

SERUM CORTISOL IN PATIENTS WITH SCHIZOPHRENIA: ASSOCIATION WITH PSYCHOPATHOLOGY AND RESPONSE TO ANTIPSYCHOTICS

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ABSTRACT

Background: Previous studies suggested that alterations in serum cortisol levels may play a role in the pathophysiology of schizophrenia. Imbalance in serum cortisol levels may be related to responsiveness to antipsychotic treatment.

Aim: To compare serum cortisol levels between patients with schizophrenia and healthy controls and to evaluate hormone association with psychopathology and response to antipsychotics in patients with schizophrenia.

Material and Methods: This clinical prospective study included 60 patients with schizophrenia and 40 healthy age and sex matched controls. All patients experienced an acute exacerbation of the illness (PANSS: P1 and P3 \geq 4). Clinical evaluation of patients was performed using the Positive and Negative Symptom Scale. A questionnaire for socio-demographic and clinical data collection was used. For the purposes of the study, the examined group was divided in two subgroups: responders and nonresponders. Serum cortisol and DHEA-S levels were measured at baseline in all participants and after 3 and 6 weeks of the antipsychotic treatment in patients with schizophrenia.

Results: Patients with schizophrenia had significantly higher serum cortisol levels compared with control group. Responders had significantly higher serum cortisol levels compared with nonresponders. From the three analyzed factors (serum cortisol, DHEA-S and cortisol/DHEA-S ratio), only serum cortisol was significant factor for antipsychotic treatment response. Responders group had significant correlation between serum cortisol and PANSS positive scale score.

Conclusion: Elevated serum cortisol levels may be considered as a biomarker for the diagnosis of schizophrenia and may be used as a significant predictor for positive response to antipsychotic treatment in schizophrenia patients with acute exacerbation. Serum cortisol levels are associated with severity of specific symptoms in patients with schizophrenia according to their responsiveness to antipsychotic treatment.

Keywords: schizophrenia, cortisol, psychopathology, antipsychotic treatment response



INTRODUCTION

Schizophrenia is a chronic and disabling mental disorder characterized by positive, negative and mood symptoms, disturbed coping abilities with elevated distress and a significant decline in cognition, quality of life and psychosocial functioning. Understanding the etiology and pathogenesis of schizophrenia is a major challenge facing psychiatry (Ritsner, 2010).

Hypothalamic-pituitary-adrenal (HPA) axis abnormalities play a key role in the etiology and pathogenesis of severe psychiatric disorders (Raison et al, 2003). The HPA axis is activated by all sorts of stressors, and this fact has represented the rationale for investigations into HPA axis function in schizophrenia, a disorder where stress could play a pivotal role in its onset and exacerbation (Hori et al, 2012). The behavioral and biological data from the previous researches indicated that stress worsens schizophrenic symptoms and that the disorder is associated with a heightened response to stressors (Ritsner et al, 2004). A neural mechanism for these phenomena is suggested by the augmenting effect of the HPA system on dopamine synthesis and receptors. Assuming that the diathesis for schizophrenia involves an abnormality in dopamine receptors, it is proposed that the HPA axis acts to potentiate schizophrenic systems by means of its effects on dopamine (Yilmaz et al, 2007).

HPA axis abnormalities may cause an increase in the baseline cortisol level (Yildirim et al, 2011). It has been demonstrated that serum baseline cortisol levels are increased in patients with schizophrenia (Hori et al, 2012; Yildirim et al, 2011; Gallagher et al, 2007; Yilmaz et al, 2007; Zhang et al, 2005; Ryan et al, 2004; Walder et al, 2000; Kaneko et al, 1992). However there are also other studies with contrary findings (Beyazyüz et al, 2014; Ritsner et al, 2004; Taherianfard et al, 2004; Kaneda et al, 2002). Authors of one study reported elevated serum cortisol levels in schizophrenic patients and their first-degree relatives and they suggested that similar physiopathologic processes occurring in the same genetic background might have a role in this increase (Yildirim et al, 2011).

Previous studies have suggested that alterations in cortisol levels may play a role in the pathophysiology of schizophrenia (Garner et al, 2011; Yildirim et al, 2011; Shulman et al, 2005). Serum cortisol levels may be used as a biological marker for the diagnosis of schizophrenia; however, further studies with larger sample sizes are warranted to support this finding (Yildirim et al, 2011).

