Adrenal gland volume assessed by magnetic resonance imaging in women with polycystic ovary syndrome and associations with gonadotropins and androgens

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Aims and objectives

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy, affecting about 5-10% of the female population in their reproductive years [1]. It is a heterogeneous endocrine/metabolic disorder characterized by hypergonadotrophism, hirsutism, obesity, and oligomenorrhea and is commonly associated with infertility [1, 2].

Androgen excess is the principal characteristic of the disease and it has been suggested that PCOS should primarily be regarded as a disorder of increased androgen synthesis, use, or metabolism [2]. While the ovary is generally considered the principal source of androgens in most of these patients, over 50% of patients with PCOS also demonstrate excess levels of adrenal androgens (AAs), particularly dehydroepiandrosterone sulfate (DHEA-S) [3, 4]. These patients show hypersecretion of adrenocortical products, both in basal conditions and in response to stimulation of adrenocorticotropic hormone (ACTH) [5-9]. However, despite extensive investigations, the main issue that has not been clarified is whether the hyperandrogenic state is due to abnormalities of hypothalamic-pituitary control or due to an alteration in the intrinsic behaviour of the adrenal cortex.

Magnetic resonance imaging (MRI) is increasingly used in clinical practice to examine the adrenal gland because of its high spatial and contrast resolution. A study performed by Wang et al. measured adrenal gland volume (AGV)'s in 81 healthy adults and noted that the left, right, and total AGV were 4.23±0.74 (range: 2.85-5.83) cm$^3$, 4.26±0.86 (2.59-6.56) cm$^3$, and 8.50±1.40 (5.80-11.39) cm$^3$, respectively [10].

It is well established that dysfunctions such as type 2 diabetes and psychiatric disorders such as depression and blumia, which are commonly seen in women with PCOS, are associated with an enlargement of the adrenal gland [11-13]. Some signs of hyperactivity of the adrenal glands should be present if the AA excess plays a major role in the pathogenesis of PCOS. AGV is suggested to be an indicator of corticotropin related adrenal gland activity [12-15], and measurement of adrenal volume may be necessary to elucidate the pathogenesis of PCOS.

The purpose of the present study was to evaluate the impact of PCOS on adrenal gland volume as measured by MRI under the hypothesis that the endocrinologic changes in PCOS can lead to morphologic changes, namely, hypertrophy of the adrenal gland. Additionally, we explored the hypothesis that adrenal gland volume can provide a surrogate measure of androgenic activity of the gland. To the best of our knowledge, this is the first study showing morphological changes of adrenal glands and their relationship to androgens in women with PCOS.
Methods and materials

Patients

This prospectively designed cross-sectional study was carried out between January 2014 and June 2014 at radiology department of our university hospital. The study was performed in accordance with the Declaration of Helsinki, and it was approved by the local Ethical Committee. Informed consent was obtained from all included subjects before participation in the study. All women with PCOS were recruited from among those who visited our Obstetrics and Gynecology outpatient clinics with a chief complaint of irregular menstrual cycles and / or clinical hyperandrogenism. All participants underwent a gynecologic examination, including transvaginal / pelvic ultrasound to investigate ovarian morphology. The diagnosis of PCOS was based on the Rotterdam criteria [16].

The patient group consisted of 27 normal-weight women with PCOS (mean age 22.1 ± 3.8 years) and 40 age and BMI-matched female volunteers with normal ovulating cycles (28 ± 2 days, blood progesterone levels >10 ng/ml in two consecutive cycles), no signs of hyperandrogenism, and normal ultrasonographic appearance of the ovaries.

Body mass index (BMI, kg/m^2) was calculated by dividing weight in kilograms (kg) by height in meters, squared (m^2) to assess obesity. All the study population had a normal abdomen MRI as evaluated by a radiologist. Also, none of the women studied had any systematic disease that could possibly affect their reproductive physiology. Exclusion criteria for all women were age <16 or >35 years, body mass index (BMI) < 17.5 kg/m^2 or >25 kg/m^2 and the possible causes of adrenal enlargement such as: congenital adrenal hyperplasia, Cushing’s syndrome, primary aldosteronism, multiple endocrine neoplasia type one, chronic infections, neoplastic processes, type 2 diabetes, or psychiatric disorders.

