IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 9 Ver. IV (Sep. 2017), PP 14-18
www.iosrjournals.org

Role of Oxidative Stress in COPD. Can We Use A Novel Biomarker to Measure It?

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Abstract : *Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable disease characterized by persistent respiratory symptoms and airway narrowing. It has been predicted by the WHO to become the 3rd leading cause of death by 2030. The chief pathogenesis at play involves an imbalance of oxidants and anti-oxidants, a term called "oxidative stress". Ischemia Modified Albumin (IMA) is a novel biomarker shown to be elevated in various states of ischemia and oxidative stress. This study was done with the aim of determining the association between IMA and COPD and also its associated factors. A cross sectional study was done on 20 consecutive patients hospitalized with COPD. The control group encompassed 20 apparently healthy volunteers. Serum samples were obtained from both groups and the levels of IMA were determined using the Albumin Cobalt-binding test. In addition, patient information was obtained from records pertaining to various covariates. On analysis, Serum IMA was very significantly reduced in patients with COPD compared to the control group {0.3068 ± 0.09924 vs 0.5908 ± 0.1351} with a p-value of < 0.0001. There was also found to be a positive correlation between the levels of IMA and the degree of smoking thereby reinstating that IMA rises with an increased exposure to smoking.(correlation coefficient r=0.6671, 95% CI:0.2561 to 0.8738, p<0.01). This study thus shows that there is some altered oxidative pattern in patients with COPD. Also, the correlation with smoking makes for a possible marker to measure the levels of oxidative stress. We recommend further large scale studies using more specific methods like ELISA to determine the exact nature of this association.*

Keywords : *COPD, Ischemia Modified Albumin, Oxidative stress, Smoking Index,*

Date of Submission: 29 -08-2017 Date of acceptance: 13-09-2017

I. Introduction

Chronic Obstructive Pulmonary Disease (COPD) has been defined as a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[1]. The World Health Organization predicts COPD to become the 3rd leading cause of death by 2030[2]. The chief risk factor for COPD worldwide is cigarette smoking. Exposure to smoke from biomass fuels, dusts and chemicals are also important risk factors in developing countries[1]. In COPD the chief pathogenesis involves an imbalance of oxidants and antioxidants – a term referred to as oxidative stress[3]. The source of these oxidants maybe endogenous as from various metabolic cycles in the body or exogenously derived from exposure of the lungs to cigarette smoke or pollutants[3-5]. The subsequent inflammatory response causes the release of Reactive oxygen species bringing about the tissue damage[5]. Ischemia Modified Albumin (IMA) is an emerging novel biomarker that has been shown to be elevated in various states of ischemia and oxidative stress such as Myocardial Infarction, Cerebrovascular accidents, obstructive sleep apnea, diabetic retinopathy and sepsis[6-10]. The aim of this study is to estimate the level of IMA in patients with COPD in comparison with a control group. In addition, we want to correlate the level of IMA with the degree of exposure to cigarette smoking. We propose to do this by correlating IMA levels with the Smoking index (S.I) which is a parameter use to express cumulative smoking exposure quantitatively[11].

I.

II. Materials and methods

The study was carried out after obtaining institutional ethics committee clearance. The study period was for four months from March to June 2017. This study is a cross-sectional study on 20 patients (17 males and 3 females) and 21 controls (18 males and 3 females). The study subjects included 20 consecutive patients in the

age range of 18-80 years clinically diagnosed with COPD by a certified Respiratory medicine specialist from the Department of respiratory medicine.

