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Original Article

The Association of Serum Lactoferrin Level with Psychological Symptoms, Cognition, and Executive Function in Schizophrenia Patients

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Abstract

Objective: Lactoferrin, a glycoprotein, has known neuroprotective effects, yet its role in the pathophysiology of neuropsychiatric disorders, particularly schizophrenia, remains unclear. This study aims to assess changes in lactoferrin levels during different phases of schizophrenia and explore its relationship with cognitive symptoms and performance.
Method: This before/after interventional study involved 30 patients diagnosed with schizophrenia. Participants were evaluated at two time points: upon hospital admission and after the resolution of acute symptoms. The Positive and Negative Syndrome Scale (PANSS) was utilized to measure symptom severity, while the Brief Assessment of Cognition in Schizophrenia (BACS) assessed the neurocognitive function. Serum lactoferrin levels were quantified using the Enzyme-Linked Immunosorbent Assay (ELISA) method.
Results: Serum lactoferrin levels significantly decreased from 130.63 ± 52.49 ng/mL at admission to 85.42 ± 29.03 ng/mL at discharge ($P < 0.001$). No significant correlation was found between lactoferrin levels and PANSS scores ($r = 0.011$, $P = 0.975$). However, an inverse correlation was observed between changes in lactoferrin levels and the executive function subscale of the BACS ($r = -0.360$, $P = 0.050$). Cognitive assessments indicated significant improvements in verbal memory ($P = 0.033$), working memory ($P = 0.002$), and executive function ($P = 0.039$) post-treatment.
Conclusion: The study demonstrates a significant reduction in serum lactoferrin levels during the acute phase of schizophrenia, suggesting its potential role in modulating cognitive functions, particularly the executive function, rather than influencing positive or negative symptoms.

Key words: *Cognitive Dysfunction; Lactoferrin; Neurodegenerative Diseases; Schizophrenia; Neuropsychiatric Disorder*

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Schizophrenia is a complex and multifaceted psychiatric disorder that affects approximately 1% of the global population. According to studies, cognitive deficits are of the main features of this disorder, mainly in the fields of executive function, thought processing speed, verbal memory, working memory, and verbal fluency (1, 2). The pathophysiology of this disease has not yet been precisely determined. In recent decades, the roles of the immune and inflammatory systems in schizophrenia have been revealed, emphasizing oxidative stress and neuroinflammation (3, 4). The central nervous system is affected by peripheral inflammation, leading to neuronal destruction in the hippocampus and cortex, which leads to cognitive disorders and memory deficits (5). Neurodegeneration and neurodevelopment are two other possible theories for describing the mechanism of schizophrenia. The main mechanism in the pathogenesis of neurodegenerative diseases consists of oxidative stress, neuronal inflammation, and iron and lipid metabolism imbalance (6). Neurodevelopmental theory suggests that brain differentiation arrests during the early stages of life which can be the reason for the onset of symptoms in the future (7). The data suggest a combination of neurodevelopmental and neurodegenerative processes in the etiology of schizophrenia (8). Studies suggest that neurodevelopmental disorders mainly lead to neuropsychiatric syndromes, especially schizophrenia and bipolar disorder (9).

Lactoferrin is a glycoprotein with a molecular weight of approximately 80 kDa, found in various biological fluids, including milk and saliva (10). It exhibits antimicrobial, anti-inflammatory, and immunomodulatory effects, which may play a crucial role in maintaining central nervous system (CNS) homeostasis (11). Studies have indicated that lactoferrin can influence neurodevelopment and protect against neurodegenerative processes, suggesting its relevance in psychiatric conditions, including schizophrenia (12, 13).

Despite the growing body of evidence supporting the involvement of lactoferrin in neuroinflammation, its specific role in schizophrenia remains largely unexplored. This limitation is related to the role of lactoferrin in the regulation of neurogenesis and neuronal proliferation, differentiation, migration, and neuronal communication. High levels of lactoferrin in patients suffering from schizophrenia indicate the function of neutrophils, eosinophils, granulocytes, macrophages/monocytes, and lymphocytes, which could indicate inflammatory responses in these patients (14).

