EVALUATING A NEW MARKER IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE. THE ISCHEMIA MODIFIED ALBUMIN PARADOX

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Abstract—Chronic Obstructive Pulmonary Disease (COPD) is a complex multisystem disorder characterized by inflammatory obstruction of the small airways as in chronic bronchitis or inflammatory destruction as in emphysema. Smoking is the main etiological factor causing COPD. Tobacco smoke causes oxidative stress and free radical damage which is central to the pathogenesis of COPD. Ischemia Modified Albumin (IMA) is a new and an upcoming biomarker that has shown be an excellent marker to quantify oxidative stress and end organ ischemic damage. The aim of our study is to estimate the levels of IMA in patients with COPD and analyze its clinical implications. The test subjects comprised of 20 patients with clinically diagnosed COPD. The control group had 20 apparently healthy individuals. Serum IMA was estimated by the Albumin Cobalt Binding (ABT) Test and represented in Absorbance Units (ABSU). Serum IMA in COPD patients (0.1054±0.0365) was significantly lower than that of the control group (0.2684±0.1103) with a p value of <0.0001. This shows that patients with COPD have altered ischemic status. While other studies evaluating IMA in pathological states associated with ischemic damage like heart failure and diabetes showed a rise in IMA levels, our study demonstrated that IMA levels were low in COPD. This emphasizes the need to carry out further research with regard to IMA and COPD.

Index Terms—Biomarker, Chronic Obstructive Pulmonary Disease, Ischemia Modified Albumin, Oxidative stress.

I. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a broad term which encompasses Chronic Bronchitis and Emphysema. COPD is a major cause of morbidity and mortality worldwide and according to World Health Organizations (WHO) predictions, COPD will be the third leading cause of death by 2020 [1]. It is characterized by gradually progressive and irreversible airflow obstruction. Smoking is the single most important etiological factor associated with COPD. Other factors like occupational exposure also seem to play a role [2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria uses post-bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) to stratify patients with COPD. While this appears practical and easy, this method appears to overestimate COPD in older individuals and underestimate it in younger individuals [3]. There is also a question on the suitability of post-bronchodilator values especially while it is being used for research purposes [4]. Thus there is a dire need to identify new strategies that can accurately grade the severity of COPD. Ischemia Modified Albumin is an upcoming biomarker with proven utility to detect end organ ischemic damage and oxidative stress. It is a conformational modification of the albumin molecule characterized by decreased affinity to cobalt ions, produced in the serum in response to ischemic damage. It has been approved by the Food and Drug Administration (FDA) for use in Cardiac Ischemia [5]. To the best of our knowledge there is no study highlighting the role of IMA in COPD. Oxidative stress is central to the pathogenesis of COPD as it is the triggering factor that causes either excess mucus production or bronchial wall destruction [6]. By studying IMA in COPD, we will be evaluating a marker that could possibly be used to quantify oxidative stress in this condition. Thus our work aims to study the levels of IMA in patients with COPD and highlight its clinical significance.

II. MATERIALS AND METHODS

This study was conducted after obtaining ethical approval from institutional Human Ethics Committee of PSG Institute of Medical Sciences and Research. The study period was for one month. 20 patients with COPD and 20 apparently healthy human volunteers as controls participated in the study. Patients who were clinically diagnosed as COPD were included. Patients with clinical conditions which are known to alter serum IMA levels namely, renal disease, diabetes mellitus, heart failure, sepsis, pulmonary embolism and cerebrovascular accidents were excluded. Control group included people who showed no clinical signs of any disease undergoing routine check-up. 5 mL of venous blood sample was collected from the subjects and serum was separated. Serum samples were stored at -20°C if not processed immediately. Serum IMA was estimated using the Albumin Cobalt Binding (ABT) Test. The test is based on the principle that a sample containing IMA will bind less cobalt and hence will have more free cobalt ions. Measuring the free cobalt is an indirect method to quantify IMA. To 200 µL of
patients serum 50 µL of cobalt chloride solution (1 g/L) was added followed by vigorous mixing and incubated for 10 minutes at room temperature. 50 µL of Dithiothreitol solution (1.5 g/L) was added followed by vigorous mixing and 2 minutes of incubation in room temperature. Dithiothreitol binds to cobalt and thus is a selective indicator of free cobalt. The last step involved adding 1 mL of normal saline to the sample. The blank was prepared similarly by excluding Dithiothreitol. The solution was read in a Gilford spectrometer at 470 nm and IMA values were recorded in Absorbance units (ABSU) [7]. Students’ t test was used for statistical analysis.

