Peripheral Non-enzymatic Antioxidants in Patients with Schizophrenia：A Case-control Study

Zhe Lu
Shandong University Cheeloo College of Medicine
Tianyang Wen
Shandong Mental Health Center
Yingtan Wang
Jining Medical University
Weijing Kan
Capital Medical University
Guanglei Xun (xungl2019@163.com)
Shandong Mental Health Center https://orcid.org/0000-0001-8024-8046

Research article

Keywords: Schizophrenia; Uric acid; Albumin; Total bilirubin

Posted Date: January 8th, 2020

DOI: https://doi.org/10.21203/rs.2.14527/v3

Version of Record: A version of this preprint was published at BMC Psychiatry on May 15th, 2020. See the published version at https://doi.org/10.1186/s12888-020-02635-8.

Abstract

Background: Recent studies show that oxidative stress is associated with the pathogenesis of schizophrenia. There are two major types of antioxidant systems in vivo, namely enzymatic antioxidants and non-enzymatic antioxidants. This study investigated differences of non-enzymatic antioxidant between schizophrenia patients and healthy controls. Methods: Peripheral UA, ALB and TBIL of 107 schizophrenic patients in acute stage and 101 in remission stage were measured respectively, so were 273 healthy controls. Results: The levels of UA (P =0.020) and TBIL (P <0.001) of schizophrenic patients in acute stage were higher than those of healthy controls, while the level of ALB (P <0.001) was lower. Similar results were detected form schizophrenic patients in remission stage. Schizophrenic patients in acute stage were divided into antipsychotics-use subgroup (n=56) and antipsychotics-naïve/free subgroup (n=51). The level of UA (P =0.001) in antipsychotics-use subgroup was higher than that in antipsychotics-naïve/free subgroup, while the level of TBIL (P =0.002) was lower than that in antipsychotics-naïve/free subgroup. 77 schizophrenic patients in acute stage were followed up, and there was no significant difference in level of UA before and after treatment, but levels of ALB (P <0.001) and TBIL (P <0.001) decreased significantly after the treatment. Conclusion: This study demonstrated that the dysfunction of peripheral non-enzymatic anti-oxidation system might be involved in the pathogenesis of schizophrenia. Keywords: Schizophrenia; Uric acid; Albumin; Total bilirubin

Background

Up to now, the pathogenesis of schizophrenia (SCZ) remains unclear. It has been proved that biological, psychological and social factors contribute to the pathogenesis of schizophrenia. Moreover, previous studies suggested that oxidative stress was related to the pathogenesis of schizophrenia[1].

Oxidative stress originates from the excessive production of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen (RNS) in vivo when subjected to various harmful stimuli, meaning that the oxidation system and antioxidant system are unbalanced, which results in damage to tissues (mainly lipids, proteins, and DNA)[2, 3]. There are two major antioxidant systems in vivo, namely enzymatic antioxidants and non-enzymatic antioxidants. The former is the main antioxidant system in the cell with three key enzymes: superoxide dismutase, catalase and glutathione peroxidase; the latter is the main antioxidant system in extracellular fluid (such as plasma, cerebrospinal fluid, etc.), mainly including vitamin A and C, tocopherol, glutathione, uric acid (UA), albumin (ALB), total bilirubin (TBIL) [4, 5]. Nervous tissue is extremely sensitive to oxidative damage caused by ROS or RNS. To be specific, the mitochondrial aerobic respiration, cellular structural component peroxidation and phagocytosis of microglia can produce a large amount of ROS and RNS to cause oxidative damage to brain tissue[6]. The mechanism of oxidative stress in schizophrenia is yet not clear, but increasing evidences suggest that oxidative stress involves in the pathophysiology of schizophrenia[7-10].

Recent studies show an elevated level of oxidative stress indicators in schizophrenia. An autopsy study conducted by Yao et al. [11] found that level of nitric oxide in caudate nucleus of schizophrenic patients was significantly higher than that of healthy controls, indicating that there was a difference in oxidative stress in different brain regions of schizophrenic patients. Radonjic et al.' result in animal study further confirmed this viewpoint [12]. They fed perinatal rats with phencyclidine to establish a model of schizophrenia, and found an evident increase in lipid peroxidation level in the hippocampus and thalamus. In summary, patients with schizophrenia are usually in a state of high oxidative stress. Specifically, their oxidative stress indicators are significantly higher than those of healthy people, and the oxidation status of different brain regions varies.

By far there is no common understanding towards that to what extent the antipsychotics affect oxidative stress in schizophrenia. Al-Chalabi et al.[13] found that olanzapine could improve plasma total antioxidant status and alleviate lipid peroxidative injury. Nevertheless, Eftekhari et al. [14] found in animal experiments that olanzapine could induce oxidative stress and hepatotoxicity, which was associated with the CYP450 enzyme. Recent study pointed out that olanzapine and clozapine had a higher antioxidant ability than risperidone, quetiapine, ziprasidone and haloperidol [15]. The effects of typical and atypical antipsychotics on oxidative stress are different. The former may aggravate oxidative damage, while the latter may improve the oxidative state[15-18]. Yet whether the effects are direct or indirect requires further study. All in all, these inconsistencies indicate that oxidative stress in schizophrenia may be independent from antipsychotic treatment.