Many researchers investigated association between serum cortisol and psychopathology in patients with schizophrenia. In some studies cortisol secretion was primarily associated with more severe positive symptoms (Walder et al, 2000; Kaneko et al, 1992; Rybakowski et al, 1991), whereas in others it was associated with higher ratings of negative symptoms (Zhang et al, 2005; Shirayama et al, 2002; Tandon et al, 1991). It has been suggested that the relation between cortisol levels and symptoms severity is due to the augmenting effects of cortisol on dopamine activity (Walker et al, 1997). Authors of one prospective study investigated circulating cortisol in patients with first episode psychosis and they concluded that decreases in cortisol over time was directly related to the improvement in depressive, negative and psychotic symptoms (Garner et al, 2011).

Authors of one study investigated association between serum cortisol, DHEA-S levels, as well as their molar ratios with PANSS dimensions in schizophrenic patients with different



response to antipsychotic treatment (Ritsner et al, 2005). They suggested that imbalance in serum cortisol and DHEA-S may be related to pathophysiological processes in schizophrenia, particularly to responsivity to antipsychotic treatment. Elevated cortisol levels and an elevated cortisol-DHEA(S) ratio have been shown to be predictive of a positive response to antipsychotic treatment according to these authors.

The aim of the study was to compare serum cortisol levels between patients with schizophrenia and healthy control subjects and to evaluate the correlation between hormone levels with psychopathology and response to antipsychotics in schizophrenic patients with acute exacerbation.

MATERIAL AND METHODS

In this clinical prospective study by its design were included 60 patients with schizophrenia and 40 healthy age and sex matched control subjects.

Examined group consisted of sixty patients with schizophrenia from both genders, age 18-50, treated as inpatients or outpatients at the University Psychiatry Clinic, Skopje, Macedonia. All patients experienced an acute exacerbation of the illness (PANSS: P1-Delusions and P3-Hallucinatory behavior ≥ 4). Patients who suffered from major physical illness, drug or alcohol abuse, epilepsy and other organic brain syndromes were not included. All patients underwent physical examination and routine laboratory tests to rule out physical illness. Clinical evaluation of patients was performed using the Positive and Negative Symptom Scale (Kay et al, 1987). Non-standardized questionnaire was used for socio-demographic and clinical data collection.

For the purposes of this study, the examined group was divided in two subgroups:

1. subgroup of subjects suffering from schizophrenia classified as responders who had no ratings of >3 on items P1, P2, P3, P5 and P6 of the PANSS.
2. subgroup of subjects suffering from schizophrenia who did not meet these criteria were defined as nonresponders.

Control group consisted of forty healthy age and sex matched control subjects. All were physically healthy and had no personal or family history of psychiatric disorder.

All participants in the study provided written informed consent to participate in this prospective study after having received a detailed explanation of the study procedures. The study was approved by the Ethics Committee of Medical University in Skopje and the Board of the University Clinic of Psychiatry.

Steroid determination

Serum cortisol and DHEA-S levels were measured in the Institute of clinical biochemistry at the Medical University in Skopje, Macedonia. Serum samples of cortisol and DHEA-S were collected between 8 a.m. and 9 a.m. hours after 20 min of rest. All participants



were instructed to abstain from unusual physical activity or stress for a period of 24 h prior to blood sampling. Blood samples were collected at baseline in all participants and after 3 and 6 weeks of the antipsychotic treatment in patients with schizophrenia. Cortisol and DHEA-S levels were measured by the IMMULITE 2000, competitive chemiluminescent enzyme immunoassay.

Statistical analysis

Several statistical methods have been used for the statistical analysis of the data obtained in the course of the study: non-parametric methods (Chi-square test, Mann-Whitney U test, Friedman ANOVA) and parametric methods (t-test for independent samples). Correlation between parameters was examined with Pearson and Spearman Rank correlation coefficients. From the multivariate methods MANOVA and Binary Logistic Regression were used. Values of $p < 0,05$ were considered statistically significant.

RESULTS

Patients with schizophrenia had significantly higher mean serum cortisol level in comparison to the control group (Table 1).

