taken as statistically significant.

RESULTS

Overall the mean age of anemic and non anemic COPD group was 46.63 \pm 14.26 and 40.89 \pm 13.38 yrs respectively ($p < 0.001$). Significant difference was found between mean Hb, MCV and MCHC between two groups. On the basis of severity of disease in anemic COPD group there was significant difference in Hb in mild, moderate and severe/very severe COPD group. Non significant differences were found in MCV, MCHC in same group. Similar results were found in non anemic mild, moderate, severe/very severe COPD groups. In both anemic and non anemic COPD groups significant difference was found in Hb and MCHC in both males and females. The antioxidant enzymes namely SOD, Catalase and GPx were significantly lower in anemic COPD group and compared to non anemic

COPD group. MDA was significantly higher in former group as compared to latter group. Overall MDA correlated negatively with Antioxidant enzymes and hematological markers. BMI correlated negatively with Hb in both male and female subjects (tables 1-4). Overall in Anemic COPD group 90(53.57%) and 78(46.43%) were male and female respectively. In non anemic group males and females were 120(71.43%) and 48(28.57%) respectively. Chi Square show $p = 0.001$ (value 11.429, df 1). Out of 90 male anemic patients 58(64.45%), 27(30%) and 05(5.55%) suffered from mild, moderate and severe anemia respectively. Out of 78 female anemic patients 24(30.77%), 44(56.41%) and 10(12.82%) had mild, moderate and severe anemia. Chi Square show $p < 0.001$ (value=19.075, df=2) (table-1). Unpaired t test show p significant at < 0.05 . Pearson correlation shows negative correlation of BMI with Hb in males ($r = -0.243$, $p = 0.04$) and females ($r = -0.114$, $p = 0.71$) (table-2).

DISCUSSION

In the present study in anemic COPD group, mild and moderate anemia was found in males and females respectively. Mild anemia was found to be more prevalent in study done by Casanova L C et al.¹⁵ Moderate anemia in females can be explained on the basis that menstrual irregularities may exist in females. Menstrual history of females was not included in the present study. Correlation between menstrual irregularities and anemia has been reported in females.¹⁶ In our study we found significant difference between age of anemic and non anemic COPD group. Similar trend was observed in a study done previously by Zavarreh RH et al.¹⁷

COPD is a slowly progressive chronic disease. Advancing age is an important identifiable risk factor associated with COPD.¹⁸ Inflammation is implicated in the pathophysiology of COPD and also there exists correlation between anemia and inflammation present in chronic diseases.¹⁹

In our study the levels of MCV and MCHC were within normal limits in anemic COPD group. Thus anemia of chronic disease was present in the patients. Normocytic normochromic anemia have been reported in COPD illnesses.²⁰ The results are similar

Variable	Anemic COPD Group(n=168)			Non Anemic COPD Group(n=168)		
	Males(n=90)	Females(n=78)	P value	Males(n=120)	Females(n=48)	P value
Age	47.88 \pm 14.47	43.50 \pm 13.35	0.01*	43.19 \pm 14.56	38.25 \pm 11.41	0.01*
BMI(Kg/m ²)	22.19 \pm 2.58	19.46 \pm 2.56	NS	22.85 \pm 2.73	19.99 \pm 2.16	NS
Hb(gm/dl)	12.03 \pm 6.06	9.82 \pm 1.50	0.002*	14.39 \pm 1.60	13.60 \pm 0.73	<0.001*
MCV(fl)	84.03 \pm 5.35	83.09 \pm 4.71	0.228	86.62 \pm 4.83	85.27 \pm 5.39	0.13
MCHC(%)	32.84 \pm 2.5	31.96 \pm 2.13	0.015*	33.48 \pm 2.26	31.95 \pm 1.86	<0.001*

Table-1: Anthropometry and Hematological data of anemic and non anemic COPD group

