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Increased androgen secretion in patients with prolactinomas: the impact of altered HPA function

Yosra Moria[1] · Rouba Kortbawi[1] · Nadine EL-Asmar[1] · Baha M. Arafah[1]

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Abstract

Background and objectives Earlier studies suggested that hyperprolactinemia was associated with elevated serum DHEA-S levels. The importance of DHEA-S measurements in the diagnosis of adrenal insufficiency prompted us to assess adrenal androgen levels in hyperprolactinemic subjects with normal or impaired function.

Methods Prospective study including 122 medically treated and 26 surgically patients with prolactinomas. Serum PRL, DHEA and DHEA-S levels were measured before and repeatedly after cabergoline therapy and also in the perioperative period of surgically treated patients.

Results Serum PRL levels decreased ($P < 0.001$) in all 101 medically treated patients with normal HPA function from 728.3 ± 1507 reaching 29.1 ± 39 and 14.9 ± 24.4 µg/L at 3 and 12 months, respectively. Concurrently serum DHEA-S levels decreased ($P < 0.001$) from 245.9 ± 196 to 216.2 ± 203.3 and to 169.7 ± 121.1 µg/dl at 3 and 12 months, respectively. These effects were reversed in 19 patients who discontinued treatment and were re-demonstrated after therapy resumption. Among the 22 surgically treated patients with normal HPA, peri-operative PRL levels decreased rapidly ($P < 0.001$) with a parallel decline in serum DHEA-S levels ($P = 0.03$). Strong correlations were noted between PRL and DHEA-S decrements observed with medical or surgical therapy. Medically ($n = 21$) and surgically ($n = 4$) patients with impaired HPA function had very low DHEA-S values that were unchanged despite marked reductions in PRL secretion.

Conclusion Hyperprolactinemia is associated with a reproducible and reversible increase in serum DHEA-S that was observed in medically- and surgically-treated patients with normal HPA function. Thus, a normal age- and gender-adjusted serum DHEA-S level continues to imply normal HPA function even among hyperprolactinemic subjects.

Keywords Prolactinoma · DHEA-S · Hypothalamic–pituitary–adrenal axis

Introduction

Secretion of dehydroepiandrosterone (DHEA) and its sulfated ester (DHEA-S) from the adrenal zona reticularis is predominantly ACTH-dependent. Thus, ACTH deficiency is characteristically associated with decreased secretion of both adrenal androgens (DHEA and DHEA-S) even when that insufficiency is partial [1–4]. Similarly, when ACTH secretion is decreased as observed in patients with cortisol secreting adrenal adenomas, serum levels of DHEA-S are characteristically low even when the hypercortisolemia is minimal and subclinical [5, 6].

Multiple studies reported by our group demonstrated the importance of measurements of serum DHEA-S levels as part of the laboratory assessment of hypothalamic–pituitary–adrenal (HPA) function [1, 3, 4]. Using insulin-induced hypoglycemia as the gold standard for the diagnosis of adrenal insufficiency, we demonstrated that ACTH deficiency, even when partial, was associated with drastic reductions in serum DHEA-S levels [1, 3, 4]. We also demonstrated that patients with partial ACTH deficiency have major reductions in baseline and ACTH-stimulated serum DHEA levels [4] indicating that loss of adrenal androgen secretion precede the decline in glucocorticoid secretion. In fact, the studies demonstrated that a normal age- and gender-adjusted serum DHEA-S level makes the diagnosis of adrenal insufficiency untenable [1, 3, 4].

✉ Baha M. Arafah
baha.arafah@case.edu

[1] Division of Clinical and Molecular Endocrinology, UH Cleveland Medical Center and Case Western University, 11100 Euclid Avenue, Cleveland, OH 44106, USA

A few earlier studies suggested that states of elevated prolactin levels could be associated with increased adrenal androgen secretion [7]. Some studies reported specifically that serum DHEA-S levels were elevated in hyperprolactinemic subjects and appeared to decline with dopamine agonist therapy [8–12]. However, this view was not universally accepted as some reports found no alterations in adrenal androgen secretion in hyperprolactinemic subjects [13–15]. For example, whereas Lobo et al. [10] reported a significant positive correlation between serum PRL and DHEA-S in women with hyperprolactinemia, a study by Metcalf and colleagues [14] concluded that hyperprolactinemic subjects did not have alterations in serum DHEA-S levels. Most of these earlier studies have serious limitations as they included a relatively small number of patients with varying degrees and different causes of hyperprolactinemia. Importantly, most such studies did not address the integrity of HPA function and its potential impact on adrenal androgen secretion.

