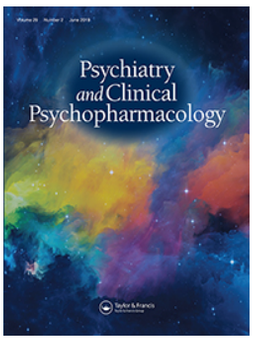

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Oxidative parameters, oxidative DNA damage, and urotensin-II in schizoaffective disorder patients

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ABSTRACT

OBJECTIVE: Complexity of schizoaffective disorder makes the identification of its pathophysiology a great challenge and there are very limited published data about the role of oxidative stress. Oxidative DNA damage has not been investigated in schizoaffective disorder. Therefore, we aimed to evaluate oxidative DNA damage together with oxidative stress and urotensin-II in patients with schizoaffective disorder.

METHODS: Fifty-four patients who were diagnosed as schizoaffective disorder bipolar type (27 of them were in symptomatic remission and 27 of them were not) and 27 healthy volunteers were included in the study. Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), serum 8-hydroxy-2′-deoxyguanosine (8-OHdG), and urotensin-II (U-II) levels were calculated and evaluated.

RESULTS: TAS and U-II levels were found to be lower in the patient group with and without remission when compared with the control group separately. There were no significant difference in terms of TOS, OSI, and 8-OHdG. Similar results were obtained when those in symptomatic remission and non-remission patient groups were combined and compared with the control group.

CONCLUSION: TAS levels in schizoaffective disorder patients were lower than controls, which may mean a vulnerability to the oxidative stress but there were no differences in terms of oxidative DNA damage. U-II levels in schizoaffective disorder patients were significantly lower than controls in contrast with our previous study.

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Introduction

Diagnosis of schizoaffective disorder has been frequently used as a distinct psychiatric diagnosis in clinical practice [1]. But it is one of the most discussed topics since it has first defined by Kasasin in nosological terms because diagnostic criteria for schizoaffective disorder were derived from schizophrenia and bipolar disorder [2–4]. In recent years, for the differential diagnosis of schizophrenia, bipolar disorder, and schizoaffective disorder, studies have been carried out in terms of symptomatology, prognosis, treatment response, and course of the disorders [5–7]. However, neurobiological data to support schizoaffective disorder as a distinct category are still very limited even though the structural and functional imaging studies have increased [8,9]. The complexity of schizoaffective disorder makes the identification of its pathophysiology a great challenge, maybe one of the most difficult challenges in psychiatry research.

Oxidative stress is accepted as a predisposing factor for various diseases in medicine by causing lipid peroxidation, cellular damage, DNA damage, enzyme inactivation, and altered inflammatory responses [10]. Oxidative stress resulting from increased oxidant levels or weak antioxidant defence mechanisms has been shown repeatedly in previous studies, suggesting that it may play a role in the etiopathogenesis of schizophrenia and bipolar disorder [11,12]. It was even hoped that oxidative stress parameters may be used as biomarkers in both disorders.

Numerous different oxidants and antioxidants can be measured in various biological samples such as blood, urine, and cerebrospinal fluid [13]. The measurement of total oxidant status (TOS) and total antioxidant status (TAS) is essential to demonstrate the relationship between a disease and oxidative stress [14]. Because of the additive effects of different antioxidant components, only TAS levels can show the antioxidant status of the plasma [15]. There are many studies which evaluated TOS and TAS levels in schizophrenia and a few studies in bipolar disorder [16,17], whereas there is only one study about schizoaffective disorder [18]. In this sole study which had investigated oxidative stress parameters, TOS levels were found to

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be higher in schizoaffective disorder patients than both schizophrenia and bipolar disorder patients.