Variable	Anemic COPD Group	Non Anemic COPD Group	P value
Age	46.63 \pm 14.26	40.89 \pm 13.38	<0.001
Hb	11.01 \pm 4.67	14.03 \pm 1.51	<0.001
BMI(Kg/m ²)	19.37 \pm 2.18	21.97 \pm 2.94	<0.05
MCV(fl)	85.66 \pm 5.26	83.53 \pm 5.02	<0.001
MCHC(%)	32.43 \pm 2.36	33.05 \pm 2.26	0.015
MDA(mmol/ml)	5.29 \pm 0.75	3.89 \pm 0.55	<0.001
SOD(units/mgm of serum proteins)	10.65 \pm 0.50	11.78 \pm 0.45	<0.001
Catalase(units/mgm of serum proteins)	12.26 \pm 0.45	13.05 \pm 0.83	<0.001
GPX(nmol NADPH oxidized/min/mgm of serum proteins)	58.99 \pm 1.22	62.03 \pm 1.69	<0.001

Table-2: Differences between anemic (n=168) and non anemic (n=168) COPD groups

Variable	Anemic COPD group				Non Anemic COPD Group			
	Mild (n=82)	Moderate (n=71)	Severe and Very Severe COPD (n=15)	P value ANOVA	Mild (n=104)	Moderate(n=44)	Severe and Very Severe COPD (n=20)	P value ANOVA
Age	44.43 ±13.62	46.66 ±13.81	48.52 ±14.76	0.21	34.72±12.40	40.45 ±8.92	43.60 ±13.71	<0.001
Hb*	11.91± 0.64	9.87± 0.94	7.4 ±0.47	<0.001	13.29±0.84	13.47± 0.96	14.42± 1.67	<0.001
MCV	83.43 ±5.09	83.27 ±4.92	85.33 ±5.14	0.345	85.36±5.30	85.88 ±5.29	86.25 ±5.20	0.633
MCHC	32.79 ±2.63	32.13 ±2.04	31.85 ±2.05	0.138	33.36±2.27	32.52 ±2.10	32.59 ±2.31	0.073
Pack Years	16.74±4.14	25.99±7.50	31.88±8.56	<0.05	12.23±1.07	14.33±6.75	16.89±2.34	Non Significant

Table-3: Differences in Anemic and Non Anemic Groups on the basis of severity of COPD

Parameter	r	P Value
SOD	-0.557	<0.001
Catalase	-0.356	<0.001
GPX	-0.535	<0.001
Hb	-0.476	<0.001
MCV	-0.126	0.02
MCHC	-0.028	0.615

Table-4: Correlation of MDA with Antioxidant Enzymes, Hb, MCV and MCHC

to study done earlier which have shown elevated MCV and low MCHC levels in COPD groups.²¹

The mean Hb in anemic and non anemic COPD groups in our study was found to be 11.01± 4.67 and 14.03 ±1.51gm/dl respectively. The results are in contrast with the study done by Attrian D et al, who found higher levels of Hb. The results can be attributed to various factors like the cut off limits for anemia used, sample size and also due to fact that majority of cases in the mentioned study were of severe COPD. With severity of disease it is expected that erythropoietin will increase but at the same time there is resistance to erythropoietin.²² The interplay of various factors like increase in prevalence of anemia with advancing age, no clear cut value to define anemia in post menopausal women and presence of relative anemia pose challenge as far as determining anemia using haemoglobin is concerned.²³ The interplay between stimulatory effects of hypoxia and suppressing effects of inflammation on erythropoiesis determines the haemoglobin levels.²⁴

Another factor to consider is that hypoxia induced EPO (Erythropoietin) increases the RBC life span by inhibiting apoptosis and at the same time it inhibits hepcidin which results in increase release of iron liver cells. All these factors may result in elevated Hb levels. This may be possible explanation for elevated Hb levels in non anemic COPD group in our study. The Hb is more in group with severe /very severe COPD.²⁵

