MINI REVIEW

# In constant hemodialysis patients, high cortisol levels are linked to oxidative stress and death

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**ABSTRACT**

One of the potential reasons of cardiovascular events and death in people with end-stage renal illness has been suggested: chronic activation of the mineralocorticoid receptor. The goal of this observational cohort study was to show that serum cortisol could be a predictor of patient death and to look at its relationship with oxidized low-density lipoprotein (ox LDL) in HD patients. Two institutions screened patients who received HD three times a week for enrollment. Before each HD session, baseline cortisol levels were assessed, and the patients were placed into two groups based on the median serum cortisol value. In patients receiving HD, serum cortisol is a useful predictor of all-cause death. In HD patients, Ox LDL is an independent marker for high serum cortisol.

**Key Words:** *Hemodialysis; Kidney disease; Lipoprotein*

## INTRODUCTION

End-stage renal disease patients have a higher risk of cardiovascular disease and death than patients with normal renal function or mild renal failure. Chronic activation of mineralocorticoid receptors by aldosterone or cortisol has been proposed as a cause of sudden cardiac mortality in diabetes individuals receiving Hemodialysis (HD). Aldosterone is a key effector hormone that has a role in heart disease. However, there has been debate concerning whether plasma aldosterone has a negative impact on cardiovascular outcomes in HD patients. Some observational studies with a small number of HD patients found a positive correlation with cardiovascular outcome and death, whereas others found a negative correlation. Another hormone that can bind to the mineralocorticoid receptor and cause negative cardiovascular outcomes in HD patients is serum cortisol. Cortisol is converted to inactive cortisone by the 11 hydroxyl steroid dehydrogenase type 2 (11HSD2) enzymes under normal conditions [1]. However, as renal function declines, 11HSD2 activity decreases, and cortisol levels rise disproportionately in comparison to aldosterone levels. Due to the low expression of 11HSD2 in the heart, cortisol rather than aldosterone may be the primary activator of cardiac mineralocorticoid receptors in HD patients. In such patients, serum cortisol levels have been shown to be one hundred to one thousand times higher than plasma aldosterone levels.

Furthermore, past research has revealed that serum cortisol has a negative impact on HD patients: High blood cortisol levels in HD patients were associated with a higher risk of cardiovascular events and mortality [2]. Low-density lipoprotein (LDL) is a primary source of cholesterol for the production of aldosterone and cortisol. LDL can be converted to oxidize LDL (ox LDL) in the presence of oxidative stress. Ox LDL is particularly atherogenic. In individuals with chronic kidney illness, the content of ox LDL is raised, in part due to the inability of high-density lipoprotein to diminish ox LDL, and in part due to the extended LDL lifespan due to impaired renal clearance. A prior study found that ox-LDL significantly reduces aldosterone secretion [3]. This conclusion could be linked to the contentious findings on the effects of aldosterone on cardiovascular outcomes in HD patients. The effect of ox LDL on the level of circulating cortisol, on the other hand, is unknown. Determining the effect of ox LDL on serum cortisol levels and patient mortality in HD patients is critical for identifying candidates who will benefit most from mineralocorticoid receptor blockers. As a result, we conducted an observational cohort study to see if serum cortisol influences patient mortality and if ox LDL is a risk factor for high cortisol in maintenance HD patients.

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## DISCUSSION

A high serum cortisol level (baseline cortisol 10 g/dL) is related with increased cardiovascular morbidity and is an independent predictor of all-cause mortality in HD patients, according to this observational analysis. Furthermore, ox LDL was found to be an independent risk factor for high serum cortisol and LVSD. Plasma aldosterone levels, on the other hand, were not linked to serum cortisol levels [4]. This study included prevalent HD patients who had been getting HD treatment three times a week for more than three months at Kangnam Sacred Heart Hospital and Chuncheon Sacred Heart Hospital. The study excluded patients who had undergone HD therapy for less than three months or at a lower frequency (three times per week). Because acute illness influences the amount of adrenal hormones, patients who were admitted to the hospital for intensive care or infection control within three months of study participation were excluded. Patients who were prescribed intravenous or oral corticosteroids for organ transplantation, glomerulonephritis, dermatitis, or asthma were also excluded for the same reason [5].

The study examined at the causes of end-stage renal disease, the existence of comorbid diseases such diabetes and hypertension, and the length of dialysis. Values from the three most recent HD treatments were used to calculate inter dialectic weight gain. The data on erythropoietin dosages was gathered on a weekly basis. Within one month after study enrolment, laboratory examinations were completed. Plasma hemoglobin, fasting glucose, serum albumin, serum calcium and phosphorus, intact parathyroid hormone (PTH), C-reactive protein, lipid profiles [6], serum sodium and potassium, and intact parathyroid hormone (PTH) were all measured. Adrenal insufficiency is a life-threatening illness caused by a decrease in the release of glucocorticoid and mineralocorticoid hormones by the adrenal glands. Primary destruction or dysfunction of the adrenal glands, as well as impairment of the hypothalamic-pituitary-adrenal axis, can cause this illness. Adrenal insufficiency results in aberrant feelings like exhaustion and appetite loss, as well as abnormal indicators like hypotension and abnormal laboratory findings including hypoglycemia, eosinophilia, and electrolyte problems like hyperkalemia. Adrenal insufficiency has been reported in Hemodialysis (HD) patients; however findings are scarce and inconsistent [7].

