Adrenal functional reserve in the full spectrum of chronic kidney disease

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Abstract

Background: Altered cortisol levels have been associated with an increase in mortality and a decrease in health-related quality of life in patients with chronic kidney disease (CKD); however, adrenal response to adrenocorticotrophic hormone (ACTH) stimulation test has not been evaluated in patients with stage 3a to 5 CKD with and without renal replacement therapy (RRT).

Objective: To evaluate adrenal function in patients with CKD. **Materials and methods:** Adults with CKD underwent a low-dose cosyntropin stimulation test (1 µg synthetic ACTH), with serum cortisol levels being measured at 0, +30 and +60 minutes post-test. **Results:** Sixty participants with stage 3, 4 and 5 CKD (with and without RRT) were included. None of the patients had adrenal insufficiency (AI). The correlation observed between cortisol concentration at baseline and 30 minutes and 1 hour after stimulation and glomerular filtration rate (GFR) was negative and statistically significant ($r: -0.39 [p = 0.002]$, $r: -0.363 [p = 0.004]$, $r: -0.4 [p = 0.002]$, respectively). **Conclusion:** Since CKD early stages, cortisol levels increase as GFR decreases. Therefore, we conclude that systematic screening for AI is not necessary in CKD patients.

KEY WORDS: Cortisol. Adrenal insufficiency Chronic kidney disease.

Reserva funcional adrenal en el espectro completo de la enfermedad renal crónica

Resumen

Antecedentes: Niveles alterados de cortisol se han asociado a un incremento en la mortalidad y disminución en la calidad de vida en pacientes con enfermedad renal crónica (ERC), sin embargo, la respuesta adrenal a la prueba de estimulación con adrenocorticotropina (ACTH) no ha sido evaluada en pacientes con ERC etapas 3a a 5 con y sin terapia de reemplazo renal (TRR). **Objetivo:** Evaluar la función adrenal de pacientes con ERC. **Materiales y métodos:** Adultos con ERC se sometieron a una prueba de estimulación con cosyntropina a dosis baja (1 µg de ACTH sintética) y se midieron los niveles séricos de cortisol a los 0, +30 y +60 minutos postestimulación. **Resultados:** 60 participantes con ERC en etapas 3, 4 y 5 (con y sin TRR) fueron incluidos. Ninguno de los pacientes presentó insuficiencia adrenal (IA). La correlación observada entre la concentración basal, a los 30 minutos y 1 hora de cortisol postestimulación y la tasa de filtrado glomerular (TFG) fue negativa y estadísticamente significativa ($r: -0.39 [p = 0.002]$, $r: -0.363 [p = 0.004]$, $r: -0.4 [p = 0.002]$, respectivamente). **Conclusión:** Desde etapas tempranas de la ERC los niveles de cortisol se incrementan a medida que la TFG disminuye. Concluimos que no es necesario un tamizaje sistemático para detectar IA en pacientes con ERC.

PALABRAS CLAVE: Cortisol. Insuficiencia adrenal. Enfermedad renal crónica.

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Introduction

Chronic kidney disease (CKD) is one of the most prevalent and devastating chronic health conditions due to an associated decrease in quality of life, and increased morbidity and mortality.^{1,2} CKD patients have been described to have alterations in the pituitary-adrenal axis³⁻⁵ that cause hormonal imbalances. In fact, aldosterone and cortisol levels imbalance has been associated with an increase in mortality and a decrease in health-related quality of life in patients with CKD.⁵⁻⁷

Symptoms and metabolic alterations present both in CKD and adrenal dysfunction may overlap. In addition, in the context of CKD and other comorbidities, adrenal insufficiency (AI) could be underdiagnosed, even by experienced physicians.

Previous studies have shown that patients with end-stage CKD have normal to high cortisol levels after a stimulation test with cosyntropin at doses ranging from 1 µg (low dose) to 250 µg (standard dose). However, these studies focused on patients undergoing renal replacement therapy (RRT), included small samples and the cosyntropin doses that were used varied in each study.⁸⁻¹⁴ In addition, adrenal functional reserve has not been studied in patients with stage 3a to 5 CKD with and without RRT.