Although extensive studies have explored the relationship between gradual aging and prevalent neurodegenerative diseases, such as Alzheimer and Parkinson, except the study conducted by Hallgren *et al*. (15), there is a lack of significant and broad evaluations of the relationship between lactoferrin and schizophrenia. Given the potential implications of lactoferrin levels in the pathophysiology of schizophrenia, this study aims to evaluate changes in serum lactoferrin levels in patients with schizophrenia during the acute phase of the disorder and after symptom resolution. Additionally, we will examine the relationship between lactoferrin levels, clinical symptoms measured by the Positive and Negative Syndrome Scale (PANSS), and cognitive performance assessed through the Brief Assessment of Cognition in Schizophrenia (BACS). This study seeks to provide insights into the potential associations between lactoferrin levels and cognitive function in schizophrenia, contributing to a better understanding of the disorder's neurobiological underpinnings.

Materials and Methods

Inclusion Criteria

The inclusion criteria consisted of patients aging between 18 and 65, diagnosed with schizophrenia using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5, SCID-5), which was confirmed by two psychiatrists. The patients were also included if at least two years had passed from the onset of their disease, they experienced a recent exacerbation, other psychiatric and neurological disorders were absent, they had a negative history of head injury and recent infectious diseases, and they had not consumed alcohol and drugs at least for the past six months.

Study Design

This study utilizes a before-and-after design with a cohort of 30 patients diagnosed with schizophrenia, hospitalized between August 2022 and December 2022. Ensuring accurate data representation, the study emphasizes reliability, honesty, and confidentiality in handling findings. Patients meeting the inclusion criteria were evaluated twice: upon hospital admission and after the subsidence of acute symptoms.

Data Collection

The samples were chosen based on their availability and adherence to the inclusion criteria. To determine the sample size, we used Cochran's formula, considering the expected change in average lactoferrin levels before and after the intervention. This calculation was informed by Eva Carro's study on lactoferrin levels in individuals with Alzheimer's, with an error margin of 0.4, resulting in a sample size of 30 participants. Collected demographic data included age, gender, body mass index (BMI), age at initial symptom onset, the interval from symptom onset to treatment initiation, history of drug side effects, smoking habits, family psychiatric history, and recent drug use. A urinary drug test (UDT) was used to identify illicit drug use relevant to the inclusion criteria. Venous blood samples were taken to determine cell blood count and inflammatory biomarkers, aiming to exclude patients with positive

results. Symptom severity and cognitive function were assessed using the PANSS and the BACS, respectively. Blood samples for serum lactoferrin levels were collected after 12 hours of fasting, between 8 and 10 AM, using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (ZellBio). Throughout hospitalization, physicians monitored patients for infections, inflammatory diseases, and treatment responses.

PANSS and BACS Descriptions

The PANSS scale includes 30 questions to which the patient provides responses through five-point Likert scales that are**:** not at all, sometimes, moderately, a lot, and very much. These questions consist of five subscales, including: negative symptoms (eight questions), positive symptoms (six questions), dissociation (seven questions), irritability symptoms (four questions), and anxiety and depression (five questions). To identify factor validity, Kai and Sui conducted PANSS on 240 patients with schizophrenia and identified two factors of negative and positive symptoms, whose eigenvalues were 7.08 and 3.74, respectively, explaining 36.1% of the total variance of schizophrenia. In a study by Ghamari Givi *et al*. conducted in 2010 in Iran (16) , Cronbach's alpha for this scale was 0.77, indicating an acceptable internal consistency for the questionnaire.

