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Original Article

A COMPARATIVE STUDY OF INSULIN RESISTANCE IN PATIENTS OF POLYCYSTIC OVARY SYNDROME

Amena Arif, Palvasha Waheed, Robina Anees*, Amir Rashid, Saleem Ahmed Khan

Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Pakistan Naval Shifa Hafeez, Islamabad Pakistan

ABSTRACT

Objective: To assess the relationship between obesity and insulin resistance in polycystic ovary syndrome affected women.
Study Design: Cross sectional comparative study.
Place and Duration of Study: Multidisciplinary Lab-I of Department of Biochemistry, Army Medical College, Rawalpindi, in collaboration with Pakistan Naval Ship Hafeez Hospital, Islamabad from Feb 2018 to Jan 2019.
Methodology: One hundred and five selected females (puberty till 25 years of age) were divided into three groups of 35 each. Blood samples were collected an overnight fast (from 8-11 AM). Serum level of insulin was measured and insulin resistance was calculated based on Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).
Results: Homeostatic Model Assessment of Insulin Resistance concentrations correlated directly with basal metabolic index (BMI), fasting plasma glucose and serum insulin levels. Mean serum insulin level was also elevated in patients with polycystic ovary syndrome (normal weight & overweight) as compared to control subjects (7.4 ± 1.2 mIU/L & 9.1 ± 0.8 mIU/L vs 6.3 ± 1.1 mIU/L; *p* as 0.003). The insulin resistance was slightly higher in patients with polycystic ovary syndrome as compared to the control subjects (1.4 ± 0.3 & 1.7 ± 0.2 vs. 1.1 ± 0.3; $p<0.001$).
Conclusion: Homeostatic Model Assessment of Insulin Resistance levels are positively associated with basal metabolic index, the intensity of peripheral insulin resistance in polycystic ovary syndrome-affected females, indicating that normal weight, and overweight patients with polycystic ovary syndrome have tendency towards insulin resistance.

Keywords: Insulin resistance, Obesity, Polycystic ovary syndrome.

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INTRODUCTION

Polycystic ovary syndrome (PCO), the most common, multifaceted endocrinopathy affecting pubertal and reproductive-aged females, exhibits diverse clinical features. The complexity of PCOS is due to interplay of ovarian abnormalities, genetic and epigenetic changes, neuroendocrine variations, and alterations of various endocrine and metabolic factors (like anti-Müllerian hormone, hyperinsulinemia and insulin resistance, adiposity and adiponectin levels, etc). The etiology of PCOS remains vague despite PCOS being a recognized, complex heterogeneous familial disorder.[1]

PCOS is diagnosed on the basis of criteria provided by Rotterdam Guidelines, Androgen Excess Society (AES) or the National Institute of Child Health and Human Development (NICHD). All criteria require exclusion of other diagnoses that exhibit identical symptoms and/or signs (Table-I).

The prevalence of PCOS in adolescents is debatable by clinicians due to diverse diagnostic criteria. Moreover, since symptoms of PCOS typically become apparent at puberty, clinical features of PCOS may overlap with normal puberty. The most common complaints of patients with PCOS are menstrual disturbances and hirsuitism. During adolescence, fluctuations in levels of hormones make the diagnosis of PCOS more difficult. The role of genetic polymorphisms or mutations in the pathogenesis of PCOS is still being investigated and requires further research.[3]

PCOS manifests itself in genetically predisposed females, activating hypothalamicpituitary-adrenal and hypothalamicpituitary-ovarian axes at puberty. This often causes an increase in weight and heightened insulin resistance at puberty. On the other hand, the hyperinsulinism in PCOS results in hyperandrogenaemia, impaired follicular and oocyte development.[4]

There exists an intricate linkage between insulin resistance, hyperandrogenism, and ovulatory disorder in PCOS affected females. PCOS and basal metabolic index (BMI) related abnormalities are linked to impaired insulin signaling due to insulin resistance.[4]

