FREQUENCY OF INSULIN RESISTANCE IN PATIENTS OF POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Objective: The objective of this study was to determine frequency of insulin resistance (IR) in patients of polycystic ovary syndrome.

Study Design: Cross sectional analytic study.

Place and Duration of Study: This study was conducted in at Department of Chemical Pathology and Endocrinology, CMH Lahore for a period of 6 months, from Oct 2015 to Mar 2016.

Material and Methods: Fifteen to thirty five years old female patients already diagnosed to have polycystic ovary syndrome (PCOS), according to Rotterdam Criteria 2003 for at least 6 months were included in this study. Patients who had pregnancy or history of childbirth less than three months back, diabetes mellitus, adrenal or thyroid dysfunction or taken insulin sensitizing agent within last three months were excluded. Two hundred patients fulfilling inclusion criteria were enrolled and blood samples were drawn for analysis of fasting plasma glucose and serum insulin from all of them. Data was entered in a specially designed proforma. The data was analyzed by using SPSS version 17.0

Results: Insulin resistance was found in 137 (69%) enrolled patients in our study. Out of 200 patients 94 (47%) were >25 years and 106 (53%) were <25 years of age.

Conclusion: The results of our study showed that a significant proportion of PCOS patients had insulin resistance. A strategy should be made to screen all patients for IR and promote treatment which could prevent IR and its adverse effects.

Keywords: Homeostasis model assessment for insulin resistance (HOMA-IR), Insulin resistance (IR), Polycystic Ovary Syndrome (PCOS).

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in females of reproductive age[1]. The prevalence of PCOS is found to be 16.6% which significantly varies with age, from 33.3% in women < 30 years to 10.2% in women ≥35 years[2]. It is a heterogeneous disorder and 80% of women with anovulatory infertility are diagnosed to have this problem[3]. PCOS which is characterized by the presence of polycystic ovaries, menstrual irregularities, and clinical/ biochemical hyperandrogenism was first recognized in 1935[4].

Rotterdam Criteria 2003 is mostly used for diagnosing PCOS[5].

According to this, a patient who has at least 2 in 3 of the following is diagnosed as case of PCOS

- Oligomenorrhea
- hyperandrogenemia and / or hyperandrogenism,
- polycystic ovaries on ultrasonography[6].

Oligomenorrhea is fewer than eight episodes of menstrual bleeding per year or menses that occur at intervals greater than 35 days.

Clinically hyperandrogenism manifests as hirsutism which is excessive terminal hair growth that takes on a male pattern distribution, acne and alopecia which is diffuse pattern of thinning hair over the vertex of the scalp with the frontal hairline commonly preserved[7].

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Biochemically hyperandrogenemia is defined as an elevated (>4.5) free androgen index (testosterone × 100 / Sex hormone binding globulin).

Polycystic ovaries were defined as 12 or more follicles (measuring 2-9 mm) per ovary, and/or an ovarian volume above 10 ml[1]. There are many short and long term health problems associated with PCOS, the main being obesity, type 2 diabetes mellitus (DM 2), cardiovascular disease, obstructive sleep apnea, complications during pregnancy, impaired fertility, and increased risk of endometrial cancer[8].

The development of PCOS has been linked to hereditary and environmental factors including genetics, insulin resistance, obesity and birth weight[9]. Decreased sensitivity or responsiveness to the metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production is known as insulin resistance[10]. Compensatory hyperinsulinemia as a result of IR leads to hyperandrogenism by stimulating ovary and increases free androgen by suppressing production of Sex Hormone Binding Globulin (SHBG) by liver[11]. Abnormalities in the hypothalamic pituitary ovarian axis seen in PCOS are also caused or contributed by the elevated insulin levels.

Degree of insulin resistance is amplified by obesity frequently associated with PCOS[12]. Insulin resistance and the metabolic abnormalities associated with it can cause metabolic syndrome (MS), type 2 diabetes mellitus and cardiovascular disease (CVD) in adults and elderly[10].

