

**Peroxiredoxin-1 Levels and Oxidative Stress in Patients with Schizoaffective Disorder***

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Objective: We aimed to evaluate the role of oxidative stress in individuals with schizoaffective disorder. In this context, serum total antioxidant level (TAS), total oxidant level (TOS), and peroxiredoxin-1 (PRDX1) levels were measured in patients; The findings were compared with those of a healthy control group and their relationship with clinical variables was examined, with the aim of contributing to the understanding of oxidative stress mechanisms in the pathogenesis of the disorder.

Materials and Methods: The study included 80 participants, consisting of 40 patients diagnosed with schizoaffective disorder and 40 healthy controls. The patients were evaluated using the Clinical Global Impression Scale, the Positive and Negative Syndrome Scale, the Hamilton Depression Rating Scale, and the Young Mania Rating Scale. TOS and TAS were determined by automatic measurement, while serum peroxiredoxin levels were measured using the ELISA method; OSI was calculated using the TOS/TAS ratio.

Results: When comparing the TAS, TOS, OSI, and PRDX1 levels between patients with schizoaffective disorder and the control group, no significant difference was found in TAS levels ($p=0.088$). However, the patient group had significantly higher TOS and OSI levels ($p=0.002$ and $p=0.001$, respectively) and significantly lower PRDX1 levels ($p=0.001$). No significant correlations were observed between continuous clinical characteristics and TAS, TOS, PRDX1, or OSI levels. Additionally, no significant correlation was observed between PRDX1 levels and TAS or TOS levels ($r=0.123$, $p=0.443$ and $r=-0.145$, $p=0.372$, respectively).

Conclusion: Our findings support increased oxidative stress and decreased PRDX1 levels in patients with schizoaffective disorder, and show no significant relationship between TAS and PRDX1; this indicates the role of PRDX1 in the oxidative stress response in patients.

Key Words: Schizoaffective disorder, oxidative stress, PRDX1, TAS, TOS, OSI

Şizoaffektif Bozukluk Tanısı Olan Hastalarda Peroksiredoksin-1 Düzeyleri ve Oksidatif Stres

Amaç: Şizoaffektif bozukluğu olan bireylerde oksidatif stresin rolünü değerlendirmeyi amaçladık. Bu bağlamda, hastalarda serum toplam antioksidan düzeyi (TAS), toplam oksidan düzeyi (TOS) ve peroksiredoksin-1 (PRDX1) düzeyleri ölçüldü; bulgular sağlıklı kontrol grubu ile karşılaştırıldı ve bozukluğun patogenezinde oksidatif stres mekanizmalarının anlaşılmasına katkıda bulunmak amacıyla klinik değişkenlerle ilişkisi incelendi.

Gereç ve Yöntem: Çalışmaya şizoaffektif bozukluk tanısı konmuş 40 hasta ve 40 sağlıklı kontrolden oluşan 80 katılımcı dahil edilmiştir. Hastalar Klinik Global İzlenim Ölçeği, Pozitif ve Negatif Sendrom Ölçeği, Hamilton Depresyon Derecelendirme Ölçeği ve Young Mani Derecelendirme Ölçeği kullanılarak değerlendirilmiştir. TOS ve TAS otomatik ölçümle belirlenirken, serum peroksiredoksin düzeyleri ELISA yöntemi kullanılarak ölçüldü; OSI, TOS/TAS oranı kullanılarak hesaplandı.

Bulgular: Şizoaffektif bozukluğu olan hastalar ile kontrol grubu arasında TAS, TOS, OSI ve PRDX1 düzeyleri karşılaştırıldığında, TAS düzeylerinde anlamlı bir fark bulunmamıştır ($p=0.088$). Ancak, hasta grubunun TOS ve OSI düzeyleri anlamlı derecede yüksek (sırasıyla $p=0.002$ ve $p=0.001$) ve PRDX1 düzeyleri anlamlı derecede düşüktür ($p=0.001$). Sürekli klinik özellikler ile serum TAS, TOS, PRDX1 ve OSI düzeyleri arasında anlamlı korelasyon gözlenmemiştir ($p>0.005$). Ayrıca, PRDX1 düzeyleri ile TAS veya TOS düzeyleri arasında anlamlı bir korelasyon gözlenmemiştir (sırasıyla $r=0.123$, $p=0.443$ ve $r=-0.145$, $p=0.372$).

