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Research Article

Exploring The Diagnostic Association Between Cortisol And DHEA-S Concentrations In Patients Experiencing Chronic Depressive Disorders.

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Abstract

Background: Chronic depression is characterized by the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and has several effects on cortisol and DHEAS production. These hormonal changes have been seen in depressive disorders, but their diagnostic value is still a matter of question.

Objective: This study evaluates the correlation between cortisol and DHEA-S levels in individuals with chronic illness and their potential as biomarkers for disease severity.

Methodology: A quantitative case-control study was done on 40 patients with chronic stress-related endocrine dysfunction and in 20 healthy controls. Electrochemiluminescence immunoassay (ECLIA) was applied for hormonal assays of cortisol and dehydroepiandrosterone sulfate (DHEA-S). A statistical analysis was performed to compare the groups.

Results: The results of the study showed that patients had reduced cortisol and DHEA-S levels. Therefore, these findings indicated the existence of a strong, significant relationship between chronic stress and endocrine disturbances.

Conclusion: These findings provide evidence for the hypothesis that HPA-DX, reduced cortisol and DHEA-S levels, is the phenotypic endophenotype of chronic depression. These changes may have effects on the diagnosis of the severity of the condition or the effectiveness of the treatment for depression. Future studies should, therefore, consider establishing their effectiveness in estimating the effectiveness of antidepressants as far as the prospect of mental health status is concerned.

Keywords : Hormonal Dysregulation, DHEA-S, Stress-Related Endocrinopathy, ECLIA, HPA Axis, Fatigue Syndrome.

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INTRODUCTION

Depression is a persistent mood disorder with several biological processes in its component, that is, the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis plays a role in stress responses and regulates cortisol, a hormone used in moods, thinking capacity and metabolism. In addition, DHEA-S, which is an adrenal androgen, counterbalances cortisol's effects on protein and mineral metabolism, while its deficiency is linked with depression. These changes can represent a sign of chronic depression; nevertheless, more research on their clinical significance is limited [1]. Short-term activation of the HPA axis allows the body to accommodate stress. Still, prolonged psychological, physical, or environmental stressors can cause a long-term imbalance of the endocrine system and, therefore, long-term health consequences [2]. One of the consequences of this is HPA axis dysregulation, or the impaired ability of the adrenal system to function appropriately, thus interfering with overall physiological well-being [3].

When the adrenal glands are strained by continuous stress, they first overproduce cortisol, and then the hormones become dysregulated. This is a condition of persistent fatigue, brain fog, disturbed sleep, compromised immunity, and metabolic dysfunction [4]. In contrast to an established endocrine disorder, Addison's disease, whose main symptom is severe adrenal insufficiency, mild to moderate adrenal insufficiency is present sub-clinically and cannot easily be identified during conventional diagnostic tests [5]. Lack of definite diagnostic criteria means that people experience symptoms whose cause cannot be explained by medicine, have delayed interventions, and are therefore subjected to ineffective treatment approaches [6].

Research Problem and Gap

The current study focuses on the endocrine changes in chronic depression states with special attention to cortisol and DHEA-S levels in clinical conditions. Although there is evidence suggesting that these hormones may be related to depressive symptoms, there is no clear definition of the HPA axis dysfunction in depression. This paper aims to fill the gap by comparing cortisol and DHEA-S levels with the severity of depressive symptoms and their effectiveness as diagnostic indices [7]. It is widely understood that many people suffer from hormonal irregularities linked to constant stress. Still, current mainstream medicine often ignores these patterns because there are no widely adopted clinical biomarkers for them [8]. Due to this uncertainty in diagnosis, Patients with persistent symptoms reduced quality of life, and increased risk of chronic diseases face diagnostic uncertainty in the diagnosis uncertainty [5].

However, the research gap is in the lack of reliable diagnostic tools and a standardized clinical framework for identifying HPA axis malfunction. However, most studies usually do not consider how prolonged stress can lead to mild to moderate hormonal imbalances [9]. Furthermore, there is very little concern regarding stress-induced adrenal dysfunction in relationship to other endocrinopathies. However, as adrenal function, it is important to establish the effects of chronic stress on overall metabolic health [10]. Without a deeper insight into these interconnections, patients may continue to get the wrong or incomplete treatment that further worsens their condition.

Stress-induced adrenal dysfunction is recognized as a critical factor for endocrine health and is needed for further medical research and improved patient outcomes. This will help bridge the gap between conventional and functional medicine opinions regarding its pathophysiology, clinical presentation, and diagnostic limitations. Therefore, this study evaluates both conventional and emerging diagnostic approaches to develop more effective treatment strategies focused on individuals with long-term stress-related endocrine alterations [11].

