

## Research article

# Dehydroepiandrosterone sulfate (DHEA-S), cortisol, and adrenocorticotrophic hormone (ACTH) levels in drug-naïve, first-episode patients with psychosis

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### ABSTRACT

The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in regulating dopamine activity in specific brain areas, particularly in the limbic system, as well as in the stress response. The assessment of the HPA axis is important for the research of biological mechanisms leading from stressful experiences to the onset of psychosis. The release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary stimulates the production of cortisol and dehydroepiandrosterone (DHEA) by the adrenal cortex as a response to stress. The co-release of DHEA may act as a protective mechanism against the damaging effects of excessive cortisol activity. We aimed to measure and compare serum DHEA-S, as well as ACTH, cortisol levels, and cortisol/DHEA-S ratio in drug-naïve FEP patients and matched controls. Data were included for 110 subjects (70 men and 40 women), comprising 55 patients and 55 controls. The mean age was 31.3 years (SD 8.7) in patients and 31.4 years (SD 8.9) in controls. Serum DHEA-S was higher in patients compared to controls [0.69 (0.40) versus 0.50 (0.19), respectively]. Serum ACTH was similar between patients and controls [28.0 pg/ml (6.2-73.9) versus 22.4 pg/ml (7.0-70.5), respectively]. Serum cortisol levels and cortisol/DHEA-S ratio were lower in patients [12.6 µg/dl (4.5) and 4.4% (1.3-19.5), respectively] compared to controls [15.4 µg/dl (3.7) and 7.0% (2.4-25.5), respectively]. Sub-analysis revealed that in men, serum DHEA-S was similar between male patients and controls [0.53 (0.23) versus 0.48 (0.17), respectively], whereas in women, serum DHEA-S was higher in patients compared to controls [0.97 (0.47) versus 0.55 (0.20), respectively]. ACTH levels were not different in the above subgroups. Serum cortisol in men was lower in patients compared to controls [12.8 µg/dl (4.4) versus 15.9 µg/dl (3.6)]. Additionally, the cortisol/DHEA-S ratio was lower in patients compared to controls in men [4.4% (1.3-19.5) versus 5.8% (2.4-15.4)], as well as in women [4.3% (1.8-15.2) versus 7.9% (4.0-25.5), respectively]. Correlation analysis was performed to examine the association between different psychopathological characteristics in patients and measured hormones. It was found that the PANSS cognitive subscale was positively correlated with DHEA-S in men, and the PANSS positive subscale was negatively correlated with DHEA-S in women. In the linear regression analysis, DHEA-S was positively associated with the PANSS cognitive subscale in men.

**KEYWORDS:** Dehydroepiandrosterone sulfate (DHEA-S), cortisol, adrenocorticotrophic hormone (ACTH), first episode psychosis, drug-naïve.

## Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the regulation of dopamine activity in certain brain areas, in particular in the limbic system, and also in response to stress.<sup>1</sup> Impaired response to stress and a pathological activation of the HPA axis have been implicated in the pathophysiology of schizophrenia.<sup>2,3</sup> Anterior pituitary hormones, among them ACTH, are involved in neurotransmission and neuroregulation, processes associated with schizophrenia.<sup>4</sup> Animal studies found that persistently increased glucocorticoid levels induce hippocampal cell damage.<sup>1</sup> Reduced hippocampal volume is one of the most robust findings observed in patients with schizophrenia and may be correlated with hypercortisolemia.<sup>1,5</sup> Hypothalamus releases corticotropin-releasing hormone (CRH), which in turn stimulates the release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary, which leads to the production of cortisol and dehydroepiandrosterone (DHEA) from the adrenal cortex. Cortisol release inhibits the production of ACTH and CRH in a negative feedback.<sup>6</sup> The co-release of DHEA may have a protective effect against the damage induced by excessive cortisol activity.<sup>7</sup> DHEA-S crosses the blood-brain barrier and acts as a neurosteroid that binds to neurotransmitter receptors  $\gamma$ -aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors in several brain areas, among them the cortex, the hippocampus, and the amygdala.<sup>8-10</sup> Except for these indirect effects, DHEA-S seems to be produced directly by glial cells and neurons in the central nervous system.<sup>11</sup> Importantly, there is a strong association between DHEA levels in cerebrospinal fluid and those in serum.<sup>12</sup>

The assessment of the HPA axis is important for the research of biological mechanisms leading from stressful experiences to the onset of psychosis.<sup>4</sup>

