Antioxidant Enzyme Deficiency and Oxidative Stress in Asthma: Implications for Therapeutic Antioxidant Strategies

Ali Abdalla Hindi [1*], Zeyad Swadi Obaid AL-isawi [2], Sameem S. M. Baker [3]

Abstract

Background: Asthma is a chronic inflammatory disorder characterized by oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and antioxidant defenses. ey oxidative stress markers, including superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and malondialdehyde (MDA), provide insights into the pathophysiology of asthma. This study aimed to evaluate oxidative stress markers in asthmatic patients by measuring antioxidant enzyme levels and lipid peroxidation products. Methods: A case-control study was conducted at Alsader Medical City in Najaf, involving 87 asthmatic patients (46 males, 41 females) and 33 healthy controls matched by age and sex. Blood samples were collected, and serum levels of SOD, CAT, GST, and MDA were measured using standardized biochemical assays. Statistical analysis was performed to assess group differences and gender-based variations, with a significance level of $p<0.05p < 0.05p<0.05$. Results: Asthmatic patients exhibited significantly lower SOD (44.1–89.38 U/L vs. 74–94.5 U/L, $p<0.001p < 0.001p<0.001$), CAT (0.015–0.106 km/min vs. 0.036–0.12 km/min, $p<0.001p < 0.001p<0.001$), and GST (3.1–18.7 U/L vs. 5.9–19 U/L, $p<0.05p < 0.05p<0.05$) levels compared to controls. In contrast, MDA levels were markedly elevated (2.2–13.46 µM vs. 0.63–6.59 µM, $p<0.001p < 0.001p<0.001$), indicating heightened oxidative stress. Gender-based comparisons among asthmatic patients revealed no significant differences in oxidative stress markers between males and females, suggesting a uniform impact of oxidative stress irrespective of sex. Conclusion: The findings highlight a significant oxidative imbalance in asthmatic patients, characterized by reduced antioxidant enzyme activities and elevated lipid peroxidation. These results underscore the role of oxidative stress in asthma pathogenesis and suggest that antioxidant-based therapeutic strategies could mitigate disease severity. Further research is needed to explore personalized approaches to managing oxidative stress in asthma.

Keywords: Asthma, Oxidative stress, Antioxidant enzymes, Malondialdehyde (MDA), Biomarker analysis .

Significance | This study reveals reduced antioxidant enzyme activity and elevated oxidative stress markers in asthma, emphasizing antioxidant therapy's potential.

*Correspondence. Ali abdalla Hindi ,Department of Biology, College of Sience, Al-Qasim Green University, Babylon, 51013, Iraq.
E-mail: Aliabdallah@science.uoqasim.edu.iq

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1. Introduction

Asthma is a chronic inflammatory disease of the respiratory system characterized by airway hyperresponsiveness and reversible airflow obstruction. The respiratory system is primarily responsible for oxygen (O_2) uptake and carbon dioxide (CO_2) elimination. It is divided anatomically into the upper and lower respiratory tracts. The upper respiratory tract includes the nose, larynx, and upper trachea, located externally to the chest cavity. The lower respiratory tract, within the chest cavity, encompasses the lungs, lower trachea, bronchi, bronchioles, alveolar ducts, and alveoli (Scanlon & Sanders, 2007). The lungs, soft and spongy organs, are enclosed by

Author Affiliation.
[1] Department of Biology, College of Sience, Al-Qasim Green University, Babylon, 51013, Iraq.
[2] Faculty of dentistry, University of Kufa, Najaf, 54003, Iraq.
[3] College of dentistry,Ahl Al Bayt University, Karbala, 56001, Iraq.

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a by a two-layered serous membrane known as the pleura. The outer parietal layer adheres to the chest wall, while the inner visceral layer is in contact with the lungs. Negative intrapleural pressure is essential to prevent lung collapse due to elastic recoil (Scanlon & Sanders, 2007).

Oxidative stress, a condition where reactive oxygen species (ROS) production overwhelms antioxidant defenses, plays a significant role in asthma pathogenesis. Elevated ROS levels in asthma can exacerbate inflammation, airway remodeling, and hyperresponsiveness. Key markers of oxidative stress, such as superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and malondialdehyde (MDA), offer insights into the oxidative imbalance in asthmatic individuals (MacPherson et al., 2001; Comhair et al., 2005).

