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Paraoxonase Activity In Patients With Chronic Obstructive Pulmonary Disease

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Abstract

Aim: We aimed to study the Paraoxonase 1 (PON1) activity in chronic obstructive pulmonary disease (COPD) patients with stable condition, had acute attack and developed respiratory failure.

Material and Method: Twenty-five patients with stable COPD (group1) (mean age 62.9±9.4), 25 cases with acute COPD attack (group2) (mean age 63.8±9.0), 25 patients with hypercapnic respiratory failure (group3) (mean age 65.0±12.9) and 25 healthy individuals for control group (mean age 34.8±9.8), totally 100 cases, were enrolled to the study. Cases with secondary lipid disorder, cardiovascular disease, diabetes mellitus, renal failure, malignancy, hepatic failure and patients who receive antilipidemic or antioxidant medicines were not included to the study. All cases enrolled to the study underwent routine biochemical analysis including PON1 activity and lipid profile.

Results: There was significant difference between groups with respect to PON1 levels ($p<0.0001$). PON1 activities of COPD patient groups (group 1=96.8±57.4U/L; group 2=51.4±32.8U/L; group 3=47.1±27.5U/L) were lower than control group (185.4±110.1U/L) ($p<0.0001$). Also, PON1 activity of stable COPD patients was higher than the COPD cases admitted with acute attack or respiratory failure (group2 and 3) ($p<0.05$).

Conclusion: These findings show that PON1 activity may have a role in COPD pathogenesis and endogen antioxidants might be depleted by increased oxidative stress in COPD. This also advocates that oxidative stress may have a role in acute COPD attacks.

Key words: COPD, oxidative stress, Paraoxonase

Introduction

The demonstration of poorly reversible airflow limitation, defined as a post-bronchodilator FEV1/FVC ,0.7 are needed the diagnosis of chronic obstructive pulmonary disease (COPD)[1]. Oxidant / antioxidant imbalance is a major problem in COPD. This imbalance causes protease / antiprotease imbalance, destruction and restructuring of parenchyma, excessive mucus secretion, change in mucus structure, increase in apoptosis, and narrowing of bronchi, which are important components of COPD pathogenesis. All these changes are also effective in COPD progression. Increased oxidative stress in COPD is not only associated with an increase in oxidants but also with a decrease in antioxidant capacity[2].

The organism gets support from endogenous antioxidant enzymes (such as superoxide dismutase, glutathione peroxidase, catalase) to protect itself against oxidant stress. Serum paraoxonase (*PON1*) is a lipophilic endogenous antioxidant enzyme synthesized in the liver and circulates with HDL in serum. *PON1* activity is protective against xenobiotic toxicity such as organophosphate. PON1 inhibits LDL oxidation and shows antiatherogenic properties as it reduces oxidative stress in atherogenic lesions. Therefore, *PON1* works as an endogenous free radical scavenger in the human body[3,4].

Changes in *PON1* activity have been reported in different diseases in which oxidative stress plays a role in the pathogenesis. Some of them are cardiovascular diseases, neurological diseases, gastrointestinal system diseases, chronic renal failure, chronic liver failure, diabetes mellitus and metabolic syndrome, different types of cancer, rheumatological diseases, pulmonary tuberculosis, asthma[4,5].

PON1 is localized in Clara cells, endothelial cells and type 1 pneumocytes in the lung. Clara cell is one of the cells most resistant to oxidants in airway cells. There is a decrease in clara cells in COPD patients and smokers[6].

It was aimed to investigate the serum *PON1* activity in patients with stable, acute and hypercapnic respiratory failure COPD and to compare it with the healthy control group in the current study.

Materials and Methods

In this case-control study, 75 patients diagnosed with COPD according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and 25 healthy people who did not have COPD or any other disease and who did not smoke were included as the control group.