The objective of this study was to examine the pathophysiology of the disrupted HPA axis, assess its impact on endocrine function, and review the effectiveness of the diagnostics and treatments that are currently used. This study provides empirical and clinical evidence on the hormonal dysregulation that is directly attributed to chronic stress to enhance knowledge on the effects of stress on health.

METHODOLOGY

Research Design

The comparative cross-sectional study design was then used to compare cortisol and DHEA-S in patients with chronic depression and healthy adults. The sample comprised 40 depressed outpatients who meet the criteria of MDD based on clinical interviews and DSM-IV and 20 controls. The Hamilton Depression Rating Scale (HDRS) was used as a reference to determine whether the subjects had CHD or not; all of them met the criterion for chronicity. [12].

Study Population

The participants of the study included 40 patients with chronic depression and 20 healthy individuals, matched by age. Study was done as a collaboration between teams in different private and governmental hospitals according to participant's affiliations between June 2024 and December 2024. There were 23 females and 17 males in the patient group (mean age 45.5±7.02 years) and 11 females and 9 males in the control group (mean age 45.4±7.51 years). Participants were recruited based on the inclusion criteria that the participants must have had a depression history of more than ten years. Depression was defined as the primary diagnosis, and exclusion criteria were any comorbid endocrine disorders like Addison's disease, Cushing's syndrome, and recent use of hormonal therapy to confirm hormonal fluctuations were solely influencing depression.

Prior research has shown that at least 30 participants per group are needed to detect meaningful endocrine variations [14] adequately, such that sampling 8 participants per group likely yields sufficient power to achieve demographic, biological, and endocrine variation in human semen. To ensure a reliable comparison group, a 2:1 case-to-control ratio has been used to increase statistical power. This distribution results in better detection of hormonal imbalances that reduce random variations. This inclusion of both genders within a similar age range will help to ensure the generalizability of findings while reducing confounding hormonal influences.

Data collection

Data collection was performed from a single center, including a detailed medical history assessment and a clinical examination of patients. The medical history included personal health information, exposure to stress for duration and severity, and underlying causes. Blood samples were taken at three points of time during the day, including in the morning (8:00 AM), after a meal (postprandial), and in the evening (before sleep) to assess daily variations of cortisol, DHEA-S.

Hormonal assay and measurement techniques

Hormonal assay and measurement techniques were performed using electrochemiluminescence immunoassay (ECLIA) for Cobas e 411 immunoassay analysers (Roche Diagnostics, USA). Since this method is particular and sensitive, it has been selected for accurate quantification of cortisol, DHEA-S. A competitive immunoassay principle was used for cortisol and DHEA-S. The process of detection included biotinylated antibodies, ruthenium-labeled hormone derivatives, and streptavidin-coated microparticles to ensure that the readings of the endocrine markers were precise with minimal interference.

Statistical analysis

Data was first normalized and assessed for distribution for statistical analysis and independent t-tests and ANOVA compared hormonal variations between the patient and control groups. Statistically significant was taken as having a p-value of <0.05. The relationships between cortisol levels, and psychological stress markers were calculated for Pearson correlation coefficients. The study aimed to enhance the accuracy of its findings by applying robust statistical methods and to avoid any spurious difference between observed differences that were clinically relevant and not due inked by random variation.

RESULTS

Demographic Data Analysis

Participants were divided into a control group (n = 20, 11 females, 9 males; M = 45.4, SD = ±7.51 years) and patient group (n = 40, 23 females; 17 males; M = 45.5, SD = ±7.02 years) with HPA Axis dysfunction. There was no significant difference between the groups in sex distribution (P = 0.821) or age (P = 0.953); both groups were well-matched. Participants in the patient group reported experiencing fatigue and a decline in energy levels throughout the day; however, they otherwise described themselves as healthy and energetic.

There was no statistical difference in the sex distribution of the two groups (**Table 1**, P-value = 0.821). There was no difference between the proportion of males and females in both groups, indicating that the presence of HPA Axis Dysfunction does not differ by sex. Many respondents were either indifferent to sex or reported no noticeable differences in energy levels or fatigue. Similarly, there was no significant difference in the reported levels of fatigue between the two groups.

Table 1. Comparison of sex of patients and control groups.

SEX	Groups						Chi-Square	
	Patients		Controls		Total			
	N	%	N	%	N	%	X2	P-value
Female	23	57.50	11	55.00	34	56.67	0.047	0.821
Male	17	42.50	9	45.00	26	43.33		
Total	40	100.00	20	100.00	60	100.00		

Regarding the age distribution, the patient's age was 35 to 58 years, and the control group was between 34 and 59 years. The mean age was approximately 45.4 years for both groups, and they had not differenced statistically significantly for age distribution (P value = 0.953) (**Table 2**). This suggests that the age factor in the two groups was well matched, which would preclude its serving as a confound in the results. Respondents from both groups reported feeling age-appropriate and did not express significant concerns regarding age-related perceived fatigue.

