# Relationship between Serum Cortisol levels and Oxidative Stress in Patients with Adrenal Disorder

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**Abstract**

Exposure to stress during critical periods in development can have severe long-term consequences, increasing overall risk on psychopathology. One of the key stress response systems mediating these long-term effects of stress is the hypothalamic-pituitary-adrenal (HPA) axis; a cascade of central and peripheral events resulting in the release of corticosteroids from the adrenal glands. A case control study conducted on a group of participants at specialist clinics and Biochemistry Laboratory in the College of Science (University of Thi-Qar) at the period between (January) to (May) 2022. The study included (152) subjects, (45) controls and (107) patients was performed. MDA revealed a significant increase in its concentrations in all patient groups when compared to the control group ($P<0.05$). Ceruloplasmin demonstrates a significant rise in serum CP concentrations in all patient groups when compared to the control group ($P<0.05$). The concentration of serum CP in the CS group is significantly higher than in the AD and CSI groups, with significant drop in serum tf concentrations ($P<0.05$) in all patient populations when compared to the control. Serum tf concentrations in the CSI group are significantly lower than in the AD group ($P<0.05$). This study aimed to investigate the relation between oxidative stress markers in patients with adrenal disorder. AS oxidative stress biomarkers; MDA appeared a role in adrenal disorder with negative relation with cortisol, and in consequence, the anti-oxidant (Cp, Tf) revealed adverse effects to compensate the oxidative damage.

Keywords: Adrenal disease, Ceruloplasmin, Cortisol, Malondialdehyde, Oxidative stress, Transferrin.

## 1. Introduction

Oxidative stress (OS) is a disruption in the equilibrium between oxidant and antioxidant status, favoring the oxidizing environment [1]. Oxidative stress causes an increased concentration of products that stimulate oxygen, which leads to critical injury of cells.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) target lipids, which sets off a chain reaction known as lipid peroxidation. Polyunsaturated fatty acid (PUFA), damages cell membranes and consequently, there is cell death [2].

Among the byproducts of LPO are stable aldehydes, malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), and acrolein. The main product of LPO are unstable hydroperoxides [2]. One of the most prevalent and trustworthy indicators of oxidative stress in medical practice is MDA [3]. It has been generally hypothesized that MDA, the main byproduct of lipid oxidation, has genotoxic effects [4].

A substance known as an antioxidant inhibits or stops other molecules from oxidizing [5-6]. Safeguarding our body against the harmful effects of free radicals [7]. Enzymatic and non-enzymatic antioxidants are the body's two main antioxidant defense mechanisms against cell damage and ROS.

A significant copper ion transporter in the plasma is ceruloplasmin (Cp), a blue multi-copper oxidase. The majority of the protein's synthesis occurs in the liver as a single-chain polypeptide, which is then released as a 2-glycoprotein into the plasma [8]. Ceruloplasmin functions to eliminate the (•O-2) superoxide radical by decreasing the copper atom in the protein, hence the amount of Cu++ in the protein determines how effective Cp is as an antioxidant [9].

The increased oxidase activity during inflammatory, infections, and damage raises the possibility that serum Cp functions as both an acute-phase protein and an antioxidant [10].

Transferin (Tf) is a main protein that binds to and transports iron . it can bind two molecules of iron produced in the liver and is primarily found in human plasma (Hayashi et al., 2006). Iron concentrations, estrogens, and dietary condition all influence the production and storage of Tf [11].

Transferrin uptake diminishes to stop additional iron absorption and excessive iron accumulation once cellular iron levels are adequate. under situations of iron overload [12].

Exposure to stress during critical periods in development can have severe long-term

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consequences, increasing overall risk on psychopathology. One of the key stress response systems mediating these long-term effects of stress is the hypothalamic-pituitary-adrenal (HPA) axis; a cascade of central and peripheral events resulting in the release of corticosteroids from the adrenal glands. Activation of the HPA-axis affects brain functioning to ensure a proper behavioral response to the stressor, but stress-induced (mal) adaptation of the HPA-axis' functional maturation may provide a mechanistic basis for the altered stress susceptibility later in life [13].

This study aimed to investigate the relation between oxidative stress markers in patients with adrenal disorder.

## 2. Materials and Methods

A case control study conducted on a group of participants at specialist clinics and Biochemistry Laboratory in the College of Science (University of Thi-Qar) at the period between (January) to (May) 2022 .The study included (152) subjects, (45) controls and (107) patients.

The study participants (patients and apparently healthy individuals) divided into four groups: Addison disease group, Cushing induced by drug group, Cushing syndrome group and Control group at age range (16 -55) years.

Five milliliters of venous blood from patients with adrenal disorders and controls were drawn, permitted to clot at room temperature in blank gel tubes, and then centrifuged at 3000 RPM for ten minutes. If not used right away, the serum were divided and refrigerated at (-30oC) for further assessment of biochemical markers.

