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RESEARCH ARTICLE

Increased Cortisol Levels in Depression: A Comparative Study Evaluating the Correlation of Hypercortisolemia with Prosocial Coping Mechanisms

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Objective: The aim of this paper was to evaluate if depressed patients have an increased level of morning serum cortisol compared to healthy persons and to assess the relation between high levels of cortisol and prosocial coping mechanisms, in the context of Recurrent Major Depressive Disorder. **Methods**: Morning serum cortisol level was measured in 15 depressed patients hospitalized in First Clinic of Psychiatry Tirgu Mures and in 15 healthy controls. We have analyzed 3 behavioral coping strategies with The Strategic Approach of Coping Scale (SACS): social joining (SJ), seeking social support (SSS) and cautious action (CA). **Results**: 30 participants were included, the mean value of the cortisol for females was Mcort_female= 16.38 μg/dl and for males Mcort_male= 16.31 μg/dl. Independent sample t test showed that the cortisol level in depressed group was higher than the cortisol level in the control group: $t = 2.394$, $p < 0.05$ (0.024). In the MDD group the Spearman correlation between the level of serum cortisol and prosocial coping strategies was: rcortisol-SJ= -0.519; rcortisol-SSS= -0.107; rcortisol-CA= -0.382. **Conclusions**: Although the studied sample patient was small, we can conclude that the patients with Recurrent Major Depressive Disorder have an increased level of morning serum cortisol compared to healthy persons. In these patients there is an inverse correlation between the increased levels of morning cortisol and the frequency of use of the effective prosocial coping strategies, particularly the social joining type.

Keywords: cortisol, depression, coping

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Introduction

Hypersecretion of cortisol, considered to be the stress hormone, is an important factor in the pathophysiology of depression. Stress itself and stressful life events may cause an increase in cortisol levels, but not necessarily determine the occurrence of a major depressive episode. Individual response is influenced by many factors and the coping mechanisms that intervene in this situation can be adaptive or maladaptive.

Most theories of personality describe prosocial and active coping, as an important marker of mental health, while the avoidant coping is more frequently associated with depression and anxiety [1].

Whether it favorizesthe installation of the disease or act as a trigger, stress is almost always involved in the development of depressive disorders, causing an activation of hypothalamic-pituitary-adrenal axis (HPAA) and an increase of cortisol, which causes important apoptotic phenomena in the brain [2].

In addition to the increased level of glutamate, hypercortisolemia is involved in neuroplasticity processes and apoptosis by decreasing the number of dendritic spines and synapses, reducing the number of glial cells and by causing dendritic atrophy. Certain areas of the brain, like hippocampus and prefrontal cortex, are more prone to neurotoxicity. In the hippocampus there are numerous glucocorticoid and mineralocorticoid receptors and in depression there is an imbalance between these receptors, with an increase of the glucocorticoid receptor density at this level [3,4].

The new generation of antidepressants has the ability to exert a neuroprotective effect and can induce neuroplasticity. In an animal model study, published in 2011, Marinescu et al. have demonstrated the neuroprotective effect of agomelatine in the hippocampus and prefrontal cortex, against the aggression of the increased level of cortisol, which is an important marker of depression [5].

Although the hippocampus exerts a negative feed-back on increased levels of cortisol, it is still unclear how hypercortisolemia as a marker of neuroendocrine stress theory and decreased hippocampal volume as a marker of neuroplacticity theory are linked together. Previous studies found smaller left hippocamapal volume associated with increased cortisol inpatients with first episode of psychosis [6,7,8,9,10] and also in depression [11,12].

Based on the theory of hyperactivation of hypothalamic-pituitary-adrenal axis (HPAA) in depression, Corticotropin Releasing Hormonreceptor ($CRHR_1$) antagonists were recently studied as potential new antidepressive drugs, but the studies have failed probably due to lack of suitable biomarkers that would help to identify depressed patients

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who have an increased signal CRH and who would benefit from these innovative drugs. An increase of the REM phase onsleep EEG of these depressed patients seemed to be an important factor associated with the response to antagonists $CRHR_1$ [13].

Therefore, in the last years it has been emphasized the need for identifying specific genetic or biological markers that provide a better understanding of disease's mechanisms and thus increase the rate of response to antidepressive treatment. Among proposed markers for depression we can mention: hypercholesterolemia and impaired suppression of the dexamethasone suppression test, decreased 5-HT1A receptor expression, increase of soluble interleukin-2 receptor and interleukin-6 in serum, decreased brain-derived neurotrophic factor (BDNF) in serum and low blood folate levels [14].

