

Diagnostic Performance of Increased Malondialdehyde Level and Oxidative Stress in Patients with Schizophrenia

Onur HURŞİTOĞLU¹, Fatma Özlem ORHAN², Ergül Belge KURUTAŞ³, Adem DOĞANER⁴, Hüseyin Toygun DURMUŞ², Hatice KOPAR³

¹Department of Psychiatry, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Turkey

²Department of Psychiatry, Faculty of Medicine, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey

³Department of Biochemistry, Faculty of Medicine, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey

⁴Department of Biostatistics and Medical Informatics, Faculty of Medicine, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey

ABSTRACT

Introduction: Schizophrenia is typically diagnosed through interviews with patients and their relatives. Thus, molecular biomarkers for this mental illness have recently become a hot topic for research. Oxidative stress and antioxidant parameters, such as catalase (CAT), superoxide dismutase (SOD) and malondialdehyde (MDA), have been investigated in schizophrenia; however, no studies have been conducted on the diagnostic performance of oxidative parameters. The goal of the present study is to examine the serum levels of SOD, CAT and MDA and to test the diagnostic performance of MDA in patients with schizophrenia.

Methods: Thirty patients with schizophrenia and 30 healthy gender- and age-matched controls were included in our study. Symptom severity in the patient group was rated using the Positive and Negative Syndrome Scale (PANSS).

Results: The serum levels of MDA, SOD and CAT were found to be significantly increased in patients with schizophrenia compared to the control group. A receiver operating characteristic curve showed a cut-off point of 2.72 nmol/ml for the MDA diagnostic measure. No significant correlation was found ($p>0.05$) between MDA, SOD and CAT activity and PANSS scores or the chlorpromazine equivalent and clinical characteristics.

Conclusion: In summary, we found higher serum levels of SOD, CAT and MDA in patients with schizophrenia compared to healthy controls. MDA is considered a very good diagnostic lipid peroxidation marker, and further studies should be done to test its validity in patients with schizophrenia.

Keywords: Schizophrenia, malondialdehyde, diagnostic, oxidative stress, superoxide dismutase, catalase

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INTRODUCTION

Schizophrenia is a serious mental disease that affects about 0.7% of the general population (1). Environmental and genetic factors are thought to play an important role in the etiopathogenesis of this destructive illness, but the particular neurochemical mechanisms involved in schizophrenia pathophysiology are not completely known.

Oxidative stress is the instability between the antioxidant defense mechanism and prooxidant processes. Increasing evidence has suggested that free radicals caused by toxicity and oxidative stress play a significant role in the pathophysiology of schizophrenia (2). Mild oxidative stress can be beneficial, as it is used by the immune system to kill pathogens. Severe oxidative stress, leading to a decrease in antioxidant levels and an increase in free radical production, can cause cell damage and, consequently, cell death (3). Deficiency in the antioxidant defense system and oxidative damage are associated with severe oxidative stress in schizophrenia patients (4).

Antioxidant enzymes or lipid peroxidation are also associated with psychopathology in schizophrenia, including positive and negative

symptoms and tardive dyskinesia (5). Malondialdehyde (MDA) is known to be the final product of lipid peroxidation. Therefore, the serum or plasma levels of MDA can be used as a marker of lipid peroxidation. An increase in free oxygen radicals can cause excessive lipid peroxidation, causing oxygen damage in tissues (4). Increased MDA levels in cerebrospinal fluid and plasma can cause oxidative damage to the brain (6). This type of damage can be prevented with antioxidants and cytoprotective enzymes. Enzymatic antioxidants, such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase, and glutathione reductase, can protect the brain against the damage caused by free radicals (7). The most studied antioxidants are CAT, which catalyzes the breakdown of hydrogen peroxide (H_2O_2) into O_2 and H_2O , and SOD, which converts superoxide radicals (O_2^-) into H_2O_2 (8).

