



Increased GDF-15 in chronic male patients with schizophrenia: correlation with body mass index and cognitive impairment

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Growth Differentiation Factor-15 (GDF-15) is a pleiotropic cytokine that plays a significant role in metabolism and inflammation. Elevated serum levels of GDF-15 have been associated with mood disorders. We propose that GDF-15 may potentially influence cognitive impairment and metabolism in male patients with chronic schizophrenia (CS), although there is limited research on this topic. This study compared serum GDF-15 levels in 72 male patients with CS and 85 healthy controls (HC). The severity of psychotic symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS), while cognitive performance was evaluated with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The male CS patients performed worse than the healthy controls in both the total score and all subscales of the RBANS. Serum GDF-15 concentrations were significantly higher in the male CS patients compared to the healthy controls. Furthermore, the log-transformed serum GDF-15 concentrations in male CS patients were positively correlated with BMI and negatively correlated with Delayed Memory scores, Immediate Memory, and the total RBANS score. This preliminary study suggests that elevated serum GDF-15 levels in male patients with chronic schizophrenia may play a role in cognitive function and BMI regulation.

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INTRODUCTION

Schizophrenia is a chronic, severe mental disorder that is often accompanied by obesity and cardiovascular disease^{1,2}. Cognitive impairment is a major contributor to persistent functional impairment in schizophrenia and is resistant to current treatments^{3–5}. Cognitive impairment affects various domains, including memory, learning, language, attention, visuospatial abilities, and executive function. Cognitive deficits are linked to poor functional outcomes⁴. Therefore, further investigation into the causes and mechanisms of cognitive deficits in schizophrenia is crucial for improving long-term clinical management.

The causes and development of cognitive impairment in schizophrenia remain unclear. Genetic risk for schizophrenia has been associated with low cognitive function^{6–10}, and a subset of these genes is linked to immune inflammation^{7,10}. The inflammation hypothesis in schizophrenia has been a major research focus^{11–16}. A comprehensive study demonstrated a significant association between the immune system and schizophrenia through the analysis of 108 schizophrenia-associated genetic loci¹¹. Recent advanced research using Mendelian studies demonstrates that pervasive, low levels of neuroinflammation may play a key role in schizophrenia¹². Additionally, another Mendelian study found that genetically determined IL-6 affects brain structure and may influence regions involved in schizophrenia¹⁶. Consequently, inflammatory cytokines represent a promising avenue for exploring cognitively relevant pathophysiological mechanisms in schizophrenia.

GDF-15 is a member of the transforming growth factor- β (TGF- β) superfamily of cytokines. GDF-15 is secreted as a 40-kDa pro-peptide, which is subsequently cleaved to release a 25-kDa active

circulating dimeric protein^{17,18}. GDF-15 regulates integrated stress response pathways, including cell activation, cellular stress, and anti-inflammatory processes^{19–21}. Many of these stresses induce GDF-15 expression via p53²² or early growth response protein-1 (EGR-1)²³ transcription factors. It is currently recognized that GDF-15 is likely involved in the pathophysiological mechanisms of obesity^{18,24–28}, cardiovascular disease^{27,29–31}, cognition^{30–34}, aging^{33,35}, and neoplasms^{18,27}. Recent studies have identified widespread associations between Body Mass Index (BMI) and brain structure in individuals with schizophrenia³⁶. Further studies have identified a significant association between Body Mass Index (BMI) and cognitive functioning in patients with first-episode schizophrenia³⁷. Figure 1 provides a preliminary overview of the inflammatory and metabolic aspects of this phenomenon. One study on cognitive issues reported a significant association between elevated GDF-15 levels and cognitive impairment within three months following acute ischemic stroke in patients³⁰. Ji et al. reported that GDF-15 is strongly associated with both baseline cognitive decline and long-term cognitive deterioration by influencing changes in brain free water content among Singaporeans aged 50 years and older³¹. However, limited research has been conducted on GDF-15 and psychiatric disorders. Kochlik et al.³⁸ found that plasma GDF-15 concentrations in older and younger citizens were associated with global cognitive function and depressive conditions. One study found elevated GDF-15 levels in men with major depression compared to healthy individuals³⁹. Another study found that among depressed individuals, those with elevated GDF-15 had higher levels of comorbid physical illness and poorer executive cognitive function³³. Yang et al.⁴⁰ found that GDF-15 levels were significantly