The results of the studies and meta-analyses regarding ACTH, cortisol, and DHEA-S levels in patients with psychosis remain inconclusive so far. Cavaleri et al (2023)<sup>4</sup> report in a recent meta-analysis, higher levels of ACTH were found in drug-naïve FEP with psychosis compared to controls. Misiak et al (2021)<sup>13</sup> report higher blood cortisol levels in patients with FEP compared to controls, but similar unstimulated salivary cortisol levels between FEPs and controls. In the meta-analysis conducted by Aymerich et al (2023),<sup>14</sup> morning cortisol levels did not differ significantly between antipsychotic naïve patients and controls. Chaumette et al (2016)<sup>15</sup> did not find any difference in cortisol levels between FEP, drug-naïve patients, controls, and Ultra High Risk (UHR)

individuals. Blunted cortisol awakening response in FEP patients,<sup>16</sup> and reduced cortisol response to stress in schizophrenia have also been reported.<sup>17</sup> Misiak et al (2018)<sup>10</sup> in his meta-analysis, which included five studies with FEP patients, report increased DHEA-S levels in FEP male patients, but neither in stable multiple episodes nor in acutely relapsed patients.

Of note, very few studies that measured DHEA-S included drug-naïve, FEP patients, and only one<sup>18</sup> measured ACTH, cortisol, and DHEA-S. Two of them,<sup>19,20</sup> report increased DHEA in the patients' group but similar cortisol levels between FEPs and controls, one finds no statistically significant difference in DHEA-S and cortisol levels and cortisol/DHEA-S ratio between patients and controls,<sup>7</sup> while Beyazyuz et al<sup>18</sup> report elevated DHEA-S but similar ACTH and cortisol levels in a group of FEPs compared both to controls and to a group of drug-free, acutely relapsed patients. Garner et al (2011)<sup>7</sup> reports a positive association between cortisol levels and psychotic symptoms, while DHEA-S levels were negatively associated with negative and depressive symptoms.

Studies in samples consisting of chronic, medicated patients with schizophrenia report higher serum cortisol and DHEA-S levels,<sup>21</sup> elevated cortisol/DHEA and cortisol/DHEA-S ratios,<sup>22</sup> elevated DHEA-S levels,<sup>23-25</sup> increased DHEA levels and decreased cortisol/DHEA ratio,<sup>26</sup> while Huang et al (2017)<sup>27</sup> found reduced levels of DHEA-S and pregnenolone in the male subgroup of patients. Huang et al<sup>27</sup> reported a positive correlation between DHEA and DHEA-S levels and age of onset and a negative one with duration of illness, while Peng et al<sup>21</sup> found a positive correlation between cortisol and the negative symptom score in PANSS and no correlation between DHEA-S and cortisol levels and age of onset or duration of illness.

Given the possible implication of the HPA axis in the onset of psychosis and the inconsistent findings reported so far, we aimed to 1. To measure DHEA-S, ACTH, and cortisol serum levels and to calculate cortisol/DHEA-S ratio in a group of drug-naïve FEP patients and matched controls, and to compare the results 2. To find possible correlations between psychopathology and stress hormone' levels

## Material and Method

### Participants

We recruited fifty-five patients from the "Early Intervention in Psychosis Unit" of the Department of Psychiatry of the University Hospital of Ioannina in Greece from September 2019 to August 2021. Inclusion

criteria were the following: (a) Diagnostic and Statistical Manual of Mental Disorders (DSM-5)<sup>28</sup> diagnosis of schizophrenia, schizophreniform disorder or brief psychotic episode, (b) patients had to experience their first psychotic episode, defined as the first experience of psychotic symptoms and the first contact with psychiatric services,<sup>29</sup> (c) they had to be antipsychotic-naïve, and (d) they were 18–48 years old. Exclusion criteria were the following: (a) past major mental illness (psychotic, mood, anxiety disorder), (b) DSM-5 diagnostic criteria for alcohol or substance abuse, (c) have serious physical disorders and/or take medications that interfere with the measurement of cortisol, DHEA-S, and ACTH, (d) patients refused to give informed consent.

Patients and controls with BMI>25 were excluded from the study. Overweight people are more likely to suffer from subclinical metabolic disorders. DHEA-S may be an insulin sensitizer, and there is also evidence that insulin changes DHEA-S levels.<sup>30</sup> DHEA-S also increases glucose uptake in adipocytes by stimulating GLUT-1 and GLUT-4 to the cellular membrane (Perrini et al 2004, Wang et al 2020).<sup>31,32</sup> It has been suggested that DHEA-S may be implicated in the pathogenesis of type-2 diabetes, and higher levels of DHEA-S are associated with a lower risk of type-2 diabetes.<sup>30</sup> Additionally, in women over 35 years, low cortisol levels have been correlated with overweight, while in women less than 35 years, DHEA-S levels have been correlated with insulin resistance. DHEA-S levels have also been associated with increased BMI in women.<sup>33</sup> For these reasons, we excluded overweight patients. We did not exclude underweight patients; however, we would like to note that no patients in our sample had a BMI<18 kg/m<sup>2</sup>.