Current studies on oxidative stress in schizophrenia mainly focus on enzymatic antioxidants, while limited studies have been carried out on non-enzymatic antioxidants. Some studies discovered that plasma non-enzymatic antioxidants (uric acid, bilirubin, and albumin) in schizophrenia are lower than those of healthy controls. Reddy et al. found that levels of UA, TBIL and ALB in schizophrenia were significantly lower than those of healthy controls and were affected by gender[19]. Widschwendter et al. carried out a retrospective study in 2016, and found that level of plasma TBIL in schizophrenic patients was significantly lower than the baseline at the end of the 2nd and the 4th week after treatment, while the latter decreased more substantially, which was correlated with positive subscale score of Positive and Negative Syndrome Scale (PANSS) [20]. But these findings were not reproduced in another similar study [7].

Previous studies on non-enzymatic antioxidants of patients with schizophrenia are limited and conflicting. Therefore, the objective of the present study is to investigate whether there are any differences in peripheral levels of non-enzymatic antioxidants between patients with schizophrenia and healthy individuals, as well as to observe the effect of antipsychotics on levels of non-enzymatic antioxidants.

Methods

Study population

A total of 107 schizophrenic patients (40 males, 67 females; mean age: 34.03±11.03 years, range: 18-57 years) in acute stage and 101 schizophrenic patients (37 males, 64 females; mean age: 35.36±11.31 years, range: 18-57 years) in remission stage were screened from outpatients and inpatients in Shandong Mental Health Center during May 2018 to May 2019. The control group consisted of 273 healthy individuals (93 males, 180 females; mean age: 34.92±9.22

years, range: 23-60 years) were invited with matched ages and genders. 107 schizophrenic patients in acute stage were followed up for 12 weeks, and their levels of non-enzymatic antioxidants were measured again at the end. Inclusion Criteria and exclusion criteria were as follows:

Inclusion criteria for schizophrenic patients in acute stage (SCZ-AS): (1) 18–60 years of age, Han Chinese; (2) Diagnosed with schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria; (3) PANSS total score ≥70.

Inclusion criteria for schizophrenic patients in remission stage (SCZ-RS): (1) 18–60 years of age, Han Chinese; (2) Previously diagnosed with schizophrenia based on

DSM-5; (3) PANSS total score ≤60, score ≤4 on 7 PANSS items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control) and Clinical Global Impressions-Severity of Illness (CGI-S) score ≤4 at least 6 months [21].

Inclusion criteria for healthy controls (HC): (1) 18–60 years of age, Han Chinese; (2) No history of psychiatric disorders.

Exclusion criteria applied for all groups: (1) Combined with brain organic diseases or brain trauma. (2) Hypertension, diabetes, gout or liver, kidney, biliary and other physical diseases or abnormal renal and liver function. (3) Combined with other mental disorders. (4) Positive in urine pregnancy test or lactating females. (5) Modified electroconvulsive therapy (MECT) treatment within 4 weeks, or long-acting antipsychotics treatment within 6 months; (6) Taking antioxidants or neurotrophic drugs within 12 weeks prior to and during enrollment.

The study protocol was approved by the Clinical Research Ethics Committee of Shandong Mental Health Center and is compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed written consent were obtained from all participants or their legal guardians after a complete and extensive description.

Measurements

The clinical psychiatric symptoms in schizophrenic patients were assessed by the Chinese PANSS. The psychiatrists (all authors) were simultaneously trained in the use of the PANSS before this study was initiated. After training, repeated assessments indicated that the inter-observer correlation coefficient was maintained at greater than 0.80 for the PANSS total score.

Five milliliters of fasting venous blood samples were drawn from participants between 7:00am and 7:30am. Serum samples were separated by centrifugation (3000 rpm for 10 min at 20 ℃) and stored at -80 ℃. Peripheral levels of UA, ALB, and TBIL were detected by Roche Cobas C702 automatic biochemical analyzer (Swiss Roche Diagnostics Co., Ltd.) according to the manufacturer's instructions.

Statistical analysis

The results were expressed as mean ± standard deviation. Differences in continuous variables among groups were assessed by the independent samples t-test and one-way analysis of variance. The chi-square test was applied to categorical data such as gender. The paired samples test was adopted to evaluate changes of UA, ALB, TBIL and PANSS total scores before and after treatment. The *Pearson* correlation analysis was adopted to analyze the relationship between antioxidant levels and PANSS. *P*-values <0.05 were considered statistically significant.