The endocrine and metabolic disorders of PCOS develop primarily due to adiposity. Adipocytokines,

Correspondence: Dr Amena Arif, Department of Biochemistry, Army Medical College, Abid Majeed Road, Rawalpindi Pakistan
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adipocytederived peptide hormones secreted by adipose tissue, exert pro-inflammatory and anti-inflammatory effects on human body.[5]

Abdominal obesity affects the level of these adipocytokines, like adiponectin and resistin. Low levels of adiponectin, seen in obesity and PCOS, correlate adversely both with insulin resistance (IR) and free androgen levels.[3]

IR is associated with conditions like obesity, Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease. Depending upon the severity of the condition, patients of PCOS are sus-ceptible to developing metabolic syndrome (hypergly-caemia, hypertension and dyslipidaemia), even during adolescence.[3]

Impairment of the action of insulin hormone in adipose tissue, mainly due to intra-abdominal fat depots is known as insulin resistance (IR), with diminished ability of tissues to respond to insulin (adipose tissue is insulin-responsive/sensitive). IR in PCOS appears to be dependent on obesity as coexisting obesity aggravates IR in PCOS. IR results in compensatory hyperinsulinemia, augmenting the hyperandrogenemia. Excessive insulin secretion inhibits hepatic synthesis of sex hormone binding globulin (SHBG), increasing testosterone bioavailability further aggravating hyperandrogenemia.[6]

Simultaneously, the compensatory hyperinsulinaemia seems to be the main metabolic anomaly in PCOS. In PCOS, hyperinsulinaemia increases the occurrence of metabolic syndrome in women leading to development of diabetes mellitus type 2 (T2DM), cardiovascular disease (CVD) and non-alcoholic fatty liver disease (NAFLD).[7] The study was performed to assess the relationship between obesity and insulin resistance in polycystic ovary syndrome affected women.

METHODOLOGY

It was a cross sectional comparative study. The study was done at the Multidisciplinary Lab-I of department of Biochemistry & Molecular Biology, Army Medical College, Rawalpindi, in collaboration with Pakistan Naval Ship Hafeez Hospital, Islamabad, from February 2018 to January 2019. The sampling technique applied was non probability purposive sampling. For assessment of biochemical parameters, 105 (calculated according to WHO calculator) patients (n=105) were selected. The selected females were divided into three groups: group-I: normal weight healthy females PCOS; controls (n=35; BMI 18.5-24.9 kg/m^2), Group-II: normal weight females with PCOS (n=35; BMI 18.5-24.9 kg/m^2), group-III: over-weight females with PCOS (n=35 BMI 25-29.9 kg/m^2).

The age and BMI were matched in all the groups. The mean age (puberty till 25 years of age) was similar in all the groups. The control subjects had a regular menstrual cycle, were not receiving any medication or hormonal therapy and were not suffering from any acute or chronic disease.

Inclusion Criteria: Diagnosed females with PCOS (diagnosed on basis of Rotterdam criteria) were included in the study.

Exclusion Criteria: All cases of hyperandrogenism due to thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumours and Cushing's syndrome were excluded from the study.

A specifically-designed questionnaire including demographic information, chief complaints, history of menstrual cycles, duration of the disorder, family history of disease, presence of hirsutism, acne and alopecia was filled for each patient at the time of enrolment of the subject into the study.

Sampling was done by convenient non-probability purposive sampling. After informed written consent, 10ml of fasting venous blood sample (overnight fast of 8-10 hours) was collected by means of 10 ml sterilized syringes. The sample blood was stored at-20oC in EDTA vacutainers (containing EDTA as anticoagulant) after proper marking with name and identification numbers given to the subjects.

Anthropometric variables for calculation of BMI were determined in all the subjects. Samples were used for the measurement of serum total testosterone, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), estradiol, and fasting glucose levels by commercially available kits based on principle of ELISA. Serum insulin was measured using radioimmunoassay techniques. HOMA-IR index was calculated by using corresponding fasting blood glucose levels. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to calculate insulin resistance (IR).