Sonuç: Bulgularımız, şizoaffektif bozukluğu olan hastalarda oksidatif stresin arttığını ve PRDX1 düzeylerinin azaldığını desteklemekte ve TAS ile PRDX1 arasında anlamlı bir ilişki olmadığını göstermektedir; bu da PRDX1'in hastalarda oksidatif stres yanıtındaki rolünü göstermektedir.

Anahtar Kelimeler: Şizoaffektif bozukluk, oksidatif stres, PRDX1, TAS, TOS, OSI

Introduction

Schizoaffective disorder, a psychiatric illness with a lifetime prevalence of 0.5% to 0.8%, clinically resembles schizophrenia in terms of symptoms but shares a course more similar to mood disorders (1). Although the exact pathophysiology of schizoaffective

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disorder is unknown, abnormalities in dopamine, serotonin, and norepinephrine have been implicated (2). While the etiology remains unclear, oxidative stress is known to play a role in the development of psychiatric disorders (3, 4). It has been shown that in schizophrenia, there is an increase in the concentrations of damaging reactive species, whereas there is a decrease in antioxidant defenses. This increased oxidative stress in schizophrenia is believed to worsen the disease symptoms by contributing to neuronal damage through lipid peroxidation (5). A study conducted on patients with bipolar disorder reported significant changes in oxidative stress markers, which the authors suggested might disrupt neurotransmitter reuptake and enzyme activities (6). Although findings related to oxidative stress in schizophrenia and bipolar disorder have been widely reported in the literature, schizoaffective disorder contains both psychotic and mood components, and therefore data obtained from these two disorders provide important clues for understanding the pathophysiology of the disease.

Oxidative stress occurs when the balance between pro-oxidant and antioxidant processes is disrupted, leading to the production of free radicals and reactive oxygen species that can damage cellular components (7). Total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI) are key factors reflecting the relationship between oxidation and antioxidation. TAS reflects the total activity of antioxidants, while TOS indicates the presence of reactive oxygen species. OSI, defined as the ratio of TOS to TAS, expresses the overall level of oxidative stress (8).

Peroxiredoxin-1 (PRDX1) belongs to the peroxiredoxin family that provides antioxidant defense by removing cellular peroxides. Through its conserved cysteine structure, PRDX1 detoxifies peroxides and contributes to oxidative balance (9). In addition, PRDX1 regulates reactive oxygen species-dependent cell signaling pathways (10). PRDX1 is an antioxidant enzyme that plays a central role in the detoxification of intracellular reactive oxygen species and is highly expressed, particularly in neuronal tissues. Therefore, it is of particular interest in understanding the pathophysiology of oxidative stress in psychiatric disorders. PRDX1's unique function in regulating redox homeostasis and its neuroprotective properties make this molecule more important than other peroxiredoxin isoforms. In patients with irritable bowel syndrome who have high levels of anxiety and depression, PRDX1 has been found to be significantly elevated (11). Although oxidative stress has been investigated in schizophrenia and bipolar disorder (12, 13), research on oxidative stress in patients with schizoaffective disorder is limited (14). Oxidative stress has been implicated as a primary etiological factor in schizophrenia and schizoaffective disorder, and it has been suggested that this oxidative mechanism has potential use for therapeutic interventions targeting this oxidative mechanism (15).

The pathophysiology of schizoaffective disorder has not been fully elucidated. Recent studies have

shown that oxidative stress may play an important role in neurological and psychiatric disorders. In this context, specifically investigating oxidative stress in schizoaffective disorder is important for better understanding the molecular and cellular mechanisms of the disease, identifying biomarkers associated with disease progression, and determining potential targets for future treatment strategies. This study fills a gap in the literature by evaluating the applicability of oxidative stress findings reported in schizophrenia and bipolar disorder to schizoaffective disorder and sheds light on the role of oxidative balance in the pathophysiology of the disease. The aim of this study is to evaluate serum levels of PRDX1, TAS, TOS, and OSI in individuals with schizoaffective disorder and to compare these findings with a healthy control group in order to elucidate the role of oxidative stress in the pathogenesis of the disorder in greater detail. This approach is expected to contribute to the understanding of oxidative stress mechanisms in schizoaffective disorder and provide valuable information for identifying potential biomarkers.