Table 2. Comparison of age in patients and control groups.

Groups	AGE						T-Test	
	Range		years	Mean	±	SD years	t	P-value
Patients	35.00	-	58.00	45.533	±	7.026	0.059	0.953
Controls	34.00	-	59.00	45.400	±	7.510		

Endocrinological Parameters

Serum cortisol and DHEA-S levels from several key endocrine markers were looked for any differences between the controls and the patient group. Among the examined hormonal markers is cortisol at various times of the day, alongside DHEA-S, a hormone linked to a stress response.

In this study, the depressed group presents a profoundly lower mean morning cortisol level; 5.84 ± 2.80 µg/dL, compared to the normal group mean of 15.02 ± 2.63µg/dL, P < 0.001). Low morning cortisol dynamics can reflect decreased HPA axis activity, which is considered a remarkable feature in patients with chronic depression. Furthermore, it was found that even at night, cortisol levels were also significantly reduced in the patient group, thus supporting the notion of HPA dysfunction in major depression.

The difference in postprandial cortisol levels between the patient and control groups was also significant (mean 6.61 µg/dL, SD ±1.48 compared to mean 8.10 µg/dL, SD ±1.37, P < 0.002). Similarly, even the evening cortisol levels for the patient showed significantly lower values (mean = 2.04 µg/dL, SD ±1.00) compared to the control (mean = 4.31 µg/dL, SD ±1.32), with a P value less than 0.001. **Table 3** highlights a significant cortisol dysregulation in the HPA Axis Dysfunction group. The respondents from the patient group reported feeling a lot drained in the evening and falling asleep.

Table 3. Serum Cortisol Levels in the AM, PP, and PM

	Group	Range (µg/dL)	Mean (µg/dL)	SD (µg/dL)	P-value
AM	Patients	2.22 - 14.01	5.84	2.8	<0.001
	Controls	10.4 -19.09	15.02	2.63	
PM	Patients	0.63 – 4.65	2.04	1	<0.001
	Controls	2.05 – 6.28	4.31	1.32	
PP	Pateints	4.51 – 10.14	6.61	1.48	0.002
	Controls	5.21 – 10.13	8.1	1.37	

Depressed patients also had reduced DHEA-S levels with an average of 66.4 µg/dL (StD±39.51) compared to the controls with 218.4µg/dL (StD± 67.85) (P<0.001). Since the DHEA-S has been previously reported as having neuroprotective and mood-regulating effects, a decrease in its level in the blood of individuals with depression may explain why mood and cognitive issues may persist for a long time. However, **Table 4** shows that other respondents who said that they were diagnosed with HPA Axis Dysfunction stated that they were stressed all the time, but they did not see themselves as an immediate stressor.

Table 4. Illustrating comparative results of DHEA-S for patients and control groups.

Groups	DHEA- S						T-Test	
	Range µg/dL			Mean	±	SD µg/dL	t	P-value
Patients	29.000	-	196.000	66.400	±	39.512	-9.515	<0.001*
Controls	97.000	-	388.000	218.400	±	67.859		

DISCUSSION

The study examines the physiological and biochemical changes associated with adrenal dysfunction, hormonal imbalances, and the symptoms that arise from chronic stress. The term adrenal dysfunction refers to a group of symptoms caused by prolonged and unremitting stress. This condition has garnered significant attention within the medical community; however, it remains a subject of debate, with widespread discussion but no consensus. This study aims to evaluate the adrenal, and other functions of patients with chronic stress in the context of chronic stress by the use of biomarkers of cortisol, DHEA-S, and other related measures. The study compares patients who have chronic stress and depression to a healthy control group to see if hormonal imbalances, specifically in cortisol, play a part in what are the symptoms of adrenal dysfunction.