The BACS test which was presented by Richard Keefe in 1999 (17). It encompasses neurocognitive tests, verbal memory components, number sequence instructions, a token motor task, semantic fluency, verbal fluency, a symbol coding task, and the Tower of London. In a study conducted by Mazhari *et al*. [18], Cronbach's alpha for the Persian version of the BACS was 0.74. All the Persian-BACS subscales were significantly correlated with the corresponding standard neurocognitive subscales and the Pearson correlation coefficient of the composite scores from the two instruments was found to be 0.71.

Statistical Analysis

Analyzes were conducted conducted using SPSS version 23. Descriptive statistics for qualitative variables are presented as frequencies and percentages, while quantitative data are summarized with means and standard deviations. A paired t-test compared the average results at the two different times, and a chi-square test assessed the qualitative variables. The study parameters' correlations were examined using the Pearson correlation test. A P-value of less than 0.05 was considered statistically significant.

Ethical Consideration

Participants were excluded from the study if they were in the acute phase of an infectious or inflammatory disease or had experienced a severe head injury. Additionally, anyone who chose to withdraw from the study for any reason was excluded. The study was approved by the Research Ethics Committees, and written consent was obtained from both the participants and their legal guardians.

The study was approved by the Research Ethics Committees of School of Medicine-Shahid Beheshti University of Medical Sciences with the ethic number of IR.SBMU.MSP.REC.1401.216 and all participants provided informed consent

Results

The study involved 30 volunteer schizophrenia patients, with an equal number of men and women and an average age of 40.77 ± 13.36 years. Baseline characteristics are detailed in Table 1. Upon admission, 18 patients (60.0%) experienced drug side effects, which decreased slightly to 17 patients (56.7%) after the acute phase was managed. Initially, 14 patients (46.7%) were treated with first-generation antipsychotic drugs (FGA), 8 patients (26.7%) with second-generation antipsychotic drugs (SGA), and 5 patients (16.7%) with a combination of both. Additionally, 8 patients (26.7%) used biperiden and 4 patients (13.3%) used benzodiazepines. During hospitalization, no patient received FGA as monotherapy; however, SGA monotherapy-controlled symptoms in 10 patients (33.3%), while a combination of FGA and SGA was used in 15 patients (50.0%). Biperiden managed drug side effects in 19 patients (63.3%), and benzodiazepines were prescribed for 5 patients (16.7%) to address sleep issues or agitation.

Table 1. Demographic and Clinical Characteristics of Study Participants

Component	Mean ± SD/n Percentage
Mean age, year	40.77 ± 13.36
Male	15 (50.0%)
Female	15 (50.0%)
Mean body mass index, kg/m^2	24.23 ± 6.04
Mean time interval between symptom onset and treatment, year	2.77 ± 5.24
The mean age at symptom appearance, year	19.60 ± 4.79
Family history of psychotic disorders	18 (60.0%)
History of smoking	17 (56.7%)

The mean PANSS score at admission was 15.78 ± 2.88, which significantly decreased to 12.48 ± 2.28 at discharge ($P < 0.001$). Significant changes were observed in the BACS component scores (Table 2),

particularly in verbal memory and learning (P = 0.033), working memory (digit sequencing) (P = 0.002), verbal fluency (category instances, controlled and word association) (P = 0.003), and executive function (Tower of London task) (P = 0.039), while other items showed no significant change. Serum lactoferrin levels decreased significantly from 130.63 ± 52.49 at admission to 85.42 ± 29.03 at discharge (P < 0.001).

Detailed changes in serum lactoferrin levels based on demographic and clinical characteristics of patients with schizophrenia are provided in Table 3. It is important to note that serum lactoferrin levels were independent of baseline characteristics such as gender, age, body mass index, illness onset or treatment duration, family history of psychotic disorders, and medications used.