### Statistical Analysis

The data was analyzed using the SPSS-25 statistical package and Excel 2013. The data was displayed using simple frequencies and percentages. To determine the significance of the difference between distinct% qualitative data, two groups, and more than two groups, the Chisquare test (two-test), independent T-test, and one way anova were used. Statistical significance was considered whenever the P-value was ≤ 0.05.

## 3. Results

Table (1) shows a significant increase in the concentration of serum cortisol. In CS group in comparison with the control group ($P < 0.05$), and there is a Significant increase in the concentration of serum cortisol CS group in comparison with the AD and CSI groups ($P<0.05$). Tables (2) reveal a significant increase in serum MDA concentrations in all patient groups when compared to the control group ($P<0.05$). Serum MDA concentrations are significantly higher in the AD group, in comparison to the CSI There is no statistically significant difference between the AD and CS groups. There is no significant statistical difference in serum levels between the CSI and CS groups ($P>0.05$).

Table (3) demonstrates a significant rise in serum CP concentrations in all patient groups when compared to the control group ($P<0.05$). The concentration of serum CP in the CS group is significantly higher than in the AD and CSI groups.

There is no statistically significant difference between the AD and CSI groups ($P>0.05$).

Table (4) shows a significant drop in serum tf concentrations ($P<0.05$) in all patient populations when compared to the control. Serum tf concentrations in the CSI group are significantly lower than in the AD group ($P<0.05$). There is no statistically significant difference between the AD, CS, and control groups ($P>0.05$).

Table (1): Comparison of adrenocorticotropic hormone and cortisol for total study groups

| Groups | N | Mean ±SD |
|---|---|---|
| | | Cortisol (pg/ml) |
| AD | 36 | 2.68±1.1c |
| CSI | 36 | 1.89 ± 1.6c |
| CS | 35 | 61.14± 27.0a |
| Control | 45 | 10.1± 3.3b |
| LSD | 6.33 | |

Table (2): Comparison of Malondialdehyde for total study groups

| Groups | N | Mean ±SD |
|---|---|---|
| | | Malondialdehyde |
| AD | 36 | 5.16 ±0.98a |
| CSI | 36 | 4.69±0.83b |
| CS | 35 | 4.91±1.07ab |
| Control | 45 | 2. 86±0.57c |
| LSD | 0.32 | |

Table (3): Comparison of Ceruloplasmin for total study groups

| Groups | N | Ceruloplasmin |
|---|---|---|
| AD | 36 | 34.9± 8.5$^{b}$ |
| CSI | 36 | 36.2 ± 6.5$^{b}$ |
| CS | 35 | 42.04± 6.3$^{a}$ |
| Control | 45 | 34.45± 3.9$^{b}$ |
| LSD | 3.5 | |

Table (4): Comparison of transferrin for total study groups

| Groups | N | Mean ±SD |
|---|---|---|
| | | Transferrin (mg/dl) |
| AD | 36 | 181.7±53.06$^{a}$ |
| CSI | 36 | 140.7 ± 48.5$^{b}$ |
| CS | 35 | 166.4± 69.6$^{ab}$ |
| Control | 45 | 172.24 ± 65.8$^{a}$ |
| LSD | 30.2 | |

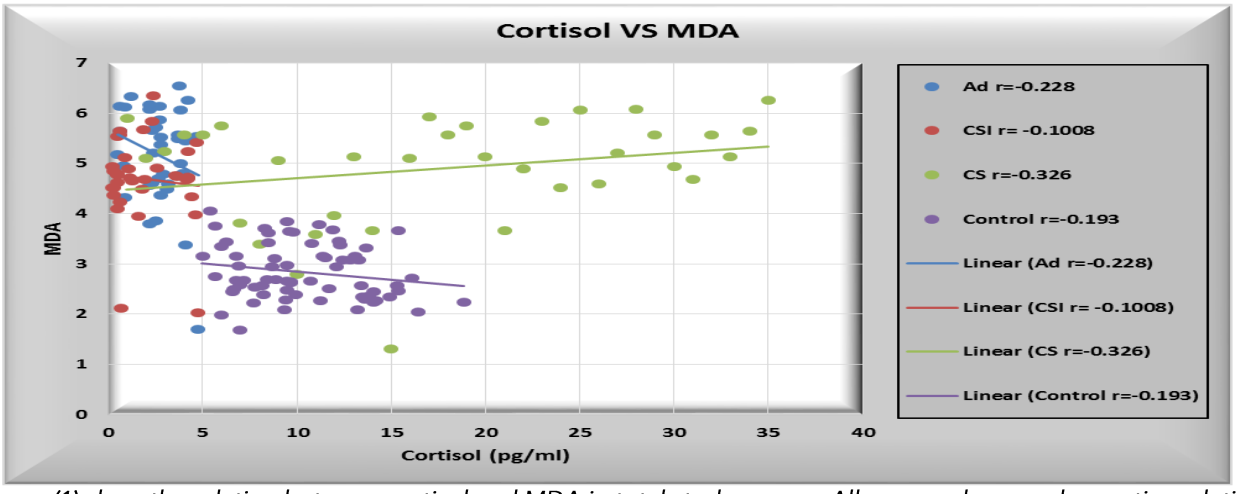


*Figure (1) show the relation between cortisol and MDA in total study groups. All groups show weak negative relation between the indicated parameters.*