Results

Demographic and clinical data

Demographic and clinical characteristics of participants are summarized in Table 1. There were no differences in demographic data (gender and age) among three groups. The differences in clinical data (smoking history, family history and duration of illness) between SCZ-AS group and SCZ-RS group were not significant.

Table 1 Demographic characteristic and clinical data (Mean ± SD) of patients with schizophrenia and healthy controls.

Variables	SCZ-AS（n=107）	SCZ-RS （n=101）	HC （n=273）
Gender (male/female)	40/67	37/64	93/180
Age (years)	34.03±11.03	35.36±11.31	34.92±9.22
Smokers/non-smokers	10/97	11/90	26/247
Family history (positive/negative)	25/82	22/79	-
Duration of illness（months）	96.70±80.48	108.23±96.605	-
Drug naïve or free/ Drug use	51/56	-	-
PANSS total scores	93.21±16.46	45.44±8.40	-

SCZ-AS, schizophrenic patients in acute stage; SCZ-RS, schizophrenic patients in remission stage; HC, healthy control; PANSS, Positive and Negative Syndrome Scale.

SCZ-AS vs. HC

Compared with HC group, the levels of UA (t=3.170, P=0.020) and TBIL(t=8.166, P<0.001) in SCZ-AS group were higher, while level of ALB(t=-13.188, P<0.001) was lower. There was no significant difference in level of UA between males in HC and SCZ-AS group. Males' level of ALB (t=-6.435, P<0.001) in SCZ-AS group was lower than that of HC group, while level of TBIL (t=4.517, P<0.001) was higher. The levels of UA (t=2.937, P=0.004) and TBIL (t=7.984, P<0.001) of females in SCZ-AS group were higher than those of HC group, and level of ALB (t=-11.841, P<0.001) was lower.

SCZ-AS were divided into antipsychotics-use (AU) subgroup and antipsychotics-naïve/free (ANF) subgroup (unmedicated first episode schizophrenia or no antipsychotics was used within 8 weeks), then compared with the HC group. It was observed that levels of UA in ANF subgroup (P=0.001) and HC group (P<0.001) were lower than those of AU subgroup, and there was no significant difference in level of UA between the ANF subgroup and the HC group. Levels of ALB of AU subgroup (P<0.001) and ANF subgroup (P<0.001) were lower than those of HC group, and there was no significant difference in level of ALB between ANF subgroup and AU subgroup. Levels of TBIL of AU (P<0.001) subgroup and ANF subgroup (P<0.001) was higher than those of HC group, and the level of TBIL in ANF subgroup was higher than that of AU subgroup (P=0.002). Analogous results were obtained when analyzing the male and the female separately (Table 2).

Table 2 Peripheral levels of uric acid, albumin and total bilirubin in schizophrenic patients in acute stage and healthy controls.

Group	UA (μmol/L)	ALB (g/L)	TBIL(μmol/L)
SCZ-AS（n=107）	308.29±78.71†*	42.79±3.55†***	18.43±9.00†***
Male（n=40）	350.45±66.54	44.02±3.36†***	19.74±10.89†***
Female（n=67）	284.72±75.45†**	42.05±3.48†***	17.65±7.65†***
AU（n=56）	330.32±81.69†***,‡**	43.13±3.17†***	16.56±5.37†***,‡**
ANF（n=51）	286.19±68.94	42.40±3.92†***	20.47±11.49†***
HC（n=273）	283.41±68.61	48.01±3.28	10.87±5.18
Male（n=93）	338.69±52.42	48.93±4.29	12.97±6.24
Female（n=180）	254.84±57.72	47.54±2.49	9.78±4.16

*P<0.05; **P<0.01; ***P<0.001.

† Compared with healthy controls group. ‡ Compared with antipsychotics-naïve/free subgroup.

SCZ-AS, schizophrenic patients in acute stage; AU, antipsychotics-use; ANF, antipsychotics-naïve/free; HC, healthy control; UA, uric acid; ALB, albumin; TBIL, total bilirubin.

SCZ-RS vs. HC

Compared with HC group, the levels of UA (t=4.125, P<0.001) and TBIL (t=5.258, P<0.001) in SCZ-RS group were higher, while level of ALB (t=-21.616, P<0.001) was lower. Males' level of ALB (t=-10.213, P<0.001) in SCZ-RS group was lower than that of HC group, while levels of TBIL (t=2.613, P=0.010) and UA (t=3.439, P=0.001) was higher. The levels of UA (t=2.937, P=0.002) and TBIL (t=7.984, P<0.001) of females in SCZ-RS group were higher than those of HC group, and level of ALB (t=-11.841, P<0.001) was lower. (Table 3).

Table 3 Peripheral levels of uric acid, albumin and total bilirubin in schizophrenic patients in remission stage and healthy controls.

