Insulin resistance and lipid profile in polycystic ovary syndrom

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ABSTRACT :

Objectives: Polycystic ovary syndrome (PCOS) is a complex heterogeneous condition, having multifactorial etiology, with contributions from genetic, endocrine, metabolic and environmental factors. Women with PCOS present most frequently with complaints of infertility, menstrual irregularity, hirsutism, acne or alopecia, alongside various metabolic derangements such as obesity, insulin resistance, dyslipidemia and hypertension. These metabolic derangements might predispose women with PCOS to earlier onset of cardiovascular diseases. So the study was undertaken to compare various biochemical parameters between women with PCOS and age matched healthy controls.

Method: Total 80 women diagnosed with PCOS were investigated for fasting plasma glucose, serum insulin, Insulin resistance (homeostasis model assessment, HOMA-IR), and lipid profile parameters and compared with 40 apparently healthy women. Cases of PCOS were divided in two groups based on BMI: PCOS with BMI 18.5 – 24.99 kg/m2 and PCOS with BMI ≥ 25 kg/m2.

Results: Serum insulin levels and HOMA-IR values were significantly ($p<0.05$) higher in PCOS women than controls. Total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) levels were also significantly ($p<0.05$) higher in PCOS women. High density lipoprotein (HDL-C) levels were significantly lower in POS group.

Conclusion: PCOS, thus, being a multifaceted disease, raising awareness of the risk factors amongst the high risk population and applying targeted screening to identify those at high risk of developing cardiovascular diseases, along with appropriate interventions to curb these parameters before the appearance of cardiovascular disease, would go a long way towards attenuating the devastating complications of the disease.

INTRODUCTION:

In 1935, Stein and Leventhal, proposed a symptom complex- Polycystic Ovary Syndrome (PCOS) consisting of amenorrhea, hirsutism, and enlarged polycystic ovaries. However, in the past few years, researchers have accumulated an abundance of clinical data that demonstrate the effects of PCOS not only on female reproductive function but also its metabolic and cardiovascular implications1.

PCOS is the most common metabolic abnormality in young women today, affecting 10% of female patients of reproductive age2,3 . Insulin resistance occurs in around 50% to 80% of women with PCOS4,5. Mechanisms involved in insulin resistance are likely to be complex with contributions from genetic and environmental factors. Abnormalities of insulin metabolism including reduced secretion, reduced hepatic extraction, impaired suppression of hepatic gluconeogenesis and abnormalities in insulin receptor signaling have been identified in PCOS. Interestingly, there is a paradoxical expression of insulin resistance in PCOS with persistence of insulin-stimulated androgen production but impaired metabolism. Therefore, insulin resistance in PCOS results in hyperinsulinemia with its associated diverse and complex effects on regulating lipid metabolism, protein synthesis and modulation of androgen production5. Hyperinsulinemia also appears to be the main contributor to the increased cardiovascular risk of women with PCOS6.

Dyslipidemia is common in PCOS characterized by higher triglycerides and lower high density lipoprotein cholesterol. The dyslipidemia occurs independent of body mass index (BMI); however there is a synergistic deleterious effect of obesity and insulin resistance in PCOS analogous to that seen in T2DM. Dyslipidemia in PCOS has multifactorial causation. Insulin resistance plays a pivotal role by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase5.

Therefore this study aimed to compare various biochemical parameters in women with PCOS and age matched controls.

MATERIALS AND METHODS:

The study was conducted in Department of Biochemistry, Government Medical College, Aurangabad (Maharashtra), India. Prior approval of Institutional Ethical Committee

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was taken. After a written informed consent, a total of 80 cases of PCOS, between the age group of 18 to 35 years were selected on the basis of Rotterdam ESHRE/ASRM revised consensus on diagnostic criteria. According to Rotterdam consensus criteria commonly used in clinical practice, two of the following three must be fulfilled for the diagnosis of PCOS: polycystic ovaries, oligo-/anovulation clinically diagnosed as oligo-/amenorrhea and hyperandrogenism (clinical or biochemical) 7.

40 apparently healthy women in the age group of 18 to 35 years with BMI between 18.5 to 24.99 kg/m2 were selected on the basis of history and clinical examination. They constituted the group 1 of the study. Cases of PCOS were divided in two groups based on BMI: Group 2- PCOS with BMI 18.5 – 24.99 kg/m2 and Group 3- PCOS with BMI ≥ 25 kg/m2.

