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Plasma Antioxidant Levels in Drug-Naïve Acute and Transient Psychotic Disorder, Risperidone-Treated Schizophrenia, and Healthy Controls: An Observational Comparative Study

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Abstract

Background: Oxidative stress has been increasingly implicated in the pathophysiology of psychotic disorders. Non-enzymatic antioxidants such as serum uric acid, bilirubin, and albumin may reflect systemic antioxidant defence and may vary across acute and chronic psychotic states.

Methods: This observational comparative study was conducted at a tertiary care psychiatric centre and included 165 participants divided equally into three groups: drug naïve first-episode acute and transient psychotic disorder (ATPD), risperidone-treated schizophrenia, and healthy controls. Socio-demographic and clinical details were recorded using a semi-structured proforma. Plasma antioxidant levels, including serum uric acid, total bilirubin, and serum albumin, were estimated in all participants. Symptom severity in patient groups was assessed using the Positive and Negative Syndrome Scale (PANSS). Data were analysed using appropriate statistical tests.

Results: Serum uric acid and bilirubin levels were lowest in the ATPD group and highest among healthy controls, with statistically significant intergroup differences. Serum albumin was also lowest in ATPD patients and higher in risperidone-treated schizophrenia patients and controls. ATPD patients had higher positive, general psychopathology, and total PANSS scores, while schizophrenia patients had higher negative symptom scores. Serum albumin showed a moderate negative correlation with total PANSS and general psychopathology scores.

Conclusion: Plasma antioxidant levels differed significantly among ATPD, risperidone treated schizophrenia, and healthy controls, suggesting altered antioxidant defence in psychotic disorders, particularly during acute untreated psychosis.

Keywords: Acute and transient psychotic disorder; Schizophrenia; Risperidone; Oxidative stress; Antioxidants; Uric acid; Bilirubin; Albumin; PANSS

Introduction

Psychotic disorders are a heterogeneous group of mental illnesses characterized by disturbances in perception, thought, affect, and behaviour. Among these, acute and transient psychotic disorder (ATPD) and schizophrenia are important diagnostic entities with overlapping symptoms but distinct course, prognosis, and therapeutic implications. ATPD usually presents with an acute onset of delusions, hallucinations, perceptual disturbances, and disorganized behaviour, with a relatively short duration and favourable outcome compared with chronic psychotic disorders.[1–3] In contrast, schizophrenia is a persistent and disabling disorder associated with positive symptoms, negative symptoms, cognitive impairment, functional decline, and substantial personal and social burden.[4] Although antipsychotic medications remain central to schizophrenia management, the biological mechanisms underlying symptom expression, illness progression, and treatment response remain incompletely understood.[5] Oxidative stress has emerged as an important biological pathway in psychotic disorders. It refers to an imbalance between the generation of reactive oxygen and nitrogen species and the capacity of antioxidant systems to neutralize them.[6,7] Excessive reactive species or inadequate antioxidant defence can damage lipids, proteins, nucleic acids, and cellular membranes.[8,9] The brain is particularly vulnerable to oxidative injury because of its high oxygen consumption, abundant lipid content, and relatively limited antioxidant reserve. Oxidative damage has therefore been proposed to contribute to altered neurotransmission, neuroinflammation, mitochondrial dysfunction, impaired synaptic plasticity, and neuronal injury in schizophrenia spectrum disorders.[10–12] Several studies have demonstrated altered oxidative stress markers and antioxidant defence mechanisms in schizophrenia. Increased lipid peroxidation, reduced antioxidant enzyme activity, and abnormalities in glutathione metabolism have been reported in both first episode and chronic schizophrenia.[13–15] A meta-analysis by Flatow et al. supported the presence of oxidative imbalance in schizophrenia and suggested its possible association with clinical dimensions such as negative symptoms and cognitive impairment.[16] Recent studies have also emphasized the relationship between oxidative biomarkers, inflammation, kynurenine pathway alterations, and psychopathological severity, indicating that oxidative stress may represent a clinically relevant biological domain in schizophrenia.[17,18] Non-enzymatic plasma antioxidants such as uric acid, bilirubin, and albumin are of particular interest because they are routinely measurable and contribute substantially to circulating antioxidant capacity. Uric acid, the final product of purine metabolism, has free radical scavenging properties but may also show pro-oxidant effects under certain conditions.[19] Bilirubin, a product of heme catabolism, is an endogenous antioxidant capable of scavenging superoxide and inhibiting lipid peroxidation.[20] Albumin, the most abundant plasma protein, contributes to redox balance through ligand binding, metal sequestration, and free-radical scavenging.[21] Alterations in these antioxidants may therefore reflect systemic oxidative burden in psychotic illnesses. Clinical studies have shown reduced plasma antioxidant levels in schizophrenia. Reddy et al. reported significantly lower albumin, uric acid, and bilirubin levels in first-episode schizophrenia patients compared with healthy controls, suggesting early antioxidant deficits independent of treatment effects.[22] Mahadik et al. observed reduced plasma albumin and bilirubin levels in schizophrenia and suggested their association with clinical symptomatology.[23] Pae et al. also reported decreased plasma antioxidant levels in schizophrenia.[24] Reduced bilirubin levels were demonstrated by Zhang et al., while Becklén et al. found lower bilirubin levels in first-episode psychosis with associations with working memory and duration of untreated psychosis.[25,26] These findings suggest that non enzymatic antioxidant deficits may be biologically relevant in psychotic disorders. The effect of antipsychotic treatment on oxidative stress is also important. Risperidone, an atypical antipsychotic with dopamine D_2 and serotonin 5-HT_2 receptor antagonistic