Group	UA (μmol/L)	ALB (g/L)	TBIL(μmol/L)
SCZ-RS（n=101）	323.19±87.48***	40.29±2.41***	14.39±7.03***
Male（n=37）	384.24±73.49**	41.41±1.98***	16.72±9.69**
Female（n=64）	287.89±74.87**	39.64±2.41***	13.03±4.45***
HC（n=273）	283.41±68.61	48.01±3.28	10.87±5.18
Male（n=93）	338.69±52.42	48.93±4.29	12.97±6.24
Female（n=180）	254.84±57.72	47.54±2.49	9.78±4.16

*P<0.05; **P<0.01; ***P<0.001.

SCZ-RS, schizophrenic patients in remission stage; HC, healthy control; UA, uric acid; ALB, albumin; TBIL, total bilirubin.

Comparison in levels of UA, ALB, TBIL and PANSS between pre- and post-treatment in SCZ-AS group

A continuous real world observation (12 weeks) of before and after treatment were performed on SCZ-AS. In this study, none limitation was conducted on the treatment, so that 30 patients in SCZ-AS group were dropped out from this part because of various reasons (such as using hypotensor, lipid-lowing drugs, hypoglycemic agents or antioxidants like vitamin E, receiving MECT, with abnormal liver function and so on).

There was no significant difference in level of UA before and after treatment, and both levels of ALB and TBIL decreased after treatment. The AU subgroup reached comparable result, but there was no significant difference in level of TBIL in males in AU subgroup before and after treatment. The level of UA increased after treatment in ANF subgroup, while both levels of ALB and TBIL decreased. There were no significant differences in levels of UA, ALB and TBIL in males in ANF subgroup before and after treatment. The difference of UA level in females in ANF subgroup before and after treatment was close to significance, and both levels of ALB and TBIL decreased after treatment. (Table 4)

There were significant differences on PANSS total scores between pre- and post-treatment. Furthermore, the relationship between PANSS total scores and antioxidant levels was not significant whether in acute stage or remission stage (acute stage: UA, *r*=-0.003, *P*=0.975; ALB, *r*=-0.042, *P*=0.666; TBIL, *r*=-0.033, *P*=0.737; remission stage: UA, *r*=0.149, *P*=0.136; ALB, *r*=0.039, *P*=0.695; TBIL, *r*=-0.196, *P*=0.050). (Table 4)

Table 4 Peripheral levels of uric acid, albumin, total bilirubin and PANSS total scores in schizophrenia before and after treatment.

Group	Before				After				$t_1/t_2/t_3/t_4$	
	UA (μmol/L)	ALB (g/L)	TBIL(μmol/L)	PANSS	UA (μmol/L)	ALB (g/L)	TBIL(μmol/L)	PANSS		
SCZ（n=77）	305.47±78.18	42.61±3.67	17.92±7.32	93.91±17.53	318.00±85.24	39.99±2.23	13.33±5.14	45.19±8.57	1.551/23.300/6.405/5.696	0.1
Male（n=27）	348.81±64.89	43.65±3.34	17.75±5.49	90.00±18.82	374.00±77.57	41.03±1.77	14.66±6.02	46.07±9.68	1.791/11.931/3.740/2.266	0.0
Female（n=50）	282.06±75.17	42.04±3.74	18.01±8.20	96.02±16.61	287.76±73.59	39.43±2.26	12.61±4.50	44.72±7.97	0.580/5.148/5.456/20.657	0.5
AU（n=36）	328.69±78.78	43.29±3.31	16.40±5.74	99.03±20.88	329.53±95.18	40.15±2.16	12.84±3.84	46.28±8.42	0.063/5.807/3.985/14.668	0.9
Male（n=15）	359.60±63.40	44.25±2.89	16.99±3.88	93.27±23.26	381.93±83.73	40.79±1.23	14.35±4.04	46.87±8.55	1.220/4.618/1.728/8.126	0.2
Female（n=21）	306.62±82.58	42.60±3.48	15.98±6.83	103.14±18.49	292.10±86.11	39.69±2.56	11.76±3.37	45.86±8.51	0.801/3.791/3.888/12.802	0.4
ANF（n=41）	285.07±72.60	42.00±3.89	19.25±8.32	89.41±12.58	307.88±75.19	39.86±2.30	12.84±6.08	44.24±8.68	2.366/3.592/4.262/20.221	0.0
Male（n=12）	335.33±66.93	42.90±3.83	19.25±8.32	85.92±10.79	364.08±71.46	41.33±2.31	12.84±6.08	45.08±11.24	1.264/1.269/1.476/9.456	0.2
Female（n=29）	264.28±65.10	41.63±3.92	19.47±8.88	90.86±13.15	284.62±64.48	39.25±2.04	13.23±5.14	43.90±7.59	2.007/3.500/4.136/18.207	0.0

AU, antipsychotics-use; ANF, antipsychotics-naïve/free; UA, uric acid; ALB, albumin; TBIL, total bilirubin; PANSS, Positive and Negative Syndrome Scale.

t1/t2/t3/t4 and P1/P2/P3/P4 are respectively the statistic of UA, ALB, TBIL and PANSS.

