HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2022.57778
Haydarpasa Numune Med J 2022;62(2):128–133

hnhtipdergisi.com

ORIGINAL ARTICLE

Association between Oxidative Stress Markers and Hospital Admission due to Asthma

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Abstract

Introduction: Asthma is a chronic respiratory disease marked by airway constriction, systemic and localized inflammation, and oxidative stress. The pathophysiological mechanism of asthma is influenced by oxidative stress, characterized by imbalance between increased reactive oxygen species and antioxidant defense. The role of oxidative stress in asthma development and control is crucial to the disease's pathogenesis and treatment. Therefore, we aimed to evaluate oxidative stress biomarkers in asthmatic patients.

Methods: Cross-sectional study, designed in tertiary care chest disease hospitals' outpatient clinic. Asthma patients, who applied to the outpatient clinic within in February 2022, were included in the study. Asthma group and control group was compared.

Results: 94 were enrolled in the study, 47 in each group. Mean age was 41±16.28 SD and body mass index (BMI) was 27.3±7.11 kg/m^2 in group asthma. Mean age was 40±24.12 SD and BMI of the control group was 28.6±8.2 kg/m^2. There was no statistically significant difference between the groups in terms of age, gender, weight, smoking status, and comorbidities ($p>0.05$). There was a statistically significant difference in total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), total thiol (TT), native Tiol (NT), and disulfide (DIS) between the control and asthma patient groups ($p=0.001$ for all variables). When compared to healthy controls, asthmatics had greater TOS, OSI, and DIS scores. Despite, healthy controls had considerably higher TAS, TT, and NT levels than the asthma group. There was no statistically significant relationship between oxidative stress markers and the comorbidities, hospital admissions in the last year and emergency admissions in the last year. Oxidative stress markers and the pulmonary function test results have no significant association ($p>0.05$) in the Asthma group.

Discussion and Conclusion: In the current study, TOS and DIS values of individuals with asthma are extremely high compared to healthy controls. Besides TAS, OSI, TT, and NT values of healthy controls were significantly higher than the asthma group. The oxidant/antioxidant balance was impaired and oxidative stress increased in asthma patients in the present study.

Keywords: Asthma; biomarker; oxidative stress

Asthma is a chronic respiratory disease marked by airway constriction, hyperactivity, systemic and localized inflammation, and oxidative stress[1]. The pathophysiological mechanism of asthma is influenced by oxidative stress, which is defined as an imbalance between increased reactive oxygen species (ROS) and antioxidant defense. Endogenous ROS are created by metabolic reactions while external ROS are produced by environmental variables in asthma[2]. Increased levels of ROS affect a variety of physiological systems and can trigger inflammatory reactions in the lungs. However, it has been proposed that one of the main causes of cell and tissue damage in asthma patients is ROS[3]. Pathological alterations in respiratory epithelial cells, increased vascular permeability, excessive mucus pro-

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Submitted Date (Başvuru Tarihi): 07.03.2022 **Accepted Date (Kabul Tarihi):** 10.04.2022

duction, smooth muscle contraction, or airway hypersensitivity arise from the resultant cell and tissue damage[4].

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 (DIS) bond is reduced, which decreases oxidative stress and keeps the thiol DIS balance in control[6]. The thiol-DIS balance has been identified as a novel biological marker of oxidative stress in recent papers.

The role of oxidative stress in asthma development and control is crucial to comprehending the disease's pathogenesis and treatment. As a response, our study's goal is to look at oxidative stress biomarkers in asthmatic patients.

Materials and Methods

Cross-sectional study, designed in tertiary care chest disease hospitals' outpatient clinic. Patients diagnosed with asthma, who applied to the outpatient clinic of the Tertiary Chest Diseases Hospital within in February 2022, were included in the study.

The study was approved by Health Sciences University Turkey Hamidiye Scientific Research Hospital Ethics Committee (04.02.2022-22/54) and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. All asthma patients and healthy control group signed informed consent.

