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Original Research Article

Evaluation of Oxidative Stress Parameters in Chronic Obstructive Pulmonary Disease before Medical Treatment

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Abstract

It is known that the pathophysiology of chronic obstructive pulmonary disease (COPD), a disease that develops against inhaled harmful chemicals and is characterized by progressive airway obstruction, is associated with oxidative stress. However, due to inconsistent findings, the oxidative status of COPD is not fully understood. It is thought that determining the oxidative state in detail may be an effective diagnostic criterion in the diagnosis of COPD. In addition, supplementing antioxidative mechanisms with diet or drugs is among the new treatment strategies. Total antioxidant status (TAS), total oxidant status (TOS), paraoxonase (PON1), arylesterase (ARES), total thiol (THIOL) levels were examined in COPD and control. Oxidative stress index (OSI) ratios were calculated. Oxidative balance did not change according to healthy individuals, although we observed a tendency to increase together in oxidative and antioxidative parameters in COPD patients. We observed that the tendency to increase antioxidative capacity in COPD patients is independent of PON1, ARES, and THIOL. When compared to the control group, the serum thiol parameter of the COPD group was shown to be significantly low. We think that the decrease in serum thiol parameter can be considered as a new indicator to confirm the diagnosis of COPD.

Keywords: Arylesterase (ARES), Chronic obstructive pulmonary disease (COPD), Paraoxonase (PON1), Total oxidative load, Total thiol (THIOL)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), known as progressive and irreversible airway obstruction, reduces the quality of life, results in death, and is becoming more common worldwide (GBD, 2020). By causing inflammation and free radicals in the respiratory tract, smoking and air pollution raise the burden of oxidative stress, which causes COPD to develop and worsen (Comandini et al., 2009; Lewis et al., 2021). It has been reported that oxidative stress alters the structure of important lung tissues as the parenchyma and the airway, causing irreparable harm (Drost et al., 2005). The imbalance between oxidative and anti-oxidative mechanisms and changes in total antioxidative stress (TAS) and total oxidative stress (TOS) levels are the primary causes of oxidative stress. The action of reactive oxygen species (ROS) has an impact on the structural properties of proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) (Liang et al., 2000; Steele et al., 2013). These actions cause biological components to deform structurally, which may cause several organs to lose their functions (Agarwal et al., 2010; de M Bandeira et al., 2013; Kluchová et al.,

2007). The majority of ROS are produced by enzymatic and nonenzymatic mechanisms (Valko et al., 2004). The oxidation of organic substances by oxygen or the exposure of cells to ionizing radiation are two other nonenzymatic ways that free radicals can be created (Dröge, 2002). Both endogenous and exogenous free radicals participate in the formation of free radicals. Numerous things, such as inflammation, ischemia, infection, cancer, excessive exercise, and emotional stress, can produce free radicals. Free radicals can be created by several environmental factors, such as pollution, heavy metals, specific chemicals, cigarette smoke, alcohol, and radiation. As a result of the body's degradation or metabolism of these exogenous substances, free radicals are produced (Genestra, 2007; Taysi et al., 2008; Taysi et al., 2019; Taysi et al., 2022).

The clinical and pathophysiological features of COPD are linked to oxidative stress in the lungs caused by external oxidants like tobacco smoke, biomass fuel, and air pollution, as well as endogenous oxidants like ROS produced by inflammatory cells and epithelium (Barnes, 2020; Barnes, 2022; Domej et al., 2014). A major source of ROS is mitochondrial respiration, and smoking leads to dysfunctional mitochondria that overproduce ROS (Aravamudan et al., 2014). Nowadays, it is widely believed that COPD is caused by an acceleration of lung aging caused by a buildup of senescent cells, which also release ROS more than intact cells (Kume et al., 2023; Barnes et al., 2019; Tsuji et al., 2004; Childs et al., 2017). As a result, many of the pathophysiological alterations in COPD are likely driven primarily by oxidative stress (Kirkham et al., 2013).

