

ORIGINAL ARTICLE

Measurements of Serum Free Cortisol in Critically Ill Patients

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ABSTRACT

BACKGROUND

Because more than 90 percent of circulating cortisol in human serum is protein-bound, changes in the binding proteins can alter measured serum total cortisol concentrations without influencing free concentrations of this hormone. We investigated the effect of decreased amounts of cortisol-binding proteins on serum total and free cortisol concentrations during critical illness, when glucocorticoid secretion is maximally stimulated.

METHODS

Base-line serum total cortisol, cosyntropin-stimulated serum total cortisol, aldosterone, and free cortisol concentrations were measured in 66 critically ill patients and 33 healthy volunteers in groups that were similar with regard to sex and age. Of the 66 patients, 36 had hypoproteinemia (albumin concentration, 2.5 g per deciliter or less), and 30 had near-normal serum albumin concentrations (above 2.5 g per deciliter).

RESULTS

Base-line and cosyntropin-stimulated serum total cortisol concentrations were lower in the patients with hypoproteinemia than in those with near-normal serum albumin concentrations ($P < 0.001$). However, the mean (\pm SD) base-line serum free cortisol concentrations were similar in the two groups of patients (5.1 ± 4.1 and 5.2 ± 3.5 μ g per deciliter [140.7 ± 113.1 and 143.5 ± 96.6 nmol per liter]) and were several times higher than the values in controls (0.6 ± 0.3 μ g per deciliter [16.6 ± 8.3 nmol per liter], $P < 0.001$ for both comparisons). Cosyntropin-stimulated serum total cortisol concentrations were subnormal (18.5 μ g per deciliter [510.4 nmol per liter] or less) in 14 of the patients, all of whom had hypoproteinemia. In all 66 patients, including these 14 who had hypoproteinemia, the base-line and cosyntropin-stimulated serum free cortisol concentrations were high-normal or elevated.

CONCLUSIONS

During critical illness, glucocorticoid secretion markedly increases, but the increase is not discernible when only the serum total cortisol concentration is measured. In this study, nearly 40 percent of critically ill patients with hypoproteinemia had subnormal serum total cortisol concentrations, even though their adrenal function was normal. Measuring serum free cortisol concentrations in critically ill patients with hypoproteinemia may help prevent the unnecessary use of glucocorticoid therapy.

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N Engl J Med 2004;350:1629-38.

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PATIENTS WITH CRITICAL ILLNESSES HAVE elevated glucocorticoid secretion marked by an increase in the serum total cortisol concentration.¹ Assays for serum cortisol measure the total hormone concentration (serum free cortisol plus the protein-bound fraction of cortisol). The current consensus is that the free cortisol, rather than the protein-bound fraction, is responsible for the physiologic function of the hormone.²⁻⁸ Because more than 90 percent of circulating cortisol in human serum is bound to proteins (corticosteroid-binding globulin and albumin), it is reasonable to suggest that alterations in the binding proteins could affect measured concentrations of serum total cortisol²⁻¹⁰ and, thus, the interpretation of tests used to assess adrenal function. The influence of other hormones — for example, estrogen — in raising the concentrations of corticosteroid-binding globulin and, subsequently, serum total cortisol without altering the concentration of free hormone is well established in other settings.^{6,10}

In contrast, the effect of decreased amounts of binding proteins on measured serum total cortisol concentrations is not commonly appreciated.^{1,11} The importance of the fall in serum corticosteroid-binding globulin on measured serum total cortisol concentrations was recently recognized in patients with sepsis,¹² those with trauma,¹² and those undergoing major surgery.¹³ These study groups recommended the use of a calculated correction factor, the free cortisol index (defined as the serum total cortisol concentration divided by the serum corticosteroid-binding globulin concentration), as a surrogate marker that better defines glucocorticoid secretion.^{12,13} These studies did not measure actual serum free cortisol concentrations and did not take into account the effect of hypoalbuminemia, which often accompanies low serum concentrations of corticosteroid-binding globulin.

In critical illness, patients are highly stressed, multiorgan dysfunction and malnutrition may develop, and the concentrations of corticosteroid-binding globulin and albumin are commonly decreased. Therefore, measured serum total cortisol concentrations can be misleadingly lower than anticipated, resulting in the incorrect conclusion that adrenal function is impaired. This mistaken conclusion would be particularly important because current standards for defining normal adrenal function are based on healthy persons who have normal concentrations of binding proteins.

We evaluated adrenal function by measuring se-

rum total cortisol and free cortisol concentrations in critically ill patients without known adrenal dysfunction. We postulated that patients with presumably normal adrenal function but decreased cortisol-binding proteins would have lower-than-expected concentrations of serum total cortisol but appropriately elevated concentrations of the free hormone. We also postulated that measurement of serum free cortisol concentrations would identify patients with normal or even increased adrenal function, who, on the basis of low total cortisol concentrations, would otherwise have been incorrectly considered to have adrenal insufficiency.

