The Value of Perioperative Levels of ACTH, DHEA, and DHEA-S and Tumor Size in Predicting Recurrence of Cushing Disease

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Context and Objectives: Despite the development of hypocortisolemia after corticotroph surgical adenomectomy, 15% to 20% patients have recurrence of Cushing disease (CD). In this study, we investigated the effect of tumor size and the value of perioperative assessment of corticotropin (ACTH) and adrenal steroid levels in predicting recurrence.

Design: Perioperatively, no glucocorticoids were administered until the serum cortisol was ≤ 3 μg/dL. Blood samples were obtained before and repeatedly after adenomectomy in 79 patients with CD. Of these, 66 had a nadir serum cortisol of ≤ 3.0 μg/dL and clinical and biochemical remissions. During a median follow-up of 131 months, 11 of 66 had disease recurrence (REC), whereas 55 of 66 did not (NO-REC).

Results: Preoperative hormone levels in the REC and NO-REC groups were similar. After adenomectomy, a brief and similar increase in ACTH, cortisol, and dehydroepiandrosterone (DHEA) levels was observed in both groups followed by gradual decline in those levels. Although REC and NO-REC patients had similar cortisol levels (3.4 ± 1.7 μg/dL vs 2.9 ± 2.2 μg/dL) at the 36th postoperative hour, their respective ACTH (33 ± 7.1 ng/L vs 12.1 ± 5.4 ng/L; $P < 0.0001$), DHEA (3.8 ± 1.7 ng/mL vs 1.2 ± 1.1 ng/mL; $P = 0.005$), and dehydroepiandrosterone sulphate (DHEA-S) (143.9 ± 45.2 μg/dL vs 48.9 ± 38.2 μg/dL; $P < 0.0001$) were higher. At nadir hypocortisolemia, perioperative ACTH levels were >20 in all REC patients and <20 ng/L in the NO-REC group. Patients with REC had larger tumors than those with NO-REC.

Conclusion: Recurrent CD is characterized by persistent perioperative ACTH secretion after adenomectomy. Higher perioperative levels of ACTH, DHEA, and DHEA-S are highly predictive of future disease recurrence, particularly in those with profound hypocortisolemia. (*J Clin Endocrinol Metab* **103: 477–485, 2018**)

After successful removal of corticotropin (ACTH)-secreting pituitary adenomas, patients develop central adrenal insufficiency requiring glucocorticoid replacement therapy for several months. In fact, the development of hypocortisolism immediately after surgery is considered a favorable indication of surgical success (1–11). However, long-term follow-up studies on patients with ACTH-secreting adenomas have shown that despite apparent initial success and evidence for hypocortisolism in the immediate postoperative period, some patients have recurrence of their disease within 2 to 5 years (7, 12–15).

Evaluating the outcome of surgery perioperatively has remained a serious challenge (4, 9–16), although the simplest approach is measurement of serum cortisol levels. In fact, the development of hypocortisolemia soon after surgery has been used a favorable marker of surgical success (4, 10–13).

We have advocated, nearly 30 years ago, that glucocorticoid administration is unnecessary during or soon

Abbreviations: ACTH, corticotropin; CD, Cushing disease; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; HPA, hypothalamic-pituitary-adrenal; ROC, receiver operating characteristics.

after surgical resection of corticotroph adenomas until documentation of need is established (17). We reasoned that even if ACTH secretion ceased completely after adenomectomy, serum cortisol levels, with a half-life of 1.5 to 2 hours (18), will not decrease to low values during the first few postoperative hours. The latter approach offered the opportunity to examine perioperative hormonal alterations (10, 11, 15).

In an earlier study, we demonstrated the predictive value of perioperative plasma ACTH measurement on disease recurrence (15). The latter study showed that despite profound perioperative hypocortisolemia, a simultaneously measured plasma ACTH of >20 ng/L accurately predicted disease recurrence (15). Limited data are available on the simultaneous alterations in ACTH levels and cortisol levels in the immediate postoperative period (19).

In a recent report, we demonstrated that in patients with ACTH deficiency, loss of adrenal androgen secretion [dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-S)] precede the decline in glucocorticoid secretion (20). Because patients with Cushing disease (CD) develop perioperative ACTH deficiency, we reasoned that this should alter adrenal androgen secretion during that period. We postulated that loss of ACTH secretion after adenomectomy would lead to a rapid decline in adrenal androgen secretion. We also postulated that persistent ACTH secretion as observed in those who had disease recurrence would lead to persistent androgen secretion. The current investigation examined the dynamic alterations in ACTH, cortisol, and adrenal androgen secretion after surgical resection of corticotroph adenomas and explored the role of such alterations in predicting future disease recurrence.

