Twenty-Four–Hour Urinary Free Cortisol in Patients With Acquired Immunodeficiency Syndrome

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Many patients with acquired immune deficiency syndrome (AIDS) have symptoms consistent with adrenal insufficiency, but only a small subset of these patients meet criteria for adrenal insufficiency during a short corticotropin (ACTH) stimulation test. We hypothesized that patients with AIDS and symptoms of adrenal insufficiency who produce normal amounts of cortisol in response to administration of 0.25 mg cosyntropin may nevertheless produce lower amounts of cortisol in a course of 24 hours than comparably sick AIDS patients without symptoms of adrenal insufficiency or comparably sick patients without AIDS. We studied four groups of male patients: AIDS patients with symptoms suggestive of adrenal insufficiency but with a normal response to cosyntropin (group I), AIDS patients without symptoms suggestive of adrenal insufficiency (group II), human immunodeficiency virus (HIV)-negative patients with serious acute or chronic illness (group III), and healthy subjects (group IV). The following variables were examined: age, CD4 cell count, Acute Physiologic and Chronic Health Evaluation (APACHE) score, serum cortisol and plasma ACTH at baseline; serum cortisol at 30 and 60 minutes after intravenous administration of 0.25 mg cosyntropin; and 24-hour urinary free cortisol. The four groups had a similar mean age and baseline plasma ACTH and serum cortisol levels. However, a change in cortisol from baseline to 30 and 60 minutes after administration of cosyntropin was significantly smaller in both groups of AIDS patients than in the sick patients without AIDS and normal subjects. There were also differences noted between the two groups of AIDS patients: both baseline and stimulated levels of cortisol tended to correlate directly with ACTH levels in patients without symptoms of adrenal insufficiency, while this relationship appeared to be inverse in patients with symptoms suggestive of adrenal insufficiency ($r = -.57$ to $-.7$, $P < .05$ to .14). The 24-hour urinary free cortisol levels were similar among all groups, but correlated strongly with baseline and stimulated serum cortisol levels only in patients with AIDS and symptoms of adrenal insufficiency ($r = .8$ to .9, $P < .002$ to .015). We conclude that (1) AIDS patients with and without symptoms of adrenal insufficiency may have either normal adrenal function or somewhat suboptimal adrenal reserve as demonstrated by a blunted cortisol response during the short ACTH stimulation test in comparison to HIV-negative comparably sick patients or healthy subjects; and (2) 24-hour urinary free cortisol is not a useful test for detection of subtle abnormalities of adrenal function in patients with AIDS.

INDICATIONS OF ABNORMAL adrenal function in patients with acquired immune deficiency syndrome (AIDS) have been noted since the early days of the AIDS epidemic.[1-8] Many patients with AIDS have a number of symptoms that may be consistent with adrenal insufficiency. These symptoms include weight loss, weakness, diarrhea, and electrolyte disturbances.[9] However, only a small fraction of these patients meet criteria for adrenal insufficiency during the short corticotropin (ACTH) stimulation test, and therefore would require glucocorticoid replacement.[10-11]

Many studies of adrenal function in patients with AIDS who do not meet criteria for adrenal insufficiency during the short ACTH stimulation test have been undertaken. These studies have demonstrated evidence for aldosterone deficiency,[12,13] somewhat subnormal glucocorticoid reserve,[14] glucocorticoid resistance,[15] or normal glucocorticoid function.[9,12,16] However, there is little information available regarding the differences between patients with AIDS who have symptoms suggestive of adrenal insufficiency and comparably sick AIDS patients without such symptoms or comparably sick patients without AIDS. Similarly, there is little information available regarding measurement of 24-hour urinary free cortisol levels in AIDS patients, even though the 24-hour urinary cortisol measurement may be the most accurate integrated test of adrenal function.[17,18]

We hypothesized that patients with AIDS and symptoms suggestive of adrenal insufficiency who respond normally to pharmacologic stimulation with cosyntropin may nevertheless produce subnormal amounts of cortisol in the course of 24 hours in response to the stress imposed by their illness. The present study was undertaken to test this hypothesis.