There are various methods to assess insulin sensitivity and insulin resistance like hyperinsulinemic euglycemic glucose clamp technique, minimal modal analysis of a frequently sampled intravenous glucose tolerance test (FSIVGTT) and indices which are derived from an oral glucose tolerance test or fasting glucose and insulin values. One of the most widely used indices is Homeostasis model assessment for insulin resistance (HOMA-IR)[13]. This estimated index is considered more suitable than the clinical parameters to detect IR in patients[14].

It is calculated using the formula:

HOMA-IR = Fasting Insulin (mIU/L) × Fasting glucose (mmol/L) /22[5].

A value above 2.0 indicates IR[6].

The purpose of this study was to estimate actual burden of the problem so that proper guidelines can be set for identification and timely treatment of IR to prevent its complications in PCOS.

PATIENTS AND METHODS

This study was conducted in Department of Chemical Pathology and Endocrinology, CMH Lahore for a duration of 6 months, from Oct 2015 to Mar 2016.

It was a cross-sectional analytical study in which non-probability consecutive sampling was done. An estimated sample size of 200 patients diagnosed with PCOS were, by using WHO sample size calculator.

Fifteen to thirty five years old females already diagnosed as PCOS (as per operational definition) for at least 6 months were included. Patients who had pregnancy, last abortion or history of childbirth less than three months back, diabetes mellitus, adrenal or thyroid dysfunction on previous medical record or taken insulin sensitizing agent within last three months were excluded.

Two hundred women with PCOS who fulfilled the inclusion criteria were enrolled in this study. Ethics committee approval and informed consent were obtained. Medical history and physical examination was carried out before blood samples were taken. Laboratory investigations of all patients were performed at CMH Lahore.

Venous blood of 2.5ml for plasma glucose fasting (FPG) was collected in the morning after overnight fast (12-14 hours) in sodium fluoride and EDTA tube. It was analyzed within 2 hours.

2.5 ml of venous blood was taken simultaneously for Serum Insulin level. Blood was allowed to clot. Clear serum was obtained by centrifugation at 3000 rpm for 5min and it was stored in plastic cups at -80 degree centigrade until analysis.

Plasma glucose level was determined photometrically by glucose oxidase method on Selectra XL (fully automated chemistry analyzer;) after ensuring Internal quality control. External quality control was ensured by results of National External Quality Assurance Program Pakistan (NEQAPP) for Plasma glucose. Serum Insulin level was detemined by chemilumiscence on fully automated immunochemistry analyzer (Immulite-1000) using Immulite Kit after ensuring Internal Quality Control by running two levels of Immulite Insulin controls. External quality control was ensured by results of National External Quality Assurance Program Pakistan (NEQAPP) for Serum Insulin.

All the data was entered in a specially designed proforma. Insulin resistance was labeled as per operational definition. All data was entered and analyzed on Statistical Package for Social Sciences SPSS 17. Mean ± SD was calculated for quantitative variables like age.

Frequency and percentage were calculated for qualitative variable like insulin resistance. Data was stratified for age, Body mass index (BMI), duration of PCOS and family history of diabetes mellitus (DM) to deal with effect modifiers, Chi-Square test was used and *p*-value of ≤0.05 was considered significant.

RESULTS

A total of 200 subjects were included in study after fulfilling the inclusion criteria. Mean age of the patients was 25 ± 4.44 years.

Among the 200 patients 94 (47%) patients were above the 25 years and 106 (53%) were below 25 years. Family history for diabetes mellitus was positive in 65 (32.5%) patients and negative in 65 (32.5%) while 70 (35%) patients were not aware about their family history of diabetes. Out of 200 patients 102 (51%) patients had a body mass index of 25 or more while the remaining 98 (49%) has a body mass index of less than 25. In 105 (52.5%) patients the duration of polycystic ovarian syndrome was between 1-5 years while in 95 (47.5%) patients the duration of polycystic ovarian syndrome was between 6-12 months.

