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Association between oxidative stress markers and lung function parameters in stable chronic obstructive pulmonary disease patients

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Abstract

Inflammation plays a role in the pathogenesis of COPD by interfering with the protease/antiprotease and oxidant/antioxidant balance. There is no adequate data about the relationship between oxidative stress biomarkers and FEV1 values in stable COPD patients. Prospective cohort study, designed in tertiary care chest disease hospitals' out-patient clinic. COPD patients were approved informed consent were included in the study. The total antioxidant status (TAS,), total oxidant status (TOS), total thiol (TT), native thiol (NT), IL1 IL6, and TNFα levels were measured. The mean age of 33 COPD patients who joined the study was 61±9,32 years, while their average body mass index (BMI) was 27±4,31 kg/m2. There was no statistically significant difference between the groups in terms of age, gender, weight, smoking status and comorbidities. According to the results of the analysis, there was a statistically significant difference in TOS, TAS, oxidative stress index (OSI), TT, NT, DIS, IL-1β, IL-6, and TNFα between the control and COPD patient groups ($p<0.001$ for all variables). Compared to healthy controls, COPD patients had greater TOS, OSI, disulfide (DIS), IL-1β, IL-6, and TNFα levels. Healthy controls, had considerably higher TAS, TT, and NT values than the COPD group. No significant correlation was detected between the pulmonary function test results and oxidative stress markers. In conclusion, no significant correlation was detected between the pulmonary function test results and oxidative stress markers besides TOS was increased while TAS was decreased, in accordance with the pathophysiology of COPD, oxidative stress markers can also be utilized in COPD patients.

Keywords: COPD, stable, oxidative stress, TOS, TAS, OSI, TT, NT, DIS, IL-1β, IL-6, TNFα

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by chronic airway obstruction and respiratory symptoms caused by gas or particle-induced airway and/or alveolar damage [1]. It is widely accepted that the abnormal inflammatory response that develops in the airways and lung parenchyma in response to harmful particles and gases is the primary pathology that contributes to the pathogenesis of COPD. This abnormal inflammatory response interferes with the lung's typical defense and repair mechanisms, causing tissue damage. This causes chronic airflow obstruction and other COPD-related physiological abnormalities [2, 3].

By interfering with the protease/antiprotease and oxidant/antioxidant equilibrium, inflammation plays an essential role in the COPD pathogenesis [3]. While oxidant stress and protease/antiprotease imbalance may be entirely due to inflammation, increased oxidative activity due to oxidant substances in cigarettes or decreased antiprotease activity due to genetic reasons such as alpha-1 antitrypsin deficiency may also have an impact on the development of these processes [4].

Reactive oxygen species (ROS) are linked to cellular metabolic damage, which results in lipid peroxidation, protein modification, and nucleic acid damage [5]. Thiols are chemical compounds that contain the sulfhydryl group and take part in the formation of ROS in cells. The thiol disulfide bond is reduced, which decreases oxidative stress and keeps the thiol disulfide balance in control [6]. The thiol-disulfide balance has been identified as a novel biological marker of oxidative stress in recent papers.

COPD is a heterogeneous disease with different clinical and pathophysiological components [7]. Therefore, biomarker studies have become increasingly important in defining different clinical subgroups in COPD and determining the endotypes of these groups based on their responses to targeted pharmacological treatment [8, 9]. The inflammatory markers that indicate oxidative stress can be useful for the management of the COPD.

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In order to develop advanced and personalized treatments, it is critical determine the underlying mechanisms triggered by oxidative stress. Therefore in this study is to examine and evaluate oxidative stress biomarkers in stable COPD patients.

Materials and Methods

After the approval of the ethics Committee Of Health Sciences University Turkey Hamidiye Scientific Research Ethics Committee dated 24/12/2021 and decision number 39/2, thirty three COPD patients were included in the study, as volunteers of varying quality. In the study, the control group was formed by choosing similar age and gender characteristics.

Inclusion criteria

1. Patients diagnosed with COPD

Exclusion criteria

1. Asthma
2. Bronchiectasis,
3. Any diagnosis of infection or inflammation,
4. Any solid or hematological malignancy,
5. Diagnosis of pulmonary embolism,
6. Autoimmune diseases,
7. Patients receiving systemic or oral corticosteroids or immunosuppressive therapy

After patients who applied to the tertiary care Chest disease hospital outpatient clinic were diagnosed with COPD signed informed consent, the remaining inert blood will be studied after the routinely requested blood is studied. Approximately 4 mL of blood was drawn and placed in sterile blood tubes containing lithium-heparin. This plasma was drawn in quantities ranging from 300 to 600 µL, placed in 1.5 mL centrifuge tubes, and stored at -80°C. The remaining lithium-heparin blood was centrifuged at 3000 x g for 10 minutes before being separated and stored at -80°C until analysis.

