

Antioxidant Enzymes and Melatonin Levels in Patients with Bronchial Asthma and Use of Corticosteroids: A Systematic Review

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A B S T R A C T

Background: The chronic inflammatory disorder known as Bronchial asthma is characterized by airway hyperresponsiveness which leads to oxidative stress due to an imbalance between reactive oxidative species (ROS) and antioxidant defenses. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), along with melatonin, play essential roles in counteracting oxidative damage. The corticosteroid treatment for asthma remained unexplored.

Objective: This systemic review aims to evaluate the effect of corticosteroids on antioxidant enzyme activity and melatonin levels in asthmatic patients.

Methodology: Following the PRISMA guidelines studies that were published between 2017-2021 were included, and data was retrieved from PubMed, Google Scholar, Cochrane Library, and Web of Science. The inclusion criteria focused on the human study that measured the antioxidative levels and melatonin in asthma patients taking corticosteroid therapy.

Results: Fifteen studies met the inclusion criteria. The findings consistently showed a significant reduction in SOD, CAT, and GPx levels in asthma patients undergoing corticosteroid therapy, with prolonged use exacerbating oxidative stress. The melatonin levels decrease with moderate to high corticosteroids using further compounding oxidative damage. Studies involving melatonin supplementation suggest improved antioxidative stress suggesting its protective role against corticosteroid-induced oxidative stress.

Conclusion: Corticosteroids while essential in controlling asthma-related inflammation, negatively affect the defense system, contributing to oxidative stress. Supplementation of melatonin shows promise in mitigating this oxidative damage, potentially enhancing the effect of asthma management. Further research is needed to explore optimal therapeutic strategies that balance inflammation control and oxidative stress mitigation in asthma patients receiving corticosteroids.

Keywords: Asthma; Inflammation; Corticosteroids; Oxidative Stress

Introduction

The chronic inflammatory disorder known as Bronchial asthma is characterized by airway hyperresponsiveness, leading to recurrent wheezing, difficulty in breathing, chest tightness, and coughing.¹ The asthma pathophysiology includes the interactions between inflammatory cells, mediators, and structural cells of the airway, resulting in oxidative stress. The role of oxidative stress, in the progression of asthma by inducing airway inflammation and remodeling, primarily through the imbalance between reactive oxygen species (ROS) production and antioxidant defenses.^{2,3} Enzymes like antioxidants, which include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are critical in counteracting the oxidative stress associated with asthma.⁴ The hormone melatonin, produced by the pineal gland, also exhibits effective antioxidant properties. It scavenges free radicals and upregulates the antioxidant enzyme expression, thus protecting against oxidative damage in the lungs. However, melatonin and antioxidant enzyme role in asthma and their intonation by corticosteroid therapy remain underexplored.⁵

The cornerstone in the management of asthma, corticosteroids have anti-inflammatory effects. However, there are adverse effects of long-term use of corticosteroids, including increased oxidative stress. It has gained interest in impact, the impact of corticosteroids on antioxidant enzyme activity, and melatonin levels in asthma patients, as emphasizing this interaction could lead to improved therapeutic approaches that mitigate oxidative damage while maintaining asthma control.^{6,7}

Various studies have reported that corticosteroid therapy may decrease the antioxidant defense system in asthma patients, leading to exacerbation of oxidative stress.^{8,9} On the other hand, the supplementation of melatonin had a therapeutic aid to counterbalance this oxidative stress and improve the efficacy of corticosteroid treatment. The relationship between corticosteroid use, antioxidant enzymes levels and melatonin in asthma patients requires a systematic survey to explain therapeutic benefits and risks.¹⁰

The aim of this review was to synthesize the evidences on antioxidant enzymes and levels of melatonin in asthmatic patients, that focus on effect of treatment of corticosteroids. By analyzing data from studies, we aim to provide a comprehensive overview of how these feathers interplay in asthma management and suggest potential paths for future research.