MRI Data Acquisition

All subjects underwent non-contrast MRI of the abdomen on a 1.5 Tesla Philips Intera MR unit (Philips Medical Systems, Amsterdam, The Netherlands) on the 3rd-7th day of their spontaneous menstrual cycle. The adrenal glands were imaged using T1-weighted fast spin echo technique with the following parameters: repetition time (TR) = 450 ms, echo time (TE) = 5.2 ms, matrix = 574x574, flip angle = 10°, field of view = 300 mm, slice thickness = 2 mm. The MRIs were evaluated by an experienced radiologist (E.K), who was blinded to group, clinical information, and sonographic findings.

Image Analysis
The MRI data were transferred to a DELL Precision Workstation for anatomical volume measurements of the right and left adrenal glands. Each adrenal gland was manually traced on axial slice of T1 sequence MRI. A segmentation process was performed in order to use images for 3D reconstruction. Segmentation was performed on a slice-by-slice basis using manual tools to define the contour around the gland. Collection of data and the segmentation process were performed using Mimics 10.1 software (Materialise, Leuven, Belgium). The segmentation process was converted to a 3D mesh model using an adapted marching cubes algorithm and the volume value was obtained (Fig.1) [17]. Measurements were performed by two radiologist with segmentation experience (EU, MBA). The overall Pearson correlation for interobserver reliability, assessed on ten randomly selected images, was 0.95 and intrarater reliability, based on 10 scans measured twice by the same rater (EU) was 0.97. All these values are well within acceptable limits.

**Serum hormone level measurements**

Fasting blood samples were collected for measurements of serum levels of FSH, LH, estradiol, DHEA-S, 17-OH progesterone, Total Testosterone (Ttest), Free Testosterone (Ftest) and prolactin between the 3rd and 7th days of the menstrual cycle in controls and after a spontaneous bleeding episode in patients with PCOS. Also 1-mg dexamethasone suppression test was performed to exclude Cushing’s syndrome.

**Statistical Analysis**

Statistical analysis was performed using SPSS, version 19.0 (SPSS, Chicago, IL). Mann-Whitney U test was used for comparison of groups for variables that were inconsistent with a normal distribution. Independent student t-test was used for comparison of groups for variables that were consistent with a normal distribution. p < 0.05 was considered statistically significant.

A multiple linear regression model was used for determination of the relation between adrenal volume and independent variables. Pearson’s Correlation Coefficient and Spearman’s correlation coefficient test was used for the comparisons of adrenal volume alterations with age and hormonal parameters. Intra observer reliability was evaluated with use of the Pearson correlation coefficient.
**Fig. 1:** Each adrenal gland was manually traced on axial slice of T1 sequence MRI. A segmentation process was performed in order to use images for 3D reconstruction and was converted to a 3D mesh model using an adapted marching cubes algorithm.

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Results

Baseline characteristics of patients with PCOS and controls are presented in Table 1. Patients with PCOS had a total AGV of 11.7 cm$^3$, whereas healthy control subjects had a volume of 7.2 cm$^3$. Statistical analysis showed total adrenal volume to be significantly higher in patients with PCOS than in healthy control subjects ($p< 0.001$) (Fig 2). Correlation analysis showed that in PCOS subjects, total AGV was significantly higher in older individuals ($r=0.42$, $p=0.05$), whereas healthy control subjects showed a trend toward decreasing AGV with age but without reaching statistical significance ($r=-0.05$, $p=0.7$, Pearson correlation coefficient) (Table 2) (Fig 3). Serum LH, LH / FSH ratio, DHEA-S, 17-OH progesterone and Ftest levels were significantly higher in the PCOS group ($p<0.05$).

AGV correlated strongly with DHEA-S levels ($r=0.51$, $p=0.008$), also with Ftest, Ttest ($r=0.43$, $p=0.03$ and $r=0.62$, $p=0.002$, respectively) and 17-OH progesterone plasma levels ($r=0.48$, $p=0.01$). However, there was a significant negative correlation between LH, LH / FSH ratio and AGV ($r=-0.55$, $p=0.02$, $r=-0.51$, $p=0.01$, respectively) (Table 2). There was no significant correlation between AGV and hormonal parameters in control group ($p>0.05$). On the other hand, LH was also negatively correlated with DHEA-S in women with PCOS ($r=-0.46$, $p=0.01$, Spearman Correlation Coefficient) whereas there was no significant correlation between LH and DHEA-S in healthy control subjects ($r=0.09$ $p=0.6$). Also multiple linear regression model results showed that there was no independent variables affecting AGV.

