Paraoxonase Activity and Phenotype Distribution in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: Paraoxonase 1 (PON1) and arylesterase (ARE) enzymes have an important role in the prevention of oxidative stress which is related to the pathogenesis of chronic obstructive pulmonary disease (COPD). PON1 levels vary widely among individuals and ethnic groups, which is in part associated with polymorphisms.

Materials and Methods: We investigated PON1 and ARE activity and phenotype distribution in COPD patients and healthy individuals. Sixty six COPD patients and 59 control subjects were involved in the study. Serum PON1 and ARE activities were detected by spectrophotometric method. The ratio of salt-induced PON1 to ARE activity was used to determine phenotypes as QQ, QR, and RR.

Results: COPD patients exhibited higher PON1 activity (199.1 vs 129.2, p=0.002) but lower ARE activity compared to control (21.3 vs 33.5, p=0.021). There was a significant difference between COPD and control group with respect to PON1 phenotype characteristics. RR phenotypic distribution was more common in the COPD group than in control (60.6% [95% CI: 48.8 - 72.3] versus 22.0 % [95% CI: 12.0 - 31.9], p=0.001). We also found that smoking (95.0% CI: 0.001-0.036, p<0.001) and RR phenotype (95.0% CI: 0.006 - 0.59, p=0.016) are independent determinants in COPD.

Conclusion: We found that RR phenotype was more common in COPD patients compared to control. Smoking and RR phenotype may be defined as independent factors associated with COPD.

Keywords: COPD, paraoxonase 1, phenotype

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of mortality and morbidity across the globe [1]. It is characterized by enhanced chronic inflammatory response in the airway to toxic particles or gases [1, 2]. Many inflammatory cells and cytokines have a role in the pathogenesis of COPD. Environmental risk factors such as smoking, air pollution, and biomass affect the genome of susceptible individuals and trigger the onset of the disease [3]. The interaction of genetic and environmental factors contributes to the formation of the phenotypes [3]. Several different clinical and pathophysiological phenotypes have been determined in COPD [2-4]. Definition of clinical phenotypes is needed to facilitate the understanding of pathogenesis and management of the disease [4].

It is well known that oxidative stress plays an important role in the pathogenesis of COPD [2]. Paraoxonase 1 (PON1) is an antioxidant enzyme associated with high-density lipoprotein (HDL) and prevents the oxidation of low-density lipoprotein (LDL) [5]. PON1 has been involved in the pathogenesis of many disorders such as asthma, COPD, cardiovascular diseases and sepsis [6-9]. PON1 is expressed in type 1 cells, endothelial cells, and Clara cells of the alveolar epithelium. Smoking may influence the expression of PON1 by epithelial damage [10]. The human plasma paraoxonase activity in a population displayed a polymorphic distribution, and polymorphisms affect plasma PON1 levels [11, 12]. PON1 polymorphism is an amino acid substitution at the active site of the enzyme. The human PON1 gene is expressed by allelic variants, a glutamine (Q allele) for arginine (R allele) at position 192 polymorphism in relation with substrate dependent [9, 13]. In a few studies, PON1 activity was studied in COPD patients but PON1 phenotypes

have not yet been determined [7, 14]. In this study, we investigated the PON1 phenotype distribution as well as PON1 activity in subjects with COPD and control subjects.

Materials and Methods

Materials

All materials and reactants were purchased from Sigma and Merck. The reactants used were high purity and measurements were determined using spectrophotometer (Bio-Tech UV, Turkey).

Methods

Study design

Sixty-six patients with COPD diagnosed according to GOLD criteria and 59 control subjects were included consecutively between Agust 2016 and February 2017 [1]. The disease was classified according to the new version of GOLD staging [1]. The mMRC dyspnea scale was fulfilled to assess the dyspnea [15]. The patients with COPD were categorized into A-D subgroups combining exacerbation risk and mMRC dyspnea score. Smokers were defined as current smokers who smoke ³2 cigarettes daily, non-smokers were defined as subjects who had never smoked, ex-smokers were defined as subjects who had a smoking history but quit smoking more than 6 months ago.

Control subjects were chosen from our hospital after undergoing a routine examination. All subjects signed written informed consent and the Institutional Ethics Committee approved the study. Physical examination, routine blood analysis, chest X-ray, and respiratory function tests were performed on all the patients. Smoking history and the number of exacerbations in the previous year were recorded. Standard blood analysis and respiratory function tests were performed for the healthy control group.

The Population of the Study

Patients over 40 years, current or former smokers of at least 10 pack-years or biomass exposure, who exhibited an FEV_1/FVC <0.7 and post-bronchodilator FEV_1 <0% were included. Individuals aged ≥40 years with a normal spirometry and who had a smoking history of <5 pack-years were recruited as the control group. Exclusion criteria included COPD exacerbation within the previous 3 months, having a chronic inflammatory disease or malignancy, and having uncontrolled concomitant disease (arrhythmia, myocardial infarction, etc.).