Most studies have reported that the serum and plasma levels of MDA increase in patients with schizophrenia (7, 9-12). However, more contradictory results have been reported in studies on the antioxidant system that may be associated with the heterogeneity of variables among participants (3-5, 13-18). Oxidative stress and antioxidant parameters,

Correspondence Address: Onur Hurşitoğlu, Kahramanmaraş Necip Fazıl City Hospital, Haydar Bey Mahallesi, Bahçeci Hoca Bulvarı Buglem Apt. No:38, Kahramanmaraş, Turkey

E-mail: onurhursitoglu@gmail.com

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like CAT, SOD and MDA, have been investigated in schizophrenia; however, no studies related to the diagnostic performance of oxidative parameters have been conducted.

Diagnosis of schizophrenia is typically based on interviews with patients and their relatives, which leads to subjectiveness and confounds objective descriptions of this mental illness. In this regard, understanding whether molecular biomarkers can assist in making clearer diagnostic decisions is a hot topic for research. On this subject, previous studies have investigated the diagnostic value of prolidase and CAT in patients with schizophrenia and bipolar disorder (19, 20). In addition, the serum levels and diagnostic performance of CAT, SOD and MDA have been studied in patients with major depression (21). The aim of the present study is to examine the serum levels of SOD, CAT and MDA and test the diagnostic performance of MDA in patients with schizophrenia. To the best of our knowledge, no study has been conducted on the diagnostic value of MDA in patients with schizophrenia.

METHODS

Thirty patients with schizophrenia and 30 healthy gender and age matched controls were included in our study. The control participants were recruited from the staff of Kahramanmaraş Sutcu Imam University Hospital. The patient group was in remission and enrolled at the outpatient clinic at the Department of Psychiatry, School of Medicine, at Kahramanmaraş Sutcu Imam University, for 4 months from late 2019 to early 2020. The patients included in the study had been receiving antipsychotic treatment for at least 6 months. The ages of the schizophrenia patients ranged from 25 to 45, and the duration of their illness was between 1 and 25 years. All patients were assessed by a qualified psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Structured Clinical Interview. We used the Positive and Negative Syndrome Scale (PANSS) to determine symptom severity in the patient group.

Approval was provided by the Scientific Research Ethics Committee at Kahramanmaraş Sutcu Imam University (approval date: 17.07.2019, number: 10). The procedure of the study was explained to both patients and control subjects, and their written informed consent was obtained. The demographic and clinical characteristics were recorded for all participants. All patients with schizophrenia were evaluated in terms of exclusion criteria, which were history of alcohol/substance abuse and diabetes mellitus, concurrent DSM-5 diagnoses other than schizophrenia, severe head injury, central nervous system infection and mental retardation.

After fasting overnight, blood samples were collected from the arm vein of the controls and patients between 8 am and 11 am. These samples were centrifuged, and the obtained serum samples were stored at -25°C until assay.

CAT activity was determined by using the Beutler method, which evaluates the reduction in H₂O₂ concentration at 230 nm (22). The analysis medium was created using 10 mmol/L H₂O₂, 1 mol/L phosphate buffer solution (pH 7) and 1.0 mol/L Tris HCl-5 mmol/L disodium ethylenediaminetetraacetic acid (EDTA) buffer solution (pH 8).

SOD activity was determined using xanthine and xanthine oxidase to produce superoxide radicals that react with p-iodonitrotetrazolium violet to create a red formazan dye measured at 505 nm, according to the method defined by Fridovich. The analysis medium was created with 3-cyclohexylaminepropanesulfonic acid (CAPS) buffer solution (0.94 mmol/L EDTA, saturated NaOH and 50 mmol/L CAPS) (pH 10.2), 0.01 mol/L phosphate buffer, 80 U/L xanthine oxidase and substrate solution

(0.025 mmol/L INT, 0.05 mmol/L xanthine). The results for SOD and CAT activities are expressed as U/ml.

Lipid peroxidation was measured by evaluating MDA, which is the end-product of lipid peroxidation. The MDA concentrations in plasma were measured by reaction with thiobarbituric acid using the Ohkawa method (23). The serum levels of MDA are expressed as nmol/ml protein.