Materials and Methods

Research and Publication Ethics: The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Gaziantep University (approval number: 2014/390, date: 15.12.2014).

Our study is a cross-sectional research, and the data were collected prospectively. In our study, a priori power analysis was performed to detect meaningful differences between groups. With 40 patients and 40 controls, an alpha level of 0.05, and a two-tailed independent samples t-test, the probability of detecting a medium-sized effect (Cohen's $d=0.5$) is approximately 80%. After receiving ethical approval, 45 patients who sought treatment at the Psychiatry Clinic of Gaziantep University Faculty of Medicine between December 2014 and August 2015 and were diagnosed with schizoaffective disorder based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), along with 43 healthy volunteers, were included. Due to the withdrawal of five patients with schizoaffective disorder and three healthy volunteers, the final sample consisted of 40 healthy controls and 40 patients diagnosed with schizoaffective disorder (total $n=80$).

Excluded from the study were individuals outside the age range of 18–65 years, those with any psychiatric disorder other than schizoaffective disorder, those with neurological or systemic diseases, pregnant individuals, those with a history of antioxidant treatment (e.g., vitamin E, vitamin C, and N-acetylcysteine) or xanthine oxidase inhibitors (e.g., allopurinol and folic acid) within the last six months, those with alcohol or drug use in the past six months, and individuals diagnosed with intellectual disability. The healthy control group was selected from individuals attending the hospital for

regular annual check-ups, who did not have any medical conditions. To eliminate potential confounding factors that could affect oxidative stress in the control group, specific exclusion criteria were applied. Accordingly, individuals with chronic inflammatory disease, hypertension, cardiovascular disease, diabetes mellitus, a history of acute or chronic infection; those who had used steroids or anti-inflammatory drugs within the past six months; those with tobacco or alcohol dependence; and those with liver or kidney dysfunction were excluded from the control group. Written informed consent was obtained from all participants and/or their legal guardians.

Data Collection Tools

Sociodemographic and Clinical Data Form: This semi-structured form, prepared by the researchers, included sociodemographic information, disease duration, medical history, mental status examination, and diagnosis according to the DSM-5 criteria.

Clinical Global Impression Scale (CGI): This scale was designed to monitor the progression of psychiatric disorders across all age groups within the context of clinical research. It comprises three items that measure the overall severity of the illness or the degree of symptomatic improvement (16).

Positive and Negative Syndrome Scale (PANSS): This semi-structured interview tool consists of 30 items, each rated on a seven-point severity scale. This scale includes seven items targeting positive symptoms, seven items focusing on negative symptoms, and 16 items addressing general psychopathology. The seven-point rating for each question reflects increasing levels of psychopathology (17). The reliability and validity analyses of the Turkish version of the scale were undertaken by Kostakoğlu et al. (18).

Hamilton Depression Rating Scale (HAM-D): This is a clinician-administered scale used to measure the severity and variation of depression levels, but it is not diagnostic. It consists of 17 items (19). The validity and reliability study of the Turkish version was conducted by Akdemir et al. (20).

Young Mania Rating Scale (YMRS): This interviewer-administered scale is designed to measure the severity and variation of manic states. It consists of a total of 11 items, with the last week being the focus of evaluation. The clinician's judgment holds more weight than the patient's statements (21). The Turkish validity and reliability study was carried out by Karadağ et al. (22).

Sample collection and laboratory measurements: Blood samples from both the patient and control groups were collected from the antecubital vein around 8 a.m., following at least 12 hours of overnight fasting. This time slot was selected to minimize circadian variations in daily hormone and metabolite levels and to ensure the standardization of measurements. After a 12-hour fasting period, blood samples were taken from the antecubital vein of both

patients diagnosed with schizoaffective disorder and the control group. The blood was transferred into gel tubes and centrifuged at 4,000 rpm for 10 minutes within six hours, and the serum was separated. The serum samples were stored at -80°C for the analysis of TAS, TOS, and PRDX1. Serum TAS (mmol Trolox equiv./L), TOS ($\mu\text{mol H}_2\text{O}_2$ equiv./L), and PRX-1 (ng/mL) levels were measured in the Biochemistry Laboratory of Gaziantep University, and OSI was subsequently calculated.

