ORIGINAL ARTICLE

RELATIONSHIP OF OBESITY WITH INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYNDROME

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Background: Polycystic ovary syndrome (PCOS) is associated with insulin resistance, hyper-insulinemia and obesity. This study was designed to find out the levels of insulin resistance (IR) and its relationship with obesity in patients of PCOS. **Methods:** Seventy-four (74) females, diagnosed as PCO were selected from the Outpatient Department of Lady Atchison Hospital and divided in two groups. Group 1, PCOS with BMI <25 Kg/m^2 and Group 2 with BMI ≥25 Kg/m^2. Blood glucose and serum insulin were determined using ELISA. Insulin resistance was calculated using HOMA-IR method. Data was analyzed using SPSS-20. Mean±SD was used to present quantitative data. Normality of data was checked by one sample Kolmogorov Simonov test. Pearson's correlation test was applied to see relationship between insulin resistance and obesity. The $p \leq 0.05$ was considered as significant. **Results:** Serum insulin in Group 2 (26.35±25.78) was statistically higher than Group 1 (16.63±13.58). Insulin resistance in Group 2 and Group 1 was 5.37±4.96 and 4.25±3.53 respectively, with no statistically significant difference (p=0.249). No significant correlation was found between IR and BMI in either cases or controls but overall a weak positive correlation was noted between the two variables. **Conclusion:** Insulin resistance and serum insulin were higher in females with polycystic ovarian syndrome. Insulin resistance and hyperinsulinaemia share the disease and might exacerbate the symptoms of disease. No significant correlation was found between insulin resistance and BMI.

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, Obesity, PCOS

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INTRODUCTION

Polycystic ovaries is one of the most common hormonal irregularity affecting 5–10% of women of child bearing age.[1–5] The prevalence of PCOS shows an increasing trend in subcontinent, with incidence of 37.3% in Indian Kashmiri women and 20.7% in Pakistani women. A local study conducted in Pakistan in 2007 reported that the occurrence of PCOS in the infertility clinic was 17.6% with an even higher rate of obesity (68.5%) and hyperinsulinemia (59%).[6]

Stein and Leventhal firstly recognized PCOS in 1935 and it was named as Stein Leventhal Syndrome.[1] There was no formal way of diagnosing PCOS before 1990. After that, a minimal criteria for diagnosis of PCOS was introduced by National Institute of Health (NIH).[7] According to NIH, PCOS is diagnosed on the basis of menstrual irregularities, oligo/ anovulation, and biochemical or clinical signs of hyperandrogenism.

The PCOS is identified by ultrasonography. Trans-vaginal ultrasound is the gold standard for diagnosis of PCOS. The presence of polycystic ovaries with one ovary having size more than 10 Cm^3 with the presence of twelve or more follicles having diameter 2–9 ηm, or ovaries containing 8 or more sub capsular follicular cysts ≤10 ηm with increased ovarian stroma characterise PCOS.[8] These findings are present in more than 80% of females with PCOS.[2,9]

The basis of the syndrome is insulin resistance and abnormal glucose handling at molecular and cellular levels. Insulin resistance is defined as defected metabolic response of the cells in which response of the cells to ordinary basal levels of insulin is highly disturbed.[10] Insulin dependent glucose transport is decreased in many tissues of the body in patients with PCOS.[7] It has been observed that there is a deficiency at molecular level that leads to insulin resistance which may be in form of increased phosphorylation of serine residues of insulin receptor or mutations in insulin receptor or insulin receptor substrate-1.[11–14] In patients with PCOS the sensitivity to insulin is reduced to 35–45%.[15] Insulin resistance, obesity and impaired insulin secretion are results of hyperglycemia.[16] This study was designed to find out the levels of insulin resistance and its relationship with obesity in patients of PCOS.

METHODOLOGY

This cross-sectional study was conducted at Lady Atchison Hospital Lahore from June 2016 to October 2016. Sample size was calculated using 5% level of significance and 90% power of test. Non-probability convenient sampling technique was used to select the subjects.

