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Effect of alpha-1 antitrypsin and alpha-1-acid glycoprotein AAT levels on prognosis in COPD exacerbation and COPD-community-acquired pneumonia patients

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is the most frequent comorbid condition that is present in patients with pneumonia. An exacerbations of chronic obstructive pulmonary disease (ECOPD) and Comminity-acquired pneumonia (CAP) are associated with high rates of hospitalizations, costs, and morbidity. Plasma levels of orosomucoid and Alpha-1 antitrypsin (AAT), also known as Alpha-1-acid glycoprotein (AGP), increase in response to inflammation and tissue necrosis. The purpose of this study is to evaluate the impact of markers in patients with ECOPD and COPD with pneumonia .

Methods: To compare the levels of AAT, and AGP, between patients diagnosed with ECOPD only and patients diagnosed with COPD and pneumonia.

Results: The study included 14 female and 22 male volunteers. The mean gender and age of groups 1 and 2 were similar. There was no statistical difference in laboratory values between the groups.

Conclusion: Alpha-1-acid glycoprotein and AAT are acute-phase proteins elevated in various inflammatory conditions such as infections, trauma, and chronic diseases such as COPD. More studies are needed on their usefulness for monitoring and/or treatment in daily practice.

Keywords: Chronic obstructive pulmonary disease, pneumonia, Alpha-1 antitripsin, Alpha-1 acid glicoprotein

INTRODUCTION

Chronic obstructive pulmonary disease is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. Chronic obstructive pulmonary disease (COPD) is a progressive but preventable disease characterized by chronic inflammation and airway restriction. It appears to be divided into two sub-phenotypes: chronic bronchitis and emphysema. Both phenotypes may be present in varying degrees in patients, increasing airflow limitation.[1]

Pneumonia is inflammation and infection of the lung parenchymal tissue and is the eighth leading cause of death and first among infectious causes of death. Inflammation is largely caused by microorganisms such as bacteria, viruses, and fungi. It can be defined as a disease that cannot be explained by other causes and is accompanied by focal lung findings on chest radiography in addition to an acutely onset cough, fever lasting more than four days, cough, sputum, chest pain, dyspnea, and/or tachypnea.[2]

Orosomucoid, also known as alpha-1-acid glycoprotein (AGP) and alpha-1 antitrypsin (AAT), are glycoproteins produced by the liver. Orosomucoid is a component of the acute phase response during systemic inflammation. Alpha-1 antitrypsin (AAT) is a highly effective protein for protecting the lungs from damage caused by enzymes released during inflammation.[3]

The aim of our study was to compare AAT and orosomucoid levels in patients with COPD-diagnosed pneumonia (Group 1) and COPD without pneumonia (Group 2), considering that they may provide information about the mechanisms underlying these conditions and potential diagnostic and prognostic markers.

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METHODS

Our study included 14 female and 22 male volunteers with COPD diagnosed with pneumonia and ECOPD without pneumonia who were admitted to our center and hospitalized. This single-center, prospective, cross-sectional study was conducted at a university hospital from May to November 2018. An exacerbation of COPD have been defined using symptom-based and event-based references and a combination of the two. Symptom-based definitions rely on patient-reported worsening of respiratory symptoms. Typical symptoms include increased dyspnoea, coughing, increased sputum volume and sputum purulence. Event-based definitions capture patients whose conditions have deteriorated enough to require a change in treatment or a hospital visit or admission. Clinical diagnosis of community-acquired pneumonia based on symptoms and signs of lower respiratory tract infection in a patient and can be confirmed by a chest X-ray showing new shadowing that is not due to any other cause (such as pulmonary oedema or infarction). This might be because of the presence of focal chest signs, illness severity or other features. Patients with interstitial pneumonia, cystic fibrosis, severe neutropenia (<0.5x10^9 neutrophils-L-1) due to chemotherapy or immunosuppressive therapy, or HIV infection with a CD4 count <200 cells/mm^3, patients who did not want to participate in the study were excluded. AGP serum levels were measured in the biochemistry laboratory of our institution using a commercially available kit based on immunoturbidimetric methods according to the manufacturers' instructions. Serum and plasma samples were stored at −80°C until they were analyzed. The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of our university hospital (Date: 28.05.2018, Decision No: 20180528/5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Numeric values with normal distribution were expressed as means±SD, whereas variables with abnormal distribution were given as median values (min-max). Categorical variables values were given as n (percentage). Chi-square tests or Fischer exact test were used to compare two independent groups for categorical data. Student's t-test or Mann-Whitney U test were used for comparison of the two groups according to distribution pattern. All directional p values were two-tailed and significance was set to values lower than 0.05.

