Increased Serum Cortisol Levels are Associated with High Tumour Grade in Patients with Renal Cell Carcinoma

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Cortisol and dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the major steroid hormones produced by the human adrenal cortex. The serum levels of cortisol and DHEAS were analysed in 211 consecutive patients with renal cell carcinoma before initiation of therapy. Serum cortisol was significantly higher in patients with renal cell carcinoma compared with that in patients with benign cysts ($p < 0.0001$). Serum cortisol was independent of disease stage, but positively correlated to tumour diameter and grade. The serum levels of DHEAS were higher in men than in women, and decreased with age, but did not correlate with disease stage, tumour diameter or grade. The prognosis of patients with elevated serum cortisol tended to be poorer ($p = 0.06$) than the prognosis of those with lower levels. In a multivariate analysis, disease stage and tumour grade were independent predictors of prognosis. Age, gender and serum levels of cortisol and DHEAS were of limited value for prognosis.

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Cortisol is secreted in response to physical and psychological stress, and the serum level is characterized by circadian rhythm and feed-back inhibition. Cortisol is potentially cytotoxic to lymphoma and leukaemia cells (1), and can suppress the production of cytokines that mediate the inflammatory reaction (2). Animal experiments (3) have shown that corticosteroids could stimulate tumour growth, and it was recently shown that dexamethasone administration significantly increased pulmonary metastasis in an experimental rat mammary tumour model (4).

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the major steroid hormones produced in human adrenal cortex. The relative androgenic activity of DHEA/S (DHEA + DHEAS) *per se* is minimal, but they act as precursors of both testosterone and oestradiol. There is a wide variation in the normal serum levels of DHEA/S, and men have slightly higher levels than women (5). The highest levels of DHEA/S are observed during young adulthood, but they steadily decline with age (6). This continuous decrease of DHEA/S with age has been associated with increased risk of cardiovascular and malignant diseases. Conflicting results concerning a possible relation between low serum DHEAS and increased risk of developing cardiovascular morbidity have been presented (7, 8). Concerning the role of DHEA/S in breast cancer, some studies suggest an association (9–11), while Zeleniuch-Jacquotte et al. (12) presented data that did not support this association. In urologic tumours, an association with low DHEA/S levels was found (13, 14), while prediagnostic levels were increased in patients with ovarian carcinoma (15). In an animal model, DHEA demonstrated an inhibitory effect on chemical carcinogenesis in the mammary gland (16), and Schulz et al. (17), demonstrated growth inhibition in human adenocarcinoma cell lines after exposure to DHEA.

Our hypothesis was that both low levels of DHEAS and high levels of cortisol may influence the clinical course in patients with renal cell carcinoma.

MATERIAL AND METHODS

Sera were collected from 211 consecutive patients (130 males and 81 females) with histologically verified renal cell carcinoma. Median patient age was 66 years (range, 25–86). The patients were admitted to the Urology Department, University Hospital, Umeå, from, 1982 to 1995. Preoperative examination included chest radiography, ul-

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Table 1

Serum cortisol and DHEAS levels in relation to gender and age in patients with renal cell carcinoma

Gender	No.	Cortisol (nmol/L)		p-value	DHEAS (μmol/L)		p-value
		Median	Range		Median	Range	
Male	130	574	<27–1 400	*	2.4	<0.81–9.9	**
Female	81	529	29–1 810		1.4	<0.81–8.7	
Total	211	562	<27–1 810		2.0	<0.81–9.9	
Age (years)							
≤66	109	539	<27–1 810	N.S.	2.7	<0.81–9.9	**
>66	102	580	29.4–1 200		1.5	<0.81–5.6	

Mann–Whitney test.
N.S. not significant ($p > 0.05$); * $p = 0.05$; ** $p < 0.0001$.

trasound and computerized tomography of the abdomen, and in the case of symptoms, also bone scans. The patients were staged according to Robson et al. (18), while tumour grading was according to Skinner et al. (19). Tumour size was measured as the maximum diameter on the surgical specimen or by computerized tomography. In all, 193 patients were operated with radical, and 4 with partial nephrectomy; 14 patients received palliative therapy, mostly with medroxyprogesterone acetate, arterial occlusion or interferon. Sera from 18 patients with benign renal cysts were used as clinical controls.

