ORIGINAL ARTICLE

Dynamics of salivary cortisol in chronic kidney disease patients at stages 1 through 4

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Summary

Context End-stage renal disease has been associated with derangement of the HPA function. The dynamics of this axis in early stages of renal disease (CKD) has not been assessed.

Objectives To evaluate in patients with CKD at stages 1–4 (KDOQI): the diurnal variation of salivary cortisol; the suppressibility of cortisol in saliva and serum after an overnight oral 1 mg dexamethasone suppression test (1 mg DST) with simultaneous measurement of circulating dexamethasone.

Design and Methods 80 CKD outpatients and 40 healthy subjects were included. All CKD collected whole saliva at 08·00 and 23·00 h (SAF_{23}) on two nonconsecutive days. Thereafter at 08·00 h, following 1 mg DST, saliva and blood were obtained. Salivary and serum cortisol as well as CBG were assessed by RIA, dexamethasone by ELISA and serum free cortisol was calculated.

Results SAF_{23} correlated negatively with glomerular filtration rate (GFR). The fraction of free cortisol in serum and saliva after 1 mg DST, correlated positively and significantly in both patients with CKD and healthy subjects (r: 0·86 and r: 0·85, respectively; $P < 0·0001$ for both). Ten percent of CKD with GFR < 90 ml/min/1·73 m^2 had false positive results unrelated to dexamethasone and CBG concentrations.

Conclusions False positive responses to 1 mg DST were associated with GFR < 90 ml/min/1·73 m^2. This could not be ascribed to either defects in dexamethasone absorption or CBG concentrations. Higher dexamethasone doses were necessary to achieve adequate HPA suppression. Salivary cortisol was useful to assess circadian cortisol levels and feed-back regulation in CKD.

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Introduction

End stage renal disease (ESRD) has been associated with derangement of the HPA function. Authors have reported elevated morning circulating cortisol levels, high late – night salivary cortisol levels due to an increase in ACTH secretion and lack of cortisol suppression after low-dose dexamethasone administration in these patients.[1–4] The lack of suppression following low-dose dexamethasone administration has been ascribed to changes in plasma binding proteins, dexamethasone bioavailability and/or clearance.[1–3] By contrast, Workman *et al.*[5] denies differences in dexamethasone metabolism in CKD. To our knowledge, the functional disturbances described in ESRD, have not been investigated in patients with earlier stages 1–4 of renal disease (CKD).[6]

Salivary cortisol reflects the free fraction of circulating cortisol and is therefore a useful noninvasive tool to investigate the status of the HPA axis. Several labs, including ours, have found that in patients with ESRD, as well as in healthy subjects, measurements of morning and late night salivary cortisol correlated well with total serum cortisol levels.[4,7] Measurements of salivary and serum cortisol after dexamethasone suppression also correlated significantly in healthy subjects and patients at risk of Cushing′s syndrome.[8–11]

Late-night salivary cortisol and the 1 mg overnight oral dexamethasone suppression test (1 mg DST) are established first-line tests for the diagnosis of endogenous hypercortisolism.[12]

An understanding of the HPA axis, and its variations, in patients with impaired renal function is critical for the management of these patients. Without this understanding, cortisol excess cannot be reliably rule out. The 1 mg DST in saliva was recently studied in a population at risk for Cushing's syndrome with glomerular filtration rate (GFR) > 60 ml/min/1·73 m^2.[11] Thus studied, this noninvasive method of screening and diagnosis of hypercortisolism is a practical way to assess ambulatory

patients in a clinical setting. However, DST in saliva has not been studied in patients with CKD.

The aims of the present study in patients with CKD are the following: (i) to assess the diurnal variation of salivary cortisol and its suppressibility after 1 mg DST; (ii) to study the correlation of salivary cortisol after 1 mg DST and the calculated free fraction of serum cortisol; (iii) to determine the concentration of circulating dexamethasone after its oral administration to ascertain an adequate absorption; (iv) to investigate the possible association of the progression of renal failure and changes in the dynamics of salivary cortisol.

