Dehydroepiandrosterone sulfate and testosterone levels correlate with negative symptoms in male patients with schizophrenia

Haitham M. Hashim and Mohmed G. Negm

Department of Psychiatry, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence to Haitham M. Hashim, Department of Psychiatry, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Tel: +01 000 089 614; fax: +055 3971039; e-mail: aboukhedry@yahoo.com

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Background
Clinical studies have shown greater sex differences in symptoms of schizophrenia, with men having more negative symptoms than women, which may be related to the action of the reproductive hormones.

Objective
The aim of this study was to determine the relationship between negative symptoms and the plasma levels of testosterone and dehydroepiandrosterone sulfate (DHEAS) in male patients with schizophrenia.

Participants and methods
The participants were 50 male patients with chronic schizophrenia. The psychopathology of the patients was assessed using the Positive and Negative Syndrome Scale (PANSS). The Calgary Depression Scale for Schizophrenia (CDSS) and the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) were also used to exclude the effects of depression or drug-induced extrapyramidal symptoms.

Results
The PANSS negative scores showed a significant inverse correlation with the serum testosterone levels without a correlation with serum DHEAS.

Conclusion
This study indicates that testosterone but not DHEAS may play an important role in the severity of negative symptoms in male patients with schizophrenia.

Keywords:
dehydroepiandrosterone sulfate, negative symptoms, schizophrenia, testosterone

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Introduction

The diagnosis of schizophrenia is currently made using criterion-based systems, including positive (e.g. hallucinations and delusions) and negative (e.g. a volition and alogia) symptoms (Shirayama *et al.*, 2002).

The correlation between negative symptoms and loss of social function among schizophrenics has been increasingly recognized. The diagnosis of schizophrenia has therefore shifted toward the presence of negative symptoms (Akhondzadeh *et al.*, 2006).

Sex differences have been reported in schizophrenia and involve various aspects of the disease. The existence of sex differences in these areas strongly suggests a vital role played by gonadal hormones; the observations of an association between age of onset and reproductive age led some researchers to suggest an important pathogenic role of both estrogen and testosterone, and their interactions with neurotransmitters' system in specific brain regions (Goldstein, 1988; Goldstein and Tsuang, 1990).

Dehydroepiandrosterone (DHEA) and its sulfate conjugate (DHEAS) are neurosteroids that mediate several neurotransmitter systems coupled to ion channels, such as γ-aminobutyric acid (GABAA), *N*-methyl-D-aspartate (NMDA), and sigma receptors (Wen *et al.*, 2001).

DHEA metabolism has been reviewed recently; briefly, DHEA sulfotransferase catalyzes the transformation of DHEA into DHEAS (Falany *et al.*, 1995). Androstenedione is synthesized from DHEA by 3h-hydroxysteroid dehydrogenase/D5–D4 isomerase and from progesterone through 17-OH-progesterone by 17a-hydroxylase and 17,20-lyase (Rupprecht, 2003). The conversion of androstenedione into testosterone is catalyzed by 17h-hydroxysteroid dehydrogenase (King *et al.*, 1999). Previous studies investigating DHEA blood levels in concentrations in psychosis or schizophrenia have reported either low (Harris *et al.*, 2001), elevated (Di Michele *et al.*, 2005), or no differences in DHEA levels (Ritsner *et al.*, 2004) compared with matched healthy controls. In addition, they have unaltered (Mason *et al.*, 1988; Markianos *et al.*, 1999) or significantly lower serum testosterone levels, especially among patients treated with high-dose first-generation antipsychotic agents (Rinieris *et al.*, 1989; Kaneda and Fujii, 2000; Kaneda, 2003), and in male schizophrenia patients before and during treatment, but not after recovery (Taherianfard and Shariaty, 2004). The inconsistencies in the findings published may be because

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of the wide clinical variability, small sample sizes, or differences in the age and duration of illness of patients (Cleare *et al*., 2004). The majority of studies do not report repeat data on serum DHEA and their key metabolites in patients compared with healthy controls over time controlling for confounding factors.