Table 5 Medication data

	Remission group		AU group		Pre- and post-treatment	
	cases	doses(mg/day)	cases	doses(mg/day)	cases	doses(mg/day)
Antipsychotics						
Perphenazine	3	17.33±8.33	5	17.60±11.52	6	19.33±10.86
Sulpiride	-	-	1	600.00	-	-
Risperidone	45	5.36±1.32	26	4.52±1.89	53	4.86±1.55
Amisulpride	7	885.71±302.37	9	600.00±300.00	14	650±295.48
Olanzapine	10	13.50±2.42	16	14.38±8.39	18	14.44±4.50
Ziprasidone	2	140±28.28	4	80±46.19	2	100±84.85
Quetiapine	7	285.71±89.97	9	327.78±207.83	14	296.43±171.49
Clozapine	13	153.85±96.74	12	176.04±162.23	10	111.25±110.62
Aripiprazole	16	15.31±9.74	22	17.05±7.82	22	18.09±10.08
Mood stabilizers						
Valproate	3	700.00±255.84	2	700.00±278.65	5	675.56±245.09
Lithium	2	425.00±206.16	1	560.00±251.00	3	478.57±191.17
Lamotrigine	-	-	1	37.50	-	-
Antidepressants						
Escitalopram	3	10.00±5.00	-	-	4	10±4.08
Fluvoxamine	-	-	1	75	-	-
Sertraline	2	50.00	5	60.00±22.36	3	50.00
Paroxetine	2	40.00	-	-	1	20.00
Trazodone	1	50.00	-	-	-	-

AU, antipsychotics-use.

Discussion

Schizophrenia has a complex pathophysiological mechanism associated with free radical-mediated neurotoxicity[4]. The effectiveness of the antioxidant defense system on ROS depends not only on its enzymatic component, but also on the non-enzymatic composition[22]. Non-enzymatic antioxidants are mainly composed of albumin, bilirubin and uric acid, which can alleviate oxidative stress by chelating with metal ions and directly capturing radicals in hydroxyl and/or carbon center, accounting for more than 85% of total plasma antioxidant capacity. Clinically, those indicators can be monitored to detect the presence of oxidative stress damage in vivo[23, 24].

UA is the end product of purine metabolism. Increased UA levels can affect the activity of other neurotransmitters, including dopamine, gamma-aminobutyric acid, glutamic acid and 5-hydroxytryptamine, which are involved in the pathophysiological mechanism of schizophrenia. Moreover, UA is also a selective antioxidant, whose level is considered as a marker of oxidative stress. Properly increased UA can enhance body's antioxidant capacity. In this study, level of UA in SCZ patients was higher than that of HC, both in acute and remission stage, which is confirmed by another recent study[25], but inconsistent with the results of Reddy et al. and Yao et al.[19, 26], in which patients involved were first-episode, but the effects of antipsychotics were not excluded in this study. Due to the

limitation of sample size, this study only reclassified SCZ-AS into AU subgroup and ANF subgroup. The results showed level of UA in AU subgroup was higher than that of ANF subgroup and HC group, and there was no difference in level of UA between HC group and ANF subgroup. This suggests that elevated level of UA may be related to the use of antipsychotics. This study also noticed that there was no statistically difference in level of UA before and after treatment in AU subgroup, but level of UA increased after treatment in ANF subgroup, which further confirmed the conclusion that the use of antipsychotics could affect level of UA. However, when analyzing by gender, there was no statistically difference in level of UA before and after treatment, whether in male or female groups. The difference of UA in female patients before and after treatment was close to significant (P=0.055), implying that female patients may be more susceptible to oxidative stress. Similar results were collected in previous studies[27, 28].

ALB is an endogenous antioxidant with radical scavenging properties that inhibits lipid peroxidation so as to directly scavenge certain radicals. In this study, whether in acute or remission stage, level of ALB in SCZ was lower than that of HC, and decreased after treatment, which was consistent with the previous study[29], indicating that ALB in patients with SCZ was constantly persistently consumed in acute and remission stage. In spite of the fact that albumin levels decreased in acute and remission stage as well as after treatment, the decline was modest, and the albumin levels of patients with SCZ in every stage were still in normal range. It may be due to the liver generating albumin continuously. Results of a five-year follow-up study of antioxidants levels in schizophrenia conducted by Dag K. Solberg et al. showed that differences on ALB levels between schizophrenic patients in remission stage and healthy individuals were not significant [30], which was not in coincidence with our result. It may be due to the observation duration of this study was relatively short that the patients might be still in an acute oxidative stress stage. Besides, there was no significant difference in level of ALB between the AU subgroup and ANF subgroup, suggesting that antipsychotics had little effect on the level of ALB.

