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Research Paper

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Correlation between serum levels of progranulin and spirometric readings in patients with chronic obstructive pulmonary disease

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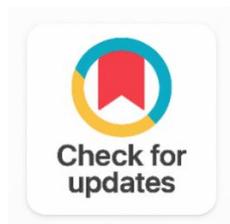
Article Info	ABSTRACT
  Check for updates	Back ground Chronic Obstructive Pulmonary Disease (COPD) is a chronic Inflammatory disease of the airways and/ or parenchyma usually characterized by progressive irreversible airflow with accompanying respiratory symptoms like dyspnea, cough, production of sputum, and/or exacerbations. The pathophysiology Of COPD involves bronchitis and /or emphysema, the effect of inflammation occurs in the lung and also have systemic effect, most common causes is tobacco smoking, occupational pollution, indoor pollution. Progranulin (PGRN) is defined as precursor of pleiotropic glycosylated protein ,it have significant role in process of inflammation ,angiogenesis, neoplasia ,cell development ,cell cycle , embryogenesis, wound healing ,modification of autoimmune process, highly found in several type of cells like respiratory epithelial cells. Objective: The aim is to study relationship between serum level of PGRN and spirometric readings in COPD patients. Patients and method: A case control study composed of 40 patients with COPD and 45 controls, demographic characteristic, pulmonary function test and plasma PGRN were measured and made comparison of data in cases with controls, data collected were statically analysis by SPSS.Result: This study found that serum PGRN was elevated in cases of COPD more than controls (230.52±189.01 VS 114.19±68.41 ng/ml) there is significant association between PGRN and COPD (P value 0.006) ,and found that PGRN negatively associated with FEV1 % (P value 0.04) Conclusions: It was concluded that PGRN may be used as blood marker that indicate severity of airflow obstruction in COPD.

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1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide in 2019, with about 3.23 million deaths occurring in middle and low-income countries. COPD prevalence is high among smokers, previous smokers, males, and those over 40 years old. The global prevalence of COPD in 2019 was 10.3% using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition [1], [2], [3], [4], [5].

COPD is a complex progressive illness that continues as an inflammatory disease of the lungs, involving multiple types of inflammatory cells and mediators. It is caused by complex, dynamic, and cumulative interactions between genes and environment during a person's lifetime, which can change normal lung development mechanisms and result in damage [6], [7], [8].

PGRN, also known as acrogranin or PC cell-derived growth factor (PCDGF), plays a crucial role in inflammatory diseases like COPD and asthma. Its anti-inflammatory action is due to its interaction with TNF R1/2 and blocking the TNF-α-TNFR1/2 signal, which inhibits neutrophil degranulation. Studies have found high concentrations of PGRN in COPD patients' serum due to the inhibition or low degree of neutrophilic inflammation. PGRN, composed of 593 amino acids, has a molecular weight of 68.5 kDa and is encoded by the GRN gene. Degradation of PGRN can occur by various proteinases, and some molecules, such as secretory leukocyte protease inhibitor (SLPI), can inhibit its anti-inflammatory action. Degradation of PGRN results in granulins with pro-inflammatory action, which can neutralize its anti-inflammatory effect [9], [10].

2. RELATED WORK

The process of inflammation in COPD affects the lungs primarily, but it also has a systemic effect, patients with COPD have higher level of inflammatory markers in systemic circulation like C-reactive protein, soluble adhesion molecules, lipopolysaccharide binding protein, TNF transmembrane receptor [11].

Tobacco Smoking considered the most common cause of COPD (about 50% of smoker complain from COPD, after consumption of more than 10 packs year) [11], despite of the smoking is consider primary cause but epidemiological studies found that about 20% - 40% of COPD patient not smoking at their life. [12], also cannabis, pipe, water pipe, cigar all consider as risk factors for COPD. [13], Genetic causes: like Alph-1 antitrypsin deficiency (AATD) [14]. Pollution due to environmental exposure to particles of gases either indoor or outdoor air pollution, previous infection like in recurrent respiratory infection mostly in lower part of respiratory airways in early childhood (2-3 times increase risk), also previous tuberculosis increase risk of occurrence COPD [15], more in poor socioeconomic conditions due to multiple compounds like decrease in nutrition and more exposed to pollution [1].

The inflammation observed in COPD patients is an altered form of the usual inflammatory response to chronic irritants like smoke inhaled from cigarettes and other particles. The main cause of this modified type of inflammation is unknown, but some studies suggest genetics may play a role [16].

The severity of airflow obstruction can be classified into stages according to criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) that depend for categorization of COPD, by examination in spirometry depend on FEV1 in patients have post bronchodilator FEV1/FVC ratio less than 0.7. It is can classified according to FEV1 value into: Mild FEV1 ≥ 80%, Moderate ≥ 50% _ < 80%, Severe ≥ 30% _<50% and Very severe < 30% [17]. [18] Found in their study a high concentration of PGRN in the serum of patients with COPD. This is due to inhibition or low degree of neutrophilic inflammation.

