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How Significant are Insulin Resistance Parameters in Subjects with Polycystic Ovarian Syndrome (PCOS)? A Cross-Sectional Study

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ABSTRACT

Objective: To evaluate insulin resistance by "Homeostasis Model Assessment for Insulin Resistance (HOMA IR)" and related cardiovascular disease risks in females with or without polycystic ovarian syndrome.

Study Design Comparative cross-sectional study.

Place and Duration of Study: Pakistan Navy Ship Hafeez Hospital, Islamabad Pakistan**,** from Jan 2018 to Dec 2019.

Methodology: Patients diagnosed to have polycystic ovarian syndrome (n=158) as per Rotterdam criteria were compared with non-PCOS patients (n=162) for HOMA IR and other CVD risks. Measurement of glucose, insulin, lipid parameters and HbA1c for all subjects was carried out in fasting. PCOS was diagnosed by "Rotterdam Criteria". Free Androgen Index was measured as FAI=(Total testosterone/SHBG) x100. Differences in insulin resistance among polycystic ovarian syndrome and non-polycystic ovarian syndrome females were measured by the non-parametric test.

Results: Our study included 158 females (49.38%) with PCOS defined as per Rotterdam criteria, while 162 subjects did not have PCOS (50.62%). The differences between PCOS and non-PCOS were LH: 5.15±3.66 vs. 4.58±2.87 IU/L (p=0.121), FSH: 5.87±3.57 vs. 7.26±4.63 IU/L (0.003), total testosterone: 1.76±0.86 vs. 1.17±0.45 nmol/L (<0.001) and SHBG: 41.59±31.94 vs. 55.50±34.76 (p<0.001). Insulin resistance was higher in PCOS [(3.81±3.58, n=156) in comparison to non-PCOS (3.11±2.49, n=162), p=0.091]. Both the presence of PCOS and obesity, as measured by BMI, were associated with higher HOMA-IR.

Conclusion: Insulin resistance was found to be higher in PCOS females than in non-PCOS females. BMI also contributed to higher insulin resistance among our study population.

Keywords: Cardiovascular Disease (CVD), Free Androgen Index (FAI), Homeostasis model assessment for insulin resistance (HOMA-IR), Polycystic ovarian syndrome (PCOS), Testosterone.

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INTRODUCTION

Syndrome X, later termed a metabolic syndrome, primarily got its nomenclature from the presence of multiple biochemical and clinical metabolic features, including obesity, hyperglycemia and lipid abnormalities.[1,2] Further research over time indicated the possibility of other associations for metabolic syndrome, which could result either directly or indirectly due to insulin resistance, including nephropathy, fatty liver disease and Polycystic Ovarian Syndrome (PCOS).[3] This disorder in recent times has emerged as one prevalent condition in reproductive-age females, with symptoms varying from menstrual disturbances to infertility to hirsutism and hormonal abnormalities.[4]

Current diagnostic criteria for both metabolic syndrome and PCOS vary in terms of both included components and various cut-offs used for diagnosis, leading to a lot of variability in existing clinical data.[5] PCOS has been hypothesised to be related to kisspeptin and GnRH-stimulated alternated functionality of hypothalamic and pituitary hormone changes defining the differing phenotypes of PCOS.[6] While the exact pathogenesis needs quality research elucidation, much ambiguity prevails due to current aetiologies focusing on insulin sensitivity, androgen excess, genetics, lifestyles, and possibly regional phenotypes.[7] However, available literature highlights multiple controversies concerning the relationship between insulin resistance and the appearance of PCOS. Bannigada *et al*. have depicted that not all clinically defined PCOS demonstrate underlying insulin resistance.[8] Studies have also shown the androgen to be the potent driver in patients with PCOS regardless of the presence of insulin resistance.[9] Others have shown the role of the leptin hormone (A surrogate for insulin resistance), and GnRH releases dynamic alteration related to

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excess androgen secretion from the ovary and adrenal glands.[10] Considering the varying nature of PCOS, as per the highlighted evidence in terms of different clinical phenotypes of PCOS and varied criteria-based diagnoses, we evaluated insulin resistance by "Homeostasis Model Assessment for Insulin Resistance (HOMA-IR)" and other cardiovascular disease (CVD) risks in subjects diagnosed with PCOS.