There are no detailed studies examining the modulating influence of hyperprolactinemia in subjects with ACTH deficiency. More specifically, it is not known whether the stimulatory effect of hyperprolactinemia discussed earlier would be observed in subjects with ACTH deficiency. This would be important to know as it could potentially confound the interpretation of serum DHEA-S levels in hyperprolactinemic subjects with suspected adrenal insufficiency.

The goal of the current study was to investigate the modulating influence of hyperprolactinemia on adrenal androgen secretion in patients with a defined cause of elevated prolactin level; namely, prolactinoma. The study was designed to investigate these effects in subjects with normal HPA function as well as others with impaired ACTH secretion. Finally, the study also investigated whether adrenal androgen levels would change when excessive prolactin secretion declines rapidly as would be the case in patients with prolactinomas undergoing surgical resection. The opportunity to examine the reversible nature of the relationship between hyperprolactinemia and adrenal androgen secretion presented itself during the course of the study when some patients discontinued therapy on their own for several months and resumed that at a subsequent date. We postulated that hyperprolactinemia causes a consistent and reversible stimulatory effect on serum DHEA-S levels only when ACTH secretion is normal.

Subjects and methods

Subjects

This was a prospective study involving consecutive patients with prolactin-secreting pituitary adenomas who were managed at our institution over an 8-year period (2010–2017). All patients included in the study underwent complete evaluation of pituitary function at enrollment. The diagnosis of prolactinoma was established based on hyperprolactinemia (serum PRL > 100 μg/L) and an MRI evidence of a pituitary adenoma. The diagnosis in surgically treated patient was further confirmed by the demonstration of positive immunostaining for PRL in the resected adenoma. While the majority of patients were treated medically with variable doses of cabergoline (0.5–4.5 mg weekly), some underwent surgical resection of their adenoma for different indications.

A total of 191 patients with newly diagnosed prolactinomas were treated medically at our institution over the study period. Of these, 49 were excluded for several reasons including intolerance to medical therapy, missing or limited pretreatment data and/or prolonged prior exposure to glucocorticoids in the preceding year. An additional 20 were also excluded because of pregnancy, use of oral contraceptive or other drugs that influence prolactin secretion within the first 3 months of medical therapy. Thus, 122 consecutive medically treated patients who were followed for a minimum of 1 year were included in the study (Table 1). Similarly, during the same period, 26 patients with prolactinomas had transsphenoidal resection of their adenoma (Table 1). In these patients, surgery was recommended based on patients' preferences, intolerance to, or failure of medical therapy and/or significant visual compromise. All surgically treated patients included in the study had immuno-histochemical confirmation of the diagnosis of prolactinomas. This study did not include patients with other types of macroadenomas who also had mild to moderate hyperprolactinemia (PRL of 25–75 μg/L) associated with variable degrees of hypopituitarism and whose adenomas had negative PRL immunostaining [16].

Medically treated patients were followed regularly while their serum levels of PRL, DHEA-S were determined at 1, 3, and 12 months. Additional biochemical data were obtained as clinically necessary including instances of dose adjustments. The dose of cabergoline was increased when serum prolactin levels were elevated at the 3 months follow up visit and was reduced in those with adverse side effects. An increase in serum PRL level after initial decline or normalization were presumed to be a sign of poor compliance. Once confirmed with the patient, repeat measurements were made and the impact of resuming therapy was investigated. A total of 19 such patients discontinued therapy for ≥ 3 months and had repeat measurements to demonstrate the reversibility of the effects of hyperprolactinemia on adrenal androgen secretion. In the latter 19 patients, repeat data were obtained 3 months after resumption of medical therapy.

For surgically treated patients, serum PRL and DHEA-S levels were obtained in the peri-operative period as described recently [17–19]. Management of patients in the perioperative period followed the same standards

Table 1 Baseline characteristics of patients with prolactinomas who were treated medically with cabergoline and others who had transsphenoidal surgery

	Medically-treated N = 122			Surgically-treated N = 26		
	Normal HPA N = 101	Abnormal HPA N = 21	P value	Normal HPA N = 22	Abnormal HPA N = 4	P value
Age (years)	36.1 ± 14	51 ± 15	0.04	28.7 ± 10.1	26.4 ± 12.1	0.21
Gender F:M	75:26	9:12	0.052	18:4	2:2	0.042
PRL level (μg/L)	745.3 ± 651.7	746 ± 863	0.83	263 ± 337	312 ± 542	0.1
DHEAS level (μg/dL)	247.6 ± 105.6	24.43 ± 12.2	< 0.001	229.6 ± 88.7	21 ± 11	< 0.001
DHEA-S/upper limits of normal	0.96 ± 0.48	0.07 ± 0.03	< 0.001	0.87 ± 0.3	0.04 ± 0.01	< 0.01
DHEA-S/lower limits of normal	5.7 ± 2.4	0.56 ± 0.24	< 0.001	6.5 ± 2.1	0.4 ± 0.2	< 0.01
AM cortisol (μg/dL)	12.8 ± 7.7	3.5 ± 2.1	< 0.001	13.1 ± 2.3	2.9 ± 2.1	< 0.01
Other pituitary hormonal deficit						
Central adrenal insufficiency	0/101	21/21	< 0.001	0/22	4/4	< 0.01
Central hypothyroidism	0/101	17/21	< 0.001	0/22	2/4	0.06
Central hypogonadism	88/101	21/21	0.28	21/22	4/4	0.45