Patient Population and Study Design

Patients included in the study

This is a prospective observational study that included patients who had transsphenoidal surgical removal of ACTH-secreting pituitary adenomas between the years 2000 and 2015 by one neurosurgeon (W.R.S.). The study was approved by the Institutional Research Board, and informed consent was obtained from participants. This study is an extension of our previous publication (15) on this patient population, and most patients included in the earlier study are enrolled in the current one. Because most recurrences occur within the first 2 to 3 postoperative years, we included those who had a minimum follow-up of >2 years. During that time frame, a total of 97 patients with established CD had pituitary surgery. Of these, 18 were excluded from the analysis because some had received medical/radiation therapy preoperatively (n = 10)

whereas others had no documented adenomas (n = 2) or had a total hypophysectomy (n = 4), and a few were on medications that alter cortisol measurements (n = 2). That left 79 hypercortisolemic patients who had visual confirmation and/or histological/immunocytochemical documentation of corticotroph pituitary adenomas. Of the latter 79 patients, 66 had a nadir serum cortisol level in the perioperative period of ≤3 μg/dL whereas the remaining 13 had levels ≥4 μg/dL (Table 1). This investigation will primarily focus on the 66 patients who had a nadir postoperative serum cortisol of ≤3 μg/dL.

Perioperative management protocol

The protocol that has been followed stipulated that glucocorticoids are not administered before and during surgery. Instead, patients were frequently evaluated clinically and biochemically for evidence for adrenal insufficiency (10, 11, 15). Blood samples for the determination of plasma ACTH, serum cortisol, DHEA, and DHEA-S levels were drawn before adenomectomy and at 2 to 4 hours, 6 to 8 hours, and every 6 hours thereafter for 48 hours after surgery. Blood samples were drawn within 1 to 2 hours of the specified time window. In three patients where there was continued decline in serum cortisol, blood draws were extended to 60 hours. In an attempt to minimize clinical symptoms of adrenal insufficiency, we used a nadir serum cortisol level of ≤3 μg/dL as an indication of early surgical success and the time to initiate glucocorticoid therapy. Patients who had a nadir serum cortisol of >4 μg/dL were managed as described earlier (15).

Although plasma ACTH and serum DHEA and DHEA-S levels were drawn in the perioperative period, the results were not immediately available and they were not used to define remissions nor the need for glucocorticoid therapy. Once glucocorticoids were administered, blood samples for hormone measurements were discontinued.

Clinical follow-up/management

All 66 patients who had a nadir serum cortisol of ≤3 μg/dL achieved clinical remission soon after surgery and were documented to have hypocortisolism requiring hydrocortisone replacement therapy for 6 to 20 months. Once off hydrocortisone replacement therapy, patients had the 1-μg cosyntropin stimulation test to document hypothalamic-pituitary-adrenal (HPA) axis recovery. Thereafter, patients had annual clinical and biochemical screening studies that included a 24-hour urinary free cortisol determination and the 1-mg dexamethasone suppression test as described earlier (15).

Patients with postoperative serum cortisol levels of >10 μg/dL (n = 5) were followed clinically, and all

Table 1.   Preoperative and Postoperative Clinical and Biochemical Characteristics in 79 Patients With CD Stratified According to Their Nadir Postoperative Serum Cortisol Levels

	Nadir Serum Cortisol of ≤3 μg/dL (n = 66)	Nadir Serum Cortisol of ≥4 μg/dL (n = 13)	P Value
Age	39.6 ± 12.9	38.9 ± 13.3	0.49
Sex (female:male)	46:20	8:5	0.28
Tumor size (cm)	0.79 ± 0.52	1.48 ± 0.72[a]	0.01
Preoperative data			
ACTH (ng/L)	80.2 ± 66.8	89.9 ± 45.7	0.93
Cortisol (μg/dL)	29.9 ± 12.3	30.6 ± 6.4	0.97
DHEA (ng/mL)	7.7 ± 5.0	9.0 ± 4.8	0.14
DHEA-S (μg/dL)	151.9 ± 57.1	171.6 ± 39.3	0.11

[a]Extrasellar extension was suspected/demonstrated in 7 of 13.

required additional therapy for hypercortisolism after modest initial clinical improvement. All patients (n = 8) with postoperative serum cortisol of >4 and <10 μg/dL were discharged on hydrocortisone therapy that was discontinued at 1 month in three subjects and at 3 to 5 months in the remaining five subjects.

Laboratory analysis

Plasma ACTH concentrations were measured using solid-phase, two-site sequential chemiluminescent immunometric assay, using the Immulite 2000XPi (Siemens, Malvern, PA). Intra-assay coefficients of variation for the lower and upper limits are 4.4% and 3.1%, respectively. Interassay coefficients of variation for the lower and upper assay ranges are 9.0% and 8.5%, respectively. The assay used two specific antibodies that detect the entire ACTH molecule.

Serum cortisol measurements were made using the direct chemiluminescent immunoassay method, using the Advia Centaur XP instrument (Siemens, Malvern, PA). Intra-assay coefficients of variation for the lower, mid, and upper assay measurement ranges are 4.7%, 3.9%, and 2.3%, respectively. The interassay coefficients of variation for the lower, mid, and upper limits are 6.1%, 8.2%, and 4.4%, respectively.