Patients with conditions such as diabetes mellitus, hyperlipidemia, history of coronary artery disease, history of stroke and history of chronic liver disease which were known to alter serum IMA levels, and those with extremes of age (below 18 and above 80) were excluded from the study. 21 apparently healthy human volunteers were used as the control group for this study.Serum was separated from 5ml of venous blood drawn from the subjects within 24 hours of admission. The samples were stored at -80^{o}C. The Albumin Cobalt Binding Test was then used to measure serum IMA. The whole procedure was scaled down to be done on microtitre plates.The Albumin Cobalt Binding Test was used to estimate the serum IMA. The principle behind the test is that the sample containing IMA will not bind to cobalt as efficiently and hence there will be more free cobalt ions. The IMA can thus be indirectly measured by the free cobalt in the solution. On a microtitre plate, 10 µL of cobalt chloride solution (1g/L) was added to 40 µL of patients serum followed by vigorous mixing. This was then incubated at room temperature for 10 mins. Then 10 µL of Dithiothretol solution (1.5 g/L) was added to the above and vigorously mixed again. The Dithiothretol is a binder of free cobalt and can thereby be used as an indicator of free cobalt. Finally 200 µL of sodium chloride solution was added to the sample. The blank solution was similarly prepared by excluding the step involving the Dithiothretol. A Gilford spectrometer was then used to read the IMA values at 470nm[7]. The IMA values were recorded in Absorbance units (ABSU). The IMA was measured for both the Test solution and the controls.

The relevant patient data such as age, gender and smoking history were collected from the patient charts. Age was measured in completed years. Smoking history was measured in number of cigarettes consumed per day into the number of years smoked. Also the values of ESR and Total leucocyte counts were obtained from the patients case records of laboratory work up within 24 hrs of admission to check for any correlation with the level of IMA. Statistical analysis was done using Medcalc software Version 12.7. Student t-test was used to compare the levels of IMA in the test and control groups. Significance was established if the p-value was < 0.05. The Correlation coefficient test was used to analyze the correlation between the various parameters done in the study and the coefficient 'r' and p-values were determined. Tables and graphs were used to express the data.

III. Results

The study was conducted on 20 patients with COPD in the age range of 18 to 80 years. Of the study subjects 16 were smokers, 2 had exposure to biomass fuel and 2 were non-smokers. The control group had 21 apparently healthy adults in the age range of 18 to 80 years. Serum IMA was very significantly reduced in patients with COPD compared to control group {0.3068 ± 0.09924 vs 0.5908 ± 0.1351} with a p-value of < 0.0001. Figure 1 is a dot and plot graph superimposed on the mean IMA values which clearly show the Decreased IMA levels in the test subjects. The correlation between Serum IMA levels and smoking index in COPD patients was done. There was found to be a positive correlation of IMA with an increased exposure to smoking (correlation coefficient $r=0.6671$, 95% CI: 0.2561 to 0.8738, $p<0.01$). Figure 2 is a scatter plot demonstrating the positive correlation between the smoking index and IMA levels.
There was no correlation between IMA and ESR or Total Leucocyte count.

II. Discussion

Ischemia modified albumin is a form of albumin modified by oxidative stress. The N-terminal end of the albumin molecule normally binds metallic ions such as cobalt[12]. Ischemia or oxidative stress is hypothesized to induce changes in the N-terminal end via the production of reactive oxygen species generating hydroxyl free radicals thereby modifying the N Asp–Ala–His–Lys sequence, resulting in a decreased ability to bind these ions[13].In our study, there was a significant decrease in serum IMA values in patients with COPD as compared to the controls. This was not in line with what is expected as COPD is a state of altered oxidative stress[14]. Other studies on the levels of IMA in COPD showed a rise in serum IMA with COPD. Can et al. discovered that serum IMA, ox-LDL and total oxidant status (TOS) were significantly increased in patients with COPD compared with healthy control subjects[15]. Also, a study by Kuang-Yao Yang et al., showed a significant correlation between the severity of COPD as per GOLD criteria and increased serum concentrations of oxidative parameters such as IMA[16].

Although there are currently no definite studies explaining the pathophysiology of the reduced levels of IMA, one possible explanation for the decreased IMA can be postulated from the following study by Roy D et al. They found the IMA levels to be decreased in patients immediately following exercise-induced skeletal muscle ischemia. This was explained by a rise in lactate which can affect the measurement of IMA. There could be similar factors at play in our study. The low IMA values in our study could also be due to different mechanisms of oxidant stress in Ischemia and in COPD. This calls for further evaluation with regard to other

substances that can interfere with accurate IMA measurement[17]. Another reason could be that patients hospitalized with COPD are usually those with acute exacerbations and are associated with hypoalbuminemia that could have falsely given a low IMA value[18,19]. Thus, more studies must be done to assess IMA in COPD preferably by correcting for altered albumin levels. The IMA/Albumin ratio can be used for that purpose, as evidenced by studies conducted on liver disease patients[20].