Sample Collection

After the patients who applied to the Istanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital outpatient clinic and were diagnosed with asthma, the blood samples were routinely requested after the informed consent was signed, and the leftover inert blood was studied. Approximately 3 mL of blood was drawn into sterile blood tubes with EDTA. 200–400 µL of blood was drawn from this blood and transferred to 1.5 ml centrifuge tubes and then stored at –80°C. The remaining EDTA blood was centrifuged at 3000× g for 10 min, then their plasma was separated and stored at –80°C until analysis.

Number of Patients and Volunteers

The study included individuals diagnosed with asthma between the ages of 18 and 65. Power analysis was used to determine the number of patients who would be included in the trial in order to attain 80% power at the 0.05 significance level. A total of 40 people were expected to participate in the study. When this number of patients was reached, the study was finalized.

Exclusion Criteria

Exclusion criteria of the study were systemic diseases such as uncontrollable cancer, hematological, neurological, or hepatic diseases, which pose an inappropriate risk to the patients or affect the results. Having a concomitant lung disease such as chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, or bronchiectasis, which has the potential to affect asthma control and cause problems in terms of differential diagnosis, were also considered as exclusion criteria.

The total antioxidant status (TAS, Rel Assay, Gaziantep, Turkey) and total oxidant status (TOS, Rel Assay, Gaziantep, Turkey) levels of the samples were determined using a photometric technique and commercially available kits. TOS/TAS was used to calculate the oxidative stress index (OSI).

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 mean standard 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

Ninety-four patients were enrolled in the study, 47 in each group. Mean age was 41±16.28 SD (standard deviation), and body mass index (BMI) was 27.3±7.11 kg/m^2 in group asthma. Mean age was 40±24.12 SD (standard deviation), and BMI of the control group was 28.6±8.2 kg/m^2.

There was no statistically significant difference between the groups in terms of age, gender, weight, smoking status and comorbidities ($p>0.05$). Demographic features and comorbidities are given in Table 1.

Table 1. Demographic features and comorbidities of the study population

Variables	n (%)
Group	
Control	47 (50)
Asthma	47 (50)
Gender	
Female	82 (83.7)
Male	12 (16.3)
Smoking history	
Never-smoker	37 (78.7)
Smoker	7 (14.9)
Ex-smoker	3 (6.4)
Comorbidities	
Present	19 (40.4)
Hypertension	4 (8.5)
Diabetes Mellitus	3 (6.4)
Other Comorbidities	15 (31.9)

Descriptive statistics are given as frequency (n) and persentage (%).

Table 2 shows on oxidative stress markers in the control and asthma 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, total thiol (TT), Native Tiol (NT), and DIS between the control and asthma patient groups (p=0.001 for all variables). When compared to healthy controls, asthmatics had greater TOS, OSI, and DIS scores. Despite, healthy controls had considerably higher TAS, TT, and NT levels than the asthma group.

In Table 3, on oxidative stress markers in Asthma group with and without comorbidities and comparison results of the groups are given. According to the analysis, there was no statistically significant difference between groups according to oxidative stress markers (p>0.05). In Table 4, comorbidities, hospital admissions in the last year, emergency admissions in the last year, and the correlation analysis findings between asthma stage and oxidative stress markers are given. Accordingly, there was no statistically significant relationship between oxidative stress markers and the comorbidities, hospital admissions in the last year and emergency admissions in the last year (p>0.05).

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

Oxidative stress markers	Group		t/Z	p
	Control (n=47)	Asthma (n=47)		
TOS	10.82±0.92	12.98±1.58	–8.302	<0.001s
TAS	1.54±0.13	1.21±0.10	14.573	<0.001s
OSI	6.97 (6.47–7.40)	10.67 (9.42–11.84)	–8.246	<0.001m
TT	573.99±50.07	452.22±54.90	11.472	<0.001s
NT	336.62±33.90	165.75±30.03	26.412	<0.001s
DIS	116.71 (102.74–128.51)	136.35 (126.81–169.70)	–4.395	<0.001m

TOS: Total oxidant status; TAS: Total antioxidant status; OSI: Oxidative stress index; TT: Total thiol; NT: Native thiol; DIS: Disulfide; t: t-test statistics; Z: Z test statistics Descriptive statistics are given as percentiles (25.–75. Percentile) or mean±standard deviation. m: Mann–Whitney U test, s: t-test.

