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ANALYSIS OF OXIDATIVE STRESS PARAMETERS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Depressive disorder is increasingly recognized as a complex systemic condition associated with oxidative-antioxidative imbalance and neurobiological alterations. The aim of this study was to evaluate oxidative stress intensity in patients with major depressive disorder by determining serum concentrations of malondialdehyde (MDA), advanced oxidation protein products (AOPP), and catalase (CAT) activity, and to compare these parameters with those observed in healthy subjects. The study included 60 participants divided into two groups: 30 patients diagnosed with major depressive disorder (MDD) according to ICD-10 criteria and 30 healthy controls. The severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAMD/HDRS). Oxidative stress biomarkers were determined spectrophotometrically. Patients with depressive disorder exhibited markedly higher HAMD/HDRS scores than healthy subjects (22.4 ± 5.1 vs. 3.3 ± 1.3; $p<0.001$). Serum concentrations of MDA and AOPP were significantly increased in the depressive disorder group, indicating enhanced lipid peroxidation, oxidative

protein modification, and disturbed redox homeostasis. Catalase activity was also significantly higher in patients with depression, suggesting activation of antioxidant defense mechanisms. These findings support the involvement of oxidative-antioxidative imbalance in the pathophysiology of depressive disorder and indicate that oxidative stress biomarkers may have potential relevance in future research on the diagnosis and treatment of depression.

Keywords: major depressive disorder; oxidative stress; malondialdehyde; advanced oxidation protein products; catalase

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ANALIZA PARAMETARA OKSIDATIVNOG STRESA KOD PACIJENATA SA DEPRESIVNIM POREMEĆAJEM

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Depresivni poremećaj se sve više prepoznaje kao kompleksno sistemsko oboljenje povezano sa oksidativno-antioksidativnim disbalansom i neurobiološkim promenama. Cilj ovog istraživanja bio je da se proceni intenzitet oksidativnog stresa kod pacijenata sa depresivnim poremećajem određivanjem serumskih koncentracija malondialdehida (MDA), uznapredovalih produkata oksidacije proteina (AOPP) i aktivnosti katalaze (CAT), kao i da se ove vrednosti uporede sa vrednostima kod zdravih ispitanika. Istraživanjem je obuhvaćeno 60 ispitanika podeljenih u dve grupe: 30 pacijenata sa dijagnostikovanim depresivnim poremećajem prema ICD-10 kriterijumima i 30 zdravih kontrolnih ispitanika. Težina depresivne simptomatologije procenjena je primenom Hamiltonove skale za procenu depresivnosti (HAMD/HDRS). Biomarkeri oksidativnog stresa određivani su spektrofotometrijskim metodama. Pacijenti sa depresivnim poremećajem imali su značajno više HAMD/HDRS skorove u poređenju sa zdravim ispitanicima (22,4 ± 5,1 prema 3,3 ± 1,3; $p<0,001$). Serumske koncentracije MDA i AOPP bile su značajno povećane u grupi sa depresivnim poremećajem, što ukazuje na pojačanu lipidnu peroksidaciju, oksidativnu

modifikaciju proteina i narušenu redoks homeostazu. Aktivnost katalaze je takođe bila značajno viša kod pacijenata sa depresijom, što ukazuje na aktivaciju antioksidativnih odbrambenih mehanizama. Dobijeni rezultati potvrđuju značaj oksidativno-antioksidativnog disbalansa u patofiziologiji depresivnog poremećaja i ukazuju da biomarkeri oksidativnog stresa mogu imati potencijalni značaj u budućim istraživanjima dijagnostike i lečenja depresije.

Ključne reči: depresivni poremećaj; oksidativni stres; malondialdehid; AOPP; katalaza.

Introduction

Depressive disorder is one of the most prevalent psychiatric illnesses worldwide and represents a major cause of disability, reduced quality of life, and increased mortality. According to the World Health Organization, depression remains a leading contributor to the global burden of disease. Although disturbances in monoaminergic neurotransmission have long been considered central to the pathophysiology of depression, increasing evidence suggests that the disorder is associated with a broad spectrum of biological abnormalities, including neuroinflammation, mitochondrial dysfunction, impaired neuroplasticity, and oxidative-antioxidative imbalance (1,2).