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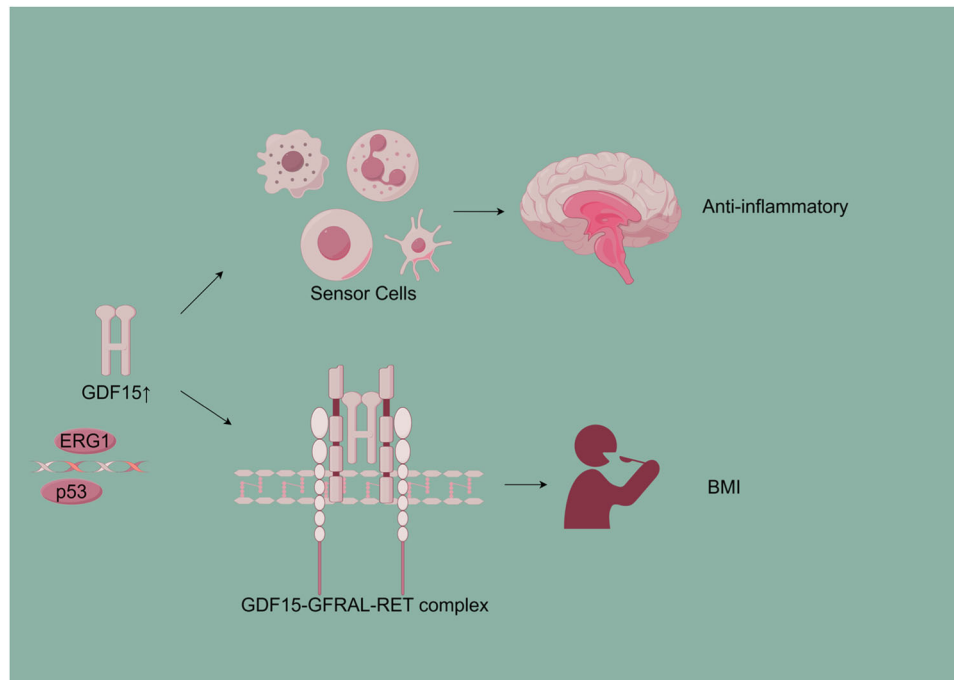


Fig. 1 Overview of GDF-15's role in inflammation and metabolism. Stress-responsive transcription factors, including p53 and early growth response transcription factor 1 (EGR1), have been identified as key regulators of growth differentiation factor -15 (GDF-15) expression. GDF-15 may function as part of a compensatory anti-inflammatory response. A model describes the formation of the GDF-15-GFRAL-RET signaling complex. GDF-15 binds to the glial cell-derived neurotrophic factor (GDNF) family receptor alpha-like (GFRAL), leading to the recruitment of RET. Full-length GFRAL is predominantly located in neurons within the posterior region of the hindbrain-brainstem and the nucleus of the solitary tract, and is essential for GDF-15-induced appetite suppression.

elevated in bipolar disorder patients compared to healthy controls. In patients with bipolar disorder, GDF-15 levels were correlated with age and disease duration. In a recent study, Yu et al.⁴¹ evaluated the cellular composition and gene expression profiles of schizophrenic brain tissue using single-cell RNA sequencing, finding that the expression changes of immune-related genes (including GDF-15) in different cell types were significantly different. Based on these findings, we hypothesize that schizophrenia may be accompanied by elevated levels of GDF-15, which likely contribute to cognitive impairment. To the best of our knowledge, this study is the first to explore the relationship between serum GDF-15 levels and cognitive function in schizophrenia, with the aim of providing a potential target for the treatment of the disorder. Therefore, the present study investigated (1) whether there are differences in serum GDF-15 levels between chronic male schizophrenic patients and matched healthy controls, and (2) whether there is a correlation between serum GDF-15 levels and cognitive impairment in chronic male schizophrenic patients.

SUBJECTS AND METHODS

Subjects

This study utilized an observational, cross-sectional, and retrospective design, employing a case-control approach. A total of 72 male inpatients, diagnosed with chronic schizophrenia (CS), were recruited from the Mental Disorder Department of Lianyungang Fourth People's Hospital. Participants were enrolled through community advertisements and referrals from local healthcare institutions. Each participant was thoroughly informed of the study's objectives and procedures and provided written informed consent, agreeing to the use of their data for research purposes. Demographic data collected included age, educational level, body mass index (BMI), age at illness onset, and duration of illness.