The purpose of this paper was to assess the relationship between elevated cortisol levels and prosocial coping mechanisms in the context of Recurrent Major Depressive Disorder (MDD).

Methods

We conducted a comparative study, on a number of 15 depressed patients hospitalized in the First Clinic of Psychiatry Tirgu Mures and 15 healthy participants, with no psychiatric history. All 15 patients were diagnosed with Recurrent Major Depressive Disorder. Major Depressive Episode, severe, without psychotic features, according to DSM IV[15]. Informed consent was obtained from all participants and the study was in accordance with the principles set out in the Declaration of Helsinki. Morning serum cortisol level was measured and all participants completed the Strategic Approach to Coping Scale (SACS). Blood samples were collected from all participants in the morning, at 08:00 AM, about 30-60 minutes after awaking and were analyzed in Bioclinica Laboratory TirguMures, the reference value being in the range of 4.3 to 22.4 μg/dl.

SACS is a self-assessment scale with 52 items which distinguishes nine behavioral coping strategies that one can use in a stressful situation: assertive action, social joining, seeking social support, cautious action, instinctive action, avoidance, indirect action, antisocial action and aggressive action. Each item can be rated on a 5-pointLikert scale, where 1 means - Not at all what I would do, and 5 means - Very much what I would do. The scale assesses the triaxial model of coping: active - passive (efforts to resolve or avoid a problem); prosocial-antisocial (personal goal achievement, taking or not taking into account the welfare and interests of the others); direct-indirect (direct, transparent approach of the issue or indirect, manipulative, "behind the scenes")[16].

The current paper analyzes 3 of the 9 coping strategies – the prosocial coping strategies: social joining (SJ), seeking social support (SSS) and cautious action (CA), the scores obtained on each subscale beeing converted later into T quotes, as per the attached tables at the end of the scale. All the collected data were analyzed using SPSS 20.

Results

30 participants were included, 17 females, with M_{age} = 42.65 and 13 males with M_{age}= 41.00. The mean value of the cortisol for females was M_{cort_female}= 16.38 μg/dl with a SD = 4.34 (Fig. 1) and for males M_{cort_male}= 16.31 μg/dl with SD = 5.54 (Fig. 2). The reference value for the morning cortisol was between 4.3 and 22.4 μg/dl.

15 healthy persons were included in the control group, where the mean age was $M_{age\_control}$= 39.6 with a SD = 7.5 and the mean of morning cortisol level was $M_{cort\_control}$= 14.4 μg/dl and SD = 4.15. In the MDD group, 15 patients suffering from MDD were included, where the mean age was M_{age_MDD}= 44.27 with SD = 12.14 and the mean level of morning cortisol was M_{cort_MDD}= 18.3 μg/dl and SD = 4.75.

Analyzing the frequency distribution of our data for the age of the participants and the cortisol level, we have seen that there was a symmetrical (bell-shaped) and normal distribution of the data.

To test the distribution of our data, we applied two normality tests (Kolmogorov-Shapiro-Wilk and Smirnov-

