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Original article

RELATION BETWEEN FAMILY HISTORY, AGE OF ONSET, RELAPSES OF THE DISORDER AND SERUM CORTISOL, DEHYDROEPIANDROSTERONE SULFAT AND THEIR RATIO IN SCHIZOPHRENIA

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Abstract

Family history of schizophrenia is considered to be the strongest risk factor for schizophrenia. Evidence for disturbances in HPA activation and abnormal HPA regulatory mechanisms in schizophrenia is accumulating.

In this clinical prospective study, 60 patients with schizophrenia and 40 healthy subjects, age- and sex-matched control subjects were included. Clinical evaluation of patients was performed using the Positive and Negative Symptom Scale. A questionnaire for socio-demographic and clinical data collection was used. Serum levels of cortisol, DHEA-S and their ratio were measured at baseline in all participants and after 3 and 6 weeks of the antipsychotic treatment in patients with schizophrenia.

Patients with schizophrenia had a significantly higher serum cortisol and DHEA-S levels in comparison to the control group. The age of onset of the disorder did not significantly correlate with serum cortisol levels, DHEA-S and cortisol/DHEA-S ratio. Number of relapses of the disorder significantly correlated with serum DHEA-S levels, but not with serum cortisol levels and cortisol/DHEA-S ratio. Positive family history did not significantly correlate with serum levels of cortisol, DHEA-S and their ratio.

Elevated serum cortisol and DHEA-S in schizophrenic patients might be associated with their role in the pathophysiology of the disorder. There was no significant difference in serum levels of cortisol, DHEA-S and their ratio according to the age of onset of the disorder and positive family history in patients with schizophrenia. Number of relapses of the disorder significantly correlated with serum DHEA-S levels.

Keywords: schizophrenia, cortisol, DHEA-S, number of relapses, age of onset, family history

Introduction

Schizophrenia is a severe, chronic and heterogeneous mental disorder that often has debilitating long-term outcomes. Its lifetime prevalence rate is estimated to be approximately 1% worldwide in the adult population[1]. Elucidation of etiological factors of schizophrenia remains a major challenge for researches. The onset is influenced by biological, psychological and social factors and their interaction is rather specific and individualistic[2]. Genetic factors have a major role in the etiology of schizophrenia, as suggested by adoption, twin and family

studies. Family history of schizophrenia is considered to be the strongest risk factor for schizophrenia with a ten-fold increased risk among first-degree relatives[3]. In the last two decades, several genome-wide association studies (GWAS) have been performed to unravel genetic causes of the disease and the role of familial genetic contribution to the disease formation[4-6]. Simultaneously, hundreds or even thousands of single nucleotide polymorphisms (SNPs) have been reported, which individually could explain only a small fraction of the genetic contribution to the disease; however, cumulative effect of these risk variants may offer a larger share in genetic architecture of disease[1,7]. Although positive family history is known to be a strong risk factor for schizophrenia, there are very few studies of its effect on the outcome[8].

According to the vulnerability-stress concept, patients with schizophrenia display increased sensitivity to stress. The hypothalamo-pituitary-adrenal (HPA) axis is one of the major hormonal systems mediating physical and psychological stress response. Evidence for disturbances in HPA activation and abnormal HPA regulatory mechanisms in psychiatric illnesses is accumulating[9].