METHODS

PATIENT POPULATION AND STUDY DESIGN

We recruited 66 consecutive critically ill patients with various illnesses and an Acute Physiology, Age, and Chronic Health Evaluation (APACHE III)¹⁴ score of 15 or higher: 60 patients from medical, surgical, or cardiac intensive care units and 6 from general medical wards. Patients were excluded if they had a history of hypothalamic–pituitary, adrenal, or liver disease, if they had taken glucocorticoids or estrogen in the preceding year or medications known to influence glucocorticoid secretion (e.g., ketoconazole) in the preceding six months, or if they were pregnant or breast-feeding.

The patients were divided into two groups according to their serum albumin concentration at the time of testing (Table 1). Group 1 was made up of patients with a serum albumin concentration of 2.5 g per deciliter or lower, and group 2 of patients with a serum albumin concentration higher than 2.5 g per deciliter. The underlying disease processes were similar in the two groups. Of the 36 patients in group 1, 11 had sepsis, 10 had cardiovascular disease, 9 had postoperative complications, and 6 had respiratory distress; of the 30 patients in group 2, 7 had sepsis, 13 had cardiovascular disease, 6 had postoperative complications, and 4 had respiratory distress. The physiological components of the APACHE III scoring system,¹⁴ with scores for the patients in our study ranging from 15 to 77, were used to determine the severity of illness, with higher scores indicating more severe illness. Because the serum albumin concentration was used to define the two groups of patients, the severity-of-illness score was determined with and without this variable, with similar results.

Similar measurements of base-line and cosy-

tropin-stimulated cortisol concentrations were performed in 33 healthy volunteers who were without known illnesses and were not receiving medications. Although the healthy volunteers were not individually matched to the patients, their sex and age distributions were similar to those of the two groups of patients. However, the mean age in the healthy volunteers was lower than that in either group of patients.

MEASUREMENTS

Published data on normal concentrations of cosyntropin-stimulated serum total cortisol vary, but normal is generally reported as 18 µg per deciliter (496.6 nmol per liter) or greater.^{1,11,15-17} Our laboratory defines a normal value as 18.5 µg per deciliter (510 nmol per liter) or greater.^{15,17}

For purposes of comparison, serum total cortisol and free cortisol concentrations were measured during acute illnesses in four patients with previously documented adrenal insufficiency and in three with newly diagnosed adrenal insufficiency. In these seven patients, the serum albumin concentrations at presentation ranged from 2.7 to 4.6 g per deciliter.

The four patients with previously diagnosed adrenal insufficiency also had chronic hypopituitarism due to surgically treated pituitary macroadenomas. Despite their having been instructed to increase (at least, double) the physiologic replacement dose of hydrocortisone (15 to 25 mg per day) during periods of stress, these four patients had not received any glucocorticoids for more than 24 hours when they presented with persistent nausea, fever, and malaise. Two of them had urinary tract infections, one had pneumonia, and one had a hip fracture.

Adrenal insufficiency was newly diagnosed in three patients who had presented with similar symptoms that are associated with infection (one had a urinary tract infection, one had pneumonia, and one had gastroenteritis), and the symptoms had failed to respond to standard treatment with intravenous fluid and antibiotic therapy. Adrenal insufficiency in these three patients was due to a corticotropin deficiency (one had a pituitary macroadenoma, one had ischemic pituitary necrosis, and one had previously undergone cranial irradiation for a meningioma).

Cosyntropin stimulation tests (with the use of 250 µg of cosyntropin administered intravenously) were performed in the two groups of patients and in the healthy volunteers between 2 p.m. and 6 p.m.

Serum total cortisol, aldosterone, and free cortisol concentrations were measured before and 30 and 60 minutes after cosyntropin was administered. The institutional review board at our hospital approved the study, and written informed consent was obtained from the healthy volunteers and from the patients, their legal guardians, or designated health care proxies.

LABORATORY ANALYSIS

The base-line plasma corticotropin concentration was measured with the use of immunoradiometric assay kits (Nichols Institute). The intra-assay and interassay coefficients of variation, determined at different ranges of values in the assays were less than 4.5 percent and less than 5.0 percent, respectively. Measurements of serum total cortisol were performed with the use of a standard radioimmunoassay.^{15,17} Serum free cortisol concentrations were measured with the use of equilibrium dialysis of undiluted serum samples for 18 hours followed

Table 1. Characteristics of Critically Ill Patients and Healthy Volunteers.*

Characteristic	Group 1 (N=36)	Group 2 (N=30)	Healthy Volunteers (N=33)
Age (yr)	65.2±14.2†	66.9±10.9†	54.6±16.6
Plasma corticotropin (ng/liter)‡	38.7±12.9§	37.8±18.8§	24.9±9.8
Corticosteroid-binding globulin (mg/liter)	17.7±5.9§¶	21.4±6.8§	26.0±3.8
Serum albumin (g/dl)	1.9±0.3§	3.1±0.4§	3.9±0.3
Total serum protein (g/dl)	4.7±0.8§**	6.0±1.0§	6.8±0.3
Duration of hospitalization before testing (days)	21.2±16.2**	6.4±5.6	NA
Severity-of-illness score	41.6±15.8	40.6±21.4	NA
No. died/no. survived	12/24	7/23	NA
Mean blood pressure (mm Hg)	78±9	81±11	82±5

* Patients in group 1 had serum albumin values less than or equal to 2.5 g per deciliter; those in group 2 had values higher than 2.5 g per deciliter. Severity of illness was measured by Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) scores, which range from 15 to 77, with higher scores indicating more severe illness. Plus-minus values are means ±SD. NA denotes not applicable. Age, corticotropin concentrations, APACHE III scores, the ratio of patients who died to those who survived, and mean blood pressures at the time of testing were similar in the two groups of patients.