Although there exist a few studies on the relationship between the plasma levels of testosterone and negative symptoms in patients with schizophrenia, the exact role of reproductive hormones in the pathophysiology of the schizophrenia is still emerging (Seeman, 1996; Shirayama *et al*., 2002; Akhondzadeh *et al*., 2003; Goyal *et al*., 2004).

The goals of this study were to determine whether alterations in serum DHEAS and testosterone occur in treated chronic schizophrenia patients compared with healthy controls and to evaluate the relationship between the plasma level of testosterone and DHEAS and the severity of negative symptoms in patients with chronic schizophrenia.

Participants and methods

Participants

Two groups of patients were invited to participate in the study.

Patients

A total of 50 patients were recruited from among consecutive attenders of the psychiatric inpatient department and outpatient clinics of Zagazig University Hospitals from April 2010 to March 2011, with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV).

All patients had chronic schizophrenia, defined as having symptoms of schizophrenia for at least 2 years before recruitment.

Their psychiatric symptoms were stable before the examination, and their doses of antipsychotic medications and other concomitant psychotropic medications such as benzodiazepines, antiparkinsonian agents, mood stabilizers, and/or hypnotics were fixed for at least 2 weeks before participation in this study.

The patients were considered symptomatically stable if there had been no appreciable change in their psychotic symptoms during the 4 weeks before participation in this study, irrespective of the severity of their symptoms.

They had no abnormal medical findings as evidenced by assessment of medical histories and physical examinations and no other chronic medical illness, substance abuse (including anabolic steroids), or substance dependence in the past year.

Patients with a BMI less than 20 kg/m^2 or more than 30 kg/m^2, those with drug-induced extrapyramidal symptoms, and depressed patients were excluded.

Controls

An equal number of apparently healthy men, matching the recruited patients as much as possible in terms of age, and with no history of treatment for any neuropsychiatric disorder were recruited.

An informed consent was obtained from all the participants after the procedures had been fully explained. The study was approved by the ethical committee of the institution.

Methods

Assessments

Clinical assessment: semistructured interview

Participants were subjected to a semistructured psychiatric interview, using a specially designed interview derived from the Psychiatric Department sheet of Zagazig University.

The semistructured interview included a full psychiatric sheet, which allowed each patient to receive a psychiatric diagnosis at the end of the interview, during which the DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of a schizophrenia disorder was confirmed.

Psychometric procedures

The following scales were administered:

Positive and Negative Syndrome Scales (*PANSS*) (Kay *et al*., 1987): This is a 30-item, psychopathology rating scale, based on a semistructured clinical interview. The scale was designed to measure positive and negative schizophrenic symptoms, and related variables such as cognitive, affective, and social functioning. It has been evaluated rigorously from a psychometric perspective and has been used widely in several clinical studies. The scale yields five scores: a positive symptom score, a negative symptom score, a general psychopathology score, a total score, and a composite score.

The Calgary Depression scale for Schizophrenia (Addington *et al*., 1990): The Calgary Depression scale for Schizophrenia (CALG) is used to assess the mood state of schizophrenic patients. The patients were asked about (a) depression (his mood over the last 2 weeks), (b) hopelessness (how do you see the future), (c) self-depreciation, (d) guilty ideas of reference, (e) pathological guilt, (f) morning depression, (g) early awakening, (h) suicide, and (i) observed depression (on the basis of interviewers' observations). These items were described according to the severity (absent, mild, moderate, and severe).

The Drug-induced Extrapyramidal Symptoms Scale (*DIEPSS*) (Inada, 1996): The DIEPSS, which consists of eight individual items and one global item, was used to assess treatment-emergent extrapyramidal symptoms.