Statistical Analysis

The Shapiro – Wilk test was used for statistical evaluation of normally distributed data. Comparison for variables with normal distribution in independent groups was examined with the independent sample t-test. Comparison for variables in independent groups was examined using the Mann-Whitney U test. The Chi-Square statistic was performed to test qualitative variables. Spearman correlation test was used when the relationship between the variables was evaluated. ROC curve was plotted to provide cut-off value for MDA to predict the presence of schizophrenia. In this study, the values were accepted statistically significant with $p < 0.05$. Statistical parameters are expressed as mean \pm standard deviation, and median (25% quartile, 75% quartile).

RESULTS

No significant difference between patients and healthy controls was found in terms of gender (patients: 21 males, 9 females; controls: 19 males, 11 females; $p = 0.584$) or age (patients: 34.77 ± 6.13 years, controls: 33.24 ± 9.64 [mean \pm SD], $p = 0.470$) (Table 1). Patients with schizophrenia had not been hospitalized in the previous 6 months and had been in remission for at least the previous 6 months. The patients in our sample were receiving second-generation and combined antipsychotics, with mild to moderate symptom severity, according to their PANSS scores (Table 1).

The MDA, SOD and CAT serum levels were significantly increased in patients with schizophrenia compared to the control group (patients: 3.31 nmol/ml, controls: 2.21 nmol/ml; patients: 5.25 U/ml, controls: 3.62 U/ml; patients: 0.60 U/mL, controls: 0.37 U/mL, respectively; $p < 0.001$) (Table 2). A receiver operating characteristic curve revealed a cut-off point of 2.72 nmol/ml for the MDA diagnostic measure (Figure 1).

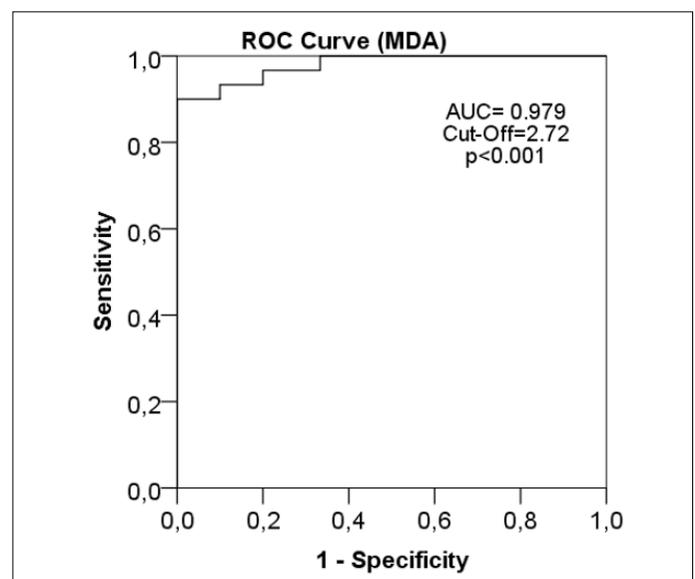


Figure 1. ROC curve for MDA (Sensitivity, 0.933; Specificity, 0.900; AUC was 0.979 for MDA. The cut-off point was detected as 2.72 ng/mL. MDA, malondialdehyde; AUC, area under curve; ROC, receiver operating characteristic).

Table 1. Demographic descriptions of subjects and clinical data and symptom measures in patients with schizophrenia.

			GROUP		P
			Schizophrenia (n: 30)	Control (n: 30)	
Age ^a Mean ± SD			34.77±6.13	33.24±9.64	0.470
Gender ^b	Male	n (%)	21.00 (70.00)	19.00 (63.30)	0.584
	Female	n (%)	9.00 (30.00)	11.00 (36.70)	
Smoke ^b	Yes	n (%)	13.00 (43.30)	6.00 (20.00)	0.052
	No	n (%)	17.00 (56.70)	24.00 (80.00)	
Smoked cigarettes daily	Mean ± SD		12.15±8.31	18.5±5.57	0.109
Duration of illness (years)	Mean		12.20±6.45		
Number of hospitalizations	Mean		3.70±3.22		
Chlorpromazine equivalent doses (mg/day)	Median (Q1-Q3)		600.00 (333.30–883.30)		
PANSS positive	Mean		15.70±5.94		
PANSS negative	Mean		17.73±5.58		
PANSS general	Mean		32.63±9.47		
PANSS total	Mean		66.07±16.57		

^aIndependent samples t-test.

