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STRESS, CORTISOL, AND HYPERTENSION: UNVEILING THE LINK AND IMPLICATIONS FORCARDIOVASCULAR HEALTH

Shiza Unab[1*], Maleeha Akram[2], Shanza Ahmed [3], Bushra Moon [4], Raniya Saleem [5], Mazhar Qayyum[6], Syed Shakeel Raza Rizvi [7]

[1] Department of Zoology, University of Mianwali, Mianwali 42200, Pakistan
[1,2,6,7]Department of Zoology, Wildlife and Fisheries, Pir Meher Ali Shah Arid Agriculture University, Rwalpindi, 46300, Pakistan.
[3] Department of Zoology, Wildlife and Fisheries, University of Agriculture Faisalabad, Pakistan
[4] School of Life Sciences, Hainan Normal University, China
[5] Department of Microbiology, University of Swabi, KPK, Pakistan

***Corresponding Author:** Shiza Unab
*Department of Zoology, University of Mianwali, Mianwali 42200, Pakistan
Email: shizaunab@umw.edu.pk

Abstract
Background: Cortisol, a stress hormone originating from the adrenal cortex's zona fasciculata, is known to exert its effects on the central nervous system, particularly in regions that regulate blood pressure. Cortisol reactivity, an indicator of hypothalamic-pituitary-adrenal function, is a potential mechanism through which psychosocial stress may impact the risk of developing hypertension.
Objectives and Methods: This study explored the association between stress and hypertension by assessing psychological stress levels using the Depression, Anxiety, and Stress Scale (DASS) and measuring physiological stress through cortisol release using Radioimmunoassay (RIA)systems.
Results: Our findings revealed that hypertensive patients exhibited significantly higher levels of psychological stress as measured by the DASS and elevated cortisol levels compared to control subjects. Additionally, we observed a significant correlation between depression, anxiety, stress, and cortisol levels within the patient group. Notably, a noteworthy association existed between depression, stress, and increased cortisol release.
Conclusion: The current study's findings elucidated a significant association between heightened depressive symptoms and psychological stress and an upregulated cortisol secretion. This intricate relationship underscores the potential contribution of cortisol dysregulation to the etiology of hypertension and associated cardiovascular disorders.

Key words: Stress, depression, anxiety, cortisol, hypertension, CVDs

Introduction

Hypertension, a public health concern, is the leading cause of disease and mortality worldwide. Estimates indicate that 1.56 billion people will have been diagnosed with hypertension by 2025 [1]. A previous study demonstrated that hypertension has significant positive relationship with depression, anxiety and stress [2]. Stress is the physiological need placed on the body when one must change a little and get better, cope, or change to fit new conditions. Acute stress, the most common form of stress, is for only a short time and comes from the demands and pressures of

the recent past and expected demands and pressures of the near future. Chronic stress, a long lasting form of stress, comes from unending feelings that there is no hope, as a result of factors such as poorness, harmful angry behaviors of family, feelings of helplessness, and/or terrible and upsetting premier childhood experience [3]. Acute stress is short-term and comes from past demands and expectations, while chronic stress is long-lasting and stems from unending feelings of hope. Factors like poverty, family behavior, helplessness, and childhood experiences can contribute to acute stress [3]. Acute stress can cause heart attacks in pre-subsisting coronary artery disease patients, with sudden emotional upsets increasing the risk [4]. Stress releases hormones like catecholamines and cortisol, the body's primary stress chemical. Long-term stress can disrupt processes and cause health issues like heart disease, obesity, diabetes, depression, learning difficulties, and inflammatory and autoimmune disorders. Cortisol directly impacts the central nervous system, controlling blood pressure [5-7]. Cortisol, a stress biological marker, is linked to various diseases like cardiovascular disease, obesity, diabetes, depression, learning difficulties, and inflammatory and autoimmune disorders. [8,9]. The etiology of hypertension hasbeen linked in a significant way to stress. It is well known that stress has a strong relationship with hypertension and contributes to many cardiac issues. An increase in heart rate is a typical cardiovascular response to stress. Stress-related blood pressure responses in young adults may indicate a future risk of developing hypertension [10,11].