Table 1. Serum levels of cortisol in the examined and control group

Hormone	Examined group	Control group	test	p-value
Cortisol	555,7±159,8	351,7±172,1	t=6,07	0,00000

t (t-test for independent samples)

The two subgroups of the examined group classified as responders and nonresponders did not significantly differ between themselves in terms of gender (men/women: 29/8 and 15/8 respectively; Pearson Chi-square=1,26 df=1, $p=0,26$), age ($t= 0,34$ $p=0,73$), marital status (Pearson Chi-square=1,41 df=2 $p=0,49$), education (Pearson Chi-square=4,21 df=3 $p=0,24$), age of onset of the disorder ($Z=0,15$; $p=0,88$), duration of illness ($Z=0,32$; $p=0,75$), number of relapses ($Z=0,11$; $p=0,9$), number of hospital treatments ($Z=0,68$; $p=0,49$) and the type of antipsychotic agents - typical/atypical (Pearson Chi-square=0,86 df=1 $p=0,35$).

Table 2 shows serum cortisol levels in the subgroup of responders compared with the subgroup of nonresponders at baseline assessment point.



Table 2. Serum cortisol levels at baseline in responders and nonresponders

Hormone	Responders N=37	Nonresponders N=23	test	p-value
Cortisol	640,6±116,4	419,1±121,2	7,05	0,000000

Across all three assessment points (baseline, after 3 and 6 weeks) the responders had a significantly higher serum cortisol levels compared with nonresponders (MANOVA, Hotelling-Lawley test, $F=16,24$; $df=6,226$; $p=0,000$).

In the responders subgroup we found significant correlation between the duration of the illness and serum cortisol levels ($r=0,4$; $p=0,014$). This correlation is positive, thus higher serum cortisol levels are associated with longer duration of the disorder.

In the nonresponders subgroup we found negative significant correlation between the age of onset of the disorder and serum cortisol, therefore younger age of the onset is associated with higher serum cortisol levels ($r=-0,41$; $p=0,05$).

To test the assumption that elevated serum cortisol levels may be related to positive response to antipsychotic treatment during acute exacerbation of schizophrenia, we used Binary Logistic Analysis to determine the predictive value of serum cortisol, DHEA-S and cortisol/DHEA-S ratio for responding to antipsychotic therapy (Table 3).

Table 3. Binary Logistic Analysis (serum cortisol, DHEA-S and cortisol/ DHEA-S ratio at baseline)

-2 Log likelihood =39,893 Nagelkerke R Square=0,661 percent correct=85,0								
	B	S.E.	Wald	df	Sig.	EXP(B)	95,0 % C.I. for EXP(B)	
							Lower	Upper
Cortisol	-0,014	0,005	8,513	1	0,004	0,986	0,977	0,995
DHEA-S	-0,008	0,005	2,558	1	0,110	0,992	0,981	1,002



Cortisol/DHEA-S	-0,188	0,395	0,227	1	0,633	0,828	0,382	1,796
Gender	1,241	1,240	1,002	1	0,317	3,459	0,305	39,301
Constant	9,679	2,624	13,603	1	0,000	15978,441		

Dependent variable: without positive response/with positive response

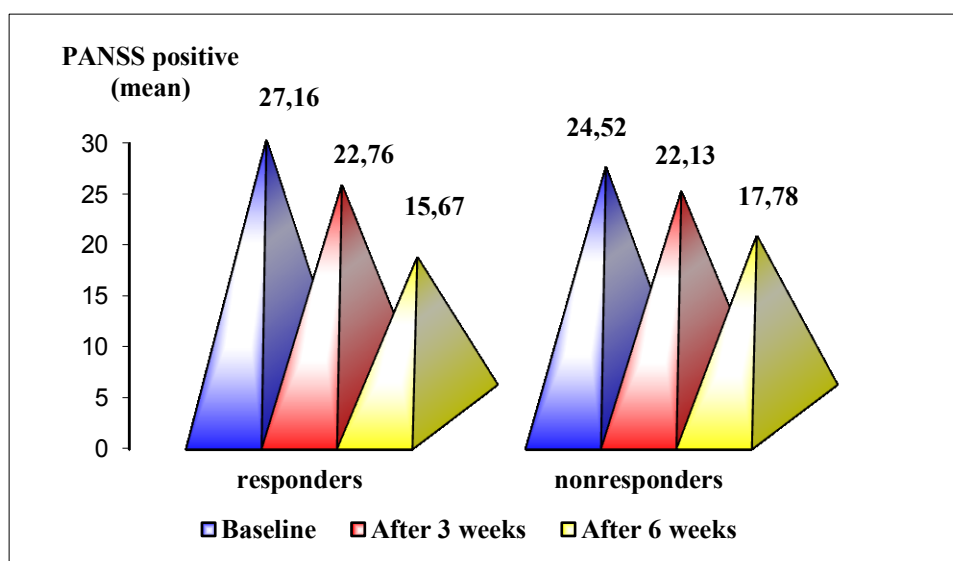
From the three analyzed factors, only serum cortisol was significant factor for antipsychotic treatment response, respectively elevated cortisol levels were associated with positive response to antipsychotic therapy.