Patients and controls had complete physical examinations by an internist and were physically healthy. A urine test was performed to exclude current substance use.

### Clinical assessment

Psychiatric diagnosis was established by an experienced psychiatrist using the Structured Clinical Interview for DSM-5 (SCID-5). Twenty-four males and 16 females were diagnosed with schizophreniform disorder, 8 males and 2 females with schizophrenia, and 3 males and 2 females with brief psychotic episode. The patients' psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS)-Greek version,<sup>34</sup> conducted by an experienced psychiatrist on the day of blood sample collection. We further evaluated psychopathology following the five-factor model

by Lykouras et al.<sup>35</sup> The participants received detailed information about the aim of the study and gave informed consent, and their anonymity has been preserved. Control group subjects were matched for age and sex. They were examined by an experienced psychiatrist who ruled out any present or past DSM-5 mental disorder. Mental health history was evaluated using the SCID NP (non-patient) edition, and only those without a past or present history of mental disorder (psychotic, mood, or anxiety disorder) were included in the study. First and second-degree relatives of persons with a history of severe mental illness were excluded as controls from the study.

### Measurements

We measured serum DHEA-S levels in FEP patients and matched controls and compared DHEA-S levels between the two groups in men and women. DHEA-S is expressed as the ratio of each DHEA-S value to the upper limit of normal for the respective age group in men and women. We also measured and compared serum ACTH and cortisol levels between patients and controls. Cortisol/DHEA-S ratio was calculated, representing the relative imbalance of the two hormones.

The study was approved by the ethical committee of the University Hospital of Ioannina, Greece, and conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

### Biochemical analysis

Blood samples were collected from all participants between 8.00 a.m. to 9.00 a.m. after a 12-hour fast. For DHEA-S and cortisol measurement, venous blood samples were placed in anticoagulant tubes, and then serum was separated by centrifugation for 10 min, 3000 rpm/min. For ACTH measurement, blood samples were placed in a separate tube with ethylene diamine tetra-acetic acid (EDTA), and then plasma was separated by centrifugation. Serum levels of DHEA-S and cortisol were measured using a Chemiluminescence Immunoassay (CLIA) technique on a CENTAUR XP (SIEMENS) automated immunoanalyzer, by SIEMENS DHEA-S and Cortisol Reagent Kit. Plasma levels of ACTH were measured using CLIA on an IMMULITE 2000 (SIEMENS) automated immunoanalyzer, by SIEMENS ACTH Reagent Kit. The normal range of Cortisol serum levels is 43,0–240,0 ng/ml. DHEAS normal range (<30 years, 18–391µg/ml, 30-50 years: 19-266µg/ml). ACTH normal range 6,0-69,0 pg/ml.

## Statistical analysis

Sample size was calculated (power 80%, significance level 5%, mean of the differences between pairs for DHEA-S 66 µg/dl, standard deviation of the differences for DHEA-S 160 µg/dl). Categorical variables are expressed as a number (percentage). Paired t-test was used for comparison of continuous variables with normal distribution [expressed as mean (standard deviation)], whereas the Wilcoxon matched pairs signed rank test was used for not normally distributed variables [expressed as median (range)]. Correlation analysis was performed to examine the association between psychopathology as expressed in the PANSS scale and subscales, duration of untreated psychosis (DUP, crudely assessed as the time (weeks) elapsed from the onset of psychotic symptoms according to information received by the patient), and different hormones (DHEA-S, ACTH, cortisol, cortisol/DHEA-S ratio). Pearson or Spearman correlation analysis was performed for parameters with or without normal distribution, respectively. Linear regression analysis was also performed using the psychopathological characteristics as the independent variable and the measured hormones as the dependent variable, adjusting for age and sex. The level of significance was set at  $p$ -value $<0.05$ . Statistical analysis was performed with Stata software version 15.1.

## Results

Data were included for 110 subjects (70 men and 40 women), comprising 55 patients and 55 controls. The mean age was 31.3 years (SD 8.7) in patients and 31.4 years (SD 8.9) in controls. Additionally, the positive, negative, cognitive, depression, and excitement subscales of PANSS (according to Lykouras et al five factor model) 35 were 26.3 (1.7), 19.8 (3.1), 13.1 (3.0), 6.4 (1.6), and 10 (5-19), respectively. Median duration of untreated psychosis was 10 weeks (3-29), with women having a longer time being untreated compared to men. Table 1 describes the different demographic, hormonal, and psychopathology data in patients and controls.