Oxidative DNA damage by oxidative stress may be particularly important because of its potential effects on the expression of a wide variety of genes [19]. Modifications caused by DNA damage can lead to cellular necrosis and increased inflammatory responses around the neurones [20]. 8-hydroxy-2'-deoxyguanosine (8-OHdG) is formed by hydroxylation of guanosine nucleoside and considered as the most sensitive and useful marker of oxidative DNA damage [21]. Oxidative DNA damage has been shown to increase in almost all studies about bipolar disorder and in most studies about schizophrenia [11,12]. We could not find any study investigating oxidative DNA damage in schizoaffective disorder.

Urotensin-II (U-II) is a neuropeptide which takes place in the oxidative system by increasing reactive oxygen species (ROS), inflammatory mediators, and pro-inflammatory cytokines [22]. Increased U-II levels have been demonstrated in the aetiology of many diseases such as diabetes mellitus, essential hypertension, and renal failure in which oxidative stress is also blamed [22,23]. U-II levels were found to be negatively correlated with TAS levels and positively correlated with oxidative stress index (OSI) levels in patients with diabetes mellitus [23]. U-II may be an important mediator in the central nervous system by means other than oxidative system. U-II was first isolated from the urophysis of teleost fish, which is an analogue of hypothalamic-pituitary axis and the receptor of U-II was found to be located throughout the central nervous system [24,25]. It has also been shown that U-II and its receptor may be a novel chemokine system that may influence the development of the central nervous system by recent studies [25]. The modulatory effect of U-II on behavioural, hormonal, oxidative, and inflammatory factors and its newly discovered migration regulatory effect suggest that U-II may play a role in the pathophysiology of psychotic disorders. U-II was researched only in schizophrenia patients with psychiatric disorders and it was found to be elevated [26]. Therefore, we investigated the levels of U-II in schizoaffective disorder patients and its association with oxidative status and oxidative DNA damage.

Methods

Patient group and study protocol

Because of the schizoaffective disorder's moderate inter-rater reliability with a kappa of 0.57 [95% CI: 0.41–0.73] [1], a total of 94 patients who were diagnosed as schizoaffective disorder bipolar type and registered in psychotic disorders unit of Gaziantep University Medical Faculty Psychiatry Department after re-evaluation by one assistant professor of psychiatry were interviewed for the study between September 2013 and February 2014; 25 patients with morbid obesity, hypertension, diabetes mellitus, hyperlipidaemia or cardiovascular disease, 2 patient with mental retardation, 2 patients with active infectious disease, 1 patient with a history of cerebrovascular disease, 1 patient with N-acetylcysteine treatment, and 9 patients who refused to participate were excluded from the study. Among the remaining 54 patients, 27 of them were in symptomatic remission and 27 of them were not. Since there are no collectively accepted remission criteria in schizoaffective disorder, remission criteria were determined by both, taking into account the remission criteria recommended for schizophrenia and bipolar disorder. Patients with a score of lower than 3 for at least 6 months in P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), N1 (blunted affect), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G5 (mannerisms and posturing), G9 (unusual thought content) components of Positive and Negative Syndrome Scale (PANSS) and those who had Hamilton Depression Rating Scale (HAM-D) score lower than 8, and Young Mania Rating Scale (YMRS) score lower than 6 for at least 6 months were accepted as in symptomatic remission. Validity and reliability of the Turkish versions of PANSS were shown by Kostakoglu et al. [27], HAM-D was shown by Akdemir et al. [28], and YMRS was shown by Karadag et al. [29]. As control group, 27 healthy people consisting of doctors, hospital staff and students were enrolled. The study was approved by ethics committee of Gaziantep University with the number 20.08.2013/283.

Laboratory measurements

Blood samples of patient and control groups were taken from antecubital vein after a 12-hour fasting period. Blood was transferred to sampling tubes with a gel separator and centrifuged at 4000 rpm for 10 minutes after a maximum of six hours storage with ice. Separated serum was immediately transferred to storage at −80°C ultra-low temperature freezer.