Serum samples were collected before initiation of any therapy between 8 and 11 a.m., and stored at −80°C until analysis at the Department of Clinical Chemistry. Hormone levels were analysed using the chemiluminescent enzyme immunoassays Immulite® Cortisol and Immulite® DHEA-SO_4, from the Diagnostic Products Corporation (Los Angeles, CA). The detection limits were 27 nmol/L, and 0.81 μmol/L for cortisol and DHEAS, respectively.

The patients were followed-up at regular intervals according to clinical routine with clinical and radiological examinations. After a median follow-up time of 102 (range, 40–176) months, 155 patients are now dead; 118 patients died of renal cell carcinoma and 37 of unrelated causes, 56 were alive at follow-up. The cause of death was based on medical records and death certificates.

Statistical analysis was performed using the Mann–Whitney U-test. Survival was calculated from admission according to the Kaplan–Meier method, and comparison of survival time was performed using the log-rank test. The level of significance for rejecting the null hypothesis of zero effect was $p = 0.05$.

RESULTS

Median serum levels of cortisol and DHEAS in patients with renal cell carcinoma were 562 (range <27–1810) nmol/L, and 2.0 (range, <0.81–9.9) μmol/L, respectively, as shown in Table 1. Nineteen patients (14 males and 5 females) had serum cortisol levels >800 nmol/L, while only 3 had undetectable serum cortisol levels (<27 nmol/L). Forty-one (19%) patients had serum DHEAS levels below the detection limit (<0.81 μmol/L). Serum cortisol levels were significantly higher in male compared to female patients, but independent of age (Table 1). As expected, DHEAS levels were higher in men compared to women, and in younger compared to elderly patients.

The relation of cortisol and DHEAS to disease stage and controls is presented in Table 2. Cortisol levels were significantly higher in cancer patients compared with those with benign cysts ($p < 0.0001$), but unaffected by disease stage. Serum DHEAS levels in patients with renal cell

Table 2

Serum cortisol and DHEAS levels in relation to disease stage in patients with renal cell carcinoma and control patients

States	No.	Cortisol (nmol/L)		p-value	DHEAS (μmol/L)		p-value
		Median	Range		Median	Range	
I	79	536	32–1 200	N.S.	2.2	<0.81–8.7	N.S.
II	9	653	416–771		1.4	<0.81–3.4	
II	48	522	29–1 400	N.S.	2.1	<0.81–7.9	N.S.
IV	75	595	<27–1 800		1.8	<0.81–9.9	
Total	211	562	<27–1 810	*	2.0	<0.81–9.9	N.S.
Cysts	18	386	104–539		2.6	<0.81–8.5	

Mann–Whitney test.
N.S. not significant ($p > 0.05$); * $p < 0.0001$.

Table 3

Serum cortisol and DHEAS levels in relation to tumor grade in patients with renal cell carcinoma

Grade	No.	Cortisol (nmol/L)		p-value	DHEAS (μmol/L)		p-value
		Median	Range		Median	Range	
1	5	463	410–612	*	1.6	<0.81–4.6	N.S.
2	42	531	<27–1 200		2.2	<0.81–8.7	
3	108	541	<27–1 810	*	2.1	<0.81–9.9	N.S.
4	50	646	<27–1 106		2.0	<0.81–7.9	

Mann–Whitney test.
N.S. not significant ($p > 0.05$); * $p = 0.03$.

carcinoma did not differ significantly from patients with benign renal cysts. Relations between serum cortisol and DHEAS levels to tumour diameter were calculated for patients with stage I–III disease. For cortisol, a weak correlation to tumour diameter ($r = 0.21$; $p = 0.015$, using the Spearman rank correlation) was found, while for DHEAS no correlation was found. Table 3 presents the relation of cortisol and DHEAS to tumour grade. The serum cortisol levels were positively correlated to tumour grade ($p = 0.012$), but for DHEAS, no significant correlations between the levels in different tumour grades were found.

