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PREVALANCE OF ADRENAL ANDROGEN EXCESS IN PATIENTS WITH THE POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Adrenal androgen excess, a significant yet underexplored aspect of hyperandrogenism in PCOS, contributes to its clinical presentation and metabolic abnormalities.

Objective: To determine the prevalence of adrenal androgen excess in women with PCOS and explore its relation with clinical and biochemical parameters.

Material & Method: This cross-sectional study was conducted at Gynae Department, Hayatabad Medical Complex & Khyber Teaching Hospital Peshawar, from March 2021 to February 2023.The study included 233 females aged between 20-55 years diagnosed as cases of PCOS according to Rotterdam criteria. Data were collected through structured questionnaire, clinical examination, biochemical analysis and pelvic ultrasonography. Serum levels of dehydroepiandrosterone sulfate (DHEAS), testosterone and androstenedione were determined. Prevalence of adrenal androgen excess was calculated while associations between it with clinical parameters as well as with biochemical parameters were assessed.

Results: Biochemical analysis indicated that 125 (53.6%) women had elevated DHEAS levels and 105 women (45.1%) demonstrated elevated values of testosterone Ninety-eight (42.1 %) participants had elevated androstenedione levels. All fasting glucose levels were 5.4 ± 0.9 mmol/L at baseline, and all mean insulin levels after a night of fasting were found to be higher than the upper limit (12.8±6 µU/mL). Lipid profile showed that 89 (38.2%) participants had high total cholesterol, and in addition to this, the percentage of those who has elevated LDL were 65 (27.9%), while it was found that 71 (30.5%) participants had reduced high-density lipoprotein (HDL) levels.

Conclusions: There is a high prevalence of adrenal but not ovarian androgen excess in PCOS, especially among the most hyperandrogenic women who are also insulin resistant. These results emphasize the importance of including adrenal contributions in PCOS treatment, and suggest an individualized medicine strategy that encompasses ovarian as well as adrenal excess androgen production.

Keywords: PCOS, Adrenal androgen excess, Androgens; DHEAS, Metabolic disturbances, Hyperandrogenemia.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a complex hormonal disorder that affects approximately 6-12 % of women in reproductive age characterized by as hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology [1]. PCOS pathogenesis is multifactorial and includes a combination of genetic, environmental, and metabolic predictors. PCOS is clinically defined by its presentation of hirsutism, alopecia and acne due to hyperandrogenemia characterized mainly as elevated levels of the sebum generating hormones dehydroepiandrosterone sulfate (DHEAS), testosterone or newly described marker androstenedione [2].

The adrenal cortex produces a great deal of androgens, mainly DHEAS the precursor for more potent androgenic steroids such as testosterone. High levels of androgen have been proposed to be the consequence of adrenal hyperactivity in PCOS patients [3,4]. In order to develop full-scale diagnostic and therapeutic approaches for adrenal androgen excess in PCOS, the question of how common this disorder is must be resolved.

According to reports, the percentage of women with PCOS who suffer from adrenal androgen excess is 20 to 60% [5,6]. Disparities in diagnostic criteria, sample populations and methodological approaches employed in hormone measurement may account for this variation. Nevertheless, it is clear that a considerable number of women with PCOS experience considerable adrenal hyperandrogenism which impacts upon clinical presentation and management of the condition [7].

Several reasons exist as to why adrenal androgen excess should be considered in patients who have PCOS. Firstly, it can help demonstrate the pathophysiology of the disorder and clarify that its development involves adrenal dysfunction. Secondly, identification of patients with adrenal hyperandrogenism may offer individualized therapeutic strategies ensuring better clinical outcomes. Thirdly, it might provide new biomarkers for early diagnosis and risk stratification of PCOS [8,9].

Our main aim was to determine the prevalence of adrenal androgen excess in PCOS and its relationship with biochemical and clinical parameters. The purpose of this research is to clarify the extent of adrenal hyperandrogenism present in PCOS that can help us better understand the syndrome and develop a directed therapy for it.

MATERIALS AND METHODS

It was a cross-sectional study completed in 2 year period from March 2021 to February 2023, conducted at the Gynae Department of Hayatabad Medical Complex and Khyber Teaching Hospital Peshawar. The study was performed in a cohort of 233 women with PCOS according to the Rotterdam criteria (modified),[10] diagnosed as such if at least two of the following are present: (1) clinical or biochemical hyperandrogenism, (2) evidence of oligo-anovulation, (3) polycystic appearing-ovarian morphology on ultrasound, with exclusion of other relevant disorders.

Inclusion Criteria:

- Women aged 20-55 years

Diagnosis of PCOS by the Rotterdam criteria

- Willingness to provide written informed consent

Exclusion Criteria:

Women with other endocrine disorders (eg, Cushing's syndrome, congenital adrenal hyperplasia or hyperprolactinemia)

Pregnancy or lactation.

