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AUTHORS: Oguz EROGLU,Nermin DINDAR BADEM,Ayse BACCIOGLU,Ertan CÖMERTPAY,Salim NESELIOGLU,Özcan EREL

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Significance of thiol/disulphide homeostasis and ischemia modified albumin levels in chronic obstructive pulmonary disease

Oğuz Eroğlu[1] , Nermin Dindar Badem[2] , Ayşe Baccıoğlu[3] , Ertan Cömertpay[1] , Salim Neşelioğlu[4] , Özcan Erel[4]

[1]Department of Emergency Medicine, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[2]Department of Medical Biochemistry, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[3]Department of Pulmonary Diseases, Division of Immunology and Allergy Diseases, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[4]Department of Clinical Biochemistry, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey

ABSTRACT

Objectives: The severity of inflammation occurring during chronic obstructive pulmonary disease (COPD) is closely associated with oxidative stress. The aim of this study was to investigate the diagnostic value of Thiol/disulphide homeostasis (TDH) and ischemia modified albumin (IMA) levels in evaluating oxidative stress in COPD patients.

Methods: This prospective study was performed with COPD patients presenting to the Kırıkkale University Hospital and with healthy volunteers. Subjects' demographic data (age, sex, body mass index, and smoking status), native thiol (NT), total thiol (TT), disulphide (Ds), IMA levels and Ds/NT, Ds/TT and NT/TT ratios were recorded. Statistical analysis was performed with SPSS 21.0 software.

Results: One hundred ninety subjects were enrolled in the study, 141 COPD patients and 49 healthy volunteers. No difference was determined between the patient and control groups in terms of age, sex or body mass index. The antioxidant markers; NT and TT levels and NT/TT ratio were significantly lower in the patient group compared to the control group ($p < 0.001$, $p < 0.001$, and $p < 0.003$, respectively). The oxidant markers; IMA levels and Ds/NT and Ds/TT ratios were significantly higher in the patient group ($p = 0.006$, p = 0.003, and $p = 0.003$, respectively). Significant negative correlation was determined between antioxidant and oxidant parameters. Sensitivity values were NT: 87.2%, TT: 83.3%, Ds/NT ratio: 68.1%, Ds/TT ratio: 68.1%, and IMA: 77.8%.

Conclusions: TDH was impaired in favor oxidants in COPD patients. TDH parameters and IMA can be used to monitor oxidative stress emerging in COPD.

Keywords: Chronic obstructive pulmonary disease, oxidative stress, thiol/disulphide homeostasis, ischemia modified albumin

Address for correspondence: Oğuz Eroğlu, MD., Assistant Professor, Kırıkkale University School of Medicine, Department of Emergency Medicine, 71850 Kırıkkale, Turkey
E-mail: oguzerogluacil@gmail.com, Tel: +90 318 3330000 (5192), Fax: +90 318 2240786

Chronic obstructive pulmonary disease (COPD) is a condition with high morbidity and mortality resulting from exposure to several harmful gasses or particles, and particularly smoking [1, 2]. Inflammation occurring during the course of COPD is closely related to the clinical course of the disease. The severity of inflammation also depends various infectious, genetic and environmental factors, and particularly oxidative stress [1]. Various cells, such as monocytes, macrophages, CD8 T-lymphocytes, neutrophils and eosinophils, and inflammatory mediators including interleukin-1, -6, and -8 and tumor necrosis factor-alpha are responsible for the development of inflammation [1, 3]. The damage caused by inflammatory products in COPD is essentially responsible for the emergence of pathological findings; reactive oxygen species (ROS) overproduction in cells makes damage in the pulmonary parenchyma resulting from oxidative stress and proteinase activity irreversible [4]. ROS are highly reactive molecules emerging as the result of enzymatic and non-enzymatic reactions. They are implicated in the pathogenesis of numerous diseases, and particularly cancers [5, 6]. ROS are eliminated from the body by antioxidant substances. These include substances with enzymatic structures such as superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase, or molecules such as glutathione, ascorbic acid, tocopherols and carotenoids [7].

