INSULIN RESISTANCE AND SECRETORY CAPACITY IN YOUNG WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

BACKGROUND

Insulin resistance is an intrinsic component in the complex pathophysiology of PCOS, causing reproductive and metabolic abnormalities. Studies on insulin secretion in PCOS are sparse and contrast.

Objective is to assess insulin resistance and insulin secretory capacity by Homeostasis Model Assessment in young women with polycystic ovary syndrome.

MATERIALS AND METHODS

Fifty young women with PCOS (mean age 21 years) and fifty control women matched as a group for age and BMI were studied. A complete hormonal assay, other laboratory parameters of glycaemic status, cholesterol status were studied in each subject. Homeostasis Model Assessment, computerised calculator used for assessing insulin resistance and secretion.

RESULTS

The mean age of PCOS women and control women was 21.18±1.8 years, 20.9±1.74 years (P value – 0.432). The mean waist circumference was non-significantly higher in PCOS women than in controls (90.44±4.15 vs 89.0±5.42, p = 0.141), whereas Waist Hip Ratio (WHR) was significantly different among PCOS and control women (0.83±0.008 vs 0.823±0.011, p = 0.002). TSH, prolactin and 17-hydroxyprogesterone were not significantly different between the groups, whereas testosterone and LH/FSH ratio was significantly different. Fasting glucose concentrations were within normal range, but significantly higher in PCOS women than control women (90.9±3.26 mg/dL vs 87.24±2.43 mg/dL, p = 0.001). The fasting insulin concentrations were higher in PCOS women than controls. HOMA-IR, HOMA-β% were significantly higher in PCOS women than control women, whereas HOMA-S% was significantly lower. PCOS women were more insulin resistant and had increased insulin secretion than controls even after adjusting for BMI. Impaired glucose tolerance was found in 12% (n=6) PCOS women. The mean serum levels of total cholesterol, LDL and triglycerides were significantly higher in PCOS women than controls, whereas HDL cholesterol were significantly lower in PCOS women and controls). HOMA–IR and HOMA-β% correlated positively well with BMI, testosterone.

CONCLUSION

HOMA-IR was higher among normal, overweight and obese PCOS women. Insulin secretion was higher among PCOS women to maintain euglycaemia. Higher prevalence of impaired glucose tolerance was found in PCOS women.

KEYWORDS

Beta Cell Function, Secretion, Homeostasis, Insulin Sensitivity, Sensitivity Index.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is clinically characterised by oligoanovulation and features of hyperandrogenism. It is the most common endocrinopathy affecting the women in the reproductive age group. Its prevalence ranges from 5-10%.[1] Insulin resistance is considered to play an important role in its pathogenesis, which has been linked to the risk of developing impaired glucose tolerance, type 2 diabetes, hypertension and dyslipidaemia in these women. Hence, PCOS is not only a reproductive disorder, but also a metabolic disorder with clustering of cardiovascular risk factors. Both lean and obese PCOS women have been shown to have insulin resistance and hyperinsulinaemia.[2,3] Obesity can exacerbate insulin resistance in PCOS. The euglycaemic-hyperinsulinaemic clamp is considered to be the gold standard for the assessment of Insulin Resistance (IR). As the procedure is cumbersome, expensive and time consuming, several indirect indices have been developed to assess insulin resistance. One such index is the Homeostatic Model Assessment (HOMA). HOMA has been validated against euglycaemic-hyperinsulinaemic clamp.[4,5] The Homeostasis Model Assessment for β-cell function is an index of insulin secretion derived from fasting plasma glucose and insulin concentrations.[6] β-cell function assessed by HOMA has been shown to correlate well with acute insulin response during intravenous glucose tolerance test.[7] Studies evaluating the insulin secretion in PCOS women are scanty and contrast. Some researchers found increased insulin secretion and some found defective insulin secretion and different results based on assessment of insulin secretion in basal state or post-absorptive state.[8,9,10] The present study aimed to assess insulin resistance and secretory capacity in PCOS women in comparison to controls.

