Original Paper

Association Between Serum Cortisol and Chronic Kidney Disease in Patients with Essential Hypertension

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Key Words

Cortisol • Relationship • eGFR • Essential hypertension • Chronic Kidney Disease

Abstract

Background/Aims: Serum cortisol level is elevated in patients with essential hypertension. We aimed at investigating the association of serum cortisol levels with parameters of renal function in essential hypertension. **Methods:** One hundred and seventy-eight patients with essential hypertension participated in the study. Fasting serum samples were collected at 8:00 am. Renal function was measured as estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine- cystatin C equation (eGFRcr-cys). Correlation analysis and stepwise regression analysis were used to detect the relationship between cortisol and eGFRcr-cys. The distributions of serum cortisol were split by the tertiles and subjects were stratified into those with low, median and high levels accordingly. **Results:** Serum cortisol levels were significantly higher in subjects whose eGFRcr-cys < 90 ml/min/1.73 m² than subjects whose eGFRcr-cys > 90 ml/min/1.73 m² (394.0 ± 93.4 vs. 343.2 ± 98.4 nmol/L, P = 0.001). Age, systolic blood pressure, and serum total cholesterol, uric acid, cortisol levels were significantly associated with eGFRcr-cys, serum levels of creatinine and cystatin C. After adjusting for clinical factors, serum cortisol level had a statistically significant negative association with the eGFRcr-cys ($\beta = -0.19$, P = 0.027), and positive associations with cystatin C ($\beta = 0.31$, P = 0.001) and creatinine ($\beta = 0.14$, P = 0.044). With the increment of cortisol tertile, the eGFRcr-cys significantly decreased (93.18 ± 14.36 vs. 84.61 ± 14.67 vs. 81.29 ± 12.36 ml/min/1.73 m² for low, median and high tertile, respectively, P = 0.001). **Conclusion:** Serum cortisol level was negatively correlated with eGFRcr-cys in subjects with essential hypertension. Further studies are needed to investigate whether cortisol plays a role in hypertensive nephropathy development.

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Introduction

With increasing prevalence and high treatment costs, chronic kidney disease (CKD) becomes a worldwide public health problem [1]. Hypertension is one of the most common causes of CKD [2-3]. The mechanism of hypertensive nephropathy remains unclear.

Cortisol is the effector end point of hypothalamic-pituitary-adrenal (HPA) axis [4]. It is well known that excessive cortisol is the main factor which causes hypertension in Cushing's syndrome. Some studies have reported that elevated levels of serum cortisol were seen in patients with essential hypertension, and cortisol is implicated in the genesis of essential hypertension [5, 6].

Cortisol is also important for the maintenance of the renal blood flow and glomerular filtration rate (GFR) [6]. It was suggested that cortisol might influence the renal function directly by its effects on glomerular and tubular function [7]. Data showed that acute effects of exogenous cortisol increased the GFR in animals and humans, while long-term effects of excessive endogenous cortisol in humans may decreased GFR [7, 8]. Whether serum cortisol correlated to CKD remains unknown. For further understanding a possible pathogenesis of hypertensive nephropathy, it is important to clarify the association between endogenous cortisol and renal function in essential hypertension.

To investigate the association of serum cortisol levels with parameters of renal function such as serum creatinine and cystatin C levels, we conducted this cross-sectional study in patients with essential hypertension.

Patients and Methods

Patients

This cross-sectional study was conducted on subjects attending the Environment, Inflammation and Metabolic Diseases Study (EIMDS). The EIMDS aimed at evaluating the influence of environmental and inflammatory factors on metabolic diseases such as obesity, type 2 diabetes, hypertension and chronic kidney disease [9, 10]. Essential hypertension was defined as an average blood pressure $\geq 140/90$ mmHg on at least two different occasions, without any evidence of secondary hypertension. Of 322 subjects with essential hypertension responded to the study questionnaire, 79 participants were excluded due to diabetes, 17 participants were excluded due to CKD stage 4 or greater (defined as eGFRcr-cys $30 \text{ ml/min/1.73 m}^2$) because dialysis was conducted in most of them, and the data of 48 participants were unavailable for measuring serum cortisol or eGFR (Figure 1). A total of 178 hypertensive patients aged 35-80 years were recruited and blood samples were collected between 7:30-8:30 am. The recruited participants provided fasting blood samples and were free of malignant tumor, severe cardiovascular diseases, acute infection or endocrine diseases at baseline. The ethical Committee of the First Affiliated Hospital of Chongqing Medical University approved the study.