SUBJECTS AND METHODS

Subjects

This controlled prospective study enrolled consecutively hospitalized male patients in the following groups: AIDS patients with symptoms suggestive of adrenal insufficiency but a normal response to cosyntropin (group I), AIDS patients without symptoms of adrenal insufficiency (group II), patients with an acute illness without AIDS (group III), and healthy normal subjects (group IV).

To qualify for the group with symptoms suggestive of adrenal insufficiency (group I), patients had to have at least five of the following symptoms: weight loss, general weakness, anorexia, diarrhea, mucocutaneous melanosis, hyponatremia, hyperkalemia, orthostatic hypotension, and documented hypoglycemia.

The two groups of AIDS patients were matched by the CD4 cell count and Acute Physiologic and Chronic Health Evaluation (APACHE) II score.[19] The sick patients without AIDS (group III) were matched to AIDS patients by the APACHE II score. All groups were matched by age.

We excluded patients treated with ketoconazole, phenytoin, glucocorticoids, or rifampin. Patient characteristics are presented in Table 1.

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Table 1. Patient Characteristics

Group	Age (yr)	CD4 Cell Count (per mL)	APACHE Score	ACTH (pg/mL)	Cortisol (μg/dL) 0 min	Cortisol (μg/dL) 30 min	Cortisol (μg/dL) 60 min	24-h Urinary Free Cortisol (μg/dL)
I (n = 8)	36.8 ± 9.2	80.3 ± 122.5	4.8 ± 4.6	12.9 ± 11.4	13.8 ± 7.2	25.5 ± 5.2	31.7 ± 8.0	58.1 ± 24.4
II (n = 8)	35.4 ± 6.0	75.8 ± 119.1	3.5 ± 2.1	18.3 ± 11.1	14.5 ± 4.9	24.5 ± 8.2	27.9 ± 9.4	69.8 ± 32.9
III (n = 9)	43.2 ± 9.4	—	4.9 ± 3.1	13.4 ± 9.4	10.3 ± 5.1	28.4 ± 6.6	33.7 ± 8.2	47.0 ± 18.4
IV (n = 9)	33.0 ± 7.3	—	—	19.4 ± 13.0	10.4 ± 5.8	27.6 ± 9.3	30.9 ± 11.2	30.9 ± 2.2

NOTE. Values are the mean ± SEM. Refer to the text for analysis of statistical differences. The groups are defined as follows: I, AIDS and symptoms of adrenal insufficiency; II, AIDS without symptoms of adrenal insufficiency; III, HIV-negative sick patients; IV, normal subjects.

Variables Examined

The following variables were examined: age, CD4 cell count, APACHE II score, serum cortisol, and plasma ACTH at baseline; serum cortisol at 30 and 60 minutes after intravenous administration of 0.25 mg cosyntropin; and free cortisol in a 24-hour urine sample.

Study Procedures

The study was approved by the institutional review boards at Cabrini Medical Center and St. Vincent's Medical Center. We identified subjects in groups I to III during their hospitalization. Normal subjects (group IV) were recruited from the hospital staff.

After informed consent was obtained, a 24-hour urine sample for urinary free cortisol was collected. A blood sample for measurement of baseline serum cortisol and plasma ACTH levels was obtained between 7 and 10 AM, and an intravenous bolus of 0.25 mg cosyntropin was then administered. Blood samples at 30 and 60 minutes were collected for measurement of serum cortisol levels.

All serum and plasma samples were frozen and stored at −20°C. Cortisol levels were measured in all samples during the same assay procedure by specific radioimmunoassay at Corning Nichols Institute (San Juan Capistrano, CA). The plasma ACTH level was measured by a highly sensitive immunoradiometric assay at Corning Nichols Institute. Urinary free cortisol levels were measured by high-performance liquid chromatography, also at Corning Nichols Institute.

Statistical Methods

ANOVA was used to determine significant differences among the four groups. If a difference existed, pairwise multiple comparisons using the Student-Newman-Keuls test (fixed at the 5% significance level) were used to identify which particular groups differed.