The eight individual items include (1) gait, (2) bradykinesia, (3) sialorrhea (increased salivation), (4) muscle rigidity, (5) tremor, (6) akathisia, (7) dystonia, and (8) dyskinesia. The global item is overall severity. Extrapyramidal syndromes, as measured by the DIEPSS,

were grouped into four categories: (a) parkinsonism, (b) akathisia, (c) dystonia, and (d) dyskinesia.

The parkinsonism syndrome consisted of DIEPSS items 1–5. The akathisia, dystonia, and dyskinesia syndromes consisted of DIEPSS items 6, 7, and 8, respectively. The severity of each item was rated from 0 (normal) to 4 (severe).

The patients filled in a questionnaire consisting of nine comprehensive questions aimed to detect typical symptoms of parkinsonism including akathisia, dystonia, and dyskinesia.

Body mass index

BMI a statistical measure of the weight of an individual scaled according to height, sometimes referred to as body weight index. It is defined as the individual's body weight divided by the square of their height.

Patients with a BMI below 18.5 kg/m^2 were categorized as underweight, 18.5–24.9 kg/m^2 were categorized as normal, 25.0–29.9 kg/m^2 were categorized as overweight, and at least 30 kg/m^2 were categorized as obese according to the WHO classification.

Laboratory Investigations

Ten milliliters of blood sample was collected in a tube to determine the levels of total testosterone and DHEAS. Blood samples for the hormone estimation were collected from 8:00 to 9:00 a.m. The sera were prepared and stored at −20°C until the time of analysis. Testosterone and DHEAS were assayed by a radioimmunoassay.

Statistical analysis

Data were statistically described in terms of mean ± SD, frequencies (number of cases), and percentages when appropriate. A comparison of the quantitative variables between the study groups was performed using the Student *t*-test for independent samples. For comparison of categorical data, the χ^2-test was carried out. The exact test was used when the expected frequency was less than 5. The correlation between various variables was determined using the Pearson moment correlation equation for a linear relation in normally distributed variables and the Spearman rank correlation equation for non-normal variables. *P* values less than 0.05 were considered statistically significant. All statistical calculations were carried out using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, USA) and statistical package for the social science (SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

The sociodemographic and clinical characteristics of the patients and the control group are presented in Table 1. Because of the selection procedures, the patients and the controls were comparable in terms of age, BMI, and education. Table 1 also shows that there was a statistically significant difference between the group of patients and the control individuals in the level of serum testosterone hormone, but there were no statistically significant differences in the DHEAS level. Table 1 indicates that the mean age at onset of the disease was 19.4 ± 3.4 years (range between 15 and 28 years) and the duration of illness was 9.3 ± 61 years (range between 2 and 23 years); the mean values of the PANSS score were as follows: total 84.8 ± 12.6, positive 20.6 ± 4.7, negative 22.1 ± 4.5, and psychopathology 41.8 ± 7.3.

Table 1 Sociodemographic and clinical characteristics of the patients and the control group

Sociodemographic data	$\bar{X}$ ± SD Patients (*N*=50)	Controls (*N*=50)	Significance
Age (years)			
X± SD	28.7 ± 6.6	29.7 ± 3.6	*t*=0.94
Range	20–40	21–37	*P*=0.34
BMI			
X± SD	25.6 ± 2.97	26.2 ± 203	*t*=1.13
Range	20–30	21–29	*P*=0.26
Education level			
0	2 ± 4.0	4 ± 8.0	*t*=5.22
1	12 ± 24.0	4 ± 8.0	*P*=0.26
2	12 ± 24.0	14 ± 28.0	
3	18 ± 36.0	22 ± 44.0	
4	6 ± 12.0	6 ± 12.0	
Serum testosterone level			
X± SD	3.88 ± 1.6	5.8 ± 1.5	*t*=5.98
Range	1.4–7.8	2.9–7.9	*P*<0.001
DHEAS level			
X± SD	223.6 ± 100.7	229.96 ± 26.6	*t*=0.43
Range	50–501	180–273	*P*=0.66
Age at onset			
X± SD	19.4 ± 3.4		
Range	15–28		
Duration of illness			
X± SD	9.3 ± 61		
Range	2–23		
PANSS			
Total	84.8 ± 12.6 (65–122)		
Positive	20.6 ± 4.7 (14–31)		
Negative	22.1 ± 4.5 (15–32)		
General	41.8 ± 7.3 (30–59)		

DHEAS, dehydroepiandrosterone sulfate; PANSS, Positive and Negative Syndrome Scale.
Statistically significant difference ($P \leq 0.05$).