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MATERIALS AND METHODS

We have enrolled fifty PCOS women from endocrinology and gynaecology outpatient department of a tertiary care teaching hospital. Age and BMI matched fifty healthy women served as controls. Informed consent was taken from all the study subjects and Institutional Ethical Committee clearance was obtained. Based on the BMI study, subjects were categorised into normal with BMI < 25 kg/m2, overweight and obese with BMI 25-30 and > 30 kg/m2 respectively. PCOS was diagnosed according to Rotterdam's criteria[11] after exclusion of other conditions like hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia, androgen secreting adrenal tumours, Cushing's syndrome and women who were using drugs causing hyperandrogenism. Detailed history, physical examination and anthropometric data which included height, weight, waist circumference and hip circumference were recorded (measured three times and average taken). Blood samples were collected in the morning (in early follicular phase of menstrual cycle) after an overnight fasting of at least eight hours for hormonal assay and for measurement of plasma glucose and insulin. Oral glucose tolerance test was done with 75 grams glucose. Abdominal ultrasonography was done for the assessment of polycystic ovarian morphology of ovaries. Hormonal assay was done with chemiluminescence with Advia Centaur Siemens Company (ECLIA). Glucose was estimated by glucose oxidase method by semiautoanalyser. Insulin resistance and insulin secretory capacity were assessed by Homeostasis Model Assessment (HOMA) – HOMA – IR (higher the value, more insulin resistance), HOMA - S% (higher the value, higher is the insulin sensitivity) and HOMA - β% (higher the value, more insulin secretion) respectively using the computerised HOMA-2 calculator (http://www.dtu.ox.ac.uk/index.html?maindoc_/homa/).[12] An ideal normal weight person less than 35 years of age has a HOMA = IR of 1 and HOMA-β of 100%.

Statistical Analysis

The statistical software 'Windostat version 9.2 from indostat services was used for statistical analysis. Results were expressed as mean±S.D. Differences between means were analysed by student's unpaired 't' test using two tailed tests for significance. P = < 0.05 was considered statistically significant. Analysis of the correlation between parameters was performed by using Pearson's bivariate correlation coefficient.

RESULTS

The age of PCOS women and control women ranged from 18-25 years with a mean of 21.18±1.8 years, 20.9±1.74 years (P value – 0.432). The mean waist circumference was non-significantly higher in PCOS women than in controls (90.44±4.15 vs 89.0±5.42, p = 0.141), whereas Waist Hip Ratio (WHR) was significantly different among PCOS and control women (0.83±0.008 vs 0.823±0.011, p = 0.002). TSH, prolactin and 17-hydroxyprogesterone were not significantly different between the groups, whereas testosterone and LH/FSH ratio was significantly different as shown in Table 1.

Among PCOS women 28% (n=14) were having normal BMI, 48% (n=24) were overweight and 24% (n=12) were obese. Although, fasting glucose concentrations were within normal range, significantly higher in PCOS women than control women (90.9±3.26 mg/dL vs 87.24±2.43 mg/dL, p=0.001). The fasting insulin concentrations were higher in PCOS women than controls indicating that higher insulin levels were required to maintain euglycaemia. HOMA-IR, HOMA-β% were significantly higher in PCOS women than control women, whereas HOMA-S% was significantly lower as shown in Table 2. After adjusting for BMI, HOMA–IR remained significantly different among PCOS women (Table 3). HOMA-β% was also significantly higher among PCOS women after adjusting for BMI (Table 4). Impaired glucose tolerance was found in 12% (n=6) PCOS women. The mean serum levels of total cholesterol, LDL and triglycerides were significantly higher in PCOS women than controls, whereas HDL cholesterol were significantly different in PCOS women and controls (Table 2). HOMA–IR correlated well with BMI (r=0.99, p=0.001), WC (r=0.35, p=0.01), testosterone (r=0.35, p=0.01). HOMA-β% also correlated positively with BMI (r=0.45, p= < 0.001), WC (r=0.40, p= < 0.05) and testosterone(r=0.303, p= < 0.05).

Characteristic	PCOS n=50 (mean±SD)	Control n=50 (mean±SD)	P-value
Age (years)	21.18±1.8	20.9±1.74	0.432
BMI (kg/m2)	26.27±3.25	26.742±3.26	0.470
Waist circumference (cms)	90.44±4.15	89±5.42	0.141
WHR (waist hip ratio)	0.83±0.008	0.823±0.011	0.002
TSH (mIU/L)	3.04±0.57	3.37±2.75	0.321
Prolactin (ng/mL)	17.16±4.83	15.88±4.23	0.16
Testosterone (ng/mL)	0.715±0.071	0.331±0.072	<0.0001
17-hydroxy progesterone (ng/mL)	0.95±0.11	0.928±0.01	0.281
LH/FSH	2.94±0.58	1.412±0.19	<0.0001