Serum DHEA levels were measured with the high-performance liquid chromatography-tandem mass spectroscopy method developed by Quest Diagnostics Nichols Institute (San Juan Capistrano, CA). The intra-assay coefficients of variation at the lower, mid, and upper limits are 13.5%, 5.2%, and 3.3%, respectively. The interassay coefficients of variation at the lower, mid, and upper limits are 14.3%, 7.7%, and 7.1%, respectively.

Serum DHEA-S levels were measured using solid-phase, chemiluminescent enzyme-labeled immunoassay, using the Immulite 2000XPi (Siemens). Intra-assay coefficients of variation at the lower, mid, and upper limits are 7.4%, 5.4%, and 4.8%, respectively. The interassay coefficients of variation at the lower and upper limits are 8.5% and 7.9%, respectively.

Statistical analysis

Data are presented as mean ± standard deviation, unless stated otherwise. The perioperative data on patients with recurrence and those without recurrences were first analyzed using the Kruskal-Wallis test, as a nonparametric alternative to analysis of variance test, and then comparisons between groups were done using the Wilcoxon rank sum test for nonparametric measurements. Categorical data were compared using χ^2 and Fisher's exact tests. Differences were considered significant when the two-sided P values were less than 0.05. The data on patients with a nadir serum cortisol of ≤3 μg/dL were further evaluated using receiver operating characteristics (ROC) curve analysis. All data analyses were made using the SPSS program.

Results

Clinical characteristics

The clinical characteristics of the 79 patients are shown in Table 1. Except for the fact that the mean tumor size of patients who had a nadir postoperative serum cortisol of ≥4 μg/dL were larger than that of patients whose postoperative levels were ≤3 μg/dL, the two groups had similar characteristics.

Perioperative serum cortisol levels

Serum cortisol levels decreased during the perioperative period to a nadir of ≤3 μg/dL in 66 of 79 and were ≥4.4 μg/dL in the remaining 13 patients (Table 1). Five of the latter 13 patients had a nadir serum cortisol of >10 μg/dL whereas the remaining 8 had levels ranging from 4.4 to 9 μg/dL.

Of the 66 patients who had a nadir serum cortisol level of ≤3 μg/dL, a few (n = 4) reached that level as early as 8 to 12 hours after surgery, but most had their lowest serum cortisol concentration 24 to 36 hours following adenomectomy with a mean of 33 ± 11 hours and a median of 36 hours.

Early clinical results

Clinical remissions were noted in all 66 patients who had a nadir serum cortisol of ≤3 μg/dL. All required

hydrocortisone replacement therapy for 6 to 20 months (median: 12 months). In contrast, only 3 of the 13 patients who had a nadir serum cortisol of >4 μg/dL had clinical remissions and required hydrocortisone replacement therapy for 3 to 5 months.

Long-term follow-up

Long-term follow-up of patients whose serum cortisol levels decreased to ≤3 μg/dL was quite interesting in that 55 of the 66 patients remained clinically and biochemically in remission at their last follow-up visit 29 to 179 months (mean: 131.3 ± 21 months; median: 131 months) after surgery. The remaining 11 patients developed clinical and biochemical confirmation of disease recurrence 26 to 66 months after adenomectomy. All five patients whose nadir serum cortisol levels were >10 μg/dL had persistent disease and required additional therapy. In contrast, three of the eight patients whose serum cortisol nadir was >4 but <10 μg/dL had initial clinical remissions but developed disease recurrence 14 and 65 months after adenomectomy, whereas the remaining five had persistent clinical and biochemical hypercortisolemia requiring additional therapy.

Perioperative data of patients who had a nadir serum cortisol of ≤3 μg/dL

Serum cortisol levels

Figure 1 illustrates the changes in serum cortisol levels in the perioperative period among these 66 patients comparing those who had remained in remission (n = 55) to others who had recurrence of their disease (n = 11). As shown in the figure, there was an increase in the mean serum cortisol level 2 to 4 hours after adenomectomy that was observed in patients with and others without future recurrence ($P < 0.01$, $P = 0.043$; respectively). Thereafter, serum cortisol in these patients declined gradually, and the levels observed in the group who remained in remission were similar to those noted in the 11 who had disease recurrence throughout the postoperative period.