and protocols established at our institution as previously described [16–19]. As reported earlier, the observed rise in serum DHEA-S during the peri-operative period returns to baseline values at the 48th postoperative hour [17–19]. Similarly, after resection of prolactinomas, serum PRL levels decline rapidly, reach their nadir, and plateau after the 48th postoperative hour [20]. Surgically treated patients were followed after surgery and had repeat measurements of serum PRL and DHEA-S at 3, 6 and 12 months. Additional biochemical studies were obtained as clinically necessary.

None of the medically or surgically treated subjects had clinical or imaging features suggestive of tumor apoplexy nor did any receive radiation therapy before enrollment. The study was approved by the Institutional Review Board.

Assessment of HPA function

HPA function was assessed in all patients according to an established published protocol [1, 3, 4] as follows. Prior to medical or surgical therapy, laboratory tests were obtained which included serum cortisol, ACTH, DHEAS, DHEA, prolactin, IGF-1, TSH, free thyroxine, FSH and LH in all patients, total and free testosterone in men and estradiol in women. Patients with a normal plasma ACTH concentration (> 15 ng/L) and a random serum cortisol of 12 μg/dL or greater were considered to have a normal HPA function [1, 3, 4]. Patients with a random serum cortisol of > 5 μg/dL and an age-appropriate serum DHEA-S levels were also considered to have a normal HPA function [1, 3, 4]. Patients with a random serum cortisol of 5–11 μg/dL but had a low or low-normal serum (< 25th percentile of the age and gender-adjusted value) DHEA-S levels had a 1 μg cosyntropin test to assure normality of the HPA function [1, 3, 4]. Patients with a serum cortisol of ≤ 5 μg/dL and a blunted (< 20 μg/dL) response to cosyntropin (1 μg) were considered to have impaired adrenal function.

Additional data confirming normality of HPA function as defined herein are included in Table 2. The data in Table 2 show that low dose (1 μg) cosyntropin stimulation testing was performed in 86/101 medically treated and in 11/22 of those who had surgery. Table 2 also show that cosyntropin-stimulated serum cortisol levels were almost identical among the three categories of patients used to define normal HPA function. Furthermore, the 22 patients who were defined to have normal HPA function and had surgery had appropriate activation of that function in the peri-operative period that was similar irrespective of category defining pre-operative normality.

In surgically treated patients, post-operative laboratory evaluation included the aforementioned laboratory tests obtained at 2, 4, 6, and every 6 h thereafter for 48 h [16–19]. The protocol stipulates that glucocorticoids are not to be administered before and during surgery to patients who have normal HPA function as previously defined [16–19]. Peri-operative HPA function was defined based on repeated measurements of serum cortisol in response to the surgical stress. A normal response to surgery was defined based on serum cortisol levels of > 15 μg/dL on multiple occasions during the first 36 postoperative hours without having values below 5 μg/dL.

Laboratory analysis

The laboratory methods followed in this study were identical to those described in several recent publications [5, 17–19]. Serum DHEA-S levels were measured using solid-phase,

Table 2 HPA Data in 101 Medically-treated and the 22 Surgically- Treated Patients with Prolactinomas considered to be Normal

	All patients (N = 123)		Serum cortisol > 12 µg/dL Plasma ACTH > 15 ng/L Serum DHEA-S > 25th percentile for age/gender (N = 89)	Serum cortisol > 5 µg/dL and < 12 µg/dL	
	Medical therapy (N = 101)	Surgery (N = 22)		Serum DHEA-S > 25th percentile for age/gender (N = 13)	Serum DHEA-S < 25th percentile for age/gender (N = 21)
Baseline/random serum cortisol (µg/dL)	12.8 ± 7.7	13.1 ± 2.3	13.8 ± 4.4	10.4 ± 3	9.8 ± 3
Serum cortisol after 1 µg cosyntropin stimulation	26.3 ± 8.3 (N = 86)[a]	26.7 ± 8.7 (N = 11)	26.5 ± 8.3 (N = 64)[a]	25.9 ± 7.5 (n = 9)[a]	26.1 ± 8.1 (n = 20)[a]
Plasma ACTH (ng/L)	24.7 ± 14	23.8 ± 11	24.3 ± 13	31 ± 16	27 ± 14