Thiols are organic compounds with a sulphydryl group exhibiting antioxidant effects [8]. These compounds form disulphide (Ds) bonds by reacting with ROS in the body. The emerging Ds bonds are reversible, and can be reduced back to thiols, depending on the oxidant-antioxidant status in the organism [8, 9]. The antioxidant effect of thiol/disulphide homeostasis (TDH) plays a critical role in signal transmission, enzymatic reactions, transcription, detoxification, and apoptosis mechanisms [8, 9]. Under normal conditions, TDH has a dynamic structure, but it can be adversely affected by pathologies involving increased oxidative stress. Studies have shown that oxidative stress, the effect of which are exacerbated by impairments in TDH, is involved in the pathophysiology of many diseases, including diabetes mellitus, cardiovascular diseases, cancer, kidney failure, rheumatoid arthritis,

Parkinson's disease, Alzheimer's disease, Friedreich's ataxia, multiple sclerosis, and amyotrophic lateral sclerosis [8-13]. Demonstrating the destructive effects of oxidative stress can elicit valuable information in terms of understanding the biochemical process involved in many diseases [14-16]. The TDH measurement method newly developed by Erel *et al*. [8, 15, 17-22] has been shown to a reliable indicator in showing oxidative stress.

Albumin is the most abundant protein in the body, and has several functions, including playing a role in the elimination of ROS [23]. In case of ischemia, changes occur in the amino acid sequence, the albumin N-terminal, and the resulting new protein is known as ischemia-modified albumin (IMA). IMA has a low binding capacity to heavy metals such as cobalt, nickel and copper, and this is closely associated with an increase in ROS, ischemia or the hypoxic process [23]. Studies have shown that IMA levels rise in several conditions, including muscle ischemia, aortic pathologies and diabetic retinopathy [24-28].

The aim of this study was to investigate changes occurring in the oxidant-antioxidant system, TDH parameters and IMA measurements in COPD.

METHODS

Study Population

Following receipt of local ethical committee approval (No.2016-08/10), this study was performed prospectively with patients with previous definite diagnosis of COPD presenting to the Kırıkkale University School of Medicine, Emergency Medicine and Chest Diseases departments and with healthy volunteers agreeing to take part of their own volition. Signed inform consent forms were received from the participants, and the study was carried out in strict accordance with the Declaration of Helsinki and Good Clinical Practice Directive.

Age, sex, body mass index (BMI), smoking status, laboratory results (complete blood count, AST, ALT, urea, creatinine, albumin and serum electrolytes), TDH parameters and IMA levels were recorded for all subjects. Spirometry measurement results were also recorded for the COPD patients.

Patients with cancer, diabetes mellitus, coronary artery disease, cerebrovascular disease, heart, liver or

kidney failure, pregnant and lactating women, patients aged under 18 and subjects refusing to take part were excluded from the study.

Specimen Collection and Analysis

We first collected 10 cc blood samples from all subjects in the patient and control groups. These were placed into biochemistry tubes (GranierBio-one, North America, Inc., North Carolina, USA) and centrifged for 6 min at 5000 rpm for serum separation. These serum specimens were subsequently placed into Eppendorf tubes and frozen at-800C until biochemical analysis. When the target participant number was reached, the specimens were transferred under appropriate conditions in iced boxes to the Kırıkkale University School of Medicine Biochemistry laboratory. All specimens were thawed at the same time, and NT, TT, Ds, and IMA levels were measured. TDH parameters levels were analyzed using the automatic measurement method newly developed by Erel and Neselioglu [8], and the results were expressed as 'µmol/L'. IMA levels were analyzed using the rapid, colorimetric method developed by Bar-Or *et al*. [29], and the results were expressed as absorbance units (ABSU).

Statistical Analysis

Data analysis was performed on SPSS 21.0 (IBM SPSS Statistics 21.0, IBM Corporation, Armonk, NY, USA) software. Compatibility with normal distribution was investigated using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as constant and discrete numeric variables and shown as mean±standard deviation (SD) or median and interquartile range (IQR). Categoric variables were expressed as number (n) and percentage (%). Parametric data were compared using Student's t test and non-parametric data using the Mann-Whitney U test, while Pearson's Chi-square test was used to analyze categorical variables, and Spearman's rho correlation test to compare numerical variables. ROC analysis was used to determined sensitivity, specificity and cut-off values. A $p < 0.05$ was regarded as statistically significant.