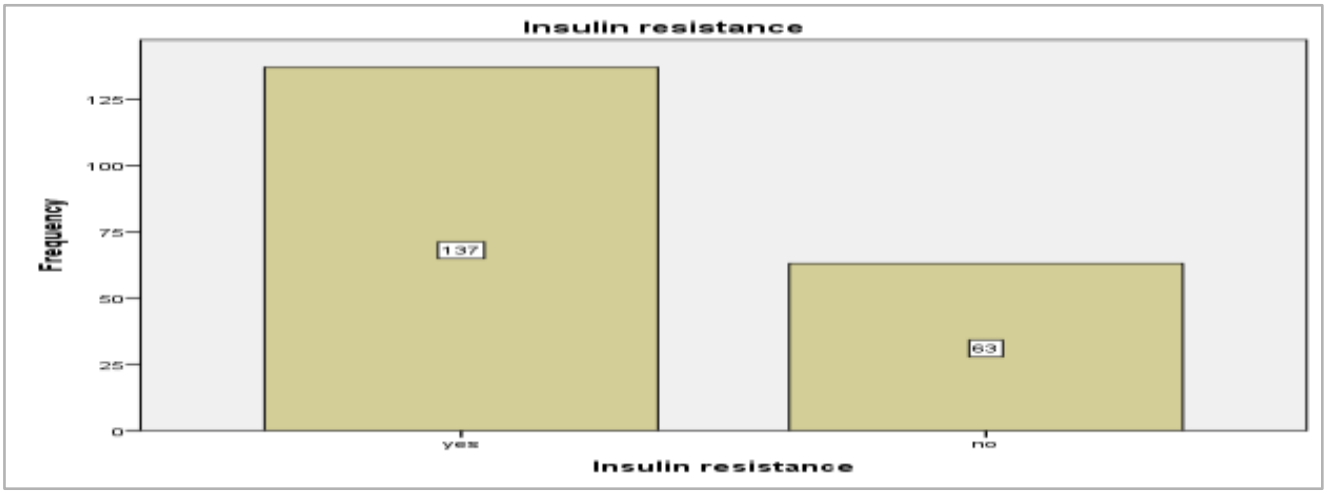

Figure: Frequency of insulin resistance in polycystic ovary syndrome patients

Insulin resistance was found in 137 (68.5%) out of all the patients (figure).

There was a statistically significant association between the presence of insulin resistance and higher body mass index (p=0.002). Comparison of higher age and presence of insulin

resistance showed a statistically significant relationship (p<0.001).

A positive of family history was not significantly associated with occurrence of insulin resistance (p=0.71). Longer duration of polycystic ovarian syndrome also did not relate with a higher detection rate of insulin resistance (p=0.21) (table).

Table: Frequency of insulin resistance in subjects by different variables.

Variable			Insulin Resistance (IR)		*p*-value
	n		Yes 137 (68.5%)	No 63 (31.5 %)	
BMI	102	Equal or >25	80 (78.4%)	22 (21.5%)	0.002
	98	< 25	57 (58.1%)	41 (41.8%)	
Age	94	Equal or >25	78 (82.9%)	16 (17.1%)	<0.001
	106	< 25	59 (55.6%)	47 (44.3%)	
Family History	65	Positive	46 (70.7%)	19 (29.2%)	0.71
	65	Negative	42 (64.6%)	23 (35.3%)	
	70	Don't know	49 (70%)	21 (30%)	
Duration of PCOS	105	1-5 yrs	76 (72.3%)	29 (27.6%)	0.21
	95	6-12 months	61 (64.2%)	34 (35.7%)	

DISCUSSION

Polycystic ovary syndrome (PCOS) is recognized as the most common endocrine disorder of reproductive-aged women around the world and Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS[14]. It is not clear how frequently this hallmark feature of insulin resistance can be found and whether IR is present in all females with PCOS[15].

A survey has showed that two-thirds (68%) physicians screen PCOS patients for IR. They also screen for diabetes and impaired glucose tolerance. Metformin therapy is used by 33% of physicians for, "all women with PCOS who have IR." The majority (68%) felt there is a need for a committee opinion on IR testing in PCOS[16].

In our study mean age of the patients was 25.41 ± 4.44 years. The mean age of PCOS patients in the study by Catherine *et al*. (2005) was 27.4 ± 7.5 which is quite similar to our study[17].

In our study 137 out of 200 (69%) patients were found to be insulin resistant.

