Increased Urinary Excretion of Cortisol and Catecholami-NES in Malnourished Cancer Patients

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Excretion of cortisol and catecholamines were measured from 24-hour urine samples collected over a period of 3 days from hospitalized cancer patients suffering from malnutrition and were compared with those of control patients equally malnourished and having a similar degree of inflammation. Compared with control patients, cancer patients had a higher excretion of cortisol, adrenaline, and noradrenaline, although noradrenaline excretion reached statistical significance only when normalized to creatinine excretion. Plasma glycerol concentrations after an overnight fast were significantly higher in cancer patients as compared with control patients, in keeping with an increased adrenal and adrenergic activity. This study demonstrates evidence of simultaneously elevated catecholamine and cortisol excretion in cancer patients, which could not be ascribed to alteration in body composition. The results may, in part, explain the mechanisms behind ongoing tissue breakdown in progressive cancer disease.

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CANCER CACHEXIA is explained by the combined effect of anorexia and elevated energy expenditure.[1-3] The subsequent alteration in body composition is thus due to an increased mobilization of body fat and amino acids for oxidation and supporting the synthesis of acute phase reactants, as well as for the new synthesis of glucose.[4-8] Such metabolic alterations in a tumor-bearing host are well-recognized changes in the physiologic response to partial starvation and inflammation.[4,9] Although it is conceivable that such metabolic alterations are communicated by the classic hormones, at present it is unclear to what extent alterations in the metabolism of insulin, glucagon, thyroid hormones, adrenergic hormones, corticosteroids, and perhaps several other hormones may be involved.[1,10]

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Evidence of elevated plasma levels of corticosteroids and catecholamines in cancer patients have been reported.[11-13] Such measurements have, however, been compared with those of well-nourished and healthy individuals. Plasma concentrations may be difficult to translate into an overall elevated daily production of hormones, particularly with regard to corticosteroids, due to their physiologic diurnal variation.[14] In addition, it has been reported that adults suffering from protein-calorie malnutrition also display signs of increased pituitary-adrenal activity.[15]

Therefore, it is important to compare hormonal alterations in cancer patients who are losing weight with measurements of similarly malnourished patients who do not have cancer.

The purpose of this study was therefore to determine the urinary excretion of cortisol and catecholamines in malnourished cancer patients as compared with that of equally malnourished patients who did not have cancer.

Materials and Methods

Patients

Patients with a history of weight loss exceeding 5% of their total body weight during the 6-month period before surgery were included. Exclusion criteria included fever and other evidence of infection or endocrine disorders and medication (alpha and beta stimulators or blockers, corticosteroids, thyroid hormones, tricyclic antidepressive drugs, sympathetic ganglioblockers, monoamine oxidase blockers), that might influence hormone status or analyses. The patients were studied after admission to the ward before any operation or other treatment was begun. They were offered an ordinary hospital diet (20% protein, 35%

fat, 45% carbohydrate) *ad libitum,* and were allowed to ambulate freely in the ward. Dietary interventions were not performed. None of the patients were bedridden. Body temperature and heart rate were measured in the morning while the patients were still in bed. Twenty-nine patients with cancer and 22 control patients received medications such as digitalis, diuretics (furosemide), nitroglycerine, and H_2-receptor blockers (two cancer patients, three control patients) or received aspirin irregularly (2 cancer patients, 3 control patients).

Fifty cancer patients with the following diagnoses were investigated: colorectal carcinoma (n = 23), gastric carcinoma (n = 8), esophageal carcinoma (n = 2) pancreatic carcinoma (n = 8), hepatocellular carcinoma (n = 4), generalized prostatic carcinoma (n = 2); soft tissue sarcoma (n = 3). Thirty-two patients had locally advanced and/or disseminated disease.

Thirty-two malnourished control patients with the following diagnoses were investigated: benign hepatobiliary disease (n = 7); peptic ulcer (n = 10); lower limb ischemia (n = 5); abdominal angina (n = 4); abdominal aortic aneurysm with intermittent pain (n = 2); Crohn's disease (n = 1), obstipation causing abdominal discomfort (n = 3).

