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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Mini Review

Oxidative Stress in Pulmonary Disease: An Underrecognized Target for Therapeutic Intervention Using Natural Glutathione Precursors

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Received: July 08, 2025; **Published:** July 22, 2025

Abstract

Oxidative stress is a fundamental yet often overlooked mechanism driving pulmonary injury and chronic inflammation across multiple respiratory diseases, including COPD, asthma, interstitial lung disease, and post-COVID-19 syndromes. Although glutathione (GSH) is the most ubiquitous intracellular antioxidant, strategies to restore GSH through supplementation remain underutilized in clinical practice. Recent data suggest that natural glutathione precursors, such as undenatured cysteine-rich whey protein isolates (CRWPI), may offer a novel, accessible, and safe adjunctive intervention for reducing oxidative stress, improving lung function, and promoting recovery in these populations.

Keywords: *Glutathione; Cysteine; Immunocal; Oxidative Stress; Pulmonary; COVID-19*

Abbreviations

GSH: Reduced Glutathione; CRWPI: Cysteine-Rich Whey Protein Isolate; ROS: Reactive Oxygen Species; COPD: Chronic Obstructive Pulmonary Disease; ARDS: Acute Respiratory Distress Syndrome; GSSG: Oxidized Glutathione-Glutathione Disulfide; CRP: C-Reactive Protein; IL-6: Interleukin 6

Introduction

The lungs are uniquely vulnerable to oxidative damage due to continuous exposure to high oxygen concentrations and environmental pollutants. Oxidative stress arises when the balance between reactive oxygen species (ROS) and the body's antioxidant defenses is disrupted. In pulmonary disease, ROS overproduction contributes to epithelial injury, mitochondrial dysfunction, and chronic inflammation [1]. Despite extensive research on oxidative stress as a pathophysiologic mechanism, few practicing physicians consider antioxidant status when managing respiratory illness. This gap between science and clinical application represents a missed opportunity.

Glutathione: The master antioxidant

Glutathione is the cornerstone of the antioxidant system, defending against oxidative damage and regulating immune function. It is synthesized intracellularly from three amino acids: glutamate, glycine, and cysteine-the latter being rate-limiting due to its low dietary availability. Glutathione deficiency has been documented in several pulmonary conditions. In COPD, for example, it is associated with

impaired GSH synthesis and reduced alveolar GSH levels [2,3] while characterized by increased ROS and decreased GSH/GSSG ratio in asthma [4,5]. In ARDS and COVID-19, high levels of oxidative stress, cytokine dysregulation, and poor GSH regeneration contribute to disease severity and poor outcomes [6,7].

The case for cysteine-rich whey protein isolates

Direct glutathione supplementation is ineffective due to poor cellular uptake. In contrast, cysteine-rich whey protein isolates, like Immunocal® (Immunotec, Inc. Montreal, Canada) deliver bioavailable cystine (a cysteine dimer), which is efficiently absorbed and converted intracellularly to cysteine. It boosts GSH synthesis without overwhelming cellular regulatory mechanisms. In clinical trials and preclinical models, Immunocal has shown promise in reducing oxidative stress, improving muscle endurance and reducing fatigue, and enhancing immune response in patients with COPD, COVID-19, exercise-induced bronchospasm, cystic fibrosis, and cancer [8-13]. Yet, CRWPI remains underrecognized in pulmonology, in part due to lack of awareness, limited pharmaceutical backing, and a focus on symptom management rather than root mechanisms.

Clinical implications and integration into pulmonary practice

The translation of glutathione-enhancing strategies into clinical respiratory care requires a multifaceted approach. First, patient selection is critical. Those with advanced COPD, poorly controlled asthma, long COVID-19 syndromes, and individuals recovering from acute respiratory infections represent key populations who may benefit from antioxidant replenishment. Second, clinicians should consider integrating oxidative stress screening into routine evaluations. While redox biomarker panels are not yet widely standardized, surrogate indicators such as elevated inflammatory markers (e.g. CRP, IL-6) and persistent fatigue may help identify candidates for intervention.

Importantly, the implementation of natural glutathione precursors should not be viewed as an alternative to standard pharmacologic therapy, but rather as a complementary measure to address the biochemical milieu underlying respiratory dysfunction. For instance, pairing CRWPI with pulmonary rehabilitation programs may enhance physical recovery, reduce exertional dyspnea, and improve patient-reported quality of life. Additionally, glutathione support may enhance host defense mechanisms, potentially lowering the risk of secondary infections or acute exacerbations.

Future directions and research priorities

Despite promising clinical anecdotes and emerging data, rigorous randomized controlled trials are needed to better define the role of natural glutathione precursors in pulmonary care. Key questions remain regarding optimal dosing regimens, duration of use, and potential synergy with inhaled therapies. Furthermore, subgroup analyses by genotype (e.g. glutathione-S-transferase polymorphisms) may help personalize antioxidant therapy for maximal benefit.

Health systems and academic centers are encouraged to initiate prospective studies evaluating glutathione precursor supplementation in chronic pulmonary disease management and post-viral recovery pathways. Outcome measures should extend beyond spirometric parameters to include functional status, hospitalization rates, and patient-reported symptom burden.

Call to Action

The mounting evidence linking oxidative stress to pulmonary dysfunction demands a shift in clinical focus. Routine assessment of redox status and proactive strategies to restore antioxidant capacity should be integrated into care, particularly for patients with chronic inflammatory or post-viral respiratory syndromes. Given their safety profile and ease of use, natural glutathione precursors like CRWPI should be explored not only as adjuncts to pharmacologic therapy but also as part of rehabilitation and prevention strategies.

Conclusion

Oxidative stress plays a central but often ignored role in the pathogenesis of pulmonary diseases. Natural glutathione precursors provide a biologically sound and clinically promising way to restore redox balance and improve respiratory health. Pulmonologists and respiratory therapists should remain informed about these emerging tools and support their integration into evidence-based practice and future trials.

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Volume 14 Issue 8 August 2025