The antioxidant balance modifies the impact of oxidative stress. A known antioxidant enzyme, paraoxonase 1 (PON1), expressed by the PON1 gene, has 354 amino acids and a molecular weight of 43 kDa (Soran et al., 2009). The substrates used to detect PON1 activity—specifically, arylesterase (ARES) (when using phenylacetate) and paraoxonase—determine the activity of this enzyme (when using paraoxon). PON1 is a lipo-lactonase that is connected to high-density lipoprotein (HDL) and exhibits flexible esterase activity (Mackness et al., 1991; Aviram et al., 1999; Sarioglu et al., 2020; Sepúlveda-Loyola et al., 2021). Studies have examined the functions of PON1 in several disease entities, such as cardiovascular disease, renal failure, diabetes mellitus, neurological disorders, and sleep apnea, based on the antioxidant effects of PON1 (Camps et al., 2009; Perła-Kaján et al., 2012; Gugliucci et al., 2012). Although the link between PON1 and COPD is also intriguing, not enough information has been provided in the literature (Watanabe et al., 2021).

Thiols are organosulfur molecules with an alkyl group or another type of organic molecule. ROS can degrade them, resulting in the formation of sulfate or disulfide (Heffner et al., 1989; Sotgia et al., 2020). Redox states of thiols in the organism reflect oxidative stress. Deterioration of redox status has been observed in various respiratory diseases such as cystic fibrosis, acute respiratory distress syndrome, asthma, and COPD (Rahman et al., 1999; Zinellu et al., 2016). Since many small-molecule thiols, including cysteine and homocysteine, can react with oxidants, a thorough study of the redox state of thiols may be more useful for determining the level of systemic oxidative stress in COPD (Zinellu et al., 2020; Jiang et al., 2022).

Although oxidative stress parameters are frequently studied in many diseases, we could not find a study in which all TAS, TOS, PON1, ARES, and total thiol (THIOL) parameters were evaluated together in untreated COPD patients. We evaluated the oxidative-antioxidative balance in newly diagnosed COPD patients who have not yet received drug therapy, to create a resource for studies on the diagnosis and treatment of COPD.

MATERIALS AND METHODS

Participants

We conducted this study on 80 subjects who were treated in the Chest Diseases Department, Kütahya Health Sciences University, Kütahya, Turkey. Fifty unrelated COPD patients (27 males, 23 females) were included in the patient group and 30 (19 males, 11 females) healthy subjects (age-matched) were included in the control group. Both the control and patient groups were chosen among the Turkish population. The diagnosis of COPD was established based on the criteria proposed by the Global Initiative for Chronic Obstructive Lung Disease used as the foundation for the diagnosis of COPD (GOLD Guideline, 2014).

Power analysis was performed by calculating the statistical power for each group using a two-tailed test and 80% power of confidence interval with alpha = 5% level of significance.

All procedures were explained to individually all subjects and written informed consent was obtained. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in prior approval by the institution's human research committee. The study procedure was approved by the AfyonKocatepe University Ethics Committee.

Enzyme-Linked Immunosorbent Assay (ELISA) Analyses and Oxidative Stress Index Calculation

Venipuncture was used to take peripheral blood samples (5 ml) from each patient. Peripheral blood samples were collected in tubes without ethylenediaminetetraacetic acid (EDTA) from all subjects. The tubes were left at room

Table 1. The comparisons of results between the patient and control groups.

GROUPS / Characteristics	COPD (n=50) Female (n=23)	COPD (n=50) Male (n=27)	Control (n=30) Female (n=11)	Control (n=30) Male (n=19)	P values
Age	45.81 ± 5.60		47.15 ± 3.15		0.348
TAS (mmol.TroloxEquiv./L)	1.25±0.31		1.17±0.21		0.790
TOS (µmol H2O2 Equiv./L)	83.02±19.45		74.91±33.09		0.687
OSI (arbitrary unit)	6730.25±4153.12		6583.04±4656.95		0.753
PON1 (U/L)	212.41 ± 145.27		274.07±151.39		0.227
ARES (U/L)	658.07 ± 173.12		681.13±170.01		0.589

Data are mean ± SEM.COPD; Chronic obstructive pulmonary disease, TAS; Total antioxidant status, TOS; Total oxidative status, OSI; Oxidative stress status, ARES; Arylesterase, PON1; Paraoxonase, THIOL; Total thiol.

