

Serum Cortisol and Folate Levels in Patients with Schizophrenia: Case Control Study in North of Iran

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Abstract

Introduction: Schizophrenia is a highly devastating condition characterized by frequent recurrences, cognitive decline, and emotional and functional disabilities. This study aimed to evaluate the serum levels of cortisol and folate in patients with schizophrenia and its comparison with healthy individuals.

Materials and methods: This is a case control study was performed on 66 individuals. Participants were divided into two groups schizophrenia (n=33) and control (n=33). The demographic information checklist, Simpson-Angus extrapyramidal Side Effect Scale (SAS), and Positive and Negative Syndrome Scale (PANSS) were used to collect demographic data, the severity of schizophrenia symptoms, and extrapyramidal symptoms. Then, blood samples were taken from each patient to measure serum levels of cortisol and folate.

Results: The level of folate in the schizophrenia group was significantly lower than in the healthy group and level of cortisol in the schizophrenia group was significantly higher than in the healthy group ($P < 0.0001$). No significant relationship was observed between both cortisol levels and folate levels and the mean total score of the SAS questionnaire as well as the mean total score of the PANSS questionnaire, positive symptom scores, negative symptoms scores, and general psychopathologic symptoms scores in the schizophrenic group and the control group. The cortisol levels in those with a history of psychiatric illness were significantly lower than in the healthy group ($P = 0.017$). The mean serum folate levels in patients with a history of hypothyroidism were significantly lower than in the healthy group ($P = 0.020$). Folate levels were significantly higher in smokers ($P = 0.036$).

Conclusion: The result showed that the serum folate level was significantly lower in the schizophrenia group and the serum cortisol level was significantly higher in schizophrenic patients. PANSS and SAS scores showed no association with serum cortisol and folate levels.

Keywords: Schizophrenia • Cortisol • Folate • Simpson-Angus • Extrapyramidal side effect scale • Positive and negative syndrome scale

Introduction

Association between serum cortisol and folate levels has been demonstrated in patients with schizophrenia. About 1% of people worldwide suffer from schizophrenia. It is a debilitating and costly disease since treatment resistant symptoms are very usual. Schizophrenia is a serious psychiatric disorder whose cause is still unknown. Evidence from animal experiments, clinical treatment courses, and neuroimaging studies suggests that abnormal neural development and gray matter deficits in different areas of the brain are involved in the pathogenesis of schizophrenia [1,2]. Clinical data shows a weakened biological response to stress in schizophrenic

patients, which is related to dysregulation and dysfunction of the Hypothalamic Pituitary Adrenal (HPA) axis and changes in cortical stress response molecules. Impaired HPA axis in patients with schizophrenia has been proposed to be related to the enzyme as well as neurotransmitter systems abnormalities, which are responsible for the HPA axis, and limbic system structural abnormalities [3,4]. It was shown that increased levels of glucocorticoids and cortisol result in neurotoxicity, inhibition of neurogenesis, atrophy, and neuronal death. Increased corticosteroids including cortisol are related to structural changes, mostly reduction in the hippocampus volume and prefrontal cortex. The hippocampus and prefrontal cortex are the main targets for glucocorticoids and cortisol, and molecular abnormalities in cortisol responses have been reported in schizophrenia. Chronically

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increased levels of cortisol can decrease neurogenesis and synaptic plasticity in the hippocampus, resulting in cognitive impairment [5,6]. A meta-analysis study revealed reduced volume as well as neuron numbers in several subfields of the left hippocampus in schizophrenic patients. Circulating cortisol has been linked to reductions in hippocampal volume in first episode psychosis, which shows the deleterious impacts of stress early in the disease. HPA axis abnormalities may lead to cortisol level elevation. Increased serum baseline cortisol levels have been reported in schizophrenic patients, however, there are other studies with opposing results [7,8].