Serum TOS and TAS levels were determined using an automatic measurement method developed by Erel, with fully automated oxidative stress kits from Rel Assay Diagnostics and the Tokyo Boeki Prestige I24 autoanalyzer. OSI was calculated by dividing TOS levels by TAS levels. Peroxiredoxin serum levels for both the patients and controls were measured at 450 nm using a Yehua (China) human enzyme-linked immunosorbent assay kit, following the manufacturer's instructions, at the Biochemistry Department of Gaziantep University.

Statistical analysis: The Kolmogorov-Smirnov test was utilized to assess the normality of variable distributions. For categorical parametric variables, the chi-square test was applied, while parametric continuous variables were analyzed using the t-test. To compare two or more independent groups with non-parametric data, the Mann-Whitney U test and the Kruskal-Wallis test were employed. Correlations between quantitative data were evaluated with Spearman's correlation test. Results were expressed as mean and standard deviation values for parametric variables and median (minimum–maximum) values for non-parametric variables. SPSS version 22.0 software was used for statistical analyses. The level of significance was set at $p < 0.05$.

Results

The study included 40 patients diagnosed with schizoaffective disorder and 40 healthy controls. Of the 40 patients, 25 (62.5%) were male, and 15 (37.5%) were female. In the control group, there were 22 males (55%) and 18 females (45%). The mean age of the patient group was 33.50 ± 5.68 (range: 22–66) years, and that of the control group was 34.00 ± 6.01 years. Among the patients, 45% ($n=18$) were married, and 55% ($n=22$) were single. Concerning educational level, 18 patients (45%) were elementary school graduates, 18 (45%) were middle or high school graduates, and four (10%) had completed university education (Table 1).

Upon comparing patients with schizoaffective disorder and healthy controls regarding age, gender, smoking status, and marital status, no significant differences were observed between the groups ($p > 0.05$). However, the body mass index was significantly higher among the patients with schizoaffective disorder compared to the controls ($p = 0.001$). The sociodemographic characteristics of the patient and control groups are presented in Table 1, and the clinical characteristics of the patient group are summarized in Table 2.

In terms of oxidative stress markers, there was no significant difference in TAS between the patients with schizoaffective disorder and the control group ($p=0.088$). However, the patient group had significantly higher TOS and OSI values ($p=0.002$ and $p=0.001$, respectively) and significantly lower PRDX1 levels ($p=0.001$, Table 3).

The patients in the study were continuing their current treatments, which included typical antipsychotics, atypical antipsychotics, mood stabilizers, and combinations of these medications. When the oxidative

stress markers were compared across these different medication classes, no significant differences were found ($p>0.005$).

Correlation analyses conducted to examine the relationships between oxidative stress markers (TAS, TOS, PRDX1, and OSI) revealed no significant correlations ($p>0.005$). There was also no relationship between PRDX1 levels and TAS or TOS ($r= -0.145$, $p=0.372$ and $r= 0.123$, $p=0.443$, respectively)(Table 4).

Table 1. Sociodemographic characteristics of the patient and control groups

		Patients with schizoaffective disorder (n = 40)	Control group (n = 40)	p value
Gender (%)	Female	15 (37.5%)	18 (45%)	0.496
	Male	25 (62.5%)	22 (55%)	
Smoking status (%)	Smoker	23 (57.5%)	19 (47.5%)	0.370
	Non-smoker	17 (42.5%)	21 (52.5%)	
Age (mean \pm SD)		33.50 \pm 5.68	34.00 \pm 6.01	0.662
Body mass index (mean \pm SD)		29.10 \pm 4.23	24.15 \pm 2.63	0.001

