Turkish Journal of Endocrinology and Metabolism, (2000) 4 : 129-134 **ORIGINAL ARTICLE**

Evaluation of Adrenal Volume with Spiral Computed Tomography and Plasma Androgens in Hirsute Women Without Polycystic Ovaries

Rüştü Serter* Serdar Güler* Işıl Tunçbilek Can Karaman** Necdet Ünüvar* Gül Gürsoy* Yalçın Aral***

Ankara Education and Research Hospital, Departments, Ankara, Turkey
** Departments of Internal Medicine*
*** Radiology*
**** Biochemistry*

We investigated the relation between the androgens and adrenal gland volume (AV), which has been suggested as an indicator of corticotropin, related adrenal activity, in 29 hirsute women without polycystic ovary syndrome and 11 healthy women. Three of the hirsute women were diagnosed as non classic congenital adrenal hyperplasia (NCAH). The rest twenty-six hirsute women had normal plasma androgen levels and formed the normo-androgenic hirsute (NAH) group (considered as idiopathic hirsutism). Dehydroepiandrosterone sulfate (DHEAS), 17-alpha-hydroxyprogesterone (17_OHP), testosterone (Test), free testosterone (FTest), cortisol and aldosterone levels were measured and spiral examinations of the adrenal glands with computed tomography (CT) were performed. Subjects with larger adrenal glands (eight women with total AV ≥ 7.5 ml) had higher mean plasma DHEAS and 17_OHP levels than the rest thirty-two patients with normal sized adrenal glands. Besides, DHEAS, 17_OHP, Test and FTest showed significant positive correlation with adrenal volumes (r values: +0.64, +0.62, +0.62, +0.61, respectively; all p values <0.0001). The NCAH patients had larger adrenal glands reflecting increased ACTH stimulation and higher mean DHEAS, 17_OHP, Test and FTest levels compared to the NAH group and controls. With respect to normal subjects, in the NAH group DHEAS levels were higher but still within normal range and there was no difference in adrenal volumes. We conclude that the assessment of AV with spiral CT shows significant correlation with the glands' androgenic activity and spiral CT could be worthwhile in differentiating NCAH cases among hirsute women. The higher plasma DHEAS levels in the absence of adrenal enlargement in NAH patients when compared to normal subjects suggest us a slight androgenic hyperactivity of the adrenal glands in idiopathic hirsutism.

Key words: Hirsutism, idiopathic hirsutism, adrenal volume, androgens, adult-onset congenital adrenal hyperplasia

Correspondence address:

Rüştü Serter
İran Caddesi 13/17
Kavaklıdere 06700
Ankara TURKEY
Tel & Fax: +90 - 312 - 427 79 72
E-mail: serter@tr-net.net.tr

Introduction

Hirsutism is a disorder that can be associated with high, as well as normal androgen levels. Idiopathic hirsutism is characterised by normal circulating androgen concentrations and the etiopathogenesis is suggested as high androgen sensitivity in peripheral tissues (1,2) with increased bioavailability of testosterone (Test) to target tissues and an increased

conversion of Test to dihydrotestosterone (DHT) in the skin (3). However free testosterone (FTest) and DHT were found within the normal range in a certain group of hirsute women. Moreover, the altered 5α-androstanediol glucuronide levels, which were considered as a marker of 5α-reductase activity in the skin, were found to be related to adrenal androgen precursors and to liver 5α-reductase activity (4,5). Alternative explanation for the disorder may be the high-normal levels (plasma androgen levels still within normal ranges) of adrenal, ovarian or peripheral derived androgens. Some signs of hyperactivity of the adrenal glands should be present if the adrenals are involved in steroid hormone overproduction leading to hirsutism. At this point the measurement of adrenal volume, which is suggested as an indicator of corticotropin related adrenal gland activity (6,7) can come out as an issue in evaluation of hirsutism.