Folate or folic acid is one of the B vitamins which are essential for cell division and maintenance. Folate facilitates the S-adenosylmethionine production, a methyl group donor for various reactions of methylation, through the conversion of homocysteine into methionine. It was shown that folate is crucial for neuronal function [9,10]. Folate insufficiencies may be associated with the increased risk of neurodevelopmental complaints, psychiatric illnesses, and dementia. Reduced levels of folate may be related to schizophrenia by acting *via* increasing homocysteine or by homocysteine independent impacts on neuronal progenitor division or through altered one carbon metabolism. Folate is a substrate for Methylene tetrahydrofolate Reductase (MTHFR), an enzyme that catalyzes the conversion of 5, 10 methyl tetrahydrofolate to 5 methyl tetrahydrofolate, which remethylated homocysteine to methionine. Therefore, the lack of folate may increase the level of homocysteine, which was shown to be associated with schizophrenia in its elevated levels [11,12]. Folate deficiency has been associated with several neuropsychiatric disorders, including schizophrenia. Evidence suggests that folate supplementation may be promising for the treatment of negative symptoms in schizophrenia while it does not appear to affect positive symptoms. On the other hand, in some studies, blood folate levels appear to decrease in patients with schizophrenia [13,14]. Because the prevalence of folate deficiency and hyperhomocysteinemia in the United States has decreased significantly since the mandatory enrichment of cereal grains with folate in 1998 and has subsequently decreased the prevalence of schizophrenia, folate deficiency has been identified as a risk factor for schizophrenia [15,16]. A review of the literature showed that such studies have been done very little in our country and the results in the world are contradictory. Therefore, we performed a study to compare the serum levels of cortisol and folate in patients with schizophrenia and healthy individuals [17].

Material and Methods

Study design and setting

The study was designed and conducted under the case control method. This study was performed on patients referred to specialized psychiatric clinics of 5th Azar Educational and Medical Center in Gorgan, North of Iran, from September 2021 to March 2022 [18].

Participants

Patients with schizophrenia were selected after approval by a psychiatrist based on inclusion and exclusion criteria and the Diagnostic and Statistical manual of mental disorders, fifth edition (DSM-5) criteria. The inclusion criteria were including, having at least

18 years of age, confirmation of schizophrenia by a psychiatrist in the schizophrenia group based on DSM-5 criteria, absence of any psychiatric symptoms [19]. Such as depression or a history of psychiatric illness in the patient or parents in the control group, obtaining informed written consent from the patient or patient caregiver, and absence of other physical and psychiatric illnesses in patients diagnosed with schizophrenia. Patients who were not referred for cortisol and folate tests and patients who were dissatisfied with participation during the study, and those use folate supplements were excluded from the study. The control group was selected from patients referred to the internal clinic of 5th Azar Hospital in Gorgan who did not have a psychiatric illness. The subjects in the control group were matched with the schizophrenia group in terms of gender and age [20].

Study size

The sample size in this study was calculated. The sampling method in this study was the convenience sampling method. Using the following formula, the sample size was defined as 66 people, of which 33 were in the case group and 33 were in the control group [21,22].

$$n = (s_1^2 + s_2^2) * (Z_{1-\alpha} / 2 + Z_{1-\beta})^2 / d^2$$

Where s_1^2 and s_2^2 are the variance of cortisol or folate levels in patients. α is Significance level and $1-\beta$ is study power. d is the minimum difference in folate/cortisol level between the patient and control groups.

Measurement

Demographic information questionnaire: A questionnaire was used to record the demographic characteristics of the patients.

Schizophrenic symptoms questionnaire

In this study, the Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of positive and negative symptoms in schizophrenic patients. For extrapyramidal symptoms of schizophrenia Simpson-Angus Extrapyramidal Side Effects Scale (SAS) was used [23,24].

- **PANSS:** This questionnaire was used to assess the severity of schizophrenia symptoms in patients, which included three question categories, 7 questions for positive symptoms, 7 questions for negative symptoms, and 16 questions for general symptoms [25]. The questions were answered based on 7-point scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme). The validity of this questionnaire in Iran was determined. And the Cronbach's alpha was defined as 0.77 [26].
- **SAS:** This questionnaire was used to assess the severity of extrapyramidal symptoms of schizophrenia in patients, which included 10 questions and symptoms. The questions of this questionnaire were scored based on a 5-point scale with a score of 0 to 4 [27]. This questionnaire is validated in Iran.