Nutritional Status

Body weight was measured on a balance with a precision of ±1%. The body weight index was calculated from the ideal weight given in a recently published report of a local reference population.[16] Triceps skinfold (TSF) was measured by a caliper on the dorsal section of the upper, nondominant arm. Mid-arm circumference (MAC) was measured halfway between the coracoid process and olecranon. Arm muscle circumference (AMC) was calculated from TSF and MAC by the following formula:

$$\text{AMC (cm)} = \text{MAC (cm} - \pi \text{X TSF cm)}.^{17}$$

The mean of three measurements of TSF and MAC was used. Total body potassium (TBK) was measured in a ^{40}K whole-body counter. The TBK index was calculated from ideal TBK, derived from the ideal weight as described above and the relation of TBK to height and weight.[18]

Urine Collection

Urine was collected from 7:00 a.m. to 7:00 a.m. of the following day (24 hours) for 3 consecutive days. The patient was urged to empty his bladder before collection commenced. During the 24-hour period of the collection, voided urine was stored at 4 C. The primary part of the urine was acidified by 14 ml of 12 M HCl, but an aliquot used for determination of cortisol was kept without acid. Analyses of the urine were undertaken the day after collection.

Blood and Serum Analyses

All samples used for blood, plasma, and serum measurements were taken after the patients had fasted overnight. Kits from Boehringer-Mannheim, West Germany were used for determination of plasma glucose and glycerol. Plasma insulin was measured by a radioimmunoassay kit (Pharmacia, Uppsala, Sweden). Hemoglobin concentration, leucocyte count, serum creatinine, and serum albumin were measured in the clinical routine laboratory.

Urine Analyses

Urinary nitrogen was measured by the Kjeldahl method.[19] Creatinine was determined by an autoanalyzer based on the Jaffé reaction.[20] Urinary cortisol excretion, which is dependent on plasma-free cortisol concentration, was quantified according to Scriba and colleagues.[21] The method used for assay of adrenaline and noradrenaline was a modification of the method described by Von Euler and Lishajco.[22] Vanilmandelic acid (VMA) was assayed according to the method of Wisser and Stamm.[23]

Noradrenaline and adrenaline in urine are derived from several sources, including the adrenal medullary tissue and sympathetic nerve endings. Catecholamines may be excreted as free nonadrenaline and adrenaline or as metabolites (metanephrines, 3-metoxi-4-hydroxy mande-lic acid), of which VMA constitutes the main part. Despite the fact that VMA excretion is over 100-fold greater than that of free catecholamines, the best indicators of sympathoadrenal function are urinary-free noradrenaline and adrenaline.[24] Acute alterations in renal blood flow, diuresis, natriuresis, and urinary acidification do not alter catecholamine excretion.[25] Because it is unusual that elevated metanephrine excretion should not be reflected by VMA measurements, metanephrines were not determined.

Statistics

Statistical computation was performed by the Student t-test. Linear regression analysis was calculated and the slopes were compared statistically by a parametric test. p-Values less than 0.05 were regarded as statistically significant.

Results

Cancer and control patients were of the same age and sex (Table 1). Cancer patients had lower body weight and TBK. Because the body weight index and TBK index were similar for the patients of both groups, this lower body weight and TBK in cancer patients was explained primarily by there being differences in height between the groups. TSF, AMC, body temperature, and resting heart rate were the same for both cancer and control patients.

TABLE 1. *Characteristics of Cancer and Control Patients (Mean ± SEM)*

	Cancer Patients (n = 50)	Control Patients (n = 32)
Age (years)	67 ± 2	68 ± 3
Male/Female	22/28	14/18
Body weight (kg)	59.5 ± 1.6†	64.8 ± 2.9
Weight index (%)	82.8 ± 1.7	84.5 ± 3.2
Weight loss (%)	12.0 ± 1.4	10.9 ± 1.8
Height (cm)	169.0 ± 1.2†	173.0 ± 1.9
TBK* (mmol)	2570.0 ± 121.0†	2935.0 ± 111.0
TBK index (%)	86.9 ± 2.8	89.7 ± 2.1
Triceps skinfold (mm)	10.1 ± 0.8	11.9 ± 1.3
AMC (cm)	25.0 ± 0.6	26.1 ± 0.7
Body temp. (C)	37.0 ± 0.1	36.9 ± 0.1
Heart rate (beats/minute)	78.0 ± 2.0	77.0 ± 2
Urinary creatinine (mmol/24 hours)	6.9 ± 0.5	8.1 ± 0.6
Urinary nitrogen (g/24 hours)	8.1 ± 0.72	7.8 ± 0.7

* Total body potassium.
† $p < 0.05$ *vs.* controls.