The total antioxidant status (TAS, Rel Assay, Gaziantep, Turkey), total oxidant status (TOS, Rel Assay, Gaziantep, Turkey), total thiol (TT, Rel Assay, Gaziantep, Turkey), native thiol (NT, Rel Assay, Gaziantep, Turkey), IL1β (BT Laboratory, China - E0143Hu), IL6 (BT Laboratory, China - E0090Hu), and TNFα (BT Laboratory, China - E0082Hu) levels were measured using different colorimetric and photometric methods using commercial kits. Oxidative stress index (TOS/TAS) and disulfide levels ((TT-NT)/2) were calculated with mathematical formulas.

Statistical Analysis

All statistical analysis will be performed using the SPSS version 25.0 program (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the quantitative variables were suitable for normal distribution. The independent samples t-test was used to compare independent groups in terms of normally distributed variables, and the Mann Whitney U test was used in terms of non-normally distributed variables. To investigate the relationship between quantitative variables, Pearson or Spearman correlation analysis was used. Descriptive statistics for quantitative variables with a normal distribution were shown as meanstandard deviation, whereas descriptive statistics for non-normally distributed quantitative variables were shown as median (25-75th percentile). The frequency distribution was used to express descriptive statistics for qualitative variables (%). Values of $p<0.05$ were considered statistically significant.

Results

The mean age of 33 volunteers who participating in the study was 61±9.32 years, while their average body mass index (BMI) was 27±4.31 kg/m². There was no statistically significant difference between the groups in terms of age, gender, weight, smoking status and comorbidities ($p>0.05$).

Demographic features are given in table 1.

Table 1. Demographic features of the patients

Variables	
Groups	
Control	33 (50)
COPD	33(50)
Gender	
Male	52(78.8)
COPD stages (according to FEV1)	**n=33**
Stage 1	5(15.2)
Stage 2	19(57.6)
Stage 3	7(21.2)
Stage 4	2(6.1)
Smoking status of COPD patients	**n=33**
Exsmoker	11(33.3)
Current smoker	22(66.7)
Comorbidities of COPD patients	**n=26 (79)**
Congestive heart failure	6(9.1)
Coronary artery disease	9(27.3)
Hypertension	12(36.4)
Atrial fibrillation	1 (3)
Diabetes	6(18.2)
Chronic renal disease	2(6.1)

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease , FEV1: Forced expiratory volume in one second.

Table 2 shows on oxidative stress markers in the control and COPD patient groups, as well as group comparison results. According to the results of the analysis, there was a statistically significant difference in TOS, TAS, OSI, TT, NT, DIS, IL-1β, IL-6, and TNFα between the control and COPD patient groups ($p<0.001$ for all variables). When compared to healthy controls, COPD patients had greater TOS, OSI, DIS, IL-1β, IL-6, and TNFα levels. Healthy controls, on the other hand, had considerably higher TAS, TT, and

Table 2. Comparison results on oxidative stress markers in the control and COPD groups

Oxidative stress markers	GROUPS		t / Z	p
	Control (n=33)	COPD (n=33)		
TOS	10.11(9.04-11.98)	13.62(13.30-14.36)	-6.534	<0.001[m]
TAS	1.17(1.05-1.24)	0.85(0.74-0.92)	-6.675	<0.001[m]
OSI	8.81(7.41-11.24)	16.65 (14.60-19.14)	-6.868	<0.001[m]
TT	526.32±62.98	467.05±45.84	-4.371	<0.001[s]
NT	318.83(262.60-384.10)	201.77(169.89-231.49)	-6.393	<0.001[m]
DIS	102.68±3.29	132.99±10.57	15.724	<0.001[s]
IL1β	300.18±60.85	467.06±57.37	11.462	<0.001[s]
IL6	101.08±12.84	174.62±17.44	19.508	<0.001[s]
TNFα	156.75(136.15-179.97)	253.94(242.68-290.26)	-6.560	<0.001[m]

t: t test statistics, Z: Z test statistics
Descriptive statistics are shown as median (25.–75. percentile) or mean±standard deviation
m: Mann Whitney U test, s:t test
Abbreviations: COPD, Chronic Obstructive Pulmonary Diseases