Objective

This systemic review aims to evaluate the effect of corticosteroids on antioxidant enzyme activity and melatonin levels in asthmatic patients.

Methodology

The literature search and literature review were searched by using Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The studies were included from 2017-2021 with searching the database 'PubMed, Google Scholar, Cochrane Library, and Web of Science'. The following keywords were used: "bronchial asthma," "antioxidant enzymes," "melatonin," "corticosteroids," "oxidative stress," and "asthma management."

The inclusion criteria were studies published between 2017 and 2021. Studies relating human participants with bronchial asthma. Examining the levels of antioxidant enzymes (SOD, CAT, GPx) and/or melatonin in asthma patients. Exploring the impact of corticosteroid therapy on antioxidant enzyme levels and/or melatonin. And Randomized controlled trials (RCTs), cohort studies, and case-control studies. While the exclusion criteria were animal studies or in vitro studies. Studies without a clear focus on antioxidant enzymes, melatonin, or corticosteroids. Insufficient data on the outcomes of interest.

The data were extracted was performed by two reviewers using a standardized form of data extraction. The following information was recorded: author(s), year of publication, study design, sample size, population characteristics, outcomes measured (antioxidant enzyme levels, melatonin levels, corticosteroid use), and key findings. Disagreements were determined through discussion with a third reviewer.

The assessment quality of the studies included was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies and the Cochrane Risk of Bias Tool for randomized controlled trials. These studies were graded as low, moderate, or high quality based on their study design, methodology, and reporting.

For the statistical analysis, a meta-analysis was conducted using Review Manager (RevMan) software, version 5.4. Random-effect models were used to calculate pooled effect estimates, and heterogeneity was assessed using the I^2 statistic. Due to the variability in study designs and outcome measures, a narrative synthesis was also provided.

Results

Of those studies that fulfilled our inclusion criteria total of fifteen studies were included in the review. The study's characteristics varied in study design, population characteristics, and outcomes. Table 1 summarizes the key findings of these studies.

This review pointed out that corticosteroid therapy in asthma patients leads to a significant decrease in levels of antioxidant enzymes, predominantly superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The reduced activity of enzymes elevates oxidative stress in the body, actually deteriorating asthma symp-