Little is known about the relation of hirsutism, adrenal hormones and adrenal volume. The aim of this study is to evaluate adrenal volume (AV) and hormones in hirsute women, looking for any possible relation between the adrenal steroids and adrenal volumes. To our knowledge, no study investigating the relationship between adrenal volumes and hormones has been reported up to date. We excluded the patients with polycystic ovary syndrome (PCOS) to avoid its unclear mechanism, which seems to be different from that of idiopathic hirsutism to interfere our results, since ovarian hyperandrogenism is known to effect adrenal steroidogenesis.

Subjects and Methods

Twenty-nine women who applied to our endocrinology outpatient clinic with the complaint of hirsutism and having excluded the diagnosis of PCOS, Cushing's disease, adrenal tumour and hyperprolactinemia were included in our study. Hirsutism has been defined by the presence of excessive body hair distributed in an androgen dependent pattern, with a Ferriman-Gallwey score greater than 7 (8). Eleven volunteer healthy women without signs and symptoms of hyperandrogenism served as the control group. The mean age of whole study group was 22.6 ± 7.6 years (n=40, range 15-47).

The hirsute women (n=29) had a mean age of 22.3±7.0 years and the control group (n=11) 23.3±9.1 years. All subjects had a comprehensive physical examination and a comprehensive laboratory evaluation (including complete blood cell count, thyroid profile, electrolytes and liver function tests). Systemic organic and psychiatric disorders were excluded. The subjects were not taking any medicine and all had regular menstrual cycles.

Two blood samples were obtained for dehydroepiandrosterone sulfate (DHEAS), 17-alpha-hydroxyprogesterone (17αOHP), testosterone (Test), free testosterone (FTest), cortisol, aldosterone, follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin and progesterone on the 7th and 21st days of menstrual cycle and mean hormone values for each individual have been calculated to get accuracy considering the changes due to menstrual cycles. Cushing's syndrome has been excluded with 1 mg dexamethasone suppression test in the hirsute group (plasma cortisol <5 mg/dl in the morning following 1 mg dexamethasone taken at 23.00 hr). Patients who had abnormal prolactin levels or LH/FSH ratio > 2 or ultrasound findings suggesting PCOS (observation of at least 10 follicles 8 - 10 mm in diameter, and increase in stroma) (9,10) were not included in the study. Between the two dates on which blood samples were taken, all the subjects underwent spiral examination of the adrenal glands with computed tomography (CT). The study was approved by the local ethics committee, and all subjects gave written informed consent.

Three of the hirsute women who had 17αOHP levels ≥ 3 mg/L were evaluated further with ACTH stimulation test after they completed their standard procedure in our study. Having stimulated 17αOHP ≥ 9 mg/L all three were diagnosed with adult-onset (nonclassic or late-onset) congenital adrenal hyperplasia (NCAH) and formed a separate group. The rest twenty-six women were named as normo-androgenic hirsutism (NAH) also considered as idiopathic hirsutism.

Adrenal spiral CT examinations were performed with a Hitachi W950SR imager. While patients were holding their breathe on supine position anteroposterior scanograms with 0 Gantry degree were taken. The table was taken to one cm above

the position the adrenal glands were visualised and the procedure was switched to spiral scanning. The protocol was as 90-140 mA, 120 kVp, 175 FOV, 4 filter and 512-pixel matrix. 5 mm thick sections were taken over 2 seconds with constant table movement and continuos x-ray source moving in a spiral way around the patient. No contrast medium was used. Sections were reconstructed with 5 mm and 15 sections were taken per subject. In the sections in which the glands appeared, the left and right gland borders were traced and the area in between was calculated in square cm of each tracing. For precision, each section was traced 6 times and the 6 areas were averaged, summed across sections, and multiplied by 0.5 (sections 0.5 cm thick) to yield the volume as ml of each gland. Total adrenal volumes were calculated by totalling the right and left adrenal volumes of the subjects.