Cortisol and folate measurements

Between 7 am to 8 am, 3 cc of venous blood was collected from each patient. The sample was stored in a tube containing 3.5%

sodium citrate to test serum cortisol and folic acid levels [28]. The samples were stored at -20°C . Measurement of cortisol is done by Cortisol AccuBind ELISA Kit (Monobind Inc., USA) and measurement of folate is done by Folate AccuBind ELISA Kits (Monobind Inc., USA) via ELISA technique. 25 μl of standards, controls, and samples were added into the wells and then 50 μl of the conjugate solution was added to all wells [29]. The plate was shaken gently for 15 seconds and incubated for 60 minutes at 37°C . After removing the plate from the incubator, 50 microliters of biotin solution were added to each well and incubated for 30 minutes at 37°C . Then the contents of the wells were emptied and then washed with 350 microliters of buffer and this repeated for 4 more times [30]. 100 μl of ready to use dye substrate was added to all wells and incubated for 15 minutes at room temperature and in a dark place, then 50 μl of the reaction stop solution was added in the same manner as the dye substrate solution. Then the absorption of each well was read at a wavelength of 450 nm after a maximum of 10 minutes with the multiple plate microplate reader URIT-660 (URIT Medical Electronic Co., China) devices [31].

Statistical analysis

Data are described by central and dispersion indices (mean, median, standard deviation), and tables and graphs. In the case of normality, the independent T-Test was used and in the absence of normality assumptions, the Mann-Whitney U test was used [32]. A correlation test was used to examine the relationship between variables and cortisol and folic acid levels in each group of patients and control. Linear regression analysis was used to compare the levels of cortisol and folic acid in the two groups of patients and controls, taking into account the age and Gender of the subjects in the study [33]. The analyzes were performed using SPSS software version 16 and at a significant level of 0.05.

Results and Discussion

Participants

Sixty-six individuals participated in this study. Participants in the study were admitted into two groups control ($n=33$) and schizophrenia ($n=33$).

Descriptive data

The mean and standard deviation of the age of the participants in the study was 39.89 ± 12.22 years with a range of 18-75 years. The mean and standard deviation of the Body Mass Index (BMI) of the participants was 24.86 ± 3.69 . Among participants, 51.5% were male, 62.1% were single, 81.3% had a diploma and under diploma level of education, 77.3% were Fars, 28.8% had medical illness history, and 45.5% had hypothyroidism [34]. Also, 28.8% had a history of Electroconvulsive Therapy (ECT). A small number had a history of smoking (6.1%) In this study, the serum levels of cortisol and folate in patients with schizophrenia referred to the psychiatric clinic were studied [35]. The level of cortisol in the schizophrenia group was significantly higher than in the healthy group. The level of folate in patients with schizophrenia was significantly lower than in healthy individuals. The cortisol levels in those with a history of psychiatric illness were significantly lower than in the healthy group. The mean serum folate levels in patients with a history of hypothyroidism were

significantly lower and in smokers were significantly higher [36]. Moreover, no significant relationship was observed between both cortisol levels and folate levels and the mean total score of the SAS questionnaire as well as the mean total score of the PANSS questionnaire, positive symptom scores, negative symptoms scores, and general psychopathologic symptoms scores in the schizophrenic group and the control group [37].

In the present study, the levels of serum folate were significantly lower in the schizophrenia group. The result of in Korea also showed that patients with schizophrenia had significantly lower levels of folate in comparison to the control group. They showed that the low folate level patient group had significantly higher homocysteine levels, which itself via neurotoxic mechanism has an effect on schizophrenia. In another study in Iran, it was found that patients with schizophrenia had significantly lower folate levels than healthy individuals. Study showed significantly lower serum levels of folate in the schizophrenia group [38]. They showed that drug naïve, first episode schizophrenia presents diminished serum levels of folate, decreased brain derived neurotropic factor, and increased homocysteine, which might play a significant role in the neurodevelopmental process of schizophrenia as well as its clinical manifestation [39]. In a meta-analysis, the levels of serum folate were significantly lower in schizophrenia patients than in controls and the reduced folate level was observed in both Asian and European patients. They suggested decreased folate as a risk factor for schizophrenia. In a meta analysis, it was reported that decreased levels of folate were associated with schizophrenia risk in total studies as well as in subgroups of Caucasians, English publications, Asians, acute schizophrenia patients, and age less than 50 with the great enough powers [40]. Another meta-analysis on 20 studies also confirmed that serum folate level was significantly lower in cases with schizophrenia than in healthy individuals. Assessed the relationship between serum folate levels in patients with schizophrenia based on sex and reported that serum folate levels might be related to schizophrenia irrespective of sex and folate administration could be advantageous for schizophrenia treatment. Study in the schizophrenia group, a significant negative relationship was found between serum levels of folate and PANSS total scores and PANSS negative symptom scores. However, in the current study, no relationship was found between folate level and PANSS negative, positive or total score [41].