When the patients were subdivided into quartiles depending on the serum cortisol level before initiation of therapy, those in the highest quartile seemed to have a worse prognosis than those with lower serum cortisol ($p = 0.06$, Fig. 1). Patients within the highest quartile of serum DHEAS levels, however, were associated with a non-significantly better prognosis (Fig. 2), In a multivariate analysis of prognostic factors, disease stage and tumour grade were identified as independent predictors of prognosis. Age, gender and serum levels of cortisol and DHEAS were not, as shown in Table 4.

DISCUSSION

A major finding in this study is that serum cortisol levels were significantly higher in patients with renal cell carcinoma in comparison with controls. The marked difference in serum cortisol level between patients with benign renal cysts and those with cancer indicates an upregulation of the hypothalamic-pituitary-adrenal axis. One possible reason for an upregulation might be an ectopic production of ACTH or ACTH-like substances derived from the tumour. However, such hormone production has mostly been observed in small cell lung cancer and neuroendocrine tumours, and only rarely in renal cell carcinoma (20). A more probable explanation may be stimulation by means of cytokines. Earlier studies have demonstrated the stimulatory effect of cytokines on the hypothalamic-pituitary-adrenal axis (21, 22). The increase in serum cortisol observed in patients with poorly differentiated tumours compared to those with differentiated tumours indicates a connection between the tumour and the HPA-axis, a signal that might be mediated by cytokines. In the present study no correlation between serum cortisol and tumour stage

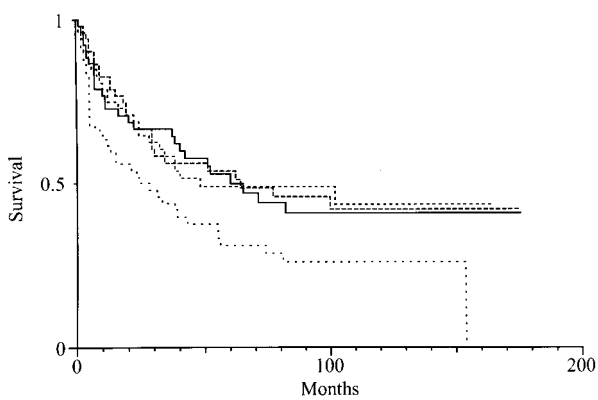

Fig. 1. Survival according to the Kaplan–Meier method in patients with renal cell carcinoma stratified in quartiles depending on serum cortisol levels. Serum cortisol < 430, (—); 430–561, (----); 562–679, (- - -); and ≥ 680 nmol/L (- - -).

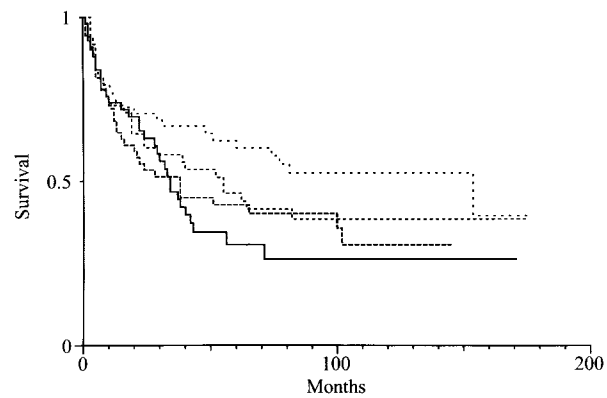

Fig. 2. Survival according to the Kaplan–Meier method in patients with renal cell carcinoma stratified in quartiles depending on serum DHEAS levels. Serum DHEAS ≤ 0.95, (—); 0.96–2.00, (----); 2.10–3.30, (- - -); and ≥ 3.4 μmol/L (- - -).

