International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Research Article

Serum Cortisol as a Predictive Biomarker of Cardiovascular Stress Reactivity and Hypertension Risk in Genetically Predisposed Individuals

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OPEN ACCESS

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Received: 02-08-2025
Accepted: 24-08-2025
Available online: 18-09-2025

ABSTRACT

Background: Increased cortisol stress reactivity may lead to cardiovascular disease and hypertension due to the consequences of frequent exposure to excessive circulating cortisol concentration. Cortisol affects areas of the brain that are involved in the control of BP, such as the hypothalamus and limbic system. Cardiovascular stress reactivity refers to the enormousness of change in heart rate and blood pressure during an aversive, challenging, or engaging laboratory stressor. Cardiovascular reactivity to stress has been revealed to be a predictor of future cardiovascular risk. During stress responses, the hypothalamic-pituitary-adrenocortical (HPA) axis is activated, further leads to increased secretion of hormones such as adrenocorticotropic hormone (ACTH) and then glucocorticoid hormones like cortisol.

Aim: To evaluate the role of serum cortisol as a biomarker for early detection of cardiovascular stress reactivity and prediction of hypertension in genetically predisposed individuals.

Methods: A total of 70 Cases (18-30 years old offspring of hypertensive parents) and 70 Controls (18-30 years old offspring of normotensive parents) were included in the study. Morning Serum Cortisol, Blood pressure (BP) and Anthropometric variables were obtained for all participants.

Results: In the present study we found that the Serum cortisol levels were significantly higher in the case group compared to controls ($p < 0.05$). Higher cortisol levels were associated with greater cardiovascular stress reactivity in at risk individuals.

Conclusion: We observed the significantly elevated level of serum cortisol which may serve as an early biomarker of cardiovascular stress reactivity and potential predictor of hypertension in genetically predisposed individuals. Delineating these mechanisms could provide insights into endothelial activation, inflammation, and the pathogenesis of hypertension.

Keywords: *Hypertension, Cortisol, Cardiovascular Stress Reactivity, HPA Axis, ACTH.*

BACKGROUND

Stress is related to development of Cardio-vascular disease through multiple pathways. Stress is related to poor health behaviours leading to increases in Cardio-vascular disease risk factors and implicated in development of atherosclerosis [1]. For example, Stress appears to be associated with endothelial dysfunction [2] or pathological changes in blood vessels that can progress to vascular abnormalities and Cardio-vascular disease. Stress also appears to be connected with increased blood pressure, reduced insulin sensitivity, and increased blood clotting [3].

During a stress response, the nervous system and the body undergo physiological changes to maintain homeostasis [4]. The response includes several physiological processes such as changes in the immune system, endocrine and metabolic

hormones, brain, and sympathetic and parasympathetic nervous system. Specifically, during stress responses, the hypothalamic-pituitary-adrenocortical (HPA) axis is activated, further leads to increased secretion of hormones such as adrenocorticotropic hormone (ACTH) and then glucocorticoid hormones like cortisol [5,6]. Stress responses also increase levels of epinephrine and norepinephrine, causing an increase in vasoconstriction and heart rate. Stress can also induce a low-grade inflammatory response in the body, leading to additional damage to endothelium [7].
Chronic stress, or persistent acute stress and accumulation of acute stress responses, results in allostatic overload leads to development of disease [8].

The stress response causes the activation of the hypothalamo–pituitary–adrenal (HPA) axis and sympathetic nervous system [9]. In acute stress the first measurable alterations are the endocrine changes because of the alteration in HPA axis. One of the HPA axis related hormone is cortisol which has a robust circadian rhythm wherein the levels peak typically in the early hours of the day and decline later on.