^bChi-Square test. α , 0.05.

PANSS, positive and negative syndrome scale.

Table 2. Oxidative parameters in participants

		GROUP		P
		Schizophrenia	Control	
MDA (nmol/ml)	Median (Q1-Q3)	3.31 (3.03–3.65)	2.21 (2.01–2.45)	$p<0.001^*$
SOD (U/ml)	Median (Q1-Q3)	5.25 (4.46–5.92)	3.62 (3.36–4.02)	$p<0.001^*$
CAT (U/ml)	Median (Q1-Q3)	0.60 (0.50–0.67)	0.37 (0.34–0.41)	$p<0.001^*$

Mann-Whitney U test. α , 0.05.

*difference is statistically significant.

SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde.

Table 3. Correlations between PANSS scores, Age, Duration of illness and MDA, SOD CAT levels

	MDA		SOD		CAT	
	R	p	r	p	r	p
PANSS positive	0.150	0.428	0.224	0.233	0.139	0.464
PANSS negative	0.063	0.739	0.056	0.768	0.260	0.165
PANSS general	-0.056	0.769	0.066	0.730	0.077	0.688
PANSS total	0.053	0.781	0.139	0.462	0.155	0.412
Duration of illness	-0.145	0.444	-0.135	0.477	-0.078	0.683
Age	-0.163	0.389	-0.320	0.085	-0.041	0.829
Chlorpromazine equivalent	0.126	0.506	0.147	0.437	0.292	0.118

Spearman correlation test.

α , 0.05.

PANSS, positive and negative syndrome scale; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase.

No significant correlation was found ($p>0.05$) between MDA, SOD and CAT activity and PANSS scores or the chlorpromazine equivalent and clinical characteristics (Table 3).

DISCUSSION

The primary finding of the present study was that the serum levels of MDA, SOD and CAT were higher in the patient group than in the control group. However, we found no correlation between MDA, SOD and CAT serum levels and PANSS scores or the chlorpromazine equivalent. Importantly, we found a very good diagnostic performance for serum MDA levels of schizophrenia according to the receiver operating characteristic (ROC) curve.

The increased serum MDA activity in chronic medicated schizophrenia patients observed in our results is consistent with the findings of most previous research. For instance, Zhang et al. reported that MDA was higher in different schizophrenia subtypes than in controls (9). Likewise, additional studies have shown increased plasma and serum MDA levels in patients with schizophrenia (10, 11, 24). Serum MDA levels were also found to be significantly higher in red blood corpuscles and cerebrospinal fluid of patients with schizophrenia (4, 25). Two additional studies found that drug-naïve patients with schizophrenia had higher levels of MDA than controls (7, 12). In contrast to the findings of the present study, some older studies found no significant differences between schizophrenia groups and healthy controls, while some even saw decreases in MDA levels (13, 26).

Increased MDA activities observed in patients with schizophrenia can be evaluated as a marker of peroxidative damage to the membrane phospholipids. Ultimately, this process may lead to neuronal membrane instability, which can result in disruption of the cell cycle and neurotransmitter release and uptake (6).

Schizophrenia is usually chronic, multiphasic and etiologically heterogeneous. There is currently no specific imaging method or blood test for patients with schizophrenia. It is, therefore, important to determine novel diagnostic biomarkers to aid in diagnosis and exclude other mental illnesses. The effectiveness of a marker in ROC analysis was assessed for its diagnostic usefulness according to the area under curve (AUC). ROC curves were categorized as follows: 0.9–1=very good, 0.8–0.9=good, 0.7–0.8=fair, 0.6–0.7=poor, and <0.6=fail (27).