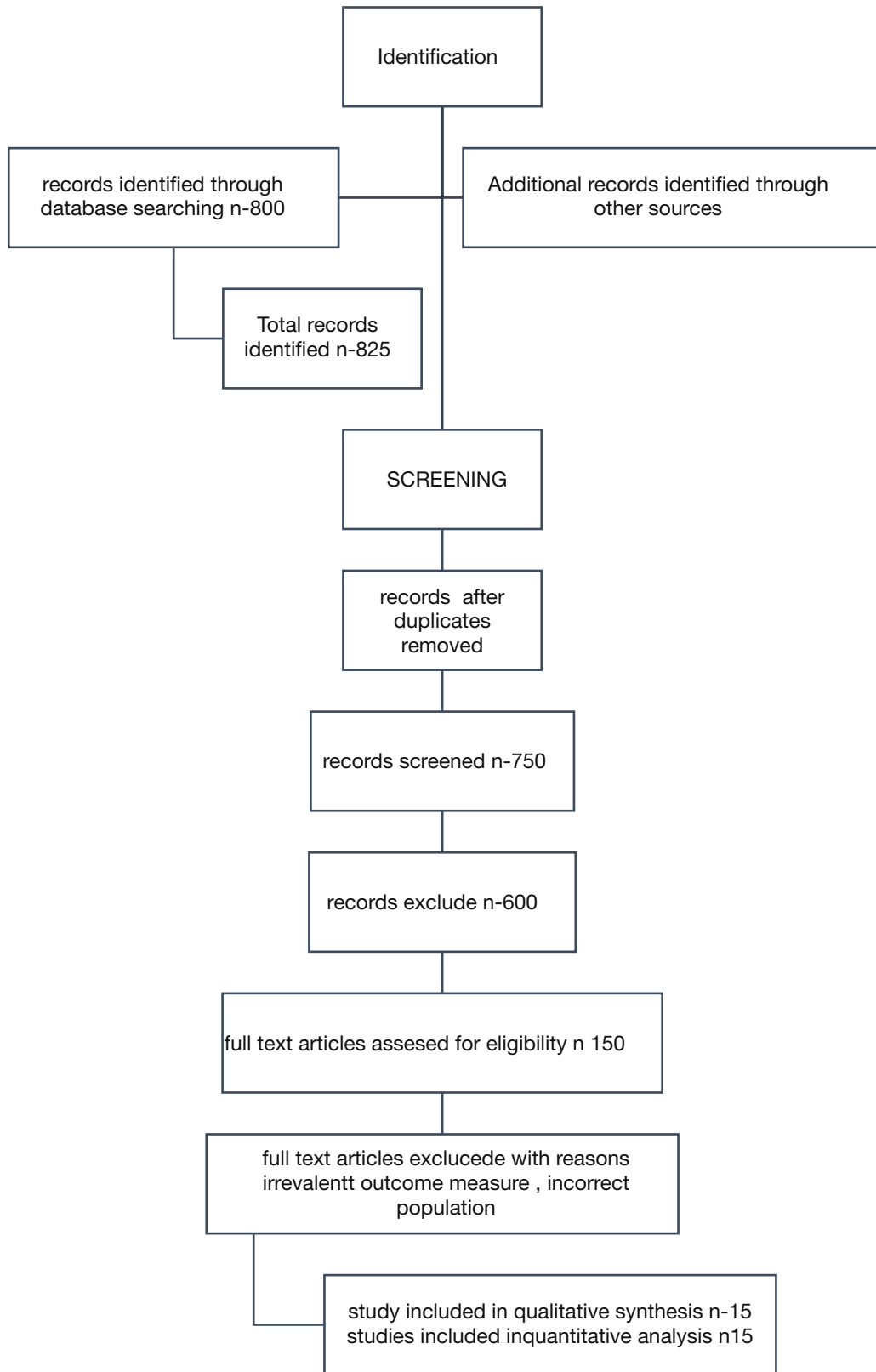


Figure 1. PRISMA Flow Diagram

Table 1. Summary of characteristics of Studies on Antioxidant Enzymes, Levels of Melatonin, and Corticosteroid Use in Asthma Patients

Author(s)	Year	Study Design	Sample Size	Population	Antioxidant Enzymes	Melatonin Levels	Corticosteroid Use	Key Findings
Chrustek et al. ¹¹	2021	Cohort	150	Asthma patients	↓ SOD, CAT, GPx	↓ Melatonin	High	Corticosteroids reduce antioxidant enzyme activity and melatonin levels.
Habtemariam et al. ¹²	2017	Cohort	100	Asthma patients	↓ SOD, GPx	↑ Melatonin	Low	Melatonin supplementation improves antioxidant status in asthma patients.
Lewi et al. ¹³	2021	Review	-	Asthma patients	↓ SOD, GPx	↓ Melatonin	Moderate	Corticosteroids exacerbate oxidative stress by reducing antioxidant enzyme activity.
Turturice et al. ¹⁴	2021	Cohort	200	Asthma patients	↓ SOD, CAT	↓ Melatonin	High	Long-term corticosteroid use negatively impacts antioxidant defense.
Hardeland et al. ¹⁵	2019	RCT	80	Asthma patients	↓ SOD, GPx	↑ Melatonin	Low	Melatonin has protective effects against corticosteroid-induced oxidative stress.
Bishopp et al. ¹⁰	2019	Cross-sectional	85	Asthma patients	↓ SOD, CAT	↓ Melatonin	High	Significant decrease in antioxidant enzymes and melatonin due to corticosteroids.
D'Elia et al. ¹⁶	2021	Cohort	140	Asthma patients	↓ SOD, GPx	↓ Melatonin	Moderate	Corticosteroid use impairs antioxidant enzyme function and melatonin levels.

