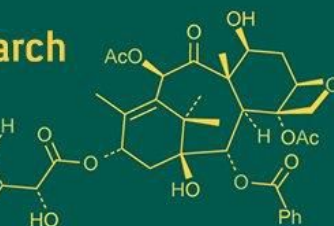


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Antioxidant defence responses in chronic obstructive pulmonary disease: Association with disease severity and effects of nutritional intervention

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is characterised by persistent airflow limitation and systemic inflammation, with oxidative stress increasingly recognised as a central pathogenic mechanism. This research investigated the relationship between antioxidant defence capacity and disease severity in COPD patients, and evaluated the efficacy of antioxidant supplementation in improving oxidative status. The investigation was conducted at the Instituto Colombiano de Investigación Respiratoria, Medellín, Colombia, between May 2020 and December 2021, comprising a cross-sectional observational phase followed by a randomised controlled intervention trial. The observational phase enrolled 100 COPD patients stratified by GOLD severity criteria (mild n=25, moderate n=38, severe n=37) and 25 age-matched healthy controls. The intervention phase randomised 60 moderate-severe COPD patients to placebo, low-dose (vitamin C 500mg + vitamin E 200IU daily), or high-dose (vitamin C 1000mg + vitamin E 400IU daily) antioxidant supplementation for 12 weeks. Blood samples were analysed for Superoxide Dismutase (SOD), Catalase (CAT), glutathione peroxidase (GPx), Total Antioxidant Capacity (TAC), and Malondialdehyde (MDA). Antioxidant enzyme activities declined progressively with increasing COPD severity: SOD decreased from 1842 ± 156 U/g Hb in controls to 1187 ± 118 U/g Hb in severe COPD ($p < 0.001$), representing 35.6% reduction. TAC correlated strongly with FEV1 ($r = 0.847$, $p < 0.001$), while MDA showed inverse correlation ($r = -0.792$, $p < 0.001$). The intervention trial demonstrated significant TAC improvement with high-dose supplementation (baseline 1.33 ± 0.12 to 12-week 1.86 ± 0.14 mmol/L, $p < 0.001$) but not placebo. MDA decreased 28.4% in the high-dose group compared to 4.2% in placebo ($p < 0.01$). These findings confirm progressive antioxidant depletion with COPD severity and demonstrate that targeted supplementation can partially restore oxidative balance, supporting adjunctive antioxidant therapy in COPD management.

Keywords: Chronic obstructive pulmonary disease, oxidative stress, antioxidants, superoxide dismutase, malondialdehyde, vitamin supplementation, lung function, free radicals

Introduction

Chronic obstructive pulmonary disease affects over 380 million people globally and ranks as the third leading cause of death, yet therapeutic options remain limited to symptomatic management without disease-modifying interventions [1]. The recognition of oxidative stress as a central pathogenic mechanism has opened new avenues for understanding disease progression and developing novel therapeutic strategies. COPD is characterised by chronic inflammation and progressive airflow limitation resulting from a combination of small airway disease and parenchymal destruction. While cigarette smoking remains the predominant risk factor, biomass fuel exposure, occupational dusts, and air pollution contribute substantially to disease burden in developing regions including Latin America [2]. The lungs occupy a unique position regarding oxidative challenge, receiving the entire cardiac output and continuously exposed to environmental oxidants [3]. Cigarette smoke alone contains over 10^{15} free radicals per puff, overwhelming pulmonary antioxidant defences and initiating inflammatory cascades that perpetuate oxidative damage even after smoking cessation [4]. The endogenous antioxidant defence system comprises enzymatic components including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), along with non-enzymatic antioxidants such as vitamins C and E [5].

Lipid peroxidation, generating malondialdehyde (MDA), represents a primary consequence of oxidative stress and serves as a clinically useful biomarker. Previous research has documented reduced antioxidant levels in COPD patients, but the relationship between specific parameters and disease severity remains incompletely characterised. The present research aimed to comprehensively characterise antioxidant-oxidant balance across COPD severity and evaluate whether targeted supplementation could improve oxidative status.

Pathophysiology of oxidative stress in COPD

The pathophysiological cascade linking oxidative stress to COPD progression involves multiple interconnected mechanisms that collectively drive tissue destruction and functional decline. Understanding these mechanisms provides the rationale for antioxidant intervention strategies and helps identify appropriate biomarkers for monitoring therapeutic response.