This information will help clinicians to rule out Cushing's syndrome in patients with predialysis CKD, in whom the usual diagnostic criteria, standardized for the normal population, may be misleading.

Subjects and Methods

Study participants

A total of 80 outpatients were randomly selected from the Endocrinology and Nephrology Departments of the University of Buenos Aires and evaluated from January 2012 to August 2014. They were grouped according their GFR and staged in accordance with KDOQI criteria to group 1–4 KDOQI.[6] A summary of clinical data including the aetiologies of CKD are described in Table 1. Those patients with diabetes had adequate metabolic control ($HBA_{1c} \leq 7{\cdot}0\%$).[6] Hypertensive patients were on one or more of the following drugs: enalapril, amlodipine and/or losartan. All patients had normal albumin levels (albumin: $5{\cdot}5 \pm 0{\cdot}4$ μM). Exclusion criteria included: major depression (patients with BDI-II score was of 19 or greater[13]; intake of anticonvulsants, major tranquilizers, glucocorticoids, adrenostatic (i.e. ketoconazole or aminoglutetimide) or adrenolytic (i.e. mitotane) drugs, alcohol or social drug abuse. The control group (C) included 40 healthy volunteers (20 women and 20 men; aged $50{\cdot}0 \pm 10{\cdot}0$ years old, range 18·0–65·0). They all had GFR > 90·0 ml/min/1·73 m^2 and no endocrine disease.

Study design

Saliva collection. Saliva samples were obtained after confirming the integrity of salivary gland function as previously described.[14] Whole saliva was collected by directly spitting in sterile polypropylene tubes. Subjects were instructed not to brush their teeth but rather to rinse their mouths with tap water 2 h before saliva collection. Samples were obtained at 08·00 h in fasting conditions (SAF_8) and at 23·00 h (SAF_{23}), at least 2-h after the last meal. Exercise, tobacco, social drugs and alcohol consumption were not allowed before sampling. Once obtained, saliva samples were frozen until delivery to the laboratory.

The CKD patients obtained basal samples of saliva on two nonconsecutive days (48-h interval) to assess the reproducibility of SAF_8 and SAF_{23}.

Low-dose dexamethasone suppression test (1 mg DST). At 23·00 h, 1 mg of dexamethasone was taken orally. The following day (at 08·00 h), samples of whole saliva and serum were obtained to measure cortisol levels (SAF_{dex} and F_{dex}, respectively) as well as CBG. After centrifugation (1000 ***g*** for 10 min), the supernatants were stored at −20 °C for further steroid analysis.

Longer low-dose dexamethasone suppression test (2 mg DST). Serum and saliva samples for measuring cortisol levels were obtained after subjects took 0·5 mg of oral dexamethasone every 6 h for a 48 h period. The criteria used to define a normal cortisol level after 2 mg DST (Endocrine Research Laboratory) were as follow: total serum cortisol ($F_{dex2\ mg}$) ≤ 40·0 nM and morning salivary cortisol ($SAF_{dex2\ mg}$) ≤ 1·5 nM as described.[11]

Assays

Salivary cortisol. SAF was measured in saliva samples by RIA (coat-a-count kit, Siemens Healthcare Diagnostics Inc, Los Angeles, CA, USA) as previously described.[15] SAF was expressed as nM, and the analytical sensitivity was 0·5 nM as reported by us.[11] In our data, the intraassay coefficients of variation (CVs) were 5·7% at 1·0 nM (low-pool) and 4·3% at 20·0 nM (high pool). The interassay CVs were for a low-pool (*n*: 20) 12·7% and for the high-pool (*n*: 20) 11·0%.

Serum cortisol. This parameter was determined by RIA using a coat-a-count kit (Siemens Healthcare Diagnostics Inc) as described by the manufacturer. In our data, the minimal detectable concentration was 6·0 nM. The intraassay coefficient of variation was 4·8% at 25·0 nM (low pool) and 4·6% at 100·0 nM (medium pool). The interassay CVs were 5·2% and 5·8%, respectively.