Cortisol is the very potent glucocorticoid and it represents 95 % of the entire glucocorticoid activity. Increased cortisol stress reactivity may lead to cardiovascular disease due to the consequences of frequent exposure to excessive circulating cortisol concentration. Cortisol affects areas of the brain that are involved in the control of BP, such as the hypothalamus and limbic system [10]. It can also directly affect BP regulation through the action of glucocorticoid receptors in the heart, vascular smooth muscle of resistance vessels, and the kidneys [11]. Acute elevation in blood cortisol via infusion results in an increase in BP [12], and excessive levels of cortisol may lead to hypertension. Hypertension is observed in individuals with Cushing's syndrome [13], and blood pressure normalizes in these patients when lowered cortisol levels are restored using medication [14]. Furthermore, urinary cortisol excretion is higher in hypertensive individuals compared to normotensive individuals [15] and plasma cortisol is reported to be elevated in young people with high BP [16].

Cortisol induced hypertension does not appear to act via enhancing sympathetic nervous activity [17], but may be mediated in part through the nitric oxide (NO) system, which helps in the regulation of blood pressure through vasodilation [18]. Cortisol may inhibit NO bioavailability in a number of ways. First, Cortisol has been demonstrated to directly block NO synthesis by down-regulating expression of NO synthase (e-NOS) within the vascular endothelium, [19] and reducing available plasma nitrate [20], a precursor to NO. Second, Cortisol may also enhance reactive oxygen species (ROS) production [21] ROS react directly with NO rendering it non-functional, and also oxidize tetrahydrobiopterin (BH4), a necessary cofactor for e-NOS [22]. In the absence of BH4, e-NOS use O2 as a substrate instead of L-arginine, and produces further ROS instead of NO [23].

Aim: To determine the role of hs-CRP as a biomarker for the early detection of endothelial dysfunction and for predicting of future development of hypertension in young healthy adults with family history of hypertension.

MATERIALS AND METHOD

The current case-control study was conducted in the Department of Physiology, Government Medical College, Kota (Rajasthan), approved from the Institutional Ethics Committee *[No.F.3.Acad/Ethicalclearance/Batch2021/2022/62]*
A total 70 normotensive participants aged 18–30 years. The study groups were defined as –

A. Case group: with a family history of hypertension.
B. Control group - without any family history of hypertension.
The subjects were recruited after applying the exclusion and inclusion criteria. After the selection of subjects informed written consent was obtained and then data were collected.

Inclusion criteria: Healthy young adults between the age group of 18-30 years, of both sexes with family history of hypertension.

Exclusion criteria: Endocrine disorders, recent infections, cardiorespiratory disorders, medications which affecting the central and autonomic nervous system.

Data Collection: Anthropometric variables were obtained for all participants. Early Morning Blood sample were collected in proper aseptic condition and transported to laboratory in ice cube container on same day. The Serum Cortisol level was estimated by fully automated Chemi Luminescent Immuno Assay (ARCHITECT- i1000 PLUS) Abbott USA.
Blood Pressure:
After the rest of 10 minutes, in supine position Blood Pressure (BP) measurement had done by using digital BP instrument (Beurer BM35).

RESULTS

Total 70 participants in which 34 (48.6%) female and 36 (51.4%) male subjects in case group while 32 (45.7%) female and 38 (54.3%) male subjects in control group.

Statistical Analysis of Demographic, Cardiovascular and Biochemical Parameters in Case vs. Control Groups					
Parameter	**Case Group (Mean ± SD / n, %)**	**Control Group (Mean ± SD / n, %)**	**t / χ^2 value**	**p-value**	**Significance**
Gender	Female: 34 (48.6%) Male: 36 (51.4%)	Female: 32 (45.7%) Male: 38 (54.3%)	$\chi^2 = 0.029$	0.8	**statistically insignificant**
Age (years)	22.8 ± 2.5	22.2 ± 3.1	t = 1.2548	0.21	**statistically insignificant**
BMI (kg/m²)	21.9 ± 3.6	21.6 ± 3.5	t = 0.50472	0.6146	**statistically insignificant**
SBP (mmHg)	132 ± 9	126 ± 9	t = 3.9181	0.00013	**Significant**
DBP (mmHg)	89 ± 10	82 ± 8	t = 4.6449	0.000008	**Significant**
Heart Rate (beats/min)	88 ± 13	79 ± 13	t = 3.877	0.0001	**Significant**
S. Cortisol (µg/dl)	13.9 ± 2.9	11.9 ± 2.1	t = 4.6042	0.00009	**Significant**

The mean ± SD values of participants age (years) in case group was 22.8 ± 2.5 and in control group was 22.2 ± 3.1. The significant difference between both case and control groups according to age were found statistically insignificant by Independent t-test and, the p-value 0.21 was greater than 0.05.

