Hyperandrogenism in Polycystic Ovary Syndrome

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Summary:

Background *The major diagnostic criteria for polycystic ovary syndrome include, in order of importance: l.hyperandrogenism 2.oligoovulation 3.exclusion of known causes of polycystic ovaries like adrenal problems or androgen secreting neoplasms 4.presence of polycystic ovaries on ultrasound. Signs of hyperandrogenism include hirsutism, android obesity, alopecia and acne.*

Objective: *To assess the different parameters of hyperandrogenism in patients with polycystic ovary syndrome patients.*

Patients and methods: *An observational case control study conducted from July 2001 to August 2002 on 60 patients demonstrating the above mentioned criteria for polycystic ovary syndrome (age 17-41) and 40 women of matching age who were menstruating regularly and of normal phenotype regarding clinical and laboratory evidence of hyperandrogenism.*

Results: *All the study group had a hirsutism score of > 6. 42 and (70%) had a score >10 but only 10 (22.22%) of the control group had hirsutism of a low score of 7-10. There was a highly significant difference in the waist hip ratio ($p < 0.0001$) being highest in the hyperinsulenemic patients (0.884 ± 0.012) and lowest in the control group (0.807 ± 0.01). There was a highly significant difference in testosterone level ($p < 0.0001$) being highest in the hyperinsulenemic patients (3.15 ± 0.13) and lowest in the control group (1.4 ± 0.09).*

Conclusion: *The high figure of hirsutism in the present study may be related to the diagnostic criteria taking a score of > 6 while other studies used a score of 8. Another factor could be related toa racial difference. Hirsutism and central obesity were the main androgenic features demonstrated in the study group.*

Keywords: *poly cystic, ovary, syndrome, hyperandrogenism*

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Introduction:

Polycystic ovary syndrome (PCOS) is a commonly diagnosed female endocrinopathy,. Particularly in the younger women.[1]

Currently, there is wide variation in the literature in the diagnosis of PCOS.

In a written questionnaire to 58 experts there was a universal agreement that the phenotype should be described accurately. The other general agreement was that the major diagnostic criteria for PCOS should include (in order of importance)

1. hyperandrogenism 2. oligoovulation 3. exclusion of known causes of polycystic ovaries like late onset adrenal congenital hyperplasia or androgen producing neoplasms
4. presence of polycystic ovaries on ultrasound scan. The presence of PCO on U/S scan without clinical features or serum androgen elevation is not sufficient to make the diagnosis of PCO. Signs of hyperandrogenism include hirsutism, android obesity, alopecia and acne.

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Patho physiology of PCOS:

Despite the hetrogenecity of the clinical presentation of women with polycystic ovaries, there are common biochemical features linking the spectrum of symptoms and signs. The endocrine hallmarks are hyperandrogenemia and, to a lesser extent, hypersecretion of luteinizing hormone. It seems likely, however that abnormal gonadotrophin secretion is the result rather than the cause of ovarian dysfunction. Although it is clear that hypersecretion of adrenal androgens may contribute to the hyperandrogenemia of women with PCOS, the majority of evidence favours the ovary as the principal source of excessive androgen secretion. Suppression of ovarian steriodogenesis by the use of gonadotrophin-releasing hormone agonists results in a decline in serum androstenedione and testosterone concentration to the range for menopausal women or those who have undergone ovariectomy [3].

Endrogens and hyperinsulinemia:

In 1980 Burghen etal [4] made the first suggestion of a relationship between hyperandrogenism of PCOS and hyperinsulinemia. There are differences of opinion in the literature concerning the

interrelationship of insulin resistance and hyperadnrogenaemia. It is suggested by some authors that hyperinsulinemia results in raised ovarian androgens while others failed to demonstrate a direct relationshipp[5,6,7]. It has been conclusively demonstrated that hyperinsulinemia is associated with decreased levels of sex-hormone binding globulins, thereby increasing the circulating free testosterone[8]. From invitro experiments Barbieri etal expounded the insulin hypothesis, stating that marked hyperinsulinemia synergizes with luteinising hormone to stimulate ovarian androgen production.[9]

The exact mechanism of insulin resistance is uncertain but a post-receptor defect in the adipose tissue has been identified. Despite insulin resistance in the adipose and skeletal muscles, the ovary remains relatively sensitive to insulin, and both insulin and insulin- like growth factor (ILGF-1) have stimulatory effect on the thecal androgen production. Some thin women with PCOS who may not have insulin resistance and hyperinsulinemia may show enhanced ovarian sensitivity to insulin[10,11,12].

