

# Efficacy of 2-hour post glucose insulin levels in predicting insulin resistance in polycystic ovarian syndrome with infertility

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## ABSTRACT

**BACKGROUND:** Insulin resistance (IR) is central to the pathogenesis of polycystic ovarian syndrome (PCOS), but tests for determining IR are elaborate, tedious and expensive. **AIMS:** To evaluate if “2-hour post-glucose insulin level” is an effective indicator of IR and can aid in diagnosing IR in infertile PCOS women. **SETTINGS AND DESIGN:** Observational study at infertility clinic of a tertiary care center. **MATERIALS AND METHODS:** 50 infertile women with PCOS and 20 females with tubal/male factor infertility were evaluated for the presence of IR, as defined by the fasting/2-hour post-glucose insulin levels cutoffs of  $>25/>41 \mu\text{U/mL}$ , respectively. The clinical, metabolic and endocrinologic profile was determined in both the groups. **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS (Chicago, IL, USA). **RESULTS:** Body mass index, post load glucose, insulin, glucose/insulin ratio, area under curve (AUC) of glucose and insulin and insulinogenic index were significantly lower in the controls as compared to the PCOS group. “2-hour post-glucose insulin levels” were elevated in 88% of PCOS individuals but were normal in all females not suffering from PCOS. These levels significantly correlated with AUC of glucose and insulin, and insulinogenic index and inversely correlated with 2-hour glucose to insulin ratio ( $r=0.827, 0.749$  and  $-0.732$ , respectively). **CONCLUSIONS:** “2-hour post-glucose insulin levels” appears to be a good indicator of IR. It can be a useful tool, especially in low resource setting where a single sample can confirm the diagnosis, thus reducing cost and repeat visits.

**KEY WORDS:** Insulin resistance, polycystic ovarian syndrome, post-glucose insulin level

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a multisystem endocrinopathy occurring in women of reproductive age group. Insulin resistance (IR) is a major factor in the development of PCOS, and the resulting hyperinsulinemia plays a role in the pathogenesis of reproductive disorders.<sup>[1,2]</sup>

It is important for the physicians to identify women with PCOS having IR so that therapeutic intervention can be initiated with insulin sensitizers since it results in clinical and metabolic improvement. Although there are many elaborate, expensive and tedious techniques available for evaluating IR, however, in resource-constrained developing countries, these tests are not widely accessible. Therefore, a single and

reliable test to screen for IR is essential. This study was planned to ascertain whether “2-hour post-glucose insulin level” can be used as a cost-effective, convenient and reliable indicator to diagnose insulin resistance, which holds the key to the pathogenesis of PCOS.

## MATERIALS AND METHODS

### Subject selection criteria

This observational clinical study was performed in an infertility clinic of a tertiary care center where consecutive 50 patients with PCOS and 20 controls were evaluated after a written informed consent was obtained from them. Patients were labeled as having PCOS<sup>[3]</sup> if any two out of the following three criteria were present: 1) oligo- or anovulation, 2) clinical and/or

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biochemical signs of hyperandrogenism, and 3) polycystic ovaries on sonography with exclusion of other etiologies. Patients in the control group included women with tubal/male factor infertility with no evidence of anovulation.

Women with associated diabetes mellitus, those on steroid hormones, on drugs known to have effects on lipid metabolism during the past 2 years, and of age <18 years or >38 years not included in the study. Clinical evaluation of each patient included detailed clinical history comprising menstrual, obstetric and personal past, family, and treatment history, followed by focused physical examination. Ferriman Gallwey scoring of  $\geq 7$  was used for grading hirsutism.<sup>[3]</sup> Anthropometric measurements were made by the same observer to obviate interobserver variation. Pelvic ultrasound (both transabdominal and transvaginal) was performed to record the status of ovaries, uterus and adnexa. Ovaries were carefully evaluated for multiple (>10) immature follicles of 2–8 mm diameter and stromal hyperplasia with/without hyperemia. Endometrial thickness was also measured in the early follicular phase.