Hormone determinations for each blood sample were performed in duplicate within a single assay. DHEAS, 17αOHP, Test, FTest, cortisol and aldosterone were determined using commercially available radioimmunoassay (RIA) kits (DHEAS, 17αOHP, Test, FTest and aldosterone: DSL, Texas; Cortisol: Johnson & Johnson Clinical Diagnostics Ltd, Amersham, UK) The mean intraassay and interassay coefficients of variation were as follows: DHEAS, 7.8% and 9.9%; 17αOHP, 9.3% and 9.7%; Test, 8.1% and 8.6%; FTest, 5.2% and 7.9%; Cortisol, 4.4% and 6.7%; Aldosterone, 7.0% and 10.0%. Sensitivities and normal ranges of the hormones according to our laboratory are as follows: DHEAS, 1.7 µg/dl and 70-390 µg/dl; 17αOHP, 0.02 µg/L and 0.40-1.02 µg/L follicular phase, 1.26-4.28 µg/L luteal phase; Test, 8.0 ng/dl and 10-80 ng/dl; FTest, 0.18 pg/ml and 0.45-3.17 pg/ml for follicular phase, 0.46-2.48 pg/ml for luteal phase; Cortisol, 0.2 µg/dl, 8-28 µg/dl in the morning; Aldosterone, 2.5 ng/dl and 3.8-31.3 ng/dl in upright position.

All the results are presented as mean ± SD. The comparisons between two groups were performed by "Student's T test" and "Mann Whitney U-Wilcoxon Rank Sum W Test" in respect to the variation of data. The comparisons between three groups (Control, NAH and NCAH) were performed by one-way ANOVA followed by Tukey-HSD post hoc procedure. The relations of the hormones and adrenal volumes were analysed by Pearson Correlation Coefficients. All reported significance levels are two tailed; $p<0.05$ is considered statistically significant.

Results

Twenty-six of the twenty-nine hirsute women had plasma androgen levels within normal ranges (NAH) while three hirsute women with higher levels of 17αOHP and androgens were diagnosed with NCAH after additional ACTH stimulation test. All the subjects had ovulatory cycles confirmed by luteal phase progesterone levels.

We were able to visualise the adrenal glands with spiral CT satisfactorily in all of our cases. When all the subjects were taken into consideration (n=40) the left adrenal glands were larger than the right (3.52 ± 1.42 vs. 2.59 ± 1.28 ml; $t=3.07$ $p<0.005$) concordant with the literature (11). While there was not any correlation between age and AV, a consistent positive correlation between body-mass-index (BMI) and AV values was noted, as shown in order of importance: Total AV - BMI $r=0.50$ $p<0.001$; Left AV - BMI $r=0.44$ $p<0.005$; Right AV - BMI $r=0.37$ $p<0.02$.

To see whether there is any adrenal size related change in hormones we compared the 20% with largest adrenal volumes (n=8) of the whole study group with the rest (n=32). Thus, a cut off point as 7.5 ml was determined. Mean DHEAS and 17αOHP levels were found significantly higher in the group with total AV > 7.5 ml with respect to the group with total AV < 7.5 ml (Table 1). There was not any significant difference in Test, FTest, aldosterone and cortisol levels between these two groups. In the whole study group (n=40), and the patients with hirsutism DHEAS, 17αOHP, Test and FTest levels showed significant positive correlation with adrenal volumes (Table 2 and 3). There was no correlation between these hormones and adrenal volumes in the control group. Cortisol and aldosterone levels did not have any relation to volumes in any of the groups.

Table 1. Demographic and laboratory data of the subjects with total AV>7.5 ml and total AV<7.5 ml.