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defense mechanisms to neutralize their harmful effects. Under physiological conditions, ROS participate in numerous cellular processes, including signal transduction, immune regulation, and cellular homeostasis. However, excessive ROS generation may result in oxidative damage to lipids, proteins, and nucleic acids. The central nervous system is particularly susceptible to oxidative injury because of its high oxygen consumption, abundance of polyunsaturated fatty acids, and relatively limited antioxidant capacity (3,4).

Among the most frequently investigated biomarkers of oxidative stress in depressive disorders is malondialdehyde (MDA), a stable end-product of lipid peroxidation. Elevated MDA concentrations have consistently been reported in patients with major depressive disorder and are considered indicators of enhanced oxidative damage to cellular membranes. Such alterations may impair membrane integrity, receptor function, and neurotransmitter signaling, thereby contributing to the development and persistence of depressive symptoms (5,6).

Oxidative stress also affects proteins through irreversible oxidative modifications, resulting in the formation of advanced oxidation protein products (AOPP). These molecules are regarded as reliable biomarkers of oxidative protein damage and disturbances in redox homeostasis. Increased AOPP concentrations have been associated with chronic inflammatory activation and altered cellular function in several neuropsychiatric disorders, including depression (1,7,8).

The antioxidant defense system constitutes a critical protective mechanism against oxidative injury. Catalase (CAT), one of the major enzymatic antioxidants, catalyzes the decomposition of hydrogen peroxide into water and oxygen, thereby limiting the formation of

highly reactive hydroxyl radicals. Altered catalase activity has been reported in depressive disorders, although available findings remain inconsistent, suggesting that antioxidant responses may vary according to disease severity, duration, treatment status, and individual biological characteristics (2,9).

Growing evidence indicates that oxidative stress represents an important component of the complex biological network underlying depressive disorder. Consequently, biomarkers reflecting lipid peroxidation, protein oxidation, and antioxidant defense may contribute to a better understanding of disease pathophysiology and may potentially serve as adjunctive diagnostic and prognostic indicators.

Therefore, the aim of this study was to evaluate the intensity of oxidative stress in patients with major depressive disorder by determining serum concentrations of malondialdehyde (MDA), advanced oxidation protein products (AOPP), and catalase (CAT) activity, and to compare these parameters with those observed in healthy subjects.

Materials and Methods

Study Design and Ethical Considerations

This case–control study was conducted between January and June 2025. Participation was voluntary and anonymous, and written informed consent was obtained from all participants prior to inclusion. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Participants

A total of 60 participants were enrolled and divided into two groups:

1) Control group (K): 30 healthy subjects recruited from voluntary blood donors at the Blood Transfusion Institute Niš.
2) Depressive disorder group (DP): 30 patients diagnosed with major depressive disorder according to the International Classification of Diseases, 10th Revision (ICD-10; F32.0, F32.1, F32.2, and F32.3).

Patients were recruited from the Center for Mental Health Protection, University Clinical Center Niš, and the Primary Health Care Center Niš. The diagnosis of major depressive disorder was established by a psychiatrist through clinical examination, medical record review, and psychiatric assessment.

Inclusion criteria for the depressive disorder group were: age ≥18 years; diagnosis of depressive disorder according to ICD-10 criteria; stable clinical condition; ability to provide informed consent.

Inclusion criteria for the control group were: age ≥18 years; absence of current or previous psychiatric and neurological disorders; absence of severe chronic systemic diseases; ability to provide informed consent.

The control group was matched to the patient group according to age and sex in order to minimize potential confounding effects of these demographic variables.

Assessment of Depressive Symptoms

The severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAMD/HDRS), one of the most widely validated clinician-administered instruments for the evaluation of depression severity (11).

The 21-item version of the scale was used in this study. The questionnaire was administered by a psychiatrist through a structured clinical interview. Total scores were interpreted as follows: 0–7 points: no depression; 8–16 points: mild depression; 17–24 points: moderate depression; >24 points: severe depression.

HAMD scores were used exclusively for the assessment of symptom severity and not for establishing the diagnosis of major depressive disorder.

Blood Sampling and Sample Processing

Venous blood samples (3 mL) were collected from all participants under standardized conditions.

Samples were transported on ice to the Department of Biochemistry, Faculty of Medicine, University of Niš. After spontaneous coagulation at room temperature for 20–30 minutes, blood samples were centrifuged at 3000 rpm for 15 minutes at +4°C. Serum was separated and stored at −80°C until biochemical analysis.

