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ORIGINAL CONTRIBUTIONS

ASSOCIATION OF OBESITY AND INSULIN RESISTANCE WITH DYSLIPIDEMIA IN INDIAN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

BACKGROUND: *Dyslipidemia, diabetes and obesity are all potent cardiovascular risk factors that tend to cluster in women with polycystic ovary syndrome (PCOS). Metabolic disorders in patients with PCOS cannot be explained solely by the presence of obesity.* ***OBJECTIVE:*** *To study the correlation between insulin resistance and serum lipid profile in Indian women with PCOS.* ***SETTING:*** *Gynecology clinic of a tertiary care hospital.* ***MATERIALS AND METHODS:*** *In this prospective study done from April 2004 to December 2004, 65 women with PCOS had their body mass index (BMI) and waist hip ratio calculated. Fasting glucose, insulin and lipid profiles were also estimated in each case. Insulin resistance was defined by fasting glucose-to-insulin ratio ≤ 4.5. The association of obesity markers and insulin resistance with lipid parameters was then studied. Statistical analysis using student 't' and Mann Whitney U tests was done as indicated.* ***RESULTS:*** *Insulin resistance was seen in 50 of the 65 PCOS women. There was no correlation seen between markers of obesity such as BMI and waist/hip ratio with various lipid parameters. But in PCOS women with insulin resistance, the lipid profile was significantly different [high triglycerides, total cholesterol and lower high-density lipoprotein (HDL)] compared to insulin-sensitive women. The difference between the two groups for total cholesterol (P = 0.002), triglycerides (P = <0.001) and HDL (P = <0.001) was statistically significant but that for low-density lipoprotein (LDL) (P = 0.07) was not statistically significant.* ***CONCLUSION:*** *Insulin resistance is associated with dyslipidemia in women with PCOS, independent of obesity.*

Key words: *Dyslipidemia, insulin resistance, lipid profile, polycystic ovarian syndrome*

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Polycystic ovary syndrome (PCOS) is not only a reproductive endocrinopathy but also a metabolic disorder. PCOS is associated with hyperinsulinemia, glucose intolerance, obesity and altered lipid profile.[1,2] 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.'[3] 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.[4] The present study was aimed to determine the correlation between lipid changes in PCOS women with insulin resistance.

MATERIALS AND METHODS

This was a prospective study done from April 2004 to December 2004 in the Department of Obstetrics and Gynecology of our teaching hospital. Sixty-five women diagnosed to have PCOS by Rotterdam ESHRE/ASRM PCOS group's revised 2003 criteria, with presence of any two of the three criteria, were recruited for the study.[5] These criteria were a) Oligo and / or anovulation, b) clinical and / or biochemical signs of hyperandrogenism c) polycystic ovaries with exclusion of congenital adrenal hyperplasia androgen secreting tumors. 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. Lipid levels were estimated by commercially available enzymatic *in vitro* assay kits and were expressed as mg/dl. Insulin levels were measured by radioimmunoassay technique and were expressed as μU/ml. A 2-hour 75 g glucose tolerance test was done in all PCOS patients. Those with impaired glucose tolerance test or type 2 diabetes were not included for this study.

Two markers for obesity - such as body mass index and waist hip ratio, which depicts central obesity were 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 65 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.[6]

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 ≥ 0.85 was considered abnormal, while <0.85 was normal.[7] 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, we divided our study population into -insulin-resistant PCOS with fasting glucose / insulin ≤ 4.5 and insulin-sensitive PCOS with fasting glucose / insulin >4.5.[1] Lipid parameters were compared in these two groups.

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Statistical analysis

All data were expressed as mean ± SD. Comparison among continuous variables was done by student *'t'* test. Mann Whitney U tests were used for comparison of parameters which are not normally distributed. One-way ANOVA was done for comparison of means when there were more than two subgroups. A '*P*' value <0.05 was considered statistically significant. However, the exact '*P*' values were reported.

RESULTS

Among the 65 PCOS women studied, there were 50 women who had fasting glucose / insulin ratio ≤ 4.5 and they were classified as insulin-resistant PCOS. Thus prevalence of insulin resistance was 76.9%. Patient profiles of both groups (insulin resistant and insulin sensitive) are depicted in Table 1.

Effect of BMI on lipid profile

Of the 65 PCOS women, 26 had normal BMI, 29 were overweight and 10 were obese. Thus only 40% of PCOS women had normal BMI. We compared all the lipid parameters in these three BMI groups. The mean total cholesterol, triglyceride, HDL and LDL cholesterol were similar in all the three BMI groups [Table 2].

