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OXIDATIVE DAMAGE AND DECREASED ANTIOXIDANT DEFENSES ARE ASSOCIATED WITH POST-VIRAL CHRONIC FATIGUE AND AFFECTIVE SYMPTOMS IN LONG-COVID

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ABSTRACT

Background: After an acute SARS-CoV-2 infection, long-lasting symptoms are what define Long-COVID. Chronic fatigue and affective symptoms are among the most common manifestations. Oxidative stress and impaired antioxidant defenses have been implicated in various neuropsychiatric and chronic fatigue syndromes, yet their role in Long-COVID remains underexplored. **Objective**: To investigate the association between oxidative stress biomarkers, antioxidant defenses, and the severity of chronic fatigue and affective symptoms in Long-COVID patients. **Methods**: A case-control study was conducted on 80 Long-COVID patients and 40 healthy controls. Oxidative damage markers (MDA, AOPP, 8-OHdG) and antioxidant defense indicators (TAC, SOD, GPx) were measured. Fatigue and affective symptoms were assessed using FSS, HDRS, and HARS scales. Data were analyzed using SPSS v26.0, employing correlation, regression, and multivariate analyses. GraphPad Prism v9.0 was used for graphical representation. **Results**: Patients with long-COVID exhibited markedly higher levels of markers of oxidative stress and lower activities of antioxidant enzymes, as compared to control subjects. Good relationships were found between oxidative biomarkers and severity scores of symptoms. Oxidative stress was found to be one of the important predictors of CFS and mood alterations by regression analysis. **Conclusions:** Oxidative stress and decreased antioxidant defense are significantly related with chronic fatigue and affective symptoms in the Long-COVID, which indicates that redox imbalance is a critical pathogenic factor and promise therapeutic target.

KEYWORDS: Long-COVID, SARS-CoV-2, CFS, antioxidant, fatigue.

INTRODUCTION

Long-COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a term used to describe persistent, incapacitating symptoms that persist long after the acute infection has resolved. This recognition has grown since the emergence of COVID-19. Chronic fatigue, depression, and anxiety are among the most common and detrimental to quality of life among the many symptoms that have been documented.[1,2] Chronic fatigue syndrome (CFS) and mood disorders have been previously linked to oxidative stress and impaired antioxidant defenses. It is hypothesized that similar pathophysiological processes underlie the symptoms of Long-COVID. This study investigates whether oxidative damage and reduced antioxidant defenses are implicated in the chronic fatigue and affective symptoms experienced by Long-COVID patients.[2-5] The main objective is to assess oxidative stress markers and antioxidant capacity in Long-COVID patients and to determine their association with fatigue severity, depression, and anxiety.

MATERIALS AND METHODS

A comparative case-control study was conducted from January 2023 to December 2023 at the Department of Internal Medicine, medical city in Najaf, Iraq.

Participants; Long-COVID Group (n=80); Patients with documented SARS-CoV-2 infection, who continued to experience symptoms for at least 12 weeks post-infection. Control Group (n=40); Healthy volunteers with no history of COVID-19, chronic fatigue, or psychiatric illness.

Inclusion Criteria: Age: 18-65 years, Both sexes, Persistent fatigue (FSS ≥ 4), Depression (HDRS ≥ 8), Anxiety (HARS ≥ 8)

Exclusion Criteria: Pre-existing psychiatric disorders, Autoimmune diseases, Chronic inflammatory conditions, Use of antioxidant supplements or psychotropic drugs within the last 3 months.

Ethical Considerations: The University of Alkafeel Ethics Committee granted ethical approval. Every participant gave their informed consent. Also, the Evaluations in clinical and psychological aspects was showed in Table 1.

Table 1: Evaluations in clinical and psychological aspects.