Some recent clinical studies have looked at diagnostic performance tests for psychiatric disorders. Gunes reported that increased serum prolidase levels might be a diagnostic biomarker for patients with schizophrenia (20). They found the AUC to be 1.0, and positive and negative predictive values were 100%. A recent study suggested that catalase may be a good diagnostic marker in patients with bipolar disorder (AUC: 0.989) (19). In another study, it was observed that the angiotensin I-converting enzyme level had fair diagnostic value in schizophrenia patients (AUC: 0.701) (28). Gadelha et al. demonstrated the significant diagnostic value of Ndel1 enzyme activity in diagnosing schizophrenia with ROC analysis (AUC: 0.70) (29). Furthermore, a previous study conducted by the authors indicated that GPER-1 has good diagnostic value for schizophrenia patients (30).

To our knowledge, this study is the first to test the diagnostic performance of MDA levels with an ROC curve in schizophrenia patients. In the present study, we found the AUC to be 0.979. This finding suggests that serum MDA levels have very good diagnostic value. As explained above, although increased MDA levels have been found in most studies, this is not a universal finding in patients with schizophrenia. We do not claim that this is a new method that should be used as a diagnostic marker in patients with schizophrenia. We suggest that further studies should be carried out in larger, more homogeneous groups to evaluate the diagnostic value of MDA in schizophrenia patients.

Among the enzymes with antioxidant effects, CAT (for detoxification of H₂O₂) and SOD (for detoxification of superoxide radicals) are key to reducing oxidative stress. In the present study, increased serum SOD and CAT activities were found in chronic medicated schizophrenia patients. While increased MDA levels have been found in most studies, this consistency is lacking for SOD. In line with our results, some studies have found that schizophrenia patients exhibit increased SOD activity in comparison with healthy subjects (3, 5, 14). In contrast, other studies have shown that schizophrenia patients exhibit decreased SOD activity compared to controls (13, 15, 16). Furthermore, studies on the CAT activity of schizophrenia patients have produced inconsistent results, showing lower, normal or elevated (4, 15, 17, 18) activities in schizophrenia patients. The differences observed in the SOD and CAT values identified in the mentioned studies may indicate an imbalance between antioxidant defense mechanisms and pro-oxidant processes in schizophrenia patients. In the present study, SOD, CAT and MDA levels were found to be increased in schizophrenia patients in comparison with healthy controls. This result suggests that attempts are made to compensate for increased free radicals in schizophrenia patients with an increase in antioxidant activities.

In summary, we found higher SOD, CAT and MDA serum levels in patients with schizophrenia. Moreover, to the best of our knowledge, this is the first study to evaluate the diagnostic value of MDA for schizophrenia.

The diagnostic value of MDA identified in this study (sensitivity: 0.933, specificity: 0.900) supports the hypothesis that cell membrane damage associated with excessive lipid peroxidation is important in the pathophysiology of schizophrenia. The diagnostic value of MDA for other psychiatric diseases, such as depression, has also been demonstrated; thus, we do not claim that the result we have obtained regarding the diagnostic value of MDA is specific to schizophrenia (21). This is an important limitation of our study. Therefore, future studies should be conducted on more homogeneous groups that include other psychiatric diseases to evaluate whether MDA can be used as a specific biomarker for schizophrenia. It should be noted that this study contained several other limitations, including the small sample size, cross-sectional design, ongoing drug use in the patient group, and non-evaluation of participant exercise, diet, and body mass index. Our findings regarding the diagnostic value of MDA should be considered new, and further research should be completed.

Committee Approval: Approval was provided by the Scientific Research Ethics Committee at Kahramanmaraş Sutcu Imam University (approval date: 17.07.2019, number: 10).

Informed Consent: The procedure of the study was explained to both patients and control subjects, and their written informed consent was obtained.

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Author Contributions: Concept – OH, FÖO, EBK; Design – OH, FÖO; Supervision – OH; Resources – OH, EBK; Materials – OH; Data Collection and/or Processing – HTD, HK; Analysis and/or Interpretation –AD; Literature Search – OH, FÖO; Writing Manuscript – OH, FÖO; Critical Review – OH, FÖO, EBK.

Conflict of Interest: There is no conflict of interest in our study.

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