Serum DHEA-S was higher in patients compared to controls [0.69 (0.40) versus 0.50 (0.19), respectively,  $p=0.0022$ ]. Serum ACTH was similar between patients and controls [28.0 pg/ml (6.2-73.9) versus 22.4 pg/ml (7.0-70.5), respectively,  $p=0.6359$ ]. Serum cortisol levels and cortisol/DHEA-S ratio were lower in patients [12.6 µg/dl (4.5) and 4.4%(1.3-19.5), respectively] compared to controls [15.4µg/dl (3.7) and 7.0% (2.4-25.5), respectively],  $p=0.0015$  and  $p=0.0003$ , respectively.

Sub-analysis revealed that in men, serum DHEA-S was similar between male patients and controls [0.53 (0.23) versus 0.48 (0.17), respectively,  $p=0.2590$ ], whereas in women, serum DHEA-S was higher in patients compared to controls [0.97 (0.47) versus 0.55 (0.20), respectively,  $p=0.0013$ ]. ACTH levels were not different in the above subgroups. Serum cortisol in men was lower in patients compared to controls [12.8 µg/dl (4.4) versus 15.9 µg/dl (3.6), respectively,  $p=0.0048$ ]. Additionally, the cortisol/DHEA-S ratio was lower in patients compared to controls in men [4.4% (1.3-19.5) versus 5.8% (2.4-15.4), respectively,  $p=0.0259$ ], as well as in women [4.3% (1.8-15.2) versus 7.9% (4.0-25.5), respectively,  $p=0.0051$ ].

Correlation analysis was performed to examine the association between different psychopathological characteristics in patients and measured hormones (table 2). It was found that the PANSS cognitive subscale was positively correlated with DHEA-S in men ( $r=0.3822$ ,  $p$ -value=0.0235) and the positive subscale was negatively correlated with DHEA-S in women ( $r=-0.4464$ ,  $p$ -value=0.0485). Additionally, the PANSS cognitive subscale was marginally negatively correlated with cortisol/DHEA-S ratio in men ( $r=-0.3323$ ,  $p$ -value=0.0511). In the linear regression analysis, DHEA-S was positively associated with the PANSS cognitive subscale in men ( $\beta=0.04$ ,  $p$ -value=0.006). The results from the linear regression analysis are presented in table 3 and the Supplementary tables.

## Discussion

In this study, we found higher serum DHEA-S levels in drug-naïve, first-episode female patients with psychosis compared to matched female controls and lower cortisol levels in male patients compared to male matched controls. In the total population cortisol/DHEA-S ratio was lower in FEP patients compared to controls. ACTH levels were similar between patients and controls. DHEA-S levels were positively associated with the PANSS cognitive subscale in men.

This is one of the very few studies in this field where DHEA-S, ACTH, cortisol, and the cortisol/DHEA-S ratio were assessed in a calculated sample of drug-naïve, first-episode patients with psychosis with relatively small DUP, and where sub-analysis in males and females was also performed.

Our findings are in accordance with Beyazyuz et al,<sup>18</sup> Strous et al,<sup>19</sup> and Solanki et al,<sup>20</sup> who report increased DHEA-S levels in FEPs compared to controls, although these studies did not provide separate analysis between

**Table 1.** Demographic, hormonal, and psychopathology data in patients and controls.

	Patients (N=55)	Controls (N=55)	p
Men:Women	35:20	35:20	–
Age (years)	31.3 (8.7)	31.4 (8.9)	–
DHEA-S <sup>1</sup>	0.69 (0.40)	0.50 (0.19)	0.00222
DHEA-S in men	0.53 (0.23)	0.48 (0.17)	0.25902
DHEA-S in women	0.97 (0.47)	0.55 (0.20)	0.00132
ACTH (pg/ml)	28.0 (6.2–73.9)	22.4 (7.0–70.5)	0.63593
ACTH in men	28.7 (8.0–73.9)	21.4 (8.6–70.5)	0.56653
ACTH in women	19.0 (6.2–56.3)	23.3 (7.0–52.8)	0.97023
Cortisol (µg/dl)	12.6 (4.5)	15.4 (3.7)	0.00152
Cortisol in men	12.8 (4.4)	15.9 (3.6)	0.00482
Cortisol in women	12.4 (4.9)	14.8 (4.0)	0.13112
Cortisol/DHEA-S (%)	4.4 (1.3–19.5)	7.0 (2.4–25.5)	0.00033
Cortisol/DHEA-S in men	4.4 (1.3–19.5)	5.8 (2.4–15.4)	0.02593
Cortisol/DHEA-S in women	4.3 (1.8–15.2)	7.9 (4.0–25.5)	0.00513
PANSS-P	26.3 (1.7)	–	–
PANSS-P in men	26.5 (1.8)	–	–
PANSS-P in women	26 (23–28)	–	–
PANSS-N	19.8 (3.1)	–	–
PANSS-N in men	20.6 (3.4)	–	–
PANSS-N in women	18.4 (1.7)	–	–
PANSS-C	13.1 (3.0)	–	–
PANSS-C in men	12 (9–19)	–	–
PANSS-C in women	13.6 (3.4)	–	–
PANSS-D	6.4 (1.6)	–	–
PANSS-D in men	6 (5–11)	–	–
PANSS-D in women	5.6 (1.4)	–	–
PANSS-E	10 (5–19)	–	–
PANSS-E in men	10 (8–14)	–	–
PANSS-E in women	11.9 (3.6)	–	–
DUP (weeks)	10.0 (3.0–29.0)	–	–
DUP in men	10.0 (3.0–29.0)	–	–
DUP in women	13.1 (6.8)	–	–