Detailed history of participants including age, marital status, history of any medications, addictions was taken. Known cases of Type 1 or Type 2 DM, history of alcoholism, cardiovascular disease, renal diseases, any endocrinological disorders, medications that increase body weight (contraceptive pills, steroids), patients on statin therapy, pancreatic disorders were excluded.

After overnight fasting, venous blood samples were collected in plain and fluoride bulbs. Plasma glucose was measured using glucose-oxidase-peroxidase method. Serum insulin quantitative estimation was done by Chemiluminescence Immunoassay (CLIA) using Acculite CLIA microwells. Assay kits from Monobind INC., Lake Forest, CA 92630, USA. Estimation of lipid profile parameter including total cholesterol, triglyceride and HDL was done using commercially available enzymatic kits. VLDL was calculated using Friedewald's formula. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR) with the formula:[8]

HOMA IR Index = [Fasting Blood Glucose (mg/dl) × Fasting Serum Insulin (μIU/ml)]/ 405

The results were analyzed by Graphpad prism software, version 5. The results were interpreted as mean ± S.D. Unpaired t test was applied for comparing between the groups and correlation coefficients were calculated (r value). P value was obtained from unpaired t test and < 0.05 was considered statistically significant. Correlation coefficients (r) were calculated among various parameters in group 2 and group 3. Positive and negative r values were interpreted as follows: r: 0 (no correlation), r: 0- 0.3 (poor correlation), r: >0.3- 0.7 (considerable correlation) and r: 0.8 or more (strong correlation).

RESULTS:

Table 1: Comparison of demographic Characters in studied Groups:

Parameter	Group 1 Healthy women with BMI 18.5-24.99 n = 40	Group 2 PCOS with BMI 18.5- 24.99 n = 40	p1 value	Group 3 PCOS with BMI ≥25 n = 40	p2 value
	MEAN ± SD			MEAN ± SD	
Age (Years)	25.63±2.38	25.58± 3.90	0.94	27.08 ± 3.94	0.09
Weight(Kg)	57.25± 5.54	57.27± 5.86	0.98	77.75 ± 7.26	**<0.0001****
Height(m)	1.59 ± 0.05	1.58 ± 0.06	0.60	1.60 ± 0.04	0.20
BMI(Kg/M²)	22.65± 1.19	22.86± 1.30	0.45	30.48 ± 2.50	**<0.0001****
WC (Cm)	76.83± 3.15	78.68± 5.15	0.06	87.85 ± 6.17	**<0.0001****
HC (Cm)	95.70± 5.16	96.06± 5.93	0.75	98.63 ± 5.08	**0.04***
W/H Ratio	0.80 ± 0.04	0.82 ± 0.04	0.09	0.89 ± 0.07	**<0.0001****

(p1 value: p value for group 1 & 2; p2 value: p value for group 2 & 3)

* Significant p value

** Highly significant p value

Table 1 shows that values of the demographic characters in Group 1 and group 2 did not differ significantly among the groups. Women in Group 2 and group 3 showed highly significant difference in the mean values of weight, BMI, waist circumference and waist hip ratios ($p < 0.0001$). Also the mean values of hip circumference ($p= 0.04$) differed significantly among the two groups.

Table 2: Comparison of BSL, serum insulin, HOMA-IR in studied groups

Parameter	Group 1 healthy women with BMI 18.5- 24.99	Group 2 PCOS with BMI 18.5- 24.99	p1 value	Group 3 PCOS with BMI ≥25	p2 value
	MEAN ±SD			MEAN ±SD	
Glucose (mg %)	92.28 ± 8.33	96.05 ± 9.83	0.07	97.33 ± 7.48	0.52
Insulin (μIU/ml)	5.71 ± 1.79	9.38 ± 2.58	**<0.0001****	11.52 ± 2.30	**0.0002****
HOMA-IR Index (< 2.5)	1.28 ± 0.36	2.26 ± 0.74	**<0.0001****	2.79 ± 0.67	**0.001****

Table 2 shows that mean values of insulin, HOMA-IR are significantly increased in group 2 as compared to their matched controls (group 1) ($p <0.0001$). The levels of fasting glucose did not differ significantly among the two groups ($p = 0.07$). Mean HOMA-IR for group 1 was 1.28 ± 0.36 and that for group 2 was 2.26 ± 0.74. The mean values of insulin ($p = 0.0002$), HOMA-IR ($p = 0.001$) were significantly higher in group 3. Mean HOMA-IR for group 2 was 2.26 ± 0.74 and that for group 3 was 2.79 ± 0.67. Threshold point for defining insulin resistance by HOMA IR Index was taken as 2.5.The above data suggests that cases of PCOS had higher levels of fasting insulin, and HOMA-IR compared to the controls.