COPD severity as assessed by GOLD criteria using values of FEV1 and FVC may indicate the extent of the damage caused by the disease on the entire body, but it does not precisely indicate the cumulative damage caused by smoking. It has been well known by the physiology of breathing tests that they depend on a lot of other patient factors like nutritional status and muscle mass. Patients with COPD often have multiple organ system dysfunctions. Disease stratification plays an essential role in all levels of management from patient counselling to treatment and in determining the level of care[21,22].It is therefore important to ascertain the damage caused by smoking. We suggest using the IMA as a measure of the cumulative damage caused by smoking. The severity of COPD correlates with the degree of smoking and hence a method to determine smoking severity can go a long way in preventive strategies. Smoking is the actual disease as COPD rarely exists without smoking[23]. In our study we found a positive correlation between the smoking index and levels of IMA. The Smoking Index is especially useful in defining risk ratio of a smoking related disease and is more suitable in Indian subjects. S.I= No. of cigarettes/bidis per day x total duration(yrs) [11]. There are innumerable toxic agents in tobacco smoke that cause free radical damage and alveolar insult. This could be from the fact that cigarette smoke damages the mitochondrial network and induces fragmentation depending on the level of oxidative stress. [24] With long term smoking and thereby increased exposure to oxidative stress, there is bound to be less available functionally active mitochondria to neutralize the oxidant imbalance consequentially leading to significantly higher IMA levels in smokers[25].

Smoking is associated with alteration in the free radical systems in our body. It not only accelerates Reactive oxygen species production, but also weakens the free radical defenses. Several inflammatory biomarkers like serum malondialdehyde (MDA) and paraoxonase (PON1) are elevated in smokers showing an altered Free radical biomechanism. But cost and feasibility of assaying them have always been issues with such biomarkers. Studies have also shown that the impaired oxidative burst mechanisms have significant implications in treatment. It is also seen that current treatment modalities do not effectively prevent chronic airway inflammation[26,27]. Therefore, the need to educate patients on smoking cessation is paramount. Cessation of smoking brings about a reduction in the oxidative stress and thereby the risk of various diseases. Thus, IMA can be investigated as a potential biomarker that can help determine the prognosis and pathophysiological changes caused by years of smoking in COPD pateints.

Figures And Tables

Figure 1: Graphical representation of IMA levels in the test group and the control group

