

**SERUM CORTISOL AND DHEA-S LEVELS IN SCHIZOPHRENIC PATIENTS  
WITH DIFFERENT RESPONSE TO ANTIPSYCHOTIC THERAPY:  
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Tel/fax: +389 (0)2 2 43 50 74; E-mail: zbabinkostova@yahoo.com**Abstract***Background:* Previous studies suggested that alterations in serum cortisol and DHEA-S levels may play a role in the pathophysiology of schizophrenia. Imbalance in serum cortisol and DHEA-S levels may be related to responsivity to antipsychotic treatment.*Aim:* To compare serum cortisol and DHEA-S levels between patients with schizophrenia and healthy controls and to evaluate their association with psychopathology in schizophrenic patients with different response to antipsychotic treatment.*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 and DHEA-S levels compared with control group. Responders had significantly higher serum cortisol and DHEA-S levels compared with nonresponders. Responders group had significant correlation between serum cortisol and PANSS positive scale score as well as between hostility and serum DHEA-S.*Conclusion:* Elevated serum cortisol and DHEA-S levels may play a role in the pathophysiology of schizophrenia. Serum cortisol and DHEA-S are associated with psychopathology in schizophrenic patients with different response to antipsychotic therapy.**Key words:** schizophrenia, cortisol, DHEA-S, psychopathology, responders, nonresponders.**Introduction**

Hypothalamic-pituitary-adrenal (HPA) axis abnormalities play a key role in the etiology and pathogenesis of severe psychiatric disorders [1]. The neuroendocrinological system, particularly the HPA axis, has been a focus of

interest for neurobiological studies aiming at elucidating the cause of schizophrenia [2]. HPA axis abnormalities may cause an increase in the baseline cortisol level [3]. It has been demonstrated that serum baseline cortisol levels are increased in patients with schizophrenia [2–9]. However

there are also other studies with contrary findings [10–11].

Recently there has been increased interest in the role of dehydroepiandrosterone (DHEA) which, in its sulfated form (DHEA-S) is the most abundant in humans [12]. It is considered both a neurosteroid, being produced in the brain, as well as a neuroactive steroid, produced in the adrenals and gonads and having its effect on the brain [13]. Dehydroepiandrosterone sulfate (DHEA-S) is a neuroactive steroid interacting with N-methyl D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptors [14]. Previous studies investigating DHEA-S blood levels in patients with schizophrenia have demonstrated elevated DHEA-S levels [3, 15–16], no different [10, 17] and decreased levels [18] in schizophrenia patients compared to healthy controls. The inconsistencies in published findings may be due to wide clinical polymorphism, small sample sizes, or differences in the age and duration of illness of patients enrolled in the studies [19].

Previous studies have suggested that alterations in cortisol and DHEA-S levels may play a role in the pathophysiology of schizophrenia [3, 16, 20–23]. Serum cortisol and DHEA-S 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 [3].

Many researchers investigated association between serum cortisol and DHEA-S levels with psychopathology in patients with schizophrenia. Authors of one study reported that serum DHEA-S levels are positively correlated with severity of dysphoric mood, positive and activation symptoms [18]. They did not find correlations between negative symptoms and serum levels of DHEA-S similar to the results of one other study [17]. On the other hand there is a study which reported correlation between DHEA-S plasma levels and negative symptoms, but not with depressive and anxiety symptoms [24].

In some studies cortisol secretion was primarily associated with more severe positive symptoms [2, 5, 25], whereas in others it was associated with higher ratings of negative symptoms [7, 17, 26]. It has been suggested that the relation between cortisol levels and symptoms severity is due to the augmenting effects of cortisol on dopamine activity [27].

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 [19]. They suggest that imbalance in serum cortisol and DHEA-S may be related to pathophysiological processes in schizophrenia, particularly to responsivity to antipsychotic treatment.

**The aim of the study** was to compare serum cortisol and dehydroepiandrosterone-sulfate levels between patients with schizophrenia and healthy control subjects and to evaluate association between these hormones and psychopathology in schizophrenic patients with different response to antipsychotic treatment.

### 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  $\geq 4$ ). 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 [28]. 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 Spearman Rank correlation coefficient. From the multivariate methods MANOVA was used. Values of  $p < 0.05$  were considered statistically significant.

### Results

Patients with schizophrenia had significantly higher mean serum cortisol and DHEA-S levels in comparison to the control group (Table 1).

