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Original Article

A Comparative Study of Serum Adiponectin and Insulin Resistance In Patients With Polycystic Ovary Syndrome

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ABSTRACT

Objective: To assess correlation between serum adiponectin levels and insulin resistance in patients with Polycystic ovary syndrome.

Study Design: Comparative Cross-Sectional study.

Place and Duration of Study: PNS Hafeez Hospital, Islamabad Pakistan, and Multidisciplinary Lab-I, Department of Biochemistry, Army Medical College Rawalpindi, Pakistan from Feb 2018 to Jan 2019.

Methodology: Three groups (35 females each) were formed from selected one hundred and five females (puberty till 25 years) who had Polycystic ovary syndrome. After overnight fast, blood samples were collected to measure serum levels of insulin and adiponectin. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to calculate insulin resistance.

Results: The over-weight PCOS subgroup displayed lowest serum adiponectin level (8.73±2.13 mg/L; 13.87±3.60 mg/L in normal weight PCOS and 15.09±3.07 mg/L in controls). There was statistical significance of serum Fasting Blood Glucose (mmol/L, p=0.002), serum Insulin (mIU/L; p=0.003) andserum Adiponectin levels (mg/L; p<0.001) and HOMA-IR (p<0.001) among three groups. The over-weight PCOS subgroup presented with highest HOMA-IR (1.71±0.19; 1.35±0.25 in normal weight PCOS subgroup and 1.12±0.26 in controls). There is negative correlation between serum adiponectin and HOMA-IR with r= -0.46.

Conclusion: In PCOS-affected females, HOMA-IR correlates inversely with serum adiponectin levels, signifying that abdominal adiposity indirectly favors insulin resistance in PCOS through decrease in adiponectin secretion. Serum adiponectin level is negatively associated with severity of IR in PCOS.

Keywords: Adiponectin, Homeostatic Model Assessment of Insulin Resistance, Insulin Resistance, Metabolic Syndrome, Polycystic Ovary Syndrome.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multidimensional endocrinal disorder, influencing the reproductive, metabolic and psychological health of females of reproductive age. It is an interplay of ovarian dysfunction, genetic andepigenetic susceptibility, neuroendocrine dysfunction, and metabolic features (adiposity, adiponectin levels, insulin resistance, etc.), although the exact etiology and pathophysiology remains unclear.[1]

The diagnosis of PCOS is based on oligo-anovulation (OA), hyperandrogenism (HA; clinical or biochemical), and polycystic ovary morphology (PCOM) on ultrasound. The Rotterdam criteria (presence of any two features) are recognized and approved by the 2018 international evidence-based guideline for assessment and management of PCOS.[2] PCOS frequently presents at puberty with distinctive reproductive and hyperandrogenic features.[3,4] Adiponectin, the major cytokine secreted by the visceral fat cells, possesses insulin-sensitizing, anti-diabetic and anti-atherogenic properties. Its levels are reduced in obese individuals and PCOS patients, which associate adversely with free androgen levels, insulin resistance (IR) and IR-associated conditions.[5] One cause of insulin resistance in PCOS is documented to be hyperandrogenism. Insulin resistance also causes hyperandrogenism and anovulation. Androgen excess accentuate visceral adiposity and insulin resistance.[6]

Females affected with PCOS often develop insulin resistance (IR), which alters insulin action at the level of the cell, leading to hyperinsulinemia (HI) as a compensatory phenomenon. In PCOS, the ovary maintains sensitivity to insulin with the concurrent stimulus causing androgen synthesis, resulting in hyperandrogenism (HA). This HA enhances the

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incidence of IR, thus, snowballing the IR-HI-HA cycle and in turn PCOS.[7,8]

The association of PCOS with obesity and insulin resistance (IR) shows that the large majority of affected females are obese or overweight, having IR and associated compensatory hyperinsulinemia. IR and hyperinsulinemia are also present in even non-obese females with PCOS. The potential to developing metabolic abnormalities is augmented by hyperinsulinemia.

METHODOLOGY

The cross-sectional study was conducted at the Multidisciplinary Lab-I, Department of Biochemistry, Army Medical College Rawalpindi, Pakistan and PNS Hafeez Hospital, Islamabad, Pakistan, from February 2018 to January 2019, following approval from the Ethical Review Committee of Army Medical College (ERC/AMC/30 May, 2018).