† P=0.01 for the comparison with the healthy volunteers.

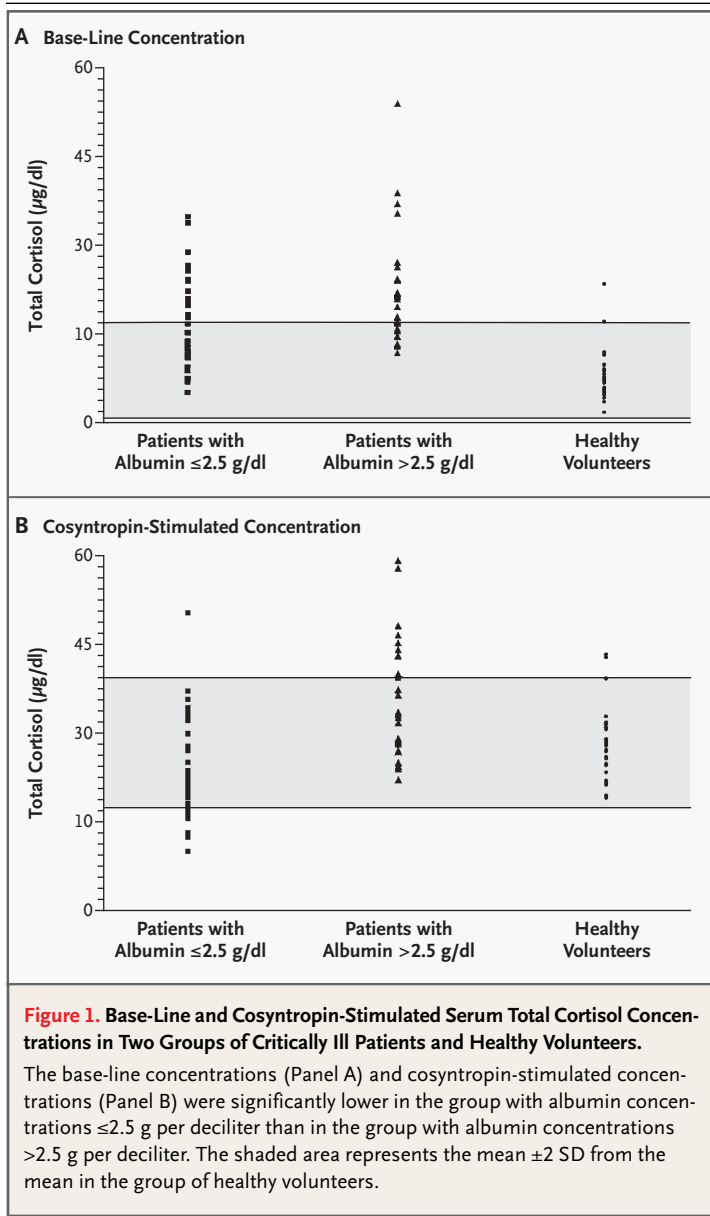
‡ To convert the values for plasma corticotropin to picomoles per liter, multiply by 0.2202.

§ P<0.001 for the comparison with the healthy volunteers, after Bonferroni's correction.

¶ P=0.03 for the comparison with group 2.

|| P<0.001 for the comparison with group 2.

** P=0.01 for the comparison with group 2.



by radioimmunoassay^{18,19}; the intra-assay and interassay coefficients of variation at various concentrations were less than 10 percent and less than 12 percent, respectively. The serum corticosteroid-binding globulin concentration was measured with the use of a radioimmunoassay with intra-assay and interassay coefficients of variation that were less than 6 percent and less than 9 percent, respectively, as determined at various concentrations.²⁰ Measurements of serum free cortisol and corticosteroid-binding globulin concentrations were performed at the Nichols Institute, San Juan Capistrano, Cali-

fornia, at the end of the study. Serum aldosterone concentrations were measured with the use of radioimmunoassay kits (Diagnostic Products).¹⁷ The intraassay and interassay coefficients of variation, determined at various concentrations, were 4.1 percent and 8.8 percent, respectively.

STATISTICAL ANALYSIS

Data are presented as means \pm SD. The data from the two groups of patients and from the controls were first analyzed with the use of the Kruskal–Wallis test, as a nonparametric alternative to analysis of variance. Comparisons between groups were performed with the use of the Wilcoxon rank-sum test for nonparametric measurements. Categorical data were compared with the use of the chi-square test and Fisher's exact test. Differences were considered significant when the two-sided P value was less than 0.05. Bonferroni's correction for multiple comparisons was used as appropriate. Linear and quadratic regressions were fit with the use of standard regression techniques; regression lines were compared between groups with the use of analysis of covariance or the mixed-models approach, which allows for heterogeneity of variance between groups. The data were analyzed with the use of the SAS and SPSS statistical programs.