When stress is acute, adaptive biochemical responses include increased adrenocortical secretion of stress hormones, prominently cortisol, and dehydroepiandrosterone takes place. Both are considered as neurosteroids, being produced in the brain, as well as a neuroactive steroid, produced in the adrenals and gonads and having its effect on the brain[9,10]. The cortisol (glucocorticoid) is a major mediator of the physiological stress response and impacts on many physiological systems to allow the body's response to a stressor. On the other hand, dehydroepiandrosterone (DHEA) mainly has anabolic effects (i.e., promoting growth and repair), thus repairing catabolic damage so long as its levels remain sufficiently high in the circulation. In humans, 99% of circulating DHEA is in its sulfated form DHEAS (together abbreviated DHEA(S)). Serum DHEAS levels are 100 or more times higher than DHEA and has a much longer life and shows no diurnal variations. Therefore, from a practical point of view, estimation of DHEA-S is preferable to DHEA as its levels are more stable. Neuroactive steroids, such as cortisol, dehydroepiandrosterone and its sulfate ester are the steroid hormones that have several notable roles in the central nervous system [11]. DHEA(S) has multiple effects in the central nervous system mediated through its non-genomic actions on several neurotransmitter systems, such as γ-amino butyric acid type A (GABAA), N-methyl-D-aspartate (NMDA) and sigma receptors[12]. Animal experiments show that DHEA-S has profound psychotropic effects, such as memory enhancement, antidepressant, anxiolytic and anti-aggression[13]. Moreover, DHEA(S) has potent anti-glucocorticoid and neuroprotective actions on the brain and can protect hippocampal neurons from glucocorticoid induced neurotoxicity. In healthy subjects, acute administration of DHEA rapidly reduces cortisol level. The concomitant release of DHEA(S) in the acute stress response is considered to protect the brain against potentially damaging effects of excessive cortisol activity. Since these acute adaptive responses to stress are designed to increase survival, yet the dysfunctional stress responses, i.e. over or under activity of HPA axis may be damaging to an individual. Failure to deactivate these stress responses within a dysfunctional stress system may result in imbalance of these steroid hormones[14].

The HPA axis abnormalities in schizophrenia are indicated by elevated basal cortisol levels, non-suppression of cortisol after dexamethasone suppression test and blunted cortisol awakening response. Increased cortisol levels observed in schizophrenia have been proposed as endophenotypic markers of illness[15].

It has been reported, although inconsistently, that the levels of DHEA and DHEA-S may impact psychopathological manifestation of schizophrenia[16-21].

We therefore decided to conduct a study of serum levels of cortisol, DHEA-S and their ratio in patients with schizophrenia, in terms of clarifying their role in the pathophysiology of the disorder.

The aim of our study was to compare serum cortisol and DHEA-S levels, and their ratio in patients with schizophrenia and healthy control subjects, and to evaluate their association with the positive family history, age of onset of the disease and relapses of the disorder.

Material and method

In this clinical prospective study, we included 60 patients with schizophrenia of both genders, aged from 18-50 years, treated as inpatients or outpatients at the University Psychiatry Clinic, Skopje, North Macedonia. All patients had experienced an acute exacerbation of the illness according to the Positive and Negative Symptom Scale (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 excluded. All patients underwent physical examination and routine laboratory tests to rule out physical illness. Clinical evaluation was performed with patients using the PANSS. As a control group, enrolled were 40 matched healthy subjects. A non-standardized questionnaire was used for collection of socio-demographic (gender, age, education, employment, marital status) and clinical data (age of onset of the disorder, duration of illness, number of relapses, number of hospital treatments, type of antipsychotic agents, treatment adherence, family history). We collected all the data in the period of one year.

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 Faculty of Medicine in Skopje (no. 03-3951/11, date: 27.09.2022).

Steroid determination

Serum cortisol and DHEA-S levels were measured at the Institute of Clinical Biochemistry at the Faculty of Medicine in Skopje, North Macedonia. Serum samples for cortisol and DHEA-S were collected between 8 a.m. and 9 a.m. after 20 min of rest. All participants were instructed to abstain from unusual physical activity or stress for a period of 24 hours prior to blood sampling. Blood samples were collected at baseline in all participants and after 3 and 6 weeks respectively of the antipsychotic treatment of patients with schizophrenia. Cortisol and DHEA-S levels were measured by IMMULITE 2000, competitive chemiluminescence enzyme immunoassay.

Statistical analysis

For statistical analysis of the data the Statistical Package for Social Sciences (SPSS) for Windows, version 17.0 was used. The statistical methods used for analysis of the data included 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. Values of $p<0.05$ were considered statistically significant.

Results

The results of this study showed that there were no significant differences between patients and controls in terms of sex (Pearson Chi-square=1.32 df=1p=0.25), males were prevailing in both groups (73.3% in patients' group; 62.5% in control group).

The mean age was 35.30 ± 9.2 years for patients with schizophrenia and 36.67 ± 7.1 years for healthy controls (t=0.79; p=0.43).