Main Points

- Arylesterase (ARE) activity could be a useful marker in COPD.
- PON1 RR phenotype was common in COPD and this result is consistent with PON1 genotype studies in COPD.
- Smoking and RR phenotype can be defined independent determinants relation with COPD.

Statistical Analysis

The results are represented as mean ± standard deviation (SD). Student t-test was used to compare the variances between two groups. The correlation analyses were performed using Pearson's correlation test. One-way ANOVA was used to analyze QR subgroups. The phenotype distribution between the groups was tested using the chi-square (χ^2) test. Logistic regression analysis with the backward elimination method was performed to identify independent determinants associated with COPD. Age, sex, smoking status, phenotype, PON1 and ARE activity were included as independent variables. p<0.05 was considered to be statistically significant. Statistical Package for the Social Sciences for Windows computing program version 22.0 (IBM SPSS Corp., Armonk, NY, USA) was used for all correlation analyses.

Blood Samples

Blood samples were obtained after an overnight fasting, and the serum separated by centrifugation at 10 min at 3.000 g was recovered following protection in aliquots at -80°C until the experiment.

Determination of Lipid Parameters

HDL, LDL, triglyceride, and total cholesterol levels were measured according to standard biochemical procedures using a COBAS Integra 800 automatic analyzer (Roche, Switzerland).

Assay of PON1 and ARE Activity

PON1 activity towards paraoxon was quantified spectrophotometrically at 412 nm [16]. The molar extinction coefficient of 17 100 M^{-1} cm^{-1} was used to determine the enzyme activity at 37°C. The micromole of p-nitrophenol formed in 1 min was considered as a unit.

ARE activity towards phenylacetate was quantified spectrophotometrically at 270 nm [17]. The molar extinction coefficient of 1310 M^{-1} cm^{-1} was used to determine the enzyme activity at 25°C. The micromole of phenylacetate formed in 1 min was considered as a unit.

PON1 Phenotype Dispersion

PON1 phenotype distribution was determined by the binary substrate process [18]. The genetic polymorphism at codon 192Q→R is liable for the presence of two isotypes: Q and R. The ratio of 1 M NaCl containing buffer paraoxonase catalysis to phenylacetate catalysis is applied to find out which of the three (QQ, QR, RR) phenotypes enters. The limit values of the phenotypes are as follows: type RR>7.0; QR: 3.0-7.0; and QQ<3.0 with RR high, QR medium, and QQ low enzyme activities.

Results

The study included 66 patients and 59 controls. Clinical, functional and biochemical parameters of subjects were shown in Table 1. The mean (SD) age of the patients was 63.9 (10) years and that of the controls was 61.0 (6.5) years. Most participants were male, and there was no significant difference between the two groups in terms of age (p=0.077) and sex (p=0.174). The proportion of smokers in the COPD group was higher than that in the control group (p=0.001) (Table 1). Twenty-five (37.9%) patients with COPD had a concomitant disease (hypertension [n=12], diabetes mellitus [n=10], and ischemic heart disease [n=3]). The mean FEV1 was 46.9% of the predicted value and mean FEV_1/FVC 55.5% in the COPD group. Incidences of comorbidities of two groups were similar (p=0.352).

As expected, pulmonary function parameters (FEV_1, FVC, FEV_1/FVC) of COPD patients were lower than controls (p=0.001). When the patients were subdivided, of the 66 patients, 30.3% were in group A, 39.4% group B, 9.1% group C, and 21.2% group D.

COPD patients exhibited higher PON1 activity (199.1 vs 129.2, p=0.002) but lower ARE activity compared to control (21.3 vs 33.5, p=0.021). Levels of LDL-C, total cholesterol, and triglycerides in the COPD group were found to be higher than those in the control (p<0.05). However, levels of HDL-C in the patient group were found to be lower than those in the control (p<0.001) (Table 1).

We observed that the phenotype distribution of the two groups was different. In the COPD group, the RR phenotype was more common compared to that of the control group (60.6% [95% CI: 48.8-72.3] versus 22.0 % [95%CI: 12.0-31.9], p=0.001) (Table 2).

The lipid parameters (HDL, LDL, triglycerides, total cholesterol) did not show any difference between the phenotype subgroups (Table 3).