The Pearson correlation coefficient was used to determine the strength of association between variables within groups. Bonferroni corrections were performed for multiple correlations.

A sample linear regression was used to fit a straight-line model for plasma ACTH as a function of the serum cortisol level separately for each of the four groups at 0, 30, and 60 minutes after administration of cosyntropin.

Values for all parameters for each group are presented as the mean ± SEM.

RESULTS

The study was conducted over a 1-year period (January 1995 to January 1996). It included 34 male subjects: eight patients in group I (mean age, 36.8 ± 9.2 years), eight patients in group II (35.4 ± 5.9), nine patients in group III (43.2 ± 9.4), and nine healthy subjects in group IV (33.0 ± 7.3). The parameters for all groups are shown in Table 1.

There were no significant differences between the groups in plasma ACTH, baseline or stimulated serum cortisol, or 24-hour urinary free cortisol levels (Table 1 and Fig 1). However, there were significant differences between the groups in the change of serum cortisol from baseline to the stimulated level at both 30 and 60 minutes. AIDS patients in both groups exhibited a reduced cortisol response compared with the sick patients without AIDS or normal subjects: the change from 0 to 30 minutes was 11.8 ± 4.7 μg/dL in group I, 10.0 ± 1.3 μg/dL in group II, 18.1 ± 1.9 μg/dL in group III, and 17.3 ± 2.5 μg/dL in group IV (P = .01 to .05 for groups I or II *v* groups III or IV, P = NS for group I *v* group II or group III *v* group IV). The change in serum cortisol from 0 to 60 minutes was 17.9 ± 2.0 μg/dL in group I, 13.4 ± 1.9 μg/dL in group II, 23.4 ± 2.3 μg/dL in group III, and 20.5 ± 2.4 μg/dL in group IV (P = .01 to .04 for group I *v* group III and group II *v* group III or IV, P = NS when other groups are compared). These results are presented in Fig 2.

Of interest was a finding of a relationship between the plasma ACTH level and both baseline and stimulated serum cortisol levels (Fig 3). This relationship tended to be positive in groups II and III (r = .40 to .65, P < .06 to .28) but negative in group I (r = −.57 to −.07, P < .05 to .14); there were no correlations between ACTH and cortisol levels in group IV. The 24-hour urinary free cortisol level correlated strongly with both baseline and stimulated serum cortisol levels only in group I (r = .81 to .9, P < .002 to .015; Fig 4). There was a positive correlation between 24-hour urinary free cortisol and baseline (but not stimulated) serum cortisol levels in group IV (r = .88, P < .002; Fig 4). After Bonferroni correction for multiple correlations, the level of statistical significance did not change.

DISCUSSION

Many studies have found great variability in adrenal function in patients with AIDS, as recently reviewed.[8,9]

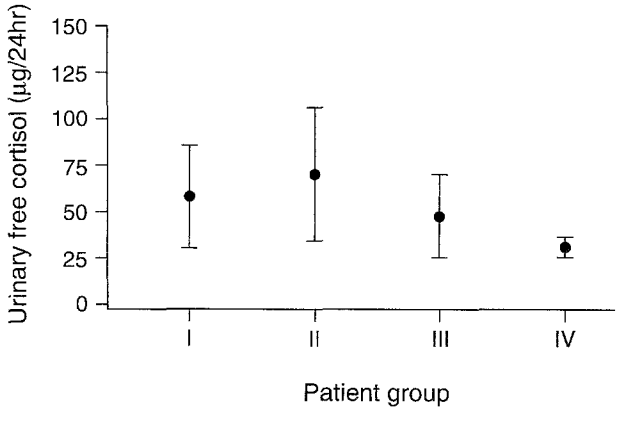

Fig 1. Twenty-four–hour free urinary cortisol levels in groups I to IV (mean ± SEM).