All participants met the following inclusion criteria: (1) aged 18–60 years, of Han Chinese ethnicity; (2) diagnosed with schizophrenia according to the Structured Clinical Interview for DSM-IV; (3) illness duration of at least 2 years; (4) consistent neuroleptic medication use at stable doses for a minimum of 12 months prior to the study; and (5) completed at least elementary school education, demonstrating adequate comprehension of study instructions, as evidenced by providing clear and relevant responses to investigator inquiries, accurately following instructions, responding consistently with the subject matter, and, when necessary, using non-verbal cues. The exclusion criteria were as follows: (1) patients with somatic disorders or substance dependence; (2) individuals who had experienced a major life event, such as divorce or widowhood, within the month prior to admission; and (3) patients who had not completed primary education.

Eighty-five healthy control (HC) participants were recruited from the local population in Lianyungang City. Although strict 1:1 matching with male CS patients was not feasible, we ensured comparability in key variables, including age, BMI, education, and smoking status. Logistic regression was used to adjust for any imbalances, thereby mitigating potential confounding effects arising from recruitment challenges. Unstructured interviews were conducted to assess the participants' current mental state and gather information on personal or family histories of mental disorders. For example, participants were asked, "With whom do you interact regularly in your daily life, and what are these interactions like?" and "What activities or routines have been part of your daily life recently?" None of the healthy control participants reported any personal or family history of psychiatric disorders. Both patients and controls provided detailed medical histories, including the use of sleep aids and antipsychotics, as well as results from physical exams (e.g., vital signs, cardiopulmonary function) and laboratory tests (e.g., blood cell analysis, electrolytes, liver, and kidney function). Only participants with

normal test results were included in the study. Participants with serious medical conditions were excluded. All healthy participants were of the same ethnicity and from the same geographic region as the patient group. A psychiatrist provided a detailed explanation of the research protocol and procedures to each patient before obtaining written informed consent. Study information was presented to maximize comprehension, taking into account participants' understanding and emotional readiness. In some cases, detailed explanations were provided to both participants and their parents or guardians. The Institutional Review Board of Lianyungang Fourth People's Hospital approved the study protocol. All methods adhered to the Declaration of Helsinki.

Psychopathological symptom assessment

Psychotic symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS), which was administered by two experienced clinicians trained in this scale. The inter-rater reliability for PANSS scores was substantial, with an Intraclass Correlation Coefficient (ICC) exceeding 0.8. To standardize medication doses for comparison, antipsychotic amounts were expressed in chlorpromazine equivalents⁴².

Cognitive assessments

The Chinese-adapted RBANS was employed to assess cognitive abilities in patients with schizophrenia and healthy controls. Given that the RBANS requires approximately 30 min and demonstrates robust reliability and validity in psychosis, its utility in clinical settings was both practical and feasible. The cognitive domains evaluated included five age-adjusted indices: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory, along with a composite total score. Neuropsychological raw scores were standardized into T-scores according to established manual criteria. Importantly, a higher RBANS score reflects better cognitive function⁴³. To mitigate the effects of medications (e.g., sleep aids) on patients' conditions, all assessments were conducted in the afternoon.

Measurement of GDF-15 levels

Both samples were analyzed by the same investigator, who was blinded to participants' clinical statuses. Venous blood samples from both patients and healthy controls were collected after overnight fasting, between 7:30 and 9:00 AM. Serum was isolated by centrifugation at $3000 \times g$ for 15 min, then stored at -80°C until analysis. Serum GDF-15 levels were quantified using a sandwich enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions (CB11271-Hu; Shanghai Coibo Bio Technology Co., Ltd., Shanghai, China). Serum GDF-15 levels are reported in pg/mL. The assay's sensitivity was 10 pg/mL, with an intra-assay CV of less than 10% and an inter-assay CV of less than 15%. All measurements were within the ELISA range of 50–1600 pg/mL specified by the manufacturer.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 25. All datasets were initially tested for normality with the Kolmogorov–Smirnov test. Since results indicated that serum GDF-15 concentrations for both CS patients and healthy controls were not normally distributed ($P < 0.05$), values underwent log-transformation for analysis. Continuous variables are presented as the mean $\pm$ standard deviation (SD). Means from normally distributed data were compared using independent t-tests or ANCOVA, and categorical variables were compared using chi-square tests. All p-values were calculated using two-tailed tests, with statistical significance set at 0.05.