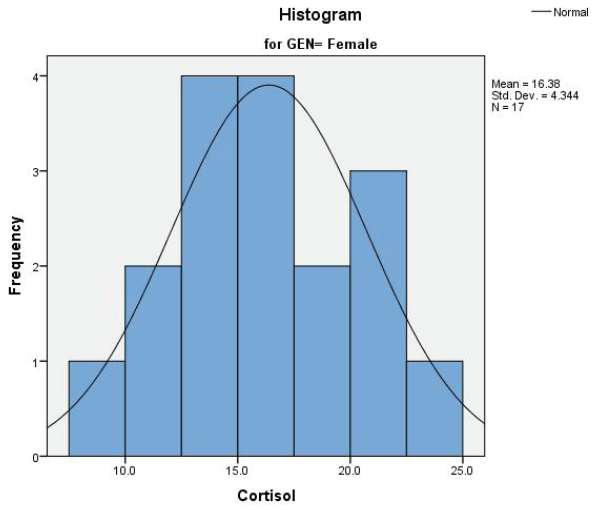

Fig. 1. Histogram of cortisol level distribution for females

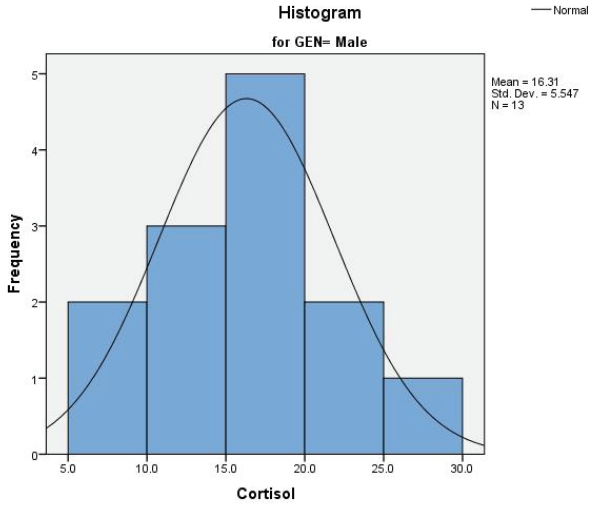

Fig. 2. Histogram of cortisol level distribution for males

Lilliefors)where the null hypothesis $H_{0\ normality}$ presumes that there is no difference between our data and the general population, while the alternative hypothesis $H_{1\ normality}$ means that there is a difference. In both MDD and control group, all of our data passed the normality tests (see Table I), so we can say that there is a normal, parametric distribution distribution of the data ($p>0.05$, H_0 is accepted).

We applied independent sample t test to evaluate if there is a difference between the mean of cortisol levels in MDD group compared to control group (Fig. 3). Because Sig was >0.05 (0.77), we used the first line to interpret our data (see Table II). In this case, the null hypothesis H_0 presumes that there is no difference between groups, while the alternative hypothesis H_1means that there is a difference. Whether the assumption of equal variances holds was evaluated using Levene's test for the equality of variances. The difference between the cortisol level in the depressed group and the control group was around 3.9. The chance of finding this or a larger absolute difference between the two means is about 2.4%. Since $p<0.05$, we rejected the null hypothesis that the mean of cortisol level in depressed group is equal to the mean of cortisol level in the control group.

The Spearman correlation between the level of serum cortisol and prosocial coping strategies was: $r_{cortisol-SJ} = -0.519$; $r_{cortisol-SSS} = -0.107$; $r_{cortisol-CA} = -0.382$ (see Table III).

Discussion

When a stress factor acts on the body, the hypothalamus secretes Corticotrophin Releasing Factors (CRF) into the portal hypothalamic-pituitary system, which determines the release of adrenocorticotropic hormone (ACTH). ACTH once released, stimulates the synthesis and release of glucocorticoids. Glucocorticoids have many effects in the body like promoting the use of energy, increase cardiovascular activity for the "flight or fight" response, and inhibitionof some functions such as growth, reproduction and immunity [17].

Although we cannot state with certainty whether it is a trigger or a secondary factor for depression, about 50% of patients with MDD have a hypersecretion of cortisol, but this percentage depends a lot on the analyzed population [18,19].

A study conducted by Bhagwagar et al shows a 25% higher secretion of cortisol in depressed patients compared to healthy controls [20]. In another study, plasma cortisol levels at baseline were significantly higher in the MDD

Table III. Correlations between cortisol level and the prosocial coping strategies: social joining (SJ), seeking social support (SSS) and cautious action (CA)

		Cortisol	T Quote_ SJ	T Quote_ SSS	T Quote_ CA
Cortisol	Correlation Coefficient	1.000	-.519	-.107	-.382
	Sig. (2-tailed)	.	.233	.819	.398
T Quote_ SJ	Correlation Coefficient		1.000	-.074	.736
	Sig. (2-tailed)		.	.875	.059
T Quote_ SSS	Correlation Coefficient			1.000	-.055
	Sig. (2-tailed)			.	.908
T Quote_ CA	Correlation Coefficient				1.000
	Sig. (2-tailed)				.

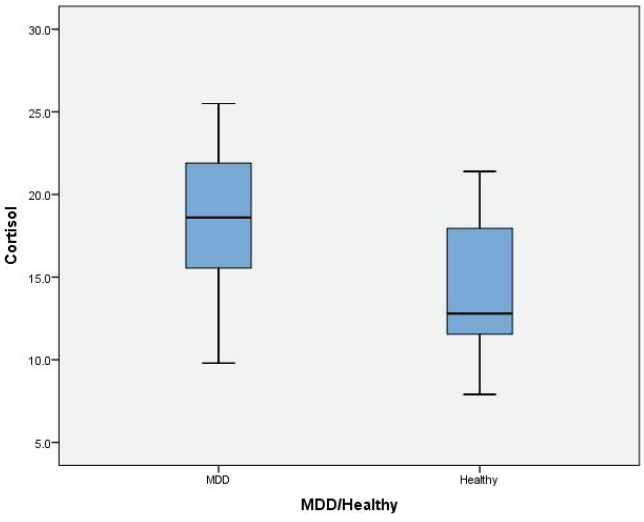

Fig. 3. Box-plot for cortisol level in MDD and control group

Table I. Tests of Normality for age and cortisol level

	MDD/ Healthy	Kolmogorov-Smirnova			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Cortisol	MDD	.122	15	.200*	.962	15	.720
	Healthy	.183	15	.187	.943	15	.423
Age	MDD	.154	15	.200*	.921	15	.203
	Healthy	.140	15	.200*	.941	15	.393