RESULTS

One hundred ninety subjects were included in the study; 141 patients with previous definite diagnosis of

**Table 1.** The groups' demographic and laboratory characteristics

	Group COPD (n = 141)	Group Control (n = 49)	*p* value
Gender	**n (%)**	**n (%)**	
male	108 (76.6)	39 (79.6)	0.843[*]
F emale	33 (23.4)	10 (20.4)	
	mean ± SD	**mean ± SD**	
Age (year)	63.8 ± 10.9	61.1 ± 7.6	0.106[†]
NT (µmol/L)	274.2 ± 88.3	427.2 ± 74.1	**< 0.001[†]**
TT (µmol/L)	315.4 ± 86.5	468.7 ± 80.3	**< 0.001[†]**
	median (IQR)	**median (IQR)**	
BMI (kg/m^2)	25.7 (5.5)	24.6 (2.6)	0.275[‡]
Ds (µmol/L)	20.4 (13.4)	20.8 (10.3)	0.153[‡]
Ds / NT	6.7 (8.2)	4.8 (2.4)	**0.003[‡]**
Ds / TT	5.9 (6.3)	4.4 (2.0)	**0.003[‡]**
NT / TT	88.3 (12.6)	91.3 (4.0)	**0.003[‡]**
IMA (ABSU)	72.5 (5.0)	72.1 (4.8)	**0.006[‡]**

BMI = body mass index, Ds = disulphide, NT = native thiol, TT = total thiol, IMA = ischemia modified albumin, IQR = interquartile range, SD = standard deviation, *Chi-square test, †Student-t test, ‡Mann-Whitney U test

Table 2. Correlation between TDH parameters and IMA

Parameters		NT	TT	NT/TT	Ds	Ds/NT	Ds/TT	IMA
NT	r	1.000	0.958[†]	–.537[†]	–.049	–.537[†]	–.537[†]	–.291[†]
TT	r		1.000	.325[†]	.184[*]	–.325[†]	–.326	–.265
NT/TT	r			1.000	–.811[†]	-1.000[†]	-1.000[†]	–.165[*]
Ds	r				1.000	.811[†]	.811[†]	.064
Ds/NT	r					1.000	1.000[†]	.166[*]
Ds/TT	r						1.000	.166[*]
IMA	r							1.000

NT = native thiol, TT = total thiol, Ds = disulphide, IMA = ischemia-modified albumin, r = Spearman rho correlation coefficient, [*]$p < 0.05$, [†]$p < 0.01$
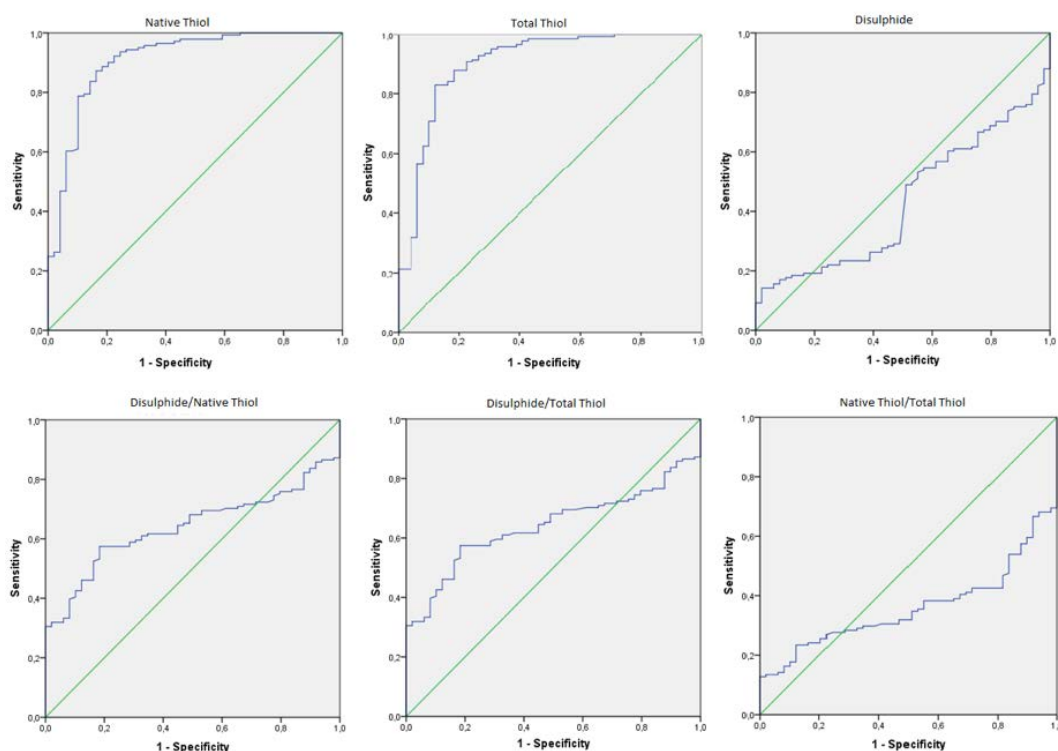
Figure 1. ROC curve analysis of thiol/disulphide homeostasis parameters