Serum TOS and TAS levels were determined using an automated measurement method developed by Erel using fully automated Rel Assay brand oxidative stress kits with Tokyo Boeki Prestige 24i chemistry analyser. Oxidative stress index (OSI) was measured by dividing TOS levels to TAS levels [OSI (arbitrary unit) = TOS (mmol H2O2 Equiv./l)/TAS (mmol Trolox Equiv./l)] [15,30].

Serum human U-II levels were assessed at ELISA laboratory (Biotek Instruments, USA) of Gaziantep University Department of Biochemistry according to the manufacturer's instructions (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China). The principle of

Table 1. Comparisons of age, gender, and smoking status of patients in symptomatic remission, non-remission and control group.

		Non-remission (*n*:27)	Remission (*n*:27)	Control (*n*:27)	*p*[a]
Gender (%)					
	Women	11 (40.7%)	10 (37%)	10 (37%)	.949
	Men	16 (59.3%)	17 (63%)	17 (63%)	
Smoking (%)					
	Yes	15 (55.6%)	14 (51,9%)	13 (48.1%)	.862
	No	12 (44.4%)	13 (48.1%)	14 (51.9%)	
Age (mean ± SD)		35.67 ± 7.43	34.96 ± 9.22	32.11 ± 5.20	.187
BMI		29.06 ± 4.33	29.32 ± 4.30	28.57 ± 4.46	.808

Note: BMI: body mass index.
[a]*p* values were obtained using χ^2 test (2xn) and ANOVA where appropriate.

the test is a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). Serum 8-OHdG was also measured in the same ELISA laboratory (Cayman Chemical, MI, USA) with an anti-mouse IgG-coated plate, which provides lower variability and higher sensitivity than antigen-coated plates.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of the variables. The chi-square test was used for parametric categorical variables, *t*-test was used for parametric continuous variables, and correlations between quantitative data were analysed by Spearman's correlation test. Mann–Whitney *U* test and Kruskal–Wallis test were used to compare two and more non-parametric independent groups. Results are expressed as mean and standard deviation (SD) for parametric and median (min–max) for non-parametric variables. SPSS for IOS version 20 software was used for statistical analyses. The level of significance was set at $p \leq .05$.

Results

There were no statistical significant differences in terms of age, gender, smoking status, and body mass index between all groups (Table 1). The schizoaffective patient groups with or without remission were not different according to onset age and duration of illness, hospitalization rates, numbers of past manic, depressive, and total mood episodes (Table 2).

The distribution of schizoaffective disorder patients who were not in symptomatic remission was as 10 (%37) in manic episode, 8 (%29.7) in depressive episode, and 9 (%33.3) in euthymic episode. PANNS and CGI scores of patients without symptomatic remission were 97.93 ± 14.57 and 5 ± 1, respectively, whereas those in symptomatic remission had a PANSS score of 51.44 ± 12.05 and CGI score of 2.44 ± 0.57. A comparison of scale scores between remission and non-remission patients was shown in Table 2.

Kruskal–Wallis test showed that TAS ($H = 9.587$, $p = .008$) and U-II ($H = 18.634$, $p = .001$) levels were significantly different across groups. While the 8-OHdG levels were lower in the control group compared to the remission and non-remission groups, the difference was not significant ($H = 4.149$, $p = .126$). There were no significant differences across groups in terms of TOS and OSI levels. Post hoc tests to test pairwise comparisons revealed that TAS levels in control group were significantly higher than remission group ($p = .015$, $d = 0.82$) and non-remission group ($p = .033$, $d = 0.83$). Also, U-II levels in control group were significantly higher than remission group ($p = .001$, $d = 0.15$) and non-remission group ($p = .001$, $d = 0.15$). There were no differences between remission and non-remission groups regarding TAS and U-II levels (Table 3).

Table 2. Sociodemographic and clinical characteristics of schizoaffective disorder patients.