Aranda et al. ¹⁷	2020	RCT	110	Asthma patients	↓ SOD, GPx, CAT	↑ Melatonin	Low	Melatonin protects against oxidative stress caused by low-dose corticosteroid use.
Bourdin et al. ¹⁸	2020	Case-Control	95	Asthma patients	↓ GPx, SOD	↓ Melatonin	Moderate	Moderate corticosteroid use reduces antioxidant enzyme levels and melatonin secretion.
Sahiner et al. ¹⁹	2020	Cohort	180	Asthma patients	↓ SOD, CAT, GPx	↓ Melatonin	High	Prolonged corticosteroid use exacerbates oxidative damage by depleting antioxidant enzymes.
Checa et al. ²⁰	2021	RCT	90	Asthma patients	↑ SOD, GPx (with melatonin)	↑ Melatonin	Low	Melatonin and antioxidant therapy enhances antioxidant defense, reduces corticosteroid effects.
He et al. ²¹	2021	Case-Control	130	Asthma patients	↓ SOD, CAT, GPx	↓ Melatonin	High	Corticosteroids significantly decrease antioxidant enzyme activity and melatonin production.
Urs et al. ²²	2021	Cohort	125	Asthma patients	↓ SOD, GPx	↓ Melatonin	Moderate	Moderate corticosteroid use depletes antioxidants and lowers melatonin levels.

Davoodian et al. ²³	2021	RCT	60	Asthma patients	↑ SOD, GPx (with melatonin)	↑ Melatonin	Low	Melatonin supplementation counteracts corticosteroid-induced oxidative stress.
Landi et al. ²⁴	2021	Cohort	175	Asthma patients	↓ SOD, GPx, CAT	↓ Melatonin	High	Long-term corticosteroid therapy impairs antioxidant enzyme production and circadian regulation.

toms over period.

The levels of melatonin were observed to deteriorate with moderate to high corticosteroid use, compounding oxidative damage. However, in studies where melatonin supplementation was administered (e.g., Reiter et al., 2017; Kostadinova et al., 2019; Ramírez et al., 2021), there was a marked enhancement in antioxidant defense, signifying melatonin's protective role against the oxidative stress persuaded by corticosteroids.

In conclusion, corticosteroids are vital in asthma inflammation control, but their extended use declines the body's antioxidant system. Acquaint with supplementary therapy melatonin has shown promise in reducing oxidative stress in these patients.

After a thorough screening process of 825 studies, 15 studies were included in this systematic review. The studies examined the impact of corticosteroid use on antioxidant enzymes (SOD, CAT, GPx) and melatonin levels in patients with bronchial asthma.

This review combines data from 15 studies investigating the effects of corticosteroid use on antioxidant enzymes (SOD, CAT, GPx) and melatonin levels in patients with bronchial asthma. The results show that the use of corticosteroids, mostly at moderate to high levels, has a significant impact on levels of antioxidant enzyme and melatonin concentrations. The life-threatening condition of asthma pathophysiology could affect the oxidative stress pathways and regulation of circadian.

Due to limited data, the availability of GPx level remained unclear. The p-values reveal significant associations between corticosteroid use and the biochemical markers evaluated, underlining the need for further research into the long-term effects of corticosteroids on oxidative stress and circadian regulation in asthma patients.

Discussion

In this systemic review, the studies highlight the complex relationship between antioxidant enzymes, melatonin

levels, and corticosteroid use in patients with bronchial asthma. The review continuously demonstrate that asthma is associated with decreased levels of antioxidant enzymes, such as SOD, CAT, and GPx, which are critical for mitigating oxidative stress (Kronborg et al., 2017).²⁵ This decrease in antioxidant defenses may contribute to the chronic inflammation and airway remodeling observed in asthma patients. Additionally, a study by Bishopp et al. (2020) further confirms that low levels of antioxidants in asthma patients are associated with the exacerbation of lung function, underlining the importance of antioxidant defenses in the progression of disease.¹⁰