According to the PANSS scores the subgroup of responders scored significantly higher on positive PANSS scale ($F=6,06$; $df=1\ 58$; $p=0,017$), delusions ($F=7,41$; $df=1\ 58$; $p=0,009$) and suspiciousness ($F=12,509$; $df=1\ 58$; $p=0,001$) compared with the subgroup of nonresponders at baseline. The differences between the subgroups according hallucinatory behavior, hostility and negative scale were not statistically significant.

The subgroup of responders showed greater reduction of the PANSS positive (Graph 1) and PANSS negative scale scores (Friedman ANOVA ANOVA Chi Sqr. $p=0\ 00000$) across all three assessment points (baseline, after 3 and 6 weeks of antipsychotic therapy) than the subgroup of nonresponders.



Graph 1. PANSS positive scale scores across three assessment points in responders and nonresponders



Correlation between serum cortisol levels with PANSS scores across all three assessment points in the two subgroups was examined with Spearman Rank Order Correlations. The results of examined correlation between hormone levels and PANSS scores in the subgroup of responders indicated statistically significant correlation between serum cortisol and PANSS positive scale score at the third assessment point (Table 4). The correlation is negative, accordingly higher serum cortisol levels significantly correlated with lower PANSS positive scale score.

Table 4. Responders - correlation serum cortisol/PANSS third assessment point

Cortisol-third assessment point	Spearman Rank Order Correlations	p-value
PANSS - delusions	-0,25	> 0,05
PANSS - hallucinatory behavior	-0,086	> 0,05
PANSS - suspiciousness	/	



PANSS - hostility	0,05	> 0,05
PANSS - positive scale	-0,35	<0,05
PANSS - negative scale	-0,022	> 0,05

Examined correlation between serum cortisol levels with PANSS scores across all three assessment points in the subgroup of nonresponders showed statistically significant correlation between cortisol and item delusions from the PANSS positive scale at the baseline ($R=0,45$; $p<0,05$). This correlation is positive, respectively higher serum cortisol levels are associated with higher scores for delusions.

DISCUSSION

The assumption that alterations in serum cortisol levels may have a role in changes in clinical presentation of several neuropsychiatric disorders, including schizophrenia, has been emphasized (Yildirim et al, 2011).

Authors of one study presented increased activity of cortisol metabolism in patients with schizophrenia compared to healthy controls and suggest that increased systemic cortisol metabolism is involved in the pathophysiology and stress vulnerability in this severe disorder (Steen et al, 2011).

Our study showed that plasma cortisol levels were significantly elevated in the group of patients with schizophrenia compared with controls, which is in agreement with the results of most of the studies (Hori et al, 2012; Yildirim et al, 2011; Gallagher et al, 2007; Yilmaz et al, 2007; Zhang et al, 2005; Muck-Seler D et al, 2004; Ryan et al, 2004; Walder et al, 2000; Kaneko et al, 1992). However there are studies reporting no significant differences between the schizophrenic patients and healthy controls in terms of cortisol levels (Beyazyüz et al, 2014; Ritsner et al, 2004; Kaneda et al, 2002), as well as lower cortisol levels in patients with schizophrenia (Taherianfard et al, 2004).

Our results showed that elevated serum cortisol levels in patients with schizophrenia may play a role in the pathophysiology of schizophrenia and may be considered as a biomarker for schizophrenia.

In the last 3 decades, several authors have posited a link between neuroactive steroids and the pathophysiology or therapeutics of schizophrenia (Beyazyüz et al, 2014).

Studies evaluating the association between serum cortisol and psychopathology in patients with schizophrenia present a variety of results. Authors of some previous studies found positive correlation between cortisol levels and negative symptoms (Zhang et al, 2005;



Shirayama et al, 2002; Newcomer et al, 1991; Tandon et al, 1991). In contrast, some other studies found a correlation between serum cortisol and positive symptoms (Walder et al, 2000; Kaneko et al, 1992; Rybakowski et al, 1991; Keshavan et al, 1989). Authors of one study did not find significant correlation between serum cortisol and symptom dimensions assessed with the PANSS (Hori et al, 2012). Authors of another study found positive correlation between cortisol levels and the rating of positive, disorganized and overall symptom severity, but not with negative symptoms (Walder et al, 2000).