Plasma ACTH

Plasma ACTH levels increased 2 to 4 hours after adenomectomy (Fig. 1) in patients with recurrences ($P = 0.043$) as well as in others who did not have a recurrence ($P < 0.001$). Following that, plasma ACTH levels declined gradually in both groups. Comparison of the respective plasma ACTH data from the two subgroups obtained at 6 hours showed that the two were significantly
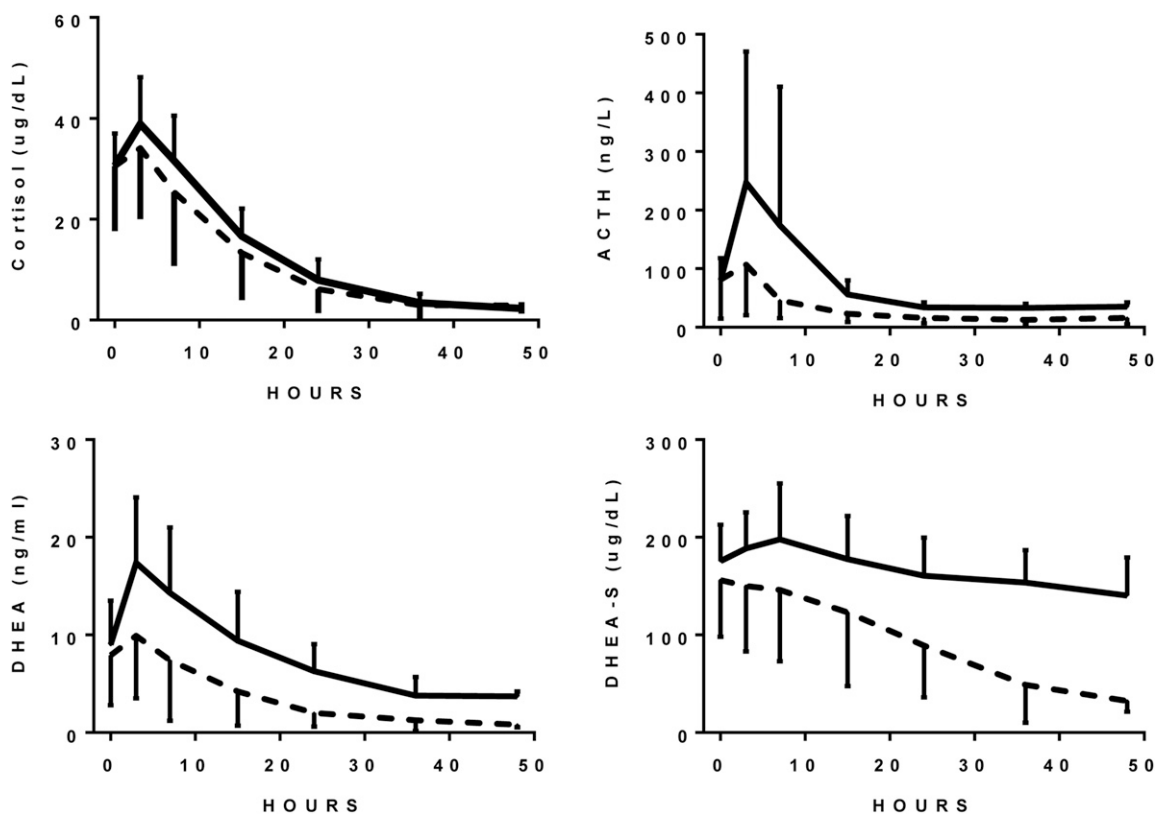

Figure 1. Mean and standard deviation of plasma ACTH (top right panel), serum cortisol (top left panel), DHEA (bottom left panel), and DHEA-S (bottom right panel) levels in 66 patients with CD obtained during the first 48 perioperative hours. Patients who had future recurrence of their disease are depicted in solid line whereas those who had sustained remissions are depicted in interrupted lines. The end of surgery was taken as time 0.

different ($P = 0.032$), whereas the respective data at 2 to 4 hours were not. Importantly, it was noted that by 12 to 18 hours after surgery and onward, patients who had future recurrences had consistently higher plasma ACTH levels than those who had no recurrences ($P < 0.001$). In contrast, serum cortisol levels in the latter two subgroups were similar at all respective time intervals (Fig. 1).

Simultaneous measurements of plasma ACTH and adrenal steroid levels obtained when serum cortisol levels reached their nadir of ≤ 3 μg/dL are illustrated in Fig. 2.

Despite similar degrees of hypocortisolemia, there were distinct differences between those who had disease recurrence and others who remained in remission. At the time patients achieved their nadir serum cortisol level, plasma ACTH concentrations were higher ($P < 0.001$) in those who had recurrences than in others who remained disease free (Fig. 2). All patients with future recurrences had plasma ACTH levels consistently >20 ng/L even though their simultaneously measured serum cortisol was ≤ 3 μg/dL.

Serum DHEA levels

Serum DHEA levels increased at 2 to 4 hours after adenomectomy (Fig. 1) in patients who remained in remission ($P = 0.008$) as well as in those who had future recurrences ($P = 0.005$). The latter increase paralleled the previously described rise in serum cortisol levels at that time. Thereafter, serum DHEA levels declined gradually throughout the perioperative period (Fig. 1). At all time periods throughout the perioperative period, mean serum DHEA levels were higher (P values <0.01 to 0.001) in patients who had future recurrences than in those who had sustained remissions. At and beyond the 24th postoperative hour, patients with sustained remissions had very low serum DHEA levels that were similar to those observed in patients with central adrenal insufficiency (20).