Abbreviations: ACTH, adrenocorticotrophic hormone; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement

<sup>1</sup>It represents the ratio of each DHEA-S value to the upper limit of normal for the respective age group in men and women

<sup>2</sup>Paired t-test was used

<sup>3</sup>Wilcoxon matched-pairs signed-rank test was used

Variables are expressed as mean (standard deviation) or median (minimum-maximum)

males and females. Misiak et al<sup>9</sup> report elevated DHEA levels but only in the male subgroup of patients. The researchers support the hypothesis that elevated DHEA-S levels in FEPs may be attributed to the increased dopaminergic activity during the acute phase of psychosis

and have a neuroprotective effect, given their anti-glucocorticoid and neuroprotective properties. This effect seems to become blunted as the disease progresses because increased DHEA-S levels were found only in FEPs and not in acutely relapsed, multiple-episode patients.

**Table 2.** Descriptive statistics of sociodemographic and clinical variables as well as of psychopathology and neurocognition.

	Total population		Men		Women	
	r	p-value	r	p-value	r	p-value
DHEA-S						
PANSS-P	-0.2207	0.1055	-0.0843	0.6303	-0.4464	0.0485
PANSS-N	0.1248	0.3641	0.2155	0.2137	-0.0141	0.9528
PANSS-C	0.3438	0.0102	0.3822	0.0235	0.2783	0.2348
PANSS-D	-0.1151	0.4029	-0.0637	0.7164	-0.0283	0.9057
PANSS-E	-0.0211	0.8785	-0.1454	0.4046	0.1246	0.6006
DUP	0.0018	0.9897	0.0223	0.8988	-0.0613	0.7974
ACTH						
PANSS-P	0.1844	0.1777	0.1798	0.3013	0.1828	0.4405
PANSS-N	0.2311	0.0896	0.2536	0.1415	-0.0781	0.7436
PANSS-C	-0.0385	0.7800	-0.0274	0.8758	0.0387	0.8714
PANSS-D	0.0828	0.5478	-0.0084	0.9617	0.0100	0.9666
PANSS-E	-0.1343	0.3282	-0.0001	0.9997	-0.1127	0.6361
DUP	0.0767	0.5776	0.0713	0.6839	0.1022	0.6682
Cortisol						
PANSS-P	-0.1733	0.2058	-0.2703	0.1163	0.0101	0.9663
PANSS-N	-0.0810	0.5564	-0.0741	0.6724	-0.2174	0.3572
PANSS-C	0.1529	0.2650	0.0505	0.7734	0.4085	0.0737
PANSS-D	0.0791	0.5659	0.1949	0.2618	-0.1672	0.4812
PANSS-E	-0.1692	0.2169	-0.2689	0.1183	-0.1210	0.6114
DUP	-0.0859	0.5327	-0.1336	0.4442	0.0077	0.9742
Cortisol/DHEA-S						
PANSS-P	0.0058	0.9665	-0.1972	0.2561	0.4184	0.0664
PANSS-N	-0.2047	0.1338	-0.2589	0.1331	-0.1692	0.4757
PANSS-C	-0.2367	0.0819	-0.3323	0.0511	0.0414	0.8626
PANSS-D	0.0763	0.5799	0.2006	0.2478	-0.1458	0.5398
PANSS-E	-0.1151	0.4025	-0.0108	0.9511	-0.2226	0.3456
DUP	0.0662	0.6311	0.0169	0.9234	0.1710	0.4710

Abbreviations: ACTH, adrenocorticotrophic hormone; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement; r, correlation coefficient

DHEA and its sulfate ester (DHEA-S) take part in brain development by promoting neuronal differentiation, synaptic connectivity, myelination, and neuron growth.<sup>36,37</sup> DHEA reduces pro-inflammatory cytokines both in vivo and in vitro.<sup>26</sup> DHEA administration decreases inflammation by the inhibition of Interleukin-6 (IL-6) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), cytokines whose levels have been found to increase in FEPs.<sup>32,38</sup> DHEA-S is the precursor of the sex hormones testosterone and estrogen, and exerts some of its actions by directly binding and activating estrogen receptors in the brain.<sup>10</sup>