There were significant differences between patients and controls, in terms of: education, with predominantly higher level of education in the control group (Pearson Chi-square=22.05 df=3 p=0.00006); employment, with predominantly employed examinees in the control group in comparison with the patients' group (Pearson Chi-square=44.74 df=2 p=0.000000), and marital status, with predominantly married examinees in the control group as opposed to the patients' group (Pearson Chi-square=8.25 df=2 p=0.016).

Patients with schizophrenia had significantly higher mean serum cortisol and DHEA-S levels in comparison to the control group. The mean cortisol/DHEA-S ratio was not significantly different between examined and control groups (Table 1).

Table 1. Serum levels of cortisol, DHEA-S and their ratio 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
Cortisol/ DHEA-S	2.1±1.95	2.3±1.49	Z= -1.57	0.11

* t (t-test for independent samples); Z (Mann-Whitney U test)

Among patients, males and females did not significantly differ between themselves in terms of the mean levels of serum cortisol, but female patients had significantly lower mean levels of DHEA-S (t=-3.12; p=0.0028) and significantly higher mean levels of cortisol/ DHEA-S ratio (Z=2.81; p=0.0049).

According to the age of the patients, there was no significant correlation with the mean serum cortisol levels, but there was a significant negative correlation of the age with serum DHEA-S (r= -0.36; p=0.004) and a significant positive correlation with cortisol/DHEA-S ratio (r=0.37; p=0.004).

The age of onset of the disorder did not significantly correlate with serum cortisol levels, DHEA-S and cortisol/DHEA-S ratio, although there was non-significant negative correlation between the age of onset and serum concentration of cortisol and DHEA-S, i.e., younger age of onset of the disorder was associated with higher serum levels of cortisol and DHEA-S (Table 2).

Table 2. Correlation between the age of onset of the disorder and serum levels of cortisol, DHEA-S and cortisol/DHEA-S ratio

	Partial correlation	
Age of onset of the disorder	**Pearson's coefficient of linear correlation**	**p-value**
Cortisol	r=-0.14	0.29
DHEA-S	r=-0.1	0.44
Cortisol/DHEA-S	r=0.14	0.27

Duration of the disorder did not significantly correlate with serum cortisol, but it had a significant correlation with serum DHEA-S levels (r= -0.35; p=0.007) and cortisol/DHEA-S ratio (r=0.31; p=0.014).

Number of hospital treatments did not significantly correlate with serum cortisol levels (r= -0.0015; p=0.99), serum DHEA-S (r = -0.13; p=0.32) and cortisol/DHEA-S ratio (r=-0.011; p=0.93).

Number of relapses of the disorder significantly correlated with serum DHEA-S levels, but not with serum cortisol levels and cortisol/DHEA-S ratio. Correlation between the

number of relapses and the value of hormone DHEA-S was negative (r=-0,26), i.e., with the increase of the relapse number of the psychiatric disorder, the serum level of the hormone DHEA-S decreased (Table 3).

Table 3. Correlation between number of relapses of the disease and serum levels of cortisol, DHEA-S and cortisol/DHEA-S ratio

Number of relapses	Partial correlation Pearson's coefficient of linear correlation	p-value
Cortisol	r=0.21	0.11
DHEA-S	r=-0.26	0.041
Cortisol/DHEA-S	r=0.09	0.48

Number of hospital treatments did not significantly correlate with serum cortisol levels (r= -0.0015; p=0.99), serum DHEA-S (r =-0.13; p=0.32) and cortisol/DHEA-S ratio (r=-0.011; p=0.93).

The difference was statistically nonsignificant between the serum levels of cortisol, DHEA-S and cortisol/DHEA-S ratio depending on the family history for presence of psychiatric disorder in patients with schizophrenia, although patients with positive family history had non-significantly higher mean cortisol serum level and cortisol/DHEA-S ratio in comparison to patients with negative family history (Table 4).