SOD and CAT are critical antioxidant enzymes that protect the airway from oxidative damage by neutralizing superoxide radicals and hydrogen peroxide, respectively. However, studies indicate that SOD activity is diminished in asthmatic airways due to increased ROS production by inflammatory cells, further reducing antioxidant capacity (Comhair et al., 2005). Similarly, GST, which detoxifies harmful metabolites, is also reported to exhibit decreased activity in asthma patients (Habig et al., 1974). MDA, a lipid peroxidation byproduct, is elevated in asthma, reflecting increased oxidative damage to membrane lipids (Rahman et al., 1996; Granic, 2001).

The interplay between oxidative stress and asthma is influenced by various factors, including disease severity, environmental exposures, and antioxidant status. For example, individuals with poorly controlled asthma or those exposed to high oxidative stress environments, such as pollution, may exhibit more pronounced deficits in antioxidant enzymes and higher oxidative damage markers (Halliwell & Gutteridge, 1989; Ozarus et al., 2000). Additionally, evidence suggests that antioxidant supplementation, either natural or synthetic, could mitigate oxidative stress and improve asthma outcomes (Mohan & Das, 1997).

Gender and age also modulate oxidative stress in asthma. Although studies reveal no significant gender-based differences in oxidative stress markers, age appears to exacerbate oxidative imbalance. Older asthmatics are more likely to exhibit reduced antioxidant enzyme activities and increased oxidative damage compared to younger individuals (Wood, Gibson, & Garg, 2003).

However, understanding oxidative stress mechanisms and their markers provides valuable insights into asthma pathophysiology. Interventions aimed at enhancing antioxidant defenses could potentially alleviate asthma severity and improve quality of life for patients.

2. Materials and Methods

2.1 Control Groups and Patients

2.1.1 Patient Group:

The study was conducted at Alsader Medical City in Najaf, involving 87 asthmatic patients (46 males and 41 females) aged 8 to 61 years. Patients with conditions such as diabetes mellitus, cardiovascular disease, hypertension, liver disease, or those using oral contraceptives were excluded to avoid confounding data. Comprehensive questionnaires were utilized to collect demographic and clinical information from the patients.

2.1.2 Control Group:

The control group included 33 healthy individuals matched to the patient group by age and sex. These participants underwent the same sample collection and analysis procedures. The control group also participated in the study at Alsader Medical City/Najaf laboratory.

2.2 Sample Collection

Blood samples were collected from both the patient and control groups using sterile disposable needles and syringes. Venipuncture was performed under standard conditions. Samples were incubated at room temperature to facilitate clotting before centrifugation at 3000 ×g for 10 minutes. The resulting serum was carefully transferred to designated tubes and stored at −17°C until further analysis.

2.3 Biochemical Measurements

Superoxide Dismutase (SOD) Activity:

The SOD activity was quantified using the SOD Test Kit – WST. This assay utilizes a water-soluble tetrazolium salt that produces a formazan dye upon reduction by superoxide anions. The inhibition of xanthine oxidase (XO) by SOD was measured as a decrease in the reduction rate of oxygen.

Catalase (CAT) Activity:

Catalase activity was measured using a method described by Aebi (1974), which monitors the reduction in absorbance due to the consumption of hydrogen peroxide (H_2O_2). This assay provided a direct assessment of the enzyme's activity in breaking down H_2O_2.

Glutathione-S-Transferase (GST) Activity:

GST activity was determined following the protocol established by Habig et al. (1974). This method evaluates the enzyme's role in catalyzing the conjugation of glutathione to various substrates.

$$\text{G - SH} + \text{CDNB} \xrightarrow{\text{GST}} \text{G - SDNB Conjugate} + \text{HCl}$$

Malondialdehyde (MDA) Levels:

MDA levels, indicative of lipid peroxidation, were determined using the modified method of Guidet and Shah. This assay measured the concentration of MDA as a marker of oxidative stress.

