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RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) CHANGES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Introduction: COPD known as Chronic Obstructive Pulmonary Disease, ranks as the third most common cause of mortality worldwide. It is a persistent and worsening illness that leads to blockage in the respiratory passages. COPD patients undergo a chronic inflammatory response in their lungs and airways, which is initiated by variables such as smoking, biomass smoke, and indoor pollutants. COPD is distinguished by persistent inflammation and stimulation of the renin-angiotensin-aldosterone system (RAAS). This leads to an elevation in pro-inflammatory cytokines and the occurrence of systemic inflammation. **Material and methods:** Standard blood tests were conducted and serum levels of renin, angiotensin Converting Enzyme 2 (ACE2), aldosterone, cortisol, IL-2, and Tumor Necrotic factor (TNF-α) were measured using the ELISA method. **Results:** The study revealed a substantial elevation in blood levels of Cortisol, Renin, Aldosterone, and Interleukin 2 (IL-2) in individuals diagnosed with COPD, with a statistical significance of $p<0.05$. The levels of TNF-α and ACE2 show non-significant rise in individuals with COPD with p › 0.05. **Conclusion**: This study established a notable association between the RAAS and COPD. The levels of serum renin, aldosterone, cortisol, and IL-2 were seen to be increased in the majority of individuals who smoke. In the near future, the components of the RAAS system, in conjunction with the inflammatory marker IL-2, have the potential to serve as predictive and diagnostic biomarkers in patients with COPD.

Keywords: COPD, RAAS, ACE 2 , IL-2 , TNF-α and ELISA.

INTRODUCTION

COPD is a medical illness that is marked by an ongoing impairment of airflow. [1] The spectrum of COPD encompasses emphysema, chronic bronchitis, and small airway disease. [2] COPD is a rapidly expanding global health issue. Currently, it ranks as the sixth leading cause of mortality, but it is projected to ascend to the third most prevalent cause of death globally in the near future. In India, COPD ranks as the second most prevalent respiratory disorder, surpassed only by pulmonary tuberculosis, which is the primary respiratory ailment. Due to their heightened propensity for smoking, middle-aged men are at a higher risk of developing COPD. The prevalence of the ailment is said to be the same in both rural and urban areas. The progress in urbanisation and assimilation, along with the growth in tobacco consumption, the utilisation of gasoline-powered vehicles, and the establishment of large-scale enterprises, has led to air pollution and therefore a significant rise in the prevalence of COPD. COPD has been associated with infants having low birth weight, malnutrition, and several respiratory illnesses during the early stages of life.

COPD is caused by chronic inflammation, which has been linked to the activation of the RAAS by the action of angiotensin II. This leads to an augmentation in the synthesis of proinflammatory cytokines, contributing to the overall inflammatory

response. [3,4] Angiotensin II-induced production of reactive oxygen species (ROS), impairment of mitochondrial function, and disruption of redox signalling pathways are all variables that contribute to the development of COPD (7,8). Xue et al. investigated the impact of Angiotensin Converting Enzyme 2 (ACE2) expression on pulmonary function and inflammatory response in rat models with Chronic COPD. Elevated ACE2 expression in the cells lining the airways enhances pulmonary function and decreases the levels of pro-inflammatory signalling molecules such as TNF-α, IL-8, IL-2, and IL-1β. In addition, a significant reduction in the expression of ACE2 mRNA was seen in the pulmonary tissue of rats with COPD.

This indicates that decreased ACE2 levels may play a role in the emergence and advancement of COPD. [5] RAAS system controls the process of salt reabsorption in the kidneys. Renin secretion is triggered by a decrease in glomerular filtration rate and a decrease in salt delivery to the distal nephrons. Renin catalyses the hydrolysis of angiotensinogen, resulting in the production of angiotensin I. ACE catalyses the conversion of angiotensin I to angiotensin II. Angiotensin II employs three distinct methods to enhance the retention of sodium. At first, it stimulates the reabsorption of sodium in the proximal tubule. Moreover, it reduces the amount of salt being filtered. Moreover, it enhances the activity of the adrenal cortex, prompting the production of aldosterone, so enhancing the reabsorption of salt. Multiple natriuretic factors regulate the process of sodium excretion. The factors comprise of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). [6]