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Table 1. Demographic features. pulmonary function tests (PFT) and arterial blood gas (ABG) values of the patients

	Stable COPD group (Mean.±SD)	COPD Exacerbation Group (Mean.±SD)	Respiratory Failure Group (Mean.±SD)
Age(years)	62.9±9.4	63.8±9.0	65.0±12.9
Disease Duration (years)	8.2±5.9	10.4±6.2	11.4±8.0
Cigarette pack (year)	49.8±26.7	44.6±24.3	61.6±30.0
Pulmonary Function Tests			
FEV1 (lt)	1.89±0.71	1.42±0.80	1.27±0.59
FEV1(%)	64.2±20.4	50.2±20.9	44.2±17.5
FVC(%)	87.2±18.3	70.5±19.2	61.4±15.7
FEV1/FVC	56.3±11.5	54.0±11.8	53.7±11.5
Arterial Blood Gas			
pH	7.42±0.03	7.43±0.05	7.29±0.07
pCO2(mmHg)	35.6±7.3	40.5±7.4	71.3±20.0
pO2(mmHg)	64.5±12.4	64.3±16.3	63.9±18.3
HCO3(mEq/L)	23.0±4.3	26.3±3.7	32.0±7.7
sO2(%)	91.3±5.7	91.7±5.0	86.0±8.9

FEV1: Forced expiratory volume in 1st second **FVC:** Forced vital capacity **SD:** Standard Deviation

Patients are divided into 3 groups as follows.

Stable COPD group; 25 outpatient clinic control cases with stable COPD

Acute COPD attack group; 25 patients hospitalized with COPD attack

Hypercapnic respiratory failure group; 25 patients hospitalized in intensive care due to hypercapnic respiratory failure depend on COPD

Exclusion Criteria: Secondary lipid disorder, Coronary artery disease, Diabetes mellitus, Kidney failure, Malignancy, Liver failure, Antilipidemic and antioxidant drug use.

The protocol and procedures of this study were approved by the Local Ethics Committee of Selcuk University Meram Faculty of Medicine. Informed consent was obtained from all individuals included in the study.

Demographic characteristics, pulmonary function tests (PFT) and arterial blood gas (ABG) values of the patients included in the study were recorded. Serum samples obtained from the patients included in the study and the control group to measure *PON1* activity were placed in the eppendorf and stored at -80 ^{0}C degrees until the study. In addition, routine biochemical examinations including lipid profile were performed in all 100 people included in the study a (COBAS Integra 800 automatic analyzer (Roche, Switzerland)).

Statistical analysis

SPSS version 23 (Statistical Package for Social Sciences) was used for statistical analysis. In addition to descriptive statistics (number, mean, standard deviation), Kruskall–Wallis test for the comparison of all groups were used. Also, and Mann–Whitney U test for pairwise comparison of groups was carried out. The $p < 0.05$ was accepted as statistically significant.

Table 2. Comparison of PON1 and Lipid Levels in the control and patient groups

	Control (Mean.±SD)	Stable COPD group (Mean.±SD)	COPD Exacerbation Group (Mean.±SD)	Respiratory Failure Group (Mean.±SD)
HDL(mg/dL)	38.7±15.9	35.5±16.6	40.8±17.7	43.7±21.6
LDL(mg/dL)	98.4±28.3	100.2±34.1	96.6±29.0	99.1±32.5
VLDL(mg/dL)	20.8±8.9	22.4±9.3	17.0±8.2	19.4±9.5
Total Cholesterol (mg/dL)	157.6±31.7	158.2±44.6	154.4±34.4	163.0±37.0
Triglyceride (mg/dL)	79.4±38.7	82.5±41.4	85.1±40.7	97.4±45.6
PON1(U/L)	185.4±110	96.8±57.4*	51.4±32.8**	47.1±27.5**

HDL: High-Density Lipoprotein **LDL:** low-density lipoprotein **VLDL:** Very-low-density lipoprotein **PON1:** Paraoxonase 1 **SD:** Standard Deviation

*p<0.001: Compared to the control group **p<0.0001: Compared to the control group

Table 3. Comparison of demographic characteristics and PON1 activities of stable and attacked patients

	STABLE (n=25) (Mean.±SD)	**ATTACK** (n=50) (Mean.±SD)	p
Age(years)	62.9±9.4	64.4±11.1	0.677
Disease Duration (years)	8.2±5.9	10.9±7.1	0.048
Cigarette pack (year)	49.8±26.7	53.1±28.3	0.565
pO2(mmHg)	64.5±12.4	64.1±17.1	0.657
sO2(%)	91.3±5.7	88.9±7.7	0.192
FEV1(%)	64.2±20.4	47.6±19.5	0.002
FEV1/FVC	56.3±11.5	53.9±11.6	0.345
PON1(U/L)	76.8±57.4	49.3±30.1	0.025

FEV1: Forced expiratory volume in 1st second **FVC:** Forced vital capacity **PON1:**Paraoxonase 1 **SD:** Standard Deviation

Results

The mean age of patients was 62.9±9.4 for stable COPD group, 63.8±9.0 for acute COPD attack group and 65.0±12.9 for hypercapnic respiratory failure group. The mean age of control group was 34.8±9.8.