First, using diagnosis as the fixed factor with age, smoking status, and years of education as covariates, ANCOVA was

performed to compare log-transformed GDF-15 concentrations and RBANS scores between male patients with CS and HC. To control for multiple comparisons, Bonferroni-corrected p-values for each RBANS score were calculated by adjusting the original p-value according to the number of comparisons ($\times 6$). Second, exploratory multiple regression analysis was conducted after adjusting for confounders like age, illness duration, smoking status, years of education, and CPZ equivalent dose⁴², examining the relationship between log-transformed GDF-15 levels, BMI, and RBANS scores. Lastly, logistic regression analysis was conducted to assess whether GDF-15 levels could independently predict case status (CS vs. controls) after adjusting for age, BMI, education level, and smoking status as confounders. Including GDF-15 in the model aimed to evaluate its significance in differentiating male CS patients from the control group.

RESULTS

Sociodemographic features and cognitive function between male CS patients and HCs

This study included 72 male participants in the "CS patient group" and 85 healthy male participants in the "HC group" (Table 1). There was no statistically significant difference between the two groups in terms of age, years of education, BMI, and smoking status (all $P > 0.05$). Furthermore, Bonferroni post-hoc testing indicated that male CS patients performed significantly worse than their control group counterparts across all neurocognitive performance tests (Table 2; all $p < 0.05$).

Serum GDF-15 concentrations

The log-transformed serum GDF-15 concentrations were significantly elevated in the male CS group compared to the healthy control group (2.18 ± 0.25 vs. 2.02 ± 0.32 pg/mL; $F = 11.656$, $P < 0.001$, Fig. 2). After adjusting for age, smoking status, and years of education using analysis of covariance, this difference remained significant ($F = 12.917$, $P < 0.001$).

Table 1. Demographic and clinical characteristics of male CS patients and healthy controls (mean $\pm$ SD).

	Male CS patients (<i>n</i> = 72)	HC (<i>n</i> = 85)	Statistic (<i>F</i> / <i>t</i> / χ^2)	<i>P</i> value
Age	39.86 $\pm$ 9.87	40.36 $\pm$ 9.23	<i>t</i> = −0.330	0.742 ^a
BMI(kg/m ²)	24.35 $\pm$ 3.86	25.30 $\pm$ 2.98	<i>t</i> = −1.711	0.089 ^a
Smoker	36	37	χ^2 = 0.656	0.418 ^b
Educations (years)	9.13 $\pm$ 2.93	9.72 $\pm$ 3.18	<i>t</i> = −1.214	0.226 ^a
Duration of illness (years)	12.93 $\pm$ 7.47			
Dose of CPZ equivalent (mg/d)	663.21 $\pm$ 284.04			
PANSS P	10.94 $\pm$ 4.50			
PANSS N	17.67 $\pm$ 6.99			
PANSS G	28.83 $\pm$ 6.20			
Log GDF- 15(pg/ml)	2.18 $\pm$ 0.25	2.02 $\pm$ 0.32	<i>F</i> = 12.917	<0.001 ^c

Significant differences ($P < 0.05$) are indicated in bold.

CS chronic schizophrenia, BMI body mass index, CPZ chlorpromazine, PANSS Positive and Negative Symptom.

^at test.

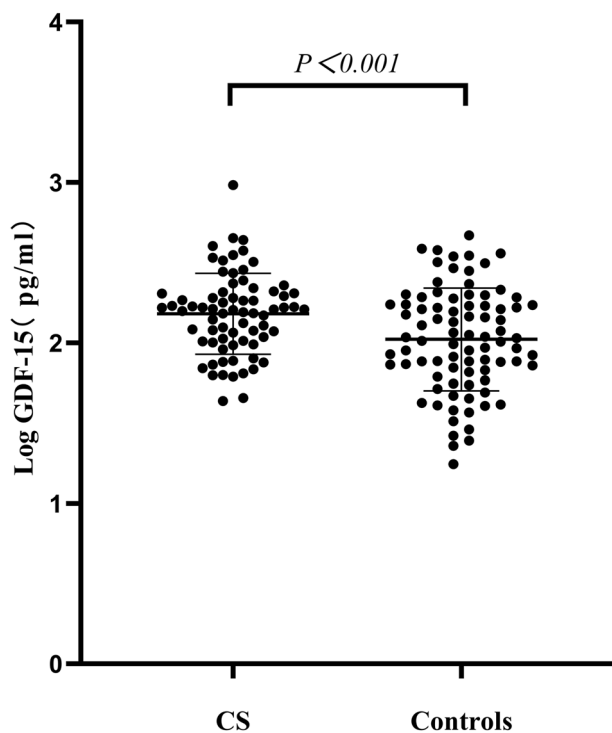
^b χ^2 test.

