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HYPERINSULINEMIC POLYCYSTIC OVARIAN SYNDROME (PCOS) PATIENTS ARE AT RISK OF DEVELOPING DIABETES & CARDIOVASCULAR DISEASE

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ABSTRACT

Background: The polycystic ovarian syndrome (PCOS) patients usually has no remarkable difference in their fasting blood sugar level but obesity play an important role. The study was designed to assess the relationship of PCOS to diabetes and cardiovascular diseases. **Objective:** To assess the relationship of diabetes mellitus and cardiovascular disease with hyperinsulinemia in polycystic ovarian syndrome patients. **Materials & Methods:** This case control study was conducted at department of Biochemistry, University of Karachi from June 2008 to June 2012. Simple random technique was used to collect the data of study. 100 diagnosed according to Rotterdam criteria polycystic ovarian syndrome patients and 100 healthy controls were screened for blood hematological parameters (Hemoglobin, Leukocyte counts and RBC Counts) and Biochemical parameters (FBS, Oral glucose tolerance test, Cholesterol, Triglycerides, Lipoproteins,and Insulin). Homeostasis model assessment of insulin resistance (HOMA-IR) and Quantitative insulin sensitivity check index (QUICKI)were calculated. **Statistical Analysis:** The statistical analysis was done by SPSS version 11.0. Pearson correlation coefficient (r) was used to correlate the biophysical and biochemical parameters with hormone and lipid profile. p-value < 0.05 was considered significant. **Result:** The QUICKI (r = -0.68) & HOMA – IR (r = -0.97) both shows a significant ($p<0.05$) correlation with serum insulin level in PCOS patients: The high insulin (>9.0 mU/L) PCOS BMI correlates significantly ($p < 0.05$) with cholesterol (r=0.29), Triglyceride (r= 0.38) and Triglycerides / LDL ratio (r= 0.39). **Conclusion:** The hyperinsulinemic PCOS women showed insulin resistance and impaired glucose tolerance, therefore they are at risk of developing type – 2 diabetes mellitus in later life. The obese hyperinsulinemic PCOS patients shown dyslipidemia and are at high risk of developing cardiovascular disease. The implication of the study is that it may produce an impact on the treatment of PCOS patients to improve their quality of life. The new aspect of study is the deranged carbohydrate metabolism leads to abnormal lipid metabolism and vice versa. PCOS is also a risk factor for stroke (cerebrovascular accident)

KEYWORD: Polycystic ovarian syndrome, Diabetes mellitus, Hyperinsulinemia, Hyperlipidemia, cardiovascular disease,

INTRODUCTION

Polycystic ovary syndrome is the common endocrine disorder characterized by ovulatory dysfunction, hyperandrogenism, and the presence of polycystic ovaries, leading to anovulatory infertility.[1] Obesity is present in about 60% PCOS patients.[2] The pathogenesis of PCOS has both genetic factors and environmental factors.[3]

The PCOS women having insulin resistance, are at high risk of developing diabetes and cardiovascular disease.[4] PCOS has great association with cardio metabolic abnormality because, in PCOS, there is central adiposity, raised blood pressure, lipid profile is pro – atherogenic, raised inflammatory markers, insulin resistance, abnormal metabolism of glucose, incidence of gestational diabetes mellitus, etc.[5]

In PCOS women, who has an ovulation, insulin resistance is much higher as compared to PCOS women who has normal ovulation.[6] The cause of severe insulin resistance is defects in insulin receptors. Hyperinsulinemia is responsible for ovarian growth and synthesis of androgen, which is independent of gonadotropins.[7] Hyperinsulinemia is responsible for producing hyperandrogenemia, by increasing androgen production in the ovaries. Insulin resistance in PCOS is responsible for producing various metabolic derangements e.g. atherosclerosis, diabetes mellitus, hypertension etc.[8] Insulin resistance occupies a major place in the pathogenesis of polycystic ovary syndrome. To identify insulin resistance, homeostasis model assessment insulin resistance (HOMA-IR) is a reliable marker.[9] Central obesity was associated with higher fasting insulin level.[10]

The aim of the present work is to assess the relationship of PCOS with the insulin resistance, which lead, diabetes mellitus type – 2 and also produces hyperlipidemia.