[a]Performed as part of an additional study

chemiluminescent enzyme-labeled immunoassay, using the Immulite 2000XPi (Siemens, Malvern, PA). Intra-assay coefficients of variation at the lower, mid and upper limits are 7.4, 5.4 and 4.8%, respectively. The inter-assay coefficients of variation at the lower and upper limits are 8.5 and 7.9%, respectively. The normal DHEA-S in this assay vary depending on the age and gender of the subject [5]. To better define serum DHEA-S levels in our relatively small patients' population with diverse age distribution, we arbitrarily divided patients into three age categories for each gender: ages 20–40, 41–60 and > 60 years. The normal respective values for men and women in the above-mentioned categories are as follows. For ages 20–40 they were 78–475 and 66–395 µg/dL while for ages 41–60 they were 70–340 and 45–240 µg/dL and for those over the age of 60 years they were 20–278 and 35–180 µg/dL, respectively.

In light of their age- and gender dependence, DHEA-S data are presented in two different ways (Table 1): one depicting the actual values while the other relates the measured level to the upper limits of normal concentration obtained in healthy subjects of similar age and gender (measured value/upper limits of respective normal subjects). Similarly, in subjects with impaired HPA function, DHEA-S data are shown as the measured values as well as a ratio of the lower limits of respective normal subjects (measured level/lower limit of normal).

Statistical analysis

Data are presented as mean ± standard deviation (SD), unless stated otherwise. The data were first analyzed using the Kruskal–Wallis test, as a nonparametric alternative to the ANOVA test. Comparisons between groups were done using the Wilcoxon rank sum test for nonparametric measurements. Categorical data were compared using Chi square (χ^2) and Fisher exact tests. Correlation of the delta change between two variables was obtained using Pearson correlation coefficient. Differences were considered significant when the two-sided P values were < 0.05. All data analysis was made using the SPSS program (SPSS Inc., Chicago, IL).

Results

Clinical characteristics

Pertinent clinical characteristics of patients included in the study are shown in Table 1 for those who were medically treated and others who had surgical resection of their prolactinomas. Although the majority of the patients with prolactinomas were females, there were more males with impaired ACTH secretion than females among the medically treated as well as the surgically treated patients. HPA function was normal in 101 and impaired in the remaining 21 medically treated patients. As shown in Table 2 86/101 of the medically treated patients had normal responses to the low dose cosyntropin stimulation test; thus confirming normality of the HPA function. Importantly, the cosyntropin-stimulated serum cortisol levels were almost identical in these patients irrespective of the category used to define normal HPA function.

The 21 medically treated patients who had impaired HPA function also had other pituitary hormone deficits (Table 1). The 101 medically treated patients had DHEA-S levels that were either high normal or clearly elevated (Table 1) while those with impaired ACTH secretion had very low levels. When expressed as a ratio of the upper limits of age- and gender-adjusted normal values, hyperprolactinemic subjects with normal HPA function had a mean ratio of 0.96 ± 0.48 (Table 1). Similar findings were observed in surgically

treated patients with prolactinomas (Table 1). The elevation in serum DHEA-S levels among hyperprolactinemic subjects was observed in both genders and in all age groups (20–40, 40–60 and > 60 years of age).

Medically treated patients with normal HPA

The dose of cabergoline had to be decreased in 5/122 patients enrolled in the study and was increased after the 3 month's visit in those (n = 45) with persistent hyperprolactinemia defined arbitrarily as serum levels of > 30 µg/L. Serum PRL and DHEA-S levels during therapy are illustrated in Fig. 1. Variable degrees of reduction in serum PRL were noted in all patients at 1 month (< 0.001) with a further reductions observed at 3 (< 0.001) and 12 months (< 0.01). Measured serum PRL decreased from a pretreatment mean level of 745.3 ± 651 to 339.5 ± 384 at 1 month and to 29.1 ± 39 and 14.9 ± 24.4 µg/L at 3 and 12 months, respectively.

A parallel decline in serum DHEA-S was noted in all patients at 1 and 3 months without further decline thereafter (Fig. 1). Serum DHEA-S levels declined from a pre-treatment levels of 247.6 ± 103.6 to 168 ± 91 and 160 ± 76 µg/dL, at 3 and 12 months, respectively. When expressed as a ratio of the upper limits of normal, DHEA-S levels at 3 and 12 months were 0.57 ± 0.28 and 0.54 ± 0.27, respectively and both were lower (< 0.001) than the pre-treatment values (Fig. 1). Baseline serum DHEA levels in hyperprolactinemic subjects (5.2 ± 2.2 ng/ml) were minimally but not significantly (P = 0.055) higher than those obtained from other patients of similar gender age and gender distribution (4.4 ± 2.5 ng/ml). After 3 months of medical therapy, baseline serum DHEA levels declined to 3.8 ± 1.9 ng/ml (p = 0.04). Importantly, serum cortisol levels obtained during the 1, 3 and 12 months follow up period (13.1 ± 6.3; 12.6 ± 8.2 and 13.6 ± 6.9 µg/dL, respectively) were similar to those obtained prior to initiation of medical therapy (12.8 ± 7.7 µg/dL).