Elevated DHEA-S levels may remain as a compensatory effect or as a neuroprotection against chronic oxidative stress or inflammation, factors strongly associated with schizophrenia and FEP. Decreased cortisol/DHEA-S ratio may represent a prolonged neuroprotective effect or a blunted cortisol response to stress.<sup>26</sup>

We did not find any statistically significant difference in ACTH levels between patients and controls. Similar findings by Beyazyuz et al,<sup>18</sup> Misiak et al,<sup>13</sup> reports increased ACTH levels in FEP patients. As the researchers state, their meta-analysis included only seven studies

**Table 3.** Linear regression analysis between different psychopathological characteristics and measured hormones in patients.

	Total population			Men			Women		
	beta	95% CI	p-value	beta	95% CI	p-value	beta	95% CI	p-value
<b>DHEA-S</b>									
PANSS-P	-0.05	-0.10, 0.01	0.110	-0.02	-0.07, 0.03	0.422	-0.10	-0.27, 0.07	0.251
PANSS-N	0.02	-0.02, 0.05	0.341	0.02	-0.01, 0.04	0.187	0.03	-0.10, 0.17	0.589
PANSS-C	0.03	0.00, 0.06	0.027	0.04	0.01, 0.07	0.006	0.02	-0.05, 0.09	0.503
PANSS-D	-0.03	-0.09, 0.03	0.342	-0.03	-0.09, 0.02	0.220	-0.04	-0.20, 0.13	0.628
PANSS-E	0.01	-0.02, 0.05	0.435	-0.03	-0.09, 0.02	0.220	0.04	-0.02, 0.10	0.139
DUP	0.00	-0.01, 0.01	0.744	0.00	-0.01, 0.01	0.877	0.02	-0.02, 0.06	0.352
<b>ACTH</b>									
PANSS-P	1.39	-1.27, 4.05	0.299	1.19	-1.83, 4.22	0.429	2.35	-4.44, 9.14	0.476
PANSS-N	0.38	-1.15, 1.90	0.621	0.56	-1.03, 2.15	0.478	-0.98	-6.17, 4.20	0.694
PANSS-C	-0.14	-1.65, 1.37	0.849	-0.19	-2.20, 1.81	0.840	-0.07	-2.72, 2.58	0.956
PANSS-D	0.98	-1.99, 3.96	0.511	1.21	-2.28, 4.71	0.484	0.49	-5.91, 6.89	0.875
PANSS-E	-0.10	-1.88, 1.68	0.911	-0.15	-3.73, 3.44	0.935	-0.11	-2.60, 2.38	0.927
DUP	0.23	-0.35, 0.82	0.424	0.16	-0.49, 0.81	0.617	0.57	-1.00, 2.14	0.453
<b>Cortisol</b>									
PANSS-P	-0.50	-1.27, 0.27	0.200	-0.66	-1.53, 0.20	0.126	0.58	-1.29, 2.44	0.523
PANSS-N	-0.17	-0.61, 0.27	0.439	-0.09	-0.56, 0.38	0.697	-0.51	-1.91, 0.89	0.453
PANSS-C	0.23	-0.21, 0.66	0.301	-0.04	-0.63, 0.54	0.881	0.49	-0.19, 1.17	0.144
PANSS-D	0.21	-0.65, 1.08	0.622	0.56	-0.45, 1.57	0.264	-0.77	-2.48, 0.94	0.358
PANSS-E	-0.28	-0.79, 0.24	0.284	-0.68	-1.70, 0.33	0.182	-0.03	-0.71, 0.65	0.931
DUP	-0.03	-0.21, 0.14	0.685	-0.08	-0.27, 0.11	0.418	0.25	-0.16, 0.67	0.218
<b>Cortisol/DHEA-S</b>									
PANSS-P	0.03	-0.58, 0.64	0.928	-0.28	-0.99, 0.44	0.437	0.88	-0.50, 2.26	0.195
PANSS-N	-0.25	-0.59, 0.09	0.150	-0.21	-0.58, 0.17	0.268	-0.69	-1.73, 0.34	0.177
PANSS-C	-0.29	-0.62, 0.04	0.086	-0.42	-0.87, 0.03	0.064	-0.11	-0.66, 0.45	0.693
PANSS-D	0.26	-0.42, 0.93	0.446	0.45	-0.37, 1.26	0.274	-0.10	-1.45, 1.24	0.876
PANSS-E	-0.17	-0.57, 0.23	0.396	0.32	-0.52, 1.16	0.446	-0.41	-0.89, 0.07	0.090
DUP	0.01	-0.12, 0.15	0.862	0.00	-0.15, 0.16	0.974	0.00	-0.33, 0.34	0.987

Abbreviations: ACTH, adrenocorticotrophic hormone; CI, confidence interval; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement

with FEP patients were included and assessment of publication bias cannot be excluded.

