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Antioxidant Therapy in Chronic Obstructive Pulmonary Disease

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Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is associated with oxidative stress. We aimed to evaluate the effect of antioxidant therapy on malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), total antioxidant capacity (TAC), and nitric oxide (NO) levels, as well as on pulmonary functions and arterial blood gases in COPD. ***Design:*** Prospective clinical study. ***Subjects/Patients:*** Twenty stable COPD patients with no comorbidities. ***Methods:*** Pulmonary functions, arterial blood gases, MDA, SOD, GSH, TAC, and NO levels were measured at baseline. After 6 weeks of treatment with an antioxidant preparation consisting of vitamins A, C, E, zinc, copper, selenium, and manganese, the tests were repeated. ***Results:*** Five patients were excluded due to exacerbations and one due to anemia. In the remaining patients, MDA levels decreased, while SOD and TAC levels increased compared to baseline. No significant changes were observed in GSH and NO levels. Pulmonary function tests improved, whereas no significant differences were found in arterial blood gases. No significant correlations were observed between pulmonary function or arterial blood gases and the biomarkers (MDA, SOD, GSH, TAC, and NO). ***Conclusion:*** Adding antioxidants to the standard treatment for COPD may help restore the oxidant-antioxidant balance, which is disrupted in favor of oxidants in COPD.

Keywords: ***Antioxidants, Arterial blood gases, COPD, Glutathione, Lung functions, Malondialdehyde, Superoxide dismutase, Total antioxidant capacity.***

Introduction

Chronic obstructive pulmonary disease (COPD), one of the leading causes of morbidity and mortality worldwide and in our country, is a preventable and treatable disease. It is typically characterized by progressive or persistent airway obstruction and may be accompanied by airway hyperreactivity. Exposure to harmful gases or particles and abnormalities in lung development can also contribute to its pathogenesis [1].

Oxidative stress can be defined as increased exposure to oxidants and/or a decrease in antioxidant capacity [2-4]. Numerous studies suggest that increased oxidative stress is associated not only with asthma [5,6], pulmonary fibrosis [6], cystic fibrosis [7], and cancer [8,9] but also with COPD [4,10-14].

When endogenous antioxidants are insufficient, dietary antioxidants are needed for support. Therefore, determining the antioxidant capacity of the body is crucial. Studies measuring antioxidants in plasma and other body fluids, identifying changes in target molecules, and detecting end products derived from these molecules will guide the therapeutic use of antioxidants.

This study aims to investigate the effect of antioxidant therapy, administered in addition to standard treatment in COPD, on plasma malondialdehyde (MDA) as a marker of oxidative stress; erythrocyte superoxide dismutase (SOD), blood glutathione (GSH), and plasma total antioxidant capacity (TAC) as indicators of antioxidant capacity; nitric oxide (NO) levels; as well as respiratory functions and arterial blood gases.

Methods

The study included 20 COPD patients who were being followed at the COPD Outpatient Clinic of the Department of Chest Diseases, Istanbul University Cerrahpaşa Faculty of Medicine. These patients had no known additional metabolic diseases, were willing to participate in the study, and had been in a stable phase for at least three weeks.

At baseline, patients underwent spirometric evaluation (FVC, FEV1, FEV1/FVC, FEF25-75%, PEF), diffusion capacity test (DLco), lung volume measurements (FRC, TLC, RV), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), reversibility test, arterial blood gas analysis, and posteroanterior

chest X-ray. Additionally, blood samples were collected for the determination of eosinophil cationic protein (ECP), total IgE, tryptase, GSH, SOD, TAC, MDA, and NO levels. On the same day, patients were instructed to take one capsule daily of an antioxidant preparation in addition to their standard treatment for six weeks. Table 1 shows the contents of this preparation.