For this reason, we decided to assess adrenal function in patients covering the full spectrum of CKD using a low-dose cosyntropin stimulation test.

Materials and methods

Participants

Adults with a previous diagnosis of stage 3a to 5 CKD according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria were consecutively recruited.¹⁵ Depending on glomerular filtration rate (GFR), estimated using the CKD-EPI equation,¹⁶ participants were divided into four groups: a) stage 3, b) stage 4, c) stage 5 without RRT, and d) stage 5 with RRT.

Patients with a history of acute infectious disease within the previous six months, oncological or thyroid disease, as well as patients taking medications that alter the pituitary-adrenal axis, were excluded. The study protocol was approved by the Research Ethics Committee of Autonomous University of Nuevo León

“Dr. José E. González” Hospital, and informed consent was obtained from all participants.

Study protocol

After obtaining a thorough medical history and confirming a fasting period of at least eight hours, 1 µg of synthetic adrenocorticotropin (ACTH) (Cortrosyn®, Amphastar Pharmaceuticals Inc., Rancho Cucamonga, CA, USA) was administered as a bolus, and blood samples were obtained at 0, 30 and 60 minutes post-test in order to measure serum cortisol levels.

Adrenal insufficiency (AI) was defined as a cortisol peak lower than 496 nmol/L at 30 or 60 minutes post-stimulation.

Measurements

Cortisol concentration was measured by electro-chemiluminescence using the Cobas® e-411 analyzer with the corresponding Roche commercial kit (Roche, SA de CV). Intra-test and inter-test coefficient of variation was 1.23 and 1.57%, respectively. All blood samples were centrifuged and stored at -20 °C for subsequent simultaneous analysis.

Statistical analysis

The sample size was calculated taking into account a difference of 8.6 µg/dL between cortisol mean peaks of patients with CKD on RRT and patients with CKD without RRT.¹² To achieve a statistical power of 80%, at least 12 patients from each CKD category were estimated to be required. Central tendency and dispersion measures were used for numerical variables, and frequencies and percentages for categorical variables. Parametric and non-parametric numerical variables between-group comparisons were obtained using ANOVA and Kruskal-Wallis test, respectively. Post hoc analyses were conducted using Bonferroni's correction. Pearson's chi-square test was used for categorical variables. Pearson's correlation coefficient was used to evaluate the correlation between GFR and serum cortisol concentration. A Pearson coefficient > 0.5 was established as evidence of a moderately strong linear correlation. A p-value < 0.05 was considered statistically significant. The analysis was performed using IBM SPSS Statistics v25 software (IBM 2019).