		Non-remission (*n*:27)	Remission (*n*:27)	*p*[a]
Education	None	0	3 (11.1%)	.289
	Primary	16 (59.3%)	11 (40.8%)	
	High School	7 (25.9%)	11 (40.8%)	
	University	4 (14.8%)	2 (7.3%)	
Marital status	Married	15 (%55.6)	10 (37.0%)	.198
	Divorced	1 (3.7%)	6 (22.2%)	
	Single	11 (40.7%)	11 (40.8%)	
Family history	Psychotic disorder	7 (25.9%)	5 (18.5%)	.199
	Mood disorder	5 (18.5%)	4 (14.8%)	
	None	15 (55.6%)	18 (66.6%)	
History of ECT	Yes	11 (40.7%)	17 (62.9%)	.086
	No	16 (59.3%)	10 (37.03%)	
Suicide attempt	Yes	11 (40.7%)	6 (22.2%)	.120
	No	16 (59.3%)	21 (77.8%)	
Age of onset (Years, mean ± SD)		20.96 ± 5.11	22.74 ± 4.91	.160
Duration of disorder (Years, mean ± SD)		14.00 ± 8.01	12.93 ± 5.69	.910
Number of hospitalizations (mean ± SD)		3.00 ± 2.55	2.37 ± 2.03	.367
Scale scores (mean ± SD)	CGI	5.00 ± 1.00	2.44 ± 0.57	.001
	YMRS	9.12 ± 1.05	2.74 ± 2.03	.006
	HAM-D	7.63 ± 7.98	3.93 ± 2.41	.171
	PANSS	97.93 ± 14.57	51.44 ± 12.05	.001
Past episodes (mean ± SD)	Manic episodes	3.41 ± 2.13	2.37 ± 1.14	.113
	Depressive episodes	3.59 ± 1.86	3.96 ± 2.51	.800

Notes: ECT: electroconvulsive treatment; CGI: clinical global impression; YMRS: Young Mania Rating Scale; HAM-D: Hamilton Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale.
[a]*p* values were obtained using χ^2 test (2xn) and *t*-test (Mann–Whitney *U* for non-parametric variables) where appropriate.

Table 3. Comparisons of TAS, TOS, OSI, U-II, and 8-OHdG levels in patients in symptomatic remission, non-remission, and control group.

	Non-remission (*n*:27) Median, [25–75%] CV	Remission (*n*:27) Median, [25–75%] CV	Control (*n*:27) Median, [25–75%] CV	*p*[a]
U-II (ng/mL)	100.51 [87.27–109.47] 1,090,810.27	98.37 [76.17–122.57] 297,543.97	231.56 [119.54–386.95] 51,999.83	.001*
TAS (mmol Trolox Eqv/L)	4.09 [1.71–4.16] 2.41	4.07 [3.08–4.18] 1.96	4.17 [4.12–4.21] 0.10	.008**
TOS (μ mol H_2O_2 Eqv/L)	46.23 [12.35–58.11] 1170.90	51.17 [20.52–80.50] 918.61	50.98 [37.56–63.35] 732.04	.485
OSI (au)	1.22 [55,560–268,900] 24.13	1.33 [0.78–2.14] 46.39	1.22 [0.90–1.50] 0.42	.798
8-OHdG (ng/mL)	13.40 [8.76–15.64] 27.36	13.14 [10.94–15.56] 16.59	10.22 [7.63–14.58] 19.36	.126

Notes: CV: coefficient of variance; U-II: urotensin-II; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; 8-OHdG: 8-hydroxy-2′-deoxyguanosine.
[a]*p* values were obtained using Kruskal–Wallis test.
*Significant at the .01 probability level.
**Significant at the .05 probability level.

Similar results were obtained when those in symptomatic remission and non-remission patient groups were combined and compared with the control group. TAS and U-II were significantly lower in the patient group ($p = .001$, $d = 0.82$ and $p = .002$, $d = 0.14$, respectively) and TOS, OSI, and 8-OHdG levels did not show any difference (Table 4).