Table 4. Family history and serum cortisol, DHEA-S and their ratio in patients with schizophrenia

Hormone	Positive family history N=25	Negative family history N=35	Test	p-value
Cortisol	563.6±157.56	546.3±165.2	t=0.39	0.7
DHEA-S	313.7±143.8	344.0±114.7	t=0.88	0.38
Cortisol/DHEA-S	2.75±3.07	1.68±0.56	Z=1.24	0.21

*t (t-test for independent samples); Z (Mann-Whitney U test)

Serum levels of the analyzed hormones significantly reduced during the 6-week period of examination in patients with schizophrenia treated with antipsychotics (F=11.251, df=6 53, p=0.000). Figure 1 presents the minimal, maximal and mean levels of cortisol in patients across the three examination points. Serum cortisol values decreased significantly after 6 weeks of antipsychotic treatment in patients with schizophrenia.

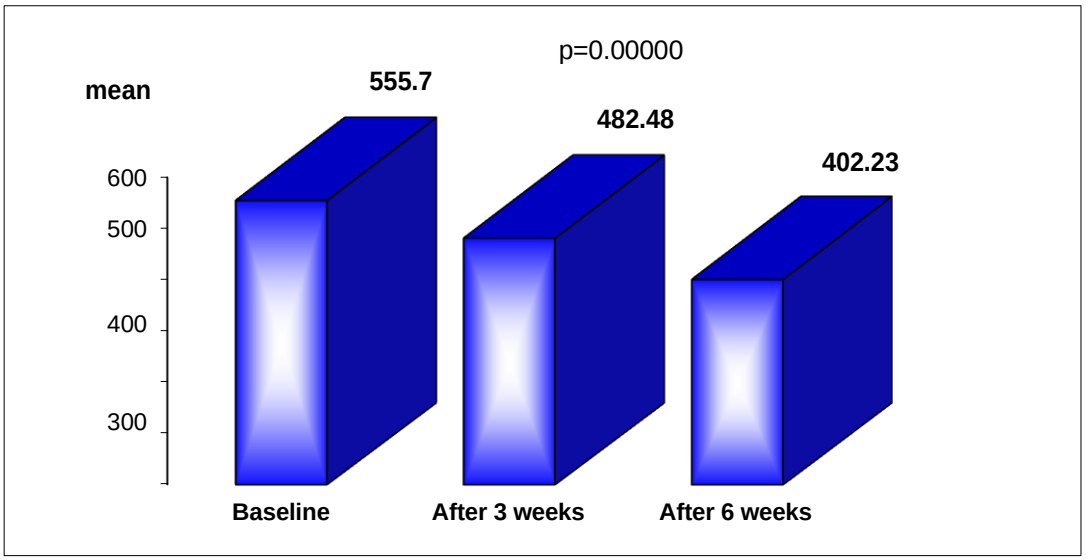

Fig. 1. Serum cortisol levels in patients with schizophrenia before and after 3 and 6 weeks of antipsychotic treatment

The average values of DHEA-S hormone at the beginning of the study were 329.5±125; after 3 weeks from the beginning of therapy it was 308.8±130.8, whereas after 6 weeks of therapy the average registered values of DHEA-S in serum were 273.7±121.6. These discrepancies registered in the DHEA-S hormone values during the analyzed period of the antipsychotic treatment were statistically significant (Friedman ANOVA Chi Sqr. (N=60, df = 2) =30.9; p=0.00000). The mean cortisol/DHEA-S ratio also decreased significantly across the three examination points of 6-week antipsychotic treatment - Friedman ANOVA Chi Sqr. (N = 60, df = 2) = 13.3; p=0.00129.

We can conclude that treatment with antipsychotics in patients with schizophrenia leads to a significant reduction of serum concentration of cortisol, DHEA-S, as well as their ratio.

Discussion

Schizophrenia is a complex psychiatric disorder with multiple clinical symptoms, including emotional disturbance, cognitive dysfunction and degradation of social activities[22].
The diathesis-stress model posits that schizophrenia results from a complex interaction of genetic, biological and environmental factors. In light of this model, it is hypothesized that family history can impact characteristics of schizophrenia through the same mechanisms that influence susceptibility[23].

Using a relatively homogeneous patient population and a parallel control group, we compared serum levels of cortisol, DHEA-S and their ratio not only among patients and controls, but also among patients before and after 3 and 6 weeks of antipsychotic treatment respectively.