Figure (1): Correlation between cortisol and MDA for total study groups

Figure (2) show the relation between cortisol and Ceruloplasmin in total study groups. All groups show weak negative relation between the indicated parameter.

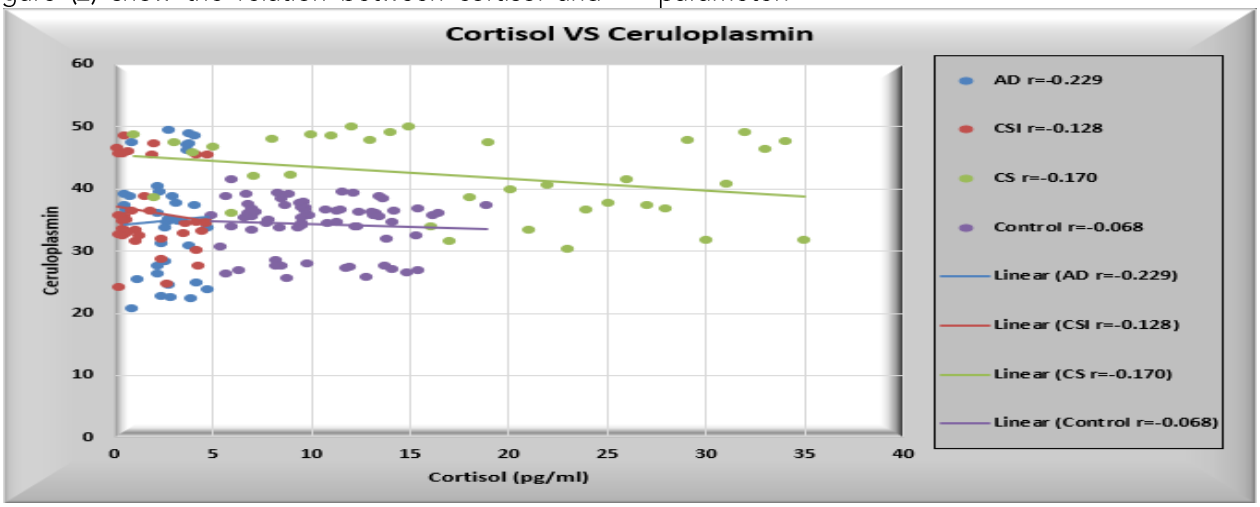


*Figure (2): Correlation between cortisol and Ceruloplasmin for total study groups*

Figure (3) show the relation between cortisol and transferrin in total study groups. The Addison and Cushing groups show weak positive relation between the indicated parameters, while the Cushing induced by drug and control groups show weak negative relation.