Determination of Malondialdehyde (MDA)

Serum malondialdehyde concentrations were determined spectrophotometrically using the thiobarbituric acid reactive substances (TBARS) assay according to the method of Ohkawa et al. (12).

The method is based on the reaction between malondialdehyde and thiobarbituric acid under acidic conditions and elevated temperature, resulting in the formation of a colored complex. Absorbance was measured at 532 nm, and results were expressed as nmol/mL of serum.

Determination of Advanced Oxidation Protein Products (AOPP)

Serum AOPP concentrations were determined spectrophotometrically according to the method described by Witko-Sarsat et al. (13).

The assay is based on the oxidation of proteins and subsequent reaction with potassium iodide under acidic conditions. Absorbance was measured at 340 nm, and results were expressed as chloramine-T equivalents (μmol/L).

Determination of Catalase (CAT) Activity

Catalase activity was determined spectrophotometrically according to the method described by Aebi (14).

The assay measures the rate of hydrogen peroxide decomposition catalyzed by CAT. Absorbance changes were monitored at 240 nm, and results were expressed as U/L of serum.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as absolute numbers and percentages. The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between the major depressive disorder and control groups were performed using the independent samples t-test for normally distributed variables. Variables not following a normal distribution were analyzed using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test. A two-tailed p-value <0.05 was considered statistically significant.

Results

Severity of Depressive Symptoms Assessed by the Hamilton Depression Rating Scale

The severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HAMD/HDRS). Patients with major depressive disorder demonstrated significantly higher HAMD scores compared with healthy controls (22.4 ± 5.1 vs. 3.3 ± 1.3, respectively; $p<0.001$).

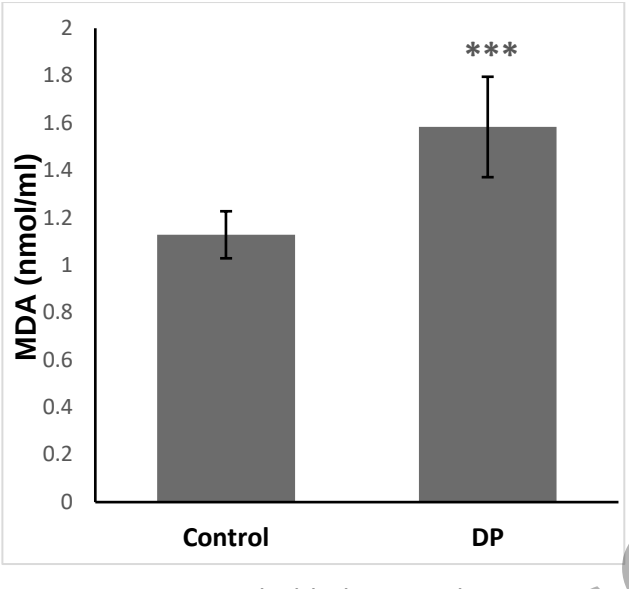
The mean HAMD score in the major depressive disorder group corresponded to moderate-to-severe depressive symptomatology, whereas scores in the control group were within the expected range for individuals without clinically significant depressive symptoms. These findings confirmed an adequate clinical differentiation between the investigated groups.

Table 1. Hamilton Depression Rating Scale (HAMD) scores in healthy controls (n=30) and patients with depressive disorder (n=30).

Study Group	n	HAMD Score (mean ± SD)
Healthy controls (K)	30	3.3 ± 1.3
Patients with depressive disorder (DP)	30	22.4 ± 5.1
p value	–	<0.001

Serum Malondialdehyde (MDA) Concentration

Serum concentrations of malondialdehyde (MDA) are presented in Figure 1. Patients with depressive disorder exhibited significantly higher MDA concentrations compared with healthy controls (1.12 ± 0.53 vs. 1.05 ± 0.31 nmol/mL, respectively; $p<0.05$).