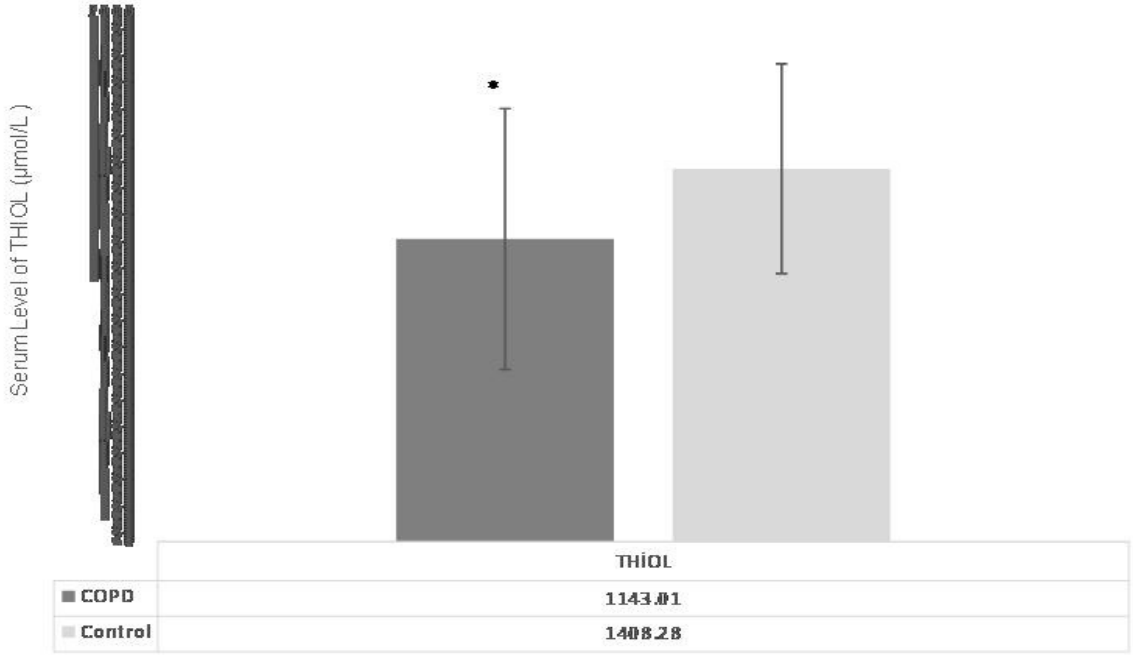

Figure 1. Serum Level of THIOL in COPD and control groups.COPD; Chronic obstructive pulmonary disease, THIOL; Total thiol.
*; $p < 0.05$ vs. control group.

temperature for 20 to 30 minutes to enable the blood to clot. We centrifuged the clot at 3000 rpm for 15 minutes, yielding serum, to extract the fibrinogen precipitate. After centrifugation, each serum sample was kept at -80 °C for enzyme-linked immunosorbent assay (ELISA) analysis.

Serum concentrations of TAS (Rel Assay Diagnostics, Turkey, REF No: RL0017, LOT No: JE 14042A), TOS (Rel Assay Diagnostics, Turkey, REF No: RL0024, LOT No: JE 14048Og), PON1 (Rel Assay Diagnostics, Turkey, REF No: RL0031, LOT No: JE14028P), ARES (Rel Assay Diagnostics, Turkey, REF No: RL0055, LOT No: JR13017AR), and THIOL (Rel Assay Diagnostics, Turkey, REF No: RL0178, LOT No: AL 13011TL) were analyzed by ELISA kits (Rel Assay Diagnostic, Gaziantep Diagnostic, Gaziantep, TURKEY) at Rel Assay Diagnostics Research Laboratories in Turkey. An ELISA microplate reader was used to assess the chemi-luminescence results (das, Digital and Analog Systems, Vimercate, MI, Italy).The oxidative stress index (OSI) was calculated according to the following formula: OSI (arbitrary unit) = TOS (µmol H2O2 Equiv./L)/TAS (mmol. Trolox Equiv./L) x100 (Zengin et al., 2014).

