Correlation between Glutathione Levels and Severity Symptoms among Bataknese Male patients with Schizophrenia

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Abstract

Background: Oxidative stress has been implicated as a part of the pathophysiological mechanisms of Schizophrenia. Oxidative stress occurs due to the imbalance of antioxidants and oxidants. Glutathione is one of the primary antioxidants that contribute to the oxidative-stress-preventable mechanism. The correlation between oxidative stress, glutathione deficiency, and schizophrenic pathophysiology has been reported in previous clinical studies. The reduction of glutathione, particularly in schizophrenic symptomatology (especially in negative and positive symptoms), has been characterized.

Methods: A cross-sectional study recruited 48 Bataknese males with Schizophrenia who have been administered atypical antipsychotic medications for at least a year. The glutathione levels were measured by the ELISA Method to calculate the quantitative results of GSH concentration within the blood plasm in *vitro*. The severity of symptoms was characterized via the Positive and Negative Syndrome Scale (PANSS).

Results: Our study found a significant correlation between glutathione levels and the severity of symptoms of Schizophrenia ($p<0.05$). The Pearson correlation value was -0.587, a negative value with medium correlation strength.

Conclusion: Our findings support the fact that oxidative stress is one of the pathophysiological mechanisms of Schizophrenia. This study also showed that a low glutathione level is associated with the severity of symptoms of Bataknese males with Schizophrenia.

Keywords: Schizophrenia, Oxidative Stress, Glutathione, GSH, Positive-Negative Symptoms, *Positive and Negative Syndrome Scale* (PANSS).

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Introduction

Schizophrenia is a severe mental disorder characterized by regular recurrence, cognitive dysfunction, and psychosocial disabilities.[1] Manifestation among patients varies. However, the schizophrenic symptoms are often severe as well as longer lasting.[2] Schizophrenic remains a global mental disorder that affects the economic burden of health. Usually, the onset of Schizophrenia begins in early life and causes significant disturbances in a long period of suffering. Therefore, it takes longer treatments and high costs due to hospital and clinical therapies, rehabilitation, and continuous support services. One systematic review reported that the economic burden due to Schizophrenia contributed to 1.7% of global disabilities. [3] Despite its poor recovery rates, those with Schizophrenia also have a significantly low life expectancy. [3],[4]

Some theories have been proposed to explain Schizophrenia, starting from the development process, neurodegenerative state, and neurotransmitter disorders to infection or autoimmune mechanisms. Schizophrenia neuropathology has different hypotheses that have been pointed out, including the neurology and neurochemistry theories. [5] Several attempts to describe the roots of molecular mechanisms of Schizophrenia have been developed. Some studies have considered that damage in nerve systems within schizophrenia pathophysiology is suspected of being related to oxidative stress. [6] This stress may occur due to excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) molecules. As a result, too many oxidants that cannot be reduced would trigger an imbalance between oxidative and antioxidant systems. [7] An increase in oxidative stress and damage in antioxidant defence systems have been characterized as early Schizophrenia. Thus, enriched antioxidant diets have been proposed as promising strategies to delay the development of Schizophrenia. [1],[6]

Glutathione (*γ-glutamyl-cysteinyl-glycine*; *glutathione disulfide;* GSH) is an abundance of low-molecules of thiol. It is the main protein based on redox reactions found in animal cells. In terms of its contribution to oxidative stress, glutathione contributes significantly in acting as a defence antioxidant, nutritional metabolism, and cellular regulator, in which ageing and many pathogenes of illness are related to the lack of glutathione.[8]

Glutathione is the major intracellular antioxidant in the brain. It has many roles in maintaining redox balance in the N-methyl-D-aspartate (NMDA) neurotransmitter involved in the pathophysiology of Schizophrenia and protecting cells against oxidative stress.[7],[8] Studies conducted by Nucifora et al. in 2017 showed a significant decrease in glutathione levels in patients with Schizophrenia and bipolar disorder compared to the control group. The decrease in glutathione levels also correlates with the total Positive and Negative Syndrome Scale (PANSS) and positive scores in patients with Schizophrenia. This study provides evidence that there is a decrease in peripheral glutathione levels in the psychosis dimension.[9]