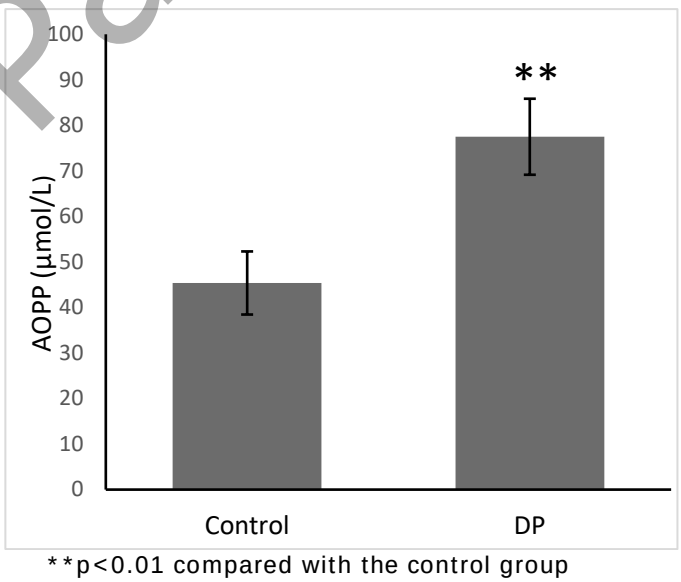


*p<0.001 compared with the control group.

Figure 1. Serum malondialdehyde (MDA) concentrations in healthy subjects and patients with depressive disorder.

Serum Advanced Oxidation Protein Products (AOPP)

Serum concentrations of advanced oxidation protein products (AOPP) are shown in Figure 2. A statistically significant increase in AOPP levels was observed in patients with major depressive disorder compared with healthy subjects (72.2 ± 9.2 vs. 45.1 ± 13.1 μmol/L, respectively; p<0.01).

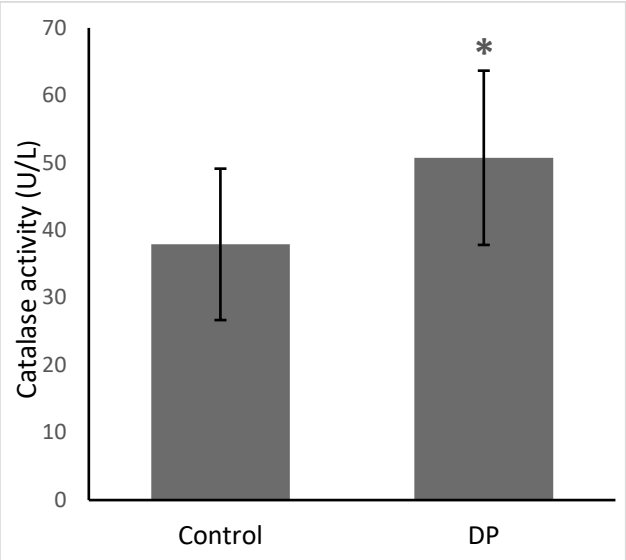


**p<0.01 compared with the control group

Figure 2. Serum advanced oxidation protein products (AOPP) concentrations in healthy subjects and patients with depressive disorder.

Catalase (CAT) Activity

Catalase activity in serum is presented in Figure 3. Patients with major depressive disorder demonstrated significantly higher CAT activity than healthy controls (42.92 ± 24.35 vs. 34.20 ± 26.07 U/L, respectively; $p<0.05$).



*p<0.05 compared with the control group.

Figure 3. Serum catalase (CAT) activity in healthy subjects and patients with depressive disorder.

Discussion

The present study demonstrated significant alterations in oxidative stress biomarkers in patients with major depressive disorder compared with healthy subjects. Patients with depression exhibited significantly higher serum concentrations of malondialdehyde (MDA) and advanced oxidation protein products (AOPP), together with increased catalase (CAT) activity, indicating the presence of oxidative-antioxidative imbalance. These findings support the growing body of evidence suggesting that oxidative stress represents an important biological component in the pathophysiology of depressive disorder (5,15,16).

Clinical differentiation between patients with major depressive disorder and healthy subjects was confirmed using the Hamilton Depression Rating Scale (HAMD/HDRS), with significantly higher scores observed in the patient group. The mean HAMD score of 22.4 ± 5.1 indicated moderate to severe depressive symptomatology, whereas healthy subjects demonstrated scores within the expected non-clinical range. These findings support the validity of the study design and appropriate stratification of the investigated groups.

One of the principal findings of the present study was the significantly higher serum concentration of MDA in patients with depressive disorder. MDA is a well-established end-product of lipid peroxidation and one of the most widely used biomarkers of oxidative damage to cellular membranes. Elevated MDA concentrations indicate enhanced oxidative degradation of membrane lipids and suggest increased oxidative stress. Oxidative damage to membrane structures may adversely affect membrane fluidity, receptor function, neurotransmitter transport, and intracellular signaling pathways, thereby contributing to neurobiological alterations associated with depressive disorder (12,16).