Table 3. ROC curve analysis of TDH parameters and IMA levels

Parameters	Area	Cut-off	Sensitivity (%)	Specificity (%)
NT (µmol/L)	0.910	368	87.2	83.7
TT (µmol/L)	0.902	368	83.3	87.8
Ds (µmol/L)	0.431	20.6	48.9	49.0
Ds/NT (µmol/L)	0.641	4.8	68.1	51.0
Ds/TT (µmol/L)	0.641	4.4	68.1	51.0
NT/TT (µmol/L)	0.641	90.5	38.3	44.9
IMA (ABSU)	0.633	71.3	77.8	62.0

NT = native thiol, TT = total thiol, Ds = disulphide, IMA = ischemia-modified albumin
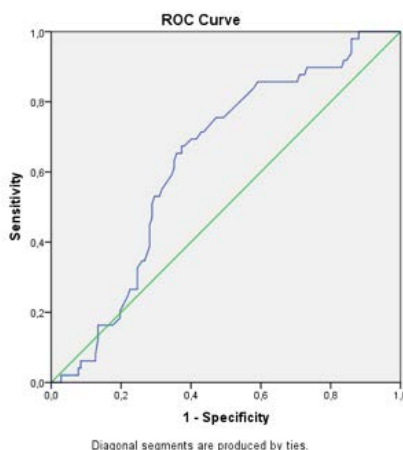
Figure 2. ROC curve analysis of ischemia-modified albumin.

COPD constituted the patient group. The control group consisted of 49 healthy volunteers similar to the patient group in terms of age, sex, and BMI. The mean age of the patient group was 63.8 ± 10.9 years, 76.6% were men, and the median BMI value was 25.7 kg/m2. The mean age of the control group was 61.1 ± 7.6 years, 79.6% were men, and the median BMI value was 24.6 kg/m2. No significant difference was determined between the two groups in terms of age, sex or BMI ($p = 0.106$, $p = 0.843$, and $p = 0.275$, respectively) (Table 1).

Mean native thiol (NT) levels were 274.2 ± 88.3 µmol/L in the patient group and 427.2 ± 74.1 µmol/L in the control group ($p < 0.001$). Mean total thiol (TT) levels were 315.4 ± 86.5 µmol/L in the patient group and 468.7 ± 80.3 µmol/L in the control group ($p < 0.001$). Mean NT/TT ratio values were 88.3% in the patient group and 91.3% in the control group ($p = 0.003$) (Table 1).

Median Ds values were 20.4 µmol/L, in the patient group and 20.8 µmol/L in the control group ($p = 0.275$). Median IMA levels were 72.5 ABSU in the patient group and 72.1 ABSU in the control group ($p = 0.006$). The median Ds/NT ratio was 6.7% in the patient group and 4.8% in the control group ($p = 0.003$), while the median Ds/TT ratio was 5.9% in the patient group and 4.4% in the control group ($p = 0.003$) (Table 1).

Antioxidant parameters (NT and TT) and oxidant parameters (Ds, Ds/NT, Ds/TT and IMA) both exhibited positive correlation among themselves, while negative correlation was determined between antioxidant and oxidant parameters (Table 2).

Sensitivity values in showing COPD were NT: 87.2%, TT: 83.3%, Ds/NT ratio: 68.1%, Ds/TT ratio: 68.1%, and IMA: 77.8% (Table 3) (Figures 1 and 2).

DISCUSSION

In this study of the relation between COPD and oxidative stress, levels of NT and TT, antioxidant markers of TDH were significantly low in the patient group, while oxidant markers Ds/NT and Ds/TT ratios increased significantly in the patient group compared to the control group. In addition, IMA levels, another oxidant parameter, were also significantly high in the patient group, and positive correlation was determined between other oxidant parameters. These findings show that TDH alters in favor of oxidants in COPD patients and that oxidative stress increases in these patients.