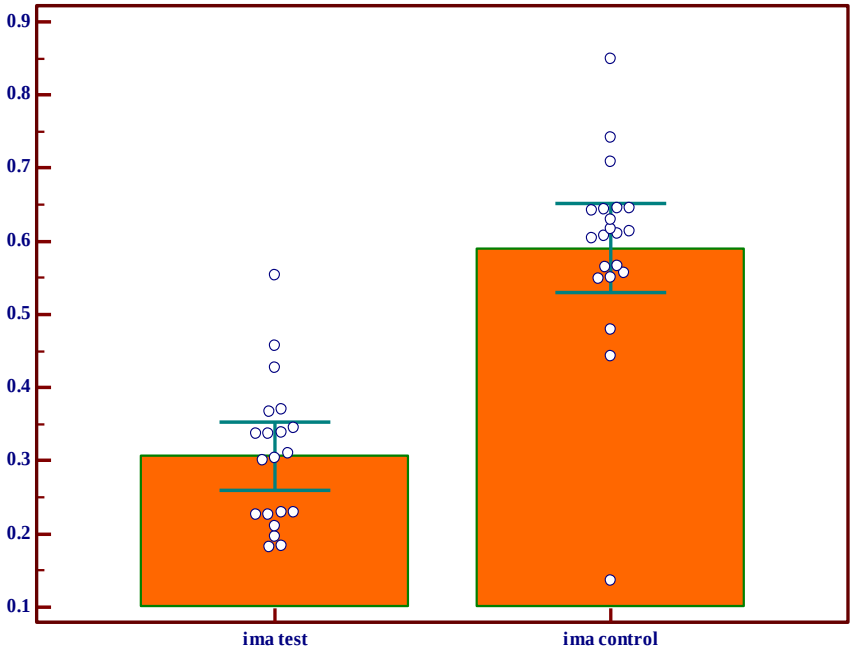
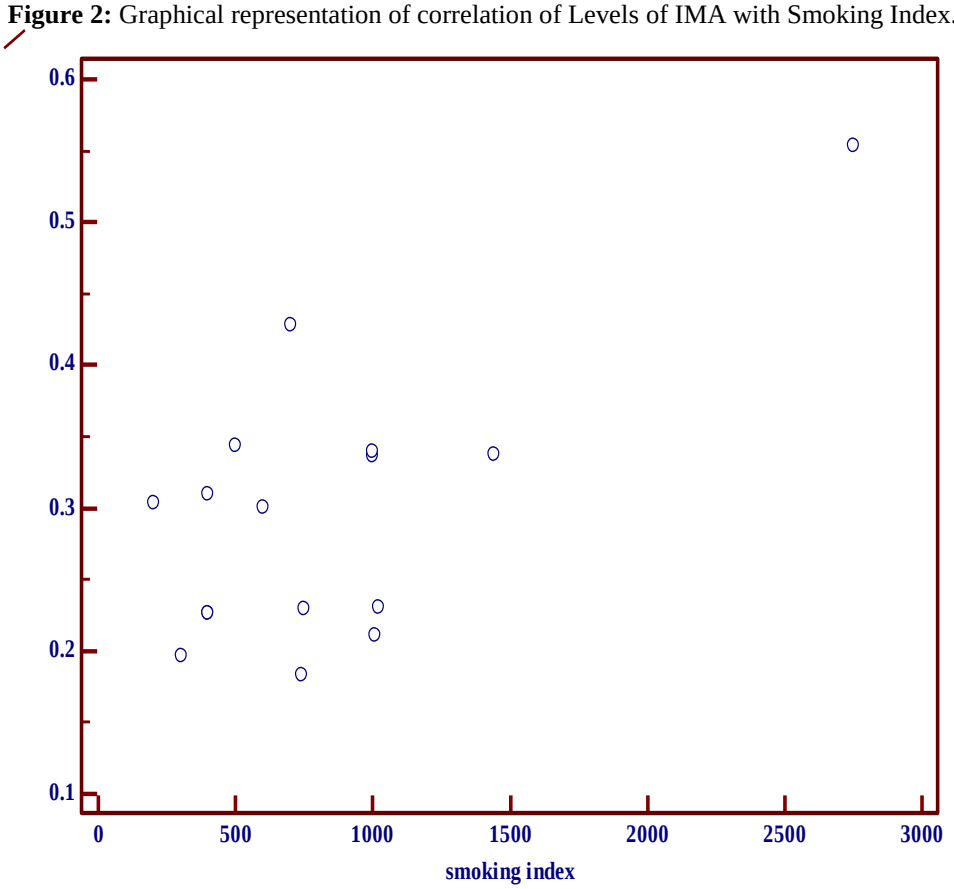


Figure 2: Graphical representation of correlation of Levels of IMA with Smoking Index.



IV. Conclusion

This study shows that there is indeed an alteration in the levels of IMA in patients with COPD. This goes on to show that there is an altered oxidative stress pattern in patients with COPD. It has also been proven that the level of Ischemia Modified has a positive correlation with smoking. Thus, IMA has a potential to be used as a biomarker that can help to determine the cumulative oxidative stress caused by smoke inhalation in COPD patients

Our study does have some limitations. Of notable mention is the small sample size and the location at a tertiary care center. There is a possibility that only patients with more severe forms of the disease present to the tertiary center. This could skew the results. These discrepancies can only be sorted out with larger sample size community based studies. Also, more specific methods to detect the IMA such as ELISA kits, and IMA/Albumin ratio can be utilized in further studies to determine the exact nature of IMA alteration in COPD.

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*Shweta Paulraj. "Role of Oxidative Stress in COPD. Can We Use A Novel Biomarker to Measure It?" IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.9 (2017): 14-18