Table 2 shows that there was no statistically significant difference between the serum testosterone level and the age of the patients, age at onset, BMI, and duration of illness, but there was a statistically significant difference in the PANSS score. The PANSS negative scores showed a significant inverse correlation with the serum testosterone level ($r = -0.481$, $P < 0.001$) and there was no significance difference between the DHEAS level and the age of the patients, age at onset, BMI, duration of illness, and the PANSS negative score.

Table 3 shows the correlation between serum testosterone and the DHEAS level and the severity of negative symptoms, and indicates that there was a highly significant negative correlation between the severity of different negative symptoms and serum testosterone level as, when testosterone decreases, the severity of negative symptoms increases, but there was no correlation between negative symptoms and the serum level of DHEAS.

Table 2 Correlation between serum testosterone, dehydroepiandrosterone sulfate, and other parameters

	Serum testosterone		DHEAS	
Patients parameters	*r*	*P*	*r*	*P*
Age of patients	−0.17	>0.05	−0.13	>0.05
Age at onset	−0.12	>0.05	−0.14	>0.05
Duration of illness	−0.11	>0.05	−0.1	>0.05
BMI	−0.19	>0.05	−0.22	>0.05
PANSS				
Total	−0.56	<0.001	0.31	<0.05
Positive	−0.40	<0.05	0.33	<0.05
Negative	−0.481	<0.001	0.19	>0.05
General	−0.48	<0.001	0.47	<0.001

DHEAS, dehydroepiandrosterone sulfate; PANSS, Positive and Negative Syndrome Scale.
Statistically significant difference ($P \leq 0.05$).

Table 3 Correlation between serum testosterone and dehydroepiandrosterone sulfate level and the severity of negative symptoms

	Serum testosterone		DHEAS	
Negative scale of PANSS	*r*	*P*	*r*	*P*
Blunted affect	−0.65	<0.001	−0.19	>0.05
Emotional withdrawal	−0.41	<0.001	−0.22	>0.05
Poor rapport	−0.42	<0.001	−0.13	>0.05
Passive social withdrawal	−0.59	<0.001	−0.12	>0.05
Difficulty in abstract thinking	−0.38	<0.001	−0.18	>0.05
Lack of spontaneity and flow of conversation	−0.02	>0.05	−0.19	>0.05
Stereotyped thinking	−0.43	<0.001	−0.11	>0.05

DHEAS, dehydroepiandrosterone sulfate; PANSS, Positive and Negative Syndrome Scale.
Statistically significant difference ($P \leq 0.05$).

Discussion

The results of this study indicate that in medicated male patients with chronic schizophrenia, compared with healthy controls, the serum concentration of testosterone was found to be increased, but the DHEAS level was normal, and that the serum total testosterone level is inversely correlated with negative symptoms. Moreover, there was no any correlation between testosterone and DHEAS or between DHEAS and the clinical characteristics of the patients. Decreased serum testosterone levels among our patients have also been reported by Ko *et al*., 2007, who found strongly decreased serum testosterone levels in a group of 35 male inpatients with schizophrenia, and the serum testosterone level was inversely correlated with negative symptoms in male patients with chronic schizophrenia. These findings suggest that lower total and free testosterone levels may reflect more severe negative symptoms in male patients with schizophrenia.

Our results are also supported by the finding reported by Akhondzadeh *et al.* (2006). The results of this study are in agreement with previous studies reporting the relationship between gonadal hormones and negative symptoms in male patients with chronic schizophrenia (Shirayama *et al*., 2002; Goyal *et al*., 2004).