There was a positive relationship between the decrements in serum PRL and DHEA-S levels measured at 3 months as illustrated in Fig. 2. Similar findings were observed for the respective data at 12 months as well. The reversibility of the relationship between serum PRL and DHEA-S levels was best illustrated in examining the data of the 19 patients who discontinued therapy for 3–6 months. In those 19 patients, serum PRL and DHEA-S levels decreased after 3 months of cabergoline therapy and increased in a parallel manner after treatment was discontinued for 3–6 months (Fig. 3). It is noted that in these patients serum PRL and DHEA-S levels increased (< 0.001) with discontinuing therapy but did not go back to their pretreatment values (Fig. 3). With resumption of therapy, there was a re-demonstration of the parallel decline in serum PRL and DHEA-S levels measured

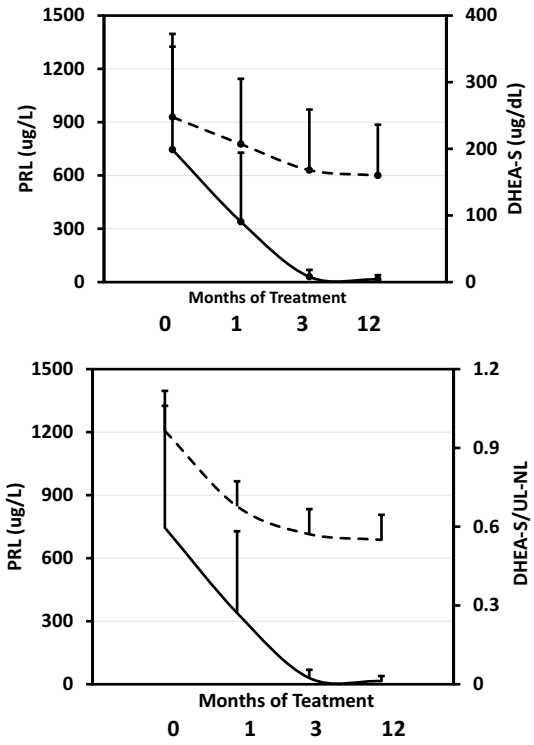

Fig. 1 Mean ± SD of serum prolactin (PRL) and DHEA-S levels (dotted lines) measured in patients with prolactinomas before and after medical therapy. The top panel graph depicts the actual values for both hormones while the lower panel of the figure shows the DHEA-S data expressed as a ratio of the upper limits of normal that was adjusted for age and gender

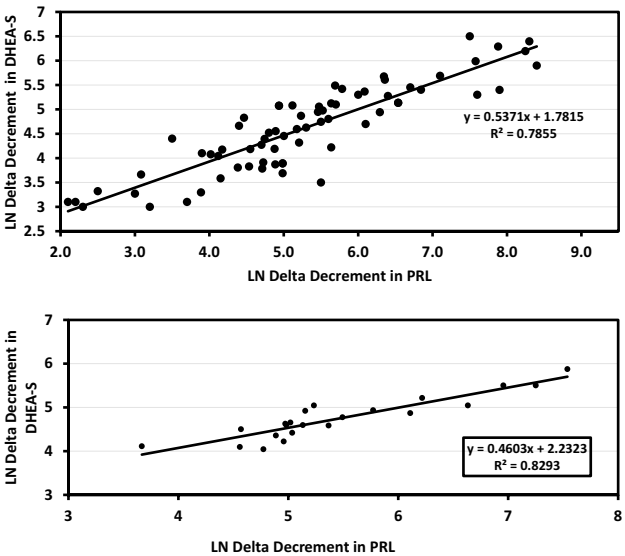

Fig. 2 Correlation between the natural logarithm (LN) of the decrement in serum prolactin and DHEA-S levels obtained at 3 months in medically (top panel) and surgically treated (lower panel) patients with prolactinomas

