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ORIGINAL ARTICLE

CORRELATION OF OBESITY, INSULIN RESISTANCE AND LIPID PROFILE IN WOMEN WITH PCOS IN KIMS HOSPITAL BANGALORE

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ABSTRACT: BACKGROUND: Polycystic ovary syndrome is a condition associated with chronic anovulation, insulin resistance and androgen excess. Dyslipidemia, diabetes, obesity are all potent cardiovascular risk factors that tend to cluster in women with PCOD. These cannot be explained by obesity alone. Thus the need arises to study the effect of insulin resistance on these factors. This will help in assessing the long term cardiovascular morbidity in PCOD patients and take necessary preventive steps. **OBJECTIVES:** To analyze the infuence of obesity on lipid profile of PCOS women. To analyze the influence of insulin resistance on lipid profile in PCOS women. **MATERIALS AND METHODS:** In this prospective study done from December 2013 to September 2014, 50 women with PCOS had their body mass index and waist to hip ratio calculated. GTT, fasting and post prandial insulin, lipid profile was also done for each case. Insulin resistance was defined by fasting glucose to insulin ratio of less than or equal to 4.5. The association of obesity markers and insulin resistance with lipid markers was then studied. Statistical analysis using Student t test and ANOVA was done as indicated. Significance is assessed at 5% level of significance. **RESULTS:** Insulin resistance was seen in 56 percent of the cases. There was no correlation between markers of obesity (BMI and Waist to Hip ratio) and the various lipid parameters. But in PCOS women with insulin resistance the lipid profile was significantly different (high triglycerides and lower high density lipoprotein) compared to the insulin sensitive women. The difference between the two groups for triglycerides and HDL was statistically significant but that for LDL and total cholesterol was not statistically significant. **CONCLUSION:** Insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity.

KEYWORDS: Obesity, insulin resistance, lipid profile.

INTRODUCTION: Polycystic ovary syndrome (PCOS) is not only a reproductive endocrinopathy but also a metabolic disorder. PCOS is associated with hyperinsulinemia, impaired glucose tolerance, obesity, hyperandrogenism and altered lipid profile.[1]

PCOS is arguably one of the most common endocrine disorders in women of reproductive age, affecting 5 -10 % of women worldwide.

Insulin resistance is thought to be the uniting pathogenic factor in the associations between hypertension, glucose intolerance, obesity, lipid abnormalities and coronary artery disease, which together constitutes metabolic syndrome or syndrome 'X.'

Studies done on Indian population, though limited, have suggested that abnormalities of the insulin receptor are more common in Indian women with PCOS compared to white women with PCOS.[2]

The present study was aimed to determine the correlation between lipid changes in PCOS women with insulin resistance.

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METHODOLOGY: The study was carried out in 50 PCOS patients – diagnosed as per the Rotterdam 2003 criteria who attended the outpatient department of Obstetrics and Gynaecology of Kempegowda Institute of Medical Sciences, Bangalore during the time period of December 2013 to September 2014. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants. Women diagnosed to have PCOS by Rotterdam ESHRE/ASRM PCOS groups revised 2003 criteria,[3] with presence of any two of the three criteria will be recruited for the study.

A) Oligo and/or anovulation.
B) Clinical and/or biochemical signs of hyperandrogenism.
C) Polycystic ovaries.

Patients with TYPE 2 diabetes mellitus (2 hour 75 gm glucose tolerance test) and patients on hormonal therapy were excluded from the study.

In these women, fasting blood was drawn for glucose, insulin and lipid profile, which included triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. A 2-hour 75 g glucose tolerance test was done in all PCOS patients. Post Prandial insulin was also taken. Those with type 2 diabetes mellitus were not included for this study.

Two markers for obesity - such as body mass index and waist hip ratio, which depicts central obesity were be used to study relationship of obesity to lipid parameters. Height (m) and weight (kg) measurements were used to calculate the body mass index (BMI = wt/ height in m^2). These women were then divided into three BMI groups based on ACOG criteria: normal - BMI <25 kg/m^2; overweight - 25-30 kg/m^2; and obese - >30 kg/m^2.