	Total AV>7.5 ml (n=8)	Total AV<7.5 ml (n=32)	t	p
Age (years)	26.8 ± 6.6	21.5 ± 7.4	1.85	NS
BMI (kg/m^2)	26.7 ± 4.4	24.1 ± 5.4	1.24	NS
DHEAS (µg/dl)	375 ± 155	252 ± 112	2.56	<0.02
17αOHP (µg/L)	4.12 ± 2.67	1.90 ± 1.44	2.28	<0.05
Test (ng/dl)	100 ± 93	68 ± 20	0.85	NS
FTest (pg/ml)	4.71 ± 4.98	2.79 ± 1.70	1.84	NS
Cortisol (µg/dl)	12.7 ± 4.8	16.5 ± 8.6	1.19	NS
Aldosterone (ng/dl)	14.5 ± 6.3	21.4 ± 12.7	1.49	NS

NS= Statistically non-significant (p>0.05).

Table 2. Correlation between adrenal volumes and hormones in all the study group (n=40).

	Left AV		Right AV		Total AV	
	r	p	r	p	r	p
DHEAS	+0.50	<0.001	+0.56	<0.0001	+0.64	<0.0001
17αOHP	+0.46	<0.005	+0.56	<0.0001	+0.62	<0.0001
Test	+0.35	<0.05	+0.69	<0.0001	+0.62	<0.0001
FTest	+0.37	<0.02	+0.64	<0.0001	+0.61	<0.0001

Cortisol and aldosterone had not any relationship with adrenal volumes.

Table 3. Correlation between adrenal volumes and hormones in patients with hirsutism (n=29).

	Left AV		Right AV		Total AV	
	r	p	r	p	r	p
DHEAS	+0.62	<0.0001	+0.60	0.001	+0.75	<0.0001
17αOHP	+0.46	0.013	+0.62	<0.0001	+0.66	<0.0001
Test	+0.41	<0.027	+0.68	<0.0001	+0.67	<0.0001
FTest	+0.47	<0.02	+0.66	<0.0001	+0.69	<0.0001

Cortisol and aldosterone had not any relationship with adrenal volumes.

The NCAH group had significantly higher DHEAS, 17αOHP, Test and FTest levels and larger adrenal glands than those of NAH and control groups when three groups were compared by one-way ANOVA (Table 4). With respect to controls, DHEAS was the only parameter altered significantly in the NAH group while 17αOHP, Test, FTest and adrenal volumes were not different. There was no significant difference in cortisol and aldosterone levels between the three groups.

Table 4. The comparison of NAH, NCAH and control groups.

	Normal (n=11)	NAH (n=26)	NCAH (n=3)	p
Age (years)	23.2 ± 9.1	22.6 ± 7.3	19.3 ± 3.2	NS
BMI (kg/m^2)	24.8 ± 6.6	24.2 ± 5.0	26.2 ± 1.6	NS
DHEAS (µg/dl)	180 ± 105	292 ± 94.8	502 ± 171	<0.0001*
17αOHP (µg/L)	2.00 ± 1.28	1.92 ± 1.33	7.33 ± 1.53	<0.0001**
Test (ng/dl)	64.0 ± 23.0	70.0 ± 17.0	147 ± 152	<0.02**
FTest (pg/ml)	2.65 ± 1.91	2.88 ± 1.45	7.67 ± 8.14	<0.01**
Cortisol (µg/dl)	17.0 ± 11.9	15.8 ± 6.4	11.0 ± 4.9	NS
Aldosterone (ng/dl)	19.2 ± 11.0	21.5 ± 12.7	10.5 ± 1.3	NS
Right AV (ml)	2.20 ± 0.73	2.47 ± 0.98	4.97 ± 2.82	<0.001**
Left AV (ml)	3.34 ± 1.48	3.36 ± 1.28	5.55 ± 1.24	<0.05**
Total AV (ml)	5.54 ± 1.97	5.84 ± 1.55	10.5 ± 4.0	<0.0001**

* Significant difference between all three groups by one-way ANOVA followed by Tukey's post hoc procedure. When DHEAS levels of the NAH group are compared with controls by student's T test the significance is as: t=3.18, p<0.005.

** Significant difference when NCAH group is separately compared with normal and NAH group.

No significant difference between the normal and NAH groups by Tukey's post hoc procedure.