Misiak et al<sup>13</sup> report higher cortisol blood levels but not unstimulated salivary cortisol levels in FEPs, while Aymerich et al<sup>14</sup> did not find any statistically significant difference in cortisol levels between FEPs and controls. According to the researchers, cortisol's little influence on dopamine secretion could explain its absence of elevation during the onset of psychosis. Cortisol level abnormalities observed in samples of chronic patients may indicate the evolution or severity of the disorder. No difference in cortisol levels is reported by

Chaumette et al,<sup>15</sup> Beyazuz et al,<sup>18</sup> Strous et al,<sup>19</sup> Solanki et al.<sup>20</sup> Hubbard and Miller<sup>6</sup> report increased blood cortisol levels in minimally treated FEPs compared to controls. In the same meta-analysis, the stratification by geographic region showed that significantly increased cortisol levels were found in studies from Europe and Asia. On the contrary, studies from the Middle East showed a trend for lower cortisol levels in FEPs compared to controls.

As DHEA-S functions as a cortisol antagonist, it may be implicated in returning cortisol levels to baseline after the stress response. DHEA-S elevations tend to be

observed after psychosocial stress and later than the cortisol peak.<sup>39</sup>

It may be suggested that the increase of DHEA-S levels in female patients may be due to a compensatory mechanism aiming at estrogen augmentation, with lower gonadal levels leading to higher DHEA production as part of negative feedback regulation<sup>26</sup> Estrogens increase synaptic plasticity and reduce neuro-inflammation, have antiapoptotic actions and increase dopamine sensitivity in the Ventral Tegmental Area (VTA), thus leading to the reduction of psychotic symptoms.<sup>40,41</sup>

Cortisol/DHEA-S ratio represents the relative imbalance between these two hormones, suggesting a possible role as an index of the HPA axis state. In our study, the cortisol/DHEA-S ratio was consistently lower in FEP patients compared to controls in the total population, as well as separately in men and women. The lower cortisol/DHEA-S ratio reflects the higher DHEA-S values in female patients and the lower cortisol levels in male patients

Our findings provide evidence for higher DHEA-S levels in females but not in males with FEP. Further studies are needed in this field to elucidate the possible implications of DHEA-S in psychosis.

Our sample consists of First-episode patients. First-episode psychosis diagnoses other than schizophrenia are quite unstable over time, although most of them shift to the diagnosis of schizophrenia (Fousar-Poli et al 2016).<sup>42</sup> Prospective studies with larger sample sizes may account for this limitation.

Hormone stress measurement at one point in time does not permit us to generalize our conclusions or to draw causal relationships. Measurements once a day

are not as reliable as multiple measurements during the day, as stress hormone levels follow a circadian rhythm. Future studies should conduct multiple daily measurements in order to account for hormonal fluctuations during the day.

We could not assess perceived anxiety in our study group during the time they were waiting for blood collection (both patients and controls). This is a limitation of our study, since anxiety could have influenced our results.

We could not take into account the phase/day of the menstrual cycle of the female participants, and this could have influenced our results.

The control group was not a random sample of the population, and this is a critical limitation of our study. Statistical analysis of many sociodemographic variables suggested no differences between our two groups, but we cannot exclude the presence of other confounding factors. Nevertheless, our study still had a higher sample size compared to similar previously published ones.

## Conclusion

Female patients with schizophrenia have a later age of onset, better response to antipsychotic treatment, and better prognosis than men. As DHEA-S acts as a compensatory, neuroprotective mechanism, higher DHEA-S values only in female FEP patients may represent a more effective, gender-dependent, compensatory process.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: <https://doi.org/10.22365/jpsych.2025.016>

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## Ερευνητική εργασία

# Συγκεντρώσεις θειικής δεϋδροεπιανδροστερόνης (DHEA-S), κορτιζόλης και αδρενοκορτικοτρόπου ορμόνης (ACTH) σε ασθενείς με πρώτο ψυχωτικό επεισόδιο άνευ αντιψυχωτικής θεραπείας