Waist-to-hip ratio was calculated after measuring waist circumference between pelvic brim and costal margin, while hip circumference was taken at the level of the greater trochanter. Waist-to-hip ratio more than 0.85 was considered abnormal, while <0.85 was considered as normal. To address the influence of obesity on the lipoprotein profile in PCOS women, we first compared lipid profile of PCOS women in different BMI groups and also tried to find its correlation with waist-to-hip ratios.

Finally, based on fasting glucose/insulin ratio and post prandial insulin we divided our study population into -insulin-resistant PCOS and insulin sensitive PCOS. Women with fasting glucose/ insulin ratio less than 4.5 were taken as insulin resistant and women with fasting glucose/ insulin ratio >4.5 were taken as insulin sensitive. Lipid parameters were compared in these two groups.

STATISTICAL ANALYSIS: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made, Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.

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Significant figures:

+ Suggestive significance (P value: 0.05<P<0.10).
* Moderately significant (P value: 0.01<P ≤ 0.05).
** Strongly significant (P value: P≤0.01).

RESULTS: In our study 56 percent of the study subjects i.e. 22 patients had Post prandial level of insulin more than 82 micro IU/ml indicating insulin resistance. As per the Post Prandial insulin levels 4 percent were insulin sensitive with values less than 82 micro IU/ml. As per the fasting glucose to insulin ratio- 27 patients or 54 percent had value less than 4.5 indicating insulin resistance. 23 patients had values more than 4.5 indicating insulin sensitivity constituting 46 percent of subjects.

EFFECT OF BMI ON LIPID PROFILE (TABLE 1): In our study – as per the BMI 40 percent of the subjects that is 20 out of 50 were overweight, whereas 16 percent (n = 8) were obese. Thus only 44 percent of the subjects had a normal BMI (n=22). The mean total cholesterol, HDL, LDL were similar in all three BMI groups. The mean triglyceride levels were 118 mg/dl, 107.05 mg/dl,138 mg/dl in groups with BMI <25, 25-30, >30 respectively with P value 0.075 suggesting significance (+Suggestive significance (P value: 0.05<P<0.10).

Lipid Parameters	BMI (kg/m^2)			Total	P value
	<25	25-30	>30		
TGL	118.55±24.38	107.05±28.59	138.50±55.13	117.14±33.51	0.075+
Total cholesterol	162.68±21.87	159.00±22.13	172.13±31.74	162.72±23.64	0.423
HDL	37.91±6.57	40.90±9.41	36.00±4.90	38.80±7.72	0.248
LDL	109.23±19.89	108.55±16.29	106.75±11.71	108.56±17.11	0.943

Table 1: Effect of BMI on lipid profile

EFFECT OF WAIST TO HIP RATIO ON LIPID PROFILE (TABLE 2): Waist-to-hip ratio more than 0.85 was considered abnormal, while <0.85 was considered normal. In our study 58 percent that is 29 out of the 50 subjects were having an abnormal waist to hip ratio of more than 0.85.21 out the 50 subjects constituting 42 percent of the sample size had normal waist to hip ratio of less than 0.85. On comparison of total cholesterol, triglyceride, HDL, LDL in patients with Waist to Hip ratio <0.85, with those having Waist to Hip ratio >/= 0.85, it was found that it was similar in both the groups, the difference being not statistically significant.

Variables	Waist Hip ratio			P value
	<0.85	>0.85	Total	
TGL	119.9±24.12	115.14±39.24	117.14±33.51	0.625
Total cholesterol	162.81±22.41	162.66±24.89	162.72±23.64	0.982
HDL	38±6.72	39.38±8.45	38.8±7.72	0.539
LDL	110.14±19.9	107.41±15.04	108.56±17.11	0.583

Table 2: Correlation of Lipid parameters according to Waist Hip ratio

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EFFECT OF INSULIN RESISTANCE ON LIPID PROFILE (TABLE 3): In order to know the association of insulin resistance on lipid profile, lipid values were compared between the insulin sensitive and resistance women. A consistent trend towards dyslipidemia was revealed in comparing insulin resistant and insulin sensitive groups. As shown in Table 3 mean levels of triglycerides were higher in insulin resistant groups which were statistically significant. HDL was significantly lower in the insulin resistant group compared to the insulin sensitive group. However LDL and cholesterol levels were not significantly different between the two groups.