Serum Corticosteroid binding globulin. CBG was determined by RIA (DIAsource, CBG-RIA-CT kit, Belgium) as described by the manufacturer. GBG was expressed in units of μM. In our laboratory the minimal detectable dose was 0·006 μM. The intraassay CV was 7·0% at 0·52 μM (low control) and 6·0% at 2·4 μM (high control). The interassay CV was 8·0% at low control and 7·0% at high control.

Calculated serum free cortisol. Two simultaneous binding equilibria determine the binding of cortisol in human serum. These are: (i) the saturable binding of cortisol to CBG and (ii) the nonsaturable binding to albumin. Free cortisol after DST (U) was calculated as described by Coolens *et al.* [16] using the equation: $U^2K\ (1 + N) + U(1 + N + K(G–T)\text{-}T: 0$. In this equation U, T and G correspond, respectively, to the μM concentrations of unbound cortisol, total cortisol and CBG; K (3×10^{-7} M^{-1}) correspond to the affinity of CBG for cortisol at 37 °C and N (1·74) the ratio of albumin-bound to unbound cortisol. Free cortisol (U) was calculated as U: $\sqrt{Z^2 + 0.0122T} - Z$, wherein *Z*: 0·0167 + 0·182 (G–T).

Serum dexamethasone. we used a competitive enzyme linking immunoabsorbent assay (corticosteroid ELISA, Europroxima, The Netherlands) using 50 μl of serum samples and following

Table 1. Summary of the study population classified according to clinical stages of chronic kidney disease

CKD stages	1	2	3	4
Patients (*n*)	20·0	20·0	20·0	20·0
Age (years)	44·0 ± 15·0 (18·0–64·0)	48·0 ± 17·0 (20·0–65·0)	49·0 ± 13·0 (24·0–65·0)	51·0 ± 21·0 (25·0–65·0)
Female/male (ratio)	15·0/5·0	16·0/4·0	13·0/7·0	15·0/5·0
BMI (kg/m^2)	29·4 ± 5·0 (19·0–40·0)	28·9 ± 5·7 (20·0–39·0)	27·0 ± 4·7 (22·0–38·0)	22·0 ± 2·0[a] (18·0–25·0)
GFR (ml/min/1·73 m$^{2)}$	102·0 ± 13·0 (90·0 ± 134·0)	75·0 ± 9·0[b] (60·0–88·0)	46·0 ± 10·0[b] (30·0–59·0)	24·4 ± 4·6[b] (15·0–29·0)
Aetiologies and associated comorbidities				
DM2			4	5
DM2 + Ob	2	4	2	
DM2 + HT + Ob	3	2	1	
UTI + Ob	2	1	1	
HT + Ob	5	2	1	
HT	2	5	7	7
HT + overweight	3			
HT + K_s		2		
K_s	2	1	1	1
K_s + Ob	1			
Nephrectomy		1		
Unknown				1
Renal polycystosis			1	2
Renal hypoplasia				1
Pyelonephritis		2	2	2
Uremic hemolytic syndrome				1

CKD, chronic kidney disease; BMI, body mass index; GFR, glomerular filtration rate; DM2, type 2 diabetes mellitus; Ob, obesity; HT, hypertension; UTI, recurrent urinary tract infection; Ks, kidney stones. Data are expressed as means ± SD (range).
[a,b]Denotes significances compared with S_1 at $P < 0{\cdot}0001$.

the instructions described by the manufacturer Dexamethasone was expressed as nM and the minimal detectable dose was 0·15 nM. The intraassay CV_S were 9·0% at 0·63 nM (low level) and 7·0% at 5·0 nM (high level). The interassay CV_s were 13·0% at low control 12·0% at high control.