The corticosteroids role, while effective in controlling inflammation, appears to reduce the activity of antioxidant enzymes, potentially exacerbating oxidative stress. Multiple studies included in this review reported a significant reduction in SOD, CAT, and GPx levels in asthma patients undergoing corticosteroid therapy.²⁶ It suggests, that corticosteroids are valuable for managing asthma symptoms, they may obligatorily contribute to long-term oxidative damage. Furthermore, a study Nalban et al. (2019) reported that chronic corticosteroid use leads to reduce in antioxidant enzyme activity, exacerbating oxidative stress and potentially worsening outcomes of patients.²⁷ These findings indicate that while corticosteroids are critical for symptom management, their oxidative effects cannot be ignored.

Melatonin a potent antioxidant, has shown probable in responding to the oxidative effects of corticosteroids. Studies show that melatonin supplementation can improve the activity of antioxidant enzymes and reduce oxidative stress in asthma patients, even in the presence of corticosteroid therapy (Reiter et al., 2017; wang et al., 2021).^{28,29} Another study by Callejo et al. (2020) pointed out that supplementation of melatonin not only improved the antioxidant enzyme levels but also improved overall lung function in patients receiving corticosteroids.³⁰ This defensive role of melatonin suggests its potential as a secretary therapy for asthma patients, predominantly

Table 2. Antioxidant Enzyme and Melatonin Levels in Patients with Corticosteroid Use

Parameter	Corticosteroid Use	Number of Studies	p-values
SOD (U/mg)	High	6	0.01, 0.03, 0.02, 0.04, 0.01, 0.05
SOD (U/mg)	Moderate	3	0.02, 0.04, 0.03
SOD (U/mg)	Low	0	Not reported
CAT (U/mg)	High	2	0.02, 0.03
CAT (U/mg)	Moderate	4	0.01, 0.04, 0.02, 0.03
CAT (U/mg)	Low	0	Not reported
GPx (U/mg)	High	0	Not reported
GPx (U/mg)	Moderate	0	Not reported
GPx (U/mg)	Low	5	0.01, 0.03, 0.04, 0.02, 0.05
Melatonin (pg/mL)	High	6	0.02, 0.01, 0.04, 0.03, 0.05, 0.02
Melatonin (pg/mL)	Moderate	4	0.02, 0.03, 0.01, 0.04
Melatonin (pg/mL)	Low	5	0.03, 0.02, 0.01, 0.04, 0.05

those on long-term corticosteroid treatment.

The change in study designs, populations, and outcome measures highlights the need for protocols in future research. Although this review provides appreciated insights, the heterogeneity among studies limits the ability to draw definitive conclusions. A meta-analysis by Liu et al. (2021) stressed the importance of uniform melatonin dosing and timing, which could help ensure consistency in results across different asthma populations.³¹ Further research is required to explore the optimum dosing and melatonin timing of supplementation and to identify which subgroups of asthma patients may benefit most from this approach.

This review underlines the importance of oxidative stress in the management of bronchial asthma, mainly in patients receiving corticosteroid therapy. In asthma treatment corticosteroids remain a cornerstone, their impact on antioxidant defenses should not be ignored. Although, studies like those of Simioni et al. (2021) emphasize that alternative or adjunct therapies such as melatonin could help balance oxidative stress without compromising the effectiveness of corticosteroids.³² Melatonin presents a promising path for mitigating the oxidative side effects of corticosteroids, possibly improving outcomes for asthma patients.

Conclusion

This review highlights the impact of corticosteroid therapy on asthma management. While effective in controlling inflammation, corticosteroids may unintentionally exacerbate oxidative stress by reducing antioxidant enzyme activity. The role of a protective agent, melatonin against oxidative stress in asthma patients is promising, suggesting that it could be considered as an adjunct therapy. However, further research is needed to fully understand the relations between corticosteroids, antioxidant enzymes, and melatonin in asthma patients.

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