

## **DIURNAL PATTERN OF SERUM CORTISOL AND ADRENAL CORTISOL RESERVE IN PATIENTS WITH NEPHROTIC SYNDROME**

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### **Summary**

In 16 patients with nephrotic syndrome without renal insufficiency, not treated with corticoids and/or immunosuppression, the absence of a normal diurnal pattern of serum cortisol was found. Functional adrenal cortisol reserve, assessed as serum cortisol increment one hour after the administration of 0.25mg of 1-24 ACTH was impaired in patients with nephrotic syndrome, compared with healthy persons. We conclude that in patients with nephrotic syndrome continuous hypersecretion of cortisol may occur and probably accounts for the diminution of functional adrenal cortisol reserve.

### **Introduction**

Very little data is available regarding the adrenal glucocorticoid function in patients with nephrotic syndrome. Musa et al [1] showed reduced 17-hydroxycorticosteroids (17-OHCS) and corticosteroid binding globulin at 9.00am in the blood of six male nephrotic subjects and increased urinary corticosteroid binding globulin. However, owing to a marked diurnal variability, plasma 17-OHCS determinations are not meaningful when performed in an isolated fashion. The evaluation of the diurnal variation of plasma cortisol is increasingly used as a diagnostic measure of adrenal glucocorticoid function. To our knowledge, the results of such investigations of adrenal function in patients with nephrotic syndrome have not been published. This study assesses the diurnal pattern of serum cortisol and evaluates the adrenal cortisol reserve in patients with nephrotic syndrome.

### **Patients and methods**

Sixteen adult patients aged 24- 53 years with nephrotic syndrome were studied. All had idiopathic types of glomerulonephritis (mesangiocapillary 8, mesangial

proliferative 3, membranous 3, focal and segmental sclerosing lesions 1, minimal change 1) and were studied within six months from the apparent onset of the nephrotic syndrome, before the institution of glucocorticoid and/or immunosuppressive therapy. Their mean 24-hour urinary protein excretion was  $7.3 \pm 2.8$ g and mean serum albumin  $23.6 \pm 4.7$ g/L. None had renal insufficiency. All patients received a diet of 2g/kg/day protein of high biological quality and of 2g of sodium chloride. During at least one week preceding the examination, the patients were not given medications. Ten healthy volunteers of comparable age served as controls.

Blood samples for serum cortisol were taken from patients and healthy controls at 8.00am, 2.00pm, 4.00pm, 0.00am and 8.00am. Functional adrenal cortisol reserve taken as the increment in serum cortisol one hour after the administration of 0.25mg 1-24 ACTH (Synacthen, Ciba-Geigy) was assessed on the day after examination of the diurnal pattern of serum cortisol. Cortisol was determined by radioimmunoassay using Biodata (Italy) kits. Serum corticosteroid binding globulin was also determined in 10 patients and healthy controls by the radioimmunological method according to Berhutz et al [2] using a double antibody technique.

## Results

The mean values  $\pm$  SD of the diurnal pattern of serum cortisol obtained in nephrotic patients and healthy controls are presented in Table I.

TABLE I. Comparison of mean values  $\pm$  SD of the diurnal pattern of serum cortisol ( $\mu$ g/dl) in nephrotic patients and healthy controls

	8.00 am	2.00 pm	4.00 pm	0.00 am	8.00 am
Patients with nephrotic syndrome (n=16)	16.7 $\pm 5.6$	16.3 $\pm 7.8$	16.4 $\pm 10.6$	13.9 $\pm 10.3$	16.9 $\pm 6.5$
Healthy subjects (n=10)	14.8 $\pm 4.6$	9.2* $\pm 3.9$	7.1*† $\pm 3.1$	4.2*† $\pm 3.0$	13.7 $\pm 2.4$

\* Significantly ( $p < 0.05$ ) lower in comparison with 8.00am value (paired Student's 't' test)

† Significantly ( $p < 0.05$ ) lower in comparison with nephrotic patients (unpaired Student's 't' test)

Serum cortisol in nephrotic patients and in healthy controls measured at 8.00am did not differ significantly. No significant differences in the mean serum cortisol was found in subsequent blood samples from patients with nephrotic syndrome. These results contrast markedly with the diurnal pattern of serum cortisol in healthy controls which showed the usual afternoon decline

by half and midnight values  $<8\mu\text{g/dl}$ . There was a significant difference in the mean plasma cortisol between nephrotic subjects and healthy controls at 4.00pm and 0.00am.

The calculated mean 24-hour serum cortisol ( $16.0\pm 7.6\mu\text{g/dl}$ ) in the nephrotic group was slightly but significantly higher than that in healthy persons ( $9.8\pm 3.0\mu\text{g/dl}$ ). The mean serum corticosteroid binding globulin concentration in nephrotic patients was  $37.0\pm 12.6\text{mg/L}$  and did not differ from the mean value in controls ( $38.4\pm 6.2\text{mg/L}$ ).

The results of the evaluation of functional adrenal cortisol reserve in patients with nephrotic syndrome and healthy subjects are presented in Table II.

