

УДК 616.895.8–07–08–02:616.89–008.45/.48
<https://doi.org/10.20538/1682-0363-2025-2-59-65>

The Relationship of Hormones of the Hypothalamic – Pituitary – Thyroid Axis with Cognitive Impairment in Patients with Schizophrenia

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ABSTRACT

Aim. To study the relationship of serum fT_3 , fT_4 and TSH levels with cognitive impairment in patients with schizophrenia.

Materials and methods. The study included 74 patients with schizophrenia. Socio-demographic and clinical data were collected, the severity of psychopathological symptoms was assessed using PANSS, and cognitive functions were evaluated using BACS. Serum levels of fT_3 , fT_4 and TSH in patients were determined using enzyme immunoassay kits.

Results. In the group of men with schizophrenia, a negative correlation was found between the concentration of fT_3 and verbal fluency ($r_s = -0.325$; $p = 0.033$), whereas in women, a positive correlation was found between the concentration of fT_4 and motor skills ($r_s = 0.372$; $p = 0.039$).

Conclusion. The study revealed a linear relationship between thyroid hormones and cognitive impairment in patients with schizophrenia, but the nature of the relationship found differed in men and women. The results of the study confirm the need for regular dynamic monitoring of thyroid hormone levels in patients with schizophrenia in order to prevent the progression of cognitive impairment.

Keywords: schizophrenia, thyroid hormones, neurocognitive disorders, verbal fluency, motor skills

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The study was conducted within the state assignment No. 075–01392–23–00 “Personalized diagnosis and therapy of polymorbid patients with schizoaffective disorders”, registration number 123041900006–4.

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Mental Health Research Institute of Tomsk NRMC (Minutes No. 157 dated November 11, 2022).

For citation: Kornetova E.G., Galkin S.A., Lobacheva O.A., Tiguntsev V.V., Mednova I.A., Kornetov A.N. The Relationship of Hormones of the Hypothalamic – Pituitary – Thyroid Axis with Cognitive Impairment in Patients with Schizophrenia. *Bulletin of Siberian Medicine*. 2025;24(2):59–65. <https://doi.org/10.20538/1682-0363-2025-2-59-65>.

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Связь гормонов гипоталамо-гипофизарно-тиреоидной оси с когнитивными нарушениями у больных шизофренией

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РЕЗЮМЕ

Цель. Изучить связь показателей тиреотропного гормона (ТТГ) и свободных фракций T_3 , T_4 в сыворотке крови с когнитивными нарушениями у больных шизофренией.

Материалы и методы. В исследование включены 74 пациента с шизофренией. Собраны социально-демографические и клинические данные, проводилась оценка тяжести психопатологической симптоматики с использованием PANSS, а также когнитивных функций с помощью BACS. Уровень свободных фракций T_3 , T_4 и ТТГ в сыворотке крови у пациентов определяли с помощью наборов для иммуноферментного анализа.

Результаты. В группе мужчин больных шизофренией выявлена отрицательная корреляция между концентрацией T_3 св. и речевой беглостью ($r_s = -0,325$; $p = 0,033$), тогда как у женщин обнаружена положительная корреляция между концентрацией T_4 св. и моторными навыками ($r_s = 0,372$; $p = 0,039$).

Заключение. Исследование показало, что существует линейная связь между гормонами щитовидной железы и когнитивными нарушениями у пациентов с шизофренией, однако характер выявленной связи отличается у мужчин и женщин. Результаты данного исследования подтверждают необходимость регулярного динамического мониторинга показателей ТТГ и тиреоидных гормонов у пациентов с шизофренией с целью предотвращения прогрессирования когнитивных нарушений.

Ключевые слова: шизофрения, тиреоидные гормоны, нейрокогнитивные нарушения, речевая беглость, моторные навыки.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проведено в рамках выполнения государственного задания No 075-01392-23-00 «Персонализированная диагностика и терапия больных полиморбидными расстройствами шизофренического и аффективного спектра», регистрационный номер 123041900006-4.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом и НИИ психического здоровья Томского НИМЦ (протокол № 157 от 18.11.2022).