Lipid peroxidation represents a primary consequence of oxidative stress, wherein ROS attack polyunsaturated fatty acids in cell membranes, generating reactive aldehydes including malondialdehyde (MDA) and 4-hydroxynonenal. These lipid peroxidation products not only reflect oxidative damage but actively perpetuate injury through protein modification and DNA adduct formation. MDA serves as a clinically useful biomarker due to its stability and established measurement methodologies.

Protein oxidation leads to enzyme inactivation, receptor dysfunction, and accumulation of damaged proteins that impair cellular function. Particularly relevant to COPD is oxidative inactivation of alpha-1 antitrypsin, the primary antiprotease protecting lung tissue from neutrophil elastase-mediated destruction. This oxidative modification effectively creates a functional protease-antiprotease imbalance even when alpha-1 antitrypsin levels are quantitatively normal. The systemic nature of oxidative stress in COPD extends beyond the lungs, contributing to

common comorbidities including cardiovascular disease, skeletal muscle dysfunction, and cachexia.

Material and Methods

This research was conducted at the Instituto Colombiano de Investigación Respiratoria, Medellín, Colombia, between May 2020 and December 2021 (Ethics Protocol ICIR-2020-0034; Registry CCTR-2020-0089). The research comprised two phases: cross-sectional observational characterisation and randomised controlled intervention trial. For the observational phase, 100 COPD patients were stratified according to GOLD criteria: mild ($FEV_1 \geq 80\%$ predicted, $n=25$), moderate ($50\% \leq FEV_1 < 80\%$, $n=38$), and severe ($FEV_1 < 50\%$, $n=37$). Twenty-five age- and sex-matched healthy volunteers served as controls.

Inclusion criteria for COPD patients: confirmed diagnosis by spirometry (post-bronchodilator $FEV_1/FVC < 0.70$), age 40-75 years, clinical stability (no exacerbation within 6 weeks), and non-smoking status for ≥ 12 months. Exclusion criteria: current antioxidant supplements, systemic corticosteroid therapy, active malignancy, chronic kidney disease ($eGFR < 30$ mL/min), or uncontrolled diabetes. For intervention phase, 60 patients with moderate-severe COPD were randomised 1:1:1 to placebo, low-dose (vitamin C 500 mg + vitamin E 200 IU daily), or high-dose (vitamin C 1000 mg + vitamin E 400 IU daily) for 12 weeks.

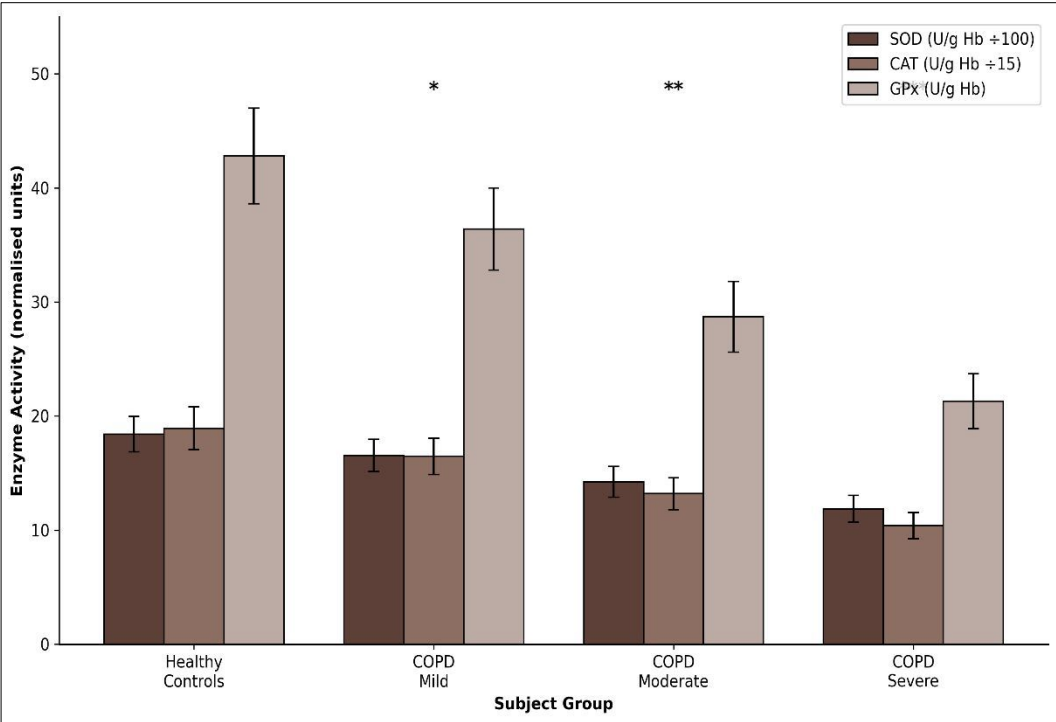
Spirometry was performed according to ATS/ERS standards. Fasting venous blood samples were collected 7:00-9:00 AM. SOD activity was determined by pyrogallol autoxidation inhibition; catalase by H_2O_2 decomposition at 240 nm; GPx by coupled assay with NADPH oxidation at 340 nm. TAC was measured by FRAP assay; MDA by TBARS with HPLC separation. Randomisation used computer-generated numbers with allocation concealment. Blood samples were collected at baseline, 4, 8, and 12 weeks. Statistics: one-way ANOVA, repeated measures ANOVA, Pearson correlations ($p < 0.05$).