SD: standard deviation

Table 2. Clinical characteristics of patients with schizoaffective disorder

		Patients with schizoaffective disorder (n = 40)
Presence of family history	Present	13 (32.5%)
	Absent	27 (67.5%)
Diagnosis in family history	Schizoaffective disorder	3 (7.5%)
	Schizophrenia	5 (12.5%)
	Major depressive disorder	2 (5%)
	Bipolar disorder	3 (7.5%)
ECT history	Present	16 (40%)
	Absent	24 (60%)
Age at disease onset (mean \pm SD)		20.96 \pm 5.11
Disease duration (mean \pm SD)		11.80 \pm 4.95
Number of hospitalizations (mean \pm SD)		2.58 \pm 3.27
Number of past manic and depressive episodes (mean \pm SD)		6.10 \pm 2.52
Number of past manic episodes (mean \pm SD)		2.65 \pm 1.61
Number of past depressive episodes (mean \pm SD)		3.45 \pm 2.09
CGI score (mean \pm SD)		3.73 \pm 1.58
YMRS score (mean \pm SD)		6.17 \pm 9.32
HAM-D score (mean \pm SD)		5.15 \pm 5.57
PANSS score (mean \pm SD)		75.05 \pm 28.87

ECT: electroconvulsive therapy, SD: standard deviation, CGI: Clinical Global Impression, YMRS: Young Mania Rating Scale, HAM-D: Hamilton Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale

Table 3. Comparison of PRDX1, TAS, TOS, and OSI values between the study groups

	Patients with schizoaffective disorder (n = 40)	Control group (n = 40)	p
TAS (mmol Trolox equiv./L) (mean ± SD)	1.93 ± 0.17	2.00 ± 0.19	0.088
TOS (µmol H ₂ O ₂ equiv./L) (mean ± SD)	97.18 ± 22.62	79.14 ± 26.60	0.002
OSI (mean ± SD)	5.08 ± 1.30	3.99 ± 1.44	0.001
PRDX1 (ng/mL) (mean ± SD)	31.75 ± 35.87	60.83 ± 35.99	0.001

TAS: total antioxidant level, TOS: total oxidant level, OSI: oxidative stress index, PRDX1: peroxiredoxin-1, SD: standard deviation

Table 4. Correlation analysis between oxidative stress markers (TAS, TOS, PRDX1, and OSI) and clinical and demographic variables

	Age	Education level	Disease duration	Number of manic episodes	Number of depressive episodes	Body Mass Index	Number of hospitalizations
TAS (mmol Trolox equiv./L)	p=0.82 r=0.025	p=0.016 r=0.269	p=0.303 r=0.167	p=0.401 r=0.136	p=0.570 r=0.093	p=0.180 r=-0.151	p=0.638 r=-0.077
TOS (µmol H ₂ O ₂ equiv./L)	p=0.179 r=-0.152	p=0.028 r=-0.246	p=0.116 r=-0.253	p=0.351 r=-0.151	p=0.537 r=0.101	p=0.006 r=0.304	p=0.696 r=0.064
PRDX1(ng/mL)	p=0.840 r=-0.023	p=0.116 r=-0.253	p=0.158 r=-0.227	p=0.968 r=0.007	p=0.501 r=-0.110	p=0.004 r=-0.316	p=0.746 r=-0.053
OSI	p=0.279 r=-0.123	p=0.023 r=-0.254	p=0.289 r=0.172	p=0.269 r=-0.179	p=0.417 r=0.132	p=0.005 r=0.308	p=0.601 r=0.085

Discussion

This study aimed to evaluate the role of oxidative stress in patients with schizoaffective disorder and showed that while there was no significant difference in serum TAS levels between the patient and control groups, the patients had significantly higher serum TOS and OSI values, as well as significantly lower serum PRDX1 levels. However, no correlation was observed between PRDX1 levels and TAS or TOS in the patient group.