In our study patients belonging to moderate and severe/very severe COPD were more. Inflammation is expected to be more as disease advances. This may be the reason why in spite of hypoxia expected with disease severity the levels of Haemoglobin are low in severe/very severe COPD group in our study. Studies have shown that anemia is more common in patients having severe COPD.²⁶ In the present study the pack years of anemic COPD group was more as compared non anemic COPD group. In cigarette smoke oxidants and free radicals are present in large quantities which in turn induce inflammation and alter repair mechanisms.¹⁸ On the other hand as a compensatory mechanism

for elevated levels of carboxyhaemoglobin in smokers the levels of Haemoglobin are raised.²⁷ Thus it is expected that with increase in smoking severity the levels of Hb should rise. But both in anemic and non anemic COPD group with increase in pack years the levels of Hb are not raised. In former group the Hb levels are less whereas in latter group the Hb is within normal limits. The reasons for this occurrence can be attributed to the dual effect of inflammation and hypoxia on Hb levels.²⁸ Erythrocytes on account of high concentration of oxygen and haemoglobin are prone to oxidative damage. Endogenous antioxidant enzyme systems like superoxide dismutase, catalase and glutathione peroxidase provide protection against oxidative stress. Vasodilatation and endothelial cell growth is altered in oxidant anti oxidant imbalance. NF KB upregulates the inflammatory cytokines which in turn results in emphysema formation.²⁹ In our present study the pack years of anemic COPD group was more than non anemic COPD group. It is worth mentioning that TNF α is implicated in the pathogenesis of anemia. Interestingly, it is a mediator of chronic inflammation and is found to be elevated in smokers.³⁰

In our study the antioxidant enzymes namely SOD, Catalase and GPx were significantly lower in anemic COPD group and compared to non anemic COPD group. Similarly, MDA (indirect marker of free radicals) was significantly higher in former group as compared to latter group. Overall MDA correlated negatively with Antioxidant enzymes (SOD, Catalase and GPx) and haematological markers (MCV and MCHC). The results can be attributed to presence of lethal triad i.e. smoking, inflammation and oxidative stress which increases the susceptibility to anemia as is evident from the results. The RBC are prone to oxidative damage in blood which may trigger the production of antibodies which in turn may result in autoimmune disease.³¹ In recent years there scientists and researchers are of view that autoimmunity may have a role in COPD.³²⁻³⁵

In the present study BMI correlated negatively with Hb in both male and female subjects. The mean BMI of anemic COPD subjects was less as compared to non anemic COPD subjects. Weight loss in COPD may be attributed to increase levels of TNF α . Low BMI can also be due to various reasons like catabolic energy state, high daily energy expenditure, increased work of breathing and above all the inflammation.³⁶ Interestingly, inflammation is also implicated in anemia in chronic inflammatory diseases like COPD.⁴ This may possibly explain the inverse relation of BMI with Hb in our study. Studies have shown that there is association between BMI and anaemia and anaemia decreases with increase in nutritional status.³⁷ Both

anemia and BMI are important prognostic markers in COPD. There is correlation between prognosis, mortality and BMI in COPD.³⁸

Nutritional deficiency in COPD may also contribute to anemia. There are multiple possible reasons for anemia in COPD. It is actually a two way sword and throws open an important research question i.e. whether anemia increases the severity of COPD or whether anemia is more common in severe COPD.²⁹

The exact mechanism of anemia in COPD remains elusive. But its concomitant occurrence in COPD negatively influences the disease outcome. It influences not only the treatment, management and prognosis but also alters quality of life. Thus it is important that assessment of anemia should be done routinely in COPD patients attending clinics.

CONCLUSION

Anemic COPD patients have altered Hemoglobin, MCV and MCHC levels. It may be due to interplay of multiple factors.

Limitation

Identification of factors associated with anemia will yield better results. Identification of exact cause of anemia or mechanism was beyond the scope of present study. Correlation of severity of disease with hematological parameters will yield better results.

ACKNOWLEDGEMENT

Authors wish the participants a happy disease free healthy life.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 12-05-2017; **Accepted:** 03-06-2017; **Published:** 24-06-2017