Table 1

*Serum levels of cortisol and DHEA-S 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
DHEA-S	329.5 ± 125.1	167.4 ± 57.5	t = 7.66	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 and DHEA-S levels in the subgroup of responders compared with the subgroup of nonresponders at baseline assessment point.

Table 2

*Serum cortisol and DHEA-S 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
DHEA-S	375.6 ± 114.4	255.4 ± 106.2	4.06	0.00014

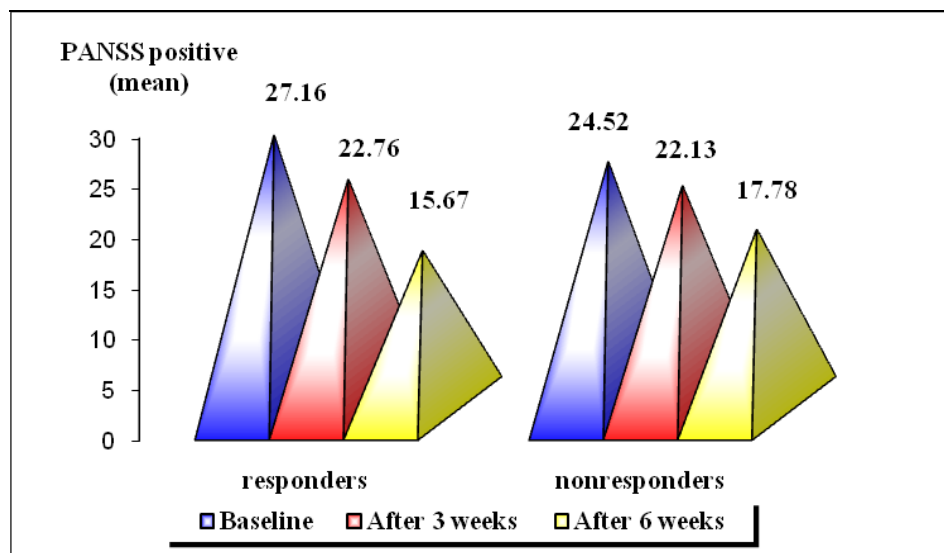
Across all three assessment points (baseline, after 3 and 6 weeks) the responders had a significantly higher serum cortisol and DHEA-S

levels compared with nonresponders (MANOVA, Hotelling-Lawley test,  $F = 16.24$ ; df = 6.226;  $p = 0.000$ ).

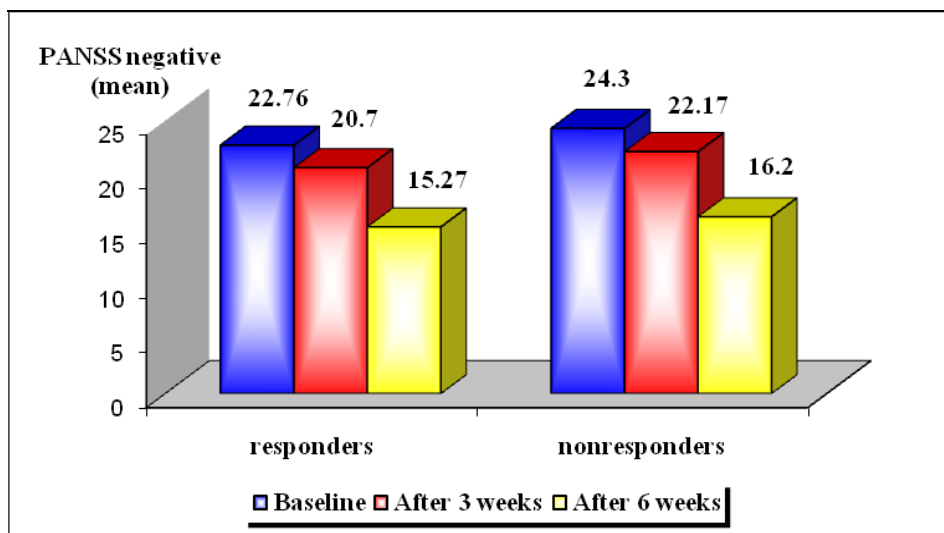
According to the PANSS scores the subgroup of responders scored significantly higher on positive PANSS scale ( $F = 6.06$ ;  $df = 158$ ;  $p = 0.017$ ), delusions ( $F = 7.41$ ;  $df = 158$ ;  $p = 0.009$ ) and suspiciousness ( $F = 12.509$ ;  $df = 158$ ;  $p = 0.001$ ) compared with the subgroup of 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 and PANSS negative scale scores across all three assessment points (baseline, after 3 and 6 weeks of antipsychotic therapy) than the subgroup of nonresponders (Graph 1; Graph 2).