Table 3: Comparison of lipid profile in studied groups:

Parameter	Group 1 Healthy women with BMI 18.5-24.99	Group 2 PCOS with BMI 18.5–24.99	p1 value	Group 2 PCOS with BMI 18.5–24.99	p2 value
	MEAN ±SD			MEAN ±SD	
TC(mg%)	170.35±10.08	176.45 ± 15.71	**0.04***	190.58±26.92	**0.005****
HDL(mg%)	55.05 ±3.94	47.75 ± 7.65	**<0.0001****	40.55 ±7.17	**<0.0001****
LDL(mg%)	91.39 ±11.40	100.32 ± 19.04	**0.01***	119.06±27.67	**0.0007****
TG(mg%)	119.58±10.37	141.90 ± 21.48	**<0.0001****	154.83±24.34	**0.01***
VLDL	23.92 ±2.07	28.38 ± 4.30	**<0.0001****	30.97 ± 4.87	**0.02***
TC/HDL	3.11 ± 0.30	3.81 ± 0.83	**<0.0001****	4.85 ± 1.13	**<0.0001****
TG/HDL	2.18 ± 0.24	3.07 ± 0.79	**<0.0001****	3.94 ± 0.97	**<0.0001****

Table 3 represents the mean values of lipid profile parameters i.e. total cholesterol (TC), HDL, LDL, VLDL, triglycerides (TG) and lipoprotein ratios i.e. TC/ HDL and TG/ HDL ratio of the studied groups. This table shows a significant difference between TC (p1 = 0.04) and LDL (p1 = 0.01) in groups 1& 2. Also, highly significant difference is found in the values of TG (p1 <0.0001), HDL (p1 <0.0001) and VLDL (p1 <0.0001) as well as that of TC/HDL and TG/HDL ratios (p1 <0.0001) in group 1 & 2. Among group 2 and group 3 a highly significant difference is found in the levels of TC (p2 =0.005), HDL (p2 <0.0001), LDL (p2 = 0.0007), TG (p2 = 0.01), VLDL (p2 = 0.02), and the lipoprotein ratios (p2 <0.0001). Mean values of TC, LDL, TG, TC/HDL and TG/ HDL ratio are increased with increasing BMI while HDL levels are decreased among the cases of PCOS.

Table 4: Correlation coefficients (r value) in Group 2: PCOS BMI 18.5-24.99

	BSL	Insulin	HOMA-IR	TC	HDL	TG
BMI	r =0.34 p= <0.05	0.26 0.1	0.32 <0.05	0.28 0.07	-0.32 <0.05	0.13 0.4
W/H	0.37 <0.05	0.36 <0.05	0.40 <0.05	0.31 <0.05	-0.19 0.20	0.39 <0.05
Insulin	0.55 **<0.001**	-	0.97 **<0.001**	0.38 <0.05	-0.38 <0.05	0.39 <0.05
HOMA-IR	0.73 **<0.0001**		-	0.37 **<0.01**	-0.34 <0.05	0.33 <0.05

We can see from table 4 that in the lean PCOS patients, BMI is positively correlated with BSL, HOMA-IR, and negatively correlated with HDL. It is poorly correlated with insulin, TC and TG. Waist/hip ratio is positively correlated with all the parameters except HDL with which it is negatively correlated. Insulin and HOMA-IR are positively correlated with all parameters except HDL with which they have a negative correlation. Insulin and HOMA-IR show a strong positive correlation with each other (r= 0.97).

Table 5: Correlation coefficients (r value) in group 3: PCOS with BMI >25

	BSL	Insulin	HOMA-IR	TC	HDL	TG
BMI	r =0.25 p= 0.2	0.44 **<0.01**	0.45 **<0.01**	0.47 **<0.01**	-0.33 <0.05	0.41 **<0.01**
W/H	0.43 **<0.01**	0.55 **<0.001**	0.61 **<0.0001**	0.46 **<0.01**	-0.42 **<0.01**	0.59 **<0.0001**
Insulin	0.40 <0.05	-	0.96 **<0.0001**	0.51 **<0.001**	-0.52 **<0.001**	0.61 **<0.0001**
HOMA-IR	0.63 **<0.0001**	-	-	0.48 **<0.01**	-0.53 **<0.001**	0.61 **<0.0001**

Table 5 correlates the parameters in overweight-obese PCOS i.e. group 3. BMI is positively correlated with insulin, HOMA-IR, TC and TG and negatively correlated with HDL. It is poorly correlated with BSL. Waist/hip ratio shows a positive correlation with all parameters except for a negative correlation with HDL. Insulin and HOMA-IR show a positive correlation with all parameters, except for a negative correlation with HDL. Insulin and HOMA-IR show a strong positive correlation with each other (r= 0.96).