Table 4

Multivariate analysis of prognostic factors according to the Cox method

Prognostic factor	Relative risk	p-value	95% confidence interval	
			Lower	Upper
Age (years)				
≤66	1.00			
>66	1.17	0.44	0.78	1.73
Gender				
Male	1.00			
Female	1.09	0.68	0.72	1.62
Stage				
I–II	1.00			
III–IV	10.82	<0.0001	5.76	20.29
Grade				
1–2	1.00			
3–4	2.35	0.04	1.04	5.32
Cortisol (nmol/L)				
≤562	1.00			
>562	1.35	0.12	0.92	1.96
DHEAS (μmol/L)				
≤2.0	1.00			
>2.0	0.79	0.25	0.53	1.18

was found. Larger studies on serum cortisol levels in patients with cancer are scarce, except for those with hyperfunctioning adrenocortical tumours (23, 24).

Our data furthermore indicate that survival is affected by serum cortisol levels. The reason for this is not clear. Hypercortisolism *per se* induces a catabolic state and is associated with a greater risk of cardiovascular morbidity. Glucocorticoids may induce tumour growth and metastasis formation, findings that have been observed in animal model systems (3, 4). They may also suppress the antitumour reactions from the host's immune system (4, 25, 26). Results presented by Spiegel et al. (27) also emphasize the negative effects of stress on survival of patients with cancer. Interestingly, it has recently been shown that antidepressant therapy may reduce glucocorticoid-related effects on increasing lung metastases after laparotomy in a rat carcinosarcoma model (28).

Our study has some limitations. The difference in serum cortisol levels observed between patients with renal cell carcinoma compared to those with benign renal cysts may be explained by a higher degree of stress exposure among cancer patients, compared to controls. However, it must be remembered that the degree of stress also may be considerable for patients with benign cysts, because at the time of sampling these patients may not have been aware of the nature of their disease. Similar observations have been presented by Gustafsson et al. (29), who studied serum cortisol and stress reactions among patients screened for prostate carcinoma. They found that serum cortisol levels were elevated at the time of biopsy, but decreased to normal levels within two weeks after screening.

Another factor that might influence serum cortisol is the increase of blood flow in the region adjacent to the tumour. An increased blood flow could have a trophic effect on the adrenal gland. However, this possibility would most likely also have resulted in an increase in the DHEAS levels.

A final potential pitfall with the present study is the fact that the assay measures total serum cortisol and makes no distinction between the active and the protein-bound fraction. Differences in corticosteroid-binding protein or albumin levels might therefore have affected our results.

In the present study we found no difference in serum DHEAS levels when patients with renal cell carcinoma were compared with those with benign renal cysts. However, among patients with cancer, those with advanced stage disease (IV) tended to have lower serum DHEAS than those with stage I disease (Table 2). This difference was not significant, and could not be explained by differences in age or gender distribution, since those parameters were similar in the two subgroups of patients. The lower serum DHEAS levels in patients with advanced disease is in accordance with findings from non-neoplastic diseases such as anorexia (30), chronic stress (31) and adrenal incidentalomas (32). Furthermore, our results do not indicate any relation of serum DHEAS to tumour grade. However, when DHEAS was related to patient survival, there seemed to be a slight, but not significant, positive correlation. The multivariate analysis further showed that serum DHEAS had no prognostic information in renal cell carcinoma. The results are in accordance with earlier reports concerning the gender dependence (5) of DHEAS,

and the inverse relation to age (6). The reason for this may be a decreased production of DHEA/S with advancing age, or an altered peripheral conversion, rather than a central influence on the hypothalamic-pituitary-adrenal axis.

In summary, our results indicate an association between increased serum glucocorticoid levels and tumour grade and size in patients with renal cell carcinoma. This finding motivates further evaluation of the hypothalamic-pituitary adrenal axis in patients with malignant diseases, and its possible influence on prognosis.

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