Numerous studies examined the relationship between stress, cortisol, anxiety, and depression levels [12-15], but the current research is unique because it simultaneously looks at all of those variables in hypertensive patients. A growing body of research on hypertension indicates that Pakistan has made some progress in controlling the condition. Determining how hypertension affects depression, anxiety, stress [2,16]. However, research into how these factors will affect hypertension in our local population is still in its infancy. Consequently, this study examined how depression, anxiety, stress, and cortisol were related to patients with hypertension in our community.

Materials and Methods

Study design

The present study was conducted at Rawalpindi Institute of Cardiology (RIC) Hospital (Rawalpindi, Pakistan) and Pakistan Institute of Engineering and Applied Sciences (PIEAS), Islamabad. The target population was all hypertensive patients who had been diagnosed with hypertension. A convenient sample of hundred hypertensive, non-diabetic cardiovascular patients were collected from RIC Rawalpindi. The study was approved by Research Ethical Committees of PMAS Arid Agriculture University Rawalpindi and Rawalpindi Institute of Cardiology (RIC) for collection of blood samples and relative information from patients. Patients aged 21-60 (years), irrespective of their genders, with a confirmed diagnosis of hypertension and current blood pressure ≥ 140/90 mmHg were included in the study. The majority of them were newly diagnosed cases of hypertension. The history of the subjects with their body weight and height was recorded in the performa especially developed for the purpose. The normal individuals constituted the control group. Hypertensive patients with cerebrovascular and neurological diseases, asthma, diabetes, chronic renal impairment, pregnant and alcoholics, advanced hepatic and renal insufficiency and those suffering from any other endocrinological disorder were excluded from the study. Hypertension symptoms along with depression, anxiety and stress cognate questions were noted. Then, the samples were analyzed for probable sodality between hypertension and psychological stress in terms of depression, anxiety and stress.

Laboratory analysis

Plasma cortisol concentrations were determined by using Beckman Coulter Cortisol RIA Czech Republic kit made in Germany (IMMUNOTECH s. r. o. - Radiova 1 102 27 Prague 10 - Czech Republic). The minimum detectable concentration of cortisol was 5 nmol/L and maximum detectable concentration of cortisol was 2000 nmol/L. Reference range for plasma cortisol was 49-724 nmol/L. The intra-assay coefficients of variation were found below or equal to 5.8 percent for

serum and inter-assay coefficients of variation were found below or equal to 9.2 percent for serum.

Statistical analysis

Unpaired 't-tests, Pearson's Correlation Coefficient' r', and analysis of variance (ANOVA) were used to examine the data, expressed as mean SD. The p value≤ 0.05 was adjusted as the level of significance.

Results

Baseline characteristics of patient's vs control group

We examined clinical parameters in 100 patients and 77 healthy people who had not been diagnosed with hypertension. Patients' and controls' demographic and baseline characteristics are depicted in (Figure 1). There was statistical significance between the age groups of 31-40, 41-50, and 51-60. When we compared the BMI of the control subjects and the patients (Figure 1B, p0.05), we observed a significant difference, with hypertension patients having a higher average BMI than healthy people. Only in the age groups 41-50 was there a non-significant difference in terms of age (Fig 1C).Similarly, the blood pressure of the patients was significantly higher than that of the control group in general and by gender (Fig 1D, E).

Hypertensive patients had high cortisol and DAAS values.

Figure 2A shows that hypertensive patients had higher cortisol levels than healthy individuals. We found the same level of significance by gender, with females releasing slightly more cortisol than males (Fig 2B). We investigated whether it could affect specific age groups based on the distribution of cortisol values in patients. We found no significant difference in cortisol levels when comparing patients aged 21-30 vs 31-40, 41-50, and 51-60, although there was a higher but non-significant release of cortisol in patients aged 51-60. (Fig 2C). Next, we want to know about the status of the patients' physiological assessment data sheets. We revealed that all three parameters have significantly higher values in patients than in controls (Fig 2D).

Type of treatment vs blood pressure and cortisol readings in patients.