According to correlation analysis, there was no strong correlation between variables but serum TAS levels showed weak negative correlation with number of past manic episodes ($r = -0.278$, $p = .042$) and U-II levels showed weak positive correlation with BMI ($r = 0.269$, $p = .049$). There were no statistically meaningful correlation between PANSS, HAM-D, YMRS scores, and oxidative parameters according to Spearman's correlation analysis.

Discussion

One of the findings of our study is that U-II levels in schizoaffective disorder patients were significantly lower than controls. This result is in contrast with our previous study in schizophrenia patients in which we claimed that increased U-II may be one of the causes of hypofrontality in schizophrenia patients by decreasing the blood flow with its strong vasoconstrictor effect [18]. Even though U-II was reported to be the most powerful vasoconstrictor ever found in mammals, this finding has not been confirmed in humans yet [31]. Hillier reported that U-II had no vasoconstrictor or dilator effects on human arteries and veins [32]. The effect of U-II on pathological processes is still controversial. It is alleged that U-II levels may be increased as a defensive response rather than being a cause for pathological process. In support of this view, there are publications reporting that U-II has a cardio-protective effect by causing beneficial effects on renal haemo-dynamics, increasing cardiac contractility, and opposing reperfusion injury [33,34]. Although the effects of U-II on cardiovascular system have been well studied, its effects on central nervous system are not clear. Behavioural and hormonal changes in animals which occur after intra-cerebrovascular injection of U-II indicate the possible role of this neuropeptide in the central nervous system regulation

Table 4. Comparisons of TAS, TOS, OSI, U-II, and 8-OHdG levels between patient and control groups.

	Schizoaffective disorder (*n*:54) Median, [25–75%] CV	Control (*n*:27) Median, [25–75%] CV	*p*[a]
U-II (ng/mL)	98.37 [76.17–120.57] 689,703.33	231.56 [119.54–386.95] 51,999.83	.001*
TAS (mmol Trolox Eqv/L)	4.09 [1.77–4.17] 2.15	4.17 [4.12–4.21] 0.01	.002**
TOS (μmol H_2O_2 Eqv/L)	46.61 [17.38–64.46] 1026.63	50.98 [37.56–63.35] 732.04	.266
OSI (au)	1.28 [0.76–2.17] 34.61	1.22 [0.90–1.50] 0.42	.638
8-OHdG (ng/mL)	13.27 [10.42–15.56] 21.85	10.22 [7.63–14.58] 19.36	.061

Notes: CV: coefficient of variance; U-II: urotensin-II; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; 8-OHdG: 8-hydroxy-2′-deoxyguanosine.
[a]*p* values were obtained using Mann–Whitney *U* test.
*Significant at the .01 probability level.
**Significant at the .05 probability level.

[35]. Mueller et al. reported that following systemic cocaine injections and intra-ventral tegmental area, microinjections of urotensin-II resulted in increased maximal evoked dopamine concentration [36].

Although studies in past decades have been focused on the vasomotor effect of U-II, recent investigations showed that U-II and its receptor may function as a chemokine system [25]. The chemotactic role of U-II/GPR-14 (G protein-coupled receptor) was first identified in cancer studies [37–40]. In these studies, it has been shown that, U-II and GPR14 were expressed in tumours, U-II increases proliferation of cancer cells and induces migration and angiogenesis [41,42]. Chemotaxis also plays a critical role in neuronal wiring in the central nervous system. Chemokines also have neurotransmitter-like, neuromodulator, neuroprotective, and neurodevelopmental effects beside chemotaxis [43]. Schizoaffective disorder may have a neurodevelopmental origin; structural imaging studies have shown decreased grey matter volume in schizoaffective disorder patients similar to schizophrenia patients [44,45]. Many chemokines have been associated with physiopathology of schizophrenia and bipolar disorder [46]. Therefore, decreased U-II levels detected in our patients and alterations in the U-II/GPR14 chemokine system may contribute to pathophysiology by affecting the development of the central nervous system. On the other hand, our results (which are in contrast with schizophrenia patients) may indicate that both disorders may have different neurobiological basis.