The mean durations of illness (years) were 8.2±5.9 for stable COPD group, 10.4±6.2 for acute COPD attack group and 11.4±8.0 for hypercapnic respiratory failure group. Additionally, the use of mean cigarette-pack (years) was 49.8±26.7 for stable COPD group, 44.6±24.3 for acute COPD attack group and 61.6±30.0 for hypercapnic respiratory failure group. Demographic characteristics, pulmonary function tests (PFT) and arterial blood gas (ABG) values of the patients included in the study were given in the table 1.

When *PON1* and Lipid Levels were compared in the control and patient groups, statistically significant differences were found between the control (185.4±110) and stable COPD group (96.8±57.4), the control (185.4±110) and acute COPD attack group (51.4±32.8) and the control (185.4±110) and hypercapnic respiratory failure group (47.1±27.5) ($p<0.001$, $p<0.0001$ and $p<0.0001$), respectively. When the

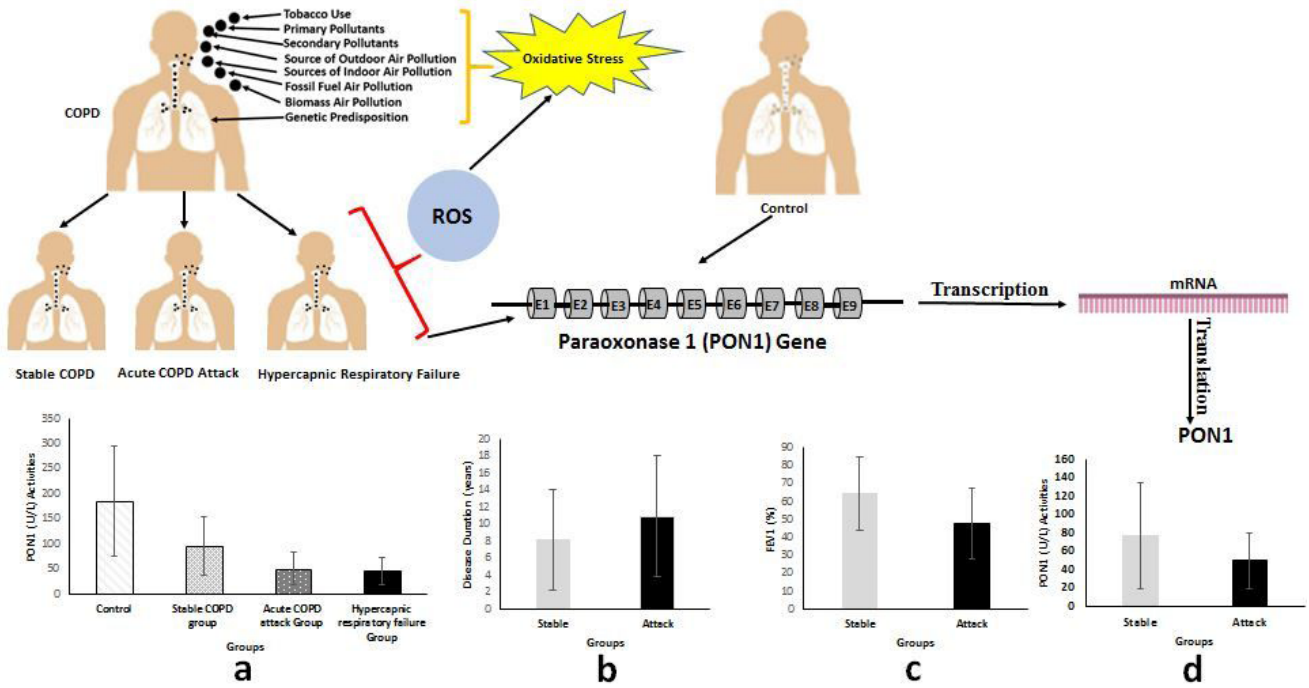

Figure -1. Risk factors for COPD (Tobacco Use, Primary Pollutants, Secondary Pollutants, Source of Outdoor Air Pollution, Sources of Indoor Air Pollution, Fossil Fuel Air Pollution, Biomass Air Pollution, Genetic Predisposition). Patients are divided into 3 groups as follows.
Stable COPD group, COPD exacerbation group and Respiratory failure group. Paraoxonase activities in patients with COPD and control groups were measured. Statistically significant differences were detected among all groups for PON1 activities (**a**). Additionally, statistically significant differences between stable and attack groups were detected for disease duration (**b**), FEV1 (**c**) and PON1 activities (**d**).