Natriuretic peptides are primarily synthesised in the cardiac and cerebral tissues. Elevated levels of atrial natriuretic peptide and B-type natriuretic peptide occur when there is an excessive amount of fluid in the extracellular space. They induce natriuresis, enhance vasodilation, and inhibit RAAS system. The main purpose of the C-type natriuretic peptide is to facilitate vasodilation. Farber and Manfredi's research team were among the first to show that individuals with COPD who experienced sustained hypercapnia faced challenges in effectively removing excess salt and water from their bodies, especially if they had edema. [7] The occurrence of salt and water retention in individuals with COPD signifies a worse prognosis. The objective of this study is to identify COPD among smokers at its first phase, with the aim of averting the progression of pulmonary hypertension and cor pulmonale. Moreover, the experiment aims to decrease the frequency of hospital admissions among patients with COPD who also have pulmonary arterial hypertension (PAH) and cor pulmonale.

MATERIALS AND METHODOLOGY

This study is an observational cross-sectional study that was done on 73 patients with COPD who were receiving outpatient or inpatient care at the General Medicine department of the School of Medical Sciences and Research, Sharda University, Greater Noida. The study took place between August 2022 and March 2024. This study included individuals who were heavy smokers with a smoking history of more than 20 pack years, as well as eligible patients aged 40-70 years who had been diagnosed with COPD using a pulmonary function test (PFT). This study excluded subjects who did not give consent to participate, non-smokers, individuals with a history of drug, substance or alcohol abuse, and patients who were already diagnosed with bronchial asthma, lung tuberculosis, hypertension, uncontrolled diabetes, thyroid disease, haematological disease, liver disease, or heart disease.

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Standard blood tests were conducted and serum levels of renin, ACE2, aldosterone, cortisol, IL-2, and TNF-α were measured using the ELISA method. Upon obtaining approval from the ethics committee, the study activity commenced on the aforementioned procedure. Utmost secrecy has been upheld throughout all stages of the study to ensure complete confidentiality of the subject's information. The acquired data was inputted into Microsoft Excel and evaluated with SPSS version 21. A Z-test was conducted to analyze a single mean. A p-value below 0.05 is deemed to be statistically significant.

RESULT

Table 1: Age distribution

Age Groups	FREQUENCY	PERCENTAGE
41-50years	40	55
51-60years	18	25
61-70years	15	20
Total	73	100.00