properties, is widely used in schizophrenia.[5] Studies suggest that risperidone may modify oxidative stress parameters through clinical improvement, antioxidant modulation, or effects on inflammatory and metabolic pathways.[27,28] Noto et al. reported antioxidant effects after risperidone treatment in drug-naïve first-episode psychosis, and Wang et al. found that changes in total antioxidant status after risperidone monotherapy were associated with symptom improvement.[29,30] However, chronic antipsychotic exposure may also be associated with metabolic adverse effects that can influence oxidative biology.[31] Compared with schizophrenia, fewer studies have examined oxidative stress in ATPD. ATPD offers an opportunity to study biochemical changes during an acute, often first-onset psychotic episode before prolonged illness progression or long-term antipsychotic exposure. Comparing drug-naïve first-episode ATPD patients with risperidone-treated schizophrenia patients and healthy controls may help clarify whether antioxidant alterations are present early in acute psychosis, persist in chronic treated psychosis, or differ according to illness course and treatment status. Assessment of antioxidant levels in relation to symptom severity using the Positive and Negative Syndrome Scale may further clarify their clinical relevance.[16–18] In this context, the present study was undertaken to compare plasma levels of serum uric acid, bilirubin, and albumin among patients with drug-naïve first-episode ATPD, risperidone-treated schizophrenia, and healthy controls. The study also assessed the association between plasma antioxidant levels and severity of clinical symptoms in ATPD and schizophrenia. By focusing on routinely available plasma antioxidant markers, this study aims to contribute to the understanding of oxidative stress in psychotic disorders and its possible relevance for illness characterization and symptom assessment.

Materials and Methods

The present observational comparative study was conducted at the Psychiatric Centre, SMS Medical College, Jaipur, after obtaining approval from the Institutional Research Review Board and Institutional Ethics Committee. The study was carried out from May 2023 to April 2024, followed by data compilation, statistical analysis, and report writing. Written informed consent was obtained from all participants or their caregivers before enrolment. The study population comprised patients attending the Department of Psychiatry who fulfilled the predefined inclusion and exclusion criteria. Participants were divided into three groups. Group A included patients with drug-naïve first-episode acute and transient psychotic disorder (ATPD), diagnosed according to ICD-10 criteria. Group B included patients with schizophrenia who had been receiving risperidone treatment for at least six months. Group C consisted of healthy controls without any psychiatric disorder or significant medical illness. Each group included 55 participants, making a total sample size of 165 subjects. The sample size was calculated at 80% power and 5% alpha error, assuming a standard deviation of 1.3 mg/dL in serum uric acid levels among the three groups, based on the seed article. Considering a minimum detectable difference of 0.8 mg/dL in serum uric acid level, a minimum of 51 participants was required in each group. This was increased to 55 participants per group. Participants aged 18–50 years were included in the study. Patients with comorbid psychiatric illness, medical conditions likely to affect serum uric acid, bilirubin, or albumin levels, substance abuse within the preceding six months except nicotine chewing, organic etiology including head injury or epilepsy, and intellectual disability were excluded. Healthy controls were also screened clinically to exclude conditions that could alter antioxidant parameters. A purposive sampling technique was used. Eligible patients and controls were recruited after explaining the purpose and methodology of the study. Socio-demographic details, including age, sex, marital status, religion, education, domicile, occupation, income, family type, number of family members, and socioeconomic status, were recorded using a semi structured proforma. Clinical details