Table 2. Cognitive Performance Changes in BACS* Components from Admission to Discharge by Paired T-Test

Component	At Admission	At Discharge	P-value**
Verbal memory and learning	22.10 ± 12.37	26.60 ± 11.35	0.033
Working memory (digit sequencing)	9.90 ± 6.09	12.27 ± 6.90	0.002
Motor speed (Token motor task)	26.10 ± 17.75	27.17 ± 17.52	0.454
Verbal fluency	10.23 ± 5.20	11.50 ± 5.51	0.003
Verbal fluency for letter D	8.00 ± 4.20	8.50 ± 5.02	0.312
Verbal fluency for letter S	6.83 ± 4.73	7.10 ± 3.85	0.531
Symbol coding	22.90 ± 15.39	23.57 ± 16.11	0.349
Executive function (Tower of London task)	2.27 ± 1.86	2.60 ± 1.85	0.039

*Brief Assessment of Cognition in Schizophrenia
**P-value < 0.05 is considered to be statistically significant

Table 3. Serum Lactoferrin Levels in Relation to Patients Baseline Characteristics

Component		At admission	p-value	At discharge	P-value
Age	≤ 41 years	125.08 ± 37.96	0.545	79.16 ± 29.93	0.212
	> 41 years	136.97 ± 66.35		92.59 ± 27.24	
Gender	Male	128.88 ± 33.16	0.859	82.03 ± 30.54	0.531
	Female	132.39 ± 67.83		88.82 ± 28.06	
BMI	≤ 24 kg/m^2	140.33 ± 67.89	0.320	94.61 ± 26.34	0.083
	> 24 kg/m^2	120.93 ± 29.94		76.23 ± 29.51	
Time between onset and treatment	≤ 3 years	159.31 ± 89.18	0.100	80.40 ± 29.91	0.086

P-value < 0.05 is considered to be statistically significant. No significant correlations were found between lactoferrin levels and the baseline characteristics of the patients including gender, age, body mass index, the time of onset of illness or time of treatment, family history of psychotic disorders, and medications.

Table 4. Correlation between BACS* Cognitive Domains and Serum Lactoferrin Levels

Component	R coefficient	P-value**
Verbal memory and learning	0.348	0.060
Working memory (digit sequencing)	-0.071	0.709
Motor speed (Token motor task)	0.020	0.916
Verbal fluency	0.179	0.343
Verbal fluency for letter D	0.001	0.999
Verbal fluency for letter S	-0.084	0.657
Symbol coding	0.021	0.910
Executive function (Tower of London task)	-0.360	0.050

*Brief Assessment of Cognition in Schizophrenia
**P-value < 0.05 is considered to be statistically significant. A significant negative correlation was found between the serum lactoferrin level and the executive function.

Our study found no correlation between changes in serum lactoferrin levels and PANSS scores (r = 0.011, P = 0.975). However, as shown in Table 4, there was an inverse relationship between changes in lactoferrin levels and performance on the executive function item (Tower of London task) in the BACS test (r = -0.360, P = 0.050).

Discussion

The study aimed to assess changes in serum lactoferrin levels in patients with schizophrenia during the acute phase and following symptom resolution. It investigated the relationship between lactoferrin levels, clinical symptoms measured by the PANSS, and cognitive performance evaluated through the BACS. The findings reveal a significant decrease in serum lactoferrin levels from admission to discharge, suggesting that lactoferrin may influence cognitive functions, particularly the executive function, rather than affecting the positive or negative symptoms of schizophrenia. Lactoferrin is a multifunctional glycoprotein with a molecular weight of about 80 kDa, known for its roles in iron regulation, antimicrobial activity, and immune modulation (19, 20). These functions are facilitated by its binding to specific receptors on various cells and targeting DNA sequences in the nucleus as a transcription factor (21). Increased lactoferrin levels can regulate genes associated with innate immune system activation, lipid metabolism, cytokine production, and lysosomal degradation (22). As an immune modulator, lactoferrin can activate transforming growth factor β (TGF-β) signaling pathways, and thus, boost innate immunity (23). It has anti-inflammatory effects by binding to specific cell receptors, influencing gene expression related to immune responses and oxidative stress. Lactoferrin's biological effects are particularly relevant in neuropsychiatric disorders, where neuroinflammation and oxidative stress are involved in the pathophysiology of schizophrenia (24). The mechanisms by which lactoferrin may impact psychological symptoms are complex. It modulates the immune system, potentially reducing neuroinflammation, a factor contributing to psychiatric symptoms. Elevated inflammatory cytokines have been linked to worsened symptoms in schizophrenia, and lactoferrin's ability to regulate these cytokines may alleviate such effects. Additionally, lactoferrin's role in enhancing the blood-brain barrier's integrity suggests it could protect neuronal health by preventing inflammatory mediators from entering the central nervous system (25, 26).

