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# Uraemia and adrenocortical function in Nigerian subjects

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**Summary**

In assessing the pituitary–adrenal axis of uraemic Nigerians, we investigated the circadian rhythm of plasma cortisol secretion, the response to the overnight dexamethasone (1 mg) suppression test and the pattern of excretion of urinary free cortisol (UFC) in 10 uraemic subjects and nine non-uraemic controls. Basal (0800 h) plasma cortisol levels were similar in both uraemic (mean ± s.e.m.; 224 ± 36 nmol/l) and non-uraemic (218 ± 47 nmol/l) subjects. The non-uraemic subjects demonstrated the normal late night (2300 h) reduction in cortisol levels but this was absent in uraemic subjects in whom the basal and late night values were similar. Post-dexamethasone (0800 h) values were suppressed by 80% in non-uraemic subjects ($P < 0.01$) from 218 ± 47 nmol/l (at 2300 h) to 44 ± 16 nmol/l (at 0800 h), whereas there was lack of suppression ($P > 0.05$) in values from uraemic subjects (224 ± 36 nmol/l at 2300 h and 210 ± 39 nmol/l at 0800 h). Irrespective of the degree of renal impairment in uraemic subjects, the 24 h UFC excretion was significantly greater ($P < 0.05$) (1126 ± 403 nmol/24 h) compared with non-uraemic subjects (342 ± 94 nmol/24 h). These results confirm previous observations in Caucasians and reaffirm the existence of a pseudo-Cushingoid state in uraemia which may contribute to the associated hypertension and electrolyte abnormalities.

**Résumé**

En analysant l'axe adrénalo–surrénal chez des Nigérians souffrant d'urémie, nous avons étudié le rythme circadien de la secrétion en cortisone dans le plasma, la réponse au test de suppression brutale de déxaméthasone (1 mg) et le type d'excrétion de cortisone urinaire libre chez 10 sujets urémiques et neuf sujets témoins non urémiques. Les niveaux de base (0800 h) en cortisone dans le plasma étaient semblables à la fois chez les sujets urémiques (224 ± (s.e.m.) 36 nmol/l) et chez les sujets non urémiques (218 ± 47 nmol/l). On a observé chez les sujets non urémiques la réduction normale de minuit (2300 h) dans les niveaux de cortisone, mais cette réduction n'a pas eu lieu chez les sujets urémiques pour qui les niveaux de base (0800 h) et de minuit (2300 h) étaient semblables. Les valeurs après déxaméthasone (0800 h) ont diminué de 80% chez les sujets non urémiques ($P < 0.01$) passant de 218 ± 47 nmol/l (à 2300 h) à 44 ± 16 nmol/l (à 0800 h), alors qu'il n'y a pas eu de diminution ($P > 0.05$) dans les valeurs chez les sujets urémiques (224 ± 36 nmol/l à 2300 h et 210 ± 39 nmol/l à 0800 h). Indépendamment du degré d'affaiblissement de la fonction rénale chez les sujets urémiques, l'excrétion sur 24 h de cortisone urinaire libre était significativement plus élevée ($P < 0.05$) (1126 ± 403 nmol/24 h) comparée avec celle des sujets non urémiques (342 ± 94 nmol/24 h). Ces résultats confirment des observations antérieures faites sur des Caucasiens et permettent de ré-affirmer l'existence dans l'urémie d'un état ressemblant à la maladie de Cushing, qui peut contribuer à une hypertension associée et à des anomalies électrolytiques.

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## Introduction

Uraemic patients demonstrate abnormalities in the secretion and metabolism of several hor-

mones including insulin [1], erythropoietin [2], testosterone [3], parathyroid hormone [4], growth hormone [5] and cortisol [6], amongst others. Erythropoietin deficiency is associated with anaemia [7] and excessive parathyroid hormone secretion contributes to renal osteodystrophy. No overt clinical effects attributable to disturbed cortisol homeostasis in uraemia have been described. McDonald *et al.* [6] suggested that uraemic patients on maintenance haemodialysis exhibited biochemical features of a Cushingoid state but this has been questioned [8]. Chronic haemodialysis may contribute independently to this putative Cushingoid state [6,9].