Although oxidative stress affects several organs, the organs most exposed to such stress are the lungs [30-32]. Oxidant substances accumulating in the airways reduce surfactant activity in addition to impairing cellular genetic structure, biological membranes, the ciliary matrix and ciliary functions, while increasing mucus and cytokine production [1, 31, 32]. Knowing the function of thiols involved in the antioxidant system is therefore becoming increasingly important in terms of understanding several diseases associated with oxidative stress, including COPD [19]. Studies investigating the relation between oxidative stress and TDH have shown that such homeostasis is impaired in oxidative terms in patients with acute

myocardial infarction, migraine, alopecia or chronic urticaria, in pregnant women with hyperemesis gravidarum (compared to normal gravidas), and in workers exposed to polycyclic aromatic hydrocarbons [14-16, 33-35]. Babaoglu *et al*. [36] assumed the presence of oxidative stress in COPD and investigated TDH in other subgroup diseases causing lower airway obstruction, such as asthma and asthma-COPD overlap syndrome (ACOS). However, in the absence of a control group for purposes of comparison, they were unable to clearly demonstrate changes in TDH [36]. Evaluated from that perspective, ours is the first study to compare TDH in patients with COPD and healthy controls.

Oxidative stress-related effects are known to be exacerbated in COPD patients for reasons such as inflammation, infection, smoking, increased hypoxia and a decreased antioxidant response [32, 37, 38]. Şahin *et al*. [39] determined an association between ROS accumulation and bronchial hyperactivity and reported that this was responsible for irreversible damage and narrowing in the airways. Rahman *et al*. [40] reported insufficient antioxidant response in COPD exacerbation and that this insufficiency persisted for 48 h. Demir *et al*. [41] reported higher than normal levels of glutathione, an antioxidant molecule, in cases of COPD, and that this elevation increased still further in the acute exacerbation period. Studies have shown that products of oxidative stress produce new radicals by removing protons from various molecules, such as thiols and also fatty acids [6, 16, 42]. A decrease in plasma thiol concentrations is therefore regarded as indicating oxidative stress and increased ROS production [16]. In our study, the Ds/NT andDs/TT ratios showing the presence of oxidative stress were significantly higher compared to in the control group, while a statistically insignificant decrease was observed in Ds levels. The antioxidant markers NT andTT levels and the NT/TT ratio were significantly lower than in the control group. At the same time, negative correlation was determined between oxidant parameters and antioxidant parameters. We interpreted these findings as indicating that the oxidant-antioxidant balance is impaired in favor of oxidants in patients with COPD, and that the organism consumes thiols in order to combat increasing oxidative stress.

Several parameters exhibiting oxidant or antioxidant characteristics have been investigated in terms of showing oxidative stress in patients with COPD. These include glutathione, glutathione peroxidase, superoxide dismutase, catalase, ferroxidase, and myeloperoxidase [43-46]. IMA is an oxidant marker resulting from the differentiation of albumin, with antioxidant properties, in situations involving increased oxidative stress [23]. Recent studies have again emphasized the relation between IMA and diseases involving increased oxidative stress. Ataş *et al*. [47] reported that IMA is superior to other biomarkers in showing oxidative stress in patients with vitiligo. In another study of the effectiveness of IMA in showing oxidative stress in COPD patients, Can *et al*. [48] determined significant elevation in IMA levels in COPD patients compared to controls and concluded that IMA may be a useful biomarker for assessing chronic inflammation and oxidative stress in COPD. IMA levels in our study were significantly higher in patients with COPD than in the control group. At the same time, IMA exhibited positive correlation with other oxidant parameters and inverse correlation with antioxidant parameters. IMA therefore shows that the increase in oxidant markers in TDH is not coincidental and may be considered as another biomarker for showing increased oxidative stress in COPD.

CONCLUSION

In conclusion, TDH is impaired in favor of oxidants in COPD, as shown by increasing Ds/NT, and Ds/TT ratios and decreasing NT and TT levels and NT/TTratios. In addition, the increase in levels of IMA, another oxidant marker, supports these findings. We therefore think that TDH parameters and IMA can be used to evaluate oxidative stress in COPD.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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