Figure 1: Gender distribution

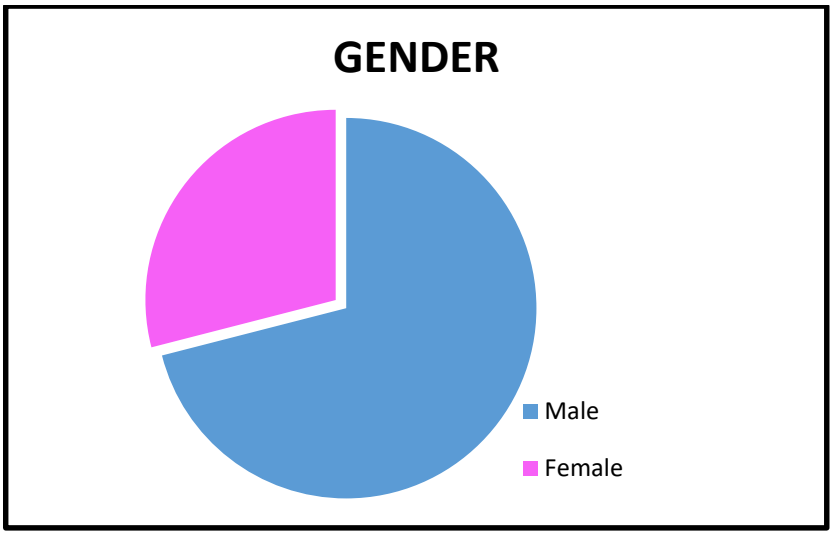

Figure 2: Distribution of smokers in the population

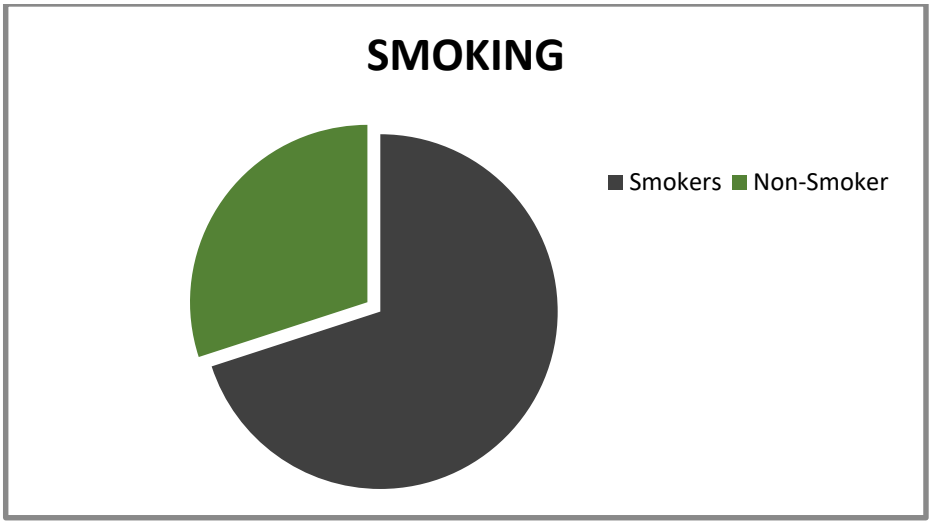

Table 2: Mean values and Standard deviations

Lab Parameters	Mean value (∑X) with Standard deviation (∑X²) of subjects	Normal Value	P-Value
Renin (ng/ml)	7.98 ± 5.27	0.29-3.7	0.00002936
ACE2 (ng/ml)	35.87 ± 9.53	3-40	0.99989
Aldosterone (pg/ml)	32.35± 14.84	3-28	0.006123
Cortisol (µg/dl)	14.46 ± 6.04	3-10	0.000658
TNF-α (pg/ml)	6.47 ± 4.61	<8	0.997652
IL-2 (pg/ml)	7.55 + 2.53	<7	0.03081

Serum Cortisol, Renin, Aldosterone and IL-2 in patients with COPD, the *p*-values are 0.00002936, 0.006123, 0.000658 and 0.03081 respectively where the result is significant as $p < 0.05$. Mean levels of TNF-α and ACE2 were recorded to be near the upper limit of normal value in patients of COPD, with non-significant p-value ≥0.05

DISCUSSION

COPD is a persistent inflammatory condition that leads to permanent harm to lung tissue and progressively limits the passage of air. [8] COPD is linked to independent risk factors such as diabetes, hypertension, and cardiovascular disease, all of which have shown a rise in prevalence in recent years. The average age of the study population was 48.25±6.78 years as mentioned in table no 1, 71% males and 29% females, 70% of the subjects are smokers while the remaining 30% are non-smokers as in figure 1, 2.

The study found that there is significant increase in the plasma renin and aldosterone levels Mean ±SD is 7.98 ± 5.27 ng/ml & 32.35 ± 14.84 pg/ml respectively with $p < 0.01$ as mentioned in table no. 2. Preeti Chauhan et al., found that individuals with COPD exhibited significantly elevated levels of plasma aldosterone Mean ±SD 182.35±364.2, in contrast to the average of 57.24±18.99 seen in the control group with $p < 0.01$ as highly significant [9]. In another study carried out in China, 75 COPD patients with or without cor pulmonale were recruited. Plasma renin activity and aldosterone were found to be higher in COPD patients when compared to 25 healthy subjects with p-value < 0.05. [10]

The present study revealed that ACE 2 activity in plasma was Mean ±SD 35.87± 9.53 ng/ml , which is non-significantly affected in COPD patient with p-value 0.99989 as mentioned in table no. 2. In a study published in the European Respiratory Journal in 2015, researchers Ümran Toru et al. found that the blood activity of ACE2 was Mean ±SD 0.1 ± 0.004 in the group with COPD and 0.08 ± 0.005 in the control group. [11] The group of individuals with COPD exhibited a statistically significant rise of ACE2. However, our study showed that the blood ACE2 level was within the normal range and was close to the upper threshold of normal. Anand et al. found that in a group of nine individuals with COPD who had low oxygen levels and high carbon dioxide levels, there was an increase in resistance in the pulmonary artery but a decrease in resistance in the peripheral blood vessels. A decrease in the amount of blood circulation that is effective in delivering oxygen and nutrients to tissues triggers the activation of the sympathetic nervous system and the RAAS system. [12] Renin is secreted into the circulatory system in response to a decrease in blood pressure and a decline in the concentration of salt in the renal tubules. Renin hydrolyzes the N-terminal region of angiotensinogen in the liver, resulting in the formation of angiotensin