Our study showed that plasma cortisol levels were significantly elevated in the group of patients with schizophrenia compared to the controls. This is in agreement with the results of most studies[15,17,24-28]. However, there are studies reporting no significant differences between the schizophrenic patients and healthy controls in terms of serum cortisol levels[29-30] as well as lower serum cortisol levels in patients with schizophrenia[31-32].
Examined serum DHEA-S levels in this study showed statistically significantly higher levels in patients with schizophrenia compared to control subjects, which coincided with the results of most studies[17,19,20,26,29,33,34], although some other studies found decreased serum DHEA-S levels[35] and no difference[24] in schizophrenia patients compared to healthy controls.

According to our results, we can conclude that elevated serum cortisol and DHEA-S levels in patients with schizophrenia may play a role in the pathophysiology of schizophrenia, and they may serve as useful biological markers potentially for diagnosing of the disease. The authors of one recent study concluded that their results further implicated the role of DHEA and HPA axis dysfunction in the pathophysiology of schizophrenia[34]. The authors of one review study also concluded that neurobiological alterations in DHEA(S) were related to the pathophysiology of schizophrenia[36].

We also found that the cortisol/DHEA-S ratio was not significantly different between patients with schizophrenia and control group, but it significantly decreased over the 6-week period of treatment with antipsychotics. Previous research suggested that the ratio of cortisol/ DHEA-S may be increased in patients with schizophrenia[37], however some studies found no difference in ratio compared to healthy controls[24,38] and the authors of a recent study have reported a significant decrease of cortisol/DHEA-S ratio in patients compared to controls[34].

From the aspect of sociodemographic and clinical data, our results showed that serum cortisol levels did not significantly differ according to gender, but there was a significant difference in serum DHEA-S levels and cortisol/DHEA-S ratio between male and female patients. Females had significantly lower mean serum levels of DHEA-S and a significantly higher mean cortisol/DHEA-S ratio. The authors of one study reported that they did not find

any statistical difference in the serum levels of cortisol and DHEA-S between males and females[33].

The age of patients showed a significant negative correlation with serum DHEA-S, which means that serum DHEA-S levels reduce with aging. We also found a significant positive correlation between the age of patients and cortisol/ DHEA-S ratio. Authors of one study did not find any variation in the serum levels of cortisol and DHEA-S in relation to age[33].

The duration of the disorder did not significantly correlate with serum cortisol, but it had a significant correlation with serum DHEA-S levels and cortisol/DHEA-S ratio in patients with schizophrenia. On the other hand, in one study the ratio was not associated with disorder duration[22].

The age of onset of the disorder did not significantly correlate with serum cortisol levels, DHEA-S and cortisol/DHEA-S ratio, although there was non-significant negative correlation between the age of onset and serum concentration of cortisol and DHEA-S, i.e., younger age of onset of the disease was associated with higher serum levels of cortisol and DHEA-S. We can conclude that the age at the beginning of the disorder was insignificantly in correlation with these parameters, i.e. changes of hormone cortisol, DHEA-S and cortisol/ DHEA-S ratio in examinees with schizophrenia do not depend upon the age when they got the first symptoms of this psychiatric disorder, although non-significant negative correlation between the age of onset and serum levels of cortisol and DHEA-S indicate that younger age of onset of the disease is associated with higher serum levels of these hormones.

Our study showed that the number of relapses of the disorder significantly correlated with serum DHEA-S levels, but not with serum cortisol levels and the cortisol/DHEA-S ratio. Correlation between the number of relapses and the value of hormone DHEA-S was negative, i.e., with increase of the relapse number of the psychiatric disorder, the serum level of the hormone DHEA-S decreased.

Family history of schizophrenia is the most important risk factor for this psychiatric disorder[1]. One meta-analysis found that estimates for schizophrenia risk were eight-fold for first-degree relatives of one proband with schizophrenia compared to healthy control probands and increasing to 11-fold for first-degree relatives with two probands with schizophrenia[39].