Для цитирования: Корнетова Е.Г., Галкин С.А., Лобачева О.А., Тигунцев В.В., Меднова И.А., Корнетов А.Н. Связь гормонов гипоталамо-гипофизарно-тиреоидной оси с когнитивными нарушениями у больных шизофренией. *Бюллетень сибирской медицины*. 2025;24(2):59–65. <https://doi.org/10.20538/1682-0363-2025-2-59-65>.

INTRODUCTION

Schizophrenia is a mental disorder characterized by the presence of positive and negative symptoms and cognitive impairment, a chronic course, and a functional decline resulting in reduced quality of life and disability [1, 2]. Studies show that cognitive impairment manifests before the onset of the illness and is present in approximately 75–84% of patients with schizophrenia [3, 4]. The etiology and pathogenesis of neurocognitive deficits in schizophrenia are not fully understood, but some studies have shown that

neuroendocrine disorders may be associated with cognitive symptoms [4–6].

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) play an important role in brain differentiation and growth and, consequently, in cognitive function. In addition, thyroid hormones maintain normal glucose metabolism, which is essential for brain function [7]. A number of researchers have shown that people with hypothyroidism have troubles in many cognitive functions, such as attention, memory, language, visual perception, and executive functions [8, 9]. Additionally, there are studies

confirming that patients with even mild or subclinical hypothyroidism have reversible cognitive impairment [8, 10]. Moreover, people with thyrotoxicosis have been found to have impaired concentration and executive function [11]. Both increased and decreased thyroid-stimulating hormone (TSH) levels are associated with cognitive impairment [12].

Neurohormonal imbalance plays an essential role in the pathogenesis of many mental disorders. Several previous studies in patients with schizophrenia have reported abnormalities in the hypothalamic–pituitary–thyroid axis in the form of decreased T_3 and T_4 , and increased thyroid autoantibody production [13, 14]. Relatively recent studies show that in female patients with schizophrenia, free T_3 ($T_{3\text{ free}}$) and T_4 ($T_{4\text{ free}}$) levels are decreased, and TSH levels are elevated [14]. Few studies have also investigated the relationship between thyroid hormones and cognitive processes in different groups of diseases due to the critical role of thyroid dysfunction in neurodegeneration and development of the nervous system [15, 16]. For example, Kapaki et al. [16] found that the direct effect of thyroxine on cholinergic neurons increases the risk of developing Alzheimer's disease. In a study of patients with early psychosis, higher levels of $T_{4\text{ free}}$ (but not TSH or thyroid autoantibodies) were associated with better cognitive performance, such as attention and thinking [15, 17]. Another study of 93 patients with schizophrenia found that $T_{3\text{ free}}$ levels were associated with better performance on the Mini-Mental State Examination (MMSE), but not with positive, negative, or general psychopathological symptoms [18].

The aim of the study was to investigate the association of serum fT_3 , fT_4 , and TSH levels with cognitive impairment in patients with schizophrenia.

MATERIALS AND METHODS

The study was conducted according to the protocol approved by the local Ethics Committee at Mental Health Research Institute of Tomsk NRMC (Minutes No.157 dated November 18, 2022). The study included 74 patients with an established diagnosis of schizophrenia receiving treatment at Mental Health Research Institute clinics. Inclusion criteria: age 18–55 years, verified diagnosis of schizophrenia according to ICD-10 criteria, patient's consent to participate in the study. Non-inclusion criteria: dependence on psychoactive substances other than tobacco, mental retardation, or dementia, neurologic history (brain injury, stroke). After obtaining patients consent, socio-demographic and clinical data were collected,

the severity of psychopathological symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) [19], and cognitive functions were assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) using normative indicators calculated for the Tomsk population [20]. Data collection and psychometric assessment of patients' condition were performed by psychiatrists.

Blood samples to determine the hypothalamic–pituitary–thyroid axis hormone levels were collected in the morning on an empty stomach from the ulnar vein into vacuum Vascette tubes. Blood serum was obtained by centrifugation at 2,000 rpm for 30 minutes. Concentrations of TSH, $T_{3\text{ free}}$, and $T_{4\text{ free}}$ in patients' serum were determined by the solid-phase enzyme-linked immunosorbent assay using reagent kits from Vector-Best JSC (Novosibirsk, Russia).