lipid levels to be considered, no statistically significant differences were found between the control and any of patient groups (p>0.05) table 2.

When the demographic characteristics of stable and attack patients and *PON1* activities were compared, the statistically significant differences were found for the duration of illness (year) (p = 0.048), forced expiratory volume in 1st second (fev1) (p = 0.02) and *PON1* (U / L) (p = 0.001) levels table 3.

Risk factors for COPD (Tobacco Use, Primary Pollutants, Secondary Pollutants, Source of Outdoor Air Pollution, Sources of Indoor Air Pollution, Fossil Fuel Air Pollution, Biomass Air Pollution, Genetic Predisposition) were shown in figure 1. Patients are divided into 3 groups as follows; Stable COPD group, acute COPD group and Hypercapnic respiratory failure group. Paraoxonase activities in patients with COPD and control groups were measured. Statistically significant differences were detected among all groups for *PON1* activities (**a**). Additionally, statistically significant differences between stable and attack groups were detected for disease duration (**b**), FEV1 (**c**) and *PON1* activities (**d**) (figure 1).

Discussion

It was suggested that the atherogenesis risk increase due to increasing the oxidized HDL particles caused by reduced *PON1* activity may not protect LDL against oxidation[7,8]. Moreover, *PON1* polymorphism and its' decreased activity have been related with several neurological diseases, including amyotrophic lateral sclerosis (ALS), ischemic stroke, white matter lesions, Parkinson's disease, and dementia[9-11]. In some study it was announced that *PON1* was lower in patients with COPD than controls[12,13]. In another study, it was reported that RR phenotype of *PON1* was more common in COPD patients compared to control. COPD patients exhibited higher *PON1* activity compared to control[5].

The current study showed that serum *PON1* activity was significantly lower in COPD patients compared to healthy people. This situation supports that the decrease in antioxidant capacity also has an effect on oxidant / antioxidant imbalance in COPD. These results suggest that changes in *PON1* activity may also play a role in the pathogenesis of COPD. In this study, it was also shown that serum *PON1* activity was significantly lower in patients with exacerbated COPD than in patients with stable COPD.

No differences of lipid parameters (HDL, LDL, triglycerides, total cholesterol) between the phenotype subgroups *PON1* gene were detected[5]. While the relation between lipid parameters and *PON1* activity was reported in some study[14], conversely, other studies showed no relation between *PON1* activity and lipid parameters[15,16]. According to our results, when the lipid levels to be considered, statistically significant differences were not found between the control and any of patient groups.

The relationship between COPD and cigarette smoke is well known. In some studies, it was reported that PON1 activity was reduced by cigarette smoke[17-19]. Conversely it was reported that *PON1* activity in smokers did not show differences from that of nonsmokers[20].

According to our results, the use of mean cigarette-pack (years) from highest to lowest was acute COPD exacerbation group, stable COPD group and hypercapnic respiratory failure group respectively. The lack of statistically significant differences between the stable and attack patient groups in terms of smoking suggest that the decrease in *PON1* activity of patients with attacks is independent from smoking. This situation supports that oxidative stress also plays a role in COPD exacerbations.

As a result, there was significant difference between groups with respect to *PON1* levels. *PON1* activities of COPD patient groups were statistically lower than control group. Also *PON1* activity of stable COPD patients was higher than the COPD cases admitted with acute attack or respiratory failure (group2 and 3). Our findings show that *PON1* activity may have a role in COPD pathogenesis. Additionally, endogen antioxidants might be depleted by increased oxidative stress in COPD. This also advocates that oxidative stress may have a role in acute COPD attacks.

However, in order to verify these relationships between *PON1* activity and COPD, more large prospective studies composed of high number of patients, in which healthy smokers as a control group are included and comparisons are made according to the GOLD staging are needed.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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