Laboratory parameters. Albumin and creatinine levels were measured by standard procedures in clinical chemistry laboratories along with the regular patients' monitoring. GFR was estimated by the clearance according to the formula of Cockcroft and Gault adjusted to 1·73 m^2 of body surface area, using the latest serum creatinine levels for each subject.[17]

Statistical analysis

Data are expressed as the mean ± SD unless otherwise specified. The intraclass coefficient of correlation (ICC) was estimated by a random-effect ANOVA model, ideally close to 1·0. Differences between samples were determined by the Mann–Whitney test and the Friedman test. The Spearman rank order test was used to estimate correlations between cortisol concentrations in different fluids and other parameters. A regression analysis was used to describe the relationship between salivary cortisol and free serum cortisol. The coefficient of determination (R^2) is a measure of how well this model fits (with a range of 0–1).

Statistical analysis were performed using the Statistical Package for Social Sciences (SPSS 11·5, SPSS Inc., Chicago, IL, USA). A $P < 0{\cdot}05$ was considered statistically significant.

Ethics approval

The study was approved by the local ethical committee of the Instituto de Investigaciones Médicas Alfredo Lanari (University of Buenos Aires) and all participants provided their written consent.

Results

Morning and late-night salivary cortisol in CKD: ratio and reproducibility

Table 2 shows morning and late-night salivary cortisol levels in CKD patients and healthy subjects. The ratio SAF8/SAF23 was significantly lower at stages 3 and 4 in comparison to controls and patients at stage 1 and 2, due to an increase in late-night salivary cortisol levels. Table S2 shows the reproducibility (≥0·91) of SAF_8 and SAF_{23} obtained from two nonconsecutive salivary samples in CKD at stages 1–4. The within-subject variation was equal to or less than 9·0%.

Correlation of salivary cortisol with anthropometric data and renal function

SAF_8 and SAF_{23} concentrations did not correlate with either age or BMI. Focusing on patient's stage of renal compromise, SAF_{23} levels correlated negatively and significantly with glomerular filtration rate (r:−0·343; $P \leq 0{\cdot}0001$), while SAF_8 did not.

Table 2. Morning and latenight salivary cortisol in CKD patients and healthy subjects

Groups	Chronic Kidney disease stages				Healthy subjects
	1	2	3	4	
n	20·0	20·0	20·0	20·0	40·0
SAF_8 (nM) (mean ± SD) (range)	10·0 ± 4·7 (4·5–18·0)	9·9 ± 5·0 (4·0–18·0)	9·9 ± 4·0 (4·0–18·0)	9·5 ± 3·2 (5·0–18·0)	11·2 ± 3·9 (5·0–18·0)
SAF_{23} (nM) (mean ± SD) (range)	1·5 ± 0·8 (0·5–3·0)	1·7 ± 1·0 (0·5–3·8)	2·2 ± 0·9[a,b] (0·5–3·8)	2·4 ± 1·0[a,b] (0·5–3·8)	1·8 ± 0·8 (0·5–3·8)
SAF_8/SAF_{23}	8·5 ± 5·5 (2·0–30·0)	8·4 ± 6·0 (2·4–26·0)	5·6 ± 3·9[a,b] (2·0–21·0)	5·2 ± 3·9[a,b] (1·6–18·0)	6·7 ± 2·9 (3·4–15·0)

CKD, chronic kidney disease; SAF_8, salivary cortisol obtained at 8·00 h; SAF_{23}, salivary cortisol obtained at 23·00 h. Data were expressed as: mean ± SD and range.
[a]Denotes significances compared with healthy subjects at $P < 0·05$.
[b]Denotes significances compared with stage1 at $P < 0·05$.

Suppressibility of hypothalamic-pituitary-adrenal axis

Circulating corticosteroid binding globulin levels in females and males with chronic renal disease and healthy subjects. CBG concentrations were assessed after 1 mg DST in CKD and controls. Mean CBG levels were not different between sexes, CKD stages, or controls ($P > 0·256$ in all cases) as seen in Fig. 1. No correlation was found between the age of the patient and CBG levels.