High levels of cortisol in the blood have been linked to cardiovascular events and death in people with end-stage renal disease. It was found that the presence of high aldosterone (>200pg/mL) and high cortisol (>21.1g/dL) levels increases the risk of all-cause death and sudden cardiac death in their post hoc analysis of the German Diabetes and Dialysis Study (4D Study). Another study found that high blood cortisol levels in HD patients were linked to inflammation and low sodium levels, and that high serum cortisol was related with a high death rate. Our research also found that elevated serum cortisol levels are associated with a higher patient mortality rate [8]. The high cortisol group also had lower serum sodium levels than the low cortisol group, according to our findings. Unfortunately, due to the small number of patients included in the trial and some missing data, we were unable to find any links between the inflammation marker and serum cortisol or patient death. Furthermore, a single C-reactive protein or serum sodium level measurement may not adequately reflect the presence of chronic inflammation. However, our research found that serum cortisol can be a helpful predictor of cardiovascular morbidity and all-cause mortality in HD patients who are exposed to oxidative stress. Only if ox LDL levels are increased in patients with chronic heart failure may serum cortisol be used as a prognostic marker for cardiac events [9].

Patients with end-stage renal illness have a nearly 10-fold higher level of ox LDL than healthy controls, according to a prior study. Ox LDL may build up in macrophages, increasing chemotactic activity and causing direct damage to endothelial cells. Ox LDL also reduces the endothelium's anti-inflammatory capabilities and increases pro inflammatory indicators such as cytokines, chemokine, and growth factors. As a result, ox-LDL may cause endothelial cell dysfunction, atherosclerosis of the microvasculature, and vascular calcification. Our research also discovered that plasma ox-LDL levels were linked to high cortisol levels and LVSD [10]. Despite the fact that our research did not aim to explain the underlying pathophysiology of ox-LDL's effect on cardiac outcomes, there may be a link between ox-LDL, serum cortisol, and cardiac dysfunction. Although plasma aldosterone levels did not alter patient mortality in our investigation, cortisol and aldosterone may be key risk factors for sudden cardiac death in HD patients. Previous research has also found a link between dialysis and poor cardiovascular outcomes. Hypertensive HD patients with low aldosterone (22.9ng/dL) had a lower survival rate (62.5% vs. 90.6%, P=0.003) than those with high aldosterone (22.9ng/dL). This perplexing link has previously been attributed to the confusing effects of volume excess, inflammation, or protein energy deficiency [11]. In our investigation, however, there were no differences in inter dialectic weight gain, serum albumin levels, or C-reactive protein levels between patients with high and low aldosterone levels. Instead, the decoupling of low circulating aldosterone levels and high tissue aldosterone levels may be to blame for aldosterone's counterintuitive effect on cardiovascular outcomes. Furthermore, in severely oxidative stress circumstances, ox-LDL may counteract aldosterone, resulting in low to normal plasma aldosterone levels. While the level of plasma aldosterone has mixed findings, the level of serum cortisol reliably predicts poor cardiovascular outcomes [12]. In pro inflammatory situations, serum cortisol may be raised, and it has an anti-inflammatory effect when ox-LDL levels are high. Furthermore, because the activity of 11HSD2, an enzyme that converts cortisol to the inert hormone cortisone, diminishes as renal function declines, serum cortisol may be significantly elevated in patients with end-stage renal failure. As a result, dialysis patients may have increased ox-LDL and serum cortisol levels while having normal to low aldosterone levels.

Our study has a number of effects. To assess the efficacy of mineralocorticoid receptor antagonists in patients with end-stage renal disease [13], serum cortisol should be combined with plasma aldosterone. Because cortisol levels in cardiac tissue may be higher due to increased ox-LDL and decreased 11HSD2 enzyme activity, cortisol may be the primary activator of cardiac mineralocorticoid receptors. As a result, it is appropriate to consider both hormone effects when evaluating the effect of mineralocorticoid receptor antagonists in patients with end-stage renal disease. Second, the therapeutic use of corticosteroids in individuals with end-stage renal disease should be reassessed. While an adequate amount of corticosteroids should be given when necessary, for patients with a significant cardiovascular risk, the duration and dose of steroids should be reduced [14].

There are a few flaws in this research. First, during the study period, we did not assess nonfatal cardiovascular events. Second, only a small percentage of patients had their ox-LDL and plasma aldosterone levels measured. Third, the duration of blood sampling differed amongst patients. Because plasma ACTH, serum cortisol, renin, and aldosterone are diurnal and can be altered by a variety of circumstances, our findings may be skewed. Fourth, in this investigation, we were unable to be

skewed. Fourth, in this investigation, we were unable to explain the direct effect of ox-LDL on cardiovascular morbidity and mortality. Finally, there was no proof of a causal link between ox-LDL and serum cortisol in this investigation [15].

## CONCLUSION

To summarize, serum cortisol is a valuable prognostic marker for all-cause death in HD patients. Increases in serum cortisol levels may be caused by oxidative stress.

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