RESULTS

The two groups of patients had similar clinical characteristics except for their serum albumin, total protein, and corticosteroid-binding globulin concentrations and the duration of hospitalization before testing (Table 1). The base-line serum total cortisol concentrations measured in the afternoon in the 66 critically ill patients varied widely (range, 5.3 to 54.0 μ g per deciliter [146.2 to 1489.9 nmol per liter]) (Fig. 1 and Table 2). Mean base-line serum total cortisol concentrations in the two groups were higher than the mean value in the group of healthy volunteers (Table 2). The base-line serum total cortisol concentrations were lower in patients with hypoproteinemia (group 1) than in those with near-normal serum protein concentrations (group 2).

Likewise, cosyntropin-stimulated serum total cortisol concentrations were lower in patients with hypoproteinemia than in the patients with near-normal serum protein concentrations or the normal volunteers (Fig. 1). The base-line serum total cortisol concentrations were lower than 15 μ g per deciliter (413.8 nmol per liter) in 4 of the 30 patients

Table 2. Base-Line and Cosyntropin-Stimulated Serum Total Cortisol and Free Cortisol Concentrations in Critically Ill Patients and Healthy Volunteers.*

Variable	Group 1 (N=36)	Group 2 (N=30)	Healthy Volunteers (N=33)
Total cortisol			
Base line ($\mu\text{g}/\text{dl}$)	15.8 \pm 7.4 \ddagger \S	22.6 \pm 8.9 \ddagger	8.6 \pm 4.2
Range	5.3–35.4	9.6–54.0	3.8–23.7
Median	13.3	21.5	7.9
After cosyntropin stimulation ($\mu\text{g}/\text{dl}$)	23.4 \pm 9.5 \P	34.4 \pm 10.3 $\ $	27.8 \pm 5.3
Range	10.0–50.2	20.0–59.8	19.1–43.3
Median	21.2	31.6	27.2
Subjects with a maximal response <18.5 μg per deciliter after cosyntropin stimulation — no./total no. (%)	14/36 (39) \ddagger \S	0/30	0/33
Free cortisol			
Base line ($\mu\text{g}/\text{dl}$)	5.1 \pm 4.1 \ddagger \S **	5.2 \pm 3.5 \ddagger	0.6 \pm 0.3
Range	1.3–12.8	1.5–13.0	0.2–1.4
Median	4.0	4.7	0.6
After cosyntropin stimulation ($\mu\text{g}/\text{dl}$)	9.3 \pm 6.3 \ddagger \S **	10.1 \pm 5.9 \ddagger	2.8 \pm 0.7
Range	3.1–29.4	4.0–29.1	1.9–4.5
Median	8.6	9.2	2.7
As a percentage of total cortisol			
At base line	31.1 \pm 14.4 \ddagger \S \P	22.6 \pm 10.2 \ddagger	8.0 \pm 2.1
After cosyntropin stimulation	38.6 \pm 18.9 \ddagger \S \P	29.5 \pm 11.2 \ddagger	10.1 \pm 2.0

* Patients in group 1 had serum albumin values less than or equal to 2.5 g per deciliter; those in group 2 had values higher than 2.5 g per deciliter. Plus–minus values are means \pm SD. Values after cosyntropin-stimulation testing are the highest concentrations at 30 and 60 minutes. To convert the values for serum total cortisol and free cortisol to nanomoles per liter, multiply by 27.59.

\ddagger P<0.001 for the comparison with the healthy volunteers.

\S The comparison was significant after Bonferroni's correction.

\P P<0.001 for the comparison with group 2.

$\|$ P=0.006 for the comparison with the healthy volunteers.

** P=0.005 for the comparison with the healthy volunteers.

** P not significant for the comparison with group 2.

\P $\|$ P=0.02 for the comparison with group 2.

\S $\|$ P=0.07 for the comparison with group 2.

with near-normal serum protein concentrations and in 21 of the 36 patients with hypoproteinemia. The base-line percentage of free cortisol in all 66 patients taken together was nearly three times as high as that in healthy volunteers.

Mineralocorticoid secretion was normal in both patient groups. Base-line and cosyntropin-stimulated serum aldosterone concentrations were similar in group 1, group 2, and the controls (base-line concentration, 10.7 \pm 18.5, 12.7 \pm 13.6, and 9.2 \pm 6.9 ng per deciliter [296.8 \pm 513.2, 352.3 \pm 377.3, and 255.2 \pm 191.4 pmol per liter], respectively; cosyntropin-stimulated concentration, 21.5 \pm 20.1, 23.0 \pm 26.5, and 26.4 \pm 7.6 ng per deciliter [596.4 \pm 557.6, 638.0 \pm 735.1, and 732.3 \pm 210.8 pmol per liter], respectively).