III. RESULTS

We conducted our study on 20 patients with COPD of which 17 were males and 3 were females. The age range of the test subjects was 18 to 80 years. The control group comprised of 20 apparently normal individuals comprising of 8 males and 12 females with an age range of 28 to 75 years.

The level of IMA in patients with COPD (0.1054±0.0365) was significantly lower than that of the control group (0.2684±0.1103) with a p value of <0.0001, which is highly significant. Fig. 1 is a Dot and plot graph representing the IMA levels of the test and the control group. It is obvious that patients with COPD had significantly lower values than normal individuals.

IV. DISCUSSION

Tobacco smoke contains innumerable toxic agents that causes free radical damage and alveolar insult in the lungs. Free radicals that are involved in the pathogenesis of COPD include superoxide dismutase, nitric oxide, N2O, α-β unsaturated aldehydes, alkyl, alkoyl and peroxyl free radicals [8]. Most cigarette smokers have some inflammation in their lungs, but those who develop COPD have an amplified response to the inhaled toxic agents which results in mucous hyper secretion in chronic bronchitis or tissue destruction as in emphysema. COPD besides being a significant cause of mortality and morbidity worldwide, presents a significant diagnostic challenge to health care workers. The main reason for this difficulty is its clinical resembles to Bronchial asthma and the lack of proper tools for its diagnosis. Though lung function tests are commonly used for its diagnosis, there is a huge variability in the parameters in the general population. It is also not sensitive for small airway abnormalities occurring in early COPD [9]. A study conducted in Europe shows that 25 to 50 % of COPD cases are under diagnosed. COPD is a complex multisystem disorder and the lack of early management will result in other systemic complications like cor pulmonale, osteoporosis and depression [10].

IMA is a structurally modified form of albumin shown to be elevated in various pathophysiological states associated with end organ ischemic damage like coronary artery disease, sepsis, diabetes mellitus and liver cirrhosis. A study conducted in patients with pulmonary embolism showed that IMA is high in such patients and can be used as an alternative to D-dimer [11]. IMA has also been shown to be elevated in carbon monoxide poisoning [12]. In a normal albumin molecule, a couple of cobalt or copper ions are bound to the N terminal end. Due to some unknown structural alteration triggered by ischemia the metal ions fail to bind to the N terminal end in IMA. This is the principle of ABT test used to estimate IMA [5], [7].

In our study, on analyzing the serum IMA in patients with COPD, it was found that IMA values were significantly reduced compared to normal individuals. This finding was in stark contrast to what was anticipated as one would expect IMA to be elevated as a result of increased oxidative stress. A study was conducted to evaluate IMA in peripheral vascular disease and skeletal muscle ischemia. It was found that IMA levels decrease immediately after muscle ischemia and returns to baseline after sometime. It was hypothesized that production of lactate interferes with estimation of IMA resulting in lower values [13]. A similar event could have occurred in our case. IMA value may be low due to production of lactate or some other unknown factors. The low value may also be due to a difference in the underlying pathophysiological and molecular mechanisms responsible of ischemic insult in different conditions and in COPD. This entails that further evaluation is required in this particular area and on the activity of IMA in varied conditions.

To our knowledge, this is the first study evaluating the role of IMA in COPD. The study highlights that IMA is significantly altered in COPD implying an altered ischemic and oxidative status. Further research if done could probably give IMA a clinical...
role in this condition. Correlating IMA levels to Arterial blood gas and spirometry values can be done to see if IMA correlates with the disease severity. Also IMA can be analyzed with respect to the course of the disease.

CONCLUSION

This is the first study to evaluate IMA in patients with COPD. The IMA levels in patients with COPD was significantly low compared to healthy controls. The exact cause for the decreased IMA levels needs to be evaluated in further studies. What can be concluded is that COPD patients will have altered and impaired ischemic status as implied by the altered IMA levels.

REFERENCES


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