such as provisional diagnosis, duration of illness, age at onset, past history, family history, substance history, current medication, and relevant investigations were collected using a clinical data sheet. Psychiatric diagnosis was confirmed using ICD-10 criteria, and the Mini International Neuropsychiatric Interview English Version 7.0.2 was used to assess psychiatric comorbidities, particularly among controls. Severity of psychotic symptoms in ATPD and schizophrenia patients was assessed using the Positive and Negative Syndrome Scale (PANSS), which includes positive symptoms, negative symptoms, and general psychopathology domains. Blood samples were collected from all participants for estimation of plasma antioxidant markers, namely serum uric acid, total bilirubin, and serum albumin. All collected data were entered and analyzed using SPSS software. Appropriate parametric and non-parametric statistical tests were applied wherever applicable. The primary outcome variables included comparison of plasma antioxidant levels among drug-naïve first-episode ATPD patients, risperidone-treated schizophrenia patients, and healthy controls. The secondary analysis assessed the association between clinical symptom severity and plasma antioxidant levels in the patient groups. Confidentiality of participant information was maintained throughout the study, and participants retained the right to withdraw from the study at any stage without any effect on their treatment.

Results

The present study included a total of 165 participants, with 55 subjects each in Group A, Group B, and Group C. Group A comprised patients with drug-naïve first-episode acute and transient psychotic disorder, Group B comprised patients with schizophrenia treated with risperidone for at least six months, and Group C comprised healthy controls. The results were analysed with respect to socio-demographic characteristics, plasma antioxidant levels, PANSS scores, and correlation of antioxidant levels with symptom severity.

Socio-demographic profile

The mean age of participants was 28.53 ± 3.08 years in Group A, 30.45 ± 9.48 years in Group B, and 30.33 ± 8.55 years in Group C. The difference in mean age among the three groups was not statistically significant (p=0.073). Males were more common than females in all three groups, with no significant difference in gender distribution (p=0.606). Most participants were married across the groups, and marital status distribution was also comparable (p=0.344). Family type, domicile, religion, educational qualification, occupation, family income, socioeconomic status, and family history of psychiatric illness were not significantly different among the groups. However, the mean number of family members differed significantly among the three groups (p=0.031), with the highest mean observed in Group C.

Table 1. Baseline socio-demographic characteristics of study participants

Variable	Group A: ATPD (n=55)	Group B: Schizophrenia onrisperidone (n=55)	Group C: Healthy controls (n=55)	p-value
Age,years,mean±SD	28.53 ± 3.08	30.45 ± 9.48	30.33 ± 8.55	0.073
Male/Female	35/20	38/17	33/22	0.606
Married/Unmarried/Divorced or separated	33/22/0	35/18/2	28/24/3	0.344

Nuclear/Joint/Extended family	18/22/15	23/19/13	19/20/16	0.870
Number of family members, mean ± SD	5.3 ± 1.2	4.9 ± 1.4	5.6 ± 1.8	0.031
Urban/Rural domicile	36/19	29/26	35/20	0.336
Hindu/Muslim/Others	41/13/1	38/16/1	34/19/2	0.684
Family history present/absent	12/43	16/39	14/41	0.681
Socioeconomic status distribution	Comparable	Comparable	Comparable	0.988

Plasma antioxidant levels Plasma antioxidant levels differed significantly among the three groups. Serum uric acid was lowest in Group A (4.67 ± 0.52 mg/dL), followed by Group B (5.34 ± 1.68 mg/dL), and highest in Group C (5.52 ± 1.50 mg/dL), with a statistically significant difference among the groups ($p<0.05$).