Clinical evaluation

The clinical information regarding medical history, smoking history was collected through physician interviews. All subjects underwent a physical ex-

Fig. 1. Flow Chart of Study Population. CKD stage 4 or greater was defined as eGFRcr-cys $< 30 \text{ ml/min/1.73 m}^2$.

amination including measurement of weight, height, waist circumference, blood pressure. Plasma glucose levels were measured with a hexokinase glucose-6phosphate dehydrogenase method by a biochemical analyzer (BS-380; Mindray Medical International, Shenzhen, China). Serum lipids including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were measured enzymatically on an automatic analyzer (Model 7080; Hitachi, Tokyo, Japan) with reagents purchased from Leadman Biochemistry Co. Ltd. (Beijing, China). Cortisol was determined with an electro-chemiluminescence method [Beckman Coulter's Dxl 800 Immunoassay System, Beckman Coulter, Inc. 250 S. Kraemer Blvd. Brea, CA 92821 U.S.A.]. Serum creatinine and cystatin C were measured with the use of an automatic biochemical analyzer (Modular DDP, Roche). Renal function was measured as eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation developed by the CKD-EPI Investigators in 2012 (eGFRcr-cys) [11]. Subjects whose eGFRcr-cys < 90 ml/min/1.73 m² was defined as low eGFR, and subjects whose eGFRcr-cys ≥ 90 ml/min/1.73 m² was defined as normal eGFR. CKD stage 1 was defined as eGFRcr-cys ≥ 90 ml/min/1.73 m², CKD stage 2 was defined as 60 ml/min/1.73 m² ≤ eGFRcr-cys < 90 ml/min/1.73 m², CKD stage 3 was defined as 30 ml/min/1.73 m² ≤ eGFRcr-cys < 60 ml/min/1.73 m² [11].

Statistical analysis

Analyses were performed using SPSS software, version 13.0, with two-tailed $p < 0.05$ indicating statistical significance. One-sample Kolmogorov-Smirnov tests were performed to test whether distributions of variables were normal. Variables distributed normally were presented as mean ± SD, while variables with skewed distribution (age, TC, TG, 2hPG and hs-CRP) were presented as medians (interquartile range) and analyzed by Mann-Whitney U test. The number of male and female who were in low eGFR or normal eGFR were reported as frequencies and further analyzed by Chi-square test. The antihypertensive medications were only reported as the total number of patients. To test the correlations between individual variables, variables which were normally distributed were analyzed by Pearson's correlation analysis, and variables with skewed distribution, namely age, TC, TG, 2hPG and hs-CRP, were analyzed by Spearman's correlation analysis. To identify the independent determinants of renal function parameters (eGFRcr-cys, cystatin C, creatinine), the clinical parameters were put into the multiple stepwise linear regression models. The criteria for including variables were: 1) significant at $P < 0.05$ level in Pearson's or Spearman's correlations (age, SBP, TC, uric acid and cortisol were included); 2) clinical confounders that might significantly influence the serum cortisol level (gender, BMI and anti-hypertensive drugs were included). In the multiple linear regression analyses, dependent variables included eGFRcr-cys, serum levels of cystatin C, serum levels of creatinine, respectively, and independent variables were age, gender, anti-hypertensive drugs BMI, SBP, TC, uric acid, cortisol. One dependent variable and all independent variables were included in a multiple linear regression analysis and stepwise regression analysis was not nested. The age and TC data were log-transformed for multiple linear regression analyses because of their skewed distributions. Serum cortisol concentration was analyzed as both a continuous and a categorical variable (in tertiles) in separate analyses. The distributions of serum cortisol were split by the tertiles and subjects were stratified into those with low, median and high levels accordingly. An analysis of variance (ANOVA) was performed to investigate the parameters of renal function according to different serum cortisol tertiles.