MATERIAL AND METHODS

The female patients having polycystic ovarian syndrome (PCOS) were selected according to Rotterdam diagnostic criteria[11] from civil Hospital, Karachi and from DR. Tehseens clinic, Garden West, Karachi, during 2008 to 2012 for the present study. The study was approved by the ethical committee of Biochemistry department Karachi University. First of all, the Patients and controls consent was taken by signing the consent form, and then the subjects were registered for the study. The female patients with the previous history of diabetes, hypertension and heart diseases using oral contraceptive, anti androgenic medicine, insulin sensitizer, lipid lowering drugs or any other illness such as renal, hepatic, and gastro intestinal disease, were not included in the study. The normal female of 15 to 45 years of age, having no symptoms of PCOS, hypertension, heart disease, diabetes mellitus or any other illness were selected, as control.

The fasting blood samples of control and PCOS patients taken on second day of menstrual cycle and was analyzed for blood sugar, Triglyceride, Cholesterol by Kits supplied by Biosciences Spain, and Lipoproteins were estimated by Kits supplied by Diagnostic system Holzheim Germany. The hormones namely Follicle Stimulating hormone (FSH), Luteinizing hormone (LH), and Insulin, were analyzed by Kits supplied by Monobind Inc. Lake Forest U.S.A.

HOMA – IR. Stands for homeostasis model assessment of insulin resistance and is calculated[12] as

$$\text{HOMA – IR} = \frac{\text{Glucose (m mole/ L) X Insulin (mU/L)}}{22.5}$$

QUICKI (Quantitative Insulin Sensitivity check index) was calculated [13] as

$$\text{QUICKI} = \frac{1}{\text{Log Fasting insulin mU/L} + \text{Log fasting glucose (mg/dl)}}$$

Statistical Analysis

The data was analyzed by SPSS (statistical package of social sciences) version II. Statistical comparison was performed by using student t – test, chi square test is applied for comparison of qualitative variables with cases and controls, Pearson correlation coefficient was used to correlate biophysical and biochemical parameters with hormones and lipid profile. The P Value < 0.05 is considered significant.

RESULT

Table – I shows age, marital status, body mass index, presenting complaints of control and PCOS patients, the table shows that, in PCOS patients the body mass index is statistically higher as compared to control subjects. Irregular periods, hirsutism, obesity and acne are the main complaints of PCOS patients. Table –2 indicates that the Total leukocyte count (TLC) is high in PCOS as compared to control. In PCOS patient the value of oral glucose tolerance tests at 1.5 hrs. Is statistically higher as compared to control subjects. The serum FSH, LH, Insulin levels in PCOS patients and control had shown no difference statistically.FSH has shown correlation with LH, RBC (per mm3), whereas LH is being correlated with LDL,and insulin level is correlated with HOMA- IR &QUICKI(Table –3). The HOMA-IR is statistically high in high insulin PCOS (>9.0 mU/L) as compared to normal insulin (0.7-9.0 mU/L) PCOS (Table-4). Higher insulin PCOS patients BMI Significantly correlates with cholesterol, and TAG / HDL ratio (Table –5).

Table 1: Age, Marital Status, Biophysical Parameters, Presenting Complaints Of Control And Pcos Patients.

Variables	PCOS (100)	Controls (100)	P-value
Age (years)	25.60 ±0.53	25.80±0.56	0.75
Height (m)	1.54±0.96	1.55±0.67	0.19
Weight (kg)	64.80±1.29	60.50±1.29	0.01*
Body Mass Index (kg/m^2)	27.70±0.66	25.10±0.53	0.002*
Marital Status			
Married	75	73	0.74
Single	25	27	
Presenting Complaints			
Irregular periods	54.00	28.00	0.001*
Hirsutism	15.00	1.00	0.001*
Obesity	29.00	16.00	0.02*
Acne	14.00	5.00	0.02*
Difficulty in conceiving	15.00	1.00	0.001*
Secondary infertility	16.00	7.00	0.04*

* Statistically significant p<0.05 as compared to control.