^cThe *p*-values for log GDF-15 were adjusted for age, Smoker, years of education and BMI.

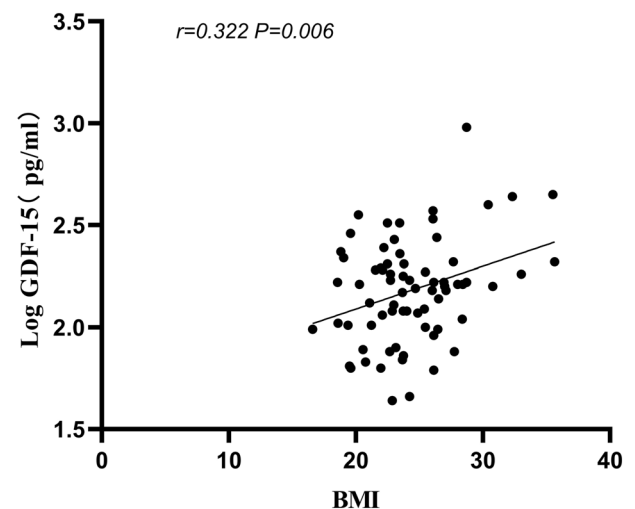
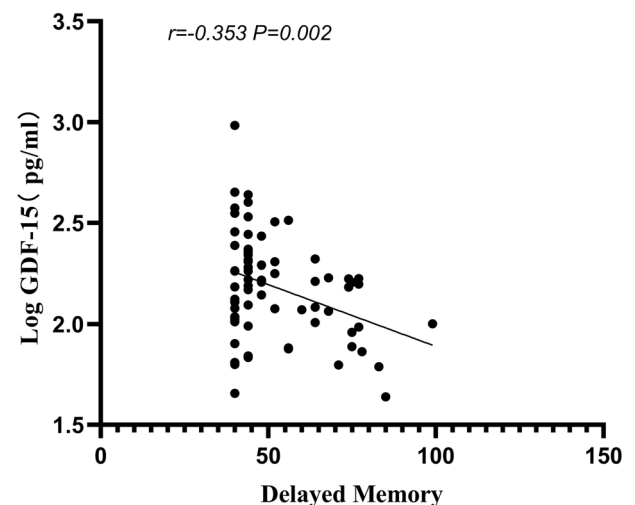
Table 2. Total and index scores on the RBANS in male CS patients vs. controls (mean $\pm$ SD).

	Male CS patients ($n = 72$)	HC ($n = 85$)	Statistic (F)	Adjusted P value
Immediate memory	50.15 $\pm$ 17.26	83.88 $\pm$ 17.31	141.972 ^a	* <0.001
Visuospatial/constructional	70.51 $\pm$ 15.49	89.92 $\pm$ 14.82	60.540 ^a	* <0.001
Language	72.49 $\pm$ 12.54	96.81 $\pm$ 11.05	168.964 ^a	* <0.001
Attention	83.04 $\pm$ 12.81	107.91 $\pm$ 14.39	127.471 ^a	* <0.001
Delayed memory	52.44 $\pm$ 14.55	84.87 $\pm$ 17.27	145.640 ^a	* <0.001
Total RBANS score	58.22 $\pm$ 10.57	88.66 $\pm$ 12.60	264.359 ^a	* <0.001

RBANS Repeatable Battery for the Assessment of Neuropsychological Status.

* $P < 0.01$.^a F -values were adjusted for age, Smoker, years of education and BMI.**Fig. 2** Serum GDF-15 concentration in CS patients and healthy controls.**Associations between serum GDF-15 concentrations, clinical variables, and cognitive function scores**