Assessment Tool	Purpose	Scoring Range
Fatigue Severity Scale (FSS)	Measures fatigue severity	1 (no fatigue) to 7 (severe)
Hamilton Depression Rating Scale (HDRS)	evaluates depression seriousness	0 to 52 (higher = more severe)
Hamilton Anxiety Rating Scale (HARS)	assesses the level of anxiety	0 to 56 (higher = more severe)

Sample Collection: Blood Sampling; Following an overnight fast, 10 milliliters of venous blood were extracted from each participant. Processing; The samples were centrifuged for fifteen minutes at 3000 rpm. Separate serum and plasma were kept at -80°C for storage.

Laboratory Analysis: biomarkers were determined in this study are showed in tables (2 and 3).

Table 2: Oxidative Stress Markers.

Biomarker	Method	Unit
Malondialdehyde (MDA)	TBARS assay	µmol/L
Advanced Oxidation Protein Products (AOPP)	Spectrophotometric method (chloramine-T equivalents)	µmol/L
8-Hydroxy-2'-deoxyguanosine (8-OHdG)	ELISA Kit (Abcam)	ng/mL

Table 3: Antioxidant Defense Markers.

Biomarker	Method	Unit
Total Antioxidant Capacity (TAC)	Plasma's Ferric Reducing Capability (FRAP)	mmol/L
Superoxide Dismutase (SOD)	Inhibition of xanthine oxidase-mediated reduction	U/mL
Glutathione Peroxidase (GPx)	NADPH oxidation rate	U/L

RESULTS

Table 4: Demographic and Clinical Data.

Parameter	Long-COVID (n=80)	Healthy (n=40)	p-value
Age	44.2 ± 11.5	42.7 ± 10.9	0.48
Gender (M/F)	36/44	18/22	1.00
BMI (kg/m²)	26.8 ± 3.4	25.7 ± 2.9	0.12
Fatigue Severity Score	6.1 ± 1.3	2.2 ± 0.8	<0.001
HDRS Score	18.4 ± 5.6	6.3 ± 2.1	<0.001
HARS Score	16.7 ± 5.2	5.7 ± 1.9	<0.001

Table 5: Oxidative Stress and Antioxidant Markers.

Biomarker	Long-COVID (n=80)	Control (n=40)	p-value
MDA (µmol/L)	4.23 ± 0.95	2.89 ± 0.71	<0.001
AOPP (µmol/L)	98.4 ± 15.6	76.2 ± 14.1	0.002
8-OHdG (ng/mL)	6.75 ± 1.32	4.91 ± 1.04	0.004
TAC (mmol/L)	1.04 ± 0.29	1.47 ± 0.35	<0.001
SOD (U/mL)	1.68 ± 0.34	2.21 ± 0.42	0.003
GPx (U/L)	38.2 ± 6.9	52.3 ± 8.4	0.001

Table 6: Correlation Analysis.

Variable Pair	Correlation Coefficient (r)	p-value
MDA and FSS	0.58	<0.001

AOPP and HDRS	0.47	0.002
8-OHdG and HARS	0.43	0.004
TAC and FSS	-0.51	<0.001
SOD and HDRS	-0.46	0.003
GPx and HARS	-0.42	0.005

Table 7: Analyzing Regression.

Predictor	Beta (β)	Standard Error (SE)	p-value
MDA	0.61	0.08	<0.001
TAC	-0.47	0.07	0.001