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



Graph 2 – PANSS negative scale scores across three assessment points in responders and nonresponders

Correlation between serum cortisol and DHEA-S 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 serum cortisol 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 3). The correlation is negative, accordingly higher serum cortisol levels significantly correlated with lower PANSS positive scale score. Investigated correlation between serum DHEA-S levels and PANSS scores in the responders subgroup showed statistically significant correlation between

enhostility and DHEA-S level at second assessment point (Table 4). This correlation is posi-

tive, respectively higher serum DHEA-S levels are associated with higher hostility scores.

Table 3

*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

Table 4

*Responders – correlation serum DHEA-S/PANSS second assessment point*

DHEA-S second assessment point	Spearman Rank Order Correlations	p-value
PANSS – delusions	-0.2	> 0.05
PANSS – hallucinatory behavior	0.29	> 0.05
PANSS – suspiciousness	0.16	> 0.05
PANSS – hostility	0.38	<0.05
PANSS – positive scale	0.21	> 0.05
PANSS – negative scale	0.11	> 0.05

Examined correlation between serum cortisol and DHEA-S 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 ( $R = 0.5$ ;  $p < 0.05$ ). This correlation is positive, respectively higher serum cortisol levels are associated with higher scores for delusions. Investigated correlation between serum DHEA-S levels and all PANSS item scores in this subgroup did not show statistically significant correlation between them across all three assessment points.

### Discussion

Recently, studies on schizophrenia have increasingly focused on potential causative factors, such as structural and functional brain abnormalities. The assumption that alterations in cortisol and DHEA-S levels may have a role in

changes in clinical presentation of several neuropsychiatric disorders, including schizophrenia, has been emphasized [3].

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 [2–9]. However there are studies reporting no significant differences between the schizophrenic patients and healthy controls in terms of cortisol levels [10, 29], as well as lower cortisol levels in patients with schizophrenia [11].

Examined serum DHEA-S levels in this study showed statistically significant higher levels in patients with schizophrenia compared to control subjects, which is in agreement with the results of most of the studies [3, 15, 16]. In contrast, some other studies found decreased serum DHEA-S levels [18] and no different [10] in schizophrenia patients compared to healthy controls.

Our results showed that elevated serum cortisol and DHEA-S levels in patients with schizophrenia may play a role in the pathophysiology of schizophrenia.

Studies evaluating the association between serum cortisol and DHEA-S levels with psychopathology in patients with schizophrenia present a variety of results. Authors of some previous studies found positive correlation between cortisol levels and negative symptoms [7, 17, 26, 30]. In contrast, some other studies found a correlation between serum cortisol and positive symptoms [2, 5, 25, 31]. It has been suggested that the relation between cortisol levels and symptom severity is due to the augmenting effects of cortisol on dopamine activity [27]. Authors of one study did not find significant correlation between serum cortisol and DHEA-S levels with symptom dimensions assessed with the PANSS [9]. Authors of other study referred positive correlation between serum DHEA-S levels and severity of dysphoric mood, positive and activation symptoms [18]. Some previous studies found no correlation between serum DHEA-S levels and negative symptoms in schizophrenia [17, 18]. On the other hand, authors of one study reported that changes in DHEA-S levels significantly correlated with total PANSS, negative and general PANSS [24].

Authors of one study investigated serum cortisol and DHEA-S levels in two groups of schizophrenia patients divided according to their responsivity to antipsychotic treatment [19]. Their results indicate that responders had significantly higher basal levels of cortisol and DHEA-S compared with nonresponders. They also examined correlation between changes in serum values of cortisol and DHEA-S with changes in PANSS dimensions. They demonstrated that among responders increased serum DHEA and cortisol concentrations significantly correlated with improvement in activation and PANSS total score. Reduction over time of PANSS total scores in their study showed significant association with increased DHEA-S levels. Among nonresponders no significant correlation was observed between changes in any hormonal measures and symptom severity according to this study.

Our study evaluated serum cortisol and DHEA-S levels and their association with psychopathology in schizophrenic patients with

different response to antipsychotic treatment. The results showed that across all three assessment points (baseline, after 3 and 6 weeks) the responders had a significantly higher serum cortisol and DHEA-S levels compared with nonresponders which is in agreement with the results of authors of one study [19]. These results indicate that elevated serum cortisol and DHEA-S levels in patients with schizophrenia may be related to responsivity to antipsychotic treatment.