RESULTS

The study included 14 female and 22 male volunteers. The mean age of the patients was 76.17±10.59 in Group 1 and 75.50±9.56 in Group 2. There were 7 females and 11 males in both groups. When groups 1 and 2 were compared, the mean gender and age were similar. There was a significant difference in smoking habits, and the rates of comorbid diseases were similar (**Table 1**). When the laboratory values of group 1 patients were compared with group 2 patients, no statistical significance was found in all parameters (**Table 2**).

Table 1. Demographic characteristics

Parameters	COPD & Pneumonia		COPD Attack		p
	N	%	N	%	
Age, years, (mean ± SD)	76.17±10.59		75.50±9.56		0.844
Gender, M	11	61.1	11	61.1	0.633
Smoking status					0.002
Never used	1	5.6	11	61.1	
Quit Smoking	12	66.7	5	27.8	
Active smoker	5	27.8	2	11.1	
Comorbid Diseases					
CAD	3	16.7	4	22.2	1.000
CHF	3	16.7	5	27.8	0.691
CKD	2	11.1	1	5.6	1.000
DM	2	11.1	6	33.3	0.228
HT	9	50	14	77.8	0.083
Malignancy	1	5.6	2	11.1	1.000

Abbreviations; CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, DM: Diabetes Mellitus, HT: Hypertension

Table 2. Laboratory results

	COPD & Pneumonia (Group 1)	ECOPD (Group 2)	P
Leukocyte	14.08±6.53	14.86±16.07	0.851
Hb	13.04±1.75	12.77±2.77	0.729
Htc	38.79±4.93	38.32±8.03	0.832
Plt	243.76±64.40	240.17±87.76	0.890
Neutrophil	11.42±5.80	8.34±6.51	0.142
Lymphocyte	1.30(0.22-3.90)	1.67(0.47-59.80)	0.389
CRP	82.25(1.5-263.2)	64.30 (0.8-351.7)	0.265
BUN	21.50 (9.0-60.0)	24.50 (9.0-87.0)	0.355
Cr	1.09±0.45	1.40±0.79	0.157
Sed	35.00±19.64	47.07±25.42	0.250
AGP	182.59±70.55	179.35±60.17	0.585
AAT	2.70±0.47	2.35±0.54	0.110

Abbreviations Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet, CRP: C- reactive protein, BUN: blood urea nitrogen, Cr: Creatinine, Sed: Sedimentation, AGP: Alpha-1-acid glycoprotein, AAT: Alpha-1 antitrypsin

DISCUSSION

According to the World Health Organization in 2014, lower respiratory tract infections and COPD represented the third and fourth leading causes of death worldwide.[3] In addition, community acquired pneumonia is cause of morbidity and mortality around the world. Therefore, it is important to understand the association between COPD and pneumonia, as well as their impact in patient's management. COPD patients may be more susceptible to develop pneumonia based on their clinical characteristics such as having chronic bronchitis with persistent mucus production, and the presence of potential pathogenic bacteria in the airways, the presence of bacteria in the airway in stable COPD patients and increased numbers during exacerbations have been associated with increased inflammation and the host immune response.[4]