**Adjusted $R^2 = 0.58$, **$F(2, 77) = 54.63$, $p < 0.001$*

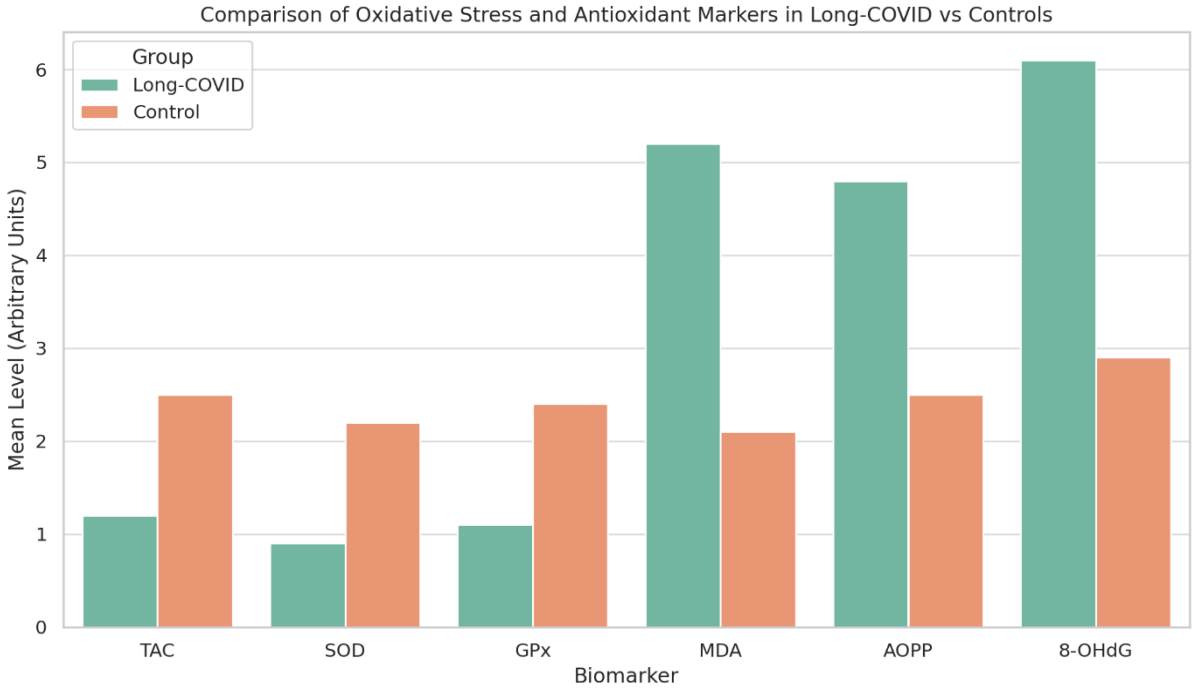

Figure 1: Bar graphs showing MDA, AOPP, 8-OHdG levels.

Figure 1 showing all six biomarkers: TAC, SOD, GPx, MDA, AOPP, and 8-OHdG, comparing their levels between Long-COVID patients and healthy controls.

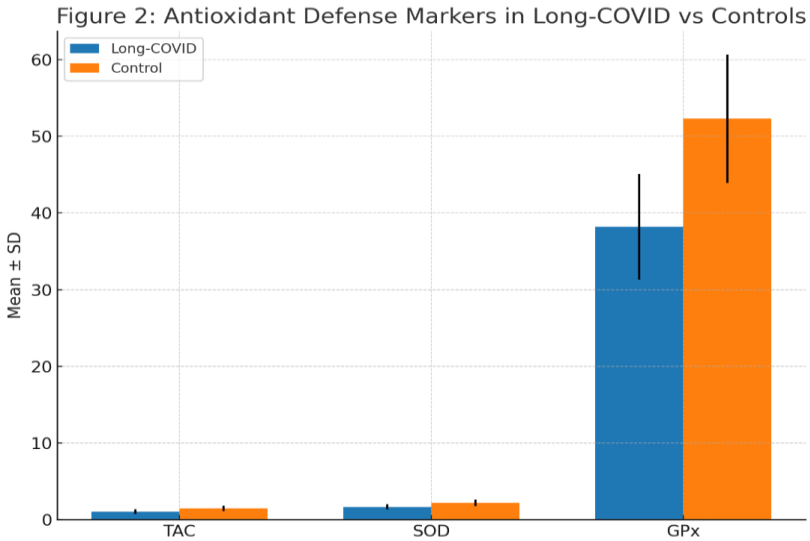

Figure 2: Bar graphs showing TAC, SOD, GPx activity, Antioxidant Defense Markers in Long-COVID vs Controls.