Statistical analysis was performed using Statistica software, version 12.0 for Windows (StatSoft, Inc.). Descriptive statistics were presented as the median and the interquartile range $Me [Q_1; Q_3]$, and the normality of variable distribution was assessed using the Shapiro–Wilk test. The Mann–Whitney U test and the factorial ANOVA were used to compare independent samples. The correlation analysis with the Spearman's rank correlation coefficient (r_s) was used to determine the linear relationship between the variables. Multiple linear regression was used to assess the effect of variables on cognitive function scores. The critical significance level p was 0.05.

RESULTS

The study included 74 patients with schizophrenia: 31 women and 43 men. The mean age of the patients was 34 [26; 43] years. Twenty-five (33.8%) patients had higher education, 8 (10.8%) – incomplete higher education, 28 (37.8%) – vocational secondary education, and 13 (17.6%) – secondary education. The duration of the disease was 9 [5; 21] years, and the age of onset was 22 [19; 27] years. The PANSS total score was 96 [88; 105], the positive symptom subscale score – 18 [16; 23], the negative symptom subscale score – 24 [22; 28], and the general psychopathological symptom subscale score – 51 [46; 56].

All patients included in the study received baseline antipsychotic therapy with atypical antipsychotics (risperidone, quetiapine, olanzapine, clozapine) – 58 (78.4%) people and conventional antipsychotics (haloperidol, chlorprothixene, trifluoperazine) – 16 (21.6%) individuals in therapeutic doses approved by the Ministry of Health of the Russian Federation.

The median total antipsychotic exposure (expressed as chlorpromazine equivalent (CPZeq)) was 360 [199; 500] mg/day, and the duration of baseline therapy was 8 [3; 20] years.

Serum $T_{3 \text{ free}}$ and $T_{4 \text{ free}}$ concentrations in patients were 5.51 [4.75; 6.65] pmol/l and 17.05 [14.67; 18.9] pmol/l, respectively, and TSH level was 2.15 [1.38; 3.16] mIU/l. $T_{3 \text{ free}}$, $T_{4 \text{ free}}$, and TSH concentrations were comparable in men and women ($p > 0.05$), whereas men and women were also comparable in age and clinical, therapeutic, and neuropsychological parameters ($p > 0.05$). A negative correlation was found between the PANSS positive symptom score and $T_{3 \text{ free}}$ ($r_s = -0.335$; $p = 0.005$) and $T_{4 \text{ free}}$ ($r_s = -0.444$; $p < 0.001$). A correlation was also revealed between the PANSS total score and the TSH concentration ($r_s = 0.245$; $p = 0.045$).

Scores on the verbal and working memory subscales were 37 [32; 43] and 18 [16; 21], respectively. The scores on the motor skill, verbal fluency, attention, and executive function subscales were 54 [44; 64], 39 [32; 49], 41 [34; 47], and 17 [15; 19], respectively. Based on the BACS [20] conducted earlier, a significant decrease in performance was observed for

all subtests ($p < 0.001$) in the studied group of patients with schizophrenia. Gender had a significant effect on all cognitive domains examined ($F(6.67) = 3.237$; $p = 0.007$). In addition, a statistically significant relationship was found in men between working memory and PANSS positive symptom scores ($r_s = -0.326$; $p = 0.048$), and between verbal fluency and PANSS negative symptom scores ($r_s = -0.547$; $p < 0.001$). In women, however, the only association found was between the duration of baseline therapy and motor skills ($r_s = 0.434$; $p = 0.023$).

We did not find statistically significant correlations between cognitive tests and the functioning of the hypothalamic–pituitary–thyroid axis in the total sample of patients with schizophrenia ($p > 0.05$). However, taking into account the patients gender, we obtained significant relationships: in the group of male patients with schizophrenia, we found a negative correlation between $T_{3 \text{ free}}$ concentration and verbal fluency ($r_s = -0.325$; $p = 0.033$), while in the group of females, we found a positive correlation between $T_{4 \text{ free}}$ concentration and motor skills ($r_s = 0.372$; $p = 0.039$) (Table 1).