As shown in Tables 2 and 3, “subnormal” co-

syntropin-stimulated serum total cortisol concentrations (less than 18.5 μg per deciliter [510.4 nmol per liter]) were measured in 14 patients, all of whom had hypoproteinemia. The findings in these 14 patients were compared with findings in the remaining 52 patients who were considered to have normal responses (18.5 μg per deciliter or more). The two patient groups had similar clinical characteristics as well as similar base-line and cosyntropin-stimulated serum free cortisol concentrations (base line, 4.6 \pm 1.3 vs. 5.2 \pm 3.6 μg per deciliter [126.9 \pm 35.9 and 143.5 \pm 99.3 nmol per liter]; cosyntropin-stimulated, 8.9 \pm 3.3 vs. 9.3 \pm 6.0 μg per deciliter [245.6 \pm 91.0 and 256.6 \pm 165.5 nmol per liter]). These levels were several times as high as the respective values in controls (Fig. 2 and Tables 2 and 3). All 14 patients with subnormal total cortisol responses (less

Table 3. Clinical Characteristics of Critically Ill Patients According to Cosyntropin-Stimulated Serum Total Cortisol Concentrations.*

Clinical Characteristic	Cosyntropin-Stimulated Serum Total Cortisol		P Value
	<18.5 µg/dl (N=14)	≥18.5 µg/dl (N=52)	
Serum total cortisol (µg/dl)			
At base line	11.5±3.6	19.2±8.7	<0.001
After cosyntropin stimulation	15.4±2.7	30.2±9.2	<0.001
Serum free cortisol (µg/dl)			
At base line	4.6±1.3	5.2±3.6	0.07
After cosyntropin stimulation	8.9±3.3	9.3±6.0	0.08
Free cortisol as a percentage of total cortisol (%)			
At base line	42.2±12.0	26.3±12.1	0.009
After cosyntropin stimulation	54.3±18.1	30.1±14.1	0.004
Serum aldosterone (ng/dl)			
At base line	11.8±13.6	11.6±16.6	0.11
After cosyntropin stimulation	21.5±18.9	22.6±32	0.13
Plasma corticotropin (ng/liter)	42.1±12.3	34.9±15.4	0.19
Serum albumin (g/dl)	1.7±0.2	2.6±0.7	<0.001
Corticosteroid-binding globulin (mg/liter)	16.7±4.8	19.8±6.7	0.03
Severity-of-illness score	44.3±18.1	41.5±21.2	0.41
Duration of illness (days)	24.8±10.1	6.9±13.0	0.007
No. of deaths/total no. of patients	6/14	13/52	0.59

* Cosyntropin-stimulated serum total cortisol concentrations ≥18.5 µg per deciliter were defined as normal, and those <18.5 µg per deciliter were defined as subnormal. Plus-minus values are means ±SD. To convert serum cortisol and free cortisol values to nanomoles per liter, multiply by 27.59. To convert serum aldosterone values to picomoles per liter, multiply by 27.74. To convert plasma corticotropin values to picomoles per liter, multiply by 0.2202.

than 18.5 µg per deciliter) had cosyntropin-stimulated serum free cortisol concentrations (minimum, 3.1 µg per deciliter [85.5 nmol per liter]) that were higher than the mean value in the controls (2.8 µg per deciliter [77.3 nmol per liter]).

Of these 14 patients, 6 were reevaluated 6 to 10 weeks after hospital discharge, at which point their serum albumin concentrations had normalized. The cosyntropin-stimulated serum total cortisol concentrations had normalized (21 to 32 µg per deciliter [537.4 to 882.8 nmol per liter]) and were higher than the values obtained when the patients had been critically ill (11.0 to 16.7 µg per deciliter [303.5 to 460.8 nmol per liter]). However, the cosyntropin-stimulated serum free cortisol concentrations in these patients were high (3.2 to 10.1 µg per deciliter [88.3 to 278.7 nmol per liter]) during critical illness and were in the high-normal range (2.6 to 4.2 µg per deciliter [71.7 to 115.9 nmol per liter]) after recovery.

The base-line and cosyntropin-stimulated serum total cortisol concentrations in the 19 patients who died (18.7±9.8 and 29.9±11.3 µg per deciliter [515.9±270.4 and 824.9±311.8 nmol per liter], respectively) were similar to those in the 47 patients who survived (18.9±8.5 and 28.1±10.8 µg per deciliter [521.5±234.5 and 775.3±298 nmol per liter], respectively). The findings were similar for base-line and cosyntropin-stimulated serum free cortisol concentrations (5.8±3.7 and 10.5±6.1 µg per deciliter [160.0±102.1 and 289.7±168.3 nmol per liter], respectively, in the group of patients who died and 5.0±3.5 and 9.2±5.5 µg per deciliter [138.0±96.6 and 253.8±151.7 nmol per liter], respectively, in those who survived).