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### ΠΕΡΙΛΗΨΗ

Ο άξονας υποθάλαμος-υπόφυση-επινεφρίδια (ΥΥΕ) παίζει σημαντικό ρόλο στη ρύθμιση της δράσης της ντοπαμίνης σε περιοχές του εγκεφάλου, ιδιαίτερα στο λιμβικό σύστημα καθώς και στην απάντηση στο στρες. Η εκτίμηση του άξονα αυτού είναι σημαντική για την αναζήτηση βιολογικών μηχανισμών που οδηγούν από τις στρεσογόνες εμπειρίες στην έναρξη της ψύχωσης. Η έκκριση της αδρενοκορτικοτρόπου ορμόνης (ACTH) από την πρόσθια υπόφυση διεγείρει την παραγωγή κορτιζόλης και δεϋδροεπιανδροστερόνης (DHEA) από τον φλοιό των επινεφριδίων ως απάντηση στο στρες. Η ταυτόχρονη έκλυση της DHEA μπορεί να δρα ως προστατευτικός μηχανισμός ως προς τις τοξικές επιδράσεις της υπερέκκρισης κορτιζόλης. Σκοπός της μελέτης ήταν η μέτρηση στον ορό συγκεντρώσεων DHEA-S, ACTH, κορτιζόλης και ο υπολογισμός του λόγου κορτιζόλης/DHEA-S σε ασθενείς πρώτου ψυχωτικού επεισοδίου που δεν είχαν λάβει αντιψυχωτική αγωγή και σε αντίστοιχη ομάδα ελέγχου και σύγκριση των αποτελεσμάτων. Συμπεριλάβαμε δεδομένα από 110 άτομα (70 άνδρες, 40 γυναίκες), 55 ασθενείς και 55 ως ομάδα ελέγχου. Η μέση ηλικία των ασθενών ήταν 31,3 έτη (8,7) και 31,4 έτη (8,9) για την ομάδα ελέγχου. Η τιμές της DHEA-S στον ορό ήταν υψηλότερες στους ασθενείς σε σύγκριση με την ομάδα ελέγχου [0,69 (0,40) έναντι 0,50 (0,19), αντίστοιχα]. Οι τιμές της ACTH του ορού ήταν παρόμοιες μεταξύ των δύο ομάδων [28,0 pg/ml (6,2–73,9) έναντι 22,4 pg/ml (7,0–70,5), αντίστοιχα]. Οι τιμές της κορτιζόλης ορού και ο λόγος κορτιζόλης/DHEA-S ήταν χαμηλότερα στους ασθενείς [12,6 mg/dl (4,5) και 4,4% (1,3–19,5), αντίστοιχα] σε σύγκριση με την ομάδα ελέγχου [15,4 mg/dl (3,7) και 7,0% (2,4–25,5), αντίστοιχα]. Η επιμέρους ανάλυση έδειξε ότι στους άνδρες, οι συγκεντρώσεις της DHEA-S στον ορό ήταν παρόμοιες μεταξύ ανδρών ασθενών και ομάδας ελέγχου [0,53 (0,23) έναντι 0,48 (0,17), αντίστοιχα] ενώ στις γυναίκες οι συγκεντρώσεις της DHEA-S στον ορό ήταν υψηλότερες στις ασθενείς σε σύγκριση με τις γυναίκες της ομάδας ελέγχου [0,97 (0,47) έναντι 0,55 (0,20), αντίστοιχα]. Οι συγκεντρώσεις της ACTH στον ορό δεν διέφεραν μεταξύ των ανωτέρω υποομάδων. Οι τιμές κορτιζόλης ορού στους άνδρες ήταν χαμηλότερες στους ασθενείς σε σύγκριση με την ομάδα ελέγχου [12,8 mg/dl (4,4) έναντι 15,9 mg/dl (3,6)]. Επιπρόσθετα, ο λόγος κορτιζόλης/DHEA-S ήταν χαμηλότερος στους ασθενείς σε σύγκριση με την ομάδα ελέγχου τόσο στους άνδρες [4,4% (1,3–19,5) έναντι 5,8% (2,4–15,4), όσο και στις γυναίκες [4,3% (1,8–15,2) έναντι 7,9% (4,0–25,5), αντίστοιχα]. Η ανάλυση συσχετίσεων πραγματοποιήθηκε για τον έλεγχο συσχετίσεων μεταξύ ψυχοπαθολογικών χαρακτηριστικών των ασθενών και των ορμονών που μετρήθηκαν. Έδειξε ότι η νοητική υποκλίμακα της PANSS συσχετιζόταν θετικά με τα επίπεδα της DHEA-S στους άνδρες και η θετική της υποκλίμακα συσχετιζόταν αρνητικά με τη DHEA-S στις γυναίκες. Στην ανάλυση γραμμικής παλινδρόμησης, η DHEA-S σχετιζόταν θετικά με τη νοητική υποκλίμακα της PANSS στους άνδρες.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Θειική δεϋδροεπιανδροστερόνη (DHEA-S), κορτιζόλη, αδρενοκορτικοτρόπος ορμόνη (ACTH), πρώτο ψυχωτικό επεισόδιο, ασθενείς άνευ θεραπείας.