Table 2. Comparison of plasma antioxidant levels among study groups

Plasma antioxidant marker	Group A: ATPD (n=55)	GroupB:Schizophrenia on risperidone (n=55)	Group C: Healthycontrols (n=55)	p-value
Serum uric acid (mg/dL),mean± SD	4.67 ± 0.52	5.34 ± 1.68	5.52 ± 1.50	<0.05
Serum bilirubin (mg/dL),mean± SD	0.76 ± 0.18	0.82 ± 0.19	1.12 ± 0.20	<0.05
Serum albumin (g/dL), mean ± SD	3.96 ± 0.39	4.45 ± 0.57	4.36 ± 0.47	<0.05

PANSS scores among patient groups

PANSS scores were assessed in Group A and Group B. Group A had higher positive symptom scores, general psychopathology scores, and total PANSS scores compared to Group B. The mean positive PANSS score was 30.24 ± 2.36 in Group A and 19.04 ± 5.70 in Group B. The mean general psychopathology score was 45.22 ± 4.07 in Group A and 28.60 ± 7.17 in Group B. The total PANSS score was also higher in Group A (89.29 ± 4.03) than in Group B (71.58 ± 9.24). In contrast, the mean negative PANSS score was higher in Group B (23.95 ± 5.69) than in Group A (13.84 ± 3.17).

Table 3. PANSS scores among ATPD and risperidone-treated schizophrenia groups

PANSS domain	Group A: ATPD	Group B: Schizophrenia on risperidone
Positive PANSS score	30.24 ± 2.36	19.04 ± 5.70
Negative PANSS score	13.84 ± 3.17	23.95 ± 5.69
General psychopathology score	45.22 ± 4.07	28.60 ± 7.17
Total PANSS score	89.29 ± 4.03	71.58 ± 9.24

Correlation of total PANSS score with plasma antioxidant levels

Correlation analysis showed weak to moderate negative correlations between total PANSS score and plasma antioxidant levels. Serum uric acid showed a weak negative correlation

with total PANSS score (r = -0.21, R^2 = 0.0441). Serum bilirubin also showed a weak negative correlation with total PANSS score (r = -0.137, R^2 = 0.0188). Serum albumin showed the strongest association among the three markers, with a moderate negative correlation with total PANSS score (r = -0.409, R^2 = 0.1676).

Table 4. Correlation between total PANSS score and plasma antioxidant levels

PANSS variable	Plasma antioxidant marker	Regression equation	R^2	Correlation coefficient(r)	Interpretation
Total PANSS score	Serum uric acid	y=-2.4151x + 96.522	0.0441	-0.210	Weak negative correlation
Total PANSS score	Serum bilirubin	y=-10.707x + 92.872	0.0188	-0.137	Weak negative correlation
Total PANSS score	Serum albumin	y=-11.079x + 131.06	0.1676	-0.409	Moderate negative correlation

Correlation of PANSS subdomains with plasma antioxidant levels

Subdomain-wise correlation analysis showed that most correlations between antioxidant levels and PANSS subscale scores were weak or very weak. Serum uric acid showed no meaningful correlation with positive PANSS score (r = 0.01), very weak negative correlation with negative PANSS score (r = -0.072), and weak negative correlation with general psychopathology score (r = -0.13). Serum bilirubin showed very weak correlations with all PANSS subdomains. Serum albumin showed very weak negative correlation with positive PANSS score (r = -0.045), very weak positive correlation with negative PANSS score (r = 0.094), and moderate negative correlation with general psychopathology score (r = -0.355).