METHODOLOGY

The comparative cross-sectional study was conducted from January 2018 to December 2019 at Pakistan Navy Ship hafeez Hospital, Islamabad Pakistan involving Gynaecology, Pathology, Radiology, and Family Outpatient Departments. Participants' selection was based upon non-probability convenience sampling.

Inclusion Criteria: Female subjects of reproductive age who presented to Outpatient Departments for any reason and who volunteered further interviewed for the presence of PCOS were included.

Exclusion Criteria: The presence of any acute/chronic medical disorder, diabetes, hypertension, heart disease, autoimmune disease, gynaecological disorder or ongoing/recent pregnancy, implied exclusion from the study.

After these initial screenings, clinical examinations and explanations about the study, the participants were asked to visit on 2nd day of their menstrual cycle around 0800 hours in the morning in medical fasting. Those participants who presented the given date and time were included in the study. On the day of the presentation, these patients were formally explained about study requirements. Females found to meet inclusion criteria were offered formally for inclusion into the study by signing a formal written consent.

History was taken for any menstrual complaints, including oligo/anovulation, which was defined to be present for a particular female subject if she had either no anovulation or periods exceeding 35 days.[11,12] These females were formally examined for exclusion of chronic disease signs and evaluation of hirsutism to calculate the modified Ferrimen-Gallwey scores questionnaire.[13] Anthropometric calculations were measured as per the referenced criteria.[14,15] After history and examination, 10 ml of blood was collected in different containers, including gel, EDTA and Na-F containers, to analyse various biochemical parameters, including lipids, glucose, uric acid, reproductive hormones and insulin. Lipids, glucose and uric acid were examined and analysed on a Selctra ProM analyser. The GPO-PAP method, GOD-PAP for triglycerides, and CHOD-PAP for cholesterol estimation were adopted for measuring glucose. We measured HDLc and LDLc using the enzymatic end-point method. All hormones except insulin were measured using chemiluminescent technology on the ARCHITECT system (Abbot Diagnostics). Insulin analysis was carried out on Immulite ® model 1000. HbA1c was analysed on Abbot Diagnostics using the methodology mentioned above. HOMA-IR calculated insulin resistance as per the method of Mathew *et al*.: HOMA-IR=Serum insulin x Fasting plasma glucose/22.2.16 PCOS was assessed by utilising the "Rotterdam Criteria".[17] Free Androgen Index (FAI) was measured by formula as FAI=(Total testosterone/SHBG) x 100.[18] BMI groups were made as Group-1 (BMI<25), Group-2 (BMI: 25 to<30), Group-3 (BMI: 30 TO <35) and Group-4(BMI: >35). We have to exclude case no 200 due to an insulin level of >200 mIU/L, but the patient was lost to follow-up.

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 20.00 and MS Excel 2016 software. Mean±SD was calculated for continuous variables using Independent sample t-statistics. Pearson's correlation was used between insulin resistance with FAI, mFG scores, waist circumference, FSH, LH, total testosterone, and SHBG, which were measured. The difference between subjects regarding with or without PCOS for HOMA-IR was measured by the Kruskal Wallis test. Finally, we evaluated the effect of BMI as an independent factor on insulin resistance in PCOS groups by developing a general linear model. The p-value of ≤ 0.05 was considered significant.