Correlation between cortisol fractions. The fraction of free cortisol in serum (FF_{dex}) and saliva (SAF_{dex}) after 1 mg DST, correlated positively and significantly in both patients with CKD and healthy subjects (*r*:0·86 and *r*:0·85, respectively; $P < 0·0001$ for both). The regression equation (dependent *y*: $SAF_{dex;}$ independent *x*:FF_{dex}) was *y*:0·1422 + 0·9141*x*; coefficient of determination R^2:0·9109. Analysis of variance renders a *F*-ratio: 1206·0315 with a significance level $P < 0·0001$.

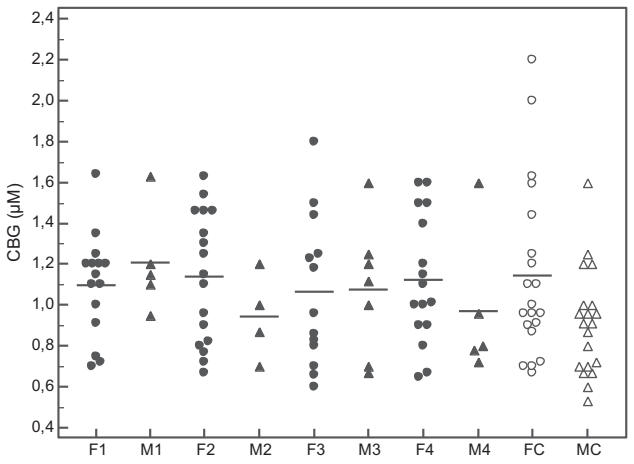

Fig. 1 Circulating corticosteroid binding globulin levels in females (F) and males (M) with chronic kidney disease at stages 1 through 4 (CKD) and in healthy subjects (C). Heathy ● CKD females; ▲ CKD males; ○ healthy females; △ healthy males. Numeral subindexes denote CKD clinical stages 1–4. Horizontal lines shows mean CBG levels.

Total circulating cortisol (F_{dex}) was also found to be positively and significantly correlated with SAF_{dex} and FF_{dex} in patients with CKD (0·70 and 0·76, $P < 0·0001$ respectively) and in healthy volunteers (*r*:0·60 and *r*:0·67, respectively; $P < 0·002$).

Dexamethasone serum concentrations. Following a 1 mg DST no significant variation was found in dexamethasone levels in CKD patients at any clinical stage (dexamethasone levels were: S_1:2·9 ± 1·2 nM; S_2:3·1 ± 1·4 nM; S_3:3·1 ± 1·2 nM and S_4:3·3 ± 1·3 nM; $P > 0·32$ in all cases). These concentrations were not different from those found in controls (3·3 ± 1·3, range: 1·53–6·40 nM; $P > 0·19$ in all cases).

Suppressors and nonsuppressors. As shown in Fig. 2(a–c) eight patients: two cases at CKD stage 2 (S_2), three cases at S_3 and three cases at S_4, had cortisol levels in serum and saliva that failed to normally suppress (DST_{neg}). The remaining CKD patients suppressed normally (DST_{pos}). The comparison of serum dexamethasone concentrations did not show differences between DST_{neg} (3·6 ± 1·4 nM), DST_{pos} (3·1 ± 1·3 nM) and healthy subjects (3·4 ± 1·3 nM), $P > 0·25$ in all cases (Fig. 3).

Primary and associated morbidities in CKD patients who did not suppress were: type 2 diabetes mellitus (3 cases) at stages S_2, S_3 and S_4; type 2 diabetes mellitus with obesity (*n*:3) at stages S_2 (*n*:2) and S_3 (*n*:1); hypertension (*n*:1 at stage S_4) and hypertension with obesity (*n*:1 at S_3). These comorbidities were similar to those found in CKD patients who suppressed normally. In addition, BMI and age were not different in DST_{neg} and DST_{pos} groups ($P > 0·33$).