Table 5. Correlation between PANSS subdomain scores and plasma antioxidant levels

PANSSscore type	Serum variable	R^2	Correlation coefficient(r)	Interpretation
Positive PANSS	Serum uric acid	0.0001	0.010	No correlation
Negative PANSS	Serum uric acid	0.0052	-0.072	Very weak negative correlation
General PANSS	Serum uric acid	0.0170	-0.130	Weak negative correlation
Positive PANSS	Serum bilirubin	0.0083	0.091	Very weak positive correlation
Negative PANSS	Serum bilirubin	0.0064	-0.080	Very weak negative correlation
General PANSS	Serum bilirubin	0.0061	-0.078	Very weak negative correlation
Positive PANSS	Serum albumin	0.0020	-0.045	Very weak negative correlation

Negative PANSS	Serum albumin	0.0089	0.094	Very weak positive correlation
General PANSS	Serum albumin	0.1262	-0.355	Moderate negative correlation

Overall, the study showed statistically significant differences in plasma antioxidant levels among drug-naïve first-episode ATPD patients, risperidone-treated schizophrenia patients, and healthy controls. Serum uric acid and serum bilirubin were lowest in the ATPD group and highest in the healthy control group. Serum albumin was lowest in the ATPD group and highest in the risperidone-treated schizophrenia group. PANSS assessment showed higher positive, general psychopathology, and total scores in ATPD patients, while negative symptom scores were higher among risperidone-treated schizophrenia patients. Correlation analysis showed that most associations between antioxidant levels and PANSS scores were weak; however, serum albumin showed a moderate negative correlation with total PANSS and general psychopathology scores.

Discussion

The present study compared plasma antioxidant levels, namely serum uric acid, serum bilirubin, and serum albumin, among patients with drug-naïve first-episode acute and transient psychotic disorder (ATPD), risperidone-treated schizophrenia, and healthy controls. The study also assessed the relationship between these antioxidant markers and severity of psychotic symptoms using PANSS scores. The principal findings were that serum uric acid and bilirubin were lowest among ATPD patients and highest among healthy controls, while serum albumin was lowest in the ATPD group and relatively higher in risperidone-treated schizophrenia patients and controls. ATPD patients had higher positive, general psychopathology, and total PANSS scores, whereas schizophrenia patients had higher negative symptom scores. Most correlations between antioxidant levels and PANSS domains were weak, although serum albumin showed a moderate negative correlation with total PANSS and general psychopathology scores. The three study groups were broadly comparable in terms of age, gender, marital status, family type, domicile, religion, family history of psychiatric illness, and socioeconomic status. The mean age was 28.53 ± 3.08 years in ATPD, 30.45 ± 9.48 years in risperidone treated schizophrenia, and 30.33 ± 8.55 years in controls, with no significant difference. This comparability is important because antioxidant markers such as uric acid, bilirubin, and albumin can be influenced by age, sex, nutrition, lifestyle, and medical comorbidities. The age profile was consistent with the usual onset pattern of acute psychosis and schizophrenia, both of which commonly affect young adults.[1–4] The significant reduction in plasma antioxidant levels among patient groups supports the role of oxidative stress in psychotic disorders. Oxidative stress results from an imbalance between reactive oxygen and nitrogen species and antioxidant defence systems, leading to damage of lipids, proteins, nucleic acids, and membranes.[6–9] The brain is particularly vulnerable because of its high oxygen consumption and lipid-rich structure.[10] In schizophrenia, oxidative stress has been linked with mitochondrial dysfunction, neuroinflammation, altered neurotransmission, membrane abnormalities, and neuronal injury.[10–12,14] The lower antioxidant levels observed in ATPD patients suggest that oxidative imbalance may be present early during acute psychosis, even before long-term illness progression or antipsychotic exposure. Reddy et al. reported reduced plasma antioxidants, including albumin, uric acid, and bilirubin, in first-episode schizophrenia patients compared with healthy controls, indicating that antioxidant deficits may occur early and independently of treatment effects.[22] Similar findings were reported by Mahadik et al. and Pae et al., who observed reduced plasma antioxidant levels in schizophrenia patients compared with controls.[23,24] The present findings are in agreement with these studies and further suggest that antioxidant depletion may not be limited to chronic schizophrenia but may also be present in acute and transient psychotic states. Serum uric acid was lowest in ATPD patients, intermediate in risperidone-treated schizophrenia patients, and highest in controls. Uric acid is a major non-enzymatic antioxidant and can scavenge reactive oxygen species; however, it may also show pro oxidant effects under certain conditions.[19] The lower uric acid level in ATPD patients is comparable to the findings of Reddy et al., who reported reduced uric acid in first-episode schizophrenia patients.[22] Yao and Keshavan also emphasized abnormalities in antioxidant defence and purine metabolism in schizophrenia.[11] The relatively higher uric acid level in the risperidone-treated group than in ATPD may reflect differences in illness stage, treatment exposure, or partial restoration of antioxidant balance, although causal inference is limited by the cross-sectional design. Serum bilirubin was also significantly lower in ATPD and schizophrenia patients compared with controls. Bilirubin is an endogenous