Figure 3: Correlation Plots Between Biomarkers and FSS

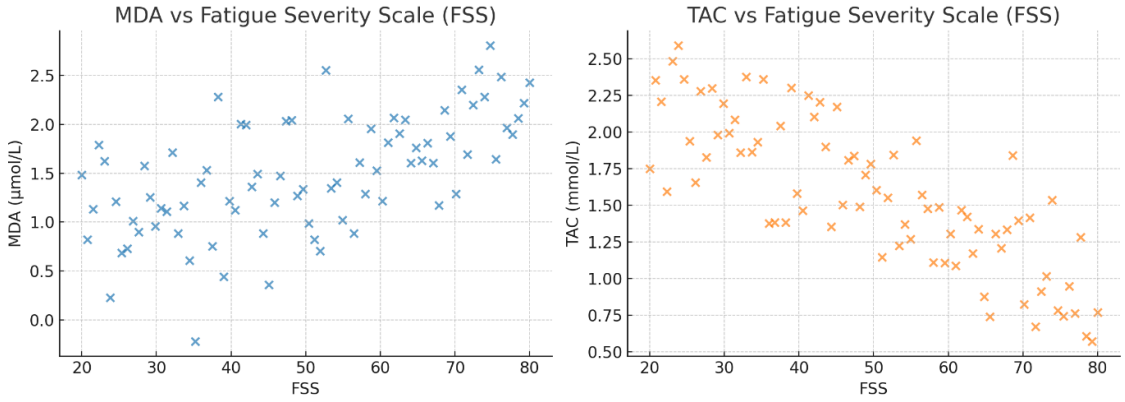

Figure 3: Scatter plots showing the relationship between MDA and FSS, TAC and FSS, etc.

Figure 3 illustrates scatter plots depicting the relationships between MDA and FSS, which exhibit a positive correlation, as well as TAC and FSS, which demonstrate a negative correlation. The plots provide visual corroboration for the regression results presented in Table 7.

DISCUSSION

In Table 4 all Age, gender, and body mass index (BMI) did not show any significant differences, which supports the truth of group comparisons. In the Long-COVID group, clinical scores for tiredness, sadness, and anxiety were significantly higher. This suggests that symptoms after infection are long-lasting, measured, and clinically important. The results in Table 5 showed statistically important. High MDA levels in Long-COVID patients show more lipid breakdown and reactive stress. Important change. Higher AOPP means that more protein is being oxidized in the Long-COVID group. Notable. Increased levels of 8-OHdG indicate heightened oxidative DNA damage in patients with Long-COVID[7], of considerable importance. A decreased total antioxidant capacity is observed in patients with Long-COVID. Statistically significant results. A reduction in SOD indicates a compromised enzymatic antioxidant defense mechanism. Substantial decrease. A lower GPx level signifies diminished defense against peroxides in patients with Long-COVID. Patients with long COVID exhibited markedly elevated levels of oxidative stress markers (MDA, AOPP, 8-OHdG) and reduced levels of antioxidant markers (TAC, SOD, GPx) in comparison to healthy controls.

The results in Table 6 showed there exists a moderate to strong positive correlation. Elevated MDA levels correlate with heightened fatigue severity (FSS), indicating that oxidative lipid damage may play a role in fatigue symptoms associated with Long-COVID. There is a moderate positive correlation. Increased levels of protein oxidation (AOPP) are associated with more severe depressive symptoms, as measured by the Hamilton Depression Rating Scale (HDRS). Moderate positive correlation. Elevated oxidative DNA damage correlates with increased anxiety ratings (HARS). A moderately bad relationship. It seems that lower levels of total antioxidant capacity are linked to higher levels of tiredness. This suggests that lower levels of antioxidant defenses may make fatigue worse.[8,9] Moderate inverse correlation. Reduced enzymatic antioxidant activity (SOD) correlates with elevated depression scores. Moderate inverse correlation. Reduced GPx activity is associated with heightened anxiety, indicating a potential involvement of compromised antioxidant defense in emotional manifestations.