The study by Langbein et al. in 2017 supports the idea of changes in the antioxidant defence of glutathione in untreated acute psychosis as a potential pathomechanism for localized brain structural abnormalities. This pathology is associated with the brain regions responsible for social cognition, affective and motivational control, and decision-making. The emergence of depressive and negative symptoms clinically accompanies it. The study found that glutathione reductase (GSR) activity in first-episode psychosis patients was lower than in the control group. GSR activity in plasma was inversely correlated with the PANSS score for negative symptoms.[10]

Subject and Method:

This correlational analytic study with a cross-sectional approach aims to assess the correlation between glutathione levels and positive-negative symptoms in 48 Bataknese male samples with Schizophrenia. The study was conducted at the Outpatient Installation of Dr. Pirngadi Regional General Hospital Medan from September 2022 to May 2023. Glutathione level examination was performed at the Integrated Research Laboratory Technical Unit of the Faculty of Medicine, Universitas Sumatera Utara. Inclusion criteria for this study were male Batak ethnicity with first-episode Schizophrenia diagnosed fulfils DSM-5 criteria for Schizophrenia, aged between 20-

40 years, able to understand Indonesian language, willing to be a respondent and be interviewed, have a smoking frequency of ≤ 10 cigarettes/day (light smoker), and have received atypical antipsychotic therapy for at least 12 weeks. After obtaining written consent from the sample, the subject's demographic data were collected, and blood samples were taken and examined using the ELISA method to determine the in vitro quantitative concentration of GSH in plasma. Then, PANSS scores were calculated, and the researchers checked for interrater reliability using the Bland-Altman plot. Statistical analyses were performed using SPSS. The Shapiro-Wilk normality test was performed on GSH levels and PANSS scores and showed normal distributions. Correlation between GSH levels and PANSS was performed using the Pearson correlation test. All data were expressed as median, mean ± standard deviation (s.d.). Statistical significance was defined as $P<0.05$.

Results

The demographic data reveals that the median age of the ODS subjects is 36.5 years old. The highest level of education attained by the ODS subjects was a high school diploma, which accounts for 72.9% of the group, followed by junior high school at 20.8% and college at 6.3%. Most ODS subjects were unmarried at 70.8%, while the remaining 29.2% were married. Most ODS subjects were unemployed, accounting for 68.8% of the group. The median duration of illness was 4.5 years, ranging from 1 to 10 years.

Table 1. Demographical Characteristics

Demographical Characteristics	Median (minimum-maximum)	N	(%)
Ages	36.5 (20-40)		
Educational Levels			
Junior High School		10	20,8
Senior High School		35	72,9
Bachelor Degree		3	6,3
Job Status			
Working		15	31,3
Not Working		33	68,8
Marital Status			
Married		14	29,2
Not-Married		34	70,8
Duration of Illness	4,5 (1-10)		

The mean glutathione level in the study subjects was 10.54 µg/ml with a standard deviation 3.85. The mean PANSS score in the study subjects was 57.92, with a standard deviation 8.45.

Table 2. Glutathione Levels and PANSS Score on Bataknese Males with Schizophrenia

	n	$mean \pm$SD (ug/ml)
Glutathione Levels	48	10.54±3,85
PANSS Score		57.92±8,45

The results of the Pearson correlation analysis between glutathione levels and severity symptoms in Batak male patients with Schizophrenia yielded an r-value of -0.587 with a p-value <0.05. This indicates that the lower the glutathione levels, the more severe the symptoms.

positive-negative symptoms in male Bataknese schizophrenia patients.
Table 3. The result of Pearson correlation analysis between glutathione levels and