Table 1: Anthropometric and Hormonal Data in PCOS and Controls

Characteristic	PCOS N=50	Control N=50	P-value
FBS (mg/dL)	90.9±3.26	87.24±2.44	<0.0001
Fasting insulin (μU/mL)	16.17±3.19	6.37±1.31	<0.0001
HOMA-IR	2.07±0.395	0.824±0.168	<0.0001
HOMA-β%	154.72±25.87	89.14±12.04	<0.0001
HOMA-S%	50.61±12.78	126.24±25.59	<0.0001
TC (mg/dL)	158.02±8.35	138.96±4.93	<0.0001
TG (mg/dL)	134.82±7.04	111.08±9.95	<0.0001
HDL (mg/dL)	41.96±1.98	43.8±1.74	<0.0001
LDL (mg/dL)	87.32±14.74	73.1±5.08	<0.0001

Table 2: Insulin Resistance, Sensitivity and Metabolic Parameters in PCOS and Control Women

BMI (kg/m2)	PCOS	Controls	P-value
<25	1.92±0.31	0.71±0.13	<0.0001
25-30	2.01±0.44	0.89±0.17	<0.0001
>30	2.38±0.17	0.80±0.14	<0.0001

Table 3: Comparison of HOMA-IR in Normal Weight, Overweight and Obese PCOS and Control Women

BMI (kg/m2)	PCOS (n=50)	Control (n=50)	P-value
<25	145.63±18.56	82.9±9.5	<0.0001
25-30	148.18±24.3	92.43±11.72	<0.0001
>30	178.39±23.03	88.45±12.94	<0.0001

Table 4: Comparison of HOMA-β% in Normal Weight, Overweight and Obese PCOS and Control Women

DISCUSSION

The role of insulin resistance and hyperinsulinaemia in PCOS has been thoroughly explored. Insulin resistance in PCOS is selectively on the intermediary metabolism, resulting in metabolic abnormalities and the consequent hyperinsulinaemia acting in synergy with luteinising hormone on theca cells of ovary to aggravate the androgen production.[13,14] Thus, the selective insulin resistance is a key component in the pathophysiology of PCOS for both reproductive and metabolic manifestations. Studies of insulin-mediated glucose disposal have shown that PCOS women have peripheral insulin resistance similar in magnitude to that seen in patients with type 2 diabetes.[2] Overweight and obesity are highly prevalent among PCOS women. The severity of obesity is positively associated with severity of insulin resistance. There have been few studies examining insulin secretion in PCOS women.

In the present study IR was higher among normal, overweight and obese PCOS women. Even after matching for BMI, PCOS women were more insulin resistant. Similarly, insulin secretion was higher among the PCOS women after adjusting for BMI, suggesting that per se PCOS women are insulin resistant and increase in weight was associated with further worsening of IR. Most insulin resistant women had high insulin secretion suggesting that these women are at higher risk of β-cell exhaustion and development of type 2 diabetes. Similar to our study, Ido Sirota et al[15] found that obese PCOS women had elevated insulin resistance and higher β-cell function than overweight and normal weight PCOS women. In another study by Jana Vrbikova et al[3] authors found significantly higher basal blood glucose levels, higher insulin resistance and higher early phase insulin secretion in both lean and obese PCOS women. In another study,[16] authors found greater degree of compensatory insulin secretion for a given increment of insulin resistance in PCOS women.

The observations on insulin resistance in lean and obese PCOS are different. We found lean and overweight and obese PCOS women were having higher insulin resistance than controls. In a study by Stovall et al[17] found insulin resistance and impaired glucose tolerance was far less common in lean young PCOS women than obese women and also BMI was highly predictive of insulin and glucose levels. Hurd et al[18] in their study found that obesity was an accurate marker of IR in PCOS women. A Japanese study[19] found insulin resistance among lean PCOS using HOMA method.

Abnormal glucose tolerance is found in obese and non-obese PCOS women. Earlier studies reported a prevalence of impaired glucose tolerance of 30-35% and a prevalence of type 2 diabetes of 7.5-10% and rate of conversion IGT to type 2 diabetes is increased 5-10 fold in PCOS.[20,21] In Indian PCOS women, higher prevalence of impaired glucose tolerance and type 2 diabetes have been reported.[22,23,24] In the present study, we found 12% of young PCOS women had IGT who were overweight and obese. None of the normal weight PCOS women had abnormal glucose tolerance and none of them had type 2 diabetes.

Limitation of the study – smaller sample size and single glucose/insulin pair in the basal state has been used for HOMA assessment. Dynamic insulin secretion was not measured during OGTT.

CONCLUSION

We found that young PCOS women have underlying insulin resistance with consequent increase in insulin secretion and increase in weight was associated with further increase in insulin resistance and insulin secretion. Higher insulin resistance and hyperinsulinaemia at an young age with possible risk of β-cell exhaustion and development of type 2 diabetes in later life in these women emphasises the need for lifestyle modification and weight reduction in these women. Larger studies to track the changes in insulin resistance and secretion in these women longitudinally are required, which will be much more informative.

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