Chronic renal disease is a major cause of morbidity and mortality in tropical African countries accounting for 2.7% of medical admissions [10], 11.4% of deaths on medical wards [11] and 7.5% of adult autopsies [12] in a Nigerian teaching hospital. The majority of these uraemic patients are still unable to benefit from the clear advantage of maintenance dialysis or replacement therapy, principally for economic reasons [13]. The clinical features of the uraemic Nigerian African are not dissimilar to those in Caucasians [13,14] but first presentation in the majority of cases is in advanced renal failure or end-stage renal disease [14].

Whilst Adadevoh [15] has indicated that there is no difference in the adrenocortical activity of Africans compared with Caucasians, there has been no study, to our knowledge, to assess the basal and stress-induced adrenocortical activity in uraemic Africans.

We undertook the assessment of the pituitary adrenal axis in uraemic Nigerians to ascertain whether there are abnormalities in cortisol homeostasis and the effects these may have on metabolic interactions. Our results should offer further information on aspects of endocrine responses in the African in general and the uraemic African in particular.

## Subjects and methods

Ten male subjects (mean age ± s.e.m. 37.2 ± 2.9 years; body mass index (BMI) 21.1 ± 1.1 kg/m$^2$) were diagnosed uraemic on the basis of (1) creatinine clearance < 30 ml/min, (2) fixed urine specific gravity, (3) bilaterally shrunken granular kidneys on ultrasound, and (4) anaemia: PCV < 30%. Diagnosis had been established in all subjects within 3 weeks to 6 months of commencement of the study. Voluntary informed consent was obtained from all subjects.

The subjects were admitted into the medical wards of the University College Hospital, Ibadan between December 1987 and January 1988 and received intermittent isotonic peritoneal dialysis for symptomatic uraemia; diet (protein 20 g/day; $Na^+$ and $K^+$ 30 meq of each/day; calories 2500–3000 kcal/day) and other drugs (folic acid, vitamin C, aluminium hydroxide, calcium carbonate, magnesium sulphate) as required. Eight of the subjects required antihypertensive treatment with oral α-methyldopa and frusemide. The studies were conducted at least 72 h into the interdialytic period.

Nine other male subjects (mean age 33.1 ± 5.3; BMI 19.0 ± 0.8 kg/m$^2$) who were convalescing on the medical wards and matched the uraemic subjects in age and BMI were recruited as controls. Six had recovered from acute infective illnesses and the other three had recovered from chronic illnesses. None of these controls was obese; none had any evidence of renal, hepatic or cardiac disease or mental illness, nor were any on specific medication at the time of the study.

### *Methods*

Baseline fasting plasma parameters (albumin, total calcium, uric acid, creatinine, blood glucose) and haematocrit were carried out on all subjects.

Twenty-four-hour urine collections (for creatinine clearance and free cortisol excretion studies) were carried out on all subjects. On completion of a 24-h urine collection, the volume was measured and aliquots stored at −20°C until analysis.

Blood specimens were collected in the semi-recumbent subject with minimal venostasis at 0800 h and 2300 h into chilled heparinized tubes. After the latter sample, 1 mg dexamethasone was ingested orally, supervised by one of us (AOO). A further blood sample was then taken at 0800 h the following morning. All samples were immediately centrifuged (2000 *g* for 5 min) and the plasma stored at −20°C until analysis. Glucose, creatinine, albumin,

calcium, uric acid and haematocrit were estimated by standard laboratory techniques.

Plasma and urinary free cortisol levels were measured by radioimmunoassay using an Amerlex kit (Amersham plc, Aylesbury, U.K.). This method is highly specific for cortisol and gives an intra-assay coefficient of variation (CV) of 4.5% and an inter-assay CV of 7.6%. By this method, 15 healthy medical students (age range 22–29 years) had a mean 0800 h plasma cortisol value of 265 ± 29 nmol/l (range 209–352 nmol/l).