To assess the feed-back mechanism using a higher dexamethasone dose, a 2 mg DST was performed in DST negative patients. They all suppressed; with cortisol levels in saliva ($SAF_{dex2\text{-}mg}$:1·25 ± 0·30 nM) and serum ($F_{dex2\text{-}mg}$: 32·0 ± 9·8 nM) after reaching dexamethasone levels that were significantly higher (6·7 ± 2·1 nM) than had been reached with 1 mg dose (*P*:0·007). In summary, 8 of 80 CKD patients required a higher dexamethasone dose (2 mg) to rule out HPA hyperactivity.

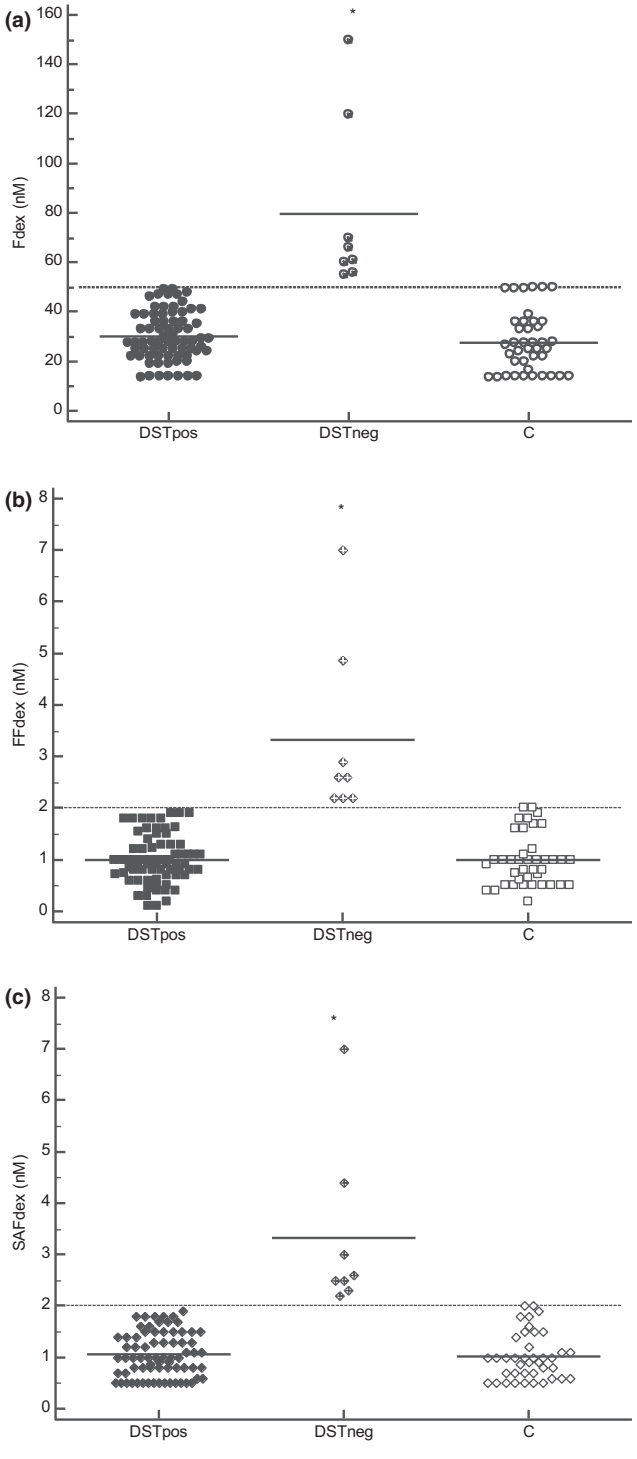

Fig. 2 Cortisol concentrations in serum (total (a) and free fraction (b) and saliva (c)) after the overnight oral 1 mg dexamethasone suppression test (DST) in CKD and healthy subjects. DST_{pos}:CKD suppressors; DST_{neg}:CKD non- suppressors; C:healthy subjects. Horizontal dotted line represents cut-off value for normal suppression. Horizontal lines show mean cortisol levels within each group. $^*P \leq 0{\cdot}05$ *vs* DST_{pos} and C.