Oxidative stress, caused by the accumulation of reactive oxygen species, has been implicated in the pathophysiology of psychiatric disorders due to its role in neuroinflammation (23). Therefore, oxidative stress is suggested as a primary etiological factor in both schizophrenia and schizoaffective disorder (24). In a study by Topak et al., higher oxidative stress and insufficient DNA repair mechanisms were reported in both patients with schizophrenia and those with schizoaffective disorder, particularly in the former (25). Similarly, a study on patients with bipolar disorder found elevated TAS, TOS, and OSI levels compared to healthy controls, and the presence of psychotic symptoms did not result in additional oxidative stress (26). In contrast, Kılıç et al. reported lower TAS levels in patients with schizoaffective disorder compared to controls but found no differences in TOS or OSI, suggesting that this could make patients with schizoaffective disorder more vulnerable to oxidative stress (27). In the current study, although not statistically significant, TAS levels were lower in the patient group. This may be due to the relatively small

sample sizes in both the patient and control groups. However, we found significantly higher TOS and OSI levels in the patient group. Previous research has demonstrated that various neuropsychiatric disorders are associated with alterations in oxidant or antioxidant levels (28). Our findings support the presence of oxidative stress and a disruption of oxidative balance in schizoaffective disorder.

PRDX1 is known to serve as an antioxidant by removing cellular peroxides (29). PRDX1 levels have been found to be significantly higher in patients with irritable bowel syndrome and comorbid anxiety or depression compared to those with irritable bowel syndrome without psychiatric conditions (11). PRDX1 deficiency has been linked to increased ischemic brain damage and microglial cell death (30). Furthermore, Park et al. demonstrated that PRDX1 exerts antioxidant effects by blocking mitochondrial fragmentation in hippocampal neurons, potentially inhibiting Alzheimer's disease-like pathology (31). Scotton et al. showed that PRDX1 could reduce oxidative damage in subjects with anhedonic behavior (32). Lower PRDX1 levels have also been documented in patients with major depressive disorder, with a significant decrease correlating with the severity of depression (33). In the current study, we similarly found significantly lower PRDX1 levels in patients with schizoaffective disorder compared to healthy controls. The deficiency of any member of the PRDX family can further compromise brain tissue, which is already vulnerable to oxidative damage due to its high lipid content and oxygen usage. This deficiency may contribute to the development of neurodegenerative diseases specific to the affected protein, region, or

function (34). Despite the increase in oxidant capacity in patients with schizoaffective disorder, the lack of a compensatory increase in antioxidant capacity (PRDX1 and TAS levels) may lead to oxidative imbalance and deterioration of various cellular structures and functional compounds, such as the auto-oxidation of dopamine. Furthermore, the low PRDX1 levels observed in this study could be one of the factors contributing to increased DNA damage in patients with schizoaffective disorder.

Previous studies have shown that as the duration and severity of neuropsychiatric disorders increase, oxidative levels tend to rise (35). However, in our study, no relationship was found between disease duration and oxidative parameters such as TOS and OSI. These discrepancies may be attributed to variations in patient populations, including differences in racial, metabolic, and physical characteristics, treatment agents used, the presence of comorbid conditions, and the assumption that schizoaffective disorder is a spectrum disorder. In our study, we observed that the body mass index (BMI) was significantly higher in patients compared to the control group. An increase in BMI, particularly due to obesity, can lead to elevated levels of systemic inflammation and oxidative stress, which may be associated with the high TOS and OSI levels observed in patients (36). Therefore, BMI should be considered a potential

confounding variable in the study, and it is important to take it into account when interpreting the findings. In this regard, our findings may shed light on studies to be conducted on individuals with similar characteristics in a large sample.

Limitations of our study include its cross-sectional design and the inclusion of patients who were already undergoing treatment with medications known to affect oxidative stress, such as antipsychotics and mood stabilizers. Another limitation of the study is that the control group was not fully matched in terms of BMI. Nonetheless, a strength of our study is that it is the first to examine the relationship between PRDX1 levels and oxidative parameters (TAS, TOS, and OSI) in patients with schizoaffective disorder without any comorbid medical conditions.

In conclusion, this study suggests that the antioxidant mechanisms may not function adequately to counterbalance the increased oxidative stress in patients with schizoaffective disorder. Elevated TOS and OSI values, accompanied by decreased PRDX1 levels, indicate a disruption in redox balance and potential oxidative damage to neuronal cells. These data highlight the importance of oxidative stress in schizoaffective disorder in terms of biological markers and targetable mechanisms. They support the need for further research to better understand the molecular basis of this disorder and to develop future treatment strategies.

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