Table 3. Comparison results on oxidative stress markers according to the presence of additional disease in the asthma group

Oxidative stress markers	COMORBIDITIES		t	p
	Absent (n=28)	Present (n=19)		
TOS	12.85±1.61	13.08±1.49	–0.493	0.624s
TAS	1.21±0.09	1.20±0.12	0.652	0.518s
OSI	10.70±1.75	11.06±1.51	–0.732	0.468s
TT	437.96±57.64	464.71±40.23	–1.751	0.087s
NT	168.10±27.30	166.17±32.69	0.216	0.830s
DIS	134.94±31.42	149.27±23.59	–1.689	0.098s

TOS: Total oxidant status; TAS: Total antioxidant status; OSI: Oxidative stress index; TT: Total thiol; NT: Native thiol; DIS: Disulfide; t: t-test statistics; s: t-test; Descriptive statistics are given as percentiles (25.–75. Percentile) or mean±standard deviation.

Table 4. Correlation analysis between comorbidities, hospital admissions, emergency admissions in last year, and oxidative stress markers

	Number of comorbidities	Hospital admission	Admission to emergency room
TOS	r=0.052	r=0.116	r=0.034
	p=0.729	p=0.439	p=0.818
TAS	r=–0.047	r=–0.040	r=0.034
	p=0.755	p=0.792	p=0.818
OSI	r=0.084	r=0.101	r=0.028
	p=0.573	p=0.499	p=0.850
TT	r=0.274	r=–0.125	r=–0.132
	p=0.062	p=0.404	p=0.377
NT	r=–0.036	r=0.184	r=0.055
	p=0.811	p=0.216	p=0.711
DIS	r=0.270	r=–0.146	r=–0.214
	p=0.067	p=0.328	p=0.149

TOS: Total oxidant status; TAS: Total antioxidant status; OSI: Oxidative stress index; TT: Total thiol; NT: Native thiol; DIS: Disulfide; r: Correlation coefficient.

The findings of the correlation study between pulmonary function test results and oxidative stress indicators in the asthma group are shown in Table 5. As a result, there was no statistically significant association between oxidative stress markers and the outcomes of the pulmonary function test (p>0.05) in the asthma group.

Discussion

Asthmatic patients are identified by inflammation, which occurs when oxidizing substances alter the structure of epithelial cells, resulting in increased mucus production. As a result, structural changes occur in the airways, leading to bronchial remodeling which triggers the release of inflammatory mediators, worsening the disease's symptoms. Pro-inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1 and IL-6 are found to be elevated in Asthma patients[7].

Pro-inflammatory mediators are also correlated with higher oxidative state, which is consistent with the features of the disease. The Th2 pathway and eosinophilic inflammation are thought to be involved in the majority of asthma patients. Non-eosinophilic asthmatics, had relationship with other leukocyte subsets, and high oxidative condition and inflammation, resulting in higher oxidative markers than control groups[7,8].

In the current study, TOS and DIS values of individuals with asthma are extremely high compared to healthy controls. On the other hand, TAS, OSI, TT, and NT values of healthy

Table 5. Correlation analysis findings between pulmonary function test results and oxidative stress markers in the asthma patients