TABLE II. Comparison of mean serum cortisol  $\pm$  SD ( $\mu\text{g/dl}$ ) at 8.00am and one hour after the administration of 0.25mg of 1-24 ACTH as well as the mean increment of serum cortisol induced in patients with nephrotic syndrome and healthy subjects

	Mean serum cortisol		Mean serum cortisol increment after stimulation
	At 8.00am (before ACTH administration)	One hour after ACTH administration	
Patients with nephrotic syndrome (n=16)	16.9 $\pm$ 6.5	22.7 $\pm$ 6.9*	5.8 $\pm$ 4.0*
Healthy subjects (n=10)	13.7 $\pm$ 2.4	31.4 $\pm$ 5.1	17.7 $\pm$ 8.1

\* Significantly ( $p<0.05$ ) lower in comparison with healthy subjects (unpaired Student's 't' test)

The mean serum cortisol after ACTH administration, as well as the calculated mean serum cortisol increment after stimulation were markedly lower in patients with nephrotic syndrome than in healthy persons.

## Discussion

Mean morning serum cortisol values in our patients with the nephrotic syndrome were not different from those found in healthy subjects. This finding is at variance with the few results reported in the literature. Musa et al [1] described six patients with rather unusual types of nephrotic syndrome and plasma 17-OHCS below the normal mean concentrations. Low 17-OHCS was associated with diminished serum corticosteroid binding globulin concentrations in four of six patients. Increased urinary excretion of corticosteroid binding globulin was found in all of them. Other authors also generally found slightly decreased serum corticosteroid binding globulin in nephrotic syndrome. Doe et al [3] had, however, pointed out that hypoalbuminaemia was not consistently associated with a low corticosteroid binding globulin concentration. In our

group of nephrotic patients mean morning corticosteroid binding globulin was not significantly different from those found in healthy subjects and this fact may account for the normal mean cortisol concentration in the morning.

The demonstration that the expected normal decline of serum cortisol in the afternoon and at bed-time in patients with nephrotic syndrome does not occur and furthermore the mean 24-hour serum cortisol in these patients remains higher than in healthy controls, suggest a hypersecretion of the hormone. In principle hypersecretion of cortisol could result from either increased circulating ACTH or from direct continuous stimulation of adrenals by other factors with subsequent suppression of pituitary ACTH release. The lack of concomitant determinations of serum ACTH in our patients does not allow differentiation of these two possibilities. Reduced functional adrenal cortisol reserve demonstrated in our patients, is also of little help in this respect. The diminished response of serum cortisol to ACTH administration seems to be a consequence of continuous adrenal hyperactivity independent of the nature of the potential stimulating factor.

When looking for a potential direct stimulator of cortisol release in patients with nephrotic syndrome angiotensin may be taken into consideration since enhanced renin activity in some nephrotic individuals has been reported [4]. Direct stimulatory effect of angiotensin on cortisol production and secretion has been suggested in several earlier studies. Kaplan and Bartter [5] incubating 'in vitro' adrenals with angiotensin have found a consistent stimulation of cortisol production when aldosterone production was stimulated. Several investigators using hypophysectomized-nephrectomized animals have noted increased glucocorticoid production when angiotensin was infused. Cade et al [6] demonstrated abnormal diurnal variation of plasma cortisol in a group of patients with renovascular hypertension, a process known to cause the release of increased amounts of renin. More detailed studies demonstrated, however, that in humans no positive corticosteroid response to angiotensin infusion 'in vivo' is seen besides a change in aldosterone and its immediate precursor [7]. This fact, together with observations indicating that elevated renin and angiotensin II are not a consistent finding in nephrotic syndrome [4], seem to reduce the potential role of angiotensin as a direct cortisol secretion stimulating factor. It should be pointed out, however, that recent papers stress the role of angiotensin as the stimulator of the secretion of vasopressin and ACTH [8]. Taken together, these observations indicate that if high renin values are present in some nephrotic subjects, angiotensin may interact with the pituitary-adrenal axis to influence the secretion of cortisol.

This mechanism could not be operative in patients with nephrotic syndrome and normal or low renin values. The demonstration of increased catecholamine excretion in the nephrotic syndrome by Oliver et al [9] suggests adrenergic stimulation, possibly associated with stressor stimuli acting in nephrotic patients. It may be suspected that long-lasting stressor stimuli, may also act through afferent neurons or directly on the hypothalamus to cause a discharge of corticotropin releasing factor, liberation of ACTH from the pituitary gland and excessive release of corticosteroids from the adrenal cortex. Further studies are needed

to identify the factor or factors responsible for the abnormal serum cortisol profile in nephrotic patients.

Independently of the pathophysiological mechanism involved in adrenal stimulation in at least some patients with nephrotic syndrome, it seems reasonable to assume that increased secretion of cortisol may occur and account for some metabolic features found. Hypersecretion of glucocorticoids may participate in the mechanisms of sodium and water retention and extracellular volume expansion. Cortisol seems to play a role in the maintenance of normal glomerular filtration rate and renal blood flow and more direct effects of its action on tubular transport processes and permeability have also been suggested [10].

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