DISCUSSION:

The association between glucose intolerance and hyperandrogenism was first made by Achard & Thiers (1921) and was called 'the diabetes of bearded women'. The association between increased insulin resistance and PCOS is now well recognized. There are several mechanisms contributing to the state of insulin resistance: peripheral target tissue resistance, decreased hepatic clearance, or increased pancreatic sensitivity.

Studies with the euglycemic clamp technique indicate that insulin resistance is a common feature of the syndrome, and both obese and nonobese women with the syndrome are more insulin-resistant and hyperinsulinemic than age- and weight-matched normal women. Insulin resistance is a common finding in women with PCOS independent of obesity and insulin resistance in obese PCOS is composed of dual contributions, one unique to PCOS and the other obesity-specific9. Hyperinsulinemia is a characteristic feature of PCOS, independent of obesity10.

Studies have revealed marked decreases in insulin sensitivity along with significant decreases in maximal rates of insulin-stimulated glucose transport secondary to a decrease in the abundance of GLUT4 glucose transporters. In at least 50% of PCOS women IR appears to be related to excessive serine phosphorylation of insulin receptor, leading to inhibition of signaling9. The ability of the PCOS-ser insulin receptors to phosphorylate an artificial substrate is also significantly reduced. Serine phosphorylation of IRS-1 appears to be the mechanism for TNF-α mediated insulin resistance. The membrane glycoprotein PC-1 also inhibits insulin receptor kinase activity without bringing about serine phosphorylation of the receptor11.

Insulin itself leads to a kind of insulin resistance; every time a cell is exposed to insulin, the production of Type 4 Glucose Transporters (GLUT4) on the cell membrane decreases somewhat. In the presence of hyperinsulinemia generally caused by insulin resistance, this down-regulation acts as a kind of positive feedback, increasing the need for insulin. At the cellular level, excessive circulating insulin appears to be a contributor to insulin resistance via down-regulation of insulin receptors. This down-regulation occurs due to prolonged and repeated elevations of circulating insulin12. Insulin resistant individuals are at increased risk of developing hypertension. Approximately 50% of patients with hypertension are insulin resistant. There is evidence that both hypercoagulability and impaired fibrinolysis are associated with insulin resistance. Plasminogen Activator Inhibitor--I (PAI-I) concentrations are higher in patients with hypertriglyceridemia, hypertension and CHD suggesting that PAI-I levels are related to insulin resistance13. Dyslipidemia is one of the most perplexing metabolic consequences in PCOS. Obesity, IR and hyperandrogenism, the pervasive features of PCOS, play significant pathophysiological roles in the lipidemic aberrations associated with the syndrome14. According to the National Cholesterol Education Program (NCEP) guidelines, approximately 70% of PCOS patients exhibit abnormal serum lipid levels14,15. The effects of IR on lipid metabolism are well known. IR impairs the ability of insulin to suppress lipolysis increasing mobilization of free fatty acids from adipose stores with consequent increased hepatic delivery of free fatty acids, thus impairing insulin inhibition of hepatic very low-density lipoprotein synthesis, and altering catabolism of very low-density lipoprotein3.

Mechanisms whereby insulin resistance influences lipid metabolism can be as follows:

1) Association of obesity and insulin resistance with hypertriglyceridemia can be via an increase in portal vein long-chain free fatty acids resulting in increased apolipoprotein (apo) B100 secretion by the liver. The long-chain fatty acids divert apoB away from degradation in the endoplasmic reticulum. This leads to increased small VLDL compared with the normal state ultimately leading to raised TG levels16.
2) Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated TG levels.
3) Subsequent exchange of TGs for cholesteryl ester (CE) by the activity of CE transfer protein (CETP) results in TG enriched high-density lipoprotein (HDL) particles that are catabolized more rapidly, and CE-enriched VLDL particles that are converted into small dense low-density lipoprotein (LDL) particles17. Insulin resistance may be responsible for the reduced levels of HDL cholesterol. Despite enhanced HDL cholesterol synthesis, the plasma HDL is low because of increase in the rate of apolipoprotein A1/HDL cholesterol degradation, which exceeds the enhanced rate of its synthesis18.