Three distinct treatments were observed in this study, which were administered to the patient group by a specialized physician. These three treatments are known as RAAS inhibitors, non- RAAS inhibitors, and combinations of these two molecules. Surprisingly, none of the treatments have been shown to be the most effective in dealing with the patients' elevated cortisol levels (Fig 3A). This is understandable because cortisol levels may be elevated for a variety of reasons. On the other hand, these treatments failed to keep patients' basic blood pressure levels stable (Fig 3B, C). Nonetheless, we found that patients on regular treatment had slightly higher values than control people. Furthermore, this effect was stronger in patients who used a combination of RAAS and non-RAAS inhibitors (Fig 3D).The significant difference observed in the current study between treatment and control patients could be attributed to other factors such as food, race, and other activities of the patients group.

Elevated cortisol levels linked to anxiety, depression, stress, and high blood pressure.

As shown in the graph, blood pressure and cortisol levels were positively correlated (Fig. 4A, B). We also looked at the correlation and found that depression and stress were positively and significantly correlated with cortisol levels in patients (Fig 4B, C). These results suggest that stress, depression, and high blood pressure all affect cortisol levels in the body, either directly or indirectly. This could involve a variety of cellular pathways and molecular biology.

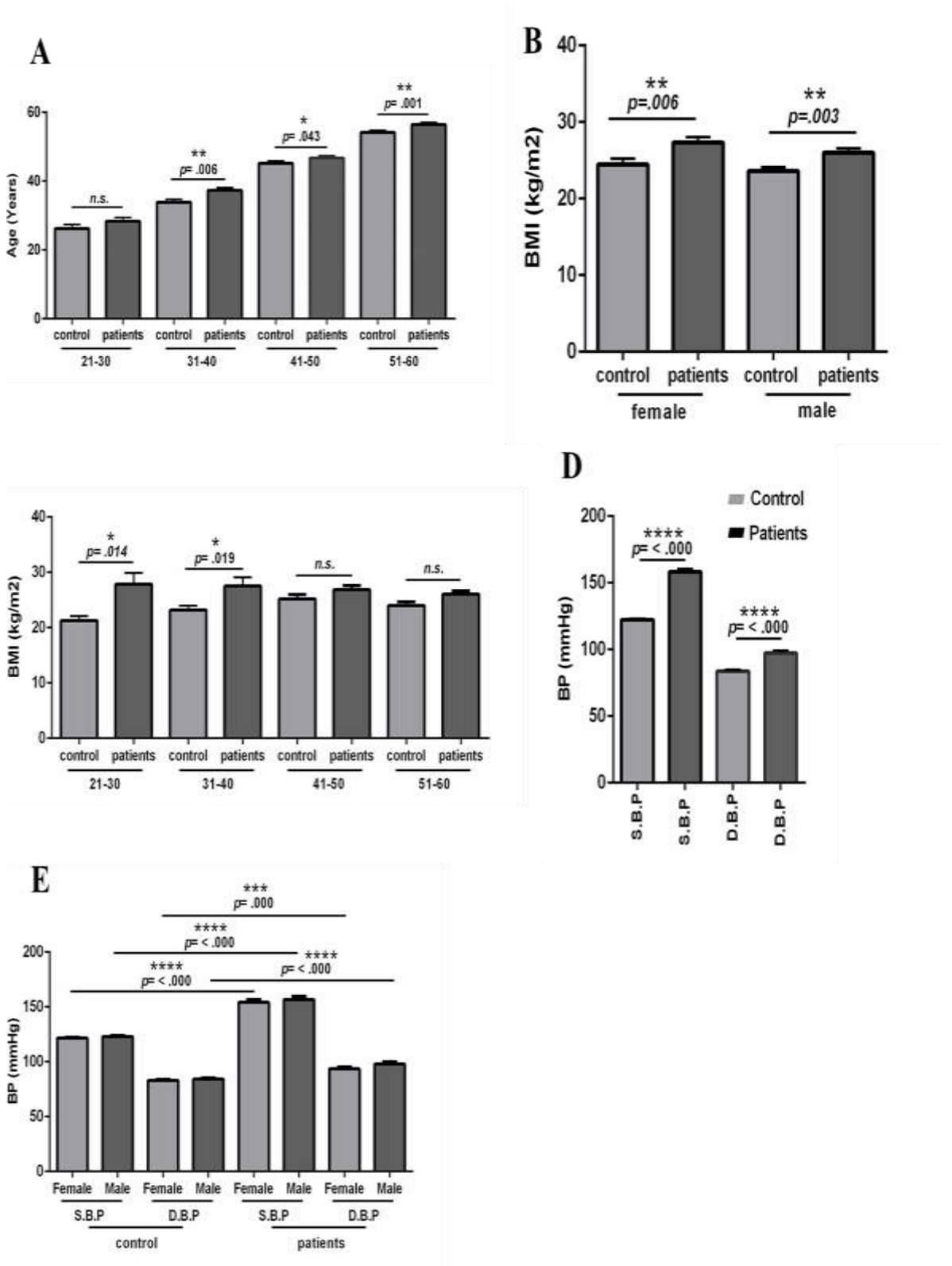

Figure 1. Age, body mass index and blood pressure of hypertensive patients and control subjects. A) Age of the patients and healthy subjects. B) BMI of patients and control subjects. C)BP of patients and control subjects in general. C) Blood pressure of patients and control subjects by age group. Data show the SEM, ANOVA, multiple comparison analysis *p<0.05.

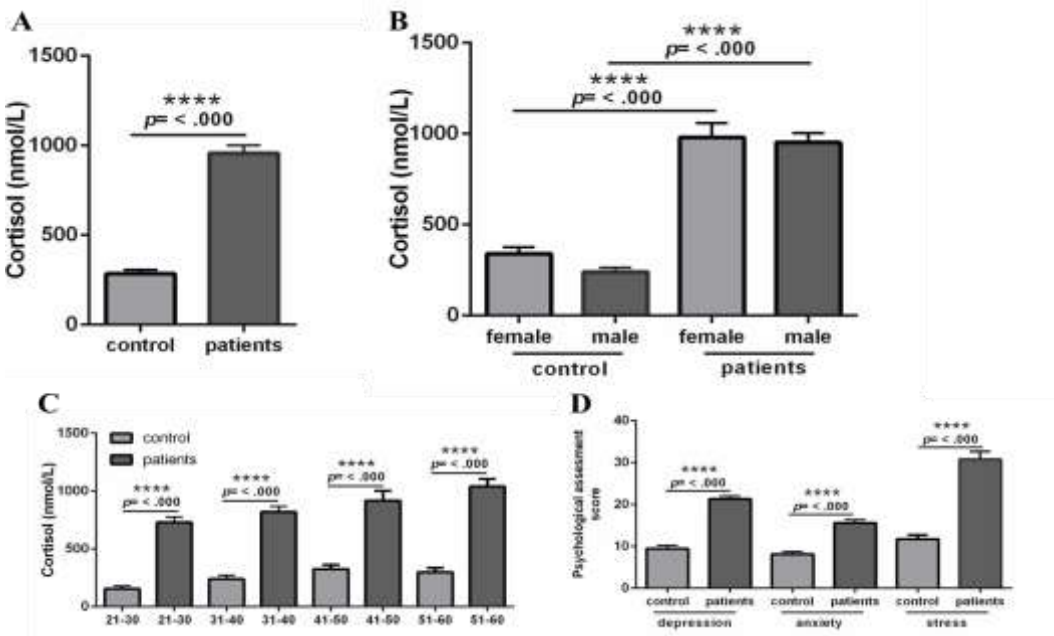

Figure 2. Cortisol and DAAS levels increased in hypertensive patients compared to controls. Cortisol or DAAS levels in healthy controls (silver column) versus hypertensive patients (light dark column). A) Cortisol levels in healthy control versus patients. B) Cortisol levels in healthy control versus patients in female and male groups. C) Graph showing cortisol readings across different age groups. D) Graph depicting the psychiatric assessment score for patients and the control group.Data show the average±SEM, T-test *p<0.05 or ANOVA, multiple comparison test.