Authors of one study investigated serum cortisol in two groups of schizophrenia patients divided according to their responsivity to antipsychotic treatment (Ritsner et al, 2005). Their results indicate that responders had significantly higher basal levels of cortisol compared with nonresponders. They also examined correlation between changes in serum values of cortisol with changes in PANSS dimensions. They demonstrated that among responders increased serum cortisol concentrations significantly correlated with improvement in activation and PANSS total score. Among nonresponders no significant correlation was observed between changes in any hormonal measures and symptom severity according to this study.

According to the PANSS scores our study showed that responders scored significantly higher on positive PANSS scale, delusions and suspiciousness compared with nonresponders which coincided with the results of other study (Ritsner et al, 2005). In our study responders showed greater reduction of the PANSS positive and negative scale scores across all three assessment points compared with nonresponders. Authors of one other study showed that responders had greater reduction in the PANSS total score than nonresponders (Ritsner et al, 2005).

Examined association between serum cortisol and psychopathology in responders subgroup in our study showed significant correlation between serum cortisol and PANSS positive scale score.

Investigated correlation between serum cortisol and psychopathology in the subgroup of nonresponders showed statistically significant correlation between serum cortisol and delusions.

Our results suggest that serum cortisol levels are associated with severity of specific symptoms in patients with schizophrenia according to their responsivity to antipsychotic treatment.

The present study also evaluated association between serum cortisol levels and response to antipsychotic treatment in schizophrenic patients with acute exacerbation. At baseline assessment point the subgroup of responders showed significantly higher serum cortisol levels compared with the subgroup of nonresponders. Across all three assessment points the responders had a significantly higher serum cortisol levels compared with nonresponders which is consistent with the results of other study (Ritsner et al, 2005). Tested predictive value of serum cortisol, DHEA-S and cortisol/DHEA-S ratio for responding to antipsychotic therapy in our study showed that only serum cortisol is a significant predictor for responsivity to antipsychotic treatment in



schizophrenia patients with acute exacerbation, respectively elevated serum cortisol levels are related to positive response to antipsychotic therapy. Authors of one previously mentioned study provided evidence that elevated serum cortisol and cortisol/DHEA-S ratio may serve as markers of biological mechanisms that are involved in responsiveness of schizophrenia patients to antipsychotic treatment (Ritsner et al, 2005).

Limited number of studies that investigate correlation between serum cortisol levels with psychopathology in patients with schizophrenia according to their responsiveness to antipsychotic therapy as well as hormone predictive value for antipsychotic response are the reasons for required similar future researches.

CONCLUSIONS

- Elevated serum cortisol levels may be considered as a specific endocrine marker for the diagnosis of schizophrenia.
- The subgroup of responders had a significantly higher serum cortisol levels compared with the subgroup of nonresponders.
- Elevated serum cortisol may be used as a significant predictor for positive response to antipsychotic treatment in schizophrenia patients with acute exacerbation.
- Responders scored significantly higher on positive PANSS scale, delusions and suspiciousness compared with nonresponders.
- Responders showed greater reduction of the PANSS positive and negative scale scores across all three assessment points compared with nonresponders.
- The responders subgroup demonstrated significant correlation between serum cortisol and PANSS positive scale score.
- The subgroup of nonresponders had significant correlation between serum cortisol and delusions.