Table I: Composition of the antioxidant preparation

Vitamin A	5000 IU
Vitamin C	250 mg
Vitamin E	200 IU
Zinc	7,5 mg
Copper	1 mg
Selenyum	15 mcg
Manganese	1,5 mg

Patients were evaluated for COPD exacerbation if they exhibited any of the following symptoms for at least 24 hours: increased cough and dyspnea, changes in the color, quantity, or viscosity of sputum, onset or worsening of wheezing, chest tightness, fatigue, reduced exercise tolerance, fever, edema, increased respiratory rate (>25/min), increased pulse rate (>110/min), cyanosis, use of accessory respiratory muscles, drowsiness, a decline in FEV1 (<1000 mL), decreased PaO2 (<60 mmHg), or reduced arterial oxygen saturation (SatO2) (<90%).

At follow-up, pulmonary function tests and arterial blood gas analyses were repeated. Blood samples were also collected for the measurement of ECP, total IgE, tryptase, GSH, SOD, TAC, MDA, and NO.

Patients who experienced COPD exacerbation or developed additional illnesses during this 6-week period were excluded from the study.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package of Social Sciences) for Windows. Results are presented as mean values ± standard deviation. Pre- and post-treatment values were compared using the student's t-test. A p-value of less than 0.05 was considered statistically significant.

Results

All 20 COPD patients included in the study were male. Five patients were excluded due to the development of exacerbations during the study, and one patient was removed after being diagnosed with iron deficiency anemia, for which iron supplementation was initiated.

Fourteen patients who completed the study without exacerbations were included in the evaluation. The mean age of these 14 patients was 64 ± 7.97 years (minimum: 45, maximum: 78), and the average disease duration was 10.57 ± 7.36 years (minimum: 1, maximum: 25).

The patients' smoking history averaged 61.86 ± 45.45 pack-years (minimum: 9, maximum: 180). Among them, four patients were still actively smoking. The ten patients who had quit smoking had an average cessation duration of 7.4 ± 6.58 years (minimum: 0.5, maximum: 20).

None of the patients had any abnormalities on their PA chest X-rays taken at the beginning of the study, except for signs of hyperinflation.

It was determined that 1 (7%) of the patients who completed the study had mild, 5 (36%) had moderate, and 8 (57%) had severe COPD.

Among the patients who completed the study, 12 (85.7%) were using theophylline, 11 (78.6%) were using ipratropium bromide, 10 (71.4%) were using long-acting inhaled β2 agonists, 8 (64.3%) were using short-acting inhaled β2 agonists, 8 (57.1%) were using inhaled corticosteroids, 4 (28.6%) were using oral β2 agonists, and 3 (21.4%) were receiving continuous home oxygen therapy.

The respiratory function tests, arterial blood gases, total IgE, ECP, tryptase, MDA, SOD, GSH, TAC and NO levels of the patients who completed the study, before and after the 6-week antioxidant treatment in addition to the standard treatment, are shown in Table 2.

Table II: Respiratory functions, arterial blood gas values and laboratory results of patients before and after antioxidant treatment

	n	Before treatment (Mean±Standard deviation)	After treatment (Mean±Standard deviation)	p
FVC (mL)	14	2534.90±668.24	2685.00±681.06	<0,05*
FVC (%)	14	71.43±18.42	76.50±19.15	<0,05*
FEV_1 (mL)	14	1310,71±512,74	1402.86±545.96	<0,05*
FEV_1 (%)	14	46.36±16.18	49.93±16.55	<0,05*
FEV_1/FVC (%)	14	52.00±12.17	51.36±10.57	>0,05
$FEF_{\%25-75}$ (L/sec)	14	0.58±0.30	0.60±0.28	>0,05
$FEF_{\%25-75}$ (%)	14	18.00±8.34	18.86±7.99	>0,05
PEF (L/sec)	9	4,10±1,83	4.23±2.18	>0,05
PEF (%)	9	53.89±20.90	55.22±25.34	>0,05
DLco (mL/mmHg/sec)	13	14.09±4.20	14.40±4.47	>0,05
DLco (%)	13	56.23±13.83	57.85±15.06	>0,05
DLco/VA(mL/mmHg/min/L)	13	3.21±0.96	3.15±0.94	>0,05
DLco/VA (%)	13	61.15±18.05	60.38±17.72	>0,05
MIP (cmH_2O)	11	72.45±21.86	75.00±25.25	>0,05
MIP (%)	11	66.64±18.85	68.91±21.79	>0,05
MEP (cmH_2O)	11	86.64±18.33	90.00±23.02	>0,05
MEP (%)	11	42.64±9.05	44.27±11.22	>0,05
FRC (L)	12	4.04±0.93	4.24±1.45	>0,05
FRC (%)	12	120.83±30.26	127.08±45.36	>0,05