Bilirubin is the end product of heme-catabolism that participates in antioxidative mechanism by efficiently scavenging peroxyl radicals and acting as a chain breaking antioxidant[31]. In this study, it was noted that level of TBIL in SCZ was higher than that of HC, both in acute and remission stage, which was confirmed by another recent study[25]. It revealed that SCZ patients may have higher oxidative stress status and the elevated serum bilirubin may be a result of the increasing fragility of erythrocyte membrane under oxidative stress[29, 32]. At the same time, the pro-oxidant effect of heme oxygenase may outrun the antioxidant property of bilirubin[33]. Contrary to our results, previous studies derived that level of TBIL in SCZ was lower than that of HC [19, 26, 34-36], which might be caused by heterogeneity of the sample. Again, this study points out that level of TBIL in AU subgroup was lower than that of ANF subgroup, and decreased after treatment. It indicated that antipsychotics may have the effect of antioxidative stress, which is in line with previous studies[13, 15]. In this study, there was no significant difference in level of TBIL before and after treatment in males in AU subgroup and ANF subgroup, while female patients had lower TBIL after treatment, confirming that females were more susceptible to oxidative stress. Although, it must be made clear that bilirubin is transported as an albumin binding complex in plasma, and the consumed plasma albumin may be the cause of the decrease in bilirubin.

There are a few limitations in this study. Firstly, the levels of peripheral albumin, bilirubin and uric acid are susceptible to diet, but this study did not strictly control the dietary. Speaking of which , a previous study did control the dietary factors, but came up with analogous findings[28]. Besides, the three non-enzymatic antioxidants can be affected by many factors, such as weight, glucose and lipid metabolism[37, 38]. Even though some controls were made in this study, there are still some influences cannot be excluded. Secondly, although previous studies showed that the antioxidant capacity of albumin, bilirubin and uric acid accounted for more than 85% of the total antioxidant capacity of plasma, more indicators should be investigated to further verify the conclusion (including total antioxidant capacity, lipid peroxides, etc.). Thirdly, some studies suggested that the peripheral antioxidant capacity is consistent with the central nervous system[39]. As a matter of fact, the peripheral status is merely an indirect evidence, which is not the same with the central nervous system. Fourthly, the study did not limit the treatment, so the types of antipsychotics in patients were various and most of patients were treated with two types of antipsychotics, therefore, it is difficult for us to analyze the relationship between non-enzymatic antioxidant levels and a certain type of antipsychotic. Fifthly, 2/3 of the included patients were female in this study, which resulted in the selection bias. Future studies should improve this part. Finally, this study only performed a 12-week observation on the SCZ-AS patients, while a longer observation is necessary. Beyond that, a larger sample size can be expected for this study.

Conclusions

This study observed that TBIL in SCZ was higher than that of HC, and decreased after treatment, suggesting that patients with schizophrenia have a higher oxidative stress status both in acute and remission stage. Antipsychotics may have an antioxidant effect. The increased level of UA in SCZ may be associated with the use of antipsychotics. Moreover, there may be a constant consumption of ALB during the acute and remission stage. In summary, the dysfunction of peripheral non-enzymatic anti-oxidation system may be involved in the pathogenesis of schizophrenia, and females may be more susceptible to oxidative stress.

Abbreviations

SCZ, schizophrenia; SCZ-AS, schizophrenic patients in acute stage; SCZ-RS, schizophrenic patients in remission stage; HC, healthy control; AU, antipsychotics-use; ANF, antipsychotics-naïve/free; UA, uric acid; ALB, albumin; TBIL, total bilirubin; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impressions-Severity of Illness; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ROS, oxygen species; RNS, reactive nitrogen; MECT, modified electroconvulsive therapy.

Declarations

Acknowledgment

The authors would like to thank patients with schizophrenia in Shandong Mental Health Center and healthy individuals in this study for their support and participation.

Authors' contributions

GLX and ZL conceived and designed the study. ZL, YTW and WJK were involved in data acquisition. ZL and TYW processed and analyzed the data. GLX and ZL discussed the results and wrote the manuscript. All authors read and approved the finalized manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This research was approved by the Human Ethics Committee of Shandong Mental Health Center. All patients were provided with written informed consents. Participation was voluntary and participants could withdraw at any time during the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Author details

[1] School of Medicine, Shandong University, 44# Wenhua Western Road, Jinan 250012, China. [2] Shandong Mental Health Center, 49# Wenhua Eastern Road, Jinan 250014, China. [3] Department of Mental Health, Jining Medical University, 133# Hehua Road, Beihu New District, Jining 272067, China. [4] Beijing An Ding Hospital, Capital Medical University, China National Clinical Research Center for Mental Disorders, Beijing, People's Republic of China.