There is a linear relationship between serum androgen levels and level of hyperinsulinemia such as fasting insulin. There has been an ongoing debate whether hyperandrogenemia or insulin resistance is primary in the evolusion of PCOS. At present the majority of evidence suggests that insulin resistance is the initiating event and that hyperandrogenism is secondary to a stimulatory effect of hyperinsulinmia on ovarian steroids production. In PCOS patients insulin stimulates the activity of ovarian P450c 17 alpha, which has a 17 alpha hydrxylase activity and 17, 20 lyase activity. These enzymes convert progesterone to 17 alpha hydroxyprogesterone and then to androstenedione, respectively. In addition elevated insulin concentrations independently act to inhibit hepatic production of SHBG.

Alternatively, hyperandrogenism could cause insulin resistance. Administration of exogenous androgens or oral contraceptives containing androgenic progestin may cause glucose intolerance.[3]

Dunaif et al[13] found that the high insulin resistance of patients with PCOS compared with that of control subjects was true for both lean and obese patients with PCOS. Therefore, it appears that insulin resistance in women with PCOS is independent of obesity, particularly if they are unovulatory.

AIM OF STUDY: to assess the different parameters of hyperandrogenism in a sample of PCOS.

PATIENTS AND METHODS:

An observational case control study conducted at a teaching hospital in Baghdad during the period July 2001-August 2002.

Sixty patients with PCOS (age range 17-41)were included in a prospective study to asses clinical features (hirsutism,acne,elopecea and central obesity), ultrasound findings, and biochemical studies. The inclusion criteria were: 1) oligoovulation/unovulation 2)androgenic features 3) Features of polycystic ovaries on ultrasound (the presence of >= 10 ovarian cysts, 2-8mm in diameter arranged peripherally in an echo-dense stroma (group 1).

Exclusion criteria were: thyroid dysfunction, hyperprolactinemia, adrenal problems and androgen secreting tumors.

The control group consisted of 45 age-matched healthy women who were menstruating regularly and were of nonnal phenotype (group 2).

None of the subjects was taking any medications known to affect hormonal or metabolic status, and none of them participated in any regular aerobic exercise. All subjects had hirsutism score evaluated according to Ferriman and Gallaway 1961 as shown in table 1 Body areas include in the evaluation were: upper lip, sideburn area, chin, jaw and neck, upper back, lower back, lower arms, thighs, chest, upper abdomen and lower abdomen. A score above 6 was regarded as hirsute. Acne was evaluated in 4 grades: 0= no acne, 1= mild acne on face only, 2= moderate acne on face only,3= severe acne on face and back or chest.

The waist-hip ratio (WHR) was determined for all the subjects and the body mass index (BMI) was recorded. The WHR was determined from the average of two measurements taken at the minimal waist circumference observed between the costal margin and the pelvic brim (at the level of the umbilicus) and the maximum hip circumference obtained at the level of the greater trochanters.

The BMI was obtained by the ratio of weight (kg) over height in m^2. A BMI of 25-29.9 was regarded as mild obesity, 30 - 39.9 was moderate obesity and BMI > 40 was regarded as morbid obesity. Alopecia was looked for in both groups.

Serum testosterone was measured by double-antibody radio-immunoassay (Cis. Bio international France).

45 patients of the study group and all the control group had fasting insulin level measured using a standardized double antibody radioimmunoassay (Immunotech: A Backman Coulter Company) Anova and F-test were used for statistical analysis.

RESULTS:

Table 2 demonstrates the androgenic features in PCOS patients and the control group. The entire study group had hirsutism score of > 6. 18(30%) had a score of 7-10, 30 (50%) had a score of 11-14, 8 (13.3) had a score of 15-18 and 4 (6.6%) had a score more than 18. Only 10 (22.22%) of the control group had hirsutism score of 7-10, and none of the control group had score of >10. 42 (70%) of the study group had

acne which was mild in 22 (36.66%), moderate m8 (13.33%), and severe in 12 (20%). Only 5 (11.11%) of the control group had acne, which was mild. Alopecia was reported in 15 (25%) of the study group while none of the control group had alopecia.

The WHR was significantly higher in the study group than in the control group being 0.830±0.02 and 0.807±0.01 respectively P< 0.001, and it was higher in the hyperinsulinemic group than the normo insulinemic 0.884±0.013 and 0.810±0.07 respectively.

The BMI was higher in the study group than the control group being 29.24±0.12 and 27.43±0.76 respectively PO.001. It was the highest in hyperinsulinemic patients (31.94±0.89)

Testosterone was significantly higher in the study group than in the control group 3.03±0.16 and 1.4±0.09 respectively (PO.0001). Testosterone was the highest in hyperinsulinemic patients (3.15±0.13)

There was highly significant difference in insulin levels between the hyperinsulinemic, the normoinsulinemic, and the control group 217.26±6.9, 64.91±4.75 and 54.82±2.72 respectively (P< 0.0001)

DISCUSSION:

Considering hirustism score above 6 [14], 25% of the control groups had mild hirustism (score 7-10), this may be due to racial factors as it has been noted that 25-33 of healthy non-Scandinavian and non-Asian women will have some terminal hair on upper lip, as well as in the peri-areolar or linea alba areas[15].In the present study there was a significant difference between the study group and the control group as all the study group had hirsutism and the majority (70%) of them had high scores

Lewis 2001 reported that hirsutism is present in 70-86% of patients with PCOS.