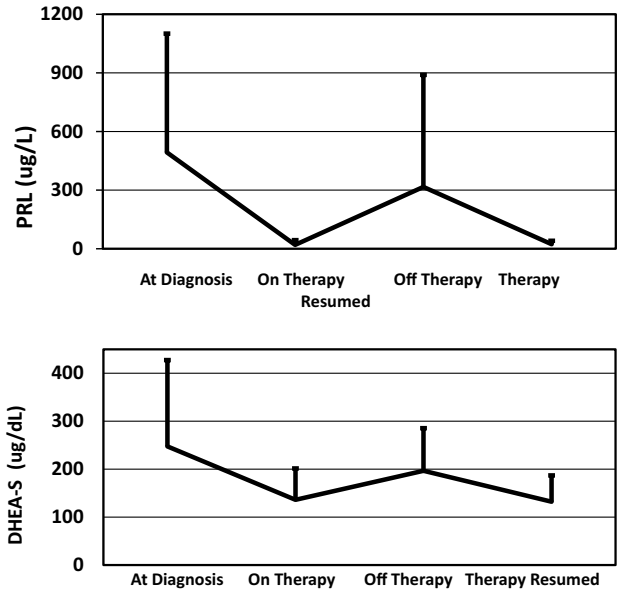

Fig. 3 Mean ± SD serum prolactin and DHEA-S levels in 19 patients treated medically with cabergoline for at least 3 months who then discontinued therapy for 3–6 months. They subsequently resumed therapy and re-tested 3 months later. The parallel changes in PRL and DHEA-S levels during and off therapy demonstrate the reversibility of the effects of hyperprolactinemia

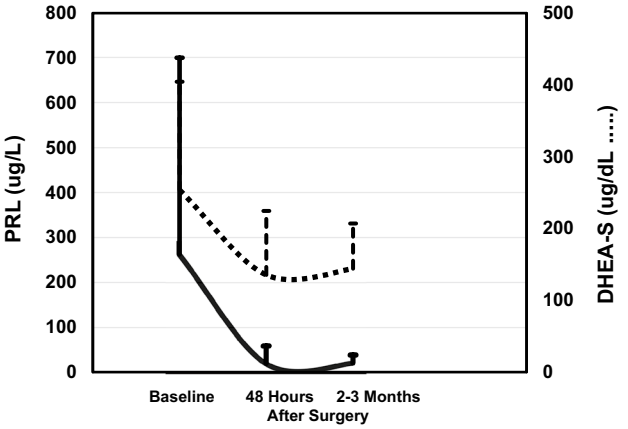

Fig. 4 Mean ± SD serum prolactin (PRL) and DHEA-S levels (dotted line) in 22 surgically-treated patients with prolactinomas who had normal HPA function obtained before surgery and at 48 h and 3 months thereafter

3 or more months later. Importantly, serum cortisol levels in those 19 subjects did not change from baseline values during the times they were on or off cabergoline therapy.

Since baseline serum DHEA-S values were incorporated in defining HPA function normality, we re-analyzed the data to examine potential confounding effects of that approach on the results. That is, the data were re-analyzed to examine the changes in the 86 medically treated patients with normal HPA function as defined by a normal serum cortisol as well as a normal cosyntropin-stimulated value of ≥ 20 µg/dL without including serum DHEA-S levels as a diagnostic feature of normal HPA function. The latter analysis revealed almost identical results. Specifically, the data on the parallel decline in serum prolactin and DHEA-S levels in these 86 patients were almost identical to that obtained when all 101 medically treated patients were included as detailed earlier. The latter finding indicate that including serum DHEA-S in defining normal HPA function did not change the results nor did it alter the interpretation.

Medically treated patients with impaired HPA function

Serum PRL levels in the 21 subjects with impaired HPA function were similar to those observed in the 101 with normal HPA axis (Table 1). With medical therapy, serum PRL levels declined from a baseline value of 746 ± 863 µg/L to 33 ± 19 and 22 ± 13 µg/L at 3 and 12 months, respectively. Before medical or surgical treatment of the hyperprolactinemia, the respective serum DHEA-S levels in patients with impaired HPA function were, as predicted, very low (Table 1) and remained as low and unchanged from their respective pre-treatment values despite the marked reductions in serum PRL levels. Although 5/21 patients regained the ability to secrete glucocorticoids as a result of tumor shrinkage, their serum DHEA-S levels remained as low. The remaining 16 continue to require hydrocortisone replacement therapy.