Serum DHEA-S levels

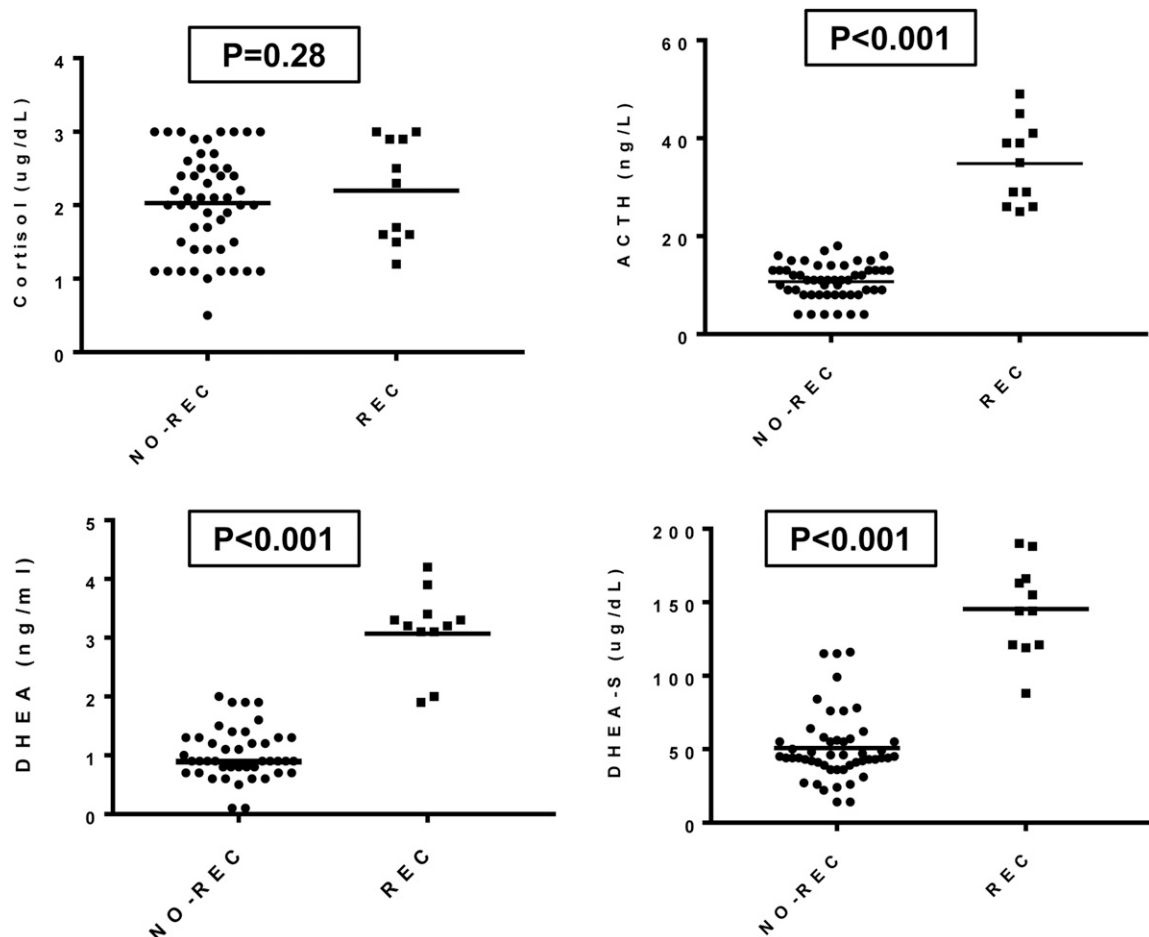During the first 8 postoperative hours, serum DHEA-S levels were unchanged in both groups of patients. However,

Figure 2. Hormone levels in all 66 patients with CD obtained simultaneously when serum cortisol levels reached their nadir of ≤ 3 μg/dL. Shown are data on serum cortisol (top left panel), ACTH (top right panel), DHEA (bottom left panel), and DHEA-S (bottom right panel). Within each of the four graphs, patients are divided into those who had no recurrence (NO-REC; n = 55) and others who had recurrence during the follow-up (REC; n = 11). Points on each of the four graphs represent data from a single patient. The horizontal line within each graph represents the mean of the respective group. The inserted boxes show the P values comparing respective groups.

thereafter, the levels declined gradually in patients without recurrences such that they reached low levels ($P < 0.001$) by 36 to 48 postoperative hours (Fig. 1). The data demonstrate that serum DHEA-S levels decreased by >50% of their respective baseline values in every patient with sustained remission such that by the 48th postoperative, the mean level reached nearly 25% of the preoperative values (Fig. 1). In contrast, there were no appreciable changes ($\pm$20%) in perioperative serum DHEA-S levels of patients who had disease recurrence.