Table 2: Variation of Hematological and Biochemical Parameters in Control and Pcos Patients.

Variables	PCOS (100)	Controls (100)	P-value
Hemoglobin(gm %)	11.60± 0.13	11.90± 0.12	0.12
RBC(per mm^3)	4.10 x 10^6 ± 0.06 x10^5	4.20 x 10^6± 0.05 x 10^5	0.20
PCV(%)	36.30± 0.52	37.80± 0.42	0.02*
MCV(μ^3)	87.30± 0.65	87.70± 0.98	0.71
MCH(pg)	28.40± 0.33	28.00± 0.28	0.42
MCHC(%)	31.80± 0.20	31.30± 0.24	0.09
TLC(per mm^3)	7.30 x 10^3 ± 1.71 x 10^2	6.75 x 10^3 ± 1.83 x 10^2	0.02*
Neutrophils(%)	59.80± 0.57	60.20 ± 0.64	0.61
Lymphocytes(%)	35.80± 0.57	35.60± 0.74	0.84
Eosinophils(%)	2.60± 0.14	2.50± 0.13	0.39
Monocytes(%)	1.50± 0.06	1.50± 0.06	0.90
Platelets(per mm^3)	251 x 10^3± 74.0 x 10^2	261 x 10^3± 76.9 x 10^2	0.37
FBS(mg/dl)	122.30 ± 3.88	119.30 ± 2.30	0.50
OGTT 1hr (mg/dl)	164.80± 5.96	152.40± 4.26	0.09
OGTT 1.5 hrs(mg/dl)	153.90± 6.24	134.80± 3.21	0.007*
Cholesterol (mg/dl)	162.90± 3.41	160.80± 2.81	0.63
Triglyceride(mg/dl)	116.30± 4.28	121.50 ±4.60	0.41
HDL (mg/dl)	44.20± 0.92	43.80± 0.69	0.73
LDL(mg/dl)	95.50± 3.02	92.80± 2.88	0.51
FSH(mU/ml)	8.60± 0.80	10.60± 0.94	0.09
LH (mU/ml)	10.20± 1.01	9.90± 0.98	0.83
Insulin (mU/L)	14.70± 2.21	13.30± 1.48	0.59
HOMA-IR	4.60± 0.79	3.80± 0.43	0.41
QUICKI	0.34± 0.004	0.33± 0.003	0.47

* Statistically significant p<0.05 as compared to normal control.

Table 3: Correlation coefficient (r) of Hormones and Lipid Profile with Biochemical Parameters In Pcos Patients.

	Hormones			Lipid profile			
	FSH	**LH**	**Insulin**	**Chole-sterol**	**Trigly-ceride**	**HDL**	**LDL**
FBS (mg/dl)	0.14	0.09	0.08	-0.01	0.11	-0.05	-0.03
OGTT 1 hr (mg/dl)	0.12	0.16	0.04	-0.07	0.17	0.02	-0.13
OGTT 1.5 hrs (mg/dl)	0.00	0.07	0.00	-0.10	0.04	-0.02	-0.12
Cholesterol (mg/dl)	0.15	0.16	0.16	1.00	0.40*	0.24*	0.94*
Triglyceride (mg/dl)	0.03	-0.09	0.10	0.40*	1.00	-0.13	0.21*
HDL (mg/dl)	0.00	-0.05	0.18	0.24*	-0.13	1.00	0.01
LDL(mg/dl)	0.16	0.22*	0.10	0.94*	0.21*	0.01	1.00
FSH(mU / ml)	1.00	0.29*	0.07	0.15	0.03	0.00	0.16
LH (mU / ml)	0.29*	1.00	-0.06	0.16	-0.09	-0.05	0.22*
Insulin (mU / ml)	0.07	-0.06	1.00	0.16	0.10	0.18	0.10
HOMA-IR	0.11	-0.03	-0.97*	0.16	0.12	- 0.15	0.10
QUICKI	- 0.12	-0.09	-0.68*	-0.26*	0.19	-0.04	0.23*

* Significant correlation p<0.05

Table 4: Biochemical Parameters of PCOS Patients With Normal and High Insulin Levels.