Serum prolactin and DHEA-S in surgically treated patients with normal HPA

PRL levels decreased rapidly in surgically treated patients with normal HPA function (n = 22) from a baseline of 263 ± 337 to 25.3 ± 22 at 48 h ($P < 0.001$) and remained unchanged (21 ± 18 µg/L) at 3 months (Fig. 4). A parallel decrease in serum DHEA-S levels was observed from a baseline of 229.6 ± 88.7 to 138 ± 87 at 48 h (< 0.001) and that remained unchanged at 3 months (144 ± 77 µg/dL). The delta decrease in serum PRL levels correlated positively with the decrement in DHEA-S observed at 48 h (Fig. 2). Although preoperative baseline serum DHEA-S levels in surgically-treated patients were higher ($P < 0.01$) than those found in other groups of patients with similar age and gender distribution who had pituitary adenomectomy, the respective baseline serum DHEA levels were not statistically different (5.1 ± 2 vs. 4.5 ± 2.2 ng/ml, respectively; $P = 0.06$). Furthermore, the postoperative pattern of serum of DHEA and DHEA-S levels in hyperprolactinemic patients were similar to normoprolactinemic subjects with pituitary tumors who had the same surgical procedure [17–19]. Peak postoperative serum DHEA levels obtained

6–8 h after surgery in patients with prolactinomas were similar to those found in normoprolactinemic subjects who had the same surgical procedure to remove non-secreting adenomas (14.2 ± 7.5 vs. 12.4 ± 9 ng/ml, respectively). Serum cortisol levels increased appropriately during the peri-operative period and were similar to those obtained in other patients who had other surgical procedures [19]. Such levels were also normal at the one, 3 and 12 months follow up visits.

Serum PRL and DHEA-S in surgically treated patients with impaired HPA function

Only four patients with impaired HPA function had surgical resection of their adenoma. In these latter patients, serum DHEA-S levels were quite low (Table 1) despite significant hyperprolactinemia. Although serum PRL levels deceased markedly to 29 ± 17 and to 19 ± 16 µg/dL at 48 h and 3 months after surgery, the respective serum DHEA-S levels remained unchanged at those two times. Two of these four patients recovered the ability to secrete glucocorticoids and were discharged without hydrocortisone replacement while their respective serum DHEA-S levels remained as low as their respective preoperative values.

Clinical follow up

At the time of enrollment, gonadal function was impaired in 88/101 medically treated and in 21/22 of those who had surgery. Clinical improvement in gonadal function as indicated by normalization/ resumption of menses in women and improved libido in men and a rise in serum testosterone level were observed in 78/88 medically treated and in 17/21 of those who had surgery at the 3 months follow up period. Gonadal function did not improve in any of the 21 medically treated or the 4 surgically treated patients who had impaired HPA function prior to treatment. However, as stated earlier 5/21 medically treated patients and 2/4 subjects who had surgery and whose HPA function was impaired prior to therapy regained the ability to secrete glucocorticoids and had to discontinue hydrocortisone therapy they were previously receiving. Despite the improvement in glucocorticoid secretion, androgen secretion and serum in these patients remained unchanged. No additional improvement in other pituitary function was demonstrated in the 21 medically or the 4 surgically treated with impaired HPA function at enrollment.

Discussion

The study demonstrates the positive impact of hyperprolactinemia on serum DHEA-S levels in patients with documented PRL-secreting pituitary adenomas. The data provide the first clear evidence that the latter effect was reversible as was re-demonstrated in patients whose therapy was interrupted. The modulating influence of hyperprolactinemia was observed only in patients with intact pituitary adrenal axis and not in those with impaired HPA function. The fact that similar reductions in serum DHEA-S levels were observed in medically and surgically treated patients with prolactinomas indicates that the alterations in serum DHEA-S levels were not caused by dopamine agonist' use but rather by the decline in serum PRL levels.

As discussed earlier, several studies reported higher serum DHEA-S levels in patients with hyperprolactinemia irrespective of its cause [7–11] although others [13–15] did not confirm such findings. Most of the earlier studies have serious limitations that include a small number of patients with variable degrees and different causes of hyperprolactinemia. Furthermore, in most of these studies hormone measurements were made before and only once and at variable times (weeks to months) after dopamine agonist therapy. In that respect, our prospective study provides repeated and consistent assessment over at least 1 year of follow up. The rapid changes observed in surgically treated hyperprolactinemic subjects indicate that the parallel decline in serum prolactin and DHEA-S levels were not due to modulation in gonadal steroid secretion resulting from lower serum prolactin levels. Our earlier study demonstrated that serum DHEA-S levels in men and women were not affected by their respective gonadal status [1]. Published studies by other investigators are consistent with the latter conclusion [21–23]. The latter statement along with the observation in surgically treated subjects wherein serum DHEA-S levels decline rapidly and in parallel to that of prolactin after adenomectomy argue strongly against any significant role played by alterations in gonadal steroid secretion in mediating the effects of lowered prolactin levels on DHEA-S secretion.