2.4 Statistical Analysis

Data analysis was performed using Minitab, Mega Statistics, and SPSS software. Results were expressed as mean ± standard deviation. A significance threshold of $P < 0.05$ was applied to all statistical tests to evaluate differences between groups.

Table 1. Superoxide dismutase (SOD), glutathione – S – transferase (GST) catalase (CAT), and "malondialdehyde (MDA) levels in asthmatic patients and the control group".

Parameter	Subject	No.	Mean ± SD	Range	P – value
SOD (U / L)	Control Patients	33 87	86.25±7.04 67.31±17.8	74 – 94.5 44.1 – 89.38	0.001
CAT(km/min)	Control Patients	33 87	0.073±0.023 0.049±0.023	0.036 – 0.12 0.015 – 0.106	0.001
GST (U / L)	Control Patients	33 87	11.05±4.2 9,02 ± 3.7	5.9 – 19 3.1 – 18.7	0.05
MDA (µM)	Control Patients	33 87	3.93±2.8 7.59±4.27	0.63 – 6.59 2.2– 13.46	0.001

Table 2. Superoxide dismutase (SOD), malondialdehyde (MDA), glutathione – S – transferase (GST) and catalase (CAT) levels in the male and female asthmatic patients.

Parameter	sex	No.	Mean ± SD	Range	P – value
SOD (U / L)	Male Female	46 41	76.13±17.41 69.09±16.9	46.3 – 83.48 44.1 – 89.38	NS
CAT(K/ min)	Male Female	46 41	0.049±0.022 0.043±0.02	0.016 – 0.106 0.015 – 0.091	NS
GST (U / L)	Male Female	46 41	9.3±3.09 8.97±4.28	4.3 – 18.7 3.1 – 15.3	NS
MDA (µM)	Male Female	46 41	6.64±3.09 8.06±4.31	2.2 – 12.38 2.42 – 13.46	NS

3. Results

3.1 Comparison of Oxidative Stress Markers Between Asthmatic Patients and the Control Group

The levels of superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and malondialdehyde (MDA) were assessed in the serum of 87 asthmatic patients and 33 healthy controls (Table 3-1).

Asthmatic patients showed significantly reduced SOD activity, with a mean range of 44.1–89.38 U/L compared to 74–94.5 U/L in the control group ($p < 0.001$). Similarly, CAT activity in asthmatic patients ranged between 0.015–0.106 km/min, markedly lower than the control group's range of 0.036–0.12 km/min ($p < 0.001$). GST activity also exhibited a significant reduction, with values ranging from 3.1–18.7 U/L in patients versus 5.9–19 U/L in controls ($p < 0.05$). Conversely, MDA levels were significantly elevated in asthmatic patients, ranging from 2.2–13.46 μM, compared to 0.63–6.59 μM in the control group ($p < 0.001$). These findings underscore the heightened oxidative stress and compromised antioxidant defenses in asthmatic patients.

3.2 Gender-Based Comparison of Oxidative Stress Markers in Asthmatic Patients

A further analysis was conducted to determine whether gender influenced oxidative stress markers among asthmatic patients (Table 3-2). The results revealed no statistically significant differences between male and female patients across all parameters. In males, SOD activity ranged from 46.3–83.48 U/L, while in females, it ranged from 44.1–89.38 U/L (p = NS). CAT activity showed similar non-significant variations, with males displaying 0.016–0.106 km/min and females 0.015–0.091 km/min (p = NS). GST activity ranged from 4.3–18.7 U/L in males and 3.1–15.3 U/L in females (p = NS). MDA levels also showed no significant differences, with ranges of 2.2–12.38 μM in males and 2.42–13.46 μM in females (p = NS).

Asthmatic patients exhibited elevated oxidative stress markers and reduced antioxidant enzyme activities compared to healthy controls. No significant gender-related differences in oxidative stress parameters were observed among the asthmatic patients, suggesting a uniform impact of oxidative stress across sexes. These findings highlight the critical role of oxidative stress in asthma and suggest that its management may benefit from targeted therapeutic interventions, irrespective of gender.