Late-night salivary cortisol and morning salivary cortisol in suppressors and nonsuppressors. The concentrations of SAF_{23} in DST_{neg} ($2{\cdot}91 \pm 0{\cdot}91$ nM) were higher than in DST_{pos}($1{\cdot}80 \pm 0{\cdot}90$ nM) and controls ($1{\cdot}8 \pm 0{\cdot}8$ nM), $P < 0{\cdot}001$ for both. No statistical differences were observed between DST_{pos} and controls.

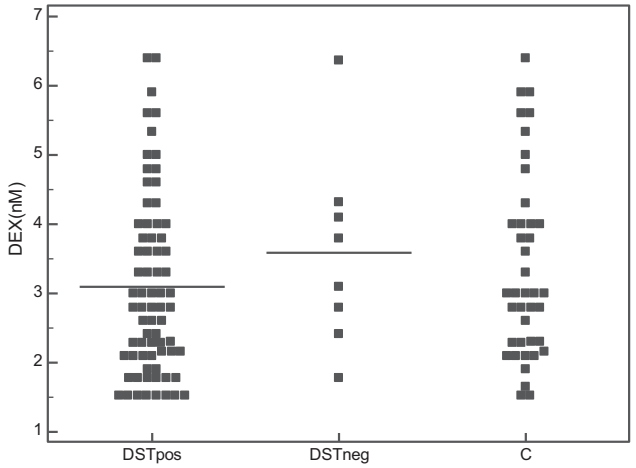

Fig. 3 Serum dexamethasone concentrations after the overnight oral 1 mg dexamethasone suppression test (DST) in CKD patients and healthy subjects. DST_{pos}:CKD suppressors; DST_{neg}:CKD nonsuppressors; C: healthy subjects. Horizontal lines show mean dexamethasone levels in each group.

SAF_8 were not different between DST_{neg}, DST_{pos} and control groups ($9{\cdot}4 \pm 3{\cdot}9$ nM, $9{\cdot}6 \pm 4{\cdot}2$ nM and $11{\cdot}2 \pm 3{\cdot}9$ nM, respectively).

Discussion

This is the first study to investigate the role of renal function on salivary cortisol dynamics in ambulatory patients with chronic kidney disease at stages 1–4. Late- night salivary cortisol showed a negative correlation with GFR leading to a reduction in the morning to late night salivary cortisol ratio at stages 3 and 4. After 1 mg overnight oral DST, the free cortisol fraction in serum and saliva and the total circulating cortisol levels correlated positively which each other in all subjects. Ten percent of patients with CKD whose GFR was <90·0 ml/min/1·73 m^2 failed to normally suppress cortisol levels in saliva and serum. However, their circulating dexamethasone and CBG concentrations did not differ significantly from suppressors. We found the appropriate screening test, suppression with a 2 day low-dose DST, unmasked the false positive nonsuppressors with 1 mg DST. The presence of associated comorbidities such as type II diabetes, generalized obesity and hypertension could not differentiate suppressors from non suppressors.

Collecting salivary cortisol, a noninvasive, stress-free method of testing allowed the CKD patients to take samples at home. Each patient was individually instructed by a laboratory technician so as to properly collect saliva reducing intra-individual variations. The good reproducibility of SAF_8 and SAF_{23} was similar to that obtained in healthy subjects, and in patients at risk of Cushing's syndrome with GFRs > 60·0 ml/min/1·73 m^2.[11]

Cortisol dynamics in patients with renal insufficiency remains debatable and most data are based on the study of patients with end stage renal disease on dialysis. At present we are not aware of reports on the diurnal variation of salivary cortisol at earlier stages of CKD. There was a reduction of SAF_8/SAF_{23} ratio in patients at stages 3 and 4 of CKD, however the relevant finding was the mean increase in SAF_{23} levels. These values remained within the 97·5% CI of healthy subjects. This finding agrees with Chiodini *et al.*[18] and Liu *et al.*[19] who found an increase in the values of cortisol at nadir in patients with type 2 diabetes. These cortisol values increased with the presence and severity of complications, as well as with increasing age.[20] Unfortunately, the authors did not show data on renal function leaving unclear the role of GFR on cortisol dynamics. Consistent with our data, total loss of renal function in ESRD was associated, with disruption of the HPA axis.[1–4,21,22] These findings highlight the importance of assessing renal function when cortisol excess is suspected using late-night salivary cortisol as a noninvasive testing strategy. Additionally the latter was markedly elevated in patients with overt Cushing′s syndrome at stage 3 of CKD (unpublished data).