Statistical analyses

The SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 16.0 package application was used to

conduct the statistical analyses. Power analysis was performed by calculating the statistical power of the two-tailed test for the study. The total sample size was 80 (COPD group n=50, Control group n=30), the power of the research was 80%, the effect size was 0.55, the interval alpha=5% level of significance, and the effect size was 0.55. Serum levels of interest parameters were given as mean ± standard error of the mean (SEM). The data obtained were evaluated using the Mann–Whitney U tests. All p-values <0.05 were accepted as statistically significant.

RESULTS

The patient group consisted of 50 unrelated COPD patients (27 males, 23 females), whereas the control group consisted of 30 (19 males, 11 females) healthy, mean ages were found as 45.81 ± 5.60 for the COPD group and 47.15 ± 3.15 for the control group, age-appropriate individuals. There were no statistically significant age or gender mean differences between the two groups ($p > 0.05$) (Table 1).

The serum levels of PON1, ARES, and THIOL were found as 212.41 ± 145.27U/L, 658.07 ± 173.12 U/L, and 1143.01 ± 493.04 µmol/L in the COPD group. The serum levels of PON1, ARES, and THIOL were found as 274.07±151.39U/L, 681.13±170.01U/L, and 1408.28 ± 395.85µmol/L in the control group. Although no statistically significant differences were found for PON1 and ARES between the two groups, THIOL was found significantly lower in the COPD group compared with the control ($p^{PON1}=0.227$, $p^{ARES}=0.589$, $p^{THIOL}=0.015$) (Table 1) (Figure 1).

The serum levels of TAS, TOS, and OSI were found as 1.25±0.31mmol/L, 83.02±19.45 µmol/L, and 6730.25±4153.12 arbitrary unit in the COPD group, and 1.17±0.21mmol/L, 74.91±33.09 µmol/L and 6583.04± 4656.95 arbitrary unit in the control group. No statistically significant differences were found for these parameters between the two groups ($p^{TAS}=0.790$, $p^{TOS}=0.687$, $p^{OSI}=0.753$) (Table 1).

DISCUSSION

Airway obstruction is caused by a chronic, irreversible illness known as COPD. The World Health Organization (WHO) stated that COPD was the third most common cause of death globally in 2019 (Lindberg et al., 2021). Apoptosis, extracellular matrix remodeling, alveolar epithelial injury, mitochondrial respiration, membrane lipid peroxidation (LPO), mucus hypersecretion, oxidative inactivation of surfactants-antiproteases, and the etiology of COPD are all affected by oxidative stress (OS) (Albano et al., 2022; Dailah et al., 2022; Rahman, 2005; Thimmulappa et al., 2019). In this context, the pathogenesis of COPD is closely linked with the increased oxidative load due to harmful oxidants and the delicate balance between the protective intracellular and extracellular antioxidant systems (Sierra-Vargas et al., 2023; Zinellu et al., 2016). Different phases of COPD severity are significantly influenced by the oxidant-antioxidant balance (Singh et al., 2017). Since this situation occurs because of insufficient antioxidants or their inability to cope with the oxidative load, the targets of treatments to be developed against oxidative stress should be to reduce oxidant formation or increase antioxidants (Rahman et al., 2012). In our study, we tried to evaluate the development of oxidant-antioxidant balance in patients with newly diagnosed COPD whose treatment was not regulated, with different antioxidative parameters belonging to the oxidative pathway.

It is difficult to measure each antioxidant and oxidative agent in different biological samples. Therefore, methods have been developed to determine TAS and TOS in serum samples (Zinellu et al., 2016; Aydemir et al., 2019). In the literature on TAS and TOS in COPD, studies are confirming the oxidant-antioxidant imbalance in COPD but offering different results. In some studies, no significant difference was found in TAS values in stable COPD patients compared to the control group (Koechlin et al., 2004; Can et al., 2015) while a significant decrease was found in other studies (Aydemir et al., 2019; ben Anes et al., 2014; Lakhdar et al., 2011), and significant increase was observed (Hlavati et al., 2020). In some studies, a significant reduction in TAS was reported only in the COPD exacerbation phase (Rahman et al., 1997; Stanojkovic et al., 2011). In other studies, it has been reported that there is no relationship between the degree of airway obstruction and TAS levels in COPD (Ben Anes et al., 2014; Ekin et al., 2017; Tavilani et al., 2012). Smoking is the main source of ROS that cause disease exacerbations and widespread tissue damage in COPD (Fischer et al., 2015). An increase in systemic oxidative stress, a decrease in antioxidants, and as a result decrease in plasma Trolox antioxidant capacity have been reported in smokers (Langen et al., 2003; Bloomer, 2007; Aydemir et al., 2019). It has also been reported that oxidative stress in COPD is associated with genetic and epigenetic factors (Fischer et al., 2015).