antioxidant that scavenges superoxide and inhibits lipid peroxidation.[20] Reduced bilirubin may therefore indicate impaired antioxidant capacity or increased utilization during oxidative stress. Zhang et al. reported decreased bilirubin levels in schizophrenia, while Mahadik et al. found reduced bilirubin and suggested its association with negative symptomatology.[23,25] Becklén et al. also reported reduced bilirubin levels in first-episode psychosis and found associations with working memory and duration of untreated psychosis.[26] The present findings support the view that bilirubin depletion may be an early biochemical feature of psychotic illness. Serum albumin was lowest in ATPD patients and higher in schizophrenia patients and controls. Albumin contributes to antioxidant defence through free-radical scavenging, ligand binding, and metal ion sequestration.[21] Reduced albumin may reflect oxidative consumption, inflammation, poor nutrition, or altered systemic physiology. The lower albumin level in ATPD patients is consistent with Reddy et al. and Mahadik et al., who reported reduced albumin in schizophrenia patients compared with controls.[22,23] In the present study, albumin showed the strongest relationship with symptom severity, with a moderate negative correlation with total PANSS and general psychopathology scores. This suggests that lower albumin levels may be associated with greater overall psychopathological burden, although albumin cannot be considered a specific biomarker because it is influenced by several systemic factors.[16–18] The PANSS profile showed higher positive, general psychopathology, and total scores in ATPD patients, while negative symptoms were higher among risperidone-treated schizophrenia patients. This pattern is clinically understandable because ATPD usually presents with sudden-onset florid psychotic symptoms, including hallucinations, delusions, emotional turmoil, and behavioural disturbance.[1–3] In contrast, chronic schizophrenia is often associated with persistent negative symptoms such as blunted affect, social withdrawal, emotional withdrawal, and reduced spontaneity.[4,5] The higher negative symptom burden in schizophrenia is also consistent with previous studies suggesting a possible relationship between antioxidant abnormalities and negative symptomatology.[13,23] Correlation analysis showed weak negative correlations of total PANSS score with uric acid and bilirubin, while albumin showed a moderate negative correlation. Subdomain correlations were mostly weak, except for albumin with general psychopathology. Flatow et al. reported oxidative stress abnormalities in schizophrenia and suggested possible links with illness state and symptomatology.[16] Więdłocha et al. and Dębowska et al. also found associations between oxidative stress biomarkers and PANSS domains.[17,18] Compared with these studies, the present correlations were weaker, possibly because only three non enzymatic plasma antioxidants were studied, whereas previous studies included broader markers such as malondialdehyde, glutathione, total oxidative status, and kynurenine pathway metabolites. The relatively better antioxidant profile among risperidone-treated schizophrenia patients compared with ATPD patients may suggest a possible antioxidant-modulating effect of risperidone or may simply reflect differences between acute untreated psychosis and chronic treated illness. Pae et al. and Zhang et al. suggested that risperidone may reduce oxidative stress and improve antioxidant enzyme activity.[27,28] Noto et al. observed antioxidant effects after risperidone treatment in drug-naïve first-episode psychosis, and Wang et al. found that risperidone monotherapy increased total antioxidant status, which was associated with symptom improvement.[29,30] However, risperidone may also cause metabolic adverse effects that can influence oxidative pathways.[31] Therefore, longitudinal studies are required to distinguish illness-related changes from treatment-related effects. An important implication of the present study is that antioxidant abnormalities may represent a transdiagnostic biological response to psychosis rather than a feature specific to schizophrenia alone. ATPD patients showed the lowest levels of all