RESULTS

Our study included 158 females (49.38%) with PCOS defined as per Rotterdam criteria, while 162 subjects did not have PCOS (50.62%) The age among our study population was 27.78±7.59 year. Table-I shows the differences measured by independent sample t-statistics between age, anthropometric profiles and reproductive hormones in subjects with PCOS or otherwise. Females with PCOS (26.58±6.94) were found to be younger in comparison to non-PCOS subjects (28.96±8.01). The differences between PCOS and non-PCOS were LH: 5.15±3.66 vs 4.58±2.87 IU/L (p=0.121), FSH: 5.87±3.57 vs 7.26±4.63 IU/L (0.003), total testosterone: 1.76±0.86 vs 1.17±0.45 (<0.001) and SHBG: 41.59±31.94 vs 55.50±34.76 (p<0.001). There was

Table-II: Glycemic and lipid indices among subjects with or without PCOS as per Rotterdam criteria (n=320)

Parameters	PCOS Diagnosis as per Rotterdam Criteria	Mean±SD	*p*-value
Fasting Plasma Glucose (mmol/L)	PCOS not diagnosed	5.31±1.64	0.411
	PCOS diagnosed	5.69±5.66	
HbA1c (%)	PCOS not diagnosed	5.71±3.65	0.329
	PCOS diagnosed	5.42±0.66	
Total Cholesterol (mmol/L)	PCOS not diagnosed	4.22±0.82	0.111
	PCOS diagnosed	4.38±0.94	
Serum Triglycerides (mmol/L)	PCOS not diagnosed	1.38±0.77	0.698
	PCOS diagnosed	1.34±0.85	
Low Density Lipoprotein Cholesterol (mmol/L)	PCOS not diagnosed	2.43±0.73	0.003
	PCOS diagnosed	2.69±0.84	
High Density Lipoprotein Cholesterol (mmol/L)	PCOS not diagnosed	1.08±0.74	0.392
	PCOS diagnosed	1.02±0.33	

Table-III: Pearson's Correlation between Insulin Resistance (HOMA-IR) and FAI, mFG, Waist Circumference and Reproductive Hormones (n=320)

Parameters		HOMA-IR
Free Androgen Index (FAI)	Correlation Coefficient	0.186**
	p-value	0.001
Modified Ferrimen Gallwey (mFG) score	Correlation Coefficient	0.075
	p-value	0.182
Waist (cm)	Correlation Coefficient	0.250**
	p-value	<0.001
LH (mIU/ml)	Correlation Coefficient	-0.045
	p-value	0.425
FSH (mIU/ml)	Correlation Coefficient	0.014
	p-value	0.802
Total testosterone (nmol/L)	Correlation Coefficient	0.110
	p-value	0.051
SHBG (nmol/L)	Correlation Coefficient	-0.172**
	p-value	0.002

Table-IV: Difference in insulin resistance among subjects with PCOS as per Rotterdam defined criteria (n=156) and without PCOS (n=162)

Parameter	PCOS diagnosis as per Rotterdam criteria	Mean±SD	*p*-value*
HOMA-IR (Insulin resistance)	PCOS not diagnosed	3.11±2.49	0.091
	PCOS diagnosed	3.81±3.58	

** Non-parametric Kruskal Wallis test*

no difference in the glycaemic and lipid indices in the two groups except for LDL-cholesterol, higher among subjects diagnosed with PCOS per Rotterdam criteria, as depicted in Table-II. Pearson's correlation identified a higher positive correlation, as shown in Table-III between insulin resistance and FAI (+0.186, p=0.001) and waist circumference (+0.250, p<0.001), while SHBG was negatively correlated (-0.172, p=0.002). Table-IV shows higher insulin resistance (HOMA-IR) among participants diagnosed with PCOS [Mean=3.81±3.58] in comparison to non-PCOS subjects [Mean=3.11±2.49]. However, the p-value was not significant (p=0.091) under non-parametric conditions. General Linear Model analysis, as depicted in Figure, shows HOMA-IR to be raised among subjects with PCOS and higher BMI, suggesting a contribution from BMI remains incremental for the causation of insulin resistance.