We compared A, B, C, and D subgroups with respect to their PON1 activity. PON1 activities in B and D groups (179.5 U mL^{-1}, 192.8 U mL^{-1}, respectively) were lower than A and C groups

Table 1. Clinical, functional and biochemical parameters of subjects

	COPD (n=66)	Control (n=59)	p
Sex (M/F)	61/5	50/9	0.174
Age	63.9 (10.7)	61.0 (6.5)	0.077
Smoking status, n (%)			
Smokers	57 (86.4)	2 (3.4)	0.001
Ex-smokers	7 (10.6)	7 (11.9)	
Non-smokers	2 (3)	50 (84.7)	
Comorbidity			
Any	41 (62.1)	45 (76.3)	0.352
Hypertension, n (%)	12 (18.2)	8 (13.6)	
Diabetes mellitus, n(%)	10 (15.2)	5 (8.5)	
Ischemic heart disease,n(%)	3 (4.5)	1 (1.7)	
FEV_1, % predicted	46.9 (16.3)	89.7 (5.5)	0.001
FVC, % predicted	66.0 (17.8)	93.2 (5.8)	0.001
FEV_1/FVC, %	55.5 (13.2)	89.9 (5.2)	0.001
Gold group, n (%)			
A	20 (30.3)		
B	26 (39.4)		
C	6 (9.1)		
D	14 (21.2)		
HDL-C (mg/dL)	48.8 (5.9)	54.9 (10.2)	0.001
LDL-C (mg/dL)	113.1 (19.5)	100.0 (26.7)	0.003
Total Cholesterol (mg/dL)	207.2 (23.8)	180.2 (34.3)	0.001
Triglyceride (mg/dl)	155.6 (30.5)	125.3 (43.7)	0.001
PON1 activity (U mL^{-1})	199.1 (134.5)	129.2 (112.5)	0.002
ARE activity (U mL^{-1})	21.3 (14.9)	33.5 (39.5)	0.021

ARE: Arylesterase; FEV_1: Forced exspiratory volume in 1 second; FVC: Forced vital capacity; COPD: chronic obstructive pulmonary disease

Table 2. PON1 phenotype distribution in patient and control subjects

	COPD		Control	
Phenotypes	n	% (95% CI)	n	% (95% CI)
QQ	12	18.2 (8.8-27.1)	24	40.7 (28.8-52.5)
QR	14	21.2 (11.3-31.0)	22	37.3 (25.6-48.9)
RR	40	60.6 (48.8-72.3)*	13	22.0 (12.0-31.9)

*RR phenotypes distribution was more common in COPD group than in contol; p=0.001 (χ^2=19.20, df=2); COPD: chronic obstructive pulmonary disease

(217.9 U mL^{-1}, 235.78 U mL^{-1}, respectively), but this difference was not statistically significant (p=0.737).

No significant correlation was found between smoking and PON1 activity (p=0.226). There was also no significant correlation between the number of exacerbations and PON1 activity (p=0.749). However, a negative association was observed between PON1 activity and mMRC dyspnea score (r=-0.25, p=0.044) (Table 4).

There was also a negative relation between PON1 activity and FEV_1/FVC (r=-0.21, p=0.019), but no similar relationship between PON1 activity and lipid parameters (HDL, LDL, triglyceride, total cholesterol) and FEV_1 or FVC was observed (Table 4).

Logistic regression analysis was performed to identify independent determinants associated with COPD. Smoking (95.0% CI: 0.001-0.036, p<0.001) and RR phenotype (95.0% CI: 0.006-0.59, p=0.016) were found to be independent factors associated with COPD (Table 5).

Discussion

In this study, we determined PON1 phenotype distribution and PON1 activity in COPD and control subjects.

As is known, reactive oxygen species (ROS) cause the oxidative deformation of basic components of the organism, which also leads to the structural damage of airway cells and connective tissues. Oxidative stress plays a crucial role in COPD and atherosclerotic disorders [2, 19-21]. Furthermore, coronary heart disease, which is related to oxidative stress is also one of the causes of mortality in COPD [20]. PON1 is an antioxidant enzyme and was examined in a few studies in COPD, but PON1 phenotypes have not been determined yet [7, 14].

Rumora et al. [7] have reported that COPD patients had lower PON-1 activity compared to the control subjects. They indicate that particularly in GOLD II-stage patients, PON1 and ARE activities significantly decrease compared to controls. The recent study reported no difference between COPD and control subjects with respect to PON1 activity [14]. However, in our study, PON1 activity in patients with COPD was found to be higher than those in the control group. These conflicting results could be explained by the patient groups did not the same with respect to disease severity.

Furthermore, previous studies demonstrated that patients with COPD had a lower ARE activity compared to that of control subjects [7, 22]. Our study also showed similar results. According to these results, we think that ARE activity could be a useful marker in COPD.

The relationship between PON1 activity and the lipid profile has been previously researched, but conflicting results have been reported [23-25]. Some studies revealed an association between PON1 activity and lipid parameters [23] whereas others did not [24, 25]. In the present study, PON1 activity was not associated with lipid parameters, which was consistent with the data from past research on type-2 diabetes mellitus [24, 25]. The inconsistent results can be explained by PON1 activity and concentration being modulated by environmental factors, lifestyle, dietary habits, and genetic properties [26-28].