A comparison of the 18 patients who had sepsis with the 48 patients who had other illnesses showed similar concentrations of serum albumin (2.4±0.7 and 2.5±0.9 g per deciliter), base-line serum total cortisol (18.2±10.0 and 19.0±10.5 µg per deciliter [502.1±275.9 and 524.2±289.7 nmol per liter]), base-line free cortisol (4.6±2.9 µg per deciliter and 5.2±3.0 µg per deciliter [126.9±80.0 and 143.5±82.8 nmol per liter]), cosyntropin-stimulated serum total cortisol (26.9±11.0 and 28.0±10.7 µg per deciliter [742.1±303.5 and 772.5±295.2 nmol per liter]), and free cortisol (8.6±5.0 and 9.4±5.5 µg per deciliter [237.3±138.0 and 259.3±151.7 nmol per liter], respectively). The seven patients with adrenal insufficiency had low or low-normal base-line total cortisol concentrations (0.2 to 5.8 µg per deciliter [5.5 to 160.0 nmol per liter]) as well as low free cortisol concentrations (0.1 to 0.56 µg per deciliter [2.8 to 15.5 nmol per liter]). The three patients with newly diagnosed adrenal insufficiency had subnormal concentrations of cosyntropin-stimulated serum total cortisol (10, 12, and 15 µg per deciliter [275.9, 331.1, and 413.9 nmol per liter]) and free cortisol (0.89, 1.1, and 1.3 µg per deciliter [24.6, 30.3, and 35.9 nmol per liter]).

The base-line serum total cortisol concentrations in the healthy volunteers were correlated with the serum concentrations of free cortisol (Fig. 3) ($r=0.85$, $P<0.001$) and serum corticosteroid-binding globulin ($r=0.59$, $P<0.001$), but not with the serum albumin concentrations. Base-line serum total cortisol concentrations in the two patient groups were correlated with the serum free cortisol concentrations (Fig. 3). In contrast to the findings in healthy volunteers, the base-line serum total cortisol concentrations in the patients in both groups were not correlated with the serum corticosteroid-binding

globulin concentrations but were instead correlated with serum albumin concentrations ($r=0.50$, $P=0.003$). Only four patients with an albumin concentration of 2.5 g per deciliter or less received glucocorticoid therapy after testing, and none of the four had clinically significant hemodynamic improvement. Thus, glucocorticoid therapy was discontinued in these patients.

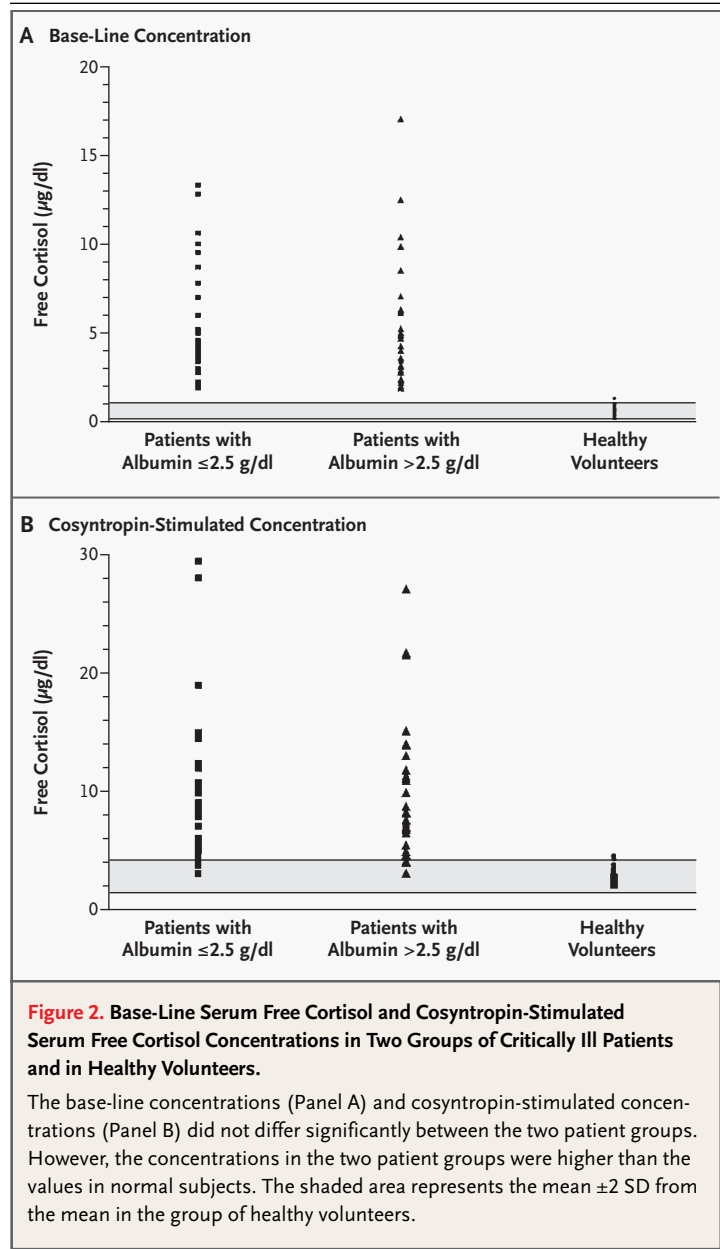
DISCUSSION

These data show that critically ill patients have an activated pituitary–adrenal axis characterized by elevated plasma corticotropin concentrations and an increase by a factor of 7 to 10 in serum free cortisol concentrations, but only a doubling or tripling of serum total cortisol concentrations. This observation was not diagnosis-specific, and the hypercortisolism persisted in patients with prolonged severe illnesses.