Correlation analyses indicated that log-transformed serum GDF-15 concentration showed no significant correlations with the PANSS total or subscale scores (all $P > 0.05$). In the male CS group, the log-transformed serum GDF-15 concentration correlated positively with BMI ($r = 0.322$, $P = 0.006$, Fig. 3) and negatively with the Delayed Memory score ($r = -0.353$, $P = 0.002$, Fig. 4), Immediate Memory ($r = -0.252$, $P = 0.032$, Fig. 5), and the Total RBANS Score ($r = -0.289$, $P = 0.014$, Fig. 6). The cognitive function scores referenced in this analysis are confirmed to be T-scores. Furthermore, multiple regression analysis, controlling for potential confounders (age, duration of illness, smoking status, years of education, and CPZ-equivalent dose), revealed that log-transformed serum GDF-15 concentration was positively associated with BMI ($R^2 = 0.104$, $F = 8.803$, $P = 0.006$) in male CS patients. Log-transformed serum GDF-15 concentration showed negative associations with Delayed Memory ($R^2 = 0.125$, $F = 9.964$, $P = 0.002$), Immediate Memory ($R^2 = 0.064$, $F = 4.766$, $P = 0.032$),

**Fig. 3** Correlation between GDF-15 concentration and BMI in male CS patients. The log-transformed GDF-15 levels in the male CS group exhibited a significant positive correlation with BMI ($r = 0.322$, $P = 0.006$).**Fig. 4** Correlation between GDF-15 concentration and Delayed Memory in male CS patients. The log-transformed GDF-15 levels in the male CS group exhibited a significant negative correlation with the Delayed Memory score on the RBANS ($r = -0.353$, $P = 0.002$).

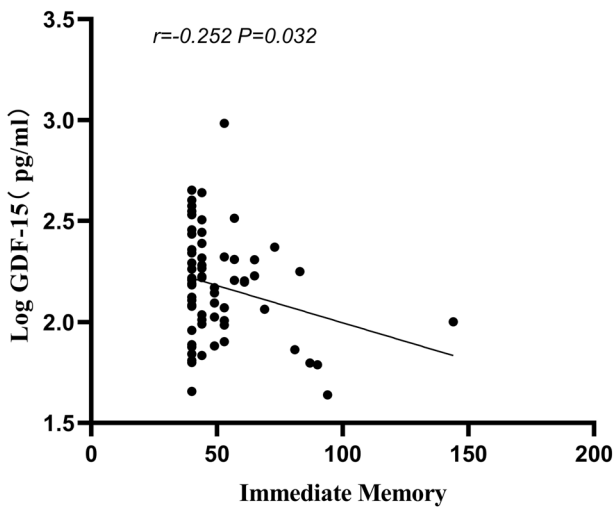


Fig. 5 Correlation between GDF-15 concentration and Immediate Memory in male CS patients. The log-transformed GDF-15 levels in the male CS group exhibited a significant negative correlation with the Immediate Memory score on the RBANS ($r = -0.252$, $P = 0.032$).

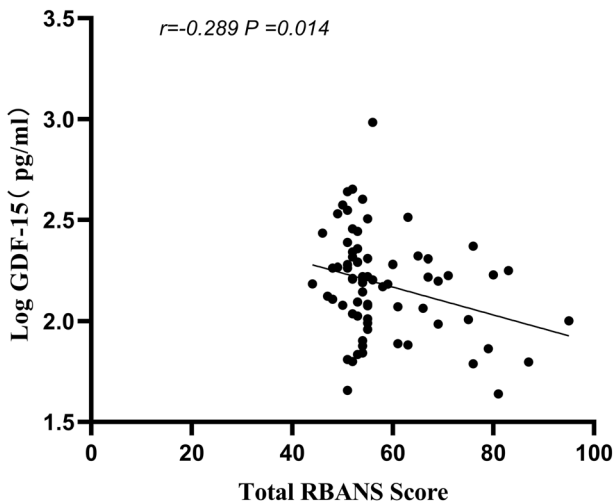


Fig. 6 Correlation between GDF-15 concentration and Total RBANS Score in the male CS patients. The log-transformed GDF-15 levels in the male CS group exhibited a significant negative correlation with the total RBANS score ($r = -0.289$, $P = 0.014$).

and the Total RBANS Score ($R^2 = 0.083$, $F = 6.367$, $P = 0.014$) in male CS patients after adjusting for various potentially confounding variables, including age, illness duration, smoking status, education, and CPZ-equivalent dose.