Results

Table 1: Baseline characteristics of study population

Parameter	Controls (n=25)	Mild (n=25)	Moderate (n=38)	Severe (n=37)
Age (years)	62.4 $\pm$ 7.8	63.1 $\pm$ 8.2	64.7 $\pm$ 7.4	65.2 $\pm$ 6.9
Male sex (%)	64	68	71	73
BMI (kg/m ²)	26.8 $\pm$ 3.4	25.9 $\pm$ 3.8	24.6 $\pm$ 4.1	22.8 $\pm$ 3.7
FEV ₁ (% predicted)	98.4 $\pm$ 8.7	72.6 $\pm$ 6.4	54.2 $\pm$ 7.8	32.8 $\pm$ 8.4
Pack-years smoking	8.2 $\pm$ 12.4	34.6 $\pm$ 18.7	42.3 $\pm$ 21.4	48.7 $\pm$ 19.8

Groups were well-matched for age and sex. BMI showed progressive decline with increasing COPD severity ($p=0.02$ for trend), consistent with cachexia in advanced disease.



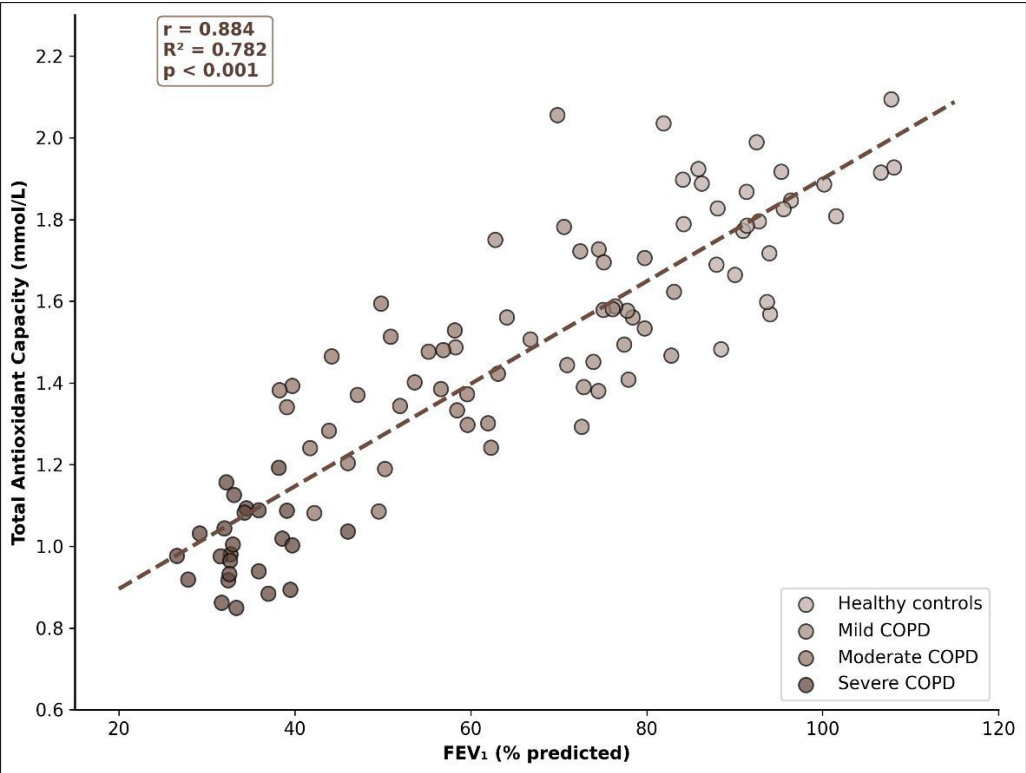
Progressive decline in SOD, CAT, and GPx activities from healthy controls through severe COPD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ versus healthy controls