TABLE 2. *Blood Measurements of Cancer and Control Patients (Mean ± SEM)*

	Control Patients (n = 50)	Control Patients (n = 32)
Hemoglobin (g/l)	123.0 ± 3.0*	131.0 ± 3.0
Blood leucocyte count (10^3)	9.6 ± 0.7	8.2 ± 0.5
Erythrocyte sedimentation rate (mm)	33.0 ± 4.0	25.0 ± 5.0
Serum creatinine (μmol/l)	84.0 ± 6.0	88.0 ± 4.0
Serum albumin (g/l)	33.7 ± 1.1	35.5 ± 1.1
Blood glucose (mmol/l)	5.0 ± 0.3	4.5 ± 0.2
Plasma glycerol (μmol/l)	155.0 ± 17.0*	120.0 ± 22.0
Plasma insulin (μU/ml)	7.0 ± 1.0	6.0 ± 1.0

* $p < 0.05$ *vs.* controls.

Nitrogen excretion in urine was almost identical in the two groups, but urinary creatinine excretion was 15% lower in the cancer group, although this was not statistically different. Nitrogen excretion per creatinine showed a trend to be elevated ($p < 0.10$) in the cancer patients.

In cancer patients, blood hemoglobin concentration was lower and serum glycerol was increased as compared with that of control patients (Table 2). Erythrocyte sedimentation rate, WBC count, serum creatinine, blood glucose, serum albumin, and plasma insulin did not differ between the two groups.

Although urine excretion of cortisol and adrenaline were significantly increased in cancer patients, the higher noradrenaline excretion did not reach statistical significance (Table 3). The noradrenaline excretion was significantly elevated in cancer patients when normalized to urine creatinine excretion. There was no difference in VMA excretion between patients of the cancer and the control groups.

For both cancer and control patients, cortisol per creatinine excretion (μmol/mol) correlated inversely to the degree of malnutrition expressed as the TBK index (Fig. 1). There tended to be a steeper slope in cancer patients compared with control patients ($p = 0.07$). Cortisol per creatinine excretion also correlated inversely to weight loss (correlation coefficient of 0.46 for cancer patients and of 0.53 for control patients, $p < 0.001$), but in this correlation, the slope for cancer patients was significantly steeper compared with that for control patients ($p < 0.001$). In cancer patients, cortisol per creatinine excretion correlated negatively to the reduction in serum albumin, but not in the control patients (Fig. 2). The urinary excretion of catecholamines was not significantly correlated to the degree of malnutrition in either cancer or control patients. We could not find any trend pertaining to stage of malignancy in any of the measured parameters.

Discussion

During recent years, the understanding of metabolic alterations in progressive cancer with associated malnutrition has improved considerably. It has been established that both anorexia and elevated energy expenditure contribute to weight loss in such patients.[1,2,4,5,8,26-29] Some metabolic alterations are secondary to anorexia, whereas others, particularly the liver and the immune reactions, are explained by the accompanying inflammation.[4] What remains to be confirmed is how the message for tissue

TABLE 3. *Urinary Cortisol and Catecholamine Excretion in Cancer and Control Patients (Mean ± SEM)*

	Cancer Patients (n = 50)	Control Patients (n = 32)	Reference Values§
Cortisol (nmol/24 hours)	317 ± 32‡	196 ± 20	30–300
Cortisol/creatinine (μmol/mol)	53 ± 5‡	31 ± 4	
Adrenaline (nmol/24 hours)	39 ± 4†	30 ± 4	0–80
Adrenaline/creatinine (μmol/mol)	6.0 ± 0.7‡	3.9 ± 0.5	
Noradrenaline (nmol/24 hours)	299 ± 44	224 ± 25	70–420
Noradrenaline/creatinine (μmol/mol)	44 ± 7†	28 ± 3	
VMA* (μmol/24 hours)	22 ± 1.5	24 ± 1.7	0–40
VMA/creatinine (mmol/mol)	3.4 ± 0.38	3.0 ± 0.2	

The mean of three consecutive 24-hour collections from each patient was used.
* Vanilmandelic acid
† $p < 0.05$ *vs.* controls
‡ $p < 0.01$ *vs.* controls
§ As defined for the methods used.