4. Discussion

4.1 Measurement of Catalase, Superoxide Dismutase, Malondialdehyde, and Glutathione-S-Transferase in Asthmatic Patients and Controls

This study evaluated the serum levels of catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione-S-transferase (GST) in 87 asthmatic patients and 33 healthy controls. Statistical analysis revealed a significant ($P < 0.001$) decrease in SOD and CAT levels, along with a moderate ($P < 0.05$) reduction in GST levels in asthmatic patients compared to controls. Conversely, MDA levels were significantly elevated ($P < 0.001$) in asthmatics, indicating heightened oxidative stress (Table 1).

Asthma is a chronic inflammatory condition associated with elevated levels of reactive oxygen species (ROS), which can overwhelm the body's antioxidant defenses and lead to oxidative stress (MacPherson et al., 2001). The significant reduction in SOD and CAT activities observed in this study aligns with findings that these enzymes serve as primary antioxidant defenses in the airway, mitigating oxidative damage (Comhair et al., 2005). The diminished SOD activity, in particular, may result from an oxidant-rich environment in asthmatic airways and excessive ROS production by inflammatory cells (Halliwell & Gutteridge, 1989).

GST, another critical antioxidant enzyme, also exhibited reduced activity in asthmatics, corroborating prior studies that reported antioxidant deficits in these patients (Comhair et al., 2005). However, variations in the severity of asthma, nutritional status, and sampling methodologies might contribute to discrepancies observed across studies (Wood et al., 2003).

MDA, a marker of lipid peroxidation and oxidative stress, was significantly elevated in asthmatic patients. This finding is consistent with studies demonstrating increased ROS-induced lipid oxidation in asthmatics (Rahman et al., 1996). The excessive ROS may lead to the oxidation of vital biomolecules, including membrane lipids, thereby contributing to airway remodeling and inflammation (Ozarus et al., 2000). Some studies, such as Mohan and Das (1997), have reported no significant changes in MDA levels, suggesting that individual variability and disease heterogeneity may influence oxidative stress markers.

Interestingly, conflicting results have been reported regarding antioxidant enzyme activity in asthmatics. Powell et al. (1994) found no significant differences in SOD activity between asthmatic and control groups, while Smith et al. (1997) reported comparable CAT activity. Such inconsistencies could stem from differences in patient demographics, disease severity, and methodologies.

4.2 Gender Differences in Oxidative Stress Markers in Asthmatic Patients

The study also assessed the influence of gender on oxidative stress markers. Among the 87 asthmatic patients (46 males, 41 females), no significant differences in SOD, CAT, GST, or MDA levels were observed between males and females. However, compared to controls, both male and female asthmatic patients exhibited significantly reduced antioxidant enzyme activities (SOD, CAT, GST) and elevated MDA levels, indicating comparable oxidative stress levels irrespective of gender (Table 2).

This lack of gender-based differences suggests that the pathological mechanisms driving oxidative stress and ROS behavior in asthma

operate similarly in males and females. These findings align with prior research indicating that gender does not significantly affect oxidative stress biomarkers in asthma (Mohan & Das, 1997). However, further studies are warranted to explore potential subtle gender-related differences that might emerge with larger sample sizes or different analytical approaches.

4.3 Clinical Implications and Future Directions

The results of this study underscore the critical role of oxidative stress in the pathophysiology of asthma. The significant reduction in antioxidant enzymes (SOD, CAT, GST) and elevated MDA levels highlight the imbalance between ROS production and antioxidant defenses in asthmatic patients. These findings suggest that therapeutic strategies aimed at enhancing antioxidant defenses or reducing ROS production could benefit asthma management.

Antioxidant supplementation, such as SOD mimetics or CAT enhancers, could potentially alleviate oxidative stress in asthmatics. However, the variability in oxidative stress markers among individuals necessitates personalized approaches to treatment. Future studies should investigate the impact of disease severity, nutritional factors, and genetic predispositions on oxidative stress biomarkers in asthma.

4.4 Study Limitations

While this study provides valuable insights, it has several limitations. The relatively small sample size may limit the generalizability of the findings. Additionally, the study did not account for dietary intake, medication use, or environmental exposures that could influence oxidative stress markers. Longitudinal studies with larger, more diverse populations are needed to validate these findings and explore potential interventions.