HOMA-IR index was calculated by standard formula: HOMA-IR = fasting concentration of insulin (μU/L)-fasting concentration of glucose(nmol/L) 22.5.[8]

The data were entered and statistically analyzed using SPSS-22. Descriptive statistics like mean and standard deviation were calculated for quantitative variables. The mean and standard deviation of serum LH, FSH, total testosterone and estradiol as well as

fasting blood glucose were calculated. The statistical significance of difference among the groups was determined by applying one way ANOVA. This was followed by applying Post Hock Tuckey's Test on the data. The *p*-value of ≤0.05 was considered to be statistically significant. For insulin resistance, HOMA-IR value of <1.0 showed insulin-sensitive which was considered optimal and HOMA-IR value of above 1.9 indicated early insulin resistance.[9]

RESULTS

Total number of individuals included in this study was 105 females (n=105), Mean age 17.23 ± 3.9 years ranging from age of puberty till 25 years. They were divided into three groups of 35 females each. HOMA-IR concentrations correlated directly with basal metabolic index, fasting plasma glucose and serum insulin levels. Mean serum insulin level was also elevated in patients with PCOS (normal weight & overweight) as compared to control subjects (7.4 ± 1.2 & 9.1 ± 0.8 VS. 6.3 ± 1.1 mIU/L; *p* as 0.003). The insulin resistance was slightly higher in patients with PCOS as compared to the control subjects (1.4 ± 0.3 & 1.7 ± 0.2 VS. 1.1 ± 0.3; *p*<0.001) shown in Table-II.

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most frequently encountered, multifaceted endocrinopathy in reproductive-aged females, manifesting as menstrual irregularities, hyperandrogenism and polycystic ovaries. Being a multifactorial disease, individual susceptibility to PCOS is determined by genetic and environmental risk factors.[10]

PCOS is a highly prevalent disorder effecting reproductive-aged women worldwide, with a prevalence of 6.5-8% in most parts of the world, using the NIH Criterion[11]. Although the etiopathogenesis of PCOS is still to be fully established, it is believed that hyperandrogenism, central obesity, and insulin resistance interplay to cause this syndrome. Adipose tissue dysfunction and chronic low-grade inflammation may be involved in the development of metabolic and reproductive dysfunctions of PCOS.[10]

The present study shows correlation of BMI and PCOS. It has been established that PCOS is associated with obesity and IR. Our study demonstrated BMI of normal weight PCOS affected females as slightly more as compared to normal weight controls. Prevalence of PCOS in normal weight females is shown in study by

Table-I: PCOS diagnostic criteria 2.

NIH Consensus 1990 (all required)	Rotterdam Consensus 2003 (two out of three required)	AEPCOS definition 2006 (androgen excess and one other criterion)
Clinical and/or	Clinical and/or	Clinical and/or
Biochemical	Biochemical	Biochemical
Hyperandrogenism	Hyperandrogenism	Hyperandrogenism
Ologo/amenorrhea, anovulation	Ologo/amenorrhea, anovulation	Ologo/amenorrhea, anovulation
	Polycystic Ovaries appearance on ultrasound	Polycystic Ovaries appearance on ultrasound

Exclusion of other androgen excess disorders: NC-CAH, Cushing's syndrome, androgen secreting tumors, hyperprolactinemia, thyroid diseases , drug-induced androgen excess. Other causes for anovulation should also been excluded

Table-II: ccomparison of mean values of biochemical parameters.