According to the PANSS scores responders scored significantly higher on positive PANSS scale, delusions and suspiciousness compared with nonresponders which coincided with the results of other study [19]. 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 [19].

Examined association between serum cortisol and DHEA-S levels with psychopathology in responders subgroup in our study showed significant correlation between serum cortisol and PANSS positive scale score as well as statistically significant correlation between hostility and serum DHEA-S.

We investigated the correlation between serum cortisol and DHEA-S with psychopathology in the subgroup of nonresponders showed statistically significant correlation between serum cortisol and delusions and no significant correlation between serum DHEA-S levels and psychopathology in this subgroup.

Our results suggested that serum cortisol and DHEA-S levels are associated with different schizophrenia symptoms in patients with schizophrenia according to their responsivity to antipsychotic treatment.

Limited number of studies that investigated the correlation between serum cortisol and DHEA-S levels with psychopathology in patients with schizophrenia according to their responsivity to antipsychotic therapy is a reason for required similar future researches.

## Conclusions

- Serum cortisol and DHEA-S levels were significantly elevated in the group of patients with schizophrenia compared with controls.

- The subgroup of responders had a significantly higher serum cortisol and DHEA-S levels compared with the subgroup of nonresponders.

- 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 responder's subgroup demonstrated significant correlation between serum cortisol and PANSS positive scale score as well as between hostility and serum DHEA-S level.

- The subgroup of nonresponders had significant correlation between serum cortisol and delusions and no significant correlation between serum DHEA-S levels and psychopathology.

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## Резиме

### **СЕРУМСКИ КОНЦЕНТРАЦИИ НА КОРТИЗОЛ И DHEA-S КАЈ ПАЦИЕНТИ СО ШИЗОФРЕНИЈА СО РАЗЛИЧЕН ОДГОВОР НА АНТИПСИХОТИЧНАТА ТЕРАПИЈА: АСОЦИЈАЦИЈА СО ПСИХОПАТОЛОГИЈАТА**

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**Вовед:** Досегашните студии укажуваат дека алтерациите на серумските концентрации на кортизол и DHEA-S може да имаат

улога во патофизиологијата на шизофренијата. Нарушувањето на серумските концентрации на кортизол и DHEA-S може да е асоцирано со одговорот на антипсихотичниот третман.

**Цел:** Да се споредат серумските концентрации на кортизол и DHEA-S меѓу пациенти со шизофренија и здрави контроли и да се евалуира нивната асоцираност со психопатологијата кај пациентите со шизофренија со различен одговор на антипсихотичниот третман.

**Материјал и методи:** Оваа клиничка проспективна студија вклучи 60 пациенти со шизофренија и 40 здрави контроли соодветни по пол и возраст. Сите пациенти манифестираа акутна егзацербација на болеста (PANSS: P1 и P3  $\geq$  4). Клиничката евалуација на пациентите беше спроведена со PANSS. Се користеше и прашалник за социодемографски и клинички податоци. За целите на студијата, испитуваната група беше поделена во две подгрупи: испитаници со позитивен и испитаници со негативен одговор на третманот. Серумските концентрации на кортизол и DHEA-S беа одредувани на почетокот на студијата кај сите испитаници и по 3 и 6 недели од антипсихотичниот третман кај пациентите со шизофренија.

**Резултати:** Пациентите со шизофренија имаа значајно повисоки серумски концентрации на кортизол и DHEA-S во споредба со контролната група. Испитаниците со позитивен одговор имаа значајно повисоки серумски концентрации на кортизол и DHEA-S во споредба со испитаниците со негативен одговор. Кај испитаниците со позитивен одговор имаше значајна корелација меѓу серумскиот кортизол и вкупниот скор на PANSS позитивната скала, како и меѓу хостилноста и серумскиот DHEA-S.

**Заклучок:** Зголемените серумски концентрации на кортизол и DHEA-S може да имаат улога во патофизиологијата на шизофренијата. Серумските кортизол и DHEA-S се асоцирани со психопатологијата кај пациентите со шизофренија со различен одговор на антипсихотичниот третман.

**Клучни зборови:** шизофренија, кортизол, DHEA-S, психопатологија, позитивен одговор, негативен одговор.