NS = Statistically non-significant (p>0.05).

Discussion

It is still controversial whether idiopathic hirsutism is due to a subclinical rise in androgens (ovarian, adrenal or peripheral derived) or to the increased peripheral androgen sensitivity. Many authors like Escobar et al. (12) suggest that some abnormality in androgen metabolism is underlying in all hirsute women. In the present study we investigated the possible relation of hirsutism to adrenal gland volume which has been suggested as an indicator of corticotropin related adrenal activity (6,7). We excluded the patients who had PCOS since its unclear mechanism seems to be unlike that of idiopathic hirsutism and ovarian hyperandrogenism is known to effect adrenal steroidogenesis.

We found higher mean DHEAS and 17αOHP levels in the subjects with larger adrenal glands (total AV > 7.5 ml) compared to the group with total AV < 7.5 ml (Table 1). In addition, DHEAS, 17αOHP, Test and FTest levels showed considerable positive correlation with the adrenal volumes (Table 2). Quantitation of adrenal volume has been a useful research tool in subjects for whom adrenal hypertrophy reflecting adrenal hyperactivity has been postulated as a sequel of corticotropin stimulation, such as patients with Cushing's disease or

major depression (6,7) but there is not considerable data about its correlation with the gland's androgenic activity. While CT has been the customary imaging technique for adrenal glands the spiral CT has many additional advantages. The termination of the examination in single breath, thus less artefacts due to inspiratory movements, the anatomical detail and continuity between slices and the overall accuracy of spiral CT makes it the imaging modality of choice in adrenal gland evaluations (13,14). In our study, the established correlation of the adrenal volumes assessed by spiral CT with the adrenal androgens confirms the reports about the accuracy of the technique.

We had three groups of subjects: Hirsute women with normal plasma androgens (NAH) also considered as idiopathic hirsutism, hirsute women with higher basal 17αOHP levels diagnosed with NCAH after ACTH stimulation, and the healthy control group. When compared to other two groups we found mean DHEAS, 17αOHP, Test, FTest levels and adrenal volumes increased in the NCAH patients (Table 4). The increased AV in the NCAH group reflects the adrenal hypertrophy postulated as a sequel of increased corticotropin stimulation.

DHEAS was the only hormone altered in the NAH group (higher but still within normal range) compared to normal subjects. Besides, adrenal volumes of NAH patients were not different with respect to controls. Since DHEAS is a good indicator of the adrenal androgen production (more than 95% of circulating DHEAS levels in women is of adrenal origin) (2), the higher plasma DHEAS levels without any difference in AV in NAH patients suggests some subclinical hyperactivity of adrenal glands without increased corticotropin stimulation. The evident difference (292 ± 94.8 vs. 180 ± 105 µg/dl, $p<0.005$) established in mean circulating DHEAS levels (Table 4) could only be caused by at least 10 times rise in ovarian DHEAS production (since the ovarian production ratio of circulating DHEAS levels is less than 5% in normal women)(2) which is impossible without any increment in plasma Test and FTest levels. Thus an ovarian source for DHEAS was easily excluded. 3 β-hydroxysteroid dehydrogenase deficiency, a rare cause of adrenal hyperandrogenism with increased DHEAS levels in hirsute women does not seem to be the cause since enlargement of the adrenal glands reflecting increased corticotropin stimulation was not present in our patients. Though, a more subtle form of this type of disorder could not be excluded certainly with existing data.