Parameters	Group-I (Controls) Mean±SD	Group II (Normal weight PCOS) Mean ± SD	Group III (Over-weight PCOS) Mean ± SD	*p*-value	Comparison of *p*-values of three groups		
					Group I -vs-		Group II -vs-
					Group II	Group III	Group III
Age (years)	17.0 ± 3.8	17.0 ± 3.9	16.8 ± 3.3	0.952	1.000	0.096	0.096
BMI (kg/m²)	23.2 ± 1.6	23.9 ± 7.14	28.1 ± 1.3	0.001	<0.001	0.038	<0.001
Leutinizing Hormone (mIU/L)	6.4 ± 1.7	8.0 ± 1.4	9.14 ± 1.1	0.001	<0.001	<0.001	0.004
Follicle Stimulating Hormone (mIU/L)	5.4 ± 1.6	5.7 ± 1.1	6.0 ± 0.8	0.166	0.595	0.140	0.617
Estradiol (pmol/L)	238.9 ± 80.8	258.9 ± 68.4	226.6 ± 60.9	0.238	0.574	0.234	0.792
Testosterone (nmol/L))	0.5 ± 0.1	0.7 ± 0.1	0.9 ± 0.2	0.003	<0.001	<0.001	<0.001
Fasting Blood Glucose (mmol/L)	4.01 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	0.002	0.030	0.004	0.753
Insulin (mIU/L)	6.3 ± 1.1	7.4 ± 1.2	9.1 ± 0.8	0.003	<0.001	<0.001	<0.001
HOMA-IR	1.1 ± 0.3	1.4 ± 0.3	1.7 ± 0.2	0.001	0.003	<0.001	<0.001

Olszanecka-Glinianowicz *et al*.[12] This is also supported in a study by Barber *et al*,[13] showing the association between PCOS and obesity, as evident from epidemiological studies revealing the majority of women (38-88%) with PCOS to be either overweight or obese. Our findings are supported by Orio *et al*,[14] who showed that there is greater occurrence of PCOS in overweight and obese women as compared to the general female population, with obesity in PCOS being influenced by various factors.

The results of our study are in concordance with study of Alfaqih *et al*,[15] who documented weight gain and central obesity as features and etiological agents of PCOS.

In this study, serum levels of fasting blood glucose and insulin were raised in normal weight and over-weight PCOS affected females as compared to normal weight healthy controls. This is documented in study by Toprak *et al*.[16]

Polycystic ovary syndrome frequently is associated with IR with compensatory hyperinsulinemia and obesity. In this study, fasting blood glucose levels were higher in PCOS patients (normal weight and over-weight) as compared to healthy controls. In a study by Ortiz *et al*,[17] fasting blood glucose levels were impaired in PCOS patients.

Insulin resistance is considered to play a major role in the etiology of PCOS. These results indicate that a significant degree of insulin resistance exists in normal weight patients with PCOS.

In the present study, fasting hyperinsulinemia with relatively higher HOMA-IR values was seen in over-weight females with PCOS as compared with the normal weight cases of PCOS and control groups. A study by Delitala *et al*,[18] IR is witnessed in about 50–80% of women with PCOS with early onset of diabetes.

In the present study, tendency to IR was documented in normal weight PCOS affected females with relatively higher HOMA-IR values as compared to normal weight healthy controls. These women may have adipose insulin resistance (adipose-IR), as labelled by Dumesic *et al*.[19]

Thus, measures to decrease insulin resistance may have to be considered earlier to decrease the potential risks of developing diabetes mellitus and coronary artery disease at later ages of life in these patients.

In this study, there was an increase in fasting blood glucose, serum insulin and HOMA-IR levels in PCOS patients (normal weight and over-weight) as compared to healthy individuals, indicating positive association between HOMA-IR levels and BMI. Thus, patients with PCOS have tendency towards insulin resistance.

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CONCLUSION

Obesity and insulin resistance are part of vicious cycle important factor in etiology/pathogenesis of PCOS. Further evaluation with larger sample size is needed to fully validate the relationship of BMI and insulin resistance in the development of morbidity associated with PCOS.

Conflict of Interest: None.

Authors' Contribution

AA: Corresponding author, PW: Critical analysis, RA: Facilitation of data collection, AR: Critical analysis, SAK: Critical analysis.

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