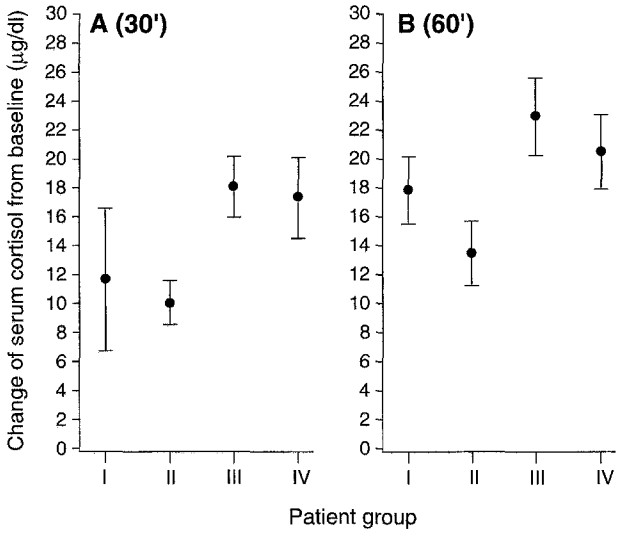

Fig 2. Change in serum cortisol from baseline at 30 minutes (30′, A) and 60 minutes (60′, B) after intravenous administration of 0.25 mg cosyntropin.

Glasgow et al[3] conducted a retrospective analysis of clinical data in deceased patients with AIDS and found a mildly blunted response to the short ACTH stimulation test in one patient and slightly elevated baseline cortisol values in five others.

Greene et al[10] studied 20 patients with symptoms of adrenal insufficiency and found four patients who had chemical evidence of adrenal insufficiency on the short ACTH stimulation test. These patients improved clinically after glucocorticoid replacement.

Mulhall[20] compared the adrenal function of 20 healthy controls and 20 asymptomatic HIV-positive patients and noted somewhat blunted responses to short ACTH stimulation tests in the HIV-positive group, although all values were within normal limits.

A prospective study by Membreno et al[21] reported an elevated basal serum cortisol level with a blunted response to a short ACTH stimulation test in AIDS patients compared with normal subjects.

Another prospective evaluation of adrenal function reported by Verges et al[14] included 63 HIV-positive patients (13 asymptomatic, 27 with AIDS-related complex, and 23 with AIDS) and 30 healthy controls and found that the asymptomatic HIV-positive group had a slightly elevated basal cortisol, but the AIDS group did not differ from the controls.

A study by Norbiato et al[15] included nine AIDS patients with a clinical picture of adrenal insufficiency but elevated levels of serum and urinary free cortisol as compared with 12 AIDS patients without clinical symptoms of adrenal insufficiency and 12 healthy controls. The study demonstrated glucocorticoid receptor abnormalities in the patients who had elevated serum