Comorbid diseases is another factor that can affect PON1 and ARE activities. However, in this study, no difference was observed between patients with COPD and healthy subjects with

Table 3. Association between lipid profile and PON1 phenotype of the subjects

Variables	QQ	QR	RR	p
HDL-C (mg/dL)				
Patient	46.9 (3.9)	52.2 (7.4)	48.0 (5.2)	0.093
Control	53.8 (8.6)	53.2 (10.1)	59.7 (12.3)	0.135
LDL-C (mg/dL)				
Patient	113.9 (17.49	110.7 (21.5)	113.9 (19.7)	0.892
Control	102.3 (24.2)	100.1 (32.3)	94.0 (26.9)	0.585
Total Cholesterol (mg/dL)				
Patient	208.6 (24.9)	210.2 (30.3)	205.6 (21.0)	0.852
Control	183.0 (35.6)	180.5 (35.4)	172.6 (31.0)	0.411
Triglyceride (mg/dL)				
Patient	164.6 (36.1)	158.5 (26.1)	151.7 (30.4)	0.468
Control	131.1 (41.0)	127.0 (48.0)	107.8 (44.5)	0.177

HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 4. Relation between PON1 activity and other parameters

Variables	r	p
FEV_1	-0.17	0.052
FVC	-0.09	0.270
FEV_1/FVC	-0.21	0.019
HDL-C (mg/dL)	-0.06	0.496
LDL-C (mg/dL)	0.13	0.153
Total Cholesterol (mg/dL)	0.11	0.216
Triglyceride (mg/dL)	-0.03	0.735
mMRC	-0.25	0.044
Smoking	0.10	0.226

mMRC: modified Medical Research Council dspnea scale; FEV_1, FVC: pulmonary function parameters; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 5. Logistic regresyon analysis of variables in COPD

					95% CI	
Variable	β	SE	p	Exp (β)	Lower	Upper
Age	0.044	0.004	0.311	1.045	0.933	1.022
Sex						
Female (ref)						
Male	1.250	0.979	0.202	3.490	0.512	23.78
Smoking						
No	-5.290	1.001	0.001	0.005	0.001	0.036
Yes (ref)						
PON	0.004	0.004	0.349	1.004	0.996	1.012
ARE	-0.024	0.023	0.311	0.977	0.933	1.022
Phenotype						
QQ (ref)						
QR	-1.190	1.317	0.366	0.304	0.023	4.016
RR	-2.814	1.167	0.016	0.060	0.006	0.590

-2 log-likelihood: 69.585; Chi-square:101.799; (p:0.001) Nagelkerke R^2: 0.74

respect to comorbidities such as hypertension, diabetes, and heart diseases.

Moreover, in our study, PON1 activity was negatively related to mMRC and FEV_1/FVC. It can be concluded that PON1 activity decreased as the disease progressed.

In a few studies, it has been reported that cigarette smoke causes a reduction in PON1 activity [29-31]. However, another study indicated that PON1 activity in smokers did not differ from that of nonsmokers [32]. In our study, the proportion of smokers in the COPD group was higher than that of control. Likewise, PON1 activity in the COPD group was higher compared to that in the control group, but no direct association was observed between smoking and PON1 activity. Our patient and control groups did not homogenous with respect to smoking status. Thus, longitudinal studies which included homogenous groups are needed.

In recent years, COPD-linked phenotypes have become the common interest area of researchers [33]. Moreover, it is recommended to choose the treatment according to clinical phenotypes. according to clinical phenotypes are being recommended [1]. In a few previous studies, the relationship between PON1 genotype and COPD [34, 35] was determined, but there is no research which examines the relationship between PON1 phenotype and COPD. We determined that RR phenotype was more common in COPD patients compared to those in the control group. Furthermore, we found that smoking and RR phenotype were independent variables of COPD.

In a previous study, a significant difference in Q192R genotype was found between patients with COPD and that of the control group [34]. In another study, Tekes et al. [35] reported that RR genotype was more prevalent in patients with COPD compared to healthy nonsmokers. They have inferred that the PON1192 gene may be related to genetic susceptibility to COPD. Our phenotype results are consistent with previous PON1 genotype studies in COPD.

One of the strengths of our study was that it is the first study investing PON1 phenotypes in COPD. The pesent study has some limitations such as, a single center study and small sample size.

The relationship between smoking and COPD is well known. In addition to other known risk factors, our results suggested that RR phenotype may be an independent risk factor associated with COPD. Further studies are needed to determine whether RR phenotype constitutes a risk in COPD progression.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Balikesir University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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