Inclusion Criteria: Based on the Rotterdam criteria, female patients of reproductive aged (1-45 years) diagnosed with PCOS were included.

Exclusion Criteria: Patients suffering from congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, hyperprolactinaemia or hyperandrogenism due to thyroid dysfunction were excluded.

WHO Sample Size Calculator calculated the sample size using the population proportion of PCOS as 6.5%-8%,[9] which came to 105. Non-probability purposive sampling was used to gather data, after obtaining written, informed consent. On the basis of total sample size, three groups were formed based on their BMI: Group-A: controls or healthy females with normal weight without PCOS (n=35; BMI 18.5-24.9 kg/m^2); Group-B: females affected by PCOS with normal weight (n=35; BMI 18.5-24.9 kg/m^2); Group-C: over-weight females affected by PCOS (n=35 BMI 25-29.9 kg/m^2).[10]

For all groups, both BMI and age were matched, respectively. In all the three groups of selected females, the mean age (puberty till 25 years of age) was comparable. Subjects in the control group had regular menstrual cycle, did not suffer from any acute or chronic illness, were not taking any drug or hormone treatment and did not suffer ailment.

Detailed particulars (demographic details, primary symptoms, menstrual history, onset/time period of the disorder, family history of PCOS, occurrence of hirsutism, acne and alopecia) were obtained on a pre-made proforma.

After an overnight fast (8–10 hours), a 10ml sample of venous blood was drawn through 10 ml sterilized syringes and placed in EDTA vacutainers (EDTA anticoagulant) and kept at -20oC. The samples were properly marked with name and identification numbers allotted to the subjects. Serum adiponectin levels were measured from the obtained blood sample by commercially available kits for ELISA technique. Direct chemiluminescent technology was used to measure serum insulin levels. Calculation of HOMA-IR index was done by incorporating corresponding levels of fasting blood glucose. The Insulin Resistance (IR) was computed by use of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

For calculation of HOMA-IR index, the following formula was applied:

HOMA-IR= (Fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl) / 22.5 11, 12

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 29. The Mean±SD deviation of serum fasting blood glucose, insulin and adiponectin levels were calculated. Independent samples t-test was applied to explore the inferential statistics. Pearson correlation coefficient was used to assess the correlation of serum adiponectin and insulin resistance. A p-value of ≤0.05 was considered significant.

RESULTS

A total of 105 subjects were included in the study after fulfilling the inclusion criteria and divided into three groups. Mean age of patients was 16.92±3.47 years which was statistically insignificant (p-value >0.05). Age and BMI characteristics of study groups is shown in Table-I. The difference in the mean BMI among all three groups displayed statistical significance with $p < 0.05$. Comparison of biochemical parameters of study groups is shown in Table-II. The mean value of fasting blood glucose (FBG) displayed statistical significance between Group-A and Group-A (p<0.04) and Group-A and Group-C (p<0.001). However, comparison of mean levels FBG among Group-B and Group-C was statistically insignificant (p=0.753). The mean levels of serum insulin levels were statistically significant among all three groups (p< 0.001). The HOMA-IR between groups A and B (p = 0.003), A and C, and B and C (p<0.001in both). Serum adiponectin levels was statistically significant

among groups A and B (p=0.022), A and C (p<0.001) and B and C (p<0.001). Comparison of biochemical parameters of study are shown in Table-III. The relation between HOMA-IR and serum adiponectin level (Pearson's correlation co-efficient) was r = -0.46, indicating an inverse relationship between the two variables.

The association between HOMA-IR and serum adiponectin as determined by Pearson's correlation co-efficient where r = -0.45 is presented in the figure.

Table-I: Age and BMI Characteristics of Study Groups (n=105)

Characteristic	Mean±SD
Age (years)	
Group-A (Controls; n = 35)	17.00±3.83
Group-B (Normal Weight PCOS; n = 35))	17.00±3.90
Group-C (Over-Weight PCOS; n = 35)	16.77±3.28
BMI (kg/m2)	
Group-A (Controls)	23.24±1.59
ii. Group-B (Normal Weight PCOS)	23.98±0.71
iii. Group-C (Over-Weight PCOS)	28.08±0.71

Table-III: Comparison of Biochemical Parameters of Study Groups (n = 105)