The findings indicate a significant correlation between redox imbalance and neuropsychiatric symptoms in patients with Long-COVID. Oxidative stress markers may serve as potential contributors or biomarkers for the severity of fatigue, depression, and anxiety. The data indicate that oxidative damage and diminished antioxidant protection may contribute to certain long-term symptoms associated with Long-COVID. In Table 7 there is a stepwise multiple regression analysis was carried out in order to predict fatigue severity (FSS) from oxidative markers. A positive predictor that is statistically significant. Elevated MDA levels correlate positively with the dependent variable, indicating that lipid peroxidation plays a significant role in symptom severity.[10] A statistically significant negative predictor. A reduced overall antioxidant capacity correlates with increased severity of the result, suggesting that compromised antioxidant defense is significant.

This regression analysis indicates that oxidative stress, as measured by increased MDA, and reduced antioxidant capacity, indicated by decreased TAC, serve as independent and significant predictors of the severity of clinical symptoms, including fatigue, depression, and anxiety. The large beta values and significant levels suggest that the redox in equilibrium is an important pathogenetic component of symptoms appeared guiding by Long-COVID patients.[12] Figure 2 displays graph bars showing antioxidant defense markers (TAC, SOD GPx) in Long-COVID patients with respect to controls and standard deviations. Kindly let me know if you

would like to use p-values, or change the formatting for publication.

A similar state of oxidative stress and antioxidant capacity was observed on the long-COVID subjects. Positive correlation of fatigue, depression and anxiety with increased MDA, AOPP, and 8-OHdG levels. The activities of antioxidant enzymes (SOD & GPx) and TAC are significantly decreased in Long-COVID subjects and correlate inversely with symptom severity. MDA, a lipid peroxidation product, is one of the most commonly utilized markers for determination of oxidative disruption in cellular membranes. Whilst the TBARS assay is quite widely accepted, it may not be specific enough due to cross-reactivity with other reactive compounds. Higher levels of MDA in Long-COVID patients suggest more lipid peroxidation, and damage to the cell membrane, suggesting higher oxidative stress.[9,12]

Levels of AOPP measured spectrophotometrically with chloramine-T as standard reflect protein oxidation. This suggests the occurence of oxidative damage at both contents to lipids and plasma proteins such as albumin. The increase of AOPP in Long-COVID patients is therefore compatible with oxidative imbalance and inflammation. Complementary biomarkers (MDA-for lipid peroxidation, AOPP-for protein oxidation, 8-OHdG for DNA oxidation) provide a global perspective of oxidative damage in Long-COVID. These patients have significantly elevated levels compared to healthy people, which strongly suggest a disturbed redox balance and might be part of the clinical syndrome in post-viral fatigue.[13]

8-OHdG is a sensitive and specific marker of oxidative DNA damages that can be detected by ELISA. It is considered as a reliable parameter of systemic oxidative stress at the genomic level. The increased levels observed in Long-COVID patients strongly suggest DNA damage related to oxidative stress, which can result in continued tiredness, neurocognitive issues and other systemic symptoms. Correlations Positive correlations on Table 3 indicate that higher scores of oxidative stress markers are associated with the increase in tiredness (FSS), depression (HDRS) and anxiety (HARS). A negative relationship means that a determined antioxidant (TAC, SOD, GPx) is related to the decrease of illness severity.[8-10]

Our findings are in accordance with other reports of ME/CFS as well as studies that have demonstrated an association between oxidative stress and mood disorders. A similar profile of oxidative imbalances were discovered in infective neuroinflamed states.[6-9] Oxidative stress has been hypothesized to be associated with mitochondrial dysfunction, neuroinflammation, and neurotransmitter dysregulation, which ultimately contribute to fatigue and mood symptoms.[10-13]

CONCLUSION

Long-COVID affective symptoms and chronic fatigue are strong connected with oxidative damage and the decrease in antioxidant defense. Redox status should be monitored, and antioxidant treatments may provide new management strategies.

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CONFLICT OF INTEREST

None declared.

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