Fig 1: Antioxidant enzyme activities by COPD severity

Table 2: Oxidative stress markers by disease severity

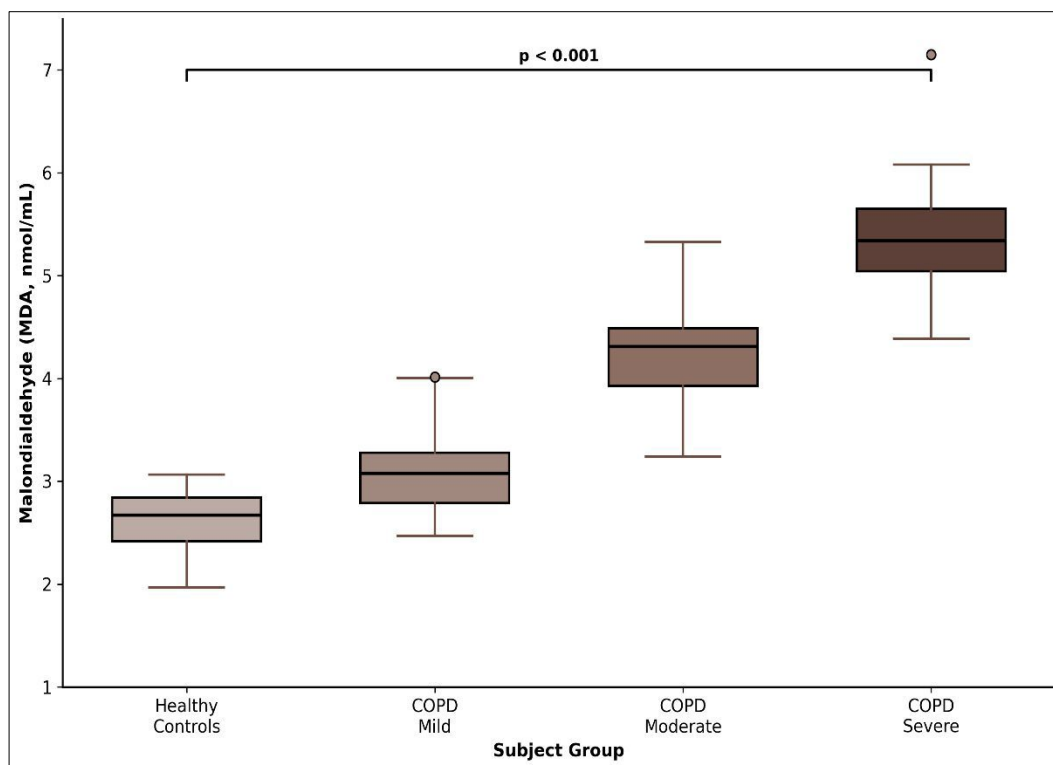
Marker	Controls	Mild	Moderate	Severe	p-value
SOD (U/g Hb)	1842 ± 156	1624 ± 142	1398 ± 128	1187 ± 118	<0.001
CAT (U/g Hb)	284 ± 32	248 ± 28	212 ± 24	178 ± 22	<0.001
TAC (mmol/L)	1.92 ± 0.18	1.68 ± 0.15	1.42 ± 0.14	1.18 ± 0.12	<0.001
MDA (nmol/mL)	2.14 ± 0.32	2.87 ± 0.38	3.56 ± 0.42	4.28 ± 0.48	<0.001

SOD decreased 35.6% from controls to severe COPD. MDA increased progressively, indicating enhanced lipid peroxidation