Corticosteroid binding globulin (CBG) is the specific high affinity plasma transport glycoprotein for cortisol. Early reports revealed that CBG levels in healthy subjects did not vary with ageing, between genders or after 1 mg DST. CBG exquisitely regulates cortisol availability and delivery. In previously reports CBG has been found to be normal or reduced in patients with renal disease.[16,23] As CBG and albumin levels remained within the normal range in our study population, the Coolens equation was used to estimate the unbound fraction of circulating cortisol after 1 mg DST.

The value of measuring the free fraction of cortisol in either serum or saliva was clearly demonstrated by the close correlation of these values in our healthy subjects as well as those with CKD. As the CBG concentrations were similar between the healthy population and the 10·0% of CKD patients that did not suppress their cortisol post 1 mg DST, a central derangement of HPA axis in the latter is suggested.

To rule out false positive results, an adequately interpret the results of the 1 mg DST, dexamethasone concentration (DEX) must be assessed.[20] Circulating dexamethasone measurements may identify subjects with low plasma DEX due to defective absorption by the gut or excessive metabolism, resulting in levels inadequate to test for suppression. Both circumstances have been reported in patients with chronic renal failure.[1,2,22,24–26] In our study dexamethasone levels were similar in suppressors and nonsuppressors and thus are not responsible for the 10·0% of CKD patients with false positive results. All nonsuppressors suppressed adequately after the 2 mg DST, suggesting the need for a higher dose of dexamethasone for a longer period as observed by Workman *et al.*[5] in end stage renal disease. Our data suggest that a subpopulation of CKD patients has a disordered feedback control of the HPA axis as reported in ESRD.[3] Other authors observed *in vitro* a diminished affinity of cytoplasmatic GC receptors to dexamethasone in ESRD.[27] It is also possible that the requirements for a higher dose of dexamethasone to adequately suppress cortisol reflected a greater stimulatory ("stress") input to the hypothalamus in some CKD patients.[28] So, a combination of increased central activation[4] and the decreased GR affinity[27] may have resulted in the need for a higher dose of dexamethasone to adequately suppress cortisol secretion". It would be interesting to ascertain if a single 2 mg overnight oral dexamethasone dose can rule out false positive 1 mg DST results in a larger population of patients with renal disease. This approach is in progress in our laboratory.

The limitations of this study are: (1) calculated circulating free cortisol by Coolens equation: (a) a constant value is used for the affinity of CBG for cortisol and abnormal forms of CBG which can be detected immunologically render a markedly underestimated cortisol, (b) only the interaction of cortisol with CBG is taken into consideration, (c) the presence of a significant amount of other steroids may interfere with the CBG cortisol equilibrium; (2) the diagnosis of depression was ruled out in the study population but we could not determine the level of chronic stress that each patient sustained; (3) subjective factors such as adaptation to disease and treatment, satisfaction with the medical staff and, social support, were not evaluated in this study; (4) the mean cortisone/cortisol concentration ratio described as progressively decreased in patients with chronic renal failure [29,30] was not evaluated.

In conclusion, cortisol dynamics were preserved in chronic kidney disease at stage 1. Changes in the regulation of the HPA axis were found in starting in stage 2 (GFR < 90·0 ml/min/1·73 m^2). In view of this, renal function should be considered by physicians when nonsuppression to 1 mg DST is observed. Salivary cortisol is a useful tool to assess cortisol nadir and feed-back regulation in CKD.

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Disclosure

The authors have nothing to disclose.

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