three antioxidants, suggesting acute antioxidant depletion during first-episode psychosis. Acute psychosis may involve agitation, insomnia, poor intake, psychological stress, autonomic activation, and inflammatory changes, all of which can increase oxidative demand. This supports the view that oxidative stress may contribute to symptom expression and illness progression across schizophrenia spectrum and related psychotic disorders.[12,22,26,29] Overall, the present study demonstrated significant differences in serum uric acid, bilirubin, and albumin among ATPD patients, risperidone-treated schizophrenia patients, and healthy controls. The findings support the presence of altered antioxidant defence in psychotic disorders, particularly during acute untreated psychosis. Although most correlations with PANSS scores were weak, serum albumin showed a moderate negative association with overall symptom severity. These findings suggest that routinely available plasma antioxidant markers may provide useful supportive information regarding oxidative imbalance in psychotic disorders, but they cannot be used as diagnostic or prognostic biomarkers at present. Larger longitudinal studies with broader oxidative stress panels are needed to clarify their clinical significance and therapeutic implications.

Strengths and limitations

A major strength of the present study was the inclusion of three clinically relevant groups: drug-naïve first-episode ATPD patients, risperidone-treated schizophrenia patients, and healthy controls. This allowed comparison between acute untreated psychosis, chronic treated psychosis, and non-psychiatric controls. The use of PANSS provided a standardized assessment of symptom severity, and measurement of commonly available plasma antioxidant markers increased the practical applicability of the findings. However, certain limitations must be considered. The study was cross-sectional; therefore, causal relationships between psychosis, risperidone treatment, antioxidant levels, and symptom severity cannot be established. Dietary intake, body mass index, smoking quantity, physical activity, inflammatory markers, and other metabolic factors may influence antioxidant levels and were not explored in detail. Only three non-enzymatic antioxidant markers were measured; inclusion of additional oxidative stress markers such as malondialdehyde, glutathione, superoxide dismutase, catalase, total oxidative status, and total antioxidant status could have provided a more comprehensive redox profile. The risperidone-treated schizophrenia group differed from the ATPD group in illness duration and treatment exposure, which may have influenced antioxidant status. Finally, ATPD is a diagnostically heterogeneous category, and follow-up is required because some cases may later convert to schizophrenia or affective psychosis.

Conclusion

The present study demonstrated significant differences in plasma antioxidant levels among drug-naïve first-episode ATPD patients, risperidone-treated schizophrenia patients, and healthy controls. Serum uric acid and bilirubin were lowest in ATPD patients and highest in controls, while serum albumin was lowest in ATPD and higher among risperidone treated schizophrenia patients and controls. These findings support the presence of altered antioxidant defence in psychotic disorders, particularly during acute untreated psychosis. Symptom analysis showed higher positive, general psychopathology, and total PANSS scores in ATPD, while negative symptoms were higher among schizophrenia patients. Most correlations between antioxidant levels and symptom severity were weak, although serum albumin showed a moderate negative correlation with total PANSS and general

psychopathology scores. Overall, the findings suggest that oxidative stress and antioxidant imbalance may contribute to the biological profile of psychotic disorders, but further longitudinal and interventional studies are required to clarify their clinical significance and therapeutic implications.

Recommendations

Future studies should be conducted with a longitudinal design to evaluate changes in plasma antioxidant levels from the acute untreated phase to follow-up after antipsychotic treatment, so that illness-related and treatment-related effects can be better differentiated. Larger multicentric studies including broader oxidative stress markers such as malondialdehyde, glutathione, superoxide dismutase, catalase, total oxidative status, and total antioxidant status are recommended to obtain a more comprehensive redox profile in psychotic disorders. Potential confounding factors such as diet, body mass index, smoking, physical activity, metabolic parameters, inflammatory markers, and duration of untreated psychosis should also be assessed. Since albumin showed a relatively stronger association with symptom severity in the present study, its role as a simple and accessible marker of systemic oxidative stress in psychosis may be explored further. Interventional studies assessing antioxidant supplementation or redox-modulating strategies as adjuncts to standard antipsychotic treatment may also help clarify whether correction of antioxidant imbalance can improve clinical outcomes in ATPD and schizophrenia.

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