Results

Characteristics of study participants

The demographic, clinical and biological characteristics of the study population are summarized in Table 1. All 118 men and 60 women were diagnosed with essential hypertension. The antihypertensive medications included angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), β -Blockers, diuretic and others (e.g., the traditional Chinese medicines), and the number of participants who used ACEI, ARB, CCB, β -Blockers, diuretic and others were 19, 35, 113, 13, 34, 40, respectively. Serum cortisol concentration was 372.6 ± 98.5 nmol/L. The median eGFRcr-cys was 85 ml/min/1.73 m². Serum cortisol level was significantly higher in subjects whose eG-

FRcr-cys<90 ml/min/1.73 m² than subjects whose eGFRcr-cys>90 ml/min/1.73 m² (394.0±93.4 vs. 343.2±98.4 nmol/L, P=0.001) (Table 1). Serum cortisol levels according to CKD stage 1-3 were 343.2±98.4 nmol/L, 390.7±95.3 nmol/L, 403.0±66.7 nmol/L, respectively.

Relationship between serum cortisol and eGFRcr-cys, cystatin C, creatinine

We estimated the relationship between eGFRcr-cys, serum cystatin C or creatinine concentration and clinical parameters. Age, systolic blood pressure, and serum total cholesterol, uric acid levels were significantly associated with eGFRcr-cys, serum creatinine and cystatin C level. Serum cortisol level was significantly associated with eGFRcr-cys (r=-0.23, P=0.012), cystatin C (r=0.24, P=0.002) and creatinine (r=0.15, P=0.045) (Table 2 and Figure 1).

A stepwise regression analysis was then conducted to identify the relationship between clinical parameters and eGFRcr-cys, cystatin C, creatinine. After adjusting for clinical factors, serum cortisol level had a statistically significant negative association with the eGFRcr-cys (β =-0.19, P=0.027), and positive associations with cystatin C (β =0.31, P=0.001) and creatinine (β =0.14, P=0.044) (Table 3).

Table 1. Demographic and clinical characteristics in patients with essential hypertension

	Total (N=178)	Low eGFR	Normal eGFR	P Value
Male/Female	118/60	68/36	50/24	0.412
Age (years)	62(53,71)	68(62,72)	54(47,63)	<0.001
Weight (kg)	63.7±11.0	62.7±10.8	66.1±11.3	0.052
BMI (kg/m ²)	24.3±3.2	24.2±3.1	24.7±3.3	0.329
WC (cm)	82.7±9.0	82.8±8.3	83.2±10.3	0.755
HC(cm)	94.3±9.8	94.8±6.4	93.6±14.0	0.462
SBP (mmHg)	128.3±20.7	132.3±18.0	121.5±22.7	0.001
DBP (mmHg)	81.3±11.7	82.5±9.5	79.5±14.6	0.112
TC (mmol/L)	4.4(3.9,4.9)	4.3(3.9,4.9)	4.4(4.1,5.1)	0.196
TG (mmol/L)	1.3(0.9,1.9)	1.2(0.8,1.6)	1.4(0.9,2.0)	0.027
HDL-c (mmol/L)	1.1±0.3	1.1±0.3	1.1±0.3	0.255
LDL-c (mmol/L)	2.9±0.6	2.9±0.7	2.9±0.6	0.410
FPG (mmol/L)	4.4±0.6	4.3±0.6	4.4±0.6	0.855
2hPG (mmol/L)	5.1(4.4,6.2)	5.20(4.4,6.5)	5.0(4.3,6.4)	0.241
hs-CRP (mg/l)	0.8(0.4,1.2)	0.8(0.4,1.2)	0.8(0.4,1.2)	0.968
Uric Acid (μmol/L)	319.0±76.2	329.5±68.6	304.0±79.5	0.028
Cystatin C (mg/L)	0.9±0.1	0.9±0.1	0.8±0.1	<0.001
Creatinine (μmol/L)	83.0±15.3	89.0±13.0	71.8±9.8	<0.001
eGFRcr-cys (ml/min/1.73 m ²)	86.1±14.3	77.1±8.6	100.7±8.1	<0.001
Fasting Insulin (μIU/mL)	5.3±4.6	5.6±5.8	4.9±2.1	0.356
Cortisol (nmol/L)	372.6±98.5	394.0±93.4	343.2±98.4	0.001

Data are mean ± SD. BMI: body mass index, WC: waist circumference, HC: hip circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, TG: triglyceride, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, FPG: fasting plasma glucose, 2hPG: 2 hours plasma glucose in oral glucose tolerance test, hsCRP: high sensitivity C reactive protein. eGFRcr-cys calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation 2012. Low eGFR defined as eGFRcr-cys<90 ml/min/1.73 m² (N=104), Normal eGFR defined as eGFRcr-cys≥90 ml/min/1.73 m² (N=74).