	Glutathione Levels
PANSS Score	r = -0.587 p < 0,05 n = 48

Discussion

In this study, the median age of the research subjects was 36.5 years old. The mean age of individuals with Schizophrenia varies across countries.[11] A study by Raffa et al. in Tunisia found a mean age of 32.2 years for individuals with Schizophrenia.[12] This study also found that the highest level of education among the research subjects was high school (72.9%), which is consistent with the findings of Pardosi et al. in a study of the Batak ethnic group, where they found that 38.1% of the subjects had completed junior high school, 57.1% had completed high school, and 4.8% had a bachelor's degree. The study also found that 70% of the subjects were unmarried and 68% were unemployed, which is consistent with a previous study by Yildiz et al. in Turkey that involved 720 individuals with Schizophrenia, which found that 68% of the subjects were never married, 56% were unemployed, and 69% lived with their parents.[13] According to Steven Marwaha and Sonia Johnson's 2004 study, deficient employment levels are not intrinsic to Schizophrenia but seem to reflect the interaction between patients' social and economic pressures, the labour market, and psychological and social barriers to employment.[14]

This study found that the mean glutathione level in individuals with Schizophrenia was 10.54±3.85 µg/ml. A previous study by Raffa et al. in Tunisia 2008 found significantly lower levels of glutathione in individuals with Schizophrenia compared to healthy controls. The mean glutathione level in healthy controls was 802.8±269.2 µmol/L, while the mean level in individuals with Schizophrenia undergoing treatment was 654.0±248.4 µmol/L.[11] Similar results were found in another study by Nucifora et al. in Washington, D.C., in 2017, which showed a decrease in glutathione levels in individuals with Schizophrenia compared to the control group (mean healthy control level 1,736±1,766 µM, mean level in individuals with Schizophrenia 0.365±0.478 µM).[9] Another study that is consistent with this study was conducted by Ivanova et al. in Russia in 2015, where glutathione levels were lower in individuals with Schizophrenia compared to the control group, both before and after treatment (mean healthy control level of glutathione 394.23±80.20 µg/ml, mean level in individuals with Schizophrenia before treatment 298.54±41.02 µg/ml and after treatment 261.64±20.32 µg/ml).[14]

This study found a correlation between glutathione levels and the severity of symptoms in Batak male patients with Schizophrenia. This correlation was statistically significant, with a moderate correlation strength. This is consistent with a study by Nucifora et al. in 2017, which showed a significant correlation between PANSS total scores and GSH levels in a population of patients with Schizophrenia.[9] Another study by Dobrin et al. in Romania 2014 also found a significant correlation between oxidative stress markers, including glutathione, and PANSS scores. The results of this study provide additional evidence of the implications of oxidative stress in patients with Schizophrenia.[15]

When glutathione levels decrease, there is a potential for increased cellular oxidative stress, characterized by an increase in reactive oxygen species (ROS). Oxidative stress is known to be involved in the pathology of Schizophrenia, which is caused by changes in dopaminergic and glutamatergic activity. Glutamate and dopamine are highly reactive redox molecules that produce ROS during normal nerve transmission. Changes in these neurotransmitter pathways can increase oxidative stress in the brain. Furthermore, mitochondrial dysfunction, as a source of oxidative stress, is also found in patients with Schizophrenia. Combining these two factors contributes to the severity of the disease symptoms.[16]

A study by Sedlak et al. in 2017 from Johns Hopkins University found that using sulforaphane supplements from broccoli sprouts may increase GSH levels, which could potentially be used to alleviate neuropsychiatric symptoms, including Schizophrenia.[17] Although it requires further research, this study opens up the

potential for combining antipsychotic medication with antioxidants as a potentially effective treatment strategy for Schizophrenia.[7] Tsugawa et al. also stated that although further research is needed better to explain the disrupted function of glutathione in Schizophrenia, it could lead to the development of new therapeutic strategies for Schizophrenia.[5]

Limitations

This study has limitations, as a healthy control group is lacking.

Conclusion

In conclusion, there is a negative correlation between glutathione levels and the severity of symptoms in Batak male schizophrenia patients. This indicates that the low glutathione levels are associated with severe symptoms in Batak male schizophrenia patients. With the significant correlation found between glutathione levels and the severity of symptoms, this can serve as a reference for considerations on education related to dietary habits and the provision of glutathione supplementation as an additional effort to improve symptoms in people with Schizophrenia. However, further studies are still needed regarding such interventions' effectiveness and potential side effects.

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