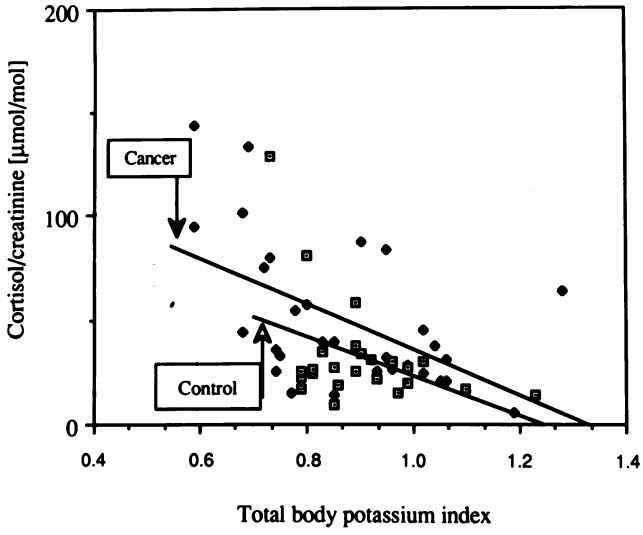

FIG. 1. The relationship between TBK index and urine cortisol/creatinine excretion.
♦ Cancer patients (y = 146 − 1.095x; r = 0.54, p < 0.01)
⊡ Control patients (y = 117 − 0.945x; r = 0.42, p < 0.05)

breakdown is communicated among organs and tissue compartments in cancer patients.

The most obvious loss of tissue compartments in cancer patients is that of skeletal muscles and subcutaneous fat. We have recently reported that the loss of muscle mass in tumor-bearing animals is parallel with the decrease of appetite, and is caused by a depressed protein synthesis rather than by elevated breakdown.[30] Similar findings have been obtained from studies of cancer patients.[31] Although we have demonstrated insulin resistance in tumor-bearing animals[32] and cancer patients[33,34] with regard to glucose homeostasis, it has been difficult to confirm that insulin is a key factor behind the wasting of skeletal muscles.[32,34] In fact, as regards protein synthesis, tumor-bearing animals have displayed normal insulin sensitivity in skeletal muscles, despite their being resistant in muscles for glucose uptake.[32] It is therefore possible that other classic hormones such as the catecholamines and glucocorticosteroids may be involved in regulation of the protein homeostasis.

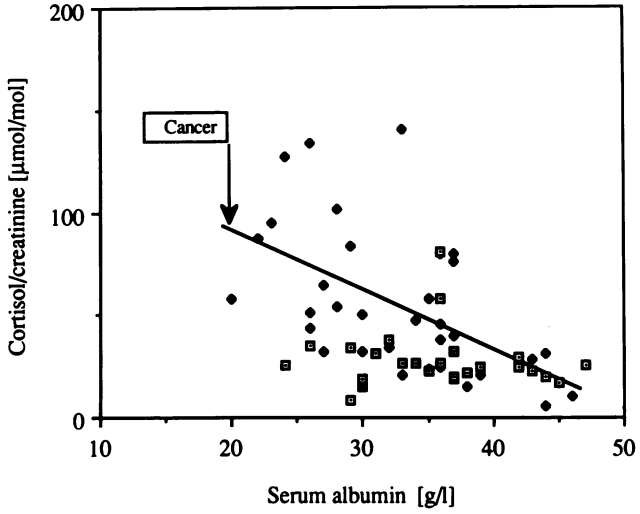

FIG. 2. The relationship between serum albumin and urine cortisol/creatinine excretion.
♦ Cancer patients (y = 149 − 2.89x; r = 0.58, p < 0.01)
⊡ Control patients (r = 0.04, NS)

The results of the present study support previous evidence of increased adrenergic and adrenal activity in cancer patients,[11-13,35] here demonstrated as increased excretion of cortisol, adrenaline, and noradrenaline as compared with that of matched control patients, although the values are not different from reference values in well-nourished, healthy individuals. These findings were obvious when measured as absolute excretion, and were even more pronounced when normalized to the creatinine excretion. Creatinine excretion is generally used as a means for accounting for variation in diuresis and incompleteness of daily urine collection under nonmetabolic ward conditions. Creatinine may also indirectly reflect the muscle mass in both humans and animals.[36,37] Our cancer patients had a lower creatinine excretion, although not significantly so when compared with the control patients. Although, with regard to age and sex, the control patients were well-matched with the cancer patients, the cancer patients had small but insignificant differences in body compositional measures that amounted to 10% of TBK, as compared with the control group. Therefore, it is possible that the lower concentration of creatinine excretion may indicate a lower but statistically insignificant reduced muscle mass in the cancer group. Perhaps more important may be the fact that our study and control patients seemed to be similar with regard to indices of inflammation, although this was evaluated by nonspecific hematologic parameters only. Therefore, we should not exclude the possibility that a higher cortisone excretion may in itself be evidence of a greater degree of inflammation in the cancer patients.