Variables	Normal Insulin PCOS (0.7-9.0 mU / ml) (55)	High Insulin PCOS (>9.0 mU / ml) (45)	P-value
Cholesterol (mg/dl)	154.30 ± 4.16	173.40 ± 5.26	0.005*
Triglyceride (mg/dl)	110.60 ± 4.31	123.30 ± 7.87	0.14
HDL (mg/dl)	43.80 ± 1.21	44.60 ± 1.41	0.69
Triglyceride/HDL ratio	2.61 ±0.12	2.95 ±0.24	0.18
LDL (mg/dl)	88.40 ± 3.73	104.20 ± 4.66	0.008*
FSH (mU / ml)	8.60 ± 1.08	8.55 ± 1.20	0.97

LH (mU / ml)	8.50 ± 1.18	12.30 ± 1.68	0.06*
LH/FSH ratio	1.32 ±0.18	2.61 ±0.65	0.04
HOMA-IR	1.41 ±0.09	8.49 ±1.59	0.001*
QUICKI	0.37 ±0.00	0.30 ±0.00	0.001*

* Statistically significant p<0.05.

Table 5: Correlation Coefficient of High Insulin Pcos BMI With Biochemical Parameters.

High Insulin PCOS BMI Correlation with following	Coefficient of correlation "r"
Cholesterol(mg/dl)	0.29*
Triglyceride(mg/dl)	0.38*
HDL(mg/dl)	0.22
Trig/HDLratio	0.39*
LDL(mg/dl)	0.27
FSH(mU / ml)	0.04
LH(mU / ml)	0.08
LH/FSH ratio	0.02
HOMA-IR	-0.08
QUICKI	0.03
OGTT 1 hr(mg/dl)	-0.08
OGTT 1.5 hr(mg/dl)	0.01

*Correlation were statistically significant p<0.05.

The table shows the correlation coefficient of high insulin (>9.0 mU / L) PCOS patients BMI with their biochemical parameters i.e. OGTT (oral glucose tolerance test) in 1 hour, OGTT (oral glucose tolerance test) in 1.5 hours, cholesterol, triglyceride, HDL (high density lipoprotein), triglyceride / HDL ratio, LDL (low density lipoprotein)., FSH (follicle stimulating hormone), LH (Luteinizing hormone), LH / FSH ratio, HOMA-IR and QUICKI.

DISCUSSION

The present study was conducted on 100 females having polycystic ovarian syndrome and 100 normal control females having no symptoms of polycystic ovarian syndrome. The mean age of control and PCOS were 25.80 ± 0.56 and 25.60 ± 0.53 years respectively. Dahiya et al[14] had shown in their studies that the mean age of control and PCOS patients were 28.28 ± 3.55 and 27.48 ± 4.22 years respectively, whereas the studies of Sarac[15] had shown the PCOS patient's age as 25.9 ± 2.7 years.

In this study the PCOS patients has presenting complaints which includes irregular, and delayed periods (54%) which is significant as compared to normal control subjects. Menstrual irregularities are common in PCOS women, 75% of PCOS patients had complaints of secondary amenorrhea.[16] Gateva and Kamenov[17] observed that in obese PCOS patients the menstrual disturbances were significantly increased as compared to obese control subjects. Polymenorrhea is a menstrual disorder, in which menstrual cycles are abnormally frequent and brief in duration.[18] About 6% PCOS patients were suffering from early periods, whereas few patients' complaint for heavy periods in the present study, but Gateva and Kamenov[17] had found no significant difference in percentages of polymenorrhea between obese PCOS patients and obese control.

In the present study 15% of PCOS patient had a hirsutism, which is statistically significant (P<0.05) as compared to normal control subject. This is in agreement of the early findings.[17] The body mass index of PCOS patients were higher as compared to control (Table – I), these results are in confirmation of the earlier studies.[14] [19]

In the present study, 14% of PCOS patients had acne (P <0.05) Majumdar and Singh[20] had shown that 74% of obese PCOS and 51% of lean PCOS had complaint of acne. Gateva and Kamenov[17] reported that in PCOS patients, the alopecia had not significantly increased as compared to obese control subjects. In the present study only 4% PCOS patients were suffering from alopecia.