Factors predicting recurrences after perioperative hypocortisolemia

We analyzed the pre- and perioperative data on the 66 patients who had a nadir postoperative serum cortisol of $\leq$3 μg/dL (Table 2; Fig. 2). Except for a significant difference in tumor size (Fig. 3), other parameters such as age, sex, and preoperative serum cortisol and plasma ACTH levels in the two subgroups were similar. Dural invasion by the tumor was not examined consistently to indicate its impact on tumor recurrences. Cavernous sinus invasion was suspected in 2 of the 11 patients who had disease recurrence and in none of the 55 who remained in remission.

The major difference between the two subgroups was in their respective perioperative hormone levels (Fig. 2). Whereas the two subgroups had similarly low serum cortisol levels when the latter reached its nadir (1.8 $\pm$ 0.8 μg/dL vs 2.1 $\pm$ 0.7 μg/dL), the simultaneously measured ACTH, DHEA, and DHEA-S levels were distinctly different. In all 11 patients who had recurrences, plasma ACTH levels drawn at the time when serum cortisol was at nadir values ($\leq$3 μg/dL) were all >20 ng/L. In contrast, all 55 patients who had sustained remissions after a median follow-up of nearly 11 years had a plasma ACTH of <20 ng/L at the time of cortisol nadir. We were unable
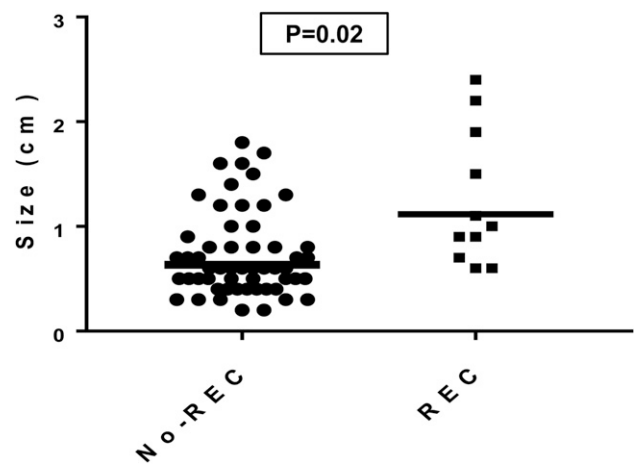

Figure 3. Tumor sizes in centimeters depicted for the 66 patients with a nadir postoperative serum cortisol of $\leq$3 μg/dL. The left panel represents data on the 55 patients with sustained remissions (NO-REC), whereas the right panel shows data of the 11 who had disease recurrence (REC).

to construct an ROC curve using ACTH plasma concentrations because there was clear separation of the levels between the two groups without any overlapping values.

Serum DHEA and DHEA-S levels were clearly low after the first 24 postoperative hours in those who had sustained remissions during the follow-up period. An ROC curve (Fig. 4) analysis on the perioperative serum DHEA data revealed that with an area under the curve of 0.99, a nadir perioperative serum DHEA level of >1.95 ng/mL predicted future recurrence with a sensitivity of 90.9%, a specificity of 97.7%, and a likelihood ratio of 39.9 ($P < 0.0001$). There was a continued decline in serum DHEA-S levels in patients with sustained remissions over the entire postoperative period whereas there was minimal and insignificant change in that level among those who had disease recurrence. ROC curve

Table 2.   Preoperative and Postoperative Clinical and Biochemical Characteristics in Patients Who Had a Postoperative Nadir Serum Cortisol of $\leq$3 μg/dL