Table 2. Correlation between eGFRcr-cys, cystatin C, creatinine and cortisol or other clinical parameters

	eGFRcr-cys		Cystatin C		Creatinine	
	R	P Value	R	P Value	R	P Value
Age	-0.52	<0.001	0.32	0.001	0.17	0.028
BMI	0.10	0.196	-0.02	0.800	-0.06	0.423
WC	0.09	0.237	0.04	0.604	0.04	0.644
HC	-0.08	0.331	0.09	0.270	0.09	0.223
SBP	-0.25	0.010	0.17	0.029	0.21	0.011
DBP	-0.07	0.403	0.11	0.165	0.17	0.028
TC	-0.19	0.021	0.18	0.023	0.20	0.017
TG	0.10	0.103	-0.04	0.656	-0.08	0.329
HDL-c	0.12	0.101	0.23	0.005	0.11	0.115
LDL-c	-0.05	0.563	0.10	0.191	0.16	0.041
FPG	-0.05	0.520	0.07	0.386	0.03	0.702
2hPG	-0.11	0.173	0.07	0.368	0.11	0.159
hs-CRP	0.02	0.967	0.08	0.313	-0.07	0.389
Uric acid	-0.34	<0.001	0.31	<0.001	0.42	<0.001
Insulin	-0.02	0.826	0.02	0.845	0.04	0.658
Cortisol	-0.23	0.012	0.24	0.002	0.15	0.045

BMI: body mass index, WC: waist circumference, HC: hip circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, TG: triglyceride, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, FPG: fasting plasma glucose, 2hPG: 2 hours plasma glucose in oral glucose tolerance test, hsCRP: high sensitivity C reactive protein. Variables which were normally distributed were analyzed by Pearson's correlation analysis. Variables with skewed distribution, namely age, TC, TG, 2hPG and hs-CRP were analyzed by Spearman's correlation analysis.

Table 4 showed the parameters of renal function according to different serum cortisol tertiles. With the increment of cortisol tertile, the eGFRcr-cys significantly decreased (93.18 ± 14.36 vs. 84.61 ± 14.67 vs. 81.29 ± 12.36 ml/min/1.73 m² for low, median and high tertile, respectively, $P=0.001$).

Discussion

This cross-sectional study is the first to demonstrate the association of serum cortisol and eGFRcr-cys in subjects with essential hypertension (Figure 2). These findings remained the same after adjusted for potential clinical confounders. Cortisol may be involving in CKD in patients with essential hypertension.

Our results were consistent with several previous studies. Cortisol excess is known to be associated with hypertension in conditions such as Cushing's syndrome [6-8]. A matched case-control study was performed on 18 patients with Cushing's disease and 18 healthy population controls. The results showed that patients

Table 3. Multiple regression analyses of relationship between clinical parameters and eGFRcr-cys, cystatin C, creatinine

	eGFRcr-cys		Cystatin C		Creatinine	
	β	P Value	β	P Value	β	P Value
Age	-0.62	<0.001	0.42	0.001	0.15	0.014
Gender, male	0.09	0.103	-0.03	0.467	0.01	0.352
Anti-hypertensive drugs						
ACEI/ARB	0.37	0.003	-0.43	0.011	-0.22	0.019
CCB	0.04	0.336	-0.02	0.421	-0.01	0.558
Others	0.11	0.075	-0.10	0.093	-0.06	0.214
BMI	0.07	0.496	-0.11	0.112	-0.04	0.318
SBP	-0.31	0.005	0.27	0.012	0.24	0.009
TC	-0.14	0.046	0.19	0.033	0.18	0.027
Uric acid	-0.42	<0.001	0.39	<0.001	0.45	<0.001
Cortisol	-0.19	0.027	0.31	0.001	0.14	0.044

BMI: body mass index, SBP: systolic blood pressure, TC: total cholesterol. Anti-hypertensive drugs included angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and other anti-hypertensive drugs included β -Blockers, diuretic and traditional Chinese medicines. Dependent variables included eGFRcr-cys, serum levels of cystatin C, serum levels of creatinine, respectively, and independent variables were age, gender, anti-hypertensive drugs BMI, SBP, TC, uric acid, cortisol.