References

1.Lohr JB. Oxygen radicals and neuropsychiatric illness. Some speculations. Arch Gen Psychiatry. 1991;48(12):1097-106.10.1001/archpsyc.1991.01810360061009

2.Lai CY, Scarr E, Udawela M, Everall I, Chen WJ, Dean B. Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics. World journal of psychiatry. 2016;6(1):102-17.10.5498/wjp.v6.i1.102

3.Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. The international journal of biochemistry & cell biology. 2007;39(1):44-84.10.1016/j.biocel.2006.07.001

4.Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxidants & redox signaling. 2011;15(7):2011-35.10.1089/ars.2010.3603

5.Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. European journal of medicinal chemistry. 2015;97:55-74.10.1016/j.ejmech.2015.04.040

6.Moniczewski A, Gawlik M, Smaga I, Niedzielska E, Krzek J, Przegalinski E, et al. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 1. Chemical aspects and biological sources of oxidative stress in the brain. Pharmacological reports : PR. 2015;67(3):560-8.10.1016/j.pharep.2014.12.014

7.Sarandol A, Sarandol E, Acikgoz HE, Eker SS, Akkaya C, Dirican M. First-episode psychosis is associated with oxidative stress: Effects of short-term antipsychotic treatment. Psychiatry Clin Neurosci. 2015;69(11):699-707.10.1111/pcn.12333

8.Pandya CD, Howell KR, Pillai A. Antioxidants as potential therapeutics for neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:214-23.10.1016/j.pnpbp.2012.10.017

9.Bulbul F, Virit O, Alpak G, Unal A, Bulut M, Kaya MC, et al. Are oxidative stress markers useful to distinguish schizoaffective disorder from schizophrenia and bipolar disorder? Acta neuropsychiatrica. 2014;26(2):120-4.10.1017/neu.2013.44

10.Koga M, Serritella AV, Sawa A, Sedlak TW. Implications for reactive oxygen species in schizophrenia pathogenesis. Schizophr Res. 2016;176(1):52-71.10.1016/j.schres.2015.06.022

11.Yao JK, Leonard S, Reddy RD. Increased nitric oxide radicals in postmortem brain from patients with schizophrenia. Schizophrenia bulletin. 2004;30(4):923-34.10.1093/oxfordjournals.schbul.a007142

12.Radonjic NV, Knezevic ID, Vilimanovich U, Kravic-Stevovic T, Marina LV, Nikolic T, et al. Decreased glutathione levels and altered antioxidant defense in an animal model of schizophrenia: long-term effects of perinatal phencyclidine administration. Neuropharmacology. 2010;58(4-5):739-45.10.1016/j.neuropharm.2009.12.009

13.Al-Chalabi BM, Thanoon IA, Ahmed FA. Potential effect of olanzapine on total antioxidant status and lipid peroxidation in schizophrenic patients. Neuropsychobiology. 2009;59(1):8-11.10.1159/000202823

14.Eftekhari A, Azarmi Y, Parvizpur A, Eghbal MA. Involvement of oxidative stress and mitochondrial/lysosomal cross-talk in olanzapine cytotoxicity in freshly isolated rat hepatocytes. Xenobiotica; the fate of foreign compounds in biological systems. 2016;46(4):369-78.10.3109/00498254.2015.1078522

15.Brinholi FF, Farias CC, Bonifacio KL, Higachi L, Casagrande R, Moreira EG, et al. Clozapine and olanzapine are better antioxidants than haloperidol, quetiapine, risperidone and ziprasidone in in vitro models. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2016;81:411-5.10.1016/j.biopha.2016.02.047

16.Parikh V, Khan MM, Mahadik SP. Differential effects of antipsychotics on expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res. 2003;37(1):43-51.10.1016/s0022-3956(02)00048-1

17.Dietrich-Muszalska A, Kopka J, Kwiatkowska A. The effects of ziprasidone, clozapine and haloperidol on lipid peroxidation in human plasma (in vitro): comparison. Neurochemical research. 2013;38(7):1490-5.10.1007/s11064-013-1050-z

18.Singh OP, Chakraborty I, Dasgupta A, Datta S. A comparative study of oxidative stress and interrelationship of important antioxidants in haloperidol and olanzapine treated patients suffering from schizophrenia. Indian journal of psychiatry. 2008;50(3):171-6.10.4103/0019-5545.43627

19.Reddy R, Keshavan M, Yao JK. Reduced plasma antioxidants in first-episode patients with schizophrenia. Schizophr Res. 2003;62(3):205-12.10.1016/s0920-9964(02)00407-3

20.Widschwendter CG, Rettenbacher MA, Kemmler G, Edlinger M, Baumgartner S, Fleischhacker WW, et al. Bilirubin concentration correlates with positive symptoms in patients with schizophrenia. The Journal of clinical psychiatry. 2016;77(4):512-6.10.4088/JCP.14m09642