Table 1: Patient characteristics of insulin-resistant and insulin-sensitive Polycystic ovary syndrome women

Parameters	*Insulin resistant (n=50) mean ± SD*	*Insulin sensitive (n=15) mean ± SD*
Age (years)	25.4 ± 3.8	23.8 ± 4.5
Weight (kilograms)	63.4 ± 7.8	59.4 ± 7
Height (centimeters)	155.7 ± 3.1	155.1 ± 3.1
*BMI (Kg/m^2)	26.1 ± 3	24.6 ± 2.5
Waist hip ratio	0.85 ± 6.1	0.82 ± 7.6
Fasting glucose (mg)	100.2 ± 9	102 ± 9.1
Fasting insulin (µU/ml)	38 ± 15.6	19 ± 2.8
Fasting G/I ratio†	2.9 ± 0.7	5.6 ± 0.8

*BMI - Body mass index, †G/I - Glucose/Insulin

Effect of waist-to-hip ratio on lipid profile

We compared total cholesterol, triglycerides, HDL and LDL cholesterol in patients with waist-to-hip ratio <0.85 with those with ratio ≥0.85. The mean total cholesterol, triglyceride, HDL and LDL cholesterol were similar in both the groups [Table 3].

Effect of insulin resistance on lipid profile

In order to know the association of insulin resistance on lipid profile, we compared the lipid values in the insulin-resistant and insulin-sensitive PCOS women. A consistent trend towards dyslipidemia was revealed in comparing insulin-resistant and insulin-sensitive groups. Mean levels of cholesterol and triglycerides were higher in the insulin-resistant group, which was statistically significant [Table 4]. HDL cholesterol was significantly lower in the insulin-resistant group compared to the insulin-sensitive group. However LDL levels were not significantly different between the two groups.

DISCUSSION

This study was attempted to understand the interrelationship between insulin resistance and lipid profile in Indian PCOS women. We noted abnormal lipid profile in PCOS women with insulin resistance, independent of obesity. Women with PCOS seem to display insulin resistance, whether they are obese or not. We had 50/65 PCOS women showing abnormal fasting glucose / insulin ratio, thus showing prevalence of insulin resistance to be 76.9% in our population. This is consistent with previous studies that showed Indian PCOS women to be more insulin resistant than their white counterparts.[4]

When we compared mean triglycerides, total cholesterol, HDL and LDL cholesterol among insulin-resistant and noninsulin-resistant PCOS women, we found significantly higher mean cholesterol and triglycerides and significantly lower HDL cholesterol in the insulin-resistant group. In our study, we could not find any significant correlation between LDL cholesterol and insulin resistance, unlike other reports, which show high LDL levels.[8] However, our borderline difference may vary with a larger sample size. HDL-C, a cardioprotective lipid, was found to be higher than controls; while LDL-C, a risk factor for cardiovascular disease, was also high in a study done by Legro *et al.*[8] They noted that LDL levels are disproportionately elevated with PCOS, when compared to other insulin-resistant states. Nevertheless, with the ethnic differences in prevalence of PCOS, insulin resistance and lipid parameters, one should know the status of their population before implementing the measures used in a different race or place.

Surprisingly in our study, we did not find any difference in lipid profile among lean or obese PCOS patients. The mean cholesterol, triglycerides, LDL and HDL cholesterol were 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 was 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.

Our results are consistent with other studies done in the past. Srezednicka *et al* drew attention to the role of insulin in lipid

Table 2: Comparison of lipid profile in the three BMI groups

Mean range Lipid parameters	*<25 kg/m^2 n = 26*	*25-30 kg/m^2 n = 29*	*> 30 kg/m^2 n = 10*	*P**
Total cholesterol (mg/dl)	172.2 ± 35.2	171.3 ± 34.9	175.5 ± 29.3	1.000
Triglycerides (mg/dl)	99.5 ± 33.1	107.1 ± 43.6	113.3 ± 21.1	0.390
†HDL (mg/dl)	42.7 ± 8	42.2 ± 9.5	41.4 ± 5.7	0.351
^{g}LDL (mg/dl)	108 ± 30.2	108.5 ± 29.4	113.3 ± 26.8	0.795

*Using one-way ANOVA, †HDL - High-density lipoprotein, ^{g}LDL - Low-density lipoprotein

Table 3: Comparison of lipid profile in the two waist-to-hip ratio groups

Mean range Lipid parameters	*< 0.85 n = 34*	*> 0.85 n = 31*	*P**
Total cholesterol (mg/dl)	169 ± 36	176.06 ± 31	0.404
Triglycerides (mg/dl)	106.3 ± 44.8	103.8 ± 26	0.786
†HDL (mg/dl)	42.8 ± 9.8	41.7 ± 6.7	0.582
^{g}LDL (mg/dl)	108.2 ± 30.4	110 ± 27.9	0.804