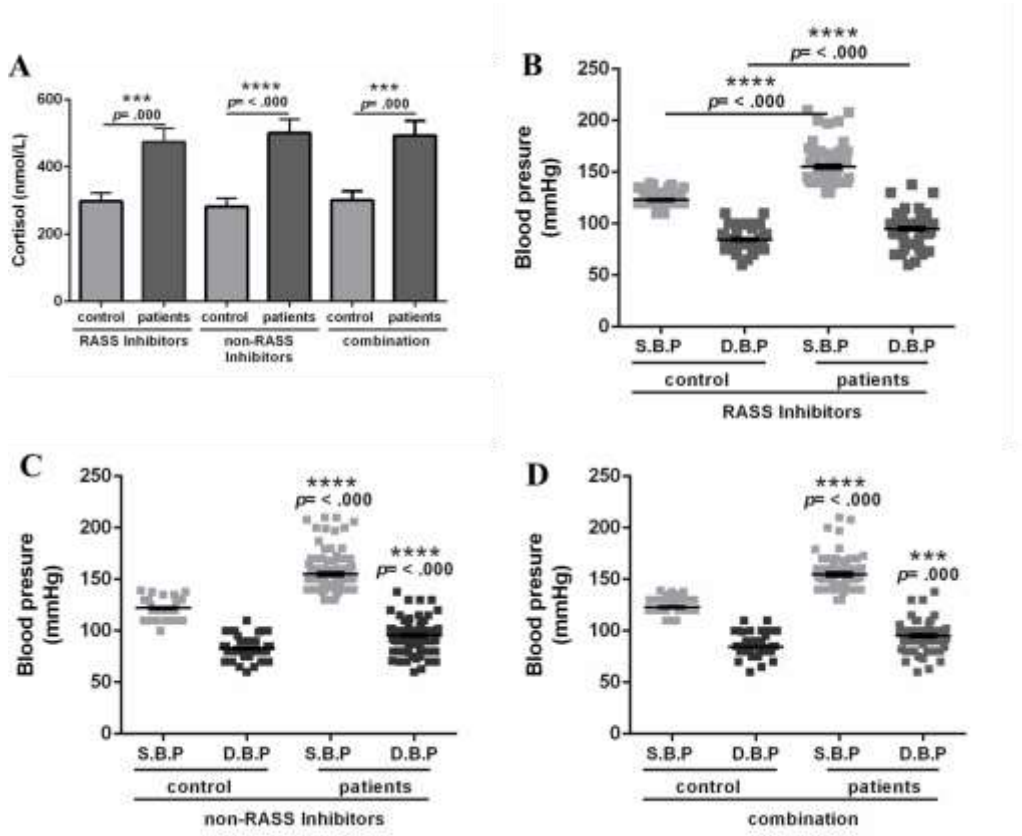

Figure 3. As controls, neither cortisol nor blood pressure were effectively maintained by the current treatment strategies. A) Cortisol levels versus treatment options. B) BP versus RAAS- inhibitor. C) BP versus non-RAAS-inhibitor. D) BP versus combination of RAAS and non- RAAS inhibitor. Data show the average±SEM, *p<0.05 or ANOVA, multiple comparison test.