|	Patients Who Had Sustained Remission (n = 55)	Patients With Recurrence (n = 11)	P Value: Sustained Remission vs Recurrence
Age	39.8 $\pm$ 12.3	39.3 $\pm$ 8.5	0.67
Sex (female:male)	39:16	7:4	0.42
Tumor size (cm)	0.74 $\pm$ 0.62	1.18 $\pm$ 0.72	0.02
Preoperative data			
ACTH (ng/L)	81.2 $\pm$ 66.8	79.9 $\pm$ 38.7	0.93
Cortisol (μg/dL)	30.5 $\pm$ 12.3	30.6 $\pm$ 6.4	0.97
DHEA (ng/mL)	7.9 $\pm$ 5.0	9.2 $\pm$ 4.8	0.44
DHEA-S (μg/dL)	155.9 $\pm$ 58.2	175.6 $\pm$ 37.3	0.11
Levels at the 36 postoperative hour			
Cortisol (μg/dL)	2.9 $\pm$ 2.2	3.4 $\pm$ 1.7	0.52
ACTH (ng/mL)	12.1 $\pm$ 5.4	33 $\pm$ 7.1	<0.001
DHEA (ng/mL)	1.2 $\pm$ 1.1	3.8 $\pm$ 1.7	0.005
DHEA-S (μg/dL)	48.9 $\pm$ 38.2	143.9 $\pm$ 45.2	<0.001
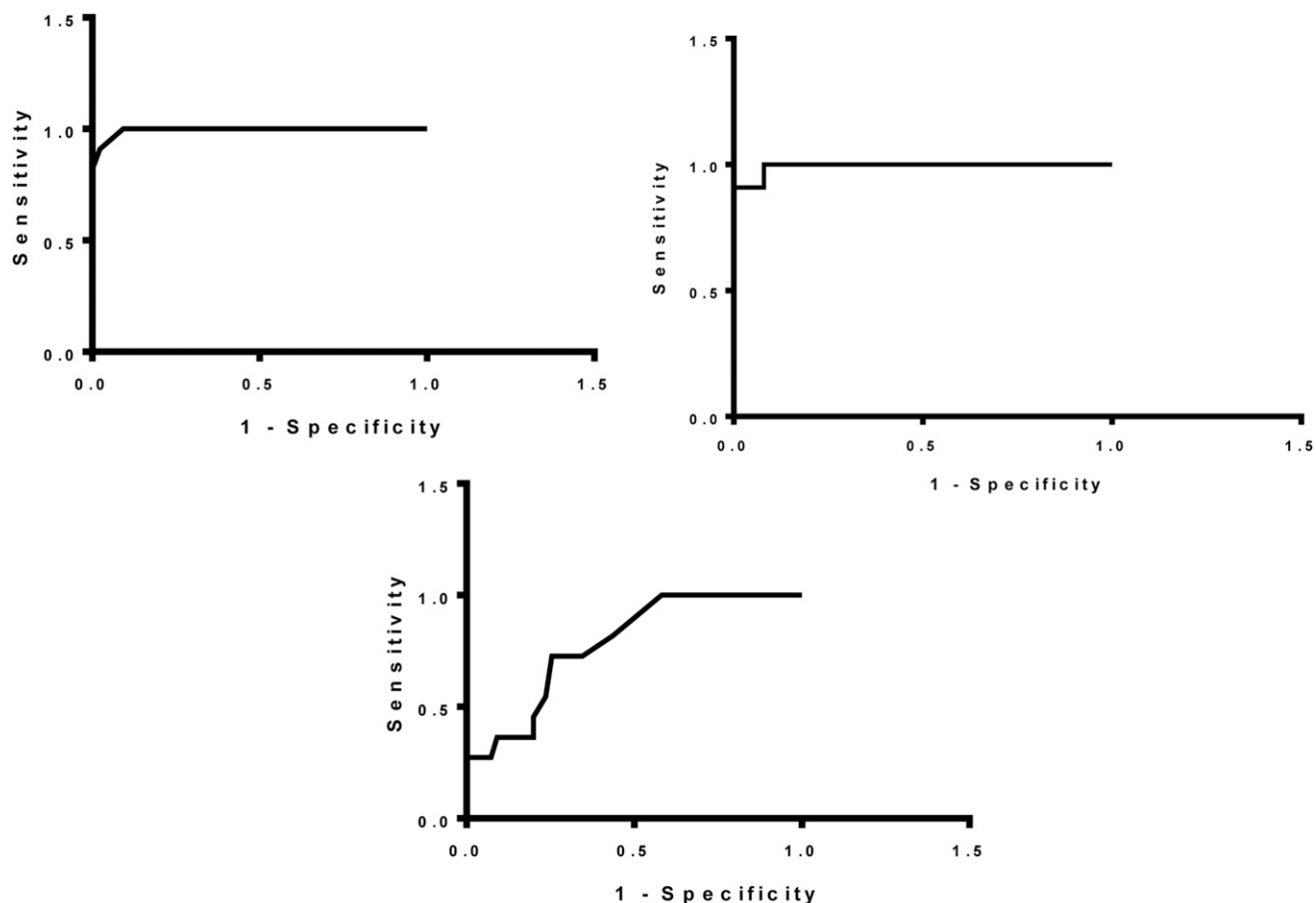
Figure 4. ROC curve analysis of the perioperative serum DHEA levels (top left panel), serum DHEA-S (top right panel), and tumor sizes (bottom panel) in 66 patients with CD who had a nadir postoperative serum cortisol of ≤3 µg/dL.

analysis of the data (Fig. 4) indicates that a nadir perioperative serum DHEA-S level of >115.5 µg/dL predicted disease recurrence with an area under the curve of 0.99, a sensitivity of 90.9%, a specificity of 98%, and a likelihood ratio of 45.5 ($P < 0.0001$).

Patients with recurrent disease had larger tumor sizes (Fig. 3). An ROC curve analysis of the latter data (Fig. 4) did not provide clear separation between the two groups. The likelihood for recurrence increases with an increase in tumor size such that a tumor size of >0.85 cm predicted recurrence with an area under the curve of 0.76, a sensitivity of 72%, a specificity of 74%, and a likelihood ratio of 2.8.