Table 1. Baseline characteristics of patients with CKD at different stages

	Stage 3	Stage 4	Stage 5 without RRT	Stage 5 with RRT	p-value
Age	58 (9.6)	55.2 (8.2)	52.4 (8.7)	51.8 (15)	0.36
Female gender	9 (60)	5 (33.3)	6 (40)	7 (46.7)	0.5
Creatinine	1.6 (.42)	3 (.57)	6.2 (2.3)	7.3 (3.3)	< 0.001
GFR	39 (7.8)	21 (4.2)	9.8 (3.9)	8 (3.3)	< 0.001
Months with CKD	12 (6-36)	12 (8-24)	12 (7-24)	24 (12-72)	0.37
Weight	75 (15)	79.4 (21.5)	76 (15)	71.2 (21.6)	0.6
BMI	30 (6.1)	29.5 (5.9)	29.2 (6.9)	26.8 (6.5)	0.53
Systolic blood pressure	144 (12.6)	136 (23)	133.8 (25.3)	148.4 (20.3)	0.2
Diastolic blood pressure	77.5 (10.3)	73.6 (1)	75.7 (14.9)	82.2 (15.7)	0.3
Hypertension	15 (100)	14 (93.3)	15 (100)	15 (100)	0.3
Diabetes mellitus	11 (73.3)	11 (73.3)	13 (86.7)	14 (93.3)	0.3
Dyslipidemia	11 (73.3)	4 (26.7)	3 (20)	5 (33.3)	0.01
Acute myocardial infarction	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)	1
Cerebrovascular event	4 (26.7)	2 (13.3)	1 (6.7)	0	0.12
Heart failure	4 (26.7)	2 (13.3)	1 (6.7)	1 (6.7)	0.32
Antihypertensive drugs	15 (100)	14 (93.3)	15 (100)	15 (100)	0.38
Glucose-lowering drugs	3 (20)	1 (6.7)	1 (6.7)	1 (6.7)	0.52
Insulin	8 (53.3)	9 (60)	10 (66.7)	8 (53.3)	0.86
Aspirin	3 (20)	3 (20)	2 (13.3)	1 (6.7)	0.69
Statins	12 (80)	10 (66.7)	8 (53.3)	2 (13.3)	0.002
Fibrates	1 (6.7)	2 (13.3)	0	1 (6.7)	0.54
Diuretics	9 (60)	12 (80)	10 (66.7)	5 (33.3)	0.06
Hemoglobin	11.6 (1.5)	11.1 (1.7)	9.8 (1.3)	9.8 (2.53)	0.014
White blood cell count	8.3 (2.5)	7.4 (1.7)	7.3 (1.3)	7.8 (2.8)	0.63
Neutrophils	5.1 (2.5)	4.3 (1.2)	4.7 (1.1)	5.5 (2.3)	0.36
Lymphocytes	2.2 (.5)	2.2 (.8)	1.6 (.6)	1.4 (.6)	0.001
Platelets	240.80 (64.79)	235.86 (57.68)	218.53 (56.72)	194.6 (99.7)	0.29
Blood urea nitrogen	25.20 (14.71)	40.13 (15.09)	64.16 (22.66)	38.51 (16.69)	<0.001
Glucose	107 (93-138)	116 (90-131)	111 (101-127)	136 (107-159)	0.25
Sodium	138.4 (3.1)	137.3 (4.4)	137.3 (4)	135.3 (5.5)	0.27
Chlorine	104.6 (4.9)	106.6 (3.6)	106.2 (5.9)	97.6 (5.7)	< 0.001
Potassium	4.5 (.6)	4.7 (.7)	4.8 (.7)	4 (.6)	0.007
Calcium	8.7 (.4)	8.6 (.7)	8.2 (.5)	8.7 (1.3)	0.34

Measurements expressed as frequencies (%), mean (standard deviation) or median (interquartile range).

CKD: chronic kidney disease; RRT: renal replacement therapy; GFR: glomerular filtration rate.

Table 2. Cortisol values (nmol/L) before and after administration of 1 µg of Cortrosyn®

	Stage 3	Stage 4	Stage 5 without RRT	Stage 5 with RRT	p-value
Baseline cortisol	418.2 (121.8)	469 (124)	594.2 (301.1)	590.6 (228)	0.05
Cortisol at 30 minutes	825.6 (165.3)	828.4 (98)	957.1 (305)	971 (201.8)	0.09
Cortisol at 1 hour	895.6 (157.1)	931.5 (164.4)	1083 (342.6)	1112.1 (221.5)	0.03
Peak	915.3 (164.8)	943.2 (146.7)	1083 (342.6)	1112.1 (221.5)	0.05
Cortisol delta	497 (160.3)	474.2 (140.5)	488.7 (163.7)	521.4 (116.4)	0.84

Values expressed as the mean (standard deviation).

RRT: renal replacement therapy.

Table 3. Cortisol values (nmol/L) before and after administration of 1 µg of Cortrosyn® in 3 groups

	Stage 3 (n = 15)	Stage 4 (n = 15)	Stage 5 with and without RRT (n = 30)	p-value
Baseline cortisol	418.2 (121.8)	469 (124)	592.4 (262.4)	0.021
Cortisol at 30 minutes	825.6 (165.3)	828.4 (98)	964.1 (254.2)	0.042
Cortisol at 1 hour	895.6 (157.1)	931.5 (164.4)	1097.5 (283.8)	0.012
Peak	915.3 (164.8)	943.2 (146.7)	1097.5 (283.8)	0.022
Cortisol delta	497 (160.3)	474.2 (140.5)	505.1 (140.6)	0.79

Values expressed as the mean (standard deviation).