21.Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. American Journal of Psychiatry. 2005;162(3):441-9.10.1176/appi.ajp.162.3.441

22.Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet. 1994;344(8924):721-4.10.1016/s0140-6736(94)92211-x

23.Miller NJ, Rice-Evans C, Davies MJ, Gopinathan V, Milner A. A novel method for measuring antioxidant capacity and its application to monitoring the antioxidant status in premature neonates. Clinical science (London, England : 1979). 1993;84(4):407-12.10.1042/cs0840407

24.Maxwell SR, Dietrich T, Chapple IL. Prediction of serum total antioxidant activity from the concentration of individual serum antioxidants. Clinica chimica acta; international journal of clinical chemistry. 2006;372(1-2):188-94.10.1016/j.cca.2006.04.015

25.Solberg DK, Refsum H, Andreassen OA, Bentsen H. A five-year follow-up study of antioxidants, oxidative stress and polyunsaturated fatty acids in schizophrenia. Acta neuropsychiatrica. 2019:1-11.10.1017/neu.2019.14

26.Yao JK, Dougherty GG, Jr., Reddy RD, Keshavan MS, Montrose DM, Matson WR, et al. Homeostatic imbalance of purine catabolism in first-episode neuroleptic-naive patients with schizophrenia. PLoS One. 2010;5(3):e9508.10.1371/journal.pone.0009508

27.Wiener C, Rassier GT, Kaster MP, Jansen K, Pinheiro RT, Klamt F, et al. Gender-based differences in oxidative stress parameters do not underlie the differences in mood disorders susceptibility between sexes. Eur Psychiatry. 2014;29(1):58-63.10.1016/j.eurpsy.2013.05.006

28.Dadheech G, Sharma P, Gautam S. Oxidative Stress-Induced Response of Some Endogenous Antioxidants in Schizophrenia. Indian J Clin Biochem. 2012;27(3):278-83.10.1007/s12291-012-0193-z

29.Chen S, Xia HS, Zhu F, Yin GZ, Qian ZK, Jiang CX, et al. Association between decreased serum albumin levels and depressive symptoms in patients with schizophrenia in a Chinese Han population: A pilot study. Psychiatry Res. 2018;270:438-42.10.1016/j.psychres.2018.10.012

30.Solberg DK, Refsum H, Andreassen OA, Bentsen H. A five-year follow-up study of antioxidants, oxidative stress and polyunsaturated fatty acids in schizophrenia. Acta Neuropsychiatr. 2019;31(4):202-12.10.1017/neu.2019.14

31.Stocker R, Glazer AN, Ames BN. Antioxidant activity of albumin-bound bilirubin. Proceedings of the National Academy of Sciences. 1987;84(16):5918-22.10.1073/pnas.84.16.5918

32.Muller N, Schiller P, Ackenheil M. Coincidence of schizophrenia and hyperbilirubinemia. Pharmacopsychiatry. 1991;24(6):225-8.10.1055/s-2007-1014472

33.Dani C, Martelli E, Bertini G, Pezzati M, Filippi L, Rossetti M, et al. Plasma bilirubin level and oxidative stress in preterm infants. Archives of disease in childhood Fetal and neonatal edition. 2003;88(2):F119-23.10.1136/fn.88.2.f119

34.Pae CU, Paik IH, Lee C, Lee SJ, Kim JJ, Lee CU. Decreased plasma antioxidants in schizophrenia. Neuropsychobiology. 2004;50(1):54-6.10.1159/000077942

35.Reddy RD, Keshavan MS, Yao JK. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naive baseline. Schizophrenia bulletin. 2004;30(4):901-11.10.1093/oxfordjournals.schbul.a007140

36.Vitek L, Novotna M, Lenicek M, Novotny L, Eberova J, Petrasek J, et al. Serum bilirubin levels and UGT1A1 promoter variations in patients with schizophrenia. Psychiatry Res. 2010;178(2):449-50.10.1016/j.psychres.2009.12.008

37.Godin O, Leboyer M, Gaman A, Aouizerate B, Berna F, Brunel L, et al. Metabolic syndrome, abdominal obesity and hyperuricemia in schizophrenia: Results from the FACE-SZ cohort. Schizophr Res. 2015;168(1-2):388-94.10.1016/j.schres.2015.07.047

38.Chiu CC, Chen CH, Huang MC, Chen PY, Tsai CJ, Lu ML. The relationship between serum uric acid concentration and metabolic syndrome in patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol. 2012;32(5):585-92.10.1097/JCP.0b013e3182664e64

39.Siciliano G, Piazza S, Carlesi C, Del Corona A, Franzini M, Pompella A, et al. Antioxidant capacity and protein oxidation in cerebrospinal fluid of amyotrophic lateral sclerosis. Journal of neurology. 2007;254(5):575-80.10.1007/s00415-006-0301-1