Discussion

In an earlier study, we demonstrated that despite the development of severe hypocortisolemia after removal of ACTH-secreting pituitary adenomas, plasma ACTH levels were still measurable and concluded that such levels were helpful in predicting disease recurrence (15). The current investigation reaffirms that observation and extends its findings to alterations in perioperative adrenal androgen levels. The data showed that patients who remained in remission had a rapid decline in serum DHEA levels during the perioperative period that paralleled the decrease observed in cortisol secretion. Although patients who had disease recurrence had hypocortisolemia to the same degree that was observed in those who remained in remission, their respective perioperative DHEA secretion persisted, albeit to a lesser degree than the preoperative values. We believe the persistent secretion of ACTH in the latter group explains the discrepancy in DHEA secretion between those who had and others who did not have recurrences. A similar pattern was observed in assessing DHEA-S where perioperative levels decreased by >50% of their respective baseline values in every patient with sustained remission such that by the 48th postoperative hour, the mean level reached nearly 25% of the preoperative values. In contrast, serum DHEA-S levels in patients who had disease recurrence were unchanged by the 48th postoperative hour. We believe that is likely due to persistent ACTH secretion in the latter group. Thus, despite the development of severe hypocortisolemia after corticotroph adenomectomy, disease recurrence can occur and this can be predicted by higher tumor sizes, and

persistent perioperative ACTH secretion. The latter can be detected by higher (>20 ng/L) ACTH, DHEA, and DHEA-S levels. One limitation to our study is the relatively small number of recurrences observed during the follow-up period.

An interesting aspect of the discordance in ACTH and cortisol levels deserves further discussion. It is difficult to explain the finding that plasma ACTH levels were still "normal" or even detectable even though serum cortisol concentrations were quite low at ≤3 μg/dL. We postulate that in patients with ACTH-secreting adenomas, adrenal cells are continuously exposed to high and sustained levels of ACTH, resulting in chronic downregulation of adrenal ACTH receptors such that a relatively sudden decrease in ACTH concentrations can result in reduction in cortisol synthesis. Additional studies are needed to further explore the exact mechanism behind this observation.

We noted that ACTH levels do not decrease immediately after resection of ACTH-producing adenomas as one would have predicted based on the short plasma half-life of ACTH. We postulated earlier (15) that a likely explanation for this phenomenon was that the source of ACTH measured during the first few hours after surgery is the normal corticotrophs. We postulated that surgical stress is powerful enough to overcome the chronic inhibition of normal corticotrophs. In other studies involving patients with normal HPA function, we found that a major spike in ACTH secretion is observed at 2 to 4 hours followed by a gradual decline to baseline values by the 24th postoperative hour (21, 22). A recent study by Asuzu et al. (23) in patients with CD reported similar findings, and the authors postulated a similar mechanism to the one we proposed earlier (15). We believe that the postoperative stress provides a powerful stimulus for HPA axis activation such that it is not suppressible even with large doses of dexamethasone (24–26). Thus it is not surprising to note that plasma ACTH levels separate out at the 24th postoperative hour such that patients with future recurrences have higher levels than those who don't recur.

Because the synthesis of DHEA is ACTH dependent, we postulated that a postoperative decline in ACTH will result in a concurrent decline in DHEA production and a subsequent decrease not only in serum DHEA, but also in DHEA-S levels. The data provided herein are supportive of this hypothesis. Patients who had a drop in their plasma ACTH levels had a parallel decline in cortisol and DHEA levels and a subsequent decrease in their serum DHEA-S levels. In contrast, serum DHEA and DHEA-S levels were higher in patients with persistent ACTH secretion who subsequently had disease recurrence. Only very limited studies examined adrenal androgen secretion

soon after resection of corticotroph adenomas (27, 28). Kleiber et al. (27) reported a decrease in serum DHEA levels in three patients with CD after adenomectomy that persisted during the follow-up period. Burkhardt et al. (28) examined data in 42 patients with CD and noted a strong correlation between the decline in DHEA-S and the decrease in ACTH and cortisol postoperatively. However, the latter study included infrequent hormone measurements without providing data on disease recurrence (28).

Our study provided a unique opportunity to examine alterations in adrenal androgen secretion in patients who develop ACTH deficiency acutely and contrast that to others with chronic secondary adrenal insufficiency (20). In the former setting, there was a parallel and equimolar decline in cortisol and DHEA secretion. In contrast, loss of adrenal androgen secretion preceded the decline in glucocorticoid secretion in patients with chronic ACTH insufficiency (20).

In summary, the data indicate that despite the development of profound hypocortisolemia (cortisol ≤3 μg/dL) after resection of ACTH-secreting adenomas, higher levels of ACTH (>20 ng/L) and persistent DHEA and DHEA-S secretion in the perioperative period are associated with high likelihood of disease recurrence.

Acknowledgments

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