Last three months use of hormonal medications or androgenic drugs.

- Sepsis, systemic illness or malignancy

Every patient who agreed to participate in the study underwent a clinical examination and a standardized questionnaire was used to collect all the data. Participants' demographics, reproductive and medical histories, and clinical symptoms associated with PCOS and hyperandrogenism were all questioned on the questionnaire. During the clinical examination, the BMI, symptoms of androgen excess, and hirsutism using the Ferriman-Gallwey score were assessed.[11]

After an overnight fast, blood samples were taken. High-performance liquid chromatography (HPLC) was used to measure the levels of androstenedione, testosterone, and dehydroepiandrosterone sulfate (DHEAS) in the blood. The lipid profile, insulin, and fasting glucose were among the other measures examined. Pelvic ultrasonography was used to assess ovarian morphology by either transvaginal or transabdominal access. Polycystic ovaries were defined by the presence of 12 or more follicles in each ovary measuring 2-9 mm diameter, and/or increased (>10 cm^3) ovarian volume.
The data was analyzed with IBM SPSS, version 25. Summary statistics using descriptive statistics for demographic and clinical characteristics were performed on the study cohort. Results were reported as means ± standard deviations (continuous variables) and frequencies and percentages (categorical variables). The prevalence of adrenal androgen excess was estimated; its link with clinical and biochemical features were tested via bivariate analysis (chi-square tests, t-tests). P value ≤0.05 was considered statistically significant. The study was approved by the Ethical Review Committee of Hayatabad Medical Complex.

Results

Total 233 women with PCOS were included. Age ranged between 20 - 55 years (mean age = 32.4 ±7.8 yrs). Mean BMI of the study participants was 27.6 ±5,4 kg/m^2; Overall, 68(29.2%) of the participants had normal BMI (< 25 kg/m^2), while 92 (39.5%) participants were overweight with a BMI of (25-29.9 kg/m^2), and 73 (31.3%) were obese (BMI ≥ 30 kg/m^2). out of the total participants, 152 (65.2%) had hirsutism as determined by Ferriman-Gallwey score with a mean score of 12.8 ± 4.5

Table 1: Demographic and Clinical Characteristics

Characteristic	Mean ± SD / n (%)
Age (years)	32.4 ± 7.8
BMI (kg/m^2)	27.6 ± 5.4
BMI < 25 kg/m^2	68 (29.2%)
BMI 25-29.9 kg/m^2	92 (39.5%)
BMI ≥ 30 kg/m^2	73 (31.3%)
Hirsutism (Ferriman-Gallwey score)	12.8 ± 4.5
Presence of Hirsutism (score ≥ 8)	152 (65.2%)

Biochemical analysis indicated that 125 (53.6%) women had elevated DHEAS levels and 105 women (45.1%) demonstrated elevated values of testosterone Ninety-eight (42.1 %) participants had elevated androstenedione levels. All fasting glucose levels were 5.4 ± 0.9 mmol/L at baseline, and all mean insulin levels after a night of fasting were found to be higher than the upper limit (12.8±6 µU/mL). Lipid profile showed that 89 (38.2%) participants had high total cholesterol, and in addition to this, the percentage of those who has elevated LDL were 65 (27.9%), while it was found that 71 (30.5%) participants had reduced high-density lipoprotein (HDL) levels.

Table 2: Biochemical Characteristics of Study Population

Biochemical Parameter	Mean ± SD / n (%)
Elevated DHEAS	125 (53.6%)
Elevated Testosterone	105 (45.1%)
Elevated Androstenedione	98 (42.1%)
Fasting Glucose (mmol/L)	5.4 ± 0.9
Fasting Insulin (µU/mL)	12.8 ± 4.6
Elevated Total Cholesterol	89 (38.2%)
Elevated Triglycerides	78 (33.5%)
Elevated LDL	65 (27.9%)
Reduced HDL	71 (30.5%)

Excess of adrenal androgens, described as DHEAS excess (serum DHEAS concentrations) was found in 125 women (53.6%). Of these, 82 (65.6%) also demonstrated an increased testosterone level and 74 (59.2%) showed elevated levels of androstenedione. Among these, obese women had higher prevalence of adrenal androgen excess than the normal weight (68.5% vs 36.8%, $p < 0.001$).

Table 3: Prevalence of Adrenal Androgen Excess.

Parameter	**n (%)**
Adrenal Androgen Excess (DHEAS)	125 (53.6%)
Elevated Testosterone with DHEAS	82 (65.6%)
Elevated Androstenedione with DHEAS	74 (59.2%)
Adrenal Androgen Excess in Obese	50 (68.5%)
Adrenal Androgen Excess in Normal Weight	25 (36.8%)

Compared with women in whom no adrenal androgen excess occurred, those who did have this had higher Ferriman-Gallwey scores (mean 14.3±4.1 versus 11.2±4.6) and BMI (mean: 28.9 ± 5.3 kg/m² vs. 26.1 ± 5.2 kg/m²). They also had higher fasting insulin levels (mean: 14.2 ± 4.8 µU/mL vs. 11.0 ± 4.1 µU/mL) and a greater degree of lipid abnormalities.