Our findings are in agreement with previous studies and meta-analyses demonstrating elevated concentrations of lipid peroxidation products in patients with depression. Jiménez-Fernández et al. reported significantly increased oxidative stress markers in individuals with major depressive disorder compared with healthy controls, while Palta et al. demonstrated a consistent association between depression and elevated biomarkers of oxidative damage. Collectively, these observations support the hypothesis that lipid peroxidation contributes to the biological processes underlying depressive disorders (5,17).

In addition to lipid peroxidation, patients with major depressive disorder demonstrated significantly higher concentrations of AOPP. These molecules are stable products of oxidative protein modification and are considered reliable biomarkers of protein oxidation and redox imbalance. Elevated AOPP concentrations indicate that oxidative damage in depression is not restricted to lipids but also involves protein structures. Oxidative modification of proteins may alter enzymatic activity, receptor function, intracellular signaling pathways, and cellular homeostasis, thereby contributing to disease-related biological disturbances (7,8,13).

The increased AOPP concentrations observed in the present study are consistent with contemporary evidence indicating that protein oxidation represents an important component of oxidative stress in psychiatric disorders. The simultaneous increase in both MDA and AOPP suggests the presence of generalized oxidative damage affecting multiple biological substrates and further supports the concept of systemic redox dysregulation in depressive disorder (1,8,15).

Another important finding of this study was the increased catalase activity observed in patients with depressive disorder. Catalase is one of the principal antioxidant enzymes responsible for the decomposition of hydrogen peroxide into water and oxygen, thereby protecting cells from oxidative injury. Previous studies investigating catalase activity in depression have yielded inconsistent results. While some authors reported decreased antioxidant enzyme activity,

suggesting exhaustion of antioxidant defenses, others described increased catalase activity, indicating activation of compensatory protective mechanisms in response to oxidative stress (2,9,19).

The increased catalase activity observed in our study most likely reflects an adaptive response to enhanced reactive oxygen species production. The coexistence of elevated MDA and AOPP concentrations together with increased CAT activity suggests that oxidative stress is sufficiently pronounced to induce activation of endogenous antioxidant defense mechanisms. This pattern may represent a compensatory attempt to limit oxidative damage and preserve cellular homeostasis.

Taken together, the simultaneous elevation of MDA and AOPP concentrations accompanied by increased CAT activity indicates enhanced oxidative damage together with activation of antioxidant defense mechanisms. These findings further support the concept that oxidative-antioxidative imbalance contributes to the biological background of major depressive disorder and may represent an important component of its pathophysiology.

The clinical significance of the present study lies in the potential utility of oxidative stress biomarkers as complementary indicators of biological alterations associated with depressive disorder. Although these biomarkers cannot replace psychiatric evaluation or established diagnostic criteria, they may contribute to a better understanding of disease heterogeneity and provide additional insight into underlying biological mechanisms. Future research may help determine whether oxidative stress biomarkers have prognostic value or can be used to monitor treatment response.

Several limitations of this study should be acknowledged. First, the relatively small sample size may limit the generalizability of the findings. Second, the cross-sectional study design does not allow conclusions regarding causal relationships between oxidative stress and major depressive disorder. Third, the potential influence of antidepressant treatment, lifestyle factors, smoking habits, dietary patterns, physical activity, and metabolic comorbidities was not comprehensively evaluated. Finally, only three oxidative stress parameters were analyzed, which does not provide a complete assessment of redox status. Future studies should include larger patient populations and a broader panel of oxidative and inflammatory biomarkers.

Despite these limitations, the present study provides evidence of increased lipid peroxidation, oxidative protein modification, and activation of antioxidant defense mechanisms in patients with major depressive disorder. The obtained findings support the growing evidence that

oxidative stress plays an important role in the pathophysiology of depression and highlight the need for further investigation of redox-related mechanisms in psychiatric disorders.

Conclusion

Patients with major depressive disorder exhibited significantly increased oxidative stress compared with healthy subjects, as evidenced by elevated serum concentrations of malondialdehyde (MDA) and advanced oxidation protein products (AOPP), accompanied by increased catalase (CAT) activity. These findings suggest that oxidative-antioxidative imbalance may contribute to the pathophysiology of depressive disorder and support the potential relevance of oxidative stress biomarkers in future research on depression.

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