Parameters	Group-A (n = 35)	Group-B (n = 35)	Group-C (n = 35)	p-value
Fasting Blood Glucose(mmol/L)	4.01±0.33	4.2±0.25	4.2±0.26	0.002
Insulin (mIU/L)	6.29±1.14	7.35±1.15	9.14± .81	0.003
HOMA-IR	1.12±0.26	1.35 ±0.25	1.71±0.19	< 0.001
Adiponectin (mg/L)	15.09±3.07	13.87±3.60	8.73±2.13	< 0.001

Table-III: Inter-Group Comparison of Biochemical Parameters (n = 105)

Parameters	Group-A VS		Group-B VS
	Group-B	Group-C	Group-C
Fasting Blood Glucose (mmol/L)	0.030	0.004	0.753
Insulin (mIU/L)	<0.001	<0.001	<0.001
HOMA-IR	0.003	<0.001	<0.001
Adiponectin (mg/L)	0.228	<0.001	<0.001

DISCUSSION

The most common endocrinal disorder observed in reproductive aged females is polycystic ovary syndrome (PCOS).[11] Its diagnosis is challenging, due to symptoms overlapping with other ailments. In PCOS, hyperinsulinaemia and insulin resistance aggravate the condition that is further exacerbated by adiposity due to hyperandrogenism, dysfunction and toxicity of adipose tissue, and oxidative stress.[12] The multifactorial disease with multiple etiological factors, increases vulnerability of affected females for dyslipidemia, impaired glucose tolerance (IGT), hypertension, T2DM, cardiovascular diseases, and eventually metabolic syndrome.[13]

The present study demonstrates that adipose tissue may disturb insulin release by the pancreas, indicated by a negative correlation between circulating adiponectin levels and serum insulin levels. Subsequently, elevated serum insulin levels correspond to raised HOMA-IR. The interrelation between the pituitary–ovarian axis and adipose tissue is reciprocal, as androgens and estrogens may influence secretion of at least some adipokines.

In all age groups, obesity affects both prevalence and degree of PCOS, with correlation between Body Mass Index (BMI) and features of PCOS.[14] According to a study by Barber *et al*., obesity and subsequent weight-gain impact progression of PCOS; the occurrence of PCOS further contributes towards weight-gain.[15]

Exposure to excess of androgens cause hypertrophy of adipocytes. Derangement of adipokines' secretion affects the pathophysiology of PCOS by virtue of its impact on gonadal steroid secretion and, hence, metabolism. PCOS is strongly associated with the operational maladies of adipose tissue. The results of the present study showed that PCOS patients have hypoadiponectinaemia. This hypoadiponectinaemia is dependent on the state of obesity. Adiponectin, secreted from the adipocyte, has insulin-sensitizing effect with some studies showing negative relationship between adiponectin and BMI.[16] A study by Baldani *et al*. demonstrated hypoadiponectinaemia in PCOS patients irrespective of obesity. The diagnosis of PCOS served as the strongest independent predictor of serum adiponectin levels with the adipocytokine being the most specific factor for a diagnosis of PCOS.[17]

In this study, women with PCOS exhibit greater insulin resistance IR than their weight and age matched counterparts. The most significant aspect of PCOS is IR, responsible for the occurrence and continuance of this disorder. IR is believed to be the root cause of the metabolic derangements linked to the metabolic syndrome.[18] Elevated testosterone

concentrations along with obesity-related inflammatory factors alter glucose homeostasis through IR and insulin secretion.[19]

Hyperandrogenaemia and IR are the strongest clinical features of PCOS, with the size of the adipocytes size being a strong marker for IR in women with PCOS. A vicious cycle is generated by presence of abdominal obesity and IR stimulated androgen production, which further exacerbates preexisting abdominal obesity and inflammation. Insulin resistance accompanied by the hyperinsulinaemia, hyperglycaemia and altered adipokines' secretion can cause dysfunction of the vascular endothelium, derangements of serum lipid profile, hypertensive disorder as well as inflammation of vascular tissue. This constellation of findings where risk factors (abdominal obesity, hyperglycaemia, dyslipidaemia and hypertension) for T2DM and CVD are present simultaneously is termed as Metabolic Syndrome (MetS).[18,19]

CONCLUSION

In PCOS-affected females, HOMA-IR correlates inversely with serum adiponectin levels, signifying that abdominal adiposity indirectly favors insulin resistance in PCOS through decrease in adiponectin secretion. Serum adiponectin level is negatively associated with severity of IR in PCOS.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AA & RA: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AR & NA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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