The mean ± SD values of BMI in case group were 21.9 ± 3.6 and the mean ± SD values of BMI in control group were 21.6 ± 3.5. We were found statistically insignificance difference between BMI and participants case and control group by using Independent t-test and p-value was 0.6146 greater than 0.05.

The Mean ± SD values of SBP in case group was 132 ± 9 and in control group was 126 ± 9. We observed that, the Mean ± SD values of SBP in case group were higher than the Mean ± SD values of SBP in control group which was statistically significant by using Independent t-test and the p-value 0.00013 (< 0.05). (Figure 1.)

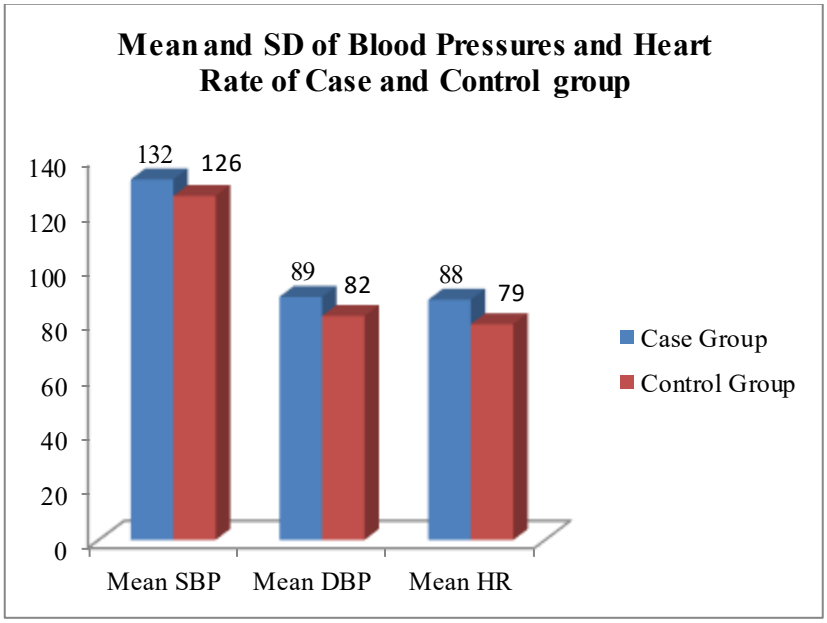

Figure 1: Mean and SD values of Blood Pressures and Heart Rates of Case and Control group.

The mean ± SD values of DBP in case group were 89 ± 10 and the mean ± SD value of DBP in control group were 82 ± 8. The higher range of DBP in case group was statistically significant and the p-value 0.000008 (< 0.05). The mean ± SD values of HR in case group were 88 ± 13 and the mean ± SD values of HR in control group were 79 ± 13.

We observed that the HR values in case group were higher than the HR values in control group. The difference between HR levels in both the groups was statistically significant the p-value 0.0001 (< 0.05).

We estimated the serum-cortisol level, the mean ± SD values in case group was 13.9 ± 2.9 and the mean ± SD values of serum-cortisol in control group was 11.9 ± 2.1. We observed the serum cortisol level in case group was increased (figure

2.). The significant difference between serum cortisol and participants groups was significant by using independent t-test and the p= 0.05. Increased serum cortisol level in case group and in control group was statistically significant.