While [19], found in their study a low concentration of PGRN in the serum of patients with asthma. This is considered as an indicator of neutrophilic inflammation and found that PGRN is negatively correlated with bronchial obstruction.

PGRN is considered as anti- inflammatory protein, it can digest by neutrophil derived proteinases, the product of digestion act on epithelial cell line and stimulate it to produce neutrophil chemoattractant interleukin IL-8. So, anti-inflammatory action of PGRN can decrease or neutralize by degradation of PGRN with neutrophil proteinases   [20].

PGRN binds to TNFR1/2 and sortilin. Sortilin acts as a regulation of PGRN concentration and uptake in the brain, mutation in the gene of PGRN can cause fronto-temporal lobar degeneration [21].

3. METHADOLOGY

Patients and Methods

From January 2023 to August 2023, 40 COPD patients (26 males and 14 females) were collected from Al-Sader Teaching Hospital in Al-Najaf city, all meeting inclusion criteria and excluded from exclusion criteria. The study involved 45 healthy participants, including 16 males and 29 females, who were recruited randomly from the general population, free from COPD, and had normal pulmonary function tests through spirometry examination. Participants provided verbal consent after understanding the study's objectives, research procedures, spirometry examination, and blood drawing. The study included COPD patients aged over 35, meeting GOLD criteria for diagnosis [22], and in a stable stage with no prior treatment with long-acting B-agonis, anti-inflammatory drugs, or oral corticosteroids [23], [24]. Individuals with connective tissue disorders, inflammatory bowel disease, and cancer in the last five years, renal or hepatic failure, or chronic diseases with systemic inflammation effects are excluded [25].

The pulmonary function test is a vital tool for diagnosing lung diseases by measuring the amount of air that can be breathed in and out of the lung. The test involves a spirometry test, which measures the amount of air that can be easily and quickly exhaled [26]. The operator measures weight and height before the test, and enters information about the participant, including date of birth, sex, weight, height, and smoking status. The subject should not be taking short-acting inhaled drugs like salbutamol or albuterol four hours prior to the examination, and oral therapy like aminophylline, slow release β-agonist, should be paused 12 hours before the examination [27]. Smoking should be stopped one hour before the examination. The operator performs the test by instructing the patient to sit upright, close their nose, and take full deep breaths. If the patient's FEV1/FVC % is less than 70%, they are instructed to take an inhaler dose of salbutamol (100 μg) in one breath, hold for 5-10 seconds, and exhale four times. The test is then done 10-15 minutes after bronchodilation. If the response to bronchodilation is less than 200 ml, it is considered no response to bronchodilation and an irreversible obstruction, confirming the diagnosis of COPD [4], [14]. A venous blood sample of 2.5 milliliters was collected from each participant and put in a gel tube, then serum progranulin was measured using the Human PGRN (Progranulin) ELISA Kit (Elabscience/USA) for all participants, following the exact manufacturing source's procedure.

The study used the Statistical Package for the Social Sciences (SPSS 23.0 for Windows) to analyze data, with descriptive statistics presented as frequency, percentage, and mean ± SD. Comparisons were made between groups using chi-square tests for categorical variables and Mann–Whitney U-test for nonparametric data. Pearson's correlation coefficient was used for normally distributed variables, and significance was set at $p < 0.05$.

4. RESULTS AND DISCUSSION

Result

The current study included a total of 85 participants (40 COPD patients and 45 as a control). Two thirds of COPD group were male against one third of the control group, Table 1.

Table 1. Demographic Characteristics of the COPD and Control Group

Characteristics		Patients n=40	Control n=45	P value
Age (years)	Below 45	13 (32.5) %	27 (60) %	0.06
	45-54	13 (32.5)	8 (17.7)	
	55-64	7 (17.5)	7 (15.6)	
	65 and above	7 (17.5)	3 (6.7)	
Gender	Male	26 (65)	16 (35.6)	0.007
	Female	14 (35)	29 (64.4)	

Progranulin Level

The analysis of data showed that there was significant statistical difference in the mean Plasma progranulin levels between the COPD and the control group Table 2, Figure 1.