### *Statistics*

Results are expressed as mean ± s.e.m. Comparison between uraemic subjects and controls was by unpaired Student's *t*-test, while within-subject variation was assessed by paired *t*-tests. The level of statistical significance was $P < 0.05$.

## Results

The age and anthropometric measurements are shown in Table 1. Initial laboratory investigation results are indicated in Table 2. The two groups of subjects were matched reasonably well for age and BMI. All the subjects were males.

As expected, the uraemics had lower haematocrits ($P < 0.01$) and higher mean arterial, systolic and diastolic blood pressures ($P < 0.01$). The expected differences in plasma calcium phosphate, creatinine and creatinine clearance were also shown (Table 2). There was no difference in the albumin levels in the two groups. Table 3 shows the plasma and urinary free cortisol levels. Plasma cortisol levels at 0800 h, 2300 h and 0800 h post-dexamethasone intake are also shown on Fig. 1. While basal (0800 h) plasma cortisol values were similar in both groups, the values in uraemic subjects were not subject to the normal circadian rhythm or to suppression by dexamethasone. Indeed, cortisol levels in these subjects remained constant irrespective of time of day or dexamethasone intake.

The non-uraemic subjects, however, exhibited the expected circadian rhythm and overnight dexamethasone suppressibility, with the values in this group of subjects at 2300 h and 0800 h significantly lower ($P < 0.01$) than corresponding values in uraemics.

As indicated in Table 3, the 24-h UFC excretion was greater ($P < 0.01$) in uraemic subjects compared with the controls. This increased excretion persisted even when the 24-h UFC excretion was expressed in relation to the 24-h urinary volume which was reduced in some uraemics.

## Discussion

We have demonstrated some abnormalities in cortisol homeostasis in uraemic Nigerians. These include the loss of normal diurnal variation, a blunted response to the overnight dexamethasone suppression test and increased 24-h UFC excretion.

Our findings of normal basal cortisol levels agree with those of some previous workers [8,9]

**Table 1.** Clinical characteristics of subjects studied

| | Age (years) | BMI† (kg/m²) | Systolic BP (mmHg) | Diastolic BP (mmHg) | MAP‡ (mmHg) |
|---|---|---|---|---|---|
| Uraemic subjects ($n$ = 10) | 37.2 ± 2.9 | 21.1 ± 1.1 | 149.5 ± 8.7 | 95.5 ± 4.4 | 86 ± 5.8 |
| Non-uraemic subjects ($n$ = 9) | 33.1 ± 5.3 | 19.0 ± 0.8 | 119.4* ± 5.4 | 75.0* ± 2.6 | 69.4* ± 3.7 |

Values represent means ± s.e.m.
*$P < 0.01$ compared to values in uraemic subjects.
†BMI = body mass index (weight/height²).
‡MAP = mean arterial pressure (0.33 × pulse pressure + diastolic pressure).

**Table 2.** Laboratory data on subjects studied

| | Haematocrit (%) | Albumin (g/l) | $Ca^{2+}$ (mmol/l) | $PO_4$ (mmol/l) | Urea (mmol/l) | Creatinine (mmol/l) | Creatinine clearance (ml/min) |
|---|---|---|---|---|---|---|---|
| Uraemic subjects ($n$ = 10) | 26.1 ± 1.6 | 35.6 ± 5.6 | 1.9 ± 0.4 | 3.1 ± 0.4 | 74.2 ± 8.7 | 1582.4 ± 212 | 1.3 ± 0.4 |
| Non-uraemic subjects ($n$ = 9) | 34.3* ± 2.3 | 38.4 ± 7.2 | 2.7* ± 0.1 | 1.1* ± 0.1 | 6.4* ± 1.1 | 97.2* ± 17.7 | 124* ± 14.8 |

Values represent means ± s.e.m.
*$P < 0.01$ compared to values in uraemic subjects