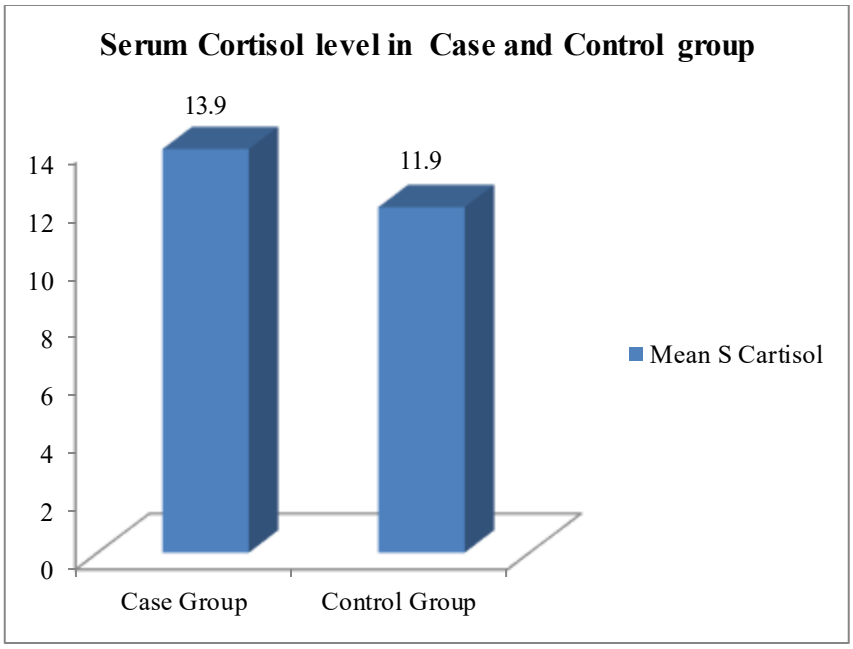

Figure 2: Mean and SD values of Serum Cortisol level in Case and Control group.

DISCUSSION

Some people are sensitive to the negative effects of stress, but others are resistant. The interacting role of serum cortisol, stress, and genetic predisposition in the development of cardiovascular diseases is essential for the development of new methods of treatments to be implemented and precautions to be taken against cardiovascular diseases [24].

Trickett et al., 2010 [25] observed that abuse has been associated with higher morning cortisol levels in childhood and lower morning cortisol levels by early adulthood even after accounting for the time elapsed since trauma disclosure. In present study serum cortisol level was increased in participants with positive family history of hypertension compared to negative family history of hypertension.

A similar finding, the Cortisol response for mental stress was greater and more persistent in persons at high risk for hypertension relative to low risk normotensives. This is because of the fact that Cortisol affects several blood pressure-related processes and regulates the expression of genes involved in blood pressure. This is accordance by Absi et al. [26]. According to Kirsch Baum et al., showed the serum Cortisol response to human and mental stress can be significantly increased by hereditary factors. [27] Chronic stress, or persistent acute stress and accumulation of acute stress responses, results in allostatic overload leads to development of disease [8].

To our knowledge, few studies have been conducted on serum cortisol levels as a biomarker for the early detection of cardiovascular stress reactivity and the prediction of hypertension in genetically predisposed individuals. The present study found the differences between the case and control groups with respect to age, gender, and BMI statistically insignificant. SBP, DBP and HR were significantly increased in offspring of hypertensive parents (OHTPs) compared to those without a family history of hypertension (ONHTPs). A better understanding of these underlying mechanisms may yield novel insights into endothelial activation, inflammatory pathways, and the pathogenesis of hypertension.

CONCLUSION

We conclude that serum cortisol levels were elevated in the case group, with a significant increase observation in OHTPs relative to ONHTPs. Our findings suggest a potential dysfunction of the HPA axis, characterized by heightened vascular and cardiac reactivity to stress, which may predispose individuals to developing hypertension. Increased serum cortisol may therefore serve as an early biomarker of cardiovascular stress reactivity and a predictor of hypertension in genetically susceptible populations. We also found no statistically significant differences in age, gender, and BMI between the groups. However, SBP, DBP, and HR values were significantly elevated in offspring of hypertensive parents (OHTPs).

Conflict of Interest

There are no conflicts of interest.

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