5. Conclusion

This study demonstrated significant oxidative stress in asthmatic patients, evidenced by reduced antioxidant enzyme activities (SOD, CAT, GST) and elevated MDA levels. These findings emphasize the role of oxidative stress in asthma pathogenesis and the potential utility of antioxidant-based therapies. Further research is needed to elucidate the complex interactions between ROS, antioxidants, and clinical outcomes in asthma.

Author contributions

A.A.H. conceived and designed the study, conducted data analysis, and drafted the manuscript. Z.S.O.A.L.contributed to data collection, performed a literature review, and revised the manuscript. S.S.M.B. assisted with the study methodology, data interpretation, and manuscript writing. All authors reviewed and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

References

Aebi, H. (1974). Methods of enzymatic analysis. New York: Academic Press.

Comhair, S. A. A., et al. (2005). Superoxide dismutase inactivation in asthmatic airway remodeling. American Journal of Pathology, 166, 663–666.

Comhair, S. A., Xu, W., Ghosh, S., Thunnissen, F. B., Almasan, A., Calhoun, W. J., Janocha, A. J., Zheng, I., Hazen, S. I., & Erzurum, S. C. (2005). Superoxide dismutase inactivation in the pathophysiology of asthmatic airway remodeling and reactivity. American Journal of Pathology, 166(3), 663–673.

Granic, P. (2001). Oxidative stress diagnostics procedures. Zagreb: Medicinska Naklada.

Habig, W. H., Pabst, M. J., & Jakoby, W. B. (1974). Glutathione S-transferase: The first enzymatic step in mercapturic acid formation. Journal of Biological Chemistry, 249(22), 7130–7139.

Halliwell, B., & Gutteridge, J. M. C. (1989). Free radicals in biology and medicine. Oxford: Clarendon Press.

Halliwell, B., & Gutteridge, J. M. C. (1989). Free radicals in biology and medicine (2nd ed.). Oxford: Clarendon Press.

MacPherson, J. C., Comhair, S. A., Erzurum, S. C., Klein, D. F., Lipscomb, M. F., Kavuru, M. S., Samoszuk, M. K., & Hazen, S. L. (2001). Eosinophils as a major source of nitric oxide-derived oxidants in severe asthma. Journal of Immunology, 166(10), 5763–5772.

MacPherson, J. C., et al. (2001). Eosinophils as a major source of nitric oxide-derived oxidants in severe asthma. Journal of Immunology, 166, 5763–5772.

Mohan, I. K., & Das, U. N. (1997). Oxidant stress and antioxidants in asthma. Medical Science Research, 25, 307–309.

Mohan, I. K., & Das, U. N. (1997). Oxidant stress, antioxidants, nitric oxide, and essential fatty acids in bronchial asthma. Medical Science Research, 25(6), 307–309.

Ozarus, R., et al. (2000). Changes in malondialdehyde levels in asthma with inhaled steroids. Respirology, 5, 289–292.

Ozarus, R., Tahan, V., Turkmen, S., et al. (2000). Changes in malondialdehyde levels in bronchoalveolar fluid and serum by the treatment of asthma with inhaled steroid and beta2-agonist. Respirology, 5(4), 289–292.

Powell, C. V. E., et al. (1994). Antioxidant status in asthma. Pediatric Pulmonology, 18, 34–38.

Rahman, I., Morrison, D., Donaldson, K., & MacNee, W. (1996). Systemic oxidative stress in asthma, COPD, and smokers. American Journal of Respiratory and Critical Care Medicine, 154(4), 1055–1060.

Scanlon, V. C., & Sanders, T. (2007). Essentials of anatomy and physiology (5th ed.). F.A. Davis Company.

Smith, L. J., et al. (1997). Reduced superoxide dismutase in lung cells of asthma patients. Free Radical Biology and Medicine, 22, 1301–1307.

Wood, L. G., et al. (2003). Biomarkers of lipid peroxidation in asthma. European Respiratory Journal, 21, 177–186.

Wood, L. G., Gibson, P. G., & Garg, M. L. (2003). Biomarkers of lipid peroxidation, airway inflammation, and asthma. European Respiratory Journal, 21(2), 177–186.