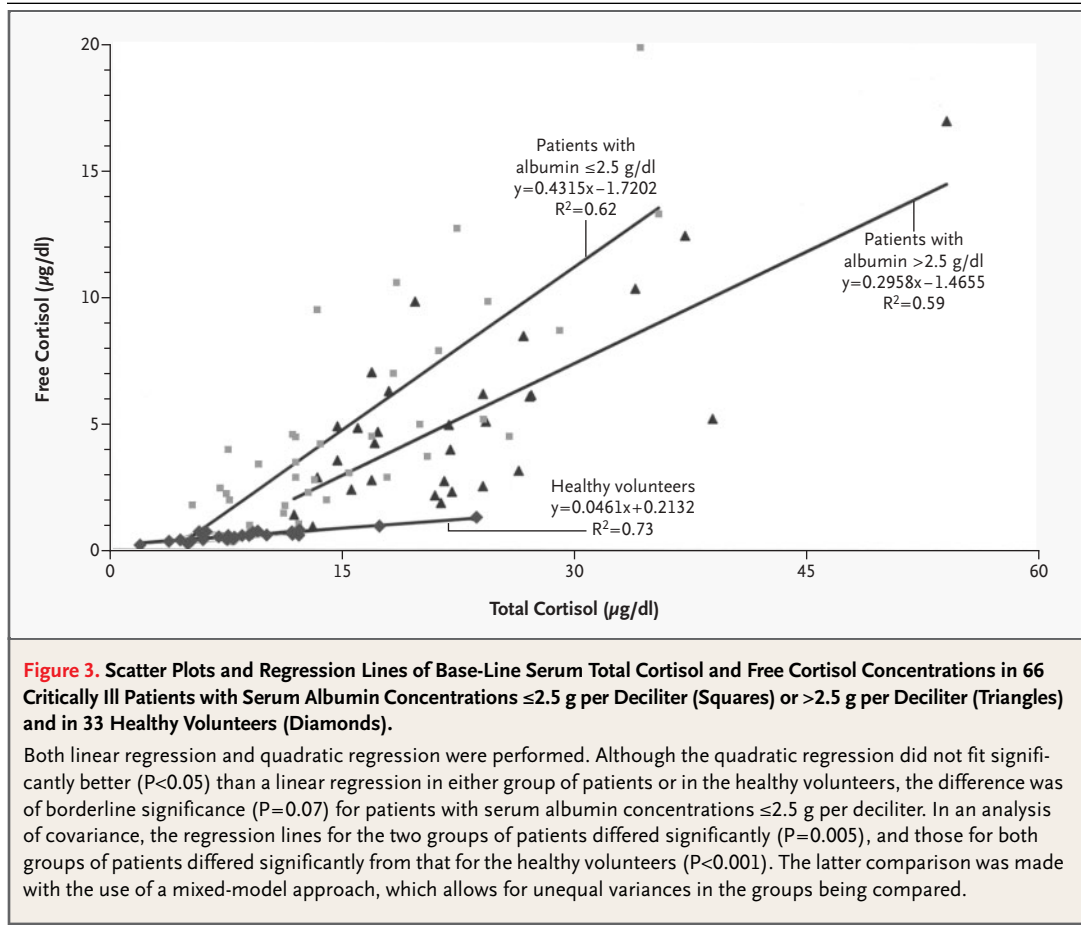
Our data also suggest that measuring base-line or corticotropin-stimulated serum total cortisol concentrations in critically ill patients with hypoproteinemia (defined as a serum albumin concentration lower than 2.5 g per deciliter) can be misleading, if the criteria for adrenal insufficiency are based on concentrations in healthy subjects with normal concentrations of serum-binding proteins. In contrast, base-line and cosyntropin-stimulated serum free cortisol concentrations in critically ill patients with hypoproteinemia do not differ significantly from those in patients with near-normal serum albumin concentrations.

It is important to attempt to define a normal adrenocorticosteroid response in critically ill patients. Despite a large increase in glucocorticoid secretion, some critically ill patients can have relative adrenal insufficiency, with elevated cortisol concentrations that are insufficient to control the inflammatory response.²¹⁻²³ Tissue-specific resistance to corticosteroids has also been postulated. Annane and colleagues^{23,24} reported that in patients with catecholamine-dependent septic shock, the failure of total serum cortisol concentrations to increase by more than 9 μg per deciliter (248.3 g per liter) above base line after cosyntropin stimulation could be used to identify those with relative adrenal insufficiency whose risk of death was reduced after one week of intravenous hydrocortisone treatment.^{23,24}

It is unknown whether these findings are unique to patients with septic shock, who might also have glucocorticoid resistance, or whether relative adre-



nal insufficiency might be seen in other critical illnesses.²⁵ Serum concentrations of free cortisol were not measured in these studies, and no albumin concentrations were reported. It is likely that serum free cortisol concentrations, as compared with serum total cortisol concentrations, offer a better reflection of activation of the hypothalamic–pituitary–adrenal axis in critically ill patients with hypoproteinemia. Whether serum free cortisol concentrations are correlated better with outcomes such as death remains speculative.