In the current study, the level of serum cortisol was significantly higher in the schizophrenia group. Evaluated the serum cortisol levels in patients with schizophrenia. In this study, 60 patients with schizophrenia, 70 healthy relatives, and 60 healthy volunteers were studied. In this study, serum cortisol levels in the schizophrenia group compared with healthy relatives and control group were significantly higher. Increasing serum cortisol levels in schizophrenic patients may be related to the role of cortisol in schizophrenic pathophysiology. Also, increasing serum cortisol levels in first degree relatives compared with the control group shows that similar pathophysiological trends may have a role in people without any symptoms but with a genetic talent for schizophrenia. Also demonstrated that in schizophrenia patients without metabolic syndrome, the cortisol blood level was significantly higher than the healthy controls 40 compared the serum cortisol in schizophrenic patients and the control group. In this study, 66 patients with chronic schizophrenia and 28 healthy men participated. Serum cortisol levels

in patients were 12.48 ± 3.2 $\mu\text{g/dl}$ and in the control group was 10.31 ± 3.1 $\mu\text{g/dl}$ which was significantly higher in schizophrenic patients than in healthy subjects, no significant difference was observed between the schizophrenia and control groups regarding serum cortisol level. Study showed that schizophrenia patients who underwent treatment and does not show important clinical symptoms of schizophrenia may have mildly lowered salivary cortisol levels. Study results, serum cortisol level were significantly lower in

schizophrenia after treatment with antipsychotics than its baseline value. Study at baseline, no association was observed between serum cortisol levels in schizophrenia patients in PANSS positive and negative sub scores. However, after treatment with antipsychotic serum cortisol level presented a strong association PANSS positive and negative sub scores. In the present study, no association was observed between serum cortisol levels and PANSS scores (Table 1).

Variables	No. (%)
Gender	
Male	24 (51.5)
Female	32 (48.5)
Marital status	
Single	41 (62.1)
Married	25 (37.9)
Education level	
Under diploma	28 (42.4)
Diploma	25 (37.9)
University education	13 (19.7)
Ethnicity	
Turkmen	4 (6.1)
Fars	51 (77.3)
Sistani	7 (10.6)
Other	4 (6.1)
History of medical illness	
Yes	19 (28.8)
No	47 (71.2)
History of hypothyroidism	
Yes	30 (45.5)
No	36 (54.5)
History of ECT	
Yes	19 (28.8)
No	47 (71.2)
History of smoking	
Yes	4 (6.1)
No	62 (93.9)

Table 1. Frequency distribution of demographic characteristics of participants in the study.

The results of SAS and PANSS questionnaires

SAS questionnaire: The mean score of the SAS questionnaire in patients was 2.98 ± 2.12 . The minimum score received from this questionnaire in patients was 0 and the maximum was 8.

PANSS questionnaire

The mean score of the PANSS questionnaire in patients was 102.12 ± 42.73 . The minimum score received from this questionnaire in patients was 33 and the maximum was 74.

- **Positive symptoms:** The mean score of schizophrenia patients was 30.51 ± 2.24 for positive symptom questions. The minimum score received from this set of questions was 20 and the maximum was 38.

- **Negative symptoms:** The mean score of schizophrenia patients was 22.03 ± 5.20 for negative symptom questions. The minimum score received from this set of questions was 15 and the maximum was 39.
- A positive and significant correlation was observed between the scores of positive and negative symptoms in patients with schizophrenia ($r=0.613$, $P<0.01$).
- **General psychopathology:** The mean score of schizophrenia patients was 49.87 ± 7.07 for psychopathologic symptom questions. The minimum score received from this set of questions was 31 and the maximum was 69 (Table 2).

Questionnaire variables	Mean \pm SD	Range
SAS	2.93 ± 2.12	0-8
PANSS		
Positive symptoms	30.51 ± 2.24	20-38
Negative symptoms	22.03 ± 5.20	15-39
General psychopathology	49.87 ± 7.07	31-69
Total	102.12 ± 42.73	74-133

Table 2. The mean and standard deviations of PANSS and SAS.

Relationship between the findings of the questionnaires

As can be seen in Table 3, a direct relationship was observed between general psychopathological symptoms or negative

symptoms and total score. A positive and significant relationship was observed between negative symptoms and total score and between positive symptoms and total score of PANSS ($P < 0.05$). On the other hand, no significant relationship was observed between the parameters of PANSS and SAS questionnaires ($P > 0.05$).