Table 4: Association of Adrenal Androgen Excess with Clinical and Biochemical Characteristics

Parameter	**With Adrenal Androgen Excess (n=125)**	**Without Adrenal Androgen Excess (n=108)**	**p-value**
Ferriman-Gallwey Score	14.3 ± 4.1	11.2 ± 4.6	0.050
BMI (kg/m²)	28.9 ± 5.3	26.1 ± 5.2	0.03
Fasting Insulin (µU/mL)	14.2 ± 4.8	11.0 ± 4.1	0.01
Elevated Total Cholesterol	56 (44.8%)	33 (30.6%)	0.081
Elevated Triglycerides	53 (42.4%)	25 (23.1%)	0.060
Elevated LDL	41 (32.8%)	24 (22.2%)	0.051
Reduced HDL	45 (36.0%)	26 (24.1%)	0.049

DISCUSSION

A prevalent endocrine condition known as polycystic ovarian syndrome (PCOS) was initially identified in 1935 by Stein and Leventhal. It affects 6 to12 % of reproductive aged women worldwide, and represents a spectrum that includes menstrual dysfunction with hyperandrogenism and polycystic ovarian morphology [12]. Hyperandrogenism is one hallmark feature of PCOS that can be either ovarian or adrenal in origin. However, despite being crucial for understanding PCOS, the idea that the disease may occur from adrenal androgen excess particularly dehydroepiandrosterone sulfate (DHEAS) has been overlooked so far [13].

The outcome of this study indicates that about 53.6% of females with PCOS have increased levels of DHEAS meaning a significant proportion might be having adrenal androgen excess. These outcomes are consistent with previous study of Carmina E et al (41%), who reported prevalence rates ranging from 20-60% for adrenal hyperandrogenism in PCOS populations.[14] We also observed that those women who had adrenocortical hyperandrogenism had higher scores in Ferriman-Gallwey assessment tool, BMI and metabolic disturbances.

A similar increase in DHEAS was observed in women with PCOS by Mariciniak A et al [15]. Findings of Sarah A et al [16] also supported our findings that women with adrenal androgen excess had high

BMI and hirsutism. Codner E et al [17] reported a correlation between elevated blood DHEAS levels and impaired metabolic phenotype in PCOS-affected females.

In addition, we observed significant interactions of adrenal androgen excess with impaired metabolic profile such as high fasting insulin level and lipid profile abnormalities. These results are also in line with the findings of O'Reilly M et al [18], which related hyperandrogenemia to metabolic syndrome in PCOS. The greater prevalence of dyslipidemia in women with adrenal androgen excess attests to the importance of full metabolic assessment.

Our results have important clinical implications. This would allow for a more personalized approach to therapy, taking adrenal androgens into account in the pathogenesis of the hyperandrogenic phenotype that characterizes PCOS. For example: If ovarian and adrenal sources of androgen excess were targeted, this might increase therapeutic efficacy leading to improved clinical outcomes. The variation in effects on metabolic health of androgen excess involving the ovaries versus those at originating from the adrenals with regard to specific interventions (e.g., life-style changes, insulin-sensitizing agents) suggests that potential benefit could be greatest for women demonstrating marked adrenal hyperandrogenemia. [19,20]

Limitation of this study include its cross-sectional design, which restricts our ability to infer causality between adrenal androgen excess and clinical/metabolic disturbances in PCOS patients. Additionally, the sample size, while sufficient for estimating prevalence, may not capture the full diversity of the PCOS population, particularly across different ethnic and geographical backgrounds. Moreover, we measured adrenal androgens at a single time point, which may not fully reflect the dynamic nature of hormone fluctuations. Future longitudinal studies are needed to confirm these findings and explore the long-term effects of adrenal androgen excess on PCOS outcomes.

CONCLUSION

Nearly half of the women with PCOS have adrenal androgen excess, as indicated by increased DHEAS levels in 53.6% of participants. Adrenal hyperandrogenism was associated with significantly increased clinical expression (Ferriman-Gallwey score, BMI) and a higher incidence of metabolic alterations like elevated fasting insulin levels and signs of disturbed lipid profile. This emphasizes the significance of acknowledging contributions made by adrenal to hyperandrogenism in PCOS, pointing towards an integrated diagnostic and therapeutic approach that includes not only ovarian but also adrenal sources of androgen excess. Thus, treatment strategies that specifically target these dual sources may ameliorate clinical outcomes and reduce metabolic risk in this population.

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