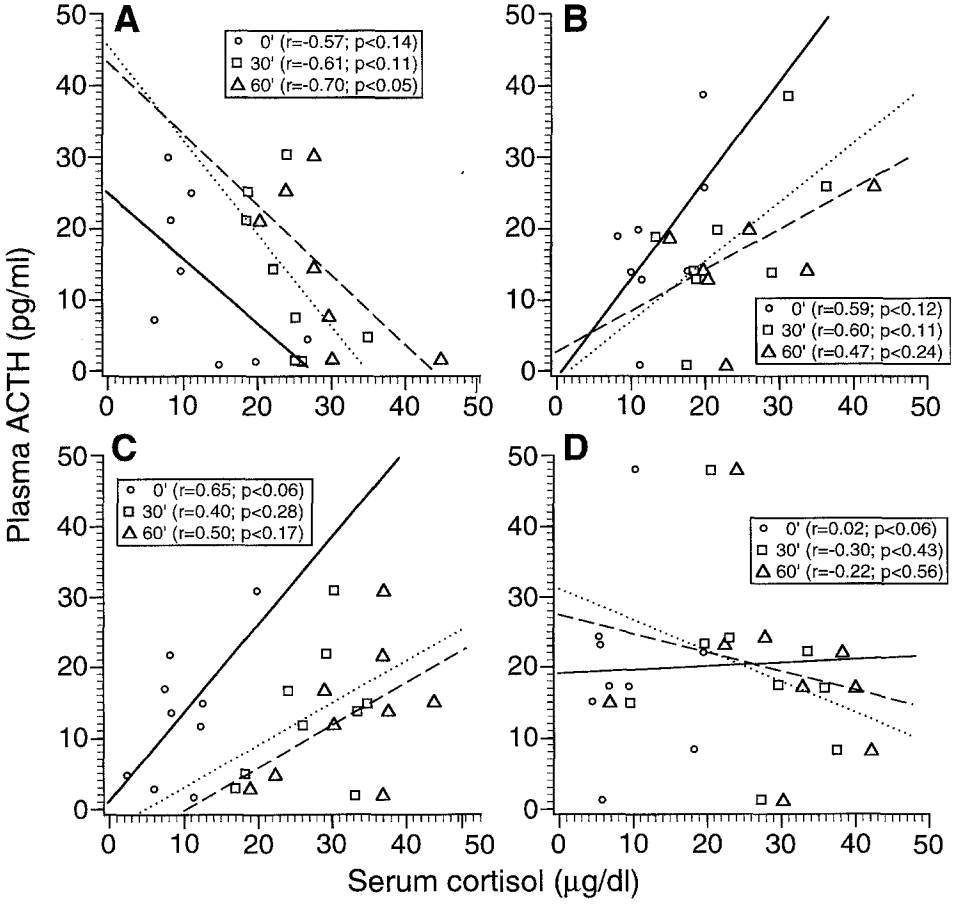

Fig 3. Relationships between plasma ACTH and serum cortisol levels at 0 minutes (0′), 30′, and 60′ after intravenous administration of 0.25 mg cosyntropin in group I (A), II (B), III (C), and IV (D).