After approval from Institutional Review Board of King Edward Medical University, Lahore, informed consent was taken from the enrolled subjects. Seventy-four females in reproductive age group aged

20–31 years[17] with BMI above 25, diagnosed of PCOS (37 patients in each group of cases and controls) were selected. After taking history and general physical examination their height in meters, weight in Kg was recorded and Body Mass Index (BMI) was calculated. On the basis of BMI they were divided into controls (normal: BMI<25 Kg/m^2), and cases (overweight: BMI ≥25 Kg/m^2). Cases included Overweight BMI: 25–29.99 Kg/m^2) and obese (BMI>30 Kg/m^2).[18] Waist circumference was measured in Cm at the thinnest depression between tenth rib and iliac crest at the level of umbilicus and 2 Cm above and below the umbilicus, and their mean was calculated. Hip circumference was taken at the level of greater trochanter and 2 Cm above and below the greater trochanter, and mean was calculated. Waist hip ratio was determined. All the ultrasound and laboratory parameters were recorded in order to confirm and support the diagnosis. Patient was called again after an overnight fast on day 3 of the menstrual cycle for the blood sample.

Fasting blood glucose was determined with glucometer. For fasting insulin levels, 5 ml of blood was taken from ante-cubital vein. For purpose of storage and centrifugation blood was transferred into yellow vacutainers. Centrifugation was done and serum was transferred into 6 aliquots and then stored in the chemical pathology laboratory of KEMU at -40 °C to be used later. Serum glucose was estimated by glucose oxidase method. All information collected was entered in a specially designed proforma.

Data was analyzed using SPSS-20. Mean±SD was used to present quantitative data. Normality of data was checked by one sample Kolmogorov Simonov test. Independent sample *t*-test was applied to compare quantitative data. Pearson's correlation was applied to see relationship between insulin and BMI, and $p \leq 0.05$ was considered as significant.

RESULTS

The mean age of cases and controls was 25.42±4.16 years and 22.98±3.35 years respectively. The mean BMI was 27.59±5.72 Kg/m^2 in cases and 22.74±4.44 Kg/m^2 in controls with significantly higher mean BMI in cases ($p<0.001$) (Table-1). The mean insulin was 26.35±25.78 µU/ml in cases and 16.63±13.58 µU/ml in controls ($p=0.038$) (Table-2).

Mean insulin resistance in cases and controls was 5.37±4.96 and 4.25±3.53 respectively with no significant statistical differences (Table-3). No significant correlation was found between IR and BMI in cases or controls but overall a weak positive correlation was noted between the two variables (Table-4).

There was no significant correlation between insulin resistance and BMI in either cases or controls, but overall there was a weak positive correlation between IR and BMI, ($r=0.248$, $p=0.027$).

Table-1: BMI in Cases and Controls

Parameter	Groups	Mean±SD	Median	IQR	*p*
BMI	Cases	27.59±5.72	28.40	6.57	<0.001*
	Control	22.74±4.44	20.90	6.68	

*Significant, Independent Sample *t*-test was applied

Table-2: Insulin in Cases and Controls

Parameter	Groups	Mean±SD	Median	IQR	*p*
Insulin	Cases	26.35±25.78	16.65	14.85	0.038
	Control	16.63±12.96	13.58	11.09	

Mann Whitney U test applied

Table-3: Insulin Resistance in Cases and Controls

Parameter	Groups	Mean±SD	Median	IQR	*p*
Insulin Resistance	Cases	5.37±4.96	4.35	4.25	0.249*
	Control	4.25±3.53	3.25	2.95	

*Mann Whitney U test applied

Table-4: Correlation between IR and BMI within Cases and Controls

Parameter		Cases	Controls	Overall
Insulin resistance with BMI	Correlation (*r*)	0.179	0.272	0.248
	p-value	0.270	0.089	0.027*

*Pearson's correlation applied

DISCUSSION

Women with PCOS with normal BMI as well as those with high BMI are insulin resistant. However, the degree of insulin resistance was high in cases. This also shows that all patients with PCOS with normal weight or obese are insulin resistant and this IR is not solely dependent on BMI. Jalalian *et al*[19] did a meta-analysis on Iranian women, which showed that obesity and overweight was a persistent factor noticed in 40–50% of females.