**Table 3.** Cortisol levels in subjects studied

| | Plasma | | | Urine |
|---|---|---|---|---|
| | 0800 h (Pre-dex; nmol/l)† | 2300 h (nmol/l) | 0800 h (Post-dex; nmol/l)‡ | 24-h UFC (nmol/24 h)§ |
| Uraemic subjects ($n$ = 10) | 224 ± 36 | 204 ± 39 | 210 ± 39 | 1126 ± 403 |
| Non-uraemic subjects ($n$ = 9) | 218 ± 47 | 77* ± 30 | 44* ± 17 | 342* ± 94 |

Values represent means ± s.e.m.
*$P < 0.01$ compared to values in uraemic subjects.
†UFC = urinary free cortisol excretion.
‡Pre-dex = sample drawn before administration of 1 mg dexamethasone.
§Post-dex = sample drawn after administration of 1 mg dexamethasone.

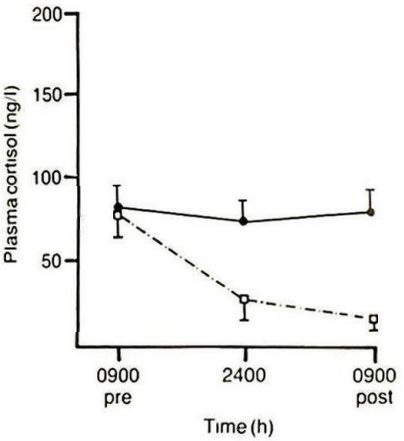


**Fig. 1.** Pre- and post-dexamethasone plasma cortisol levels in uraemic (●, $n$ = 10) and non-uraemic (□, $n$ = 9) subjects.

but contrast with those in whom the majority of patients studied were on long-term haemodialysis [6,16]. As our subjects were on intermittent peritoneal dialysis and not maintenance haemodialysis, possibly with more efficient clearance of 'middle molecules', the role of the latter in the pattern of our results and the uraemic syndrome remains controversial and awaits further clarification [6,9].

The loss of normal diurnal variation in cortisol secretion would appear to be consequent upon the deranged homeostatic profile of cortisol in uraemia. It has been postulated that hypothalamic reactivity to increasing cortisol levels is blunted in uraemics [16].

In Cushing's syndrome, the earliest recognizable change is an inability to suppress evening values of cortisol, resulting in the loss of the normal circadian rhythm [17]. This may even antedate dexamethasone suppressibility, and having demonstrated these abnormalities in our subjects, it is tempting to speculate that a pseudo-Cushingoid state exists in uraemia, possibly contributing to the electrolyte and blood pressure abnormalities seen characteristically. This may have important prognostic implications.

The 24-h UFC excretion correlates well with the physiologically active (free) plasma cortisol [18]. It is also less subject to fluctuation than urinary group steroid metabolites measured hitherto, which are more dependent on hepatic function [17]. The greater 24-h UFC excretion observed in the uraemics suggests increased cortisol levels, and the greater 24-h UFC excretion would support the possibility of increased cortisol secretion in uraemia, especially as the hepatic metabolism of cortisol in our subjects did not appear impaired.

In these preliminary observations we have not found any clinical evidence of obesity, depression, liver disease or heart failure in the subjects. It seems possible, however, that subclinical forms of these conditions may have

been present with variable effects on our results.

The possibility of poor gastrointestinal absorption of dexamethasone in uraemic patients has led Ramirez *et al.* [8] to postulate that the blunted suppression observed in uraemia is attributable to this. Pharmacokinetic studies will be required before definite inferences can be drawn in this respect in the Nigerian uraemic.

In conclusion, Nigerian uraemics demonstrate abnormal cortisol regulatory responses suggestive of a biochemical Cushingoid state similar to observations in Caucasians. This abnormality appears to be unrelated to the degree of renal impairment and possibly extracorporeal haemodialysis. It may thus be considered to be a component of the uraemic syndrome.

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