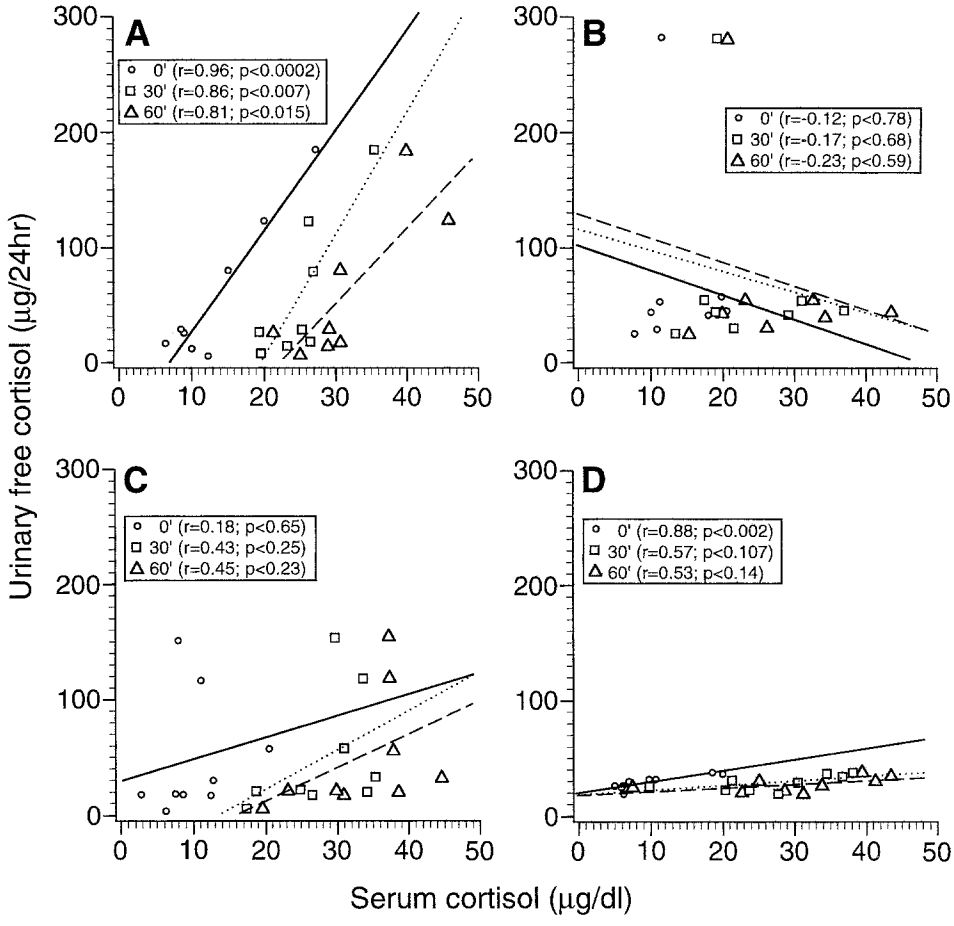

Fig 4. Relationships between urinary free cortisol and serum cortisol levels in group I (A), II (B), III (C), and IV (D).

and urinary free cortisol levels. Other measures of adrenal function in the study were variable, including ACTH levels, which were elevated, suppressed, or normal.

A study by Azar and Melby[22] examined the response to ovine corticotropin-releasing hormone in 25 non-AIDS patients with advanced HIV infection. They found that cortisol and ACTH responses in these patients were divided into three different patterns: 25% had reduced pituitary reserve but elevated basal cortisol and ACTH levels, another 25% had reduced adrenal reserve with high basal cortisol and an inappropriately normal ACTH response, and 50% had normal responses.

In the present study, we examined 24-hour urinary free cortisol excretion and found no statistical differences between patients with AIDS (with or without symptoms suggestive of adrenal insufficiency) and either comparably sick patients without AIDS or normal controls, and 24-hour urinary cortisol excretion in all groups, except for normal controls, was highly variable. Nevertheless, there were differences among the groups that may be of interest.

First, the change in the cortisol level from baseline to 30 or 60 minutes after stimulation by cosyntropin was significantly smaller in AIDS patients, indicating subnormal adrenal reserve and supporting previous reports of similar abnormalities in patients with AIDS.[3,20,21] Since 24-hour urinary free cortisol levels and both basal or stimulated serum cortisol levels did not differ between the groups, an alternative explanation would be that none of these patients had abnormal adrenal function.

Second, the relationship between plasma ACTH and either baseline or stimulated serum cortisol levels in patients with AIDS and symptoms of adrenal insufficiency tended to be negative, whereas a similar correlation tended to be positive in AIDS patients without symptoms of adrenal insufficiency and in comparably sick patients without AIDS. Although this finding, which did not reach statistical significance, is difficult to interpret with certainty, it may indicate that the pituitary/adrenal axis in patients with AIDS and symptoms of adrenal insufficiency is strained, and that this group may consist of a mixture of patients: those whose adrenals are about to fail (high-normal ACTH and low-normal cortisol), those who have tissue-specific peripheral resistance to cortisol,[15,23] or those in whom factors other than ACTH stimulate cortisol release[21] (high-normal cortisol and low-normal ACTH in the latter two subgroups). An alternative explanation would be that glucocorticoid feedback dominated all other relationships between ACTH and cortisol in this group of patients.

Third, a very strong correlation between urinary free cortisol and both baseline and stimulated serum cortisol levels existed only in patients with AIDS and symptoms of adrenal insufficiency. This observation suggests that cortisol clearance in this group was increased for unknown reasons.

The above relationships between plasma ACTH, serum

cortisol, and urinary free cortisol levels, although statistically significant, are not necessarily clinically meaningful. Further studies may be needed to determine whether these relationships may be of clinical significance in any particular subgroup of patients.

We conclude that (1) AIDS patients with or without symptoms of adrenal insufficiency have either normal adrenal function or somewhat suboptimal adrenal reserve as demonstrated by a blunted serum cortisol response during the short ACTH stimulation test when compared with comparably sick patients without AIDS or normal individuals; and (2) the 24-hour urinary free cortisol determination is not a useful test for the detection of subtle abnormalities of adrenal function in patients with AIDS.

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