The plasma level of glycerol was significantly higher in the cancer group, and this is consistent with our findings in previous studies of cancer cachexia.[38-40] Elevated glycerol concentrations may reflect an increased lipolysis in cancer disease,[40] perhaps due to increased adrenergic activity and insulin resistance,[34] although it may also reflect decreased lipogenesis.[41]

We have previously speculated that elevated energy expenditure in cancer patients may be secondary to their increased adrenergic activity.[42,43] It may be questioned, however, whether the urinary levels of catecholamines in the cancer patients are high enough to explain the increased energy metabolism. In patients with myocardial infarction and increased energy expenditure, the excretion

of adrenaline and noradrenaline may be around fivefold higher during the acute period than that found in our cancer patients.[44] A simple index of catecholamine activity, such as pulse rate, did not support any difference among our patient groups, and since we did not measure energy expenditure directly in the present study, we cannot be certain whether the cancer patients differed significantly from the control patients in this respect. Therefore, the possible relationship between elevated energy expenditure and increased adrenergic tone in cancer disease remains speculative, although we have some circumstantial evidence to support this hypothesis. We have recently reported increased cardiac sensitivity to B-agonists in tumor-bearing animals,[42,45] and we have obtained preliminary evidence of increased reactivity to adrenaline infused in cancer patients who lose weight.[43] An interesting observation of the present study was that of adrenaline excretion being inversely correlated to serum albumin concentrations in cancer patients. Such findings should also be seen in light of a pronounced down-regulation of thyroid hormones in those cancer patients who lose weight and have a serum albumin of less than 35 g/l.[46] Thus, the presence of a malignant tumor may for some reason create an increasing adrenergic drive which, in order to save energy in a substrate deficient condition such as cancer cachexia, is counteracted by a down-regulation in thyroid hormones.

It is difficult to evaluate whether the clearly higher cortisol excretion of our cancer patients is high enough to explain accelerated tissue breakdown. At best, this question can be evaluated by indirect comparison with other conditions where a more direct relationship has been reported between plasma concentrations and metabolic regulation. It has been clearly established that plasma cortisol levels within 300–500 μg/l can increase whole-body proteolysis after single drug infusions in healthy volunteers.[47] Plasma levels of approximately 200–300 μg/l have been associated with urinary cortisol excretion corresponding to 250–300 μg/day during the postoperative period.[48] This corresponds approximately to a twofold higher concentration of excretion than that found in our cancer patients. It has been reported that the mean elevated concentration of plasma cortisol was 165 ± 69 μg/l for cancer patients, but was considerably higher in patients with metatstatic disease as compared with patients who had solitary tumors.[12,13] Finally, there has been evidence suggesting that even mood changes can be registered in the pattern of urinary excretion of cortisol and catecholamines.[14]

The results of the present study agree with our recent studies of tumor-bearing animals, in which we likewise demonstrated an elevated excretion of glucocorticoids.[49] In those experiments, however, it was obvious that the major part of the elevated cortisol excretion could be explained by the stress that anorexia elicited in tumor-bearing animals. Because we did not measure food intake in our present study, we cannot exclude the possibility that anorexia-related stress influenced cortisol excretion in cancer patients. Yet, irrespective of the reason behind increased pituitary-adrenal function in cancer patients, we regard it as a physiologic means by which a tumor can translate anorexia into negative host tissue balances, although it is well-recognized that malignant tumors may sometimes produce substances similar to ACTH.[35] In addition to normal physiology, it is worth emphasizing that the combined small changes in several hormones, such as insulin, glucagon, thyroid hormones, growth hormone, catecholamines, and glucocorticoids may act synergistically and thereby amplify the response. It has been demonstrated that the combined infusion of stress hormones leads to a larger metabolic response than a single hormone infusions.[50–52]

In conclusion, this study demonstrates higher catecholamine and cortisol excretion in malnourished cancer patients as compared with malnourished control patients, although the values reported are not different from reference values for well-nourished healthy individuals. In cancer patients, this increased urinary excretion could not be ascribed to alterations in body composition. However, one cannot exclude the possibility that the higher excretion of catecholamines may be explained by impaired extraneuronal catabolism in the liver and the kidneys. It is possible, although not yet proven, that these hormonal alterations, in part, explain the ongoing tissue breakdown in progressive cancer disease. This question must await future, randomized studies with hormone blockers.

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