RRT: renal replacement therapy.

Results

A total of 60 patients with CKD were included (15 in each group). Baseline characteristics are shown in table 1.

Prevalence of adrenal insufficiency and serum cortisol comparison

None of the included patients showed AI (Table 2). However, a significant difference was found in plasma cortisol concentration at 60 minutes post-stimulation between all four groups ($p = 0.03$). A trend towards an increase in baseline cortisol levels was observed across all different CKD categories. When stage 5 patients (with and without RRT) were analyzed as a single group, we observed a statistically significant difference in cortisol peaks ($p = 0.02$), and in baseline concentration ($p = 0.02$), and at 30 ($p = 0.042$) and 60 minutes ($p = 0.012$) between the three groups (Table 3). The correlation observed between cortisol baseline concentration, at 30 minutes and 1 hour post-stimulation and GFR was negative and statistically significant (r : -0.39 [$p = 0.002$], r : -0.363 [$p = 0.004$], r : -0.4 [$p = 0.002$], respectively).

Table 4 shows baseline and post-stimulation cortisol levels according to blood urea nitrogen serum levels.

Discussion

Previous literature had focused on the relationship between cortisol levels and GFR rather than with the incidence of AI in patients with CKD.⁸⁻¹⁴ In our study, no participant met the criteria for AI in response to the stimulation test with low-dose cosyntropin (1 µg).¹⁷ However, we found significant differences between the different CKD groups (stages 3, 4 and 5 with and without RRT) in baseline cortisol levels and at 30 and 60 minutes post-stimulation.

The prevalence of AI in patients on RRT who had hypotension was 26% in studies where salivary cortisol was measured.¹⁸⁻²⁰ In our study, the absence of AI might be explained by the lack of patients with hypotension and by serum cortisol measurement. For this reason, it would be valuable to evaluate the concordance between serum and salivary cortisol levels in patients with CKD in order to validate the use of this method as a screening test for AI.²¹

Cortisol levels are expected to increase in stressful situations such as CKD,²² which could be explained by

Table 4. Cortisol values (nmol/L) before and after administration of 1 µg of Cortrosyn® in groups divided according to blood urea nitrogen level*

	< 60	> 60	p-value
Baseline cortisol	479.8 (167.4)	688.3 (321.7)	0.01
Cortisol at 30 minutes	876.1 (180.2)	1022.4 (299.4)	0.84
Cortisol at 1 hour	971.6 (198.5)	1156.7 (371.4)	0.04
Peak	981.2 (193.3)	1156.7 (371.4)	0.033
Cortisol delta	501.4 (138)	468.3 (171.5)	0.46

Values expressed as the mean (standard deviation).

a decrease in renal clearance and by 11-beta-hydroxysteroid dehydrogenase type 2 inactivity.²³ However, studies in which patients with CKD and healthy controls were included did not find statistically significant differences between salivary cortisol levels.^{9,14,18} Our results show that, since CKD early stages, cortisol concentration increased as GFR decreased, which had not been previously reported. These findings suggest a protective effect against AI at CKD terminal stages.⁸⁻¹⁴

The strengths of our study include the use of a superior sample of patients belonging to CKD full spectrum with few demographic and biochemical differences between all four groups, none of which has been previously associated with adrenal gland dysfunction.²⁴ As a limitation, most our patients had diabetes and were relatively young (50-55 years).

Conclusions

Our results suggest that adrenal function evaluation is not necessary in patients with CKD. A negative correlation was observed between serum cortisol levels and GFR; however, further studies are required in order for the clinical significance of this association to be clarified.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures that were followed adhered to the ethical standards of the responsible committee for experimentation on human beings and were in agreement with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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