The results indicated significantly higher GDF-15 levels in the male CS group compared to the control group. Consequently, GDF-15 was included as a variable in logistic regression analysis to evaluate its potential as an independent predictor, adjusting for age, BMI, education level, and smoking status. Participants were categorized into high- and low-level GDF-15 groups based on the mean GDF-15 value, with the high-level group coded as 1. The analysis demonstrated a significant association between elevated GDF-15 levels and an increased likelihood of schizophrenia ($B = 0.844$, Wald statistic = 6.372, $p = 0.012$, OR = 2.326, 95% CI = 1.208–4.481). Furthermore, BMI was identified as a confounding factor ($B = -0.100$, Wald statistic = 4.069, $p = 0.044$, OR = 0.905, 95% CI = 0.821–0.997). These findings support GDF-15 as an independent factor significantly associated with

schizophrenia, with this association remaining robust even after adjusting for potential confounders.

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the relationship between serum GDF-15 concentration and cognitive function in male inpatients with chronic stable schizophrenia. The major findings of this study were as follows: (1) male CS patients performed significantly worse than controls on all neurocognitive performance tests; (2) serum GDF-15 concentrations were significantly higher in the male CS group than in the healthy control group after adjusting for age, smoking status, and years of education; (3) moreover, multiple regression analyses, adjusting for age, duration of illness, smoking status, years of education, and CPZ equivalent dose as control variables, revealed that log-transformed serum GDF-15 concentration was positively correlated with body mass index (BMI) in male CS patients, while being negatively correlated with Delayed Memory, Immediate Memory, and Total RBANS score. Thus, alterations in serum GDF-15 levels may provide mechanistic insights into these cognitive deficits and BMI.

GDF-15 is a cytokine involved in cell activation and stress responses, belonging to the glial cell lineage-derived neurotrophic factor family within the TGF- β superfamily. It functions through GFRAL, a recently identified orphan receptor of the GFR α family, and signals via Ret co-receptors. Cellular stress and disease lead to elevated serum levels of GDF-15, which are associated with anorexia, weight loss, and metabolic changes, primarily through its actions on the hindbrain region²¹. GDF-15 is suggested to have an overall anti-inflammatory effect and is elevated in inflammatory conditions associated with cancer, cardiovascular disease, insulin resistance, and obesity⁴⁴ as a compensatory mechanism^{19,20}. Previous studies have demonstrated that GDF-15 is positively correlated with IL-6 and CRP in inflammatory diseases^{45–47}. Previous studies have demonstrated that GDF-15 levels in cerebrospinal fluid correlate with serum levels⁴⁸.

Cognitive deficits are a significant predictor of long-term poor prognostic outcomes in patients with schizophrenia^{3,4}. Patients in this study performed worse in processing immediate memory, visuospatial/structural tasks, verbal abilities, attention, delayed memory, and composite total scores compared to healthy matched controls, consistent with the findings of Li et al.⁴⁹. Overall, these findings reflect a comprehensive profile of cognitive impairment in chronic male patients with schizophrenia, highlighting the pervasive and multifaceted nature of cognitive dysfunction associated with the disorder.

In this study, we found that serum GDF-15 levels were significantly higher in male CS patients compared to healthy controls. In previous studies, a Swedish study comparing 120 psychiatric patients (including those with schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder, and unspecified psychosis) with 120 healthy controls found significantly elevated plasma GDF-15 levels in the patient group. However, no further studies have been conducted focusing exclusively on schizophrenia⁵⁰. Several studies have shown that plasma or serum GDF-15 levels are significantly higher in elderly patients with depression than in healthy controls^{33,47,51}. Additional studies have found significantly higher plasma GDF-15 levels in patients with bipolar disorder compared to healthy controls⁴⁰. In our study, male patients with chronic schizophrenia exhibited elevated serum GDF-15 levels compared to healthy controls. In conjunction with the analysis of GDF-15 properties and previous studies, we speculate that this elevation may represent a compensatory anti-inflammatory response⁴⁸. Naturally, further experiments are needed to validate these findings more thoroughly in the future.