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REFERENCES

- Beyazyüz M, Albayrak Y, Beyazyüz E, Ünsal C, Göka E (2014). Increased serum dehydroepiandrosterone sulfate in the first episode but not in subsequent episodes in male patients with schizophrenia. *Neuropsychiatr Dis Treat* 10: 687-93.
- Gallagher P, Watson S, Smith MS, Young AH, Ferrier IN (2007). Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. *Schizophr Res* 90(1-3): 258-65.
- Garner B, Phassuliotis C, Phillips LJ, Markulev C, Butselaar F, Bendall S, Yun Y, McGorry PD (2011). Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis. *J Psychiatr Res* 45(2): 249-55.
- Hori H, Teraishi T, Sasayama D, Fujii T, Hattori K, Ishikawa M, Kunugi H (2012). Elevated cortisol level and cortisol/DHEAS ratio in schizophrenia as revealed by low-dose dexamethasone suppression test. *The Open Neuropsychopharmacology* 5: 18-24.
- Kaneda Y, Fujii A, Ohmori T (2002). The hypothalamic-pituitary-adrenal axis in chronic schizophrenic patients long-term treated with neuroleptics. *Prog Neuropsychopharmacol Biol Psychiatry* 26: 935-8.
- Kaneko M, Yokoyama F, Hoshino Y, Takahagi K, Murata S, Watanabe M, Kumashiro H (1992). Hypothalamic-pituitary-adrenal axis function in chronic schizophrenia: association with clinical features. *Neuropsychobiology* 25: 1-7.
- Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 13: 261-7.
- Keshavan MS, Brar J, Ganguli R, Jarrett D (1989). DST and schizophrenic symptomatology. *Biol Psychiatry* 26: 847-58.
- Muck-Seler D, Pivac N, Crncevic Z, Jakovljevic M, Sagud M (2004). Platelet serotonin and plasma prolactin and cortisol in healthy, depressed and schizophrenic women. *Psychiatry Res* 127(3): 217-226.
- Newcomer JW, Faustman WO, Whiteford HA, Moses JA, Csernansky JG (1991). Symptomatology and cognitive impairment associate independently with post-dexamethasone cortisol concentrations in unmedicated schizophrenic patients. *Biol Psychiatry* 29: 855-64.



Raison CL, Miller AH (2003). When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry* 160:1554-65.

Ritsner M (2010). Pregnenolone, Dehydroepiandrosterone, and Schizophrenia: Alterations and Clinical Trials. *CNS Neurosci Ther* 16: 32-44.

Ritsner M, Gibel A, Maayan R, Ratner Y, Ram E, Biadys E, Modai I, Weizman A (2005). Cortisol/Dehydroepiandrosterone ratio and responses to antipsychotic treatment in schizophrenia. *Neuropsychopharmacology* 30: 1913-22.

Ritsner M, Maayan R, Gibel A, Strous RD, Modai I, Weizman A (2004). Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *Eur Neuropsychopharmacol* 14: 267-73.

Ryan MC, Sharifi N, Condren R, Thakore JH (2004). Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. *Psychoneuroendocrinology* 29: 1065-70.

Rybakowski J, Linka M, Matkowski K, Kanarkowski R (1991). Dexamethasone suppression test and the positive and negative symptoms of schizophrenia. *Psychiatr Pol* 25: 9-15.

Shirayama Y, Hashimoto K, Suzuki Y, Higuchi T (2002). Correlation of plasma neurosteroids to the severity of negative symptoms in male patients with schizophrenia. *Schizophrenia Res* 58: 69-74.

Shulman Y, Tibbo P (2005). Neuroactive steroids in schizophrenia. *Can J Psychiatry* 50: 695-702.

Steen NE, Methlie P, Lorentzen S, Hope S, Barrett EA, Larsson S, Mork E, Almas B, Lovas K, Agartz I, Melle I, Berg JP, Andreassen OA (2011). Increased systemic cortisol metabolism in patients with schizophrenia and bipolar disorder: a mechanism for increased stress vulnerability? *J Clin Psychiatry* 72(11): 1515-21.

Taherianfard M, Shariaty M (2004). Evaluation of serum steroid hormones in schizophrenic patients. *Indian J Med Sci* 58(1): 3-9.

Tandon R, Mazzara C, DeQuardo J, Craig KA, Meador-Woodruff JH, Goldman R, Greden JF (1991). Dexamethasone suppression test in schizophrenia: relationship to symptomatology, ventricular enlargement and outcome. *Biol Psychiatry* 29: 953-64.



Walder DJ, Walker EF, Lewine RJ (2000). Cognitive functioning, cortisol release, and symptom severity in patients with schizophrenia. *Biol Psychiatry* 48: 1121-32.

Walker EF, Diforio D (1997). Schizophrenia: a neural diathesis-stress model. *Psychol Rev* 104: 667-85.

Yıldırım O, Dogan O, Semiz M, Kilicli F (2011). Serum cortisol and dehydroepiandrosterone-sulfate levels in schizophrenic patients and their first-degree relatives. *Psychiatry Clin Neurosci* 65: 584-91.

Yilmaz N, Herken H, Cicek HK, Celik A, Yürekli M, Akyol O (2007). Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. *Med Princ Pract* 16(2): 137-41.

Zhang XY, Zhou DF, Cao LY, Wu GY, Shen YC (2005). Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. *Neuropsychopharmacology* 30(8): 1532-8.