In addition, lipid metabolism in women with PCOS may also be affected by ovarian and/or adrenal secretion of sex steroids and obesity17. Androgens affect lipids not only directly, but also by affecting obesity, catecholamines, and insulin19. Hyperandrogenism has been associated with increased hepatic lipase (HL) activity17. HL hydrolyses phospholipids on the surface of HDL mediating the conversion of HDL-2 to the smaller denser HDL-3. This being a better substrate for the liver, increases the clearance of HDL. Androgens, through interaction with the androgen receptor, also decrease the catabolic removal of LDL by attenuating estrogen receptor mediated induction of LDL receptor activity14.

In the present study it was found that women with PCOS, nonobese and obese, had higher levels of fasting insulin and were insulin resistant. We found that lean women with POCS were insulin resistant when compared to healthy women ($p < 0.0001$) Ahmed M. Mohamadin et al, in their study found that women with PCOS had significantly higher fasting serum insulin levels compared to healthy controls ($p < 0.001$)20. Saip Toprak et al found that the mean serum insulin level was elevated in lean PCOS patients as compared with control subjects ($p < 0.05$). The insulin sensitivity was lower in patients with PCOS as compared with the control subjects ($p < 0.001$)21. Orio et al found that women with PCOS had significantly higher

levels of glucose, insulin and HOMA-IR as compared to controls (p <0.0001)22.M Yilmaz et al in their study found that nonobese women with PCOS had significantly higher HOMA-IR values than nonobese controls (p <0.001). They also found that obese women with PCOS had higher values of HOMA-IR than nonobese PCOS (p <0.005), suggesting that insulin resistance as possible risk factor for CVD in both obese and nonobese women with PCOS23.

In the present study we found that the mean values of the lipid profile components and the lipoprotein ratios were significantly higher in the lean PCOS group as compared to healthy women except HDL which was lower in lean PCOS. The mean values of lipid profile parameters were raised in overweight-obese PCOS cases as compared to lean PCOS cases except for HDL which was found to be even lower in overweight-obese PCOS The findings of our study are in accordance with those of Kader NA et al who suggested that this compromised metabolic profile in PCOS puts these women at higher cardiovascular risk24. Kalra et al , in their study found that insulin resistant PCOS women had high triglycerides (p <0.001), total cholesterol (p =0.002) and lower high-density lipoprotein (p <0.001) compared to insulin-sensitive women. They concluded that insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity25. The presence of an atherogenic lipid profile in women with PCOS was also confirmed by Valkenburg et al 17.

In the present study we found that serum insulin levels and HOMA-IR values showed positive correlation with TC, TG, LDL-C and VLDL-C, and negative correlation with HDL-C. They also correlated with TC/HDL ratio and TG/HDL ratio.TG, HDL and TC/HDL ratio are important predictors of CVD26. Increased TG/HDL ratios can identify insulin resistant overweight individuals with normal glucose tolerance and are markers of insulin resistance with specificities and sensitivities similar to those for fasting plasma insulin concentration. Increased TG/HDL-C ratios also indicate the presence of atherogenic small, dense LDL particles and could serve as a good predictor of myocardial infarction and the presence of coronary atherosclerotic lesions27.

Goodzari et al in their study found that among the PCOS cases HOMA-IR correlated with HDL (p = 0.13), TG (p = 0.0014) and TC/HDL (p =0.12)28. Djuro Macut et al found that values of TG, HDL, TC/HDL and TG/HDL were significantly higher in overweight PCOS women compared to normal weight PCOS women (p <0.001). They also had higher values of basal insulin (p =0.003) and HOMA (p <0.001) compared to normal weight counterparts. Basal insulin and HOMA showed positive correlation with TC/HDL (r = 0.38, p <0.001; r =0.4, p <0.001 respectively) and TG/HDL (r = 0.34, p <0.001 for both) 29.

CONCLUSION:

The findings of present study show significant elevations in serum insulin levels and HOMA-IR values in PCOS group. They also suggest the presence of atherogenic lipid profile in PCOS group independent of obesity. All these factors lead to increased risk of cardiovascular disease in the women with PCOS. Therefore, raising awareness of the risk factors amongst the high risk population and applying targeted screening to identify those at high risk of developing cardiovascular diseases, alongwith interventions in the form of therapeutic lifestyle changes before the appearance of cardiovascular disease, would go a long way towards attenuating the devastating complications of the disease.

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