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Table II. Independent sample t test for the cortisol level of MDD group compared to Control group

		Independent Samples Test							
		Levene's Test for Equality of Variances	t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Cortisol	Equal variances assumed	.082	.777	2.39	28	.024	3.9000	1.6288	.5635	7.2365
	Equal variances not assumed			2.39	27.503	.024	3.9000	1.6288	.5607	7.2393

compared to a control group, but depressed patients did not showed significantly higher levels of 24-hour urinary free cortisol compared to healthy participants [21].

Measuring cortisol level was proposed as a marker of depression and studies have proved that there is an important association between increased cortisol levels and vulnerability to depression [22]. There are many ways to measure cortisol: from blood, saliva, urine and recently, from hair. In the current research the morning serum cortisol was measured, due to lack of availability of alternative methods. In the last years cortisol level from saliva was used to determine the cortisol awaking response (CAR), but the use of morning basal serum cortisol levels as an alternative to dynamic testing for assessment of hypothalamic-pituitary-adrenal axis has previously been reported[23].Serum basal cortisol levels may be used as the first-line test in the assessment of thehypothalamic-pituitary-adrenal axis both preoperatively and postoperatively [24].

It is known that the lowest level of cortisol is between 10 PM and 04 AM and the highest is at 30 to 60 minutes after awakening. In our study all blood samples were collected in a fasting state in the morning, at 08 AM, about 30-60 minutes after awaking. Samples were collected 2-3 days after hospitalization to minimize the stress of being an inpatient.

Certain features of one's personality, like high neuroticism and hopelessness reactivity were proved to be associated with increased cortisol levels from +30 to +60 minutes post awakening [25,26].History of depression in the family was associated with higher cortisol awaking response even if the participants were asymptomatic at the evaluation moment [27]. Follow up studies on a longer period in patients who experienced at least one depressive episode have shown that the risk of recurrence was higher in those with higher levels of cortisol [28,29].

It is well known that major stressful life events act as a trigger especially in the first depressive episode, while in the case of recurrent episodes the stress factor can be a minor or even missing [30,31].

The aim of our study was to evaluate if there is a higher secretion of cortisol in depressed patients compared to healthy controls. Our results showed no gender differences between the mean value of the cortisol of the male and the female participants. Our results were consistent with those found by previous studies and the cortisol level in depressed group was significantly different to the cortisol level in the control group. Regarding the onset of depression it is not the severity and number of stressors that correlate with the increased cortisol level, but it is more important the degree of the perceived stress and the degree that one can cope with a stressor [32,33].

The social support is an important factor for the evolution of chronic diseases. In a 12 months study, conducted on a number of 65 patients suffering from HIV/AIDS, the social support proved to be an important predictor of disease progression and the patients with a more satisfactory social support reported a smaller increase in physical symptoms related to HIV [34].

A poor social support network both qualitatively and quantitatively is associated with increased severity of depressive episodes and an unfavorable long term evolution of depression.

Previous studies have shown that more frequent use of the 3 prosocial strategies analyzed in this paper - social joining (SJ), seeking social support (SSS) and cautious action (CA) may be associated with an increased level of good mood [35].

Our results indicated the existence of a negative correlation with moderate association between the level of cortisol and social joining and weak association with the other two strategies: seeking social support and cautious action. The negative correlations that we obtained showed an inverse relationship between the parameters analyzed, the morning serum cortisol level and the frequency of use of the prosocialcoping strategies. Because the correlations obtained was mild to moderate type, we can say that in the case of depressed patients, there are other factors involved in the relationship between the body's endocrine response to stress and the behavioral response linked to the choice of the appropriate coping mechanism.

Conclusions

Although the studied sample patient was small, we can conclude that the patients with Recurrent Major Depressive Disorder have an increased level of morning serum cortisol compared to healthy persons. In these patients there is an inverse correlation between the increased levels of morning cortisol and the frequency of use of the effective prosocial coping strategies, particularly the social joining type. We can presume that a more frequent use of this strategy by the depressed patients may result in decreasing the serum cortisol levels and might be a protective factor for the occurrence of new major depressive episodes.

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