Other factors, in addition to marked stress and variation in concentrations of binding proteins, can potentially influence the “normal” concentrations of serum total cortisol or free cortisol during critical illness. Such factors include possible tissue-specific resistance to corticosteroids, which can vary according to the illness.²⁵⁻²⁸ Our data suggest that the cosyntropin-stimulated serum total cortisol and free cortisol concentrations are higher in critically ill patients than in healthy volunteers. Accordingly, it is important to define normal serum total cortisol concentrations in critically ill patients. Many believe that a threshold value of 15 μg per deciliter (413.9 nmol per liter) best identifies critically ill patients with adrenal insufficiency.¹ Although this may be true for patients with normal concentrations of binding proteins, the threshold may be lower in those with severe hypoproteinemia, in which case measurements of serum free cortisol concentrations are more valuable.

Other than the present data and reports based

on a few patients,⁶ no published studies have determined normal serum free cortisol concentrations during critical illness. Given these limitations, an attempt to define normal values during various critical illnesses would be premature. In highly stressed, critically ill patients, base-line serum free cortisol concentrations would be expected to exceed cosyntropin-stimulated concentrations in normal, unstressed subjects (1.9 μg per deciliter [52.4 nmol per liter] or higher). We therefore recommend that a base-line serum free cortisol concentration of 2.0 μg per deciliter (55.2 nmol per liter) be considered as a threshold that identifies patients at risk for adrenal insufficiency during critical illness. Further testing (for example, measurement after cosyntropin stimulation) may be necessary in critically ill patients with lower concentrations. Since the cosyntropin-stimulated serum free cortisol concentrations in the critically ill patients in our study were 3.1 μg per deciliter (85.3 nmol per liter) or higher, we recommend that this value be used to define

normal cosyntropin-stimulated serum free cortisol concentrations in critically ill patients until additional data from studies of larger numbers of patients become available.

Until serum free cortisol measurements become widely available, the use of serum total cortisol concentrations would seem reasonable. Obviously, clinical judgment must be exercised in deciding whether to administer glucocorticoids to critically ill patients both before and after serum total cortisol or free cortisol concentrations are available, even in the case of patients with apparently normal values. This decision would be clinically important in treating patients with hypotension or those who do not have a response to volume or pressor therapy. Such patients, particularly those with septic shock, are at risk for relative adrenal insufficiency and might benefit from therapy with exogenous glucocorticoids, as was recently demonstrated.²³ Thus, instead of long-term therapy, the administration of glucocorticoids should be limited to only a few days in selected patients.

Corticosteroid-binding globulin has a low capacity and a high affinity for binding cortisol, whereas albumin has a high capacity and a low affinity for binding cortisol.^{2,6-9,29} In humans and at physiologic concentrations, corticosteroid-binding globulin can bind up to 25 μ g of circulating cortisol per deciliter (689.8 nmol per liter). As corticosteroid-binding globulin becomes saturated, a larger proportion of circulating serum-bound cortisol will be bound to albumin. A steady reduction in the percentage of bound cortisol was noted when albumin concentrations in isolated albumin solutions or in plasma were reduced to less than 2.0 g per deciliter.⁹

Our data on the correlation between serum free cortisol and total cortisol concentrations are consistent with this concept. The fact that measured concentrations of serum total cortisol can be misleadingly low only when hypoproteinemia is severe is also consistent with this concept. Earlier studies showed that corticosteroid-binding globulin activity is decreased in certain types of stress, such as shock due to bacterial or fungal infection or septic shock, major burns, and recent abdominal or thoracic surgery.³⁰⁻³⁸ The decrease in binding activity was attributed, by some, to a reduction in the concentration of corticosteroid-binding globulin — and perhaps also to the presence of factors that inhibit binding or to structural changes in corticosteroid-binding globulin, leading to an increased dissociation from cortisol.^{1,29-38}

In summary, our study indicates that severe hypoproteinemia results in lower-than-expected concentrations of serum total cortisol in 39 percent of critically ill patients. Nevertheless, serum free cortisol concentrations are consistently elevated, suggesting a substantial increase in glucocorticoid secretion in such patients. Caution should be exercised in interpreting base-line and cosyntropin-stimulated serum total cortisol values in critically ill patients with hypoproteinemia.

Supported in part by a grant (M01RR000080) to the Clinical Research Center of Case Western Reserve University from the National Center for Research Resources.

Presented in part at the 82nd meeting of the Endocrine Society, Toronto, June 21–24, 2000.

We are indebted to the staff and nurses at the Clinical Research Center and Intensive Care Units at the University Hospitals of Cleveland for their help in completing the study, to Dr. Mark Schluchter for help with the statistical analysis of the data, and to Drs. F. Ismail-Beigi and S. Genuth for reviewing the manuscript.

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