The main finding of this study is the differences in cortisol levels between the patient and control groups. The control group showed higher morning and evening cortisol levels compared to the patients with chronic stress. This agrees with Henry et al., who also observed disrupted cortisol rhythms in people with adrenal dysfunction [13]. However, cortisol produced by the adrenal glands as a response to stress has a diurnal rhythm in which it tends to peak in the morning and decrease at night. This rhythm is usually disrupted in adrenal dysfunction, resulting in lower morning and different evening cortisol levels. The findings of Walker et al. indicate that disrupted cortisol circadian rhythm may be a feature of the overall dysfunction [14]

The study showed that both cortisol and DHEA-S levels are involved in the pathogenesis of chronic depression. These results are in accordance with previous works that revealed that baseline cortisol levels are lower in MDD than in healthy controls. Also, the significantly lower level of DHEA-S in the depressives suggests that adrenal dysregulation could be involved in mood disorder. These changes indicate that cortisol and DHEA-S may be useful markers that facilitate the identification of depressive disorder as well as the evaluation of its severity [15]. However, some medical professionals argue there is no sufficient evidence that one commonly describes as adrenal dysfunction does exist. Medical professionals said most of the symptoms often attributed to adrenal insufficiency might be due to another disease, such as chronic fatigue syndrome (CFS), major depressive disorder [16]. Interpretation of the study's results needs to take into account these critiques since a portion of cortisol disruption may be caused by these alternate diagnoses that share the same symptoms rather than specific to adrenal dysfunction. It is critical to have these competing perspectives scrutinized to understand if adrenal dysfunction is an independent entity or a subset of stress-related disorders.

Additionally, the study examined the levels of DHEA-S, a hormone of the adrenal gland that has a counter-regulatory function to cortisol. The findings from Geiger et al. reveal that in the patient group, DHEA-S levels were significantly lower than in the control group, which is in agreement with the results [17]. DHEA-S, together with cortisol, plays an integral role in the body's ability to respond to stress, and the decline in its levels amplifies symptoms of adrenal dysfunction. Lee et al. describe that when increased cortisol from chronic stress causes an elevation of cortisol levels, DHEA-S helps balance cortisol's catabolic effects [18]. However, in adrenal dysfunctions, the adrenal glands do not secrete enough of DHEA-S, causing prolonged catabolism that leads to chronic fatigue, weight gain, and impaired immune function.

The results of this study suggest how adrenal dysfunction may occur. The study does confirm that cortisol and DHEA-S do not operate as they should in persons with chronic stress and adrenal dysfunction. Coluzzi et al. agree that hormonal imbalances play a role in the pathophysiology of adrenal dysfunction. Still, a critical evaluation of the existing evidence appears to hold that adrenal dysfunction continues to be a controversial diagnosis [19]. These symptoms also overlap with those of such alternative conditions as chronic fatigue syndrome and depression. The study also emphasizes the critical point that a comprehensive treatment approach will have to include adrenal dysfunction as well as no adrenal, including factors such as infection and nutritional deficiency.

The findings of this study point to the fact that adrenal dysfunction is a physiological syndrome rather than a psychological phenomenon, making diagnosis and treatment multifactorial [20]. Further research should be conducted to clarify the link between stress, hormonal imbalances, and adrenal dysfunction, as well as to find possible therapeutic measures to reverse adrenal dysfunction. Considering the profound effect of adrenal dysfunction on one's quality of life, healthcare providers must give proper attention to both the physical and emotional dimensions of adrenal dysfunction. Understanding adrenal dysfunction and its underlying causes will further aid us in developing better treatments for people to acquire their health and well-being.

Future Recommendations and Limitations

Future research should include ones with larger sample sizes and longitudinal studies to improve generalizability and allow long-term studies of adrenal dysfunction. Moreover, when there is a broader consideration of biomarkers, i.e., neuropeptides or genetic factors, it would give a more complete understanding of the condition. Also, other personalized treatment strategies, such as the combination of endocrinology, psychology, and lifestyle interventions, should be investigated to enhance patient outcomes. In addition, it would be helpful to establish standardized diagnostic criteria for adrenal dysfunction in future studies.

A few limitations are involved with this study, including a relatively small sample and dependence on cross-sectional data, thus limiting generalizability and causality. Also, there is no psychological assessment in this research, which hinders an in-depth understanding of the link between mental health and adrenal dysfunction. Moreover, diagnostic criteria for adrenal dysfunction lack uniformity, which makes the reliability and comparability of findings unreliable across the studies.

CONCLUSION

This study emphasizes the profound physiological and biochemical alterations with adrenal dysfunction, especially cortisol rhythm and DHEA S reduction in chronic stress. The findings are consistent with existing research and provide support for adrenal dysfunction being a multifactorial condition affecting the adrenal systems but also indicate the importance of critical assessment with overlap of symptoms with chronic fatigue syndrome and depression. This indicates that adrenal dysfunction is a real physiological syndrome, not something merely psychological, and hence should be treated comprehensively. Future work should explore the mechanisms of adrenal dysfunction, refine diagnostic criteria, and pursue ways to treat adrenals to rebalance the hormones, to improve clinical outcomes for this affected population.

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