*Student *'t'* test, †HDL - High-density lipoprotein, ^{g}LDL - Low-density lipoprotein

Table 4: Comparison of lipid profile among insulin-resistant and noninsulin-resistant Polycystic ovary syndrome patients

Mean range Lipid parameters	*Insulin resistant n = 50*	*Insulin sensitive n = 15*	*P**
Total cholesterol (mg/dl)	178.8 ± 35.2	152.5 ± 18.6	0.002
Triglycerides (mg/dl)	116.2 ± 35.4	71 ± 12	<0.001
†HDL (mg/dl)	39 ± 5.7	52.4 ± 7.6	<0.001
^{g}LDL (mg/dl)	112.8 ± 30.5	97.7 ± 20.6	0.071

*Student 't' test, Mann Whitney U test, †HDL - High-density lipoprotein, ^{g}LDL - Low-density lipoprotein

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abnormalities observed in women with PCOS.[9] In their study, 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. In a similar study done by Robinson *et al,* they found that insulin insensitivity contributes significantly beyond BMI to the low HDL cholesterol in women with polycystic ovaries.[10] They concluded in their study that polycystic ovary syndrome is associated with biochemical risk factors for premature vascular disease that cannot be explained by obesity alone. But a study done in India by Bhattacharya *et al* found no correlation between the fasting glucose / insulin ratio and the triglyceride levels.[11] Their study differed from ours in that they had taken only adolescent girls and not the adult population. Their cutoff for fasting glucose / insulin ratio was 7 (adolescent population) unlike our value of 4.5, which is used for adult population. The cutoff for adolescents is different to allow for the physiological changes occurring around puberty.[11]

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 this 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.[12] Thus all PCOS women require assessment of insulin resistance and dyslipidemia.

We acknowledge the limitations of this study, the most important factor being the small number and the selection bias of including PCOS women seen primarily for infertility and menstrual disturbances. We used only fasting glucose-to-insulin ratio and not HOMA (homeostasis model assessment) or QUICKI (quantitative insulin sensitivity check index), which are widely used. The reason for choosing fasting glucose-to-insulin ratio is that it is simple to calculate for office use. Fasting glucose-to-insulin ratio is reliable in women without hyperglycemia.[1] This study did not include women with impaired glucose tolerance or diabetes. All our subjects were of same ethnicity where fasting glucose-to-insulin ratio is reliable. HOMA and QUICKIE are preferred in multiethnic populations. Using BMI and waist-to-hip ratio to describe obesity 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 of the metabolic syndrome than subcutaneous fat. Increased visceral fat has been observed in Asian Indians, which is not apparent from their BMI.[13]

The general prevalence of insulin resistance in our women with PCOS is quite high. More research is needed to find out the reason for insulin resistance and dyslipidemia in the Indian population. South Asian immigrants in Britain and Durban have also shown high prevalence of PCOS.[14] They not only have higher prevalence and severe degree of insulin resistance but also tend to manifest symptoms at an earlier age than their Caucasian counterparts. They also tend to

have high prevalence of diabetes and coronary artery disease. Both hyperinsulinemia and dyslipidemia are risk factors for cardiovascular disease. Evidence of subclinical cardiovascular disease has been reported in overweight PCOS women.[15] Talbott *et al* noted in a review that women with PCOS had dyslipidemia, increased blood pressure, plasminogen activator inhibitor and coronary artery calcification. An interesting observation that they made was that abnormal lipid profile difference between PCOS cases and controls was mainly seen in women aged less than 45 years, while carotid artery changes were seen in PCOS women after 45 years. This indicates that dyslipidemia occurring at a younger age translates into atherosclerosis and cardiovascular disease later in life. Although obesity is often associated with metabolic disorders, lean women with PCOS also have been found to have hyperinsulinemia and dyslipidemia.[16] Lipid profile is also required if combined pill is being considered in PCOS women as it is contraindicated when triglyceride level is elevated. Thus screening for dyslipidemia in PCOS women is essential. This will enable clinicians to implement some preventive measures such as diet, exercise and lifestyle modifications that may help in preventing long-term health risks in these women. If that doesn't work, pharmacotherapy with either metformin or lipid-reducing agents may have to be considered.

CONCLUSION

Our study confirms that insulin resistance is associated with dyslipidemia in women with PCOS. This is independent of obesity markers such as BMI and waist-to-hip ratio. The prevalence of insulin resistance in our PCOS women was 76.9% and this emphasizes the importance of screening for insulin resistance and dyslipidemia in Indian women with polycystic ovary syndrome.

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