The highest figure in the present study may be explained by the strict diagnostic criteria; a score of >6 as hirsutism while in many studies the scores >8.[16]

Alopecia and acne are less common in PCOS patients with a prevalence of approximately 20-25% and 15-20% respectively[17], and in the present study, only 15(25%) of the study group had alopecia and 42(70%) had acne.

Hyperandrogenism is associated with preponderance of fat localized to truncal abdominal sites[12]. Women with PCOS have a greater truncal and abdominal fat distribution as demonstrated by an increased WHR[12,14,18]. The central distribution of fat in these studies was independent of body mass index and was associated with higher plasma insulin and triglyceride concentration and reduced HDL cholesterol concentration[18].

In the present study, the study group in general had mild obesity and the hyperinsulinemic sub-group had moderate obesity. The WHR showed highly significant difference between the control group and the study group; the difference being more pronounced in the hyperinsulinemic women.

Table 1: Hirsutism rating scale (Ferriman and Gallwey, 1961):

Site	Severity (points) and description			
	1	2	3	4
Upper lip	Scattered hairs outer margin	Small moustache covers less than half of upper lip	Moustache extends halfway or to midline from outer margin	Moustache covers most of upper lip
Sideburn area	Few scattered hairs	Scattered hairs with concentrated areas	Complete but light coverage	Heavy complete coverage
Chin	Few scattered hairs	Scattered hairs with concentrated areas	Complete but light coverage	Heavy complete coverage
Jaw and neck	Few scattered hairs	Scattered hairs with concentrated areas	Complete but light coverage	Heavy complete coverage
Upper back	Few scattered hairs	Scattered hairs with concentrated areas	Complete but light coverage	Heavy complete coverage
Lower back	Midline hair	Lateral extension one-half to three-fourths of area	Three-fourth coverage	Complete covered
Upper arms	Sparse hairs one-fourth of surface	Incomplete coverage greater than one-fourth of area	Complete but light coverage	Complete dense hair growth
Thighs	Sparse hairs less than one-fourth of surface	Incomplete coverage greater than one-fourth of area	Complete but light coverage	Complete dense hair growth
Chest	Midline or periareolar hair	Midline and periareolar hair	Three-fourth coverage	Completely covered
Upper abdomen	Scattered midline hairs	Moderate amount of hair all midline	One-half covered	Fully covered
Lower abdomen	Scattered midline hairs	Thin band of midline hair	Wide band of hair less than one half width of pubic hair	Inverted V, greater than one-half width of pubic hair

Table 2: Androgenic features in the study group and control group

Variable	PCOS		Control	
	n=60	%	n=45	%
Hirsutism	60	100%	10	22.22%
Hirsutism score:				
7-10	18	30%	10	22.22%
11-14	30	50%	0	0%
15-18	8	13.3%	0	0%
>18	4	6.6%	0	0%
Acne	42	70%	5	11.11%
Acne severity				
Mild	22	36.66%	4	8.88%
Moderate	8	13.3%	1	2.22%
Severe	12	20%	0	0%
Alopecia	15	25%	0	0%

Table 3: Findings in hyperinsulinemic group, normoinsulinemic group and the control group

Variable	Hyperinsulinemic PCOS	Normoinsulinemic	Control
WHR	0.884±0.012	0.810±0.07	0.807±0.01
BMI (kg/m^2)	31.94±0.89	28.14±0.83	27.43±0.76
F.B.S (mmol/L)	5.77±0.14	4.91±0.95	4.63±0.044
Insulin (pmol/L)	217.26±6.9	64.91±4.75	54.28±2.72

Table 4: Comparison of hormonal measures in PCOS patients and controls

Variable	PCOS n = 60	Controls n = 45
LH (IU/L)	15.33±0.79	4.99±0.27*
FSH (IU/L)	7.57±0.42	4.96±0.24*
LH/FSH	2.12±0.49	0.94±0.29*
Oestradiol (pmol/L)	235.3±34.55	332.4±11.6*
Testosterone (nmol/L)	3.03±0.16	1.4±0.09*
Prolactin (μIU/ml)	335±39.3	188.9±9.4*

* $p < 0.0001$

CONCLUSION:

Hirsutism was the most common androgenic feature in the study group being more severe in the hyperinsulinemic patients.

Central obesity as demonstrated by high WHR showed highly significant difference being highest in the hyperinsulinemic group.

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