Table 1. Baseline characteristics of patients with PCOS and controls.

<table>
<thead>
<tr>
<th></th>
<th>PCOS(n=27)</th>
<th>CONTROL(n=40)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.1±3.8</td>
<td>23.1±1.5</td>
<td>0.1$^a$</td>
</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
<td>24.5±2.1</td>
<td>22.1±1.7</td>
<td>0.8$^a$</td>
</tr>
<tr>
<td>Adrenal volume (cm$^3$)</td>
<td>11.7±4.4</td>
<td>7.2±1.9</td>
<td>0.00*$^a$</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>10±10.8</td>
<td>5±6.8</td>
<td>0.00*$^b$</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>6.1±2.1</td>
<td>5.2</td>
<td>0.7$^a$</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>1.59±1.82</td>
<td>0.9±0.8</td>
<td>0.03*$^b$</td>
</tr>
<tr>
<td>DHEAS (µg/dL)</td>
<td>311±133</td>
<td>242±100</td>
<td>0.01*$^a$</td>
</tr>
<tr>
<td></td>
<td>Free Testosterone (ng/dl)</td>
<td>Total Testosterone (ng/dl)</td>
<td>P</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>2.7±2.3</td>
<td>1.0±0.4</td>
<td>0.00*a</td>
</tr>
<tr>
<td></td>
<td>37.9±23.6</td>
<td>35±28.6</td>
<td>0.2*b</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>39.3±33</td>
<td>42.5±35</td>
<td>0.9*b</td>
</tr>
<tr>
<td>17-OH Progesterone (ng/ml)</td>
<td>0.95±0.4</td>
<td>0.39±0.7</td>
<td>0.03 *a</td>
</tr>
</tbody>
</table>

* Significant differences were signed (if p<0.05)

\[ ^a \text{Independent sample t-test (was used for normally distributed variables that was showed as mean±standart deviation), } ^b \text{Mann Whitney U-test (was used for not-normally distributed variables that was showed as median (interquartile range) (IQR))} \]

BMI: Body mass index, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, DHEA-S: Dehydroepiandrosterone Sulfate

**Table 2.** Correlation coefficients between total adrenal volume and age, hormonal parameters in women with PCOS.

<table>
<thead>
<tr>
<th></th>
<th>rho</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.42</td>
<td>0.05*a</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>-0.55</td>
<td>0.02*b</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>-0.51</td>
<td>0.01*b</td>
</tr>
<tr>
<td>DHEA-S (µg/dL)</td>
<td>0.51</td>
<td>0.008*a</td>
</tr>
<tr>
<td>Free Testosterone (ng/dl)</td>
<td>0.43</td>
<td>0.03*a</td>
</tr>
<tr>
<td>Total Testosterone (ng/dl)</td>
<td>0.62</td>
<td>0.002*b</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>-0.18</td>
<td>0.3*b</td>
</tr>
<tr>
<td>17 OH Progesterone (ng/ml)</td>
<td>0.48</td>
<td>0.01*a</td>
</tr>
</tbody>
</table>

\[ ^a \text{Pearson’s correlation coefficient, } ^b \text{Spearman’s correlation coefficient} \]
Fig. 1: Each adrenal gland was manually traced on axial slice of T1 sequence MRI. A segmentation process was performed in order to use images for 3D reconstruction and was converted to a 3D mesh model using an adapted marching cubes algorithm.

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**Fig. 2:** Adrenal gland volumes across groups. Adrenal volumes are significantly higher in patients with PCOS than in healthy control subjects (p< 0.00)

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**Fig. 3:** Correlations of adrenal gland volumes with age. Total adrenal gland volume was significantly higher in older individuals in patients with PCOS (r = 0.42, p = 0.05) whereas healthy control subjects showed a trend toward decreasing gland volume with age (r: -0.05, p=0.7).

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Conclusion

The main findings of the present study are as follows: an increase in AGV in normal weight PCOS patients compared with age and BMI matched healthy controls was noted. Furthermore, AGV’s were positively correlated with DHEA-S, 17-OH progesterone, Ttest, and Ftest and were negatively correlated with LH levels in PCOS patients, but there was no significant correlation between these parameters in healthy subjects. Finally, a significant positive correlation between AGV and age was noted in PCOS patients, whereas healthy control subjects showed a trend toward decreasing AGV with age. The findings were consistent with our previous hypothesis that increased androgen levels in PCOS are associated with hypertrophy of the adrenal gland, which can be an issue in PCOS pathogenesis.