	FEV1 (ml)	FEV1 (%)	FVC (ml)	FVC (%)	PEF	FEV1/FVC (%)
TOS	r=–0.059	r=–0.201	r=–0.096	r=0.136	r=–0.123	r=0.194
	p=0.694	p=0.175	p=0.521	p=0.450	p=0.410	p=0.192
TAS	r=0.103	r=0.072	r=0.110	r=0.279	r=0.083	r=–0.011
	p=0.491	p=0.628	p=0.462	p=0.116	p=0.579	p=0.939
OSI	r=–0.100	r=–0.238	r=–0.138	r=–0.249	r=–0.151	r=0.155
	p=0.505	p=0.107	p=0.355	p=0.163	p=0.312	p=0.297
TT	r=–0.115	r= 0.041	r=–0.114	r= –0.148	r=0.044	r=–0.021
	p=0.443	p=0.785	p=0.446	p=0.413	p=0.767	p=0.890
NT	r=–0.096	r= –0.284	r=–0.164	r= –0.181	r=–0.076	r=0.232
	p=0.522	p=0.053	p=0.270	p=0.313	p=0.613	p=0.116
DIS	r=–0.055	r=0.191	r=–0.019	r=0.076	r=0.079	r=–0.113
	p=0.715	p=0.199	p=0.899	p=0.972	p=0.600	p=0.450

TOS: total oxidant status; TAS: total antioxidant status; OSI: oxidative stress index; TT: total thiol; NT: native thiol; DIS: disulfide.

controls were significantly higher than the asthma group.

There are no adequate study which demonstrate a relationship between antioxidant indicators and asthmatic lung function/disease severity[8]. Both in the lung and in the blood, superoxide dismutase (SOD) activity has been demonstrated to be favorably linked with lung function[8]. Excessive ROS production causes SOD inactivation, which could be associated with lung function loss. In addition, circulating leukocytes may be involved in SOD inactivation and oxidant production, leading to a reduction in lung function[9,10]. Other enzymatic antioxidants and lung function are not found to have any meaningful relationships in many studies[9,10]. The enzymes lower (SOD) oxidative susceptibility or differential gene regulation in response to oxidative harm. In our study, we also did not find any relation with the lung functions, but a difference between healthy and diseased subjects. In our study, we did not find any relationship between lung functions of asthmatic patients and oxidative stress markers, but we found a difference in oxidative stress markers between healthy and diseased individuals.

Several investigations have found an increased oxidative burden in asthmatic patients. Cluzel et al.[11] studied at the respiratory burst of alveolar macrophages in bronchoalveolar lavage (BAL), finding that it was much higher in asthma patients, and that there was a link between alveolar macrophage ROS production and asthma severity. In several studies, revealed that changes in antioxidant enzymes are relatively common in asthmatic airways[11]. Because there has no adequate data about the oxidative level of the peripheral blood and the oxidative condition of alveolar macrophages in asthmatic patients[11]. In the current study, respiratory burst of alveolar macrophages in BAL was not evaluated, besides peripheral blood, and the oxidative condition of alveolar macrophages in asthmatic patients was determined.

There were some limitations. First, it was a cross-sectional, single-center study. Nonetheless, it provides crucial clinical information due to the sample size and specific patient group such as asthma. Second, the study was undertaken using only asthma patients and the results were not be generalized. These results may be helpful for physicians managing the relationship between Asthma patients and oxidative stress markers during their follow-up period.

Smoking has a significant impact on the lungs' oxidative state. Exogenous causes of oxidative stress in the lungs include smoking, air pollution, and biomass smoke; nevertheless, oxidative stress remains even in ex-smokers, demonstrating that oxidative stress can arise endogenously. Smoking was not evaluated as an interfering factor in our study because the number of smoker patients is quite low, and the oxidative state is associated to disease itself.

CONCLUSION

In our study, we found that the oxidant/antioxidant balance was impaired and oxidative stress increased in asthma patients. Future research should focus on the development of innovative therapeutic strategies that combine antioxidant therapy with asthma treatment.

Ethics Committee Approval: The study was approved by Health Sciences University Turkey Hamidiye Scientific Research Hospital Ethics Committee (04.02.2022-22/54) and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.A.B.; Design: S.A.B.; Data Collection or Processing: S.A.B.; Analysis or Interpretation: S.A.B., B.N.Ö.; Literature Search: B.N.Ö.; Writing: S.A.B., B.N.Ö.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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