Gateva and Kamenov[17] had shown the ultrasound scanning of obese PCOS patients who had significant increased presence of polycystic ovaries as compared to obese control subjects. Robert[21] had reported that the ovaries of PCOS women had more follicles more volume and greater width. In the present study we had found the cystic ovaries with multiple follicles and more volume.

The mean TLC of PCOS patients were statistically significant (P <0.05) as compared to normal control subjects (Table –2). The mean level of eosinophils, lymphocytes,monocytes and platelets in PCOS patients were not significant as compared to control in the present study as was found by previous worker.[17] There was no significant difference of RBC count, MCV, MCH, MCHC in PCOS and control groups as was the finding of the previous studies.[17]

In the present study the mean OGTT (oral glucose tolerance test) after 1.5 hrs. was significantly increased (P<0.05) as compared to normal control subjects. The higher values of OGTT at 1.5 hrs. in PCOS patients is the indication of impaired glucose tolerance. PCOS patients had increased prevalence of impaired glucose tolerance, type 2 diabetes mellitus and metabolic syndrome in obese and non obese females.[16] The obese patients with PCOS had shown higher insulin resistance, hypertension and hyper lipidemia as compared with non obese patients.[22]

The cholesterol level and LDL level were significantly high in PCOS patients having high insulin level (>9.0mU/L) as compared to normal insulin level (0.7 – 0.9 mU/L) in PCOS cases as was found earlier.[19] The level of triglyceride is not high in PCOS patients which

is in accordance to the observation of Oh et al.[23] HDL levels are not significantly different from the controls (Table –2) as was found by sarac.[15]

FSH level is a direct method to judge ovarian morphology and reproductive potential.[14] High LH level during follicular growth phase causes premature formation of oocyte, which causes reduction in the chances of fertilization and implantation. In the present study high LH / FSH ratio was found in PCOS patients having high insulin level as compared to low insulin level PCOS patients. Earlier studies also reported high level of LH.[14, 19] In the present study 24% PCOS patients had higher testosterone levels, which is associated with hyperandrogenism, and only 45% PCOS had shown a high insulin level (>0.9 mU/L), where as previous studies[14, 18] had shown higher serum insulin levels percentage in PCOS as compared to control subjects

In PCOs patients having high insulin level, the HOMA-IR is high and QUICKI values are low as compared to normal insulin PCOs patients (Table 4), so these patients showed insulin resistance. The cause of severe insulin resistance is defect in insulin receptors. PCOS status intensifies the adverse effects of obesity on insulin resistance.[24] There is an impaired insulin action and hyperandrogenism, favoured by specific intrinsic abnormalities in PCOS womens.[25]

The PCOS women present higher risk for the type-2 diabetes and higher prevalence of cardiovascular risk factors that seems to be associated with the classic phenotype.[26] Studies had shown that patients having hyperinsulinimea, having reduced insulin sensitivity lead to diabetes mellitus and cardiovascular disease.[27] In the present study 57% of PCOS patients had reduced insulin sensitivity as their QUICKI values were <0.35 and were considered insulin resistant so the risk of type – 2 diabetes in PCOS is present only in women who has obesity and metabolic abnormalities and not to all women suffering from PCOS.

CONCLUSION

The conclusion is that the hyperinsulinemic PCOS women has insulin resistance and impaired glucose tolerance, therefore, they have, chances of developing Type – 2 diabetes mellitus in later life. Also hyperinsulinemic patients BMI correlates with cholesterol, TG and TG / HDL ratio, so in this way the hyperinsulinemic obese PCOS showed dyslipidemia and are at high risk of developing cardiovascular diseases. There is a need for long term studies.

Implications for practice and/policy

The study may produce an impact on the treatment of PCOS patients that not only the hormone levels (follicle stimulating hormone, luteinizing hormone, testosterone) but also insulin, blood sugar level, oral glucose tolerance test, lipid profile may be included as a part of PCOS patient's routine evaluation, so that the risk factors can be identified and PCOS patients may be treated accordingly in order to make their quality of life better.

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Author Disclosur Statement

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