The study shows lactoferrin levels increase during the acute phase of the disease and decrease with drug treatment during hospitalization, indicating a link between disease severity and serum lactoferrin levels.

Previous research found higher serum lactoferrin levels in schizophrenia patients compared to healthy controls. Animal studies demonstrate its anti-inflammatory effects, thus reducing stress-induced anxiety and depressive behaviors and lowering Brain-Derived Neurotrophic Factor (BDNF) levels, which is a key factor in mood disorders (15, 27). The observed improvement in cognitive performance, particularly in verbal and working memories, supports the hypothesis that lactoferrin may play a crucial role in cognitive recovery during treatment. While earlier studies reported elevated lactoferrin levels in patients with schizophrenia compared to healthy controls, these findings suggest that lactoferrin levels may be more closely related to cognitive function than to the severity of positive or negative symptoms. This distinction emphasizes the need for further research into the specific cognitive domains affected by lactoferrin and its potential therapeutic implications (28). Lactoferrin is present in brain capillary endothelial and nerve cells and can cross the blood-brain barrier into nerve tissues. It has been found that lactoferrin levels significantly increase in the brains of patients with Parkinson's and Alzheimer's diseases. The effectiveness of such a protein in patients with schizophrenia might operate through a mechanism similar to that of those diseases. However, further studies are necessary to confirm this theory (29-32). In conclusion, our study provides evidence of a significant reduction in serum lactoferrin levels during the acute phase of schizophrenia, suggesting its potential role in cognitive modulation rather than symptom severity. Future research should focus on elucidating the precise mechanisms by which lactoferrin influences cognitive functions and its potential as a therapeutic target in the treatment of schizophrenia. Understanding these pathways could pave the way for novel interventions aimed at improving cognitive outcomes in patients with this complex disorder.

Limitation

This study provides valuable insights into the relationship between serum lactoferrin levels and cognitive functions in schizophrenia, though several limitations may influence the interpretation of our findings. The small and homogeneous sample size restricts the generalizability of our results, as a more diverse population might yield different outcomes, particularly regarding how lactoferrin levels are related to demographic factors such as age, gender, and ethnicity. This lack of diversity limits the applicability of our findings to broader populations. Additionally, the cross-sectional nature of the study prevents us from establishing causality between changes in lactoferrin levels and cognitive performance. Longitudinal studies are needed to determine whether fluctuations in lactoferrin levels directly affect cognitive outcomes over time. Without temporal data, it is challenging to ascertain whether lower lactoferrin levels result from improved cognitive function or contribute to cognitive recovery. Moreover, factors such as medication adherence, the type of antipsychotic treatment, and comorbid medical conditions were not fully controlled in

this study, which could significantly influence both lactoferrin levels and cognitive performance, potentially confounding our results. Future research should aim to control for these variables to isolate the specific effects of lactoferrin. Individual differences in lactoferrin metabolism and response to treatment may also introduce variability in our findings. Genetic factors, lifestyle choices, and nutritional status can all impact lactoferrin levels and its biological effects. A detailed exploration of these individual differences could enhance our understanding of lactoferrin's role in schizophrenia.

Conclusion

Changes in serum lactoferrin levels can predict different phases of schizophrenia. During the active phase, lactoferrin levels increase. As symptoms improve with treatment, these levels decrease. While lactoferrin appears to enhance executive function, it has little impact on the positive or negative symptoms of the disease.

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Conflict of Interest

None.

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