Variable	PANSS					SAS		
	Negative symptoms		Positive symptoms		Total Score	Total Score		
PANSS	Correlation coefficient	P	Correlation coefficient	P	P	Correlation coefficient	P	
General psychopathology	0.678	0	0.191	0.288	0.897	0	0.193	0.281
Negative symptoms			0.125	0.488	0.827	0	0.196	0.275
Positive symptoms					0.49	0.004	0.167	0.345
Total score							0.243	0.173

Table 3. Relationship between questionnaire findings in the schizophrenia group.

Serum levels of cortisol and folate

The level of cortisol in the schizophrenia group was significantly higher than in the healthy group ($P < 0.0001$). Also, the level of folic

acid in patients with schizophrenia was significantly lower than in healthy individuals ($P < 0.0001$) (Table 4).

Variable	Schizophrenia patients	Healthy individuals	P-value
	Mean ± SD	Mean ± SD	
Serum Cortisol levels	54.98 ± 26.90	18.84 ± 9.16	<0.0001
Serum folate levels	2.21 ± 2.20	14.69 ± 11.68	<0.0001

Table 4. Mean serum levels of Cortisol and folate in the patients with schizophrenia and healthy individuals.

Correlation between serum cortisol levels and questionnaire parameters

Relationship between serum cortisol levels and PANSS questionnaire: In this study, no significant relationship was observed between cortisol levels and the mean total score of the PANSS questionnaire, positive symptom scores, negative symptoms scores, and general psychopathologic symptoms scores in the schizophrenic group and the control group.

Relationship between serum cortisol levels and SAS questionnaire: No significant relationship was observed between cortisol levels and the mean total score of the SAS questionnaire.

Correlation between serum folate level and questionnaire parameters

Relationship between serum folate levels and PANSS questionnaire: In this study, no significant relationship was observed between folate levels and the mean total score of the PANSS questionnaire, positive symptom scores, negative symptoms scores, and general psychopathologic symptoms scores in the schizophrenic group and the control group.

Relationship between serum folate levels and SAS questionnaire: No significant relationship was observed between folate levels and the mean total score of the SAS questionnaire (Table 5).

Questionnaire variable	Serum cortisol levels		Serum folate levels	
	Correlation coefficient	P value	Correlation coefficient	P-value
SAS Total	0.12	0.506	0.253	0.156
PANSS Positive symptoms	0.102	0.571	0.072	0.691
Negative symptoms	0.243	0.172	-0.228	0.202

General psychopathologic Symptoms	0.141	0.433	-0.111	0.537
Total	0.212	0.236	-0.131	0.467

Table 5. Correlation between serum cortisol and Serum folate levels and questionnaire parameters.

Relationship between demographic variables and cortisol and folate levels

The results of the Mann-Whitney test showed that the mean serum folate levels in patients with a history of hypothyroidism were

Variable	Yes	No	Z	P-value
Cortisol levels				
History of psychiatric illness	12.16 ± 10.27	57.77 ± 26.45	-2.38	0.017
History of using psychiatric drugs	27.12 ± 10.16	77.45 ± 57.26	-2.38	0.017
Folate levels				
History of hypothyroidism	1.94 ± 1.89	5.30 ± 2.78	-2.318	0.02
History of smoking	4.70 ± 2.73	1.94 ± 1.86	-2.097	0.036

Table 6. Relationship between demographic variables and cortisol and folic acid levels.

The results of logistic regression analysis for the relationship between measured serum cortisol and folate levels and schizophrenia showed that there was no significant relationship, one of the reasons could be the small sample size.

Conclusion

According to the result of the present study, the serum cortisol was significantly higher and folate levels was significantly lower in the schizophrenia group. It is suggested that in future studies the effect of supplements on schizophrenia be investigated and that clinical trials be performed on this issue.

Limitations

Due to the COVID-19 pandemic and health protocols, there was a decrease in the number of referrals to health centers and as a result, the lack of patients referred to psychiatric clinics and reduced hospitalization of psychiatric patients in the ward led to a prolongation of the sampling process. The sample size of this study was small and it is recommended to perform the future studies with larger sample size.

Ethical consideration

This study is approved by the ethics committee of Golestan University of Medical Sciences.

significantly lower than in the healthy group ($P=0.020$). Also, cortisol levels in those with a history of psychiatric illness were significantly lower than in the healthy group ($P=0.017$). Folate levels were significantly higher in smokers ($P=0.036$) (Table 6).

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Conflicts of Interest

There are no conflicts of interest to declare.

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