A study conducted on Congolese women with PCOS showed 39.3% prevalence of IR using HOMA-IR which is much less than our study. This difference can be attribute to ethnic difference in the group that had been studied and also due to the lack of well accepted criteria for diagnosis of POCS.

Carmina and Rogerio (2004) found the prevalence of insulin resistance in three groups of 25 women with PCOS from the U.S. (primarily Hispanic Americans), southern Italy, and Japan using

HOMA – IR. Insulin Resistance was found in 77% of PCOS patients which is quite similar to our study. In this study IR was detected in 65.4% of the women if glucose / insulin (G / I) ratio is used and 79.2% of women by QUICKI score . Another study from Karachi showed 34.78% prevalence using G/I ratio[11]. Thus detection of IR is found to be significantly high using the calculated indices HOMA and QUICKI as compared to G/I[16]. In Iraq (Baghdad) insulin resistance is found in 76.5% females by HOMA-IR, which is quite similar to over study. A study from Karachi used HOMA-IR, QUICKI and McAuley value in patients of PCOS to detect IR which were 65%, 88% and 51.2% respectively. Thus frequency varies with the method used to determine IR. Here again IR by HOMA-IR matches our results[13]. Moghetti P in 2016 estimated 70% of PCOS patients to be insulin

resistant which is almost same as in our study[18]. Tosi F in 2017 identified insulin resistant in 74.9% of PCOS patients using euglycaemic hyper-glycaemic clamp method which is very close to our study[19].

IR might be absent in a minority of patients with PCOS. Milder forms of IR might reduce insulin action only at the level of adipose tissue and not at the level of muscle, which was where we found IR using the various methods describe.

Our study suggested that positive family history of diabetes mellitus did not significantly associates with occurrence of insulin resistance (p=0.71). Similarly longer duration of polycystic ovarian syndrome also has no influence on detection rate of IR. (p=0.21). Inadequate data was available on association of family history of DM and duration of syndrome with IR in PCOS.

In our study 102 (51%) were obese (BMI = or >25) whereas 98 (49%) had BMI <25. In study conducted by Carmina *et al*. 52% of the women with PCOS were of normal weight and 48% of women with PCOS were obese[20].

In our study 80 (78.4%) out of 102 obese women were found insulin resistant but Carmina *et al*. suggested 95.3% prevalence of IR in obese patients which was much higher than in our study[20].

In our study 57 (58.1%) out of 98 non- obese women were found insulin resistant. Higher body mass index was significantly associated with presence of insulin resistance in our study (p-value 0.002)[13]. A study from Lahore revealed 60% prevalence in obese and 33% in non-obese[12].

Our study showed a significant correlation between increasing age and Insulin resistance (p-value <0.001). This was inconsistent with result of Popovska-Dimova *et al*. who found no significant association between age and IR[21]. This was similar to findings of De Ugarte *et al*., who found that in both controls and cases an association between IR and age was either absent or weak[17].

CONCLUSION

The results of our study showed that the majority of PCOS patients were Insulin resistant. Thus subjects with PCOS were at higher risk of insulin resistance.

All women with PCOS require evaluation for insulin resistance and metabolic syndrome and its components, including type-2 diabetes, hypertension, hyperlipidemia, and the possible risk of clinical events, including acute myocardial infarction and stroke. A strategy should be developed to screen for IR simply by fasting plasma glucose and serum insulin levels and promote treatment which could prevent from IR and thereby diseases like metabolic syndrome, diabetes mellitus and cardiovascular problems.

LIMITATION OF STUDY

The main limitation of the study was that the study population only represented patients enrolled to Combined Military Hospital, Lahore.

Use of single measurements of glucose and insulin for estimation of HOMA-IR was also a limitation. The pulsatile pattern of insulin secretion and the relatively high within-person make the use of a single sample less than ideal and ideally insulin should be estimated from 3 samples collected at 5-min intervals.

Lack of traceability of different commercial methods with differences in assay specificity and sensitivity, the lack of a standardized inter-national insulin assay reference method, and preanalytical and analytical factors affecting the reproducibility of the results should also be taken into consideration when comparing our estimates of HOMA with other studies.

CONFLICT OF INTEREST

There is no conflict of interest as declared by the authors.

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