Another finding of our study is that TAS levels in schizoaffective disorder patients were significantly lower than controls. Reduction in antioxidant capacity due to the effect of genetic and environmental factors are thought to contribute to the development of diseases by causing vulnerability to the oxidative stress. Several pathological mechanisms such as aberrant migration, synapse formation, myelination, and neuro-transformation have been shown to occur due to oxidative damage [12]. For example, TAS levels were found to be generally low in studies evaluating schizophrenia [17,46,47]. In addition, antioxidants such as vitamins and fish oil (long-chain omega-3 polyunsaturated fatty acids [PUFAs]) have shown beneficial effects on some symptoms of schizophrenia [48–50]. There have been accumulating evidence for aberrant reactive oxygen species and inflammation in schizophrenia. Increased lipid oxidation (thiobarbituric acid reactive substances), protein oxidation, and NO signalling related molecules were reported in multiple studies [12]. There are also studies showing increased levels of antioxidants in schizophrenia and bipolar disorder patients [16,51]. In these studies, increased antioxidant levels were explained as a sign of compensatory mechanism to counteract a preceding cellular oxidative stress process.

Nucleotides are one of the main targets of oxidative stress. It causes scissions, breaks, and base modifications in DNA [11]. DNA mutations may affect the intracellular messenger systems leading to abnormal metabolic activity, alterations in gene expression, and membrane dysfunctions [19,52]. There are studies that reported changes in expression levels of genes in schizophrenia and bipolar disorder. For example, increased expression of neuronal calcium sensor-1 gene coding in the prefrontal cortex of subjects with both disorders was reported [53] and decreased expression of synapsin IIa and IIIa were in the hippocampus of subjects with both disorders were reported [54]. Although we detected an increase in oxidative DNA damage in schizoaffective disorder patients in our study, this difference did not show statistical significance. This is maybe because of our patient population was not big enough to reach statistical significance due to difficulties in adequate diagnosis. Oxidative DNA and RNA damage was shown in many studies in schizophrenia and bipolar disorder patients consistently in different samples such as blood and cerebrospinal fluid [52,55,56]. Reduced antioxidant capacity in our patients may have made their DNA susceptible to the damaging effects of oxidative stress. We have not identified any differences in terms of OSI and TOS levels between schizoaffective patients and control group. In the sole study with schizoaffective disorder patients, OSI and TOS levels were found higher in schizoaffective patients when compared with schizophrenia and bipolar disorder patients [26]. Our results were not compatible with the previous study, but when we consider the low TAS levels we have found in schizoaffective disorder patients, our results may also indicate an oxidative imbalance that is claimed to be disrupted in the previous study. In schizophrenia, a meta-analysis proposed that TAS levels were found to be lower in the first psychotic episode but significantly increased with antipsychotic treatment, therefore TAS levels may be a state marker [57]. Even though our study is not a prospective one, lower TAS levels we have found in schizoaffective patients in both symptomatic remission and non-remission may support the idea that TAS is more likely a trait marker rather than being a state marker and may play a role in disease pathophysiology.

Limitations

There are some limitations of our study. All of our patients were allowed to take their medications, including antipsychotics and mood stabilizers because of ethical issues, which are known to affect oxidative status. It was also not possible to control environmental factors such as dietary intake and exercise, which are also known to affect our results, as in previous studies. Finally, our sample size was not large enough and

moderate inter-rater reliability for the diagnosis decreases the chance of reaching conclusions that can be generalized. Despite our limitations, this is the first study investigating the U-II and 8-OHdG levels in schizoaffective disorder.

Disclosure statement

No potential conflict of interest was reported by the authors.

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