I. Angiotensin I lacks any acknowledged biological action. Angiotensin I undergoes conversion to angiotensin II through the activity of ACE (Angiotensin Converting Enzyme), which is mostly produced by vascular endothelial cells in the pulmonary circulation. Angiotensin II impacts extracellular volume and blood pressure regulation through different specific mechanisms. Firstly, it induces the contraction of smooth muscles in arterioles, resulting in vasoconstriction via the AT 1 receptor in blood vessels. Secondly, it stimulates the release of aldosterone from the zona glomerulosa of the adrenal cortex. Thirdly, it enhances sodium reabsorption by increasing the activity of the Na-H antiporter in the proximal convoluted tubule of the kidney, again through the AT 1 receptor. Lastly, Angiotensin II promotes inflammation throughout the body and causes oxidative damage. It induces smooth muscle spasms in blood vessels, disrupts the functioning of the inner lining, leads to tissue scarring, and enhances cell proliferation and survival. [13]

In the present study serum cortisol was found to be significantly increased with Mean±SD 14.46 ± 6.04 µg/dl and p-value < 0.01 as mentioned in table no. 2. Meshram PL, Shinde SN, et al. (2018) examined the concentrations of inflammatory markers in individuals diagnosed with COPD. [14] The study revealed that people with COPD exhibited significantly elevated levels of cortisol, TNF-α, IL-6, lactate dehydrogenase, and CRP in comparison to individuals in the control group. In this study, the levels of TNF-α were within the normal range, however they were close the upper limit, whereas IL-2 was significantly increased Mean± SD was7.55 ± 2.53 pg/ml & p-value = 0.03081 .

In a research conducted in 2018 by Wei B, Sheng Li C et al., show that people suffering from COPD had elevated levels of IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE compared to individuals with stable COPD or those without the condition. [15] There were significantly higher levels of IL-2 identified in the group being compared to the levels observed in healthy individuals. Rybka et al., found that patients with both COPD and depression had substantially elevated levels of IL-2 Mean± SD 3.20 ± 0.389 pg/ml compared to the control group Mean± SD 2.20 ± 0.184 pg/ml, with a p-value of less than 0.05. [16]

In 2014, researchers Wafaa S. El-Shimy, Ayman S. El-Dib, and his colleagues show that IL-6, IL-8, and TNF-α can be used as indicators of inflammation in individuals suffering from COPD. [17] Individuals with severe COPD had considerably elevated levels of serum TNF-α Mean± SD 54.472 ± 12.972 pg/ml compared to those with mild and moderate COPD mean = 43.833 ± 10.531 pg/ml and control participants. A research conducted in Kashmir by Shah et al. found that patients with COPD had significantly elevated levels of TNF-α in their blood compared to the control group Mean± SD 8.0 ± 10.1 ng/ml vs. 3.3 ± 0.42, p-value ≤ 0.0001. [18]

The suggested explanation for these comorbidities in COPD patients is the presence of hypoxia, oxidative stress, and systemic inflammation. Consequently, individuals with COPD are anticipated to see an increase in systemic inflammatory markers. Studies indicate that persons with COPD exhibit elevated levels of inflammatory markers, including CRP, fibrinogen, IL-6, IL-8, and TNF-α, in comparison to healthy individuals. [19, 20] Higher levels of these markers are linked to sudden worsening of symptoms and poor prognosis.

CONCLUSION

Serum Renin, Aldosterone, Cortisol and IL-2 levels were found to be elevated in majority of COPD patients specially who are smokers. **.** ACE2 and TNF-α were recorded to be near the upper limit of normal value in study participants**.** The components of RAAS system along with inflammatory marker IL-2 maybe considered for use as potential prognostic and diagnostic biomarkers in COPD patients in the near future.

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