An exacerbation of COPD is defined as an increase in symptoms of cough, sputum, and/or dyspnea that may be accompanied by tachypnea and/or tachycardia as a result of increased local and systemic inflammation due to air pollution, infection, or other exposure.[5] ECOPD is usually associated with increased airway inflammation, increased mucus production, and marked air trapping. These changes contribute to the increase in dyspnea, which is the main symptom of exacerbation.[6] Characteristically, inflammation is characterized by increased numbers of macrophages, activated neutrophils, and B and T lymphocytes in the

peripheral airways, lung parenchyma, and pulmonary circulation. Together with epithelial cells and other structural cells, they secrete numerous inflammatory mediators, such as tumor necrosis factor-a (TNF-a) and interleukins (IL-1b, IL-6, and IL-8).[7] The risk of developing pneumonia in COPD patients is much higher than in the healthy population. This is due to damaged airways and decreased lung function. In addition, the weakened immune system in COPD makes patients more susceptible to respiratory tract infections such as pneumonia. In addition, pneumonia can exacerbate COPD symptoms, increase the number of attacks, and worsen lung function. Molecular tests and improved imaging techniques are very helpful in classifying the disease group and identifying causative organisms. Investigations such as CRP, procalcitonin, and cytokine measurement are auxiliary laboratory tests used in the diagnosis of pneumonia in clinical practice.[8] Although there are studies showing that leukocyte and CRP values were found to be higher in COPD patients presenting with pneumonia compared to patients without pneumonia, no significant difference was found between both groups in our study.

The protein AAG (orosomucoid), which is in the α1-globulin band of serum proteins, is mostly made by parenchymal cells in the liver. Its plasma level increases in response to inflammation and tissue necrosis. CRP is the first to rise as an acute-phase reactant, and its plasma level starts to rise within the first 24 hours after α1-antichymotrypsin. Since it has a low molecular weight that can easily pass into the glomerular filtrate, its plasma half-life is 3 to 5 days. As the inflammation improves, the orosomucoid level decreases in parallel.[9] Alpha-1 antitrypsin (AAT) is produced by the liver, and one of its main functions is to inhibit an enzyme called neutrophil elastase that can break down connective tissue in the lungs. Genetic deficiency of Alpha-1 antitrypsin leads to AAT-associated emphysema. This condition causes progressive tissue damage in the lung. Individuals with COPD and alpha-1 antitrypsin deficiency have an increased risk of both pneumonia and severe lung damage. AAT deficiency impairs the ability of the lung to resist the effects of inflammation and enzyme activity, making the lungs more susceptible to infections such as pneumonia and accelerating the progression of COPD.[10] Since both AAT and AGT levels play a role in immune response and inflammatory regulation, they may vary in patients with COPD and pneumonia. Especially in pneumonia, both AAT and AGT levels are typically increased due to an acute inflammatory response. Many studies have shown an inverse correlation between elevated inflammatory biomarkers and lung function.[11] In our study related to AAT and orosomucoid levels in both groups of patients, the results were similar between the two groups. This was thought to be primarily due to the fact that the groups included a small population. Another reason was that acute-phase reactants may increase together in cases of exacerbation and pneumonia, which increase inflammation.

CONCLUSION

AAT and AGP (orosomucoid) are several acute-phase proteins that are elevated in the bloodstream in response to various inflammatory conditions such as infections, trauma, and chronic diseases such as COPD. Inflammation can cause further damage to lung tissue, exacerbating symptoms and reducing lung function. In cases of pneumonia, especially in individuals with COPD, the immune response triggers an increase in the production of acute-phase proteins, and elevated glycoprotein levels may indicate a more intense inflammatory response. Distinguishing among pneumonic and non-pneumonic exacerbations in COPD patients is still a matter of controversy. For all that reasons, further studies are needed on the potential of such markers to clarify this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Ufuk University Clinical Researches (Date: 28.05.2018, Decision No: 20180528/5).

Informed Consent

All patients voluntarily signed the informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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