Table 2. Comparison of Progranulin Level between Patient and Control

Variable		Mean ± SD	P value
Plasma progranulin level (ng/ml)	Patients	230.52 ± 189.01	0.006
	Control	114.19 ± 68.41	
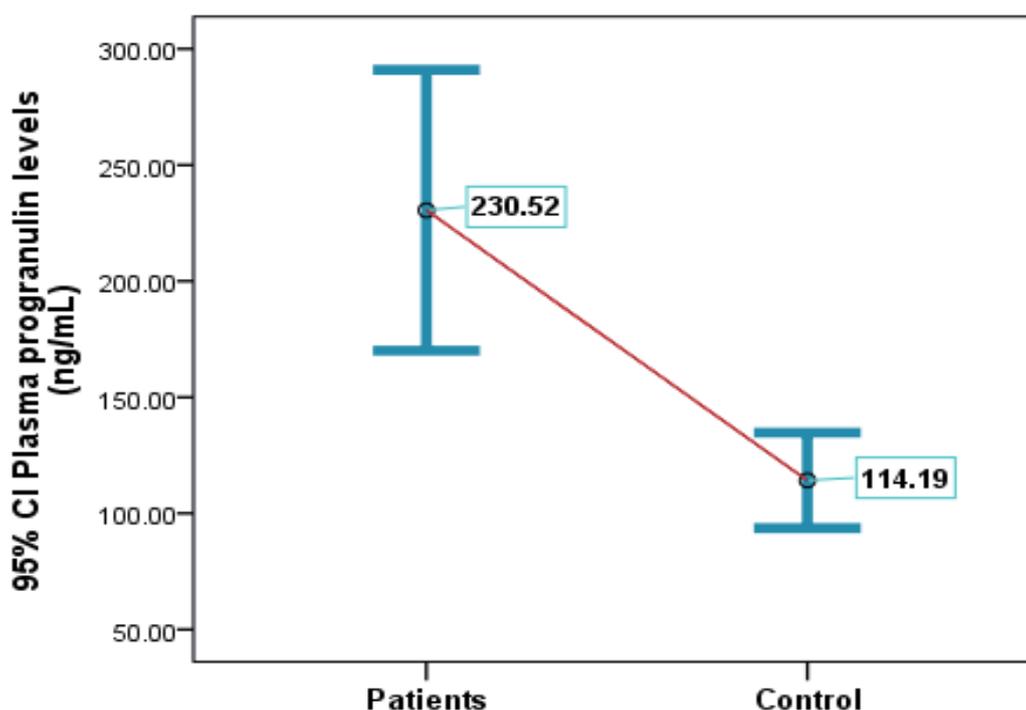
Figure 1. Plasma Progranulin Levels in COPD and Control Group

There was significant negative correlation between the mean progranulin level and the FEV1 in patients group Table 3.

Table 3. Correlations between Progranulin Level and Spirometric Reading in Patient and Control

Variables	Patients		Control	
	Pearson Correlation (r)	P value	Pearson Correlation (r)	P value
FEV1 predicted	-0.320	0.044	0.011	0.943

Discussion

This study involved 40 COPD patient (patient group) and 45 non COPD subjects. There is no difference in age between patients and controls P value (0.06) ,the age consider as risk 0.factor for developing of COPD due to either the lung function decline with increase age or due to increase time of exposures to the other causes such as tobacco smoking ,air pollution and occupational pollution during the life [1], this consistent with other studies [13], 65% of the patients in this study were males ,this consistent with study of [19], systemic review composed of more than 150 previous study ,that found prevalence of COPD was larger in males than females but the difference in prevalence between males and females in developed countries and high income countries was not significant statistically, this appear due to environmental factors and behavioral factors , genetic factors and prevalence of smoking high in men all these causes lead to difference in prevalence of COPD between genders, the diagnosis of COPD in developing countries still higher in males than females, but because of increase in smoking among females and working in males occupations that have risk of develop COPD due to pollution [6], but in other research [4], that found no difference in prevalence of COPD between men and women. [19] Explain in high income countries prevalence of COPD higher in females than males ,due increase exposure to tobacco smoking and found females have more susceptibility to harmful effect of tobacco smoking due to smaller size of lung in female so become more susceptible to oxidative stress [23].

This study showed a significant difference in progranulin level between cases of COPD and controls (230.52± 189.01 vs 114.19 ± 68.41 , P value 0.006) ,which is similar to finding of other study which found that progranulin level higher in acute exacerbation of COPD than stable COPD than controls and also found there is significant negative correlation between PGRN level and FEV1% ,this similar with finding of other study [8], [11], [21], due to PGRN may reflect the inflammatory and fibrotic changes in the airways which increase as severity of COPD increase and subsequently FEV1 decrease [26], [27].

5. CONCLUSION

We concluded for this study that elevated levels of PGRN are linked to COPD and are significantly correlated with severity of airflow obstruction.

Recommendation

We recommend using of spirometry for patients with clinical evidence of COPD especially in young age people that are have risk factor for develop COPD and using of spirometry as routine examination in people age more than 35 and have risk factors and also we recommended further studies with larger sample size are recommended for clarify the effect of PGRN on the severity of COPD.

Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Fatima Ali Alkyoon	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	
Falah Mahdi Dananah	✓	✓	✓	✓	✓		✓	✓		✓	✓		✓	

C: **C**onceptualization	I: **I**nvestigation	Vi: **Vi**sualization
M: **M**ethodology	R: **R**esources	Su: **Su**pervision
So: **So**ftware	D: **D**ata Curation	P: **P**roject administration
Va: **Va**lidation	O: Writing- **O**riginal Draft	Fu: **Fu**nding acquisition

Fo: **Fo**rmal analysis   E: Writing- Review& **E**diting

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and approved by the relevant institutional authorities.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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