Table 4. The parameters of renal function in patients with essential hypertension according to different serum cortisol tertiles

	Low (n=59)	Median(n=59)	High(n=60)	P value
Cystatin C (mg/L)	0.81 ± 0.1	0.84 ± 0.12	0.88 ± 0.12	0.002
Creatinine (μ mol/L)	79.81 ± 14.7	82.84 ± 14.94	85.82 ± 13.59	0.091
eGFRcr-cys (ml/min/1.73 m ²)	93.18 ± 14.36	84.61 ± 14.67	81.29 ± 12.36	0.001

Cortisol tertile: The range for low, median, high tertile were 166.8- 335.2, 335.3-414.0, 414.1-666.8 nmol/l, respectively.

Fig. 2. Correlation between serum cortisol and eGFRcr-cys.

with Cushing's disease had lower GFR, which measured by 24-h creatinine clearance [8]. On the other hand, cortisol might perform a direct effect on cystatin C and creatinine [12, 13]. Some clinical data suggested that glucocorticoid administration leads to increased cystatin C levels in patients with chronic and acute disease [13-15]. Both plasma creatinine concentration and urinary creatinine excretion were increased in patients receiving glucocorticoid [16, 17]. Furthermore, evidence indicated that patients with resistant hypertension had a relatively high prevalence of subclinical hypercortisolism, and its presence is associated with 1.74-fold risk of CKD [18]. Even though catabolic effect of cortisol could not be excluded, the relationship between serum cortisol and eGFRcr-cys in subjects with essential hypertension suggested that cortisol might be involving in CKD.

We revealed that serum cortisol level had a statistically significant negative association with the eGFRcr-cys ($\beta = -0.24$), and positive associations with cystatin C ($\beta = 0.26$) and creatinine ($\beta = 0.19$). The relationship between cortisol and parameters of renal function have not been explored in previous studies, thus its mechanism reminded unknown. It was shown that aldosterone and cortisol are positively associated with blood pressure in patients with early end-stage CKD [19]. Cortisol may promote hypertension by acting on mineralcorticoid receptor (MR) in endothelial cells and kidney. These pathogenesis might be involved in kidney diseases in chronic hypercortisolemic states [7, 20]. A functional defect in the ability to convert cortisol to cortisone existed in patients with essential hypertension and chronic kidney diseases (CKD), which would result in the activation of mineralocorticoid receptor [21]. MR antagonists not only improve the prognosis for patients with cardiovascular diseases, but also been used in patients with CKD due to its potential effects on reducing proteinuria and kidney damage [22-25].

Some explanations were needed to be clarified for our main findings. Firstly, it has been confirmed that acute effects of cortisol increases the GFR in animals and humans [16, 26], while long-term effects of cortisol excess could be totally different [7, 8]. Secondly, as serum creatinine or cystatin C levels was influenced by many factors such as muscular atrophy and obesity, using equation that combined creatinine-cystatin C to calculate eGFR was more accurate than singly use creatinine or cystatin C [11]. Thirdly, as a cross-sectional study, we could not prove the causality between elevated serum cortisol and development of CKD.

The main strengths of this study was the use of the combined creatinine-cystatin C equation to calculate eGFR, and we ruled out the influence of diabetes on the results. Definitely, this cross-sectional study has several limitations that needed to be noted. One of the major limitations was that a cross-sectional study could not be good enough for studying whether cortisol plays a role in the decline of renal function, and further prospective studies were needed to demonstrate this issue. Another important limitation was that we did not collect the urinary samples, and albuminuria or proteinuria could not be interpreted. Furthermore, measurements of adrenocorticotrophic hormone (ACTH) and cortisol circadian rhythm were not performed and our study could not comprehensively reflect the function of HPA axis. Cortisol and cortisone are excreted in the urine as tetrahydrocortisol and tetrahydrocortisone, and these metabolites might be crucial for further illustration of our results.

Conclusion

This study indicates that higher levels of serum cortisol is associated with decreased eGFRcr-cys in patients with essential hypertension. Further high-quality studies are needed to investigate whether cortisol plays a role in hypertensive nephropathy development.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the reported research.

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