The mean fasting serum insulin levels were raised in cases as well as in controls. However, mean insulin resistance in cases and controls was almost the same with no statistically significant differences, ($p=0.249$). Although the levels were higher than normal cut-off value but no significant correlation was found between BMI and IR in either cases or controls; however, a weak positive correlation was observed overall (combining cases and controls). This shows that fasting insulin levels as well as insulin resistance are high in all patients of PCOS irrespective of their BMI. It suggests that BMI does not affect insulin sensitivity in cells directly. In addition, some other factors like ethnicity and family history can play role in hyper-insulineamia and IR. A study by Al-Watify[20] showed that serum insulin levels and IR by HOMA-IR in PCOS patient was high as compared to healthy controls.

In females with PCOS, 30–40% of cases experience glucose intolerance or diabetes mellitus before they reach the age of 40 years. Women with PCOS are at high risk of developing metabolic abnormalities.[20] Maryam *et al*[21] reported that 6% of overweight and 39% of obese females have insulin resistance and females with normal weight have no IR. They found a positive correlation between IR and

BMI.[21] In PCOS patient the gonadotropin axis is disturbed which is further exacerbated by hyperinsulineamia and IR might not have any effect on it.[22] Areej and Catherine[23] also found IR and hyperinsulineamia in both lean as well as obese females with PCOS. According to their study the degree of IR was more in obese PCOS females. In our study 79% of Cases had IR compared to 67% IR in Controls. Katsikis *et al*[24] concluded that no significant correlation exists between serum insulin level, glucose to insulin ratio, or HOMA-IR.

In this study, overall 26% were normal with no insulin resistance and 74% were insulin resistant. When classified according to BMI, 67% of Controls were insulin resistant and 79% of Cases had IR. Ryes *et al*[25] demonstrated a positive correlation between IR and BMI.[25] deLeo *et al*[26] reported that the fasting insulin in obese PCOS women was higher as compared to non-obese PCOS women. In addition the fasting glucose was also found higher in between the groups. They found a positive linear relationship between log of HOMA-IR and BMI. Their study also reported BMI to be a better predictor of IR.[26]

Our results are further supported by Dasgupta *et al*[27] who showed IR to be greater in obese and overweight females compared to lean females. They concluded that BMI is a predictor of IR. Cupisti *et al*[28] also demonstrated that patient with BMI >25 Kg/m^2 have prominent changes in metabolic profile, e.g., IR as compare to lean patients.

If IR is responsible for PCOS and its complications then it should affect only those individuals who have PCOS, but it is found that obese subjects irrespective of gender have some degree of IR. IR does not seem to be a feature peculiar to PCOS; BMI contributes to IR. Literature available shows contrary results which suggests pattern of obesity is the key factor. Subjects who have central or visceral obesity are more prone to suffer from IR and PCOS and such patients have more chances of having metabolic diseases such as type-II diabetes.

Future work may be done on a larger sample for a better insight to the problem. Regular screening for insulin resistance may be advised especially for obese females who are prone to develop PCOS for prevention of its complications.

CONCLUSION

Serum insulin as well as insulin resistance are raised in females with PCOS suggesting that hyperinsulinemia and insulin resistance are part of disease and might exacerbate the symptoms of disease. No significant correlation was found between IR and BMI in either cases or controls but overall a weak positive correlation was noted between the two variables. In PCOS patients, levels of serum insulin and IR should be monitored and the disease should be treated as metabolic syndrome and not merely as gynaecological disorder.

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