Variables	Fasting Glucose to insulin ratio			P value
	Resistant	Sensitive	Total	
TGL	126.79±28.6	104.86±35.87	117.14±33.51	0.020*
Total cholesterol	168.18±23.89	155.77±21.92	162.72±23.64	0.065+
HDL	35.71±6.29	42.73±7.72	38.8±7.72	0.001**
LDL	111.54±15.51	104.77±18.63	108.56±17.11	0.168

Table 3: Correlation of Lipid parameters according to Fasting Glucose to insulin ratio

Lipid profile parameters – total triglycerides, cholesterol, HDL, LDL were similar in groups divided on the basis Post Prandial insulin into resistant and sensitive categories.

Variables	Post Prandial insulin			P value
	Resistant >82microU/mL	Sensitive <82microU/mL	Total	
TGL	116.90±41.18	117.32±26.87	117.14±33.60	0.966
Total cholesterol	157.14±24.64	167.01±22.29	162.72±23.64	0.140
HDL	39.18±6.62	38.50±8.60	38.8±7.72	0.760
LDL	104.27±13.70	111.93±18.93	108.56±17.11	0.117

Table 4: Correlation of Lipid profile with PP Insulin

DISCUSSION: This study was attempted to understand the interrelationship between insulin resistance, obesity, and lipid profile in PCOS women. We noted abnormal lipid profile in PCOS women with insulin resistance independent of obesity. Women with PCOS display insulin resistance whether they are obese or not. We had 27/50 PCOS women showing abnormal fasting glucose/ insulin ratio thus showing prevalence of insulin resistance to be 54 percent. Out of 50, 28 had raised post prandial insulin levels (56 percent of the study subjects). This is consistent with previous studies that showed Indian PCOS women to be more insulin resistant than their white counterparts.[4] Out of the insulin resistant patients (as per the FGI ratio) 14 were obese (50 percent of the patients. Out of the insulin resistant patients as determined by the post prandial insulin level, 57.14 percent (n=16) were obese.

On comparing mean triglycerides, total cholesterol, HDL, LDL levels among insulin resistant and insulin sensitive PCOS women we found significantly higher mean triglycerides and significantly lower HDL levels in the insulin resistant group. In our study we could not find any significant correlation between total cholesterol and LDL cholesterol levels unlike other reports which show high LDL and cholesterol levels[5]. However our borderline difference may vary with larger sample size.

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In our study we did not find any difference in lipid profile among lean or obese PCOS patients. The mean cholesterol, triglycerides, LDL, HDL cholesterol was similar among lean, overweight and obese PCOS women. We also did not find any correlation between waist to hip ratio and lipid parameters. Thus it is seen that presence of insulin resistance was a separate risk factor, independent of other markers of obesity such as BMI and waist to hip ratio as a cause for dyslipidemia in these PCOS women. No significant correlation was found between the post prandial insulin levels and lipid profile. Ingelsson et al suggest that hyperinsulinemia associated with impaired glucose metabolism represents a risk factor through various mechanisms. Insulin acts as a growth factor in myocardium, leads to sodium retention leading to blood volume expansion and subclinical myocardial dysfunction. Postprandial hyperinsulinemia leads to sympathetic nervous system activation. It also causes increased effectiveness of angiotensin II on blood pressure.

Our results were consistent with other studies done in the past. Robinson et al found that insulin resistance contributes significantly to low HDL C levels independent of BMI in PCOS women. Thus they concluded that PCOS is associated with biochemical risk factors for premature vascular disease which cannot be explained by obesity alone.[6] In a study by Apridonidze et al 68 percent of the PCOS patients had low HDL-C and 35 percent had hypertriglyceridemia. Low serum HDL –C is known to predict increased risk of cardiovascular disease independent of LDLC. It has been suggested that it provides cardiovascular protection by direct endothelial effects via nitric oxide synthase.[7] Srezednicka et al drew attention to the role of insulin in dyslipidemia observed in women with PCOS.[8] After adjustment for age, BMI, and sex steroids, fasting insulinemia was a significant explanatory variable for total triglycerides suggesting that hyperinsulinemia independent of obesity might play a role in the lipid disturbances of PCOS.