It was of interest to note that 5/21 medically treated patients who had impaired HPA function prior to initiation of therapy regained the ability to secrete glucocorticoids 2–3 months after cabergoline therapy as a result of profound reduction in their tumor sizes. Similar observations were reported by other investigators in patients with prolactinomas treated medically with dopamine agonists [24]. The latter findings are also analogous to that observed in patients with ACTH deficiency and large non-functioning pituitary tumors who had [16, 25] well-documented recovery of glucocorticoid secretion after pituitary adenomectomy. There are, to our knowledge no published data on adrenal androgen secretion in patients with this setting. The dissociation between glucocorticoids and adrenal androgen secretion is well known to occur in patients treated for several weeks with the former steroids [26, 27]. In the latter situation, glucocorticoid secretion can normalize while androgen

secretion remains suppressed. We are not aware of a known specific mechanism for this phenomenon.

The exact mechanisms through which hyperprolactinemia modulates serum DHEA-S levels are not well established although some studies suggested multiple potential possibilities [9–12] that lead to increased secretion of the latter steroid. Such mechanisms include decreased activity of 17, 20 desmolase [11] and more likely that of 3 β-hydroxysteroid dehydrogenase (3-β-HSD) [9, 11, 12]. Additional steroidogenic enzymes modulated by hyperprolactinemia include the 5-α reductase whereby the enzyme activity was decreased in those with elevated prolactin levels [12]. Other studies suggested an additional mechanism whereby hyperprolactinemia was associated with increased sulfokinase activity [8, 11]. The latter conclusion was supported by the authors' findings of increased DHEA/DHEA-S ratios after medical therapy for hyperprolactinemia [11]. Our study showed that serum DHEA levels decreased only modestly with medical treatment of hyperprolactinemia although the decline in serum DHEA-S concentrations was quite impressive. The latter findings are consistent with potential stimulation of sulfokinase activity in hyperprolactinemic subjects being an important mechanism altering adrenal androgens. However, since serum DHEA declined, albeit modestly, with medical therapy one can speculate that such findings are also consistent with additional effects of hyperprolactinemia on adrenal steroid synthetic pathway as suggested by earlier studies [9, 11]. A major limitation for relying on single serum DHEA measurements is that the latter steroid is not protein- bound and thus has a relatively short half-life in the circulation. Furthermore, serum DHEA levels can vary a great deal depending on the ambient plasma ACTH concentration at the time of blood sampling. In contrast, DHEA-S in the circulation is albumin-bound with a long half-life and thus its serum levels are dependent on the time of the day or the concurrent plasma ACTH concentrations. Despite the limitations of random serum DHEA levels, our data and that of others [9, 11] suggest that hyperprolactinemia is associated with increased concentration of the latter adrenal steroid.

Earlier studies have indicated the identification of prolactin receptors on adrenal cortical cells [28]; a finding that supports potential direct prolactin influence on adrenal function. In an in vitro study, Higushi and colleagues found that the addition of prolactin to primary cultures of human adrenal cells resulted in increased DHEA and DHEA-S secretion that was observed only when ACTH was concurrently added to the media [22]. Thus, the authors suggested the influence of high concentrations of prolactin is synergistic to the effects of ACTH on adrenal androgen secretion [29]. The authors also noted that despite the increase in DHEA and DHEA-S secretion, there were no changes in androstenedione secretion in the media; suggesting partial inhibition of 3-β HSD activity as a potential mechanism mediating the effects of hyperprolactinemia [29]. The latter finding is consistent with our observation that the stimulatory influence of hyperprolactinemia was observed only in those with intact or normal HPA function. Thus, we believe that our data are consistent with the view that the dominant mechanisms mediating the influence of hyperprolactinemia on adrenal androgen secretion involve stimulation of sulfokinase and partial inhibition of 3-β HSD.

Multiple earlier studies from our institution demonstrated the value of measurements of serum androgens (DHEA and DHEA-S) in defining the integrity of HPA function [1, 3, 4] particularly in patients with partial ACTH deficiency. Given the fact that loss of adrenal androgen secretion precedes the decline in glucocorticoid production, we and others have advocated that measurements of serum androgens be utilized to define HPA function [1–4, 30, 31]. We do not believe that measurements of serum DHEA-S should in any way replace determinations of cortisol and ACTH levels in the assessment of HPA function. Instead, we advocate that serum DHEA-S measurements should be an additional approach in that assessment. Serum DHEA-S measurements are particularly helpful when they are normal and a low level does not necessarily imply impaired glucocorticoid function. The current investigation indicates that the effects of hyperprolactinemia on serum DHEA-S levels were observed only in patients with normal or intact HPA function and are not demonstrated in those with impaired axis. Thus, one can still rely on serum DHEA-S levels in assessing HPA function in hyperprolactinemic patients as much as in others with high or low serum prolactin concentration.

In summary, our data demonstrate that hyperprolactinemia is associated with increased adrenal androgen secretion that resolves with medical or surgical treatments. The effect is reversible and is only observed when HPA function is normal. Thus, measurements of adrenal androgen levels continue to be important addition in the diagnosis of adrenal insufficiency even in patients with prolactinomas.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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