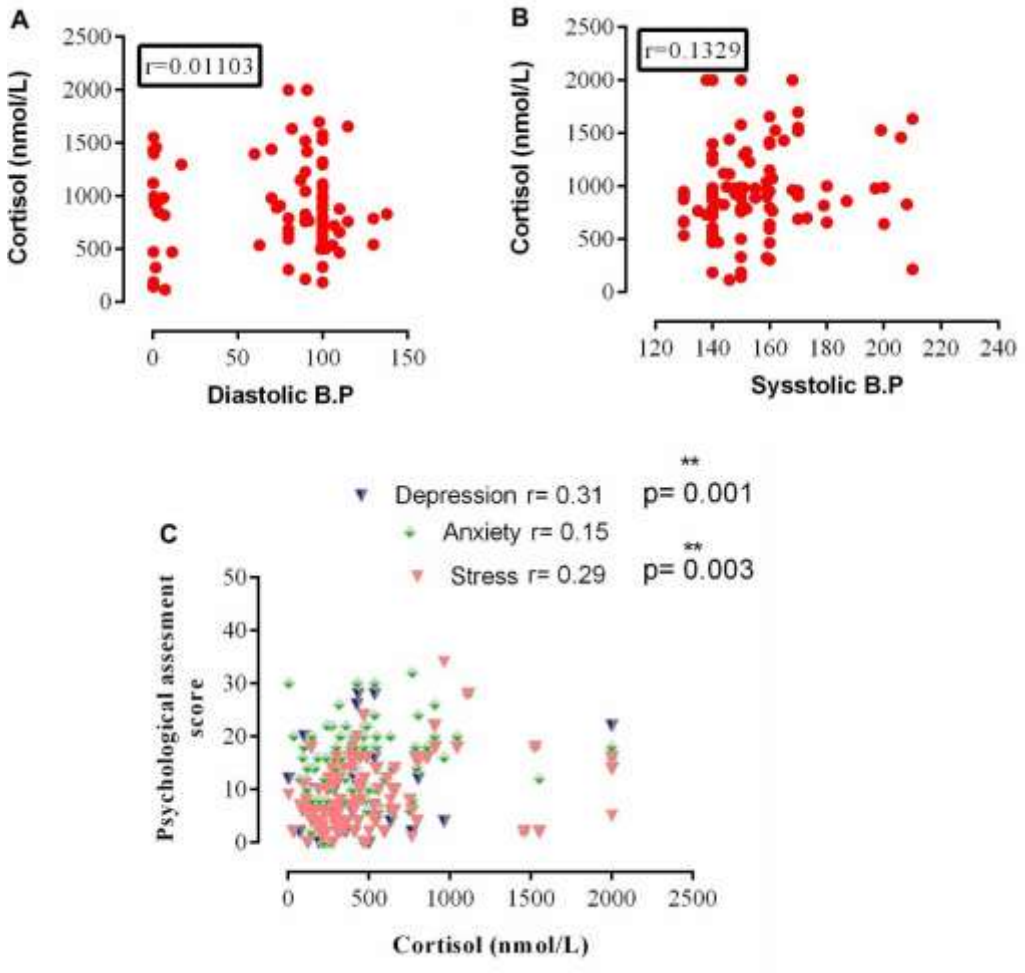

Figure 4. Cortisol, blood pressure, depression, and stress were all found to be positively related in patients. A) Cortisol levels versus systolic blood pressure. B) Cortisol levels versus diastolic blood pressure. C) Cortisol levels versus psychological assessment score. *p<0.05.

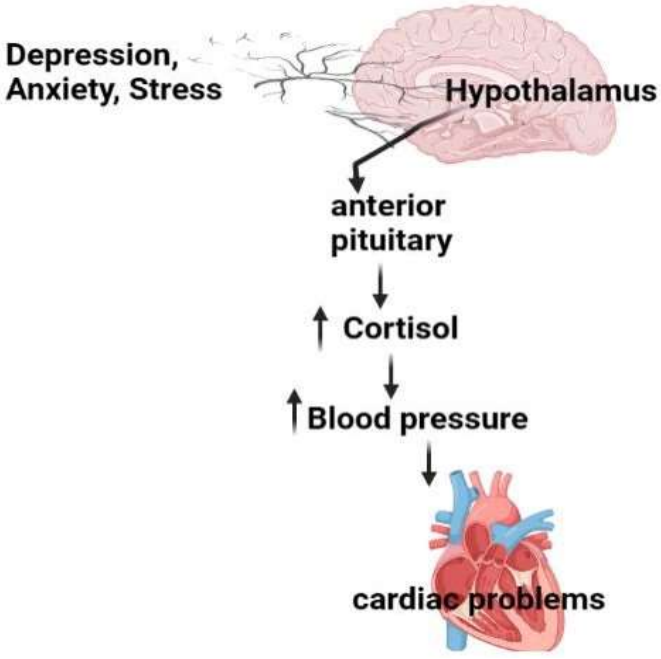

Fig 5. Model depicting the mechanisms by which psychosocial events trigger the physiological events.

Discussion

The adrenal cortex of the kidney produces the essential catabolic hormone cortisol, which is released throughout the day, with blood levels peaking in the morning to promote arousal and then gradually declining. The stress response is primarily influenced by cortisol. Although a short-term increase in cortisol secretion by stress is adaptive, excessive or prolonged cortisol secretion can harm the body and mind. Cortisol, a hormone with a complex action on metabolizing carbohydrates, proteins, and lipids and acting on inflammatory and immunological responses, is released when the HPA axis is activated in stressful situations. Cortisol has been used as a stress evaluator in numerous studies. One of the primary etiological factors for many diseases is stress.