In our study, we found an insignificant increase in TAS and TOS levels in the serum COPD group compared to the control group. Although the increase in oxidative stress is an expected situation in COPD, we have obtained results that are compatible with the literature in our study. The increase in the serum TAS level in the COPD group was found to be consistent with some literature data. It is not possible to definitively interpret the increase in the serum TAS level in COPD because the individuals in our patient groups were newly diagnosed, COPD grading was not done, and it was not significant. We think that this increase is a homeostatic response to

compensate for the oxidative stress associated with the pathophysiology of the disease in the COPD group. We observed almost no difference between the control and COPD groups in terms of OSI. We think that the absence of any difference between the groups in terms of OSI parameters is an indication that the antioxidative response to oxidative stress in COPD is an effective homeostatic regulation, at least in newly diagnosed and untreated COPD patients. We will try to explain the increase in antioxidant capacity with the results of the antioxidative agents we examined.

PON1 prevents the oxidation of low-density lipoprotein (LDL) as an antioxidant enzyme associated with high-density lipoprotein (HDL), which has a function in the pathogenesis of many diseases such as asthma, COPD, cardiovascular diseases, and sepsis (Kappelle et al., 2012; Sarioglu et al., 2015; Rumora et al., 2014; Wysocka et al., 2017; Rodríguez-Esparragón et al., 2005). Plasma PON1 activity shows genetic polymorphism among populations (Costa et al., 2005; Richter et al., 2009). Studies are showing that PON1 activity is lower (Rumora et al., 2014), unchanged (Zinellu et al., 2016), and higher (Sarioglu et al., 2020) in COPD patients compared to healthy individuals. Like PON1, ARES has an antioxidant impact. Its function is not influenced by genetic variation like PON1 (Saeidi et al., 2017). It has been reported in the literature that there is a decrease in ARES activity in COPD patients compared to control individuals (Sarioglu et al., 2020; Gumusyayla et al., 2008; Menini et al., 2014). Thiols are organic molecules containing a sulfhydryl group. Thiols constitute an important part of the antioxidants in the body in defense against ROS (Prakash et al., 2009). A decrease in THIOL levels in individuals with COPD compared to healthy individuals has been reported in the literature (Kabuto et al., 2003).

In our study, we found an insignificant decrease in serum PON1 and ARES levels, but a significant decrease in THIOL in the COPD group compared to the control group. Although there are conflicting results in the literature regarding PON1, the decrease in the PON1 level is compatible with some studies. In terms of ARES and THIOL, we have obtained consistent results compared to the general literature. We think that the increase in TAS we observed in COPD occurs independently of PON1, ARES, and THIOL.

CONCLUSION

In our study, we found a non-significant increase in antioxidative and oxidative capacity in the patient. However, the OSI values between groups were a natural consequence of the increase in both parameters together, we determined oxidative states that did not change between groups. The results show that the oxidative status of newly diagnosed and untreated COPD individuals does not change compared to healthy individuals. We believe that PON1, ARES, and THIOL, which are the parameters we examined, have no effect on increased antioxidant capacity, although it is not significant in COPD patients. In addition, the significant decrease in serum level of THIOL, an antioxidative agent, in COPD patients can be considered as a new indicator to support the diagnosis of COPD. We believe that future research should focus on developing methods to reduce reactive stress in COPD patients. For this reason, in COPD patients, antioxidant capacity can be supported in terms of PON1, ARES, and THIOL to provide effective treatment of the disease.

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