Family history also could act as an environmental stressor via conflictual interactions between an affected family member and the patient[23]. Authors of one study[40] found that the presence of a family history was associated with elevated emotional distress in patients, hypothesizing that this was due to the impact of family history on the emotional reactivity to stressful life events. On the other hand, one meta-analysis provided evidence of a small influence of family history on several clinical features of schizophrenia[23].

In our study, we had referred to the information of positive family history of both patient and one family member. The existence of a familial history positive for psychiatric disorders was performed by diagnostic interviews conducted with the patient's parents in most cases, or with other family members. We have collected the family history data by interview only, as very few families can provide medical documentation on family members.

Our study showed that the difference in the serum levels of cortisol, DHEA-S and cortisol/DHEA-S ratio depending on the family history for presence of psychiatric disorder in patients with schizophrenia was statistically non-significant, although patients with positive family history had higher mean cortisol serum level and cortisol/DHEA-S ratio in comparison to patients with negative family history.

Authors of one recent study stated that a family history positive for psychiatric conditions proved to be an important risk factor both for an early onset of the disease and for severity of the symptoms in their study group[41]. Authors of another study concluded that family history of psychiatric disorders had a small association with outcome in schizophrenia. They stated that despite family history of psychosis being a strong risk factor for schizophrenia,

after years of illness it does not seem to affect outcome[42]. On the other hand, authors of one recent study concluded that positive family history for psychiatric disorders was associated with worse prognosis in schizophrenia patients. Their study results showed that schizophrenia patients with positive family history were more associated with younger age at onset, male sex, substance abuse, negative symptoms and lower education[1].

Our study also showed that treatment with antipsychotics in patients with schizophrenia during the examination period of 6 weeks led to a significant reduction of serum concentration of cortisol, DHEA-s as well as their ratio.

This study has some limitations. One of the limitations relates to the assessment of diurnal rhythmicity of hormones. Future studies should collect blood samples taken more frequently during the day. Failure to investigate whether the family members suffer from other mental disturbances except psychotic disorders is also limitation of our study. Another limitation is the possible influence of menstrual status, use of oral contraceptives and hormone replacement therapy that might affect cortisol. Smoking also influences serum cortisol levels and is more prevalent in schizophrenic patients. Excluding smokers would have provided better results.

Nonetheless, the complex interaction between neurosteroids, dopamine pathways and neurotransmitters in the brain and their role as biomarkers in schizophrenia demand further investigation. Further assessment of the association between the age of onset, number of relapses and family history in patients with schizophrenia and serum levels of cortisol, DHEA-S and their ratio need to be conducted with larger samples.

Conclusion

Our study provides evidence that serum levels of cortisol and DHEA-S may serve as biomarkers for diagnosing schizophrenia. Elevated serum cortisol and DHEA-S in schizophrenic patients might be associated with the role of cortisol and DHEA-S in the pathophysiology of the disorder.

Serum DHEA-S levels and cortisol/DHEA-S ratio significantly correlate with age, and gender of patients, as well as with schizophrenia duration.

Changes of hormone cortisol, DHEA-S and cortisol/DHEA-S ratio in patients with schizophrenia do not depend on the age when patients got the first symptoms of this psychiatric disorder, although younger age of onset of the disease is non-significantly associated with higher serum levels of cortisol and DHEA-S.

Number of relapses of the disorder significantly correlates with serum DHEA-S levels; with increase of the relapse number of the psychiatric disorder, the serum level of the hormone DHEA-S decreases.

The difference in the serum levels of cortisol, DHEA-S and cortisol/DHEA-S ratio depending on the family history for presence of psychiatric disorder in patients with schizophrenia was statistically non-significant, although patients with positive family history had higher mean cortisol serum level and cortisol/DHEA-S ratio in comparison with patients with negative family history.

The results obtained in this study may add to our existing knowledge about the pathophysiology of schizophrenia. However, the complex interaction between neurosteroids, dopamine pathways and neurotransmitters in the brain warrants further investigation. Further assessment of the association between the age of onset, number of relapses and family history in patients with schizophrenia and serum levels of cortisol, DHEA-S and their ratio need to be conducted with larger samples.

Conflict of interest statement. None declared.

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