We demonstrated that cortisol and blood pressure were positively but not significantly correlated in the current study. Intravenous or oral cortisol can mimic the hypertensive effects of adrenocorticotropic hormone (ACTH) infusion in humans. Blood pressure is raised by oral cortisol in a dose-dependent manner. Systolic pressure increases by about 15 mmHg at doses of 80 to 200 mg per day. Within 24 hours, blood pressure increases become noticeable. When cortisol is administered, both direct and indirect measures of sympathetic activity are either unaffected or suppressed, indicating that increased sympathetic tone is not a mediator of cortisol- induced hypertension [8]. The idea that cortisol may contribute to some types of essential hypertension is of great interest, and it has been suggested that cortisol may be responsible for about 30% of all cases of hypertension [17-20].

In the current study we found that cortisol, stress, depression and anxiety levels were correlatedin hypertensive patients. The relationship between stress and increased cortisol levels has been established with a high degree of certainty [21], and depression is exacerbated by hypertension [22]. Here we found that anxiety and the level of cortisol was positively but non significantly correlated. No significant correlation between the anxiety levels, either state- or trait-anxiety, and the studied periods was found in earlier study [23]. Anxiety is the leading single cause of hypertension, according to a sufficient body of research [24]. According to reports, participants who go on to develop hypertension at a later stage have significantly more anxiety at the baseline stage than participants who don't go on to develop hypertension [25]. We could not locate relevant data that demonstrated a connection between anxiety and cortisol in patients with hypertension.

Three distinct treatments were administered to the patient group by a specialized physician. These three treatments are known as RAAS inhibitors, non-RAAS inhibitors, and combinations of these two molecules. Surprisingly, none of the treatments have been shown to be the most effective in dealing with the patients' elevated cortisol levels and patients' basic blood pressure levels stable. Due to a high degree of sequence homology between aldosterone synthase inhibitors and mitochondrial cytochrome P450 11B1, also known as steroid 11-hydroxylase and encoded by the CYP11B1 gene, the two enzymes may suppress cortisol release [26]. LCI699 has been tested in human studies as an orally active, nonselective aldosterone synthase inhibitor. A daily dose of LCI699 of 0.5 mg was well tolerated in phase I studies and reduced plasma and urinary aldosterone levels without affecting cortisol secretion [27]. However, cortisol secretion dropped at higher doses. Phase II studies showed that LCI699 therapy lowers plasma and urinary aldosterone levels while upregulating the RAAS and causing slight hyponatremia and elevated serum potassium levels [28]. LCI699 inhibits aldosterone synthase while maintaining normal cortisol levels [27]. Renin and angiotensinogen synthesis and release are necessary for the RAS to regulate blood pressure. Additionally, the active metabolite, angiotensin II, must be produced from angiotensinogen [29]. As a result, it is reasonable to assume that the RAS has a smaller impact on blood pressure variability than the sympathetic nervous system [30]. In fact, it has been proposed that the RAS influences cardiovascular variability at a very low frequency (0.04 Hz in dogs). This idea is consistent with research by Elghozi et al., [31-34] who showed that very low frequency blood pressure variability (0.02-0.2 Hz) increased in conscious rats when the RAS was stimulated experimentally and that this increase could be stopped by angiotensin AT1 receptor antagonists [34-36].

Previous studies had several limitations, including using participants from single or random age groups without control groups and an average disease period that was too short to study the connection between serum cortisol levels and the psychosocial characteristics of the patients—including healthy controls and the concurrent analysis of the correlation between cortisol levels and patient psychosocial factors strengthened our study. The current study had several drawbacks, including a small sample size and a single study site. This study did not consider alpha-lactalbumin, an active protein, and variations in the SERPINA6/A1 gene, which may affect serum cortisol levels. Even though there is insufficient evidence in our research to infer a causal relationship, the intriguing associations we found can still offer insightful recommendations for future research.

Conclusion

According to our investigation, cortisol levels were higher in hypertensive patients than in healthy individuals and positively correlated with blood pressure. Our findings also show a positive correlation between cortisol levels and stress, anxiety, and depression. Even so, we discovered that none of the drugs used to maintain the patient's blood pressure were successful. However, more extensive prospective cohort studies should be conducted to assess this finding further.

Conflict of interest:

The authors declare no conflicts of interest.

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