Table 3. Comparison results on the presence of comorbidities

Oxidative stress markers	Comorbidities		t / Z	p
	Absent (n=7)	Present (n=26)		
TOS	13.81(13.34-14.82)	13.59(13.22-14.18)	-1.145	0.268[m]
TAS	0.85±0.11	0.81±0.13	0.723	0.475[s]
OSI	17.01±2.48	17.43±3.61	-0.290	0.774[s]
TT	442.91±48.43	473.54±43.82	-1.608	0.118[s]
NT	170.05(157.05-208.28)	203.72(172.30-238.61)	-1.938	0.054[m]
DIS	132.11±10.48	133.23±10.79	-0.244	0.809[s]
IL1β	459.72±43.27	469.04±61.19	-0.376	0.709[s]
IL6	166.79±19.45	176.73±16.63	-1.356	0.185[s]
TNFα	242.91(240.16-255.87)	255.47(243.64-291.39)	-1.057	0.308[m]

t: t test statistics, Z: Z test statistics
Descriptive statistics are shown as median (25.–75. percentile) or mean±standard deviation
m: Mann Whitney U test, s: t test

Table 4. Findings of correlation analysis between the number of hospital admissions, the number of emergency admissions in the last year, and the stage of COPD and oxidative stress markers

	Hospital admission	ED admission	COPD stage
TOS	r=-0.117	r=-0.142	r=-0.236
	p=0.516	p=0.429	p=0.186
TAS	r=0.148	r=-0.041	r=-0.304
	p=0.412	p=0.822	p=0.085
OSI	r=-0.206	r=-0.041	r=0.164
	p=0.250	p=0.822	p=0.361
TT	r=0.146	r=0.000	r=0.144
	p=0.419	p=0.999	p=0.424
NT	r=0.128	r=-0.001	r=0.147
	p=0.479	p=0.993	p=0.413
DIS	r=0.066	r=0.101	r=-0.089
	p=0.716	p=0.576	p=0.620
IL1β	r=0.043	r=-0.246	r=-0.067
	p=0.812	p=0.167	p=0.712
IL6	r=-0.051	r=-0.267	r=0.144
	p=0.780	p=0.132	p=0.425
TNFα	r=0.130	r=-0.120	r=-0.125
	p=0.470	p=0.506	p=0.489

r: Correlation coefficient, ED: emergency department
Abbreviations: ED admission, Emergency Department admission; COPD, Chronic Obstructive Pulmonary Disease

NT values than the COPD group.

Descriptive data for oxidative stress markers in groups with and without comorbid disease and group comparison results are shown in Table 3. According to the results of the analysis, there was no statistically significant difference in oxidative stress markers between patients with and without comorbidities (p>0.05).

Table 4 shows the number of hospital admissions, emergency visits, and findings of the association analysis between COPD stages and oxidative stress indicators . There was no statistically significant association between oxidative stress levels and previous-year hospital admissions, emergency admissions, or COPD stage (p>0.05).

Correlation analysis findings between pulmonary function test results and oxidative stress markers are shown in table 5 (p>0.05).

Table 5. Correlation analysis findings between pulmonary function test results and oxidative stress markers

	FEV1 (ml)	FEV1 (%)	FVC (ml)	FVC (%)	FEV1/FVC (%)
TOS	r=0.118	r=0.165	r=0.082	r=0.136	r=0.328
	p=0.512	p=0.358	p=0.650	p=0.450	p=0.063
TAS	r=0.328	r=0.310	r=0.250	r=0.279	r=0.250
	p=0.062	p=0.079	p=0.161	p=0.116	p=0.160
OSI	r=-0.275	r=-0.246	r=-0.244	r=-0.249	r=-0.147
	p=0.121	p=0.168	p=0.172	p=0.163	p=0.414
TT	r=-0.125	r=-0.158	r=-0.083	r=-0.148	r=-0.094
	p=0.489	p=0.380	p=0.646	p=0.413	p=0.602
NT	r=-0.198	r=-0.187	r=-0.154	r=-0.181	r=-0.158
	p=0.268	p=0.298	p=0.392	p=0.313	p=0.380
DIS	r=0.150	r=0.092	r=0.092	r=0.076	r=0.107
	p=0.404	p=0.611	p=0.611	p=0.972	p=0.552
IL1β	r=0.263	r=0.148	r=0.262	r=0.125	r=0.016
	p=0.140	p=0.411	p=0.141	p=0.487	p=0.930
IL6	r=-0.235	r=-0.271	r=-0.247	r=-0.300	r=0.081
	p=0.187	p=0.127	p=0.165	p=0.090	p=0.652
TNFα	r=0.224	r=0.115	r=0.275	r=0.121	r=0.018
	p=0.211	p=0.522	p=0.122	p=0.503	p=0.921

r: Correlation coefficient
Abbreviations: FEV1: Forced expiratory volume in one second; FVC, Forced vital capacity