Although many studies have examined AA excess in patients with PCOS [3-5, 7-9], the role of the adrenal gland in the genesis of PCOS and the mechanisms responsible for the adrenal hyperandrogenism in these women are still unresolved problems. To date, the main focus of interest concerning patients with PCOS has been on metabolic and hormonal alterations and thus have been extensively studied. Since AA overproduction plays a major role in the pathogenesis of PCOS, some signs of hyperactivity of the adrenal glands should exist. Our analysis showed that volume of the adrenal gland, which we investigated by means of 1.5T MRI, was significantly larger in patients with PCOS than in control subjects. To the best of our knowledge, this is the first study showing objective measurable morphological changes in the adrenal gland and its relationship to androgens in women with PCOS.

In a healthy population, the synthesis and release of dehydroepiandrosterone (DHEA) and DHEA-S in the adrenal cortex declines linearly with age [3]. However, we found that PCOS patients showed a significant increase in adrenal volume with age whereas our control group showed a trend toward decreasing gland volume with age which is in line with this finding. Also our data support the findings of Puurunen et al. who found that serum adrenal steroid levels and adrenal steroid production capacity remain enhanced at least up to menopause in women with PCOS [9]. Therefore, it is reasonable for us to speculate that enlargement of the adrenal gland with age in PCOS may reflect more chronically elevated levels of DHEA-S and an ongoing process of gland hypertrophy in the course of time and duration of the disease from puberty to menopause.

MRI is increasingly used in clinical practice to examine the adrenal gland because of its high high-contrast, high-resolution and multiplanar imaging capability. Although the adrenal gland is a small structure, its volume can be measured using MRI. According to Wang et al, in healthy adults, the normal total AGV pituitary gland is approximately 8.50 cm$^3$ [10]. Our analysis showed that patients with PCOS have significantly enlarged adrenal glands with a total volume of 11.7 cm$^3$. 

DHEA-S is the most abundant androgen produced by the adrenal cortex and therefore is used as a marker of AA secretion. Also 17-OH progesterone is primarily produced in the adrenal glands and to some degree in the gonads [1]. Our analysis showed that serum DHEA-S, 17-OH progesterone and Ftest levels were significantly higher in the PCOS women and also the patients with higher DHEA-S and 17-OH progesterone levels have larger adrenal volumes. Azziz et al. reported that AA excess in PCOS patients was not due to increased response of the pituitary to CRH or increased sensitivity of these androgens to ACTH stimulation [4]. Our data are in line with the findings of Azziz et al. because they suggested that hyperresponsivity to ACTH for these steroids might be secondary to increased zona reticularis mass [4]. They found no significant differences in terms of ACTH levels between PCOS and the healthy control group, which is in line with other studies [4]. We therefore hypothesized that subtle but chronic overactivity of the HPA axis could result in subclinical hypertrophy and / or hyperplasia of the zonae reticularis / fasciculata, with a consequent overresponse to ACTH stimulation.

There are limitations of the present study that must be observed. Firstly, we designed our study with basal androgens and routine hormonal parameters which was sufficient for the diagnosis of PCOS. For this reason, laboratory findings concerning, insulin and IGF-1 levels which may contribute to adrenal gland enlargement and also ACTH levels were not available. Although our study was performed with normal-weight women to exclude the possibility of hyperinsulinemia, further research with a full endocrine assessment is warranted. The other weakness of our study was the limited number of subjects fulfilling the inclusion criteria (BMI, hormonal status, and age). On the other hand, statistically significant correlations were found even though the sample size was small.

We have found a significant increase of AGV in patients with PCOS compared to healthy individuals, previously not reported, as well as a positive correlation of adrenal gland size and androgens. Adrenal androgen excess in PCOS appears to be due to an alteration in the intrinsic behavior of the adrenal cortex (subclinical hypertrophy and / or hyperplasia of zonae reticularis / fasciculata) and hyperactivity of the adrenal glands. Also, we conclude that PCOS should be kept in mind when adrenal enlargement is detected incidentally on MRI, before unwarranted interventions are initiated. Understanding the relations between adrenal volume and adrenal steroidogenesis in PCOS might provide novel insights into the pathophysiology of the syndrome.
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