Table 1

Correlations between TSH, Thyroid Hormones, and Cognitive Function in Patients with Schizophrenia, R_s							
Parameter		I	II	III	IV	V	VI
Total sample of patients with schizophrenia, $n = 74$							
TSH	r_s	-0.033	-0.032	0.029	-0.138	0.027	0.026
	p	0.777	0.788	0.808	0.242	0.817	0.826
$T_{3 \text{ free}}$	r_s	-0.036	-0.024	-0.013	-0.228	-0.167	0.064
	p	0.763	0.841	0.911	0.051	0.156	0.589
$T_{4 \text{ free}}$	r_s	0.035	0.148	0.148	-0.004	0.009	0.099
	p	0.764	0.209	0.209	0.974	0.936	0.401
Men with schizophrenia, $n = 43$							
TSH	r_s	-0.122	0.143	-0.084	-0.199	0.062	-0.127
	p	0.434	0.360	0.592	0.200	0.692	0.419
$T_{3 \text{ free}}$	r_s	-0.075	-0.108	-0.158	-0.325*	-0.266	0.029
	p	0.633	0.492	0.310	0.033*	0.085	0.852
$T_{4 \text{ free}}$	r_s	-0.080	0.219	-0.046	-0.126	-0.117	0.044
	p	0.609	0.158	0.772	0.420	0.456	0.781
Women with schizophrenia, $n = 31$							
TSH	r_s	0.148	-0.254	0.143	-0.034	-0.028	0.152
	p	0.426	0.168	0.442	0.854	0.883	0.413
$T_{3 \text{ free}}$	r_s	0.058	0.134	0.124	0.018	0.011	-0.058
	p	0.755	0.472	0.505	0.921	0.954	0.757
$T_{4 \text{ free}}$	r_s	0.147	0.040	0.372*	0.150	0.210	0.194
	p	0.429	0.830	0.039*	0.421	0.258	0.295

Note: I – memorization of a list of words, II – a sequence of numbers, III – a motor test with chips, IV – verbal fluency, V – “Cipher”, VI – “Tower of London”. * – statistically significant differences.

Based on the correlation analysis data, in order to determine the influence of clinical and biochemical parameters on cognitive function in male and female

patients with schizophrenia, a series of separate regressions were additionally conducted, where the following were used as independent variables: scores

on the PANSS positive (1) and negative (2) symptom subscales, and $T_{3 \text{ free}}$ concentration (3) for men; duration of baseline therapy (1) and $T_{4 \text{ free}}$ concentration (2) for women. In the male group, the predictive model for the verbal fluency parameter was statistically significant ($F(3,33) = 4.714$; $p = 0.007$). The R^2 value was 0.301, indicating that scores on the PANSS positive and negative symptom subscales and serum $T_{3 \text{ free}}$ concentration explained approximately 30% of the variability in verbal fluency in male patients with schizophrenia. Statistically significant predictors were the scores on the PANSS negative symptom subscale ($t = -2.515$; $p = 0.016$) and the $T_{3 \text{ free}}$ concentration ($t = -2.985$; $p = 0.011$) (Table 2).

Table 2

Coefficients of the Multiple Linear Regression Model for the Relationship of Verbal Fluency with Clinical and Biochemical Parameters in Men with Schizophrenia				
Parameter	Coefficient B	Standard Error	Significance (t)	Significance (p)
Constant	75.997	12.539	6.061	0.001
PANSS _p (score)	-0.104	0.428	-0.243	0.808
PANSS _n (score)	-1.118	0.444	-2.515	0.016
$T_{3 \text{ free}}$ (pmol / l)	-1.348	0.369	-2.985	0.011
$R = 0.547$; $R^2 = 0.301$				

Note: PANSS_p – scores on the positive symptom subscale, PANSS_n – scores on the negative symptom subscale.

In the female group, the model for predicting the motor skill scores was statistically significant ($F(2,34) = 3.545$; $p = 0.039$). R^2 was 0.272, indicating that the duration of therapy and the concentration of $T_{4 \text{ free}}$ in the blood serum explain approximately 27% of the variability in the motor skill scores in female patients with schizophrenia. Both predictors were statistically significant: the duration of baseline therapy ($t = 2.038$; $p = 0.049$) and the $T_{4 \text{ free}}$ concentration ($t = 2.816$; $p = 0.032$) (Table 3).