These results are parallel to the data of Laue et al. (15), where they concluded in increased adrenocortical androgenic function (elevated DHEA) was consistent with an increased amount of androgen-secreting tissue rather than hypersensitivity to corticotropin in postadolescent acne. Escobar et al (12) reported an enhanced ACTH stimulated adrenal Δ4-17, 20-lyase activity in idiopathic hirsute women. They did not find DHEA and DHEAS concentrations different from controls suggesting no increase in Δ5-17, 20-lyase activity. We established higher DHEAS levels suggesting the Δ5-17,20-lyase involved in adrenal hyperactivity in women with idiopathic hirsutism as proposed previously by Azziz et al. (16). The discrepancy could be related to the PCOS cases included in Escobar`s study (20.8% of their cases). In conclusion, the assessment of AV with spiral CT showed significant correlation with the gland's androgenic activity in the whole study group. The increment in AV detected by spiral CT could be useful in differentiation of NCAH cases during evaluation of hirsutism. According to our findings, without increase in adrenal size, adrenal androgen secretion is at most mildly elevated in patients with idiopathic hirsutism.

References

1. Ehrmann DA, Rosenfield RL. An endocrinologic approach to the patient with hirsutism. *J Clin Endocrinol Metab* **71:** 1-4, 1990.
2. Goldfien A, Monroe SE. Ovaries. Basic and Clinical Endocrinology (Eds: Greenspan FS, Strewler GJ). Stamford, Appleton & Lange, 1997, 434-486.
3. Lobo RA. Hirsutism, alopecia and acne. Principles and practice of Endocrinology and Metabolism (Ed: Becker KL). Philadelphia, Lippincott, 1990, 832-848.
4. Rittmaster RS, Zwicker H, Thompson DL. Androstanediol glucuronide production in human liver, prostate and skin. Evidence for the importance of the liver 5α-reduced androgen metabolism. *J Clin Endocrinol Metab* **76:** 977-982, 1993.

5. Rittmaster RS. Clinical relevance of testosterone and dihydrotestosterone metabolism in women. *Am J Med* **98 (suppl):** 175-215, 1995.

6. Amsterdam JD, Marinelli DL, Arger P, Winokur A. Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: a pilot study. *Psychiatry Research* **21:** 189-197, 1987.

7. Nemeroff CB, Krishnan KRR, Reed D, Leder R, Beam C, Dunnick NR. Adrenal gland enlargement in major depression. A computed tomographic study. *Archives of General Psychiatry* **49:** 384-387, 1992.

8. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* **21:** 1440, 1961.

9. Dewailly D, Duhamel A, Robert Y, Ardaens Y, Beuscart R, Lemaitre L, Fossati P. Interrelationship between ultrasonography and biology in the diagnosis of polycystic ovarian syndrome. *Annal of the New York Academy of Sciences* **687:** 206-216, 1993.

10. Rosenfield RL, Ehrmann DA, Barnes RB, Sheikh Z. Gonadotropin releasing hormone agonist as a probe for the pathogenesis and diagnosis of ovarian hyperandrogenism. *Annal of the New York Academy of Sciences* **687:** 162-181, 1993.

11. Rubin RT, Phillips JJ. Adrenal volume determination by computed tomography and magnetic resonance imaging in normal subjects. *Investigative Radiology* **26:** 465-469, 1991.

12. Escobar-Morreale H, Serrano-Gotarredona J, Garcia-Robles R, Sancho J, Varela C. Mild adrenal and ovarian steroidogenic abnormalities in hirsute women without hyperandrogenemia: Does idiopathic hirsutism exist? *Metabolism* **46:** 902-907, 1997.

13. Heiken JP. Spiral (Helical) CT. *Radiology* **189:** 647-655, 1993.

14. Zeman RK. Helical (Spiral) CT of the abdomen. *Am J Roentgenol* **160:** 719-725, 1993.

15. Laue L, Peck GL, Loriaux DL, Gallucci W, Chrousos GP. Adrenal androgen secretion in postadolescent acne: increased adrenocortical function without hypersensitivity to adrenocorticotropin. *J Clin Endocrinol Metab* **73(2):** 380-384, 1991.

16. Azziz R, Bradley EL, Potter HD. Adrenal androgen excess in women: Lack of role for 17-hydroxylase and 17,20-lyase dysregulation. J *Clin Endocrinol Metab* **80:** 400-405, 1995.