A study conducted by Berneis et al. showed low HDL-C is commonly found in PCOS cases but hypertriglyceridemia was relatively uncommon. To the contrary, they also found that the most classic lipid alteration determining cardiovascular risk, increase of LDL-C, is not common in all populations with PCOS. Beyond total LDLC concentrations, the quality of LDL may exert a direct influence on the CV risk. The National Cholesterol Education Program Adult Treatment Panel III accepts that small, dense LDL has an approximately 3-fold increased risk for coronary artery disease and is stated as an emerging Cardiovascular risk factor.

HDL-C, A cardioprotective lipid was found to be lower than controls, while LDL-C and total cholesterol levels a risk factor for cardiovascular disease were also high in study done by Legro et al. These parameters especially LDL –C were significantly increased in PCOS women as compared to controls, independent of obesity. However, ethnic differences in the prevalence of PCOS, insulin resistance and lipid parameters may have role to play accounting for this difference of results.

Thus one should analyze the status of their population before implementing the measures in a different race or place. In a study done by Bhattacharya et al adolescent girls with PCOS were studied. No correlation was found between the FGI ratio and TGL levels or between FGI ratio and TGL: HDL ratio. The FGI ratio of less than 7 was selected as the main marker of insulin resistance to account for the physiological insulin resistance occurring during puberty.[9]

Our study is done on Indian PCOS women in the reproductive age group and we have shown that insulin resistance in these women is associated with abnormal lipid changes and is irrespective of the presence or absence of obesity. Hyperinsulinemia has been found to correlate with a profile of increased cardiovascular risk factors in PCOS independent of obesity.[10] Thus all PCOS women require

assessment of insulin resistance and dyslipidemia. Limitations of the study – we have used fasting glucose to insulin ratio and post prandial insulin levels and not HOMA (homeostasis model assessment) or QUICKI (quantitative insulin sensitivity check index) which are widely used. FGI ratio is simple to calculate and is more suitable for office use. HOMA and QUICKI are more suited and are more reliable in multi ethnic populations. Using BMI and waist to hip ratio may be flawed as it does not include visceral fat which may be related to dyslipidemia. It has been observed that abdominal visceral fat correlates better with insulin resistance and markers for metabolic syndrome than subcutaneous fat. Increased visceral fat has been observed in Asian Indians, which is not apparent from BMI.[11]

The general prevalence of insulin resistance in our women with PCOS is very high. More research is needed to find out the reason behind increased incidence of insulin resistance and dyslipidemia in Indian population. Indian women also tend to manifest symptoms at an earlier age than their Caucasian counterparts. The prevalence of diabetes mellitus and coronary artery disease is also high in Indian PCOS women. Several studies have reported unfavorable lipoprotein pattern, more carotid plaques and higher carotid intima-media thickness and a predicted increased risk for developing CVD in women with PCOS. Talbott et al noted in a review that women with PCOS had dyslipidemia, increased blood pressure, plasminogen activator inhibitor and coronary artery calcification. Abnormal lipid profile difference between PCOS cases and controls were seen in women below 45 years of age whereas carotid artery changes were mainly seen in PCOS women more than 45 years of age. This implies that dyslipidemia occurring at a younger age culminates into atherosclerosis and cardiovascular disease later in life. Even though obesity is associated with metabolic disorders lean PCOS women also have hyperinsulinemia and dyspidemia. OCPs also have to be given a second thought in such women when the triglyceride levels are raised. Thus screening for dyslipidemia becomes essential. This will help in stressing on certain preventive measures like diet, exercise and lifestyle changes that may in turn prevent long term health risks in PCOS patients. Drugs like metformin and lipid lowering agents can also be considered.

CONCLUSION: Our study concludes that dyslipidemia is strongly associated with insulin resistance in PCOS women irrespective of obesity. The prevalence of insulin resistance in our study was as high as 56 percent. Thus our study emphasizes on the need for screening for insulin resistance and dyslipidemia in PCOS women in an endeavor to stress on lifestyle changes that would reduce the burden of long term health risks such as cardiovascular diseases in these women.

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