TLC (L)	12	6.12±0.94	6.39±1.23	>0,05
TLC (%)	12	99.67±18.40	105.17±24.80	>0,05
RV (L)	12	3.43±0.85	3.54±1.26	>0,05
RV (%)	12	149.83±43.45	152.67±56.70	>0,05
Reversibility (%)**	4	6.75±3.30	1.50±2.08	>0,05
pH	14	7.41±0.03	7.41±0.02	>0,05
$PaCO_2$ (mmHg)	14	38.96±6.15	39.80±4.56	>0,05
PaO_2 (mmHg)	14	72.33±10.45	72.99±9.46	>0,05
$SatO_2$ (%)	14	93.96±2.69	94.37±2.26	>0,05
Bicarbonate (mEq/L)	11	24.33±2.18	25.01±2.22	>0,05
IgE (IU/mL)	13	74,46±69,52	68,77±48,78	>0,05
ECP (µg/L)	14	16,07±11,11	14,64,80±11,91	>0,05
Triptaz (µg/L)	14	5,25±2,20	5,03±2,25	>0,05
MDA (nmole/mL)	9	4,95±2,33	2,64±1,02	<0,01*
SOD (U/gHb)	11	690,41±169,21	866,41±200,36	<0,05*
GSH (mmole/L/gHb)	10	2,84±1,10	2,87±1,03	>0,05
TAC (mmole/L)	11	1,18±0,23	1,71±0,38	<0,001*
NO (mmole/L)	9	39,44±8,06	38,44±5,08	>0,05

** Statistically significant*

***The difference in FEV_1 compared to the baseline value after administering 200 mcg of inhaled Salbutamol, 15-20 minutes later*

Discussion

Recent studies have focused on the role of oxidants in COPD pathogenesis, recognizing smoking as a significant source of oxidants. Morrow et al. identified increased levels of F2-isoprostanes in smokers, suggesting oxidative stress as a contributor to lung damage [9]. Li et al. indicated that smoking elevates airway epithelial permeability through oxidants, while GSH offers protective effects [15]. Lapenna et al. observed a positive correlation between smoking intensity (pack-years) and lipid peroxidation products in smokers [16].

Our study did not show a correlation between smoking (pack-years), smoking cessation, disease duration, and oxidative stress markers (MDA, TAC, NO, erythrocyte SOD, blood GSH). Similarly, Schunemann et al. found no correlation between TAC and FEV1 but observed a negative correlation between lipid peroxidation and lung function [17]. Rahman's study also found no correlation between TAC and lung function parameters [18]. In line with these findings, our study showed no correlation between oxidative stress markers and pulmonary function tests or arterial blood gases.

Regarding MDA, a key oxidative stress indicator, we observed a significant decrease from 4.95 ± 2.33 nmole/mL to 2.64 ± 1.02 nmole/mL after six weeks of antioxidant therapy, in line with Demir et al.'s findings showing higher MDA levels during acute exacerbation compared to stable COPD [19]. Our pre-treatment MDA values were higher than both stable and acute exacerbation values from Demir's study.

Superoxide dismutase (SOD), another important antioxidant, showed a significant increase from 690.41 ± 169.21 U/gHb to 866.41 ± 200.36 U/gHb post-treatment ($p<0.05$). Demir's study reported lower SOD values in both acute exacerbation (896 ± 243 U/gHb) and stable phase COPD (856 ± 203 U/gHb), with our pre-treatment values being lower than these, but the post-treatment values were comparable to stable COPD levels [19].