With respect to DHEAS (sulfate conjugate of DHEA), some studies have reported low DHEA levels in schizophrenic patients compared with healthy controls (Harris *et al*., 2001); however, other studies have not reported any differences between patients with schizophrenia and normal controls (Brophy *et al*., 1983; Ritsner *et al*., 2004, 2006). Another study reported higher DHEAS levels in young male patients with schizophrenia (Oades and Schepker, 1994) and higher DHEAS levels in first-episode schizophrenia patients (Strous *et al*., 2004). Plasma levels of DHEA were found to be strongly elevated in a group of schizophrenic patients compared with that of control individuals as reported by Di Michele *et al*. (2005).

However, Goyal *et al.* (2004) reported that both serum testosterone and DHEAS levels were lower in a patient group with predominantly negative symptoms than in a patient group with predominantly positive symptoms.

Previous studies investigating DHEA and testosterone blood levels in psychosis or schizophrenia have reported either low DHEA (Harris *et al*., 2001), elevated DHEA (Di Michele *et al*., 2005), or no differences in DHEA levels (Ritsner *et al*., 2004) compared with matched healthy controls. DHEAS levels have been reported to be elevated (Strous *et al*., 2004) or in the control range (Ritsner *et al*., 2004).

In addition, unaltered (Markianos *et al*., 1999) or significantly lower serum testosterone levels have been reported (Kaneda, 2003). The inconsistencies in published findings may be because of the wide clinical variability, small sample sizes, or differences in the age and duration of illness of patients (Cleare *et al*., 2004). The majority of studies have not reported repeat data on serum DHEA and their key metabolites in patients compared with healthy controls.

Many factors affect serum androgen levels as serum testosterone levels decrease with age, starting from the fifth decade of life (Gray *et al*., 1991). Maximal values of circulating DHEAS are attained between the ages of 20 and 30 years (Orentreich *et al*., 1984); the serum testosterone level has a diurnal variation, with the highest values at 8:00 a.m. and the lowest values in the late afternoon (Bremner *et al*., 1983); adiposity, as assessed by the BMI, is a negative determinant of serum testosterone levels (Zumoff *et al*., 1990).

Therefore, to reduce the effects of these factors on androgen levels, we recruited young male schizophrenic patients aged between 20 and 39 years, taking blood samples between 8:00 and 9:00 a.m., and excluded patients who were obese, that is, those with a BMI of over 30 kg/m^2 in this study.

Previous studies have reported controversial results on the relationship between serum testosterone level and negative symptoms in male schizophrenia patients.

However, these previous studies provide possible explanations for the role of testosterone in the negative symptoms of schizophrenia through its effects on

receptors of gonadal hormones that are concentrated in hypothalamic and limbic systems involved in perception, cognition, and behavior (Stevens, 2002).

Testosterone modulates the action of various neurotransmitters and neuropeptides (Białek *et al*., 2004) and through the neuroprotective or neurotrophic actions of testosterone on motor and autonomic neurons (Białek *et al*., 2004).

This study had some limitations. First, we did not measure other related hormone levels, including the gonadotropin-releasing hormone, luteinizing hormone, adrenocorticotropic hormone, prolactin, cortisol, and estradiol, and thus we did not identify their associations with testosterone and DHEAS levels. Second, the number of participants in this study was small; therefore, a larger sample size is recommended for further studies.

Finally, all patients included in our study received antipsychotic drugs; therefore, it is recommended that in further studies, patients who are not under any treatment be studied in order to exclude the effect of those drugs on the level of serum hormones.

However, this study indicates that testosterone but not DHEAS may play an important role in the severity of negative symptoms in male patients with schizophrenia.

Conclusion

There is a need to determine the serum total testosterone hormone level in male schizophrenia patients with predominantly negative symptoms as it may reflect an associative relationship of testosterone with the severity of negative symptoms in male schizophrenic patients.

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Conflicts of interest

There are no conflicts of interest.

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