The current study also found a positive correlation between serum GDF-15 concentration and BMI in male patients with chronic schizophrenia, whereas no such correlation was observed in the healthy control group. It is well-established that GDF-15 plays a role in biological pathways such as energy homeostasis, stress response, and inflammatory regulation⁵². Human genetic studies have established a link between GDF-15 and obesity. A genome-wide association study involving 339,224 individuals focused on BMI and identified 97 BMI-associated loci, one of which was associated with GDF-15. Two genome-wide association studies involving approximately 700,000 participants demonstrated that the GDF-15 intronic variant rs10424912 and downstream variant rs16982345 were associated with BMI²⁵. Previous studies by Mastrobattista et al.³³ in elderly depressed patients did not show a correlation between GDF-15 levels and BMI. Kempf et al.⁵³ identified a positive correlation between GDF-15 levels and BMI in obese nondiabetic individuals. Meanwhile, GDF-15 mRNA was found to be negatively correlated with body mass index and body fat in healthy individuals⁵⁴. The results of our study suggest that elevated GDF-15 levels in male patients with chronic schizophrenia may be associated with an elevated body mass index. One possible explanation is that studies have shown an association between p53 and schizophrenia^{55–57}, where p53 is activated in adipose tissue to promote the secretion of pro-inflammatory cytokines and insulin resistance. p53 also mediates GDF-15 expression in adipose tissue⁵⁸, which is further up-regulated by high glucose supplementation in HUVEC cells in a p53-dependent manner^{22,59}. Another plausible explanation for BMI modulation in schizophrenia patients concerns the GDF15-GFRAL-RET signaling complex, which engages neurons in the posterior hindbrain-brainstem region, particularly within the nucleus accumbens and nucleus tractus solitarius, ultimately influencing appetite regulation⁶⁰. Nevertheless, further in-depth research is needed to validate this in the future.

In this study, we identified a negative correlation between serum GDF-15 levels and delayed memory, immediate memory, and total RBANS scores among male patients with chronic schizophrenia. Prior research exploring the association between GDF-15 and cognitive function in schizophrenia remains limited. One study involving both older and younger adults demonstrated an inverse association between plasma GDF-15 levels and global cognitive performance³⁸. Our findings suggest that elevated GDF-15 levels may contribute to memory deficits and impaired cognitive function among male patients with chronic schizophrenia. The inflammatory hypothesis, a prominent theory regarding cognitive impairment in schizophrenia, posits that microglial hyperactivation leads to excessive synaptic pruning and cortical gray matter loss, ultimately impacting cognitive function^{13,61}. GDF-15 synthesis occurs in lesioned neurons, microglial cells, and the choroid plexus in the central nervous system⁶², as demonstrated in non-neuronal cells and the choroid plexus of the hippocampus in murine models. In unilateral cortical cryoinjury lesions, GDF-15-producing cells exhibit immunocytochemical markers consistent with neurons, macrophages, and activated microglia, suggesting that GDF-15 contributes to the anti-inflammatory cytokine network activated by CNS injury⁶³. In older populations, degeneration of gray and white matter structures may underlie the inverse correlation between GDF-15 levels and cognitive function^{64,65}. The expression of GDF-15 may reflect a homeostatic response to cerebral atrophy or may serve as a marker of systemic inflammation impacting the brain. We propose that elevated GDF-15 levels observed in our study may act as an anti-inflammatory factor and a compensatory response to neural injury. This mechanism could involve microglial activation, impairing neuronal plasticity and affecting gray and white matter, potentially compromising cognitive

function in male patients with chronic schizophrenia. Further studies are essential to elucidate this relationship.

This study has several limitations. First, the relatively small sample size may limit the statistical power of the findings. Second, the participants had chronic schizophrenia and were undergoing antipsychotic treatment, which may affect both cognitive function and BMI. While antipsychotic doses were standardized using a conversion factor, residual effects may still influence these outcomes. Third, the cross-sectional design of this study limits causal inference regarding the relationship between elevated GDF-15 levels, BMI, and cognitive function. Longitudinal or prospective studies are necessary to explore potential causal associations. Finally, this study only evaluated GDF-15 levels; additional related factors and pathways should be explored in future research to provide a more comprehensive understanding of GDF-15's mechanisms in schizophrenia.

CONCLUSION

In conclusion, this preliminary study indicates that male patients with chronic schizophrenia exhibit higher serum GDF-15 levels compared to healthy matched controls. Furthermore, elevated GDF-15 levels may be associated with both cognitive impairment and increased BMI in this patient population. Together, these findings support the hypothesis that GDF-15 may play a role in modulating cognitive function and BMI in schizophrenia. Further research is warranted to elucidate the mechanisms underlying the relationship between serum GDF-15 and schizophrenia.

DATA AVAILABILITY

The data supporting the results of this study are available upon request from the corresponding author.

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AUTHOR CONTRIBUTIONS

X.Z., P.C., T.G. and H.Y. were responsible for study design, statistical analysis and writing of the manuscript. T.G. and P.C. were responsible for laboratorial analysis. L.C., H.Y., W.S. and J.L. were responsible for recruiting the patients, performing the clinical

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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