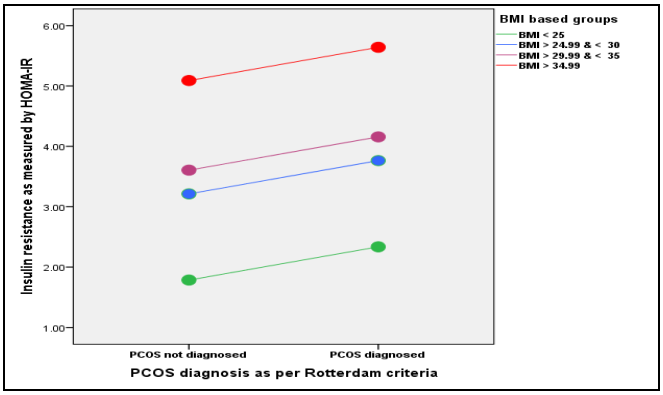

Figure: General Linear Model (GLM) Showing Differences in Insulin Resistance (HOMA-IR) with Presence or Absence of PCOS and BMI as Independent Variables. (Model Significance <0.001)

DISCUSSION

Our study depicted higher insulin resistance among subjects with PCOS in comparison to females without PCOS. However, we also observed that higher BMI among females increased insulin resistance. The contribution to insulin resistance comes from both obesity and PCOS. There is available data which contradicts in many ways the relationship between insulin resistance and the development of polycystic ovaries.[8,9] One study stated that insulin resistance is the key driver in polycystic ovarian pathogenesis but

argue that underlying resistance to insulin is not demonstrated in all patients with the key factor being the lean and obese PCOS phenotype where the former category only demonstrated insulin resistance in up to 20-25%.[19] Similarly, Aye *et al*. in experimental studies, showed that regular exercise reduced insulin resistance among PCOS subjects and ameliorated the disease's clinical features.[20] Provided contrasting data. We feel confident that our findings follow supporting data as we were able to show that the presence of PCOS is associated with being obese and having a higher degree of insulin resistance.

Our data also showed higher testosterone, FAI and LH levels with lower SHBG and FSH levels, thus suggesting hyperandrogenemia is associated with PCOS in our subjects. Though no novelty lined with this observation, it points out various neuroendocrine factors, including an altered Kisspeptin-GnRH-LH axis, which various stress-related hormones could alter to cause higher LH with low FSH levels as observed in our study.[21] Probable mechanisms to higher LH levels as observed against low FSH among PCOS vs Non-PCOS include altered triggers to kisspeptin neurons leading to downstream effects in terms of higher GnRH to LH pulsations leading to the appearance of PCOS phenotype.[22]

We observed that insulin resistance, while showing some degree of correlation with free androgen index, anthropometric markers like waist circumference and SHBG were not associated with Ferryman-Gallwey score for hirsutism, thus pointing towards the interplay involving other factors including ethnicity, genetics, race and maybe unknown etiologies.[23,12] These findings suggest differences in the PCOS phenotypes along with genotypes among the Asian population and other ethnic or race groups, which in future could have specific criteria for defining this disorder.

Associating our findings with shared literature identifies the pathogenesis as multifactorial. Apparent phenotypic issues could include hyperandrogenism and insulin resistance, with underlying genetic alterations all converging to specific PCOS phenotypes.

Our study makes a significant contribution towards local data for PCOS. The study can guide physicians in terms of considering obese and non-obese PCOS phenotypes in clinical consideration during diagnostic testing and for therapeutics. Furthermore, the study highlights the need to find specific criteria for diagnosing PCOS, which needs better quality trials.

LIMITATION OF STUDY

Certain limitations to our work must be acknowledged: Firstly, a cross-sectional small sample study requires replication to generate wholesome data to incorporate all possible etiological factors discussed. Secondly, we believe the Rotterdam criteria needs an ethnic and race-specific adjustment in terms of cut-offs, especially for the mFG score.

CONCLUSION

Polycystic ovarian syndrome in our studied population was associated with both hyperandrogenemia and insulin resistance. Moreover, BMI, age, and the presence of PCOS contribute to insulin resistance.

Conflict of Interest: None.

Authors Contribution

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

SHK & RS: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

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

RA & TC: Conception, data acquisition, drafting the manuscript, 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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