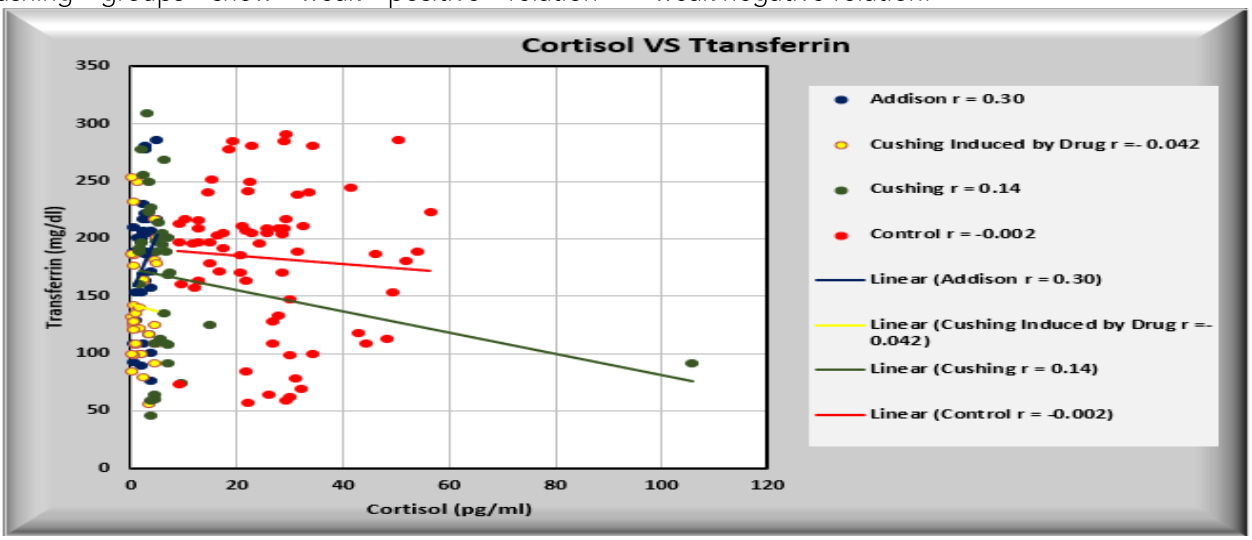


*Figure (3): Correlation between cortisol and transferrin for total study groups*

## 4. Discussion

In matching with the results of [15]. An increase in the production of c ortisol from the adrenal cortex occurs in Cushing syndrome (CS) or Cushing's disease, due to an increase in the adrenocorticotropic hormone that stimulates the production of cortisol ,and it was found that about

70% of cause is tumor in the pituitary gland that produces an increase in the adrenocorticotropic hormone.Cushing syndrome can occur due to excessive intake of glucocorticoids called exogenous Cushing syndrome. Chronic glucocorticoid administration resulting in hypothalamic-pituitary dysfunction only cortisol deficiency [15-16]. The different etiologies for Cushing syndrome can be categorized as ACTH-dependent or ACTH-independent [17].

These findings are backed up by studies that show significantly higher levels of malondialdehyde (MDA), an indicator of OS, in patients with overt CS when compared to cured CS and healthy subjects [18].

Lipid peroxidation is the oxidative degeneration of lipids, while one of the most abundant carbonyl products produced by lipid peroxide is MDA that is an indicator of oxidative damage [19]. Rising lipid peroxidation could result from increased generation of free radicals and an inhibited scavenging mechanism [20].

The relevance of lipid peroxidation and antioxidant changes during myocarditis has provided new insight into the pathogenesis of heart disease [21].

Increased the amount of free radical generating systems and MDA and decreased levels of free-radical scavenging systems appear to play an important role in ischemic heart disease [22], during times of increased oxygen flux (i.e. exercise).

The exact pathophysiology of atherosclerosis and CVD is influenced by oxidative stress [23-24]. The loss of the regular homeostatic balance among ROS and antioxidant defensive lines causes an increase in the production of ROS that are harmful and toxic to cells and tissues, causing membrane lipid peroxidation and, consequently, lipid and DNA damage, which induces apoptosis and protein impairment [25-26].

Ceruloplasmin is a liver-produced enzyme that is accountable for the transport of circulating copper. It binds 95% of the Cu in serum [27]. Ceruloplasmin also participates in iron metabolism and has oxidant and antioxidant characteristics [28].

It is occasionally increased as just an acute phase reactant in a variety of conditions [29]. Ceruloplasmin's antioxidant activities include the conversion of Fe++ to Fe+++ and the blocking of oxidant properties of many molecules via Cu reduction [30].

In another research, but can also contribute to the production of free radicals, which may be at the root of a variety of diseases including myocardial infarction, arteriosclerosis, unstable angina, abdominal aortic aneurysm, vacuities, peripheral arterial disease, and even dementia [31]. Elevated CP levels were linked to an increased risk of atrial fibrillation hospitalization [32].

In consistent with previous research [33], that explains why, at low transferrin concentrations, free iron does not really find Tf to bind to for transport, causing oxidation and the generation of the more free - radical. In humans, lower plasma Tf occurs when iron stores are risen [34].

The low plasma Tf level observed in humans with increased iron stores could be attributed to a negative feedback effect of storage iron status on Tf synthesis [35]. Serum tf levels were found to be significantly lower in heart failure patients in an another study [36].

According to Van Campenhout et al, low levels of Tf can improve iron's pro-oxidative effects. They argue that these consequences are the most worthwhile issues underlying lipid peroxidation and raise the risk of CVD [37].

Transferrin is an antioxidant that aids in preventing formation of free radicals. It keeps the related metal iron from reacting with H2O2 to form free radicals, together with Tf, which tends to work to remove O-2, the underlying cause of superoxide anion. Transferrin works to reduce the oxidative stress that happens in Patients, so its tiers will be reduced [38].

## 5. Conclusion

AS oxidative stress biomarkers: MDA appeared a role in adrenal disorder with negative relation with cortisol, and in consequence, the anti-oxidant (Cp, Tf) revealed adverse effects to compensate the oxidative damage.

### Ethical Clearance and financial support

Lastly the ethical approval for this study was issued by the ethical committee of college of science of Thi-Qar University. Moreover, there was a financial support from college of science in Thi-Qar University.

Conflict of Interest: Nil

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