Table 3

Coefficients of the Multiple Linear Regression Model for the Relationship of Motor Skills with Clinical and Biochemical Parameters in Women with Schizophrenia				
Parameter	Coefficient B	Standard Error	Significance (t)	Significance (p)
Constant	24.281	11.038	2.199	0.034
Duration of therapy (years)	0.534	0.262	2.038	0.049
$T_{4 \text{ free}}$ (pmol / l)	1.164	0.641	2.816	0.032
$R = 0.415$; $R^2 = 0.272$				

DISCUSSION

The present study investigated the relationship between indices of cognitive function and hormones of the hypothalamic–pituitary–thyroid axis, as well as some clinical and dynamic parameters in patients with schizophrenia. The results of the study revealed a linear relationship between thyroid hormones and cognitive functions, but the direction of this relationship differed between male and female patients. In males, high levels of $T_{3 \text{ free}}$ in the blood serum were associated with lower indices of verbal fluency, whereas in females, the concentration of $T_{4 \text{ free}}$ correlated directly with motor skill scores. The study also found that factors influencing cognitive function differed between males and females with schizophrenia. In the resulting regression model, the significant predictors of verbal fluency in males were the $T_{3 \text{ free}}$ concentration and the severity of negative symptoms. In females, the predictors of the motor skill score were the duration of baseline therapy and the $T_{4 \text{ free}}$ concentration.

Thyroid hormone levels are known to be important for cognitive abilities, including motor function and language. Studies investigating the relationship between thyroid hormone levels and cognition in patients with mental disorders are limited. One study of patients with psychosis found that changes in $T_{3 \text{ free}}$ within the normal range (reference values) had a significant effect primarily on the attention [15]. Another study in patients with schizophrenia showed that higher $T_{3 \text{ free}}$ levels were associated with higher MMSE scores [18]. The same study emphasized that T_3 replacement therapy could improve cognitive function in patients with schizophrenia. However, in our study, inverse relationships were found for $T_{3 \text{ free}}$ only in males, suggesting that $T_{3 \text{ free}}$ levels are more strongly associated with cognitive symptoms in males with schizophrenia than $T_{3 \text{ free}}$ concentrations.

Some studies have shown that changes in $T_{4 \text{ free}}$ in patients with psychosis affect some cognitive functions [15, 17]. Increased $T_{4 \text{ free}}$ levels in patients with psychosis are associated with improved attention, but no such relationship was found in the healthy control group [15]. In our study, we found a linear relationship between $T_{4 \text{ free}}$ levels and motor function scores only in females, suggesting that $T_{4 \text{ free}}$ levels play a more important role in cognitive function in patients with schizophrenia than $T_{3 \text{ free}}$.

We also found significant relationships between thyroid hormone levels and positive symptoms on the PANSS, although some authors have previously reported no such relationships [5, 18]. The study

it confirms the effect of thyroid hormones not only on cognitive functions, but also on the severity of psychopathological symptoms of schizophrenia.

However, our study has some limitations. Although the study used a comprehensive neurocognitive test battery, the number of patients was relatively small, which could have a negative effect on statistical significance. Moreover, due to the cross-sectional nature of the study, it was impossible to establish a causal relationship between the changes found. In addition, we studied a group of chronic patients with schizophrenia who were receiving long-term antipsychotic therapy, and we cannot exclude the influence of therapy on our results, nor can we be sure that patients adhered to the treatment regimen in the long term.

CONCLUSION

The study showed that there is a linear relationship between thyroid hormones and cognitive impairment in patients with schizophrenia, however, the nature of the relationship identified differs between male and female patients. The results of this study confirm the need for regular dynamic monitoring of TSH and free thyroid hormone levels in patients with schizophrenia to prevent progression of cognitive impairment. Further studies with larger numbers of patients are needed to better understand the relationship between thyroid dysfunction and cognitive symptoms and to consider the possibility of including hormone replacement therapy in the treatment strategy for patients with schizophrenia.

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Author contribution

Kornetova E.G. – conception and design, clinical, psychopathological, and psychometric examination of the sample, review of publications on the topic of the article, critical revision of the manuscript for important intellectual content. Galkin S.A. – drafting of the manuscript, statistical analysis of the data. Lobacheva O.A. – laboratory analysis of the parameters, review of publications on the topic of the article. Tiguntsev V.V. – preparation of the sample, maintenance of the database. Mednova I.A. – examination of the sample, maintenance of the database. Kornetov A.N. – study design, editing of the manuscript, final approval of the manuscript for publication.

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Received 31.10.2024;
approved after peer review 07.11.2024;
accepted 14.11.2024