GSH levels in our study were 2.84 ± 1.10 mmole/L/gHb before treatment and 2.87 ± 1.03 mmole/L/gHb after treatment, showing no significant change. Demir reported much higher GSH levels in both acute exacerbation (10.2 ± 2.15 mmole/L/gHb) and stable phase COPD (8.72 ± 2.41 mmole/L/gHb) [19]. In smokers, GSH levels in epithelial fluid were found to be twice as high as in non-smokers [20].

Chow et al. found that smokers had lower plasma levels of vitamin C and total carotene, with vitamin A negatively correlating with smoking [21]. In our study, the plasma TAC level increased significantly from 1.18 ± 0.23 mmole/L to 1.71 ± 0.38 mmole/L post-treatment, reaching the normal range of 1.28-1.83 mmole/L ($p<0.001$). Rahman et al. also found lower TAC levels in smokers, with a positive correlation between TAC and lung function post-smoking cessation [22].

NO levels in our study were 39.44 ± 8.06 mmole/L before treatment and 38.44 ± 5.08 mmole/L after treatment, showing no significant difference. Both values were lower than normal plasma levels (51 ± 26 mmole/L) [23]. Studies have shown that NO levels do not increase in stable COPD but increase during exacerbations, with eosinophils playing a role in these changes.

The use of antioxidants in COPD treatment has been proposed for years, although there has been little clinical implementation [24]. Various antioxidant strategies have been suggested, including reducing leukocyte migration, inhibiting radical release from leukocytes, and antioxidant treatment. Potential therapeutic antioxidants include vitamins C and E, thiol compounds (e.g., N-acetylcysteine), antioxidant enzymes (e.g., recombinant SOD), and pro-oxidant inflammatory cytokine inhibitors [24,25].

Studies have explored the link between dietary antioxidants and lung function. Morabia et al. reported that a vitamin A-rich diet was associated with an increased risk of airway obstruction [26]. Britton et al. found that daily vitamin C intake positively correlated with FEV1 and FVC [27]. Similarly, in the NHANES II study, higher vitamin C intake was linked to better lung function, and a study by Hu found that higher levels of vitamins C, E, and selenium were associated with better lung function [28]. In the general population, increased dietary vitamin C intake was associated with improved FVC and FEV1 [29].

Studies also show that smokers have lower dietary intake of antioxidants such as vitamin C and carotenoids compared to non-smokers, which affects their lung function. Faruque et al. found smokers had significantly lower plasma vitamin C levels [30]. Lothian

et al. demonstrated that supplementation with GSH precursors improved lung function in patients with corticosteroid-responsive obstructive lung disease [31].

N-acetylcysteine (NAC) has been widely studied as an antioxidant. It scavenges free radicals and stimulates cellular glutathione synthesis, protecting against oxidative damage in respiratory diseases [32]. Studies have shown that NAC reduces exacerbations in COPD and improves pulmonary function in certain patients [33,34]. Similarly, Ambroxol, another antioxidant, reduces oxidative stress and enhances surfactant production [32].

In conclusion, the findings suggest that integrating antioxidant therapy into the treatment protocol could offer an adjunctive benefit in managing COPD, potentially enhancing lung function and overall patient outcomes. Future studies with larger sample sizes and longer follow-up periods are needed to validate these results and further explore the therapeutic potential of antioxidants in COPD management. These findings emphasize the importance of personalized treatment strategies to optimize care for COPD patients, particularly those with more advanced disease.

Declarations

Conflict of Interest

The author(s) declare that there are no conflicts of interest regarding the publication of this manuscript. No financial or personal relationships have influenced the work presented in this study.

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Contributors

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Ethical Clearance

We strictly adhered to all the necessary ethical standards throughout the course of this study. Prior to its initiation, explicit permission was obtained from the head of the department and the faculty, ensuring full compliance with institutional guidelines. In addition, all participants were thoroughly informed about the study's purpose, procedures, and potential risks. Each patient provided written informed consent, and they were explicitly assured that their participation was voluntary. Furthermore, they were informed that their decision to decline participation or withdraw from the study at any point would not result in any harm or repercussions. We ensured the anonymity of all participants by keeping their personal information confidential, and their records were securely classified and stored in a manner that protected their privacy.

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