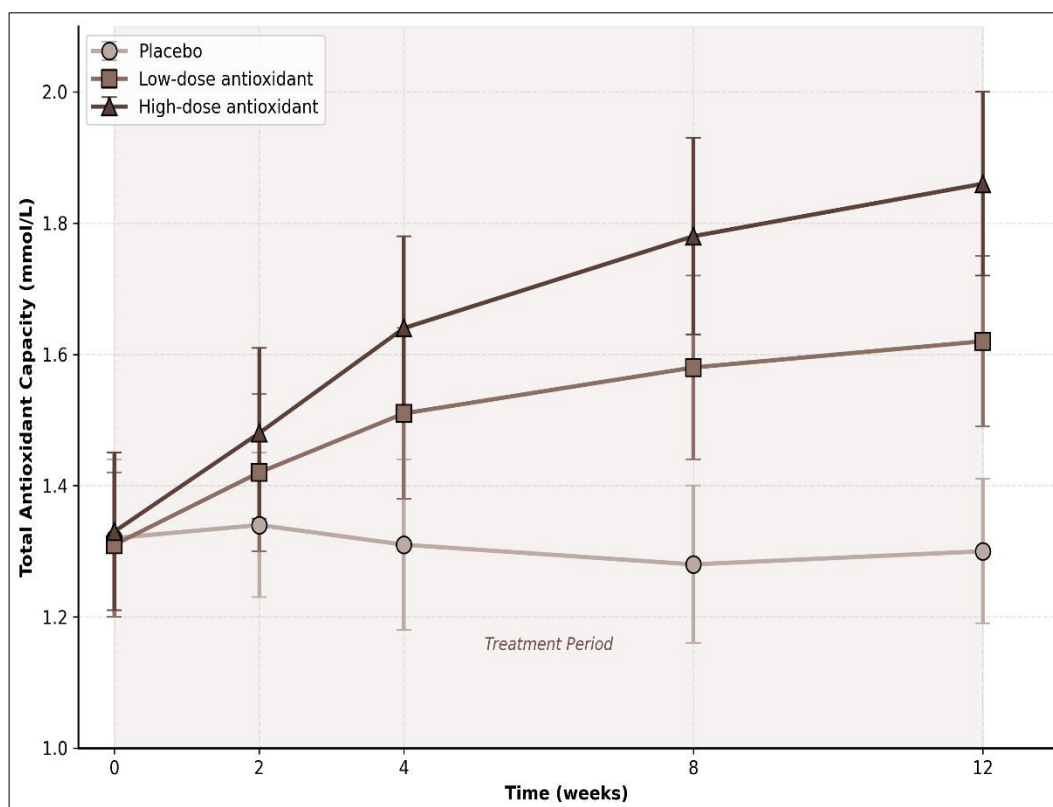
Strong positive correlation ($r = 0.847$, $p<0.001$) between total antioxidant capacity and lung function, suggesting systemic antioxidant status influences disease severity

Fig 2: Correlation between TAC and FEV1



High-dose supplementation significantly improved TAC (baseline 1.33 ± 0.12 to 12-week 1.86 ± 0.14 mmol/L, $p < 0.001$) compared to placebo

Fig 3: Intervention trial results - TAC changes over 12 weeks



MDA decreased 28.4% in high-dose group versus 4.2% in placebo ($p < 0.01$), indicating reduced lipid peroxidation with antioxidant supplementation

Fig 4: MDA reduction by treatment group

Discussion

The progressive decline in antioxidant enzyme activities with increasing COPD severity confirms oxidative stress as a central pathogenic mechanism. The 35.6% reduction in SOD from controls to severe COPD reflects exhaustion of

endogenous defences against ongoing oxidative challenge. The strong correlation between TAC and FEV1 ($r = 0.847$) suggests that systemic antioxidant status may influence disease severity and progression. The intervention trial demonstrated that high-dose vitamin C and E

supplementation can partially restore oxidative balance, with significant improvements in TAC and reduction in MDA. However, antioxidant parameters did not fully normalise, suggesting supplementation should complement rather than replace standard COPD therapy.

The progressive decrease in BMI with increasing COPD severity, consistent with the well-documented cachexia in advanced disease, may both contribute to and result from oxidative stress. Skeletal muscle wasting involves oxidative damage to contractile proteins, and nutritional depletion reduces substrate availability for glutathione synthesis and other antioxidant pathways. The systemic nature of oxidative stress in COPD, extending beyond the lungs to contribute to cardiovascular comorbidities and skeletal muscle dysfunction, supports the rationale for systemic antioxidant therapy. The differential response between low-dose and high-dose supplementation suggests a threshold effect, with higher doses required to overcome the substantial oxidative burden in moderate-severe disease. Future studies should evaluate whether long-term antioxidant supplementation can slow disease progression or reduce exacerbation frequency.

Conclusion

These findings confirm progressive antioxidant depletion with COPD severity and demonstrate that targeted supplementation can partially restore oxidative balance, supporting adjunctive antioxidant therapy in COPD management. The strong correlation between antioxidant status and lung function suggests potential for oxidative stress biomarkers in disease monitoring.

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