Discussion

In the current study, in the COPD group, TOS was increased while TAS was decreased, in accordance with the pathophysiology of COPD, oxidative stress markers can also be utilised in patients diagnosed with the disease. No significant correlation was detected between the pulmonary function test results and oxidative stress markers.

Oxidative stress is a major contributor to COPD pathogenesis and has a number of consequences for the lungs. It has a significant role in the start and progression of the disease. The equilibrium of oxidative and antioxidative products is altered in COPD. Oxidative stress causes increased inflammation, corticosteroid resistance, accelerated aging and cellular damage, autoimmunity, and DNA mutation [10].

Oxidative stress is higher in COPD patients, especially during acute exacerbations. Smoking, air pollution, and biomass smoke are exogenous causes of oxidative stress in the lungs, yet oxidative stress persists even in ex-smokers, suggesting that oxidative stress can develop endogenously. The number of alveolar macrophages in COPD patients is significantly higher, and they are more active than in control subjects, generating more ROS in the form of superoxide anions and hydrogen peroxide [11]. Patients with COPD have more activated neutrophils in their alveoli and active neutrophils in their peripheral circulation, produce more reactive oxygen species (ROS), especially during exacerbations [12]. Other intracellular ROS sources include membrane-associated NADPH oxidases, cytoplasmic ROS-producing enzymes including the xanthine/xanthine oxidase system, and neutrophil-derived myeloperoxidases [13].

Proinflammatory cytokines are produced by activated macrophages and are involved in the up-regulation of inflammatory processes. Pro-inflammatory cytokines such as IL-1, IL-6, and TNFα are implicated in the pathogenesis of COPD, according to a series of studies [3]. Monocytes and macrophages, as well as non-immune cells including fibroblasts and endothelial cells, release IL-1β following cell damage, infection, invasion, and inflammation. Given that immune system cells are the primary endogenous sources of oxidative stress, our results are as expected.

In this study, oxidative stress levels between patients with COPD and the control group were examined.

In the COPD group, TOS and OSI were high, but TAS and TT were low, as expected. Due to increased oxidative products and/or

impairment of antioxidant systems, these findings suggested that COPD has a high oxidative environment. Furthermore, the fact that proinflammatory cytokines were found to be elevated in the COPD group, along with oxidative indicators, implies that the two conditions may be related.

In previous studies, cigarette smoking has also been proven to enhance oxidative stress. TOS and OSI were found to be high in our COPD group, which comprised both exsmokers and smokers, in the current study [14]. TAS values in individuals with COPD have also been reported to be low in previous studies, similar to these results shown here [15,16].

In healthy nonsmokers, smokers, and COPD patients, our correlation an.

alyses found no significant connection between spirometry results and antioxidant status, confirming earlier findings [16,17]. Unlike previous research, no relationship was found between comorbidities, emergency department admissions, hospitalization, and COPD stages with oxidative stress [14]. This situation can be explained by the fact that the majority of our COPD patients are in stages 1 and 2.

The limitations of our study were the limited number of patients when divided into subgroups such as comorbidity, single-centered, the absence of nonsmoker patients, and the inability to balance the distribution of patients between COPD stages. Its strengths were that there was a control group that was very similar in age and gender, and that proinflammatory markers were included along with oxidative markers.

Conclusion

Our findings back up the theory that oxidative stress is more prevalent in COPD patients. Furthermore, there was a significant oxidant/antioxidant imbalance. Patients with COPD at all stages, with and without comorbidities, had higher levels of oxidative stress, antioxidant defense, and systemic inflammation. The development of novel therapeutic techniques that combine antioxidant therapy with COPD treatment should be a focus of future study.

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Conflict of interests
The author contribute to the study and work with preparing the manuscript. And the author declare to have no conflict of interest directly or indirectly related to the manuscript contents

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Ethical approval
The approval of the ethics Committee Of Health Sciences University Turkey Hamidiye Scientific Research Ethics Committee dated 24/12/2021 and decision number 39/2.

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