### Sample collection and estimation

Patients were advised to have carbohydrate diet of at least 300 g for 3 days prior to the test. The fasting blood sample was analyzed for serum lipid profile, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin and testosterone on day 2 or 3 of menstrual cycle, while serum progesterone was measured on day 21. Blood sugar values and serum insulin values were determined during a 75 g oral glucose tolerance test (OGTT). Values of OGTT were assessed according to WHO, 2002.<sup>[4]</sup> Presence of IR was defined by fasting or post-load insulin levels >25 and >41  $\mu\text{U}/\text{mL}$ , respectively (DRG diagnostic instrument, GmbH, Germany). These levels have been calculated after calibration of the kits and standardizing the kits for many years. Area under curve (AUC) for glucose and insulin during OGTT, Insulinogenic Index (AUC<sub>i</sub>/AUC<sub>g</sub>), fasting and 2-hour glucose to insulin ratio were charted as determinants of IR in these patients. Hormonal estimation was done by chemiluminescence assay. Lipid profile was estimated by using enzymatic colorimetric technique and criteria adopted were in consonance with the NCEP-ATP III guidelines.<sup>[5]</sup>

### Statistical analysis

The statistical analysis was performed using SPSS (Chicago, IL, USA). Clinical, hormonal and metabolic parameters were compared between the PCOS and the control groups, employing the two-tailed unpaired student's *t* test. To identify whether "2-hour post-glucose load insulin levels" correlated significantly with fasting and 2 hours glucose/insulin ratio, AUC of glucose and insulin and insulinogenic index, correlation between different variables

was determined using Pearson's coefficient of correlation. *P* value <0.05 was taken as the cut-off level for significance.

## RESULTS

The prevalence of various clinical features in the two groups is given in Table 1. In the PCOS group, 18% patients had a family history of diabetes as against 5% controls, 8% had impaired glucose tolerance as against none in controls and 32% had deranged serum lipids as against 10% in the control group. The hormonal and metabolic parameters are also outlined in Tables 2 and 3, respectively. The hormonal profile of all subjects in the control group was in the normal range. Body mass index (BMI), 2-hour glucose, fasting and

**Table 1: Clinical profile of study subjects**

Indicators	Controls (n=20)	Cases (n=50)	<i>P</i> value
Age	26±3.4	28.4±4.2	0.27
Hirsutism	2 (10)	36 (72)	<0.05
Irregular cycles	Nil	47 (94)	<0.001
Acne	Nil	9 (18)	<0.05
PCOS on sonography of pelvis	Nil	48 (96)	<0.001
Acanthosis nigricans	Nil	6 (12)	0.173
Clitoromegaly (clitoris>10 mm)	Nil	1 (2)	0.52

PCOS = Polycystic ovarian syndrome, Figures in parentheses are in percentage

**Table 2: Hormonal assessment of study group subjects**

Mean serum value	Controls (n=20)	Cases (n=50)	Unpaired <i>t</i> -test <i>P</i> value
LH (mIU/mL)	7.8±4.0	11.6±3.4	<0.001
LH/FSH	1.1±0.7	1.9±0.8	<0.001
Testosterone (ng/dL)	0.6±0.2	1.5±0.6	<0.001
Progesterone (ng/dL)	8.4±2.6	2.3±1.0	<0.001
FSH (mIU/mL)	7.5±1.8	6.7±2.1	0.15
Prolactin (ng/dL)	17.2±4.1	13.7±3.6	0.004
TSH (mIU/mL)	2.4±0.9	2.4±1.5	0.9

Values given are Mean±SD, NS = Not significant, LH = Luteinizing hormone, FSH = Follicle stimulating hormone, TSH = Thyroid stimulating hormone

**Table 3: Metabolic assessment of both the groups**

Indicators	Control (n=20)	Cases (n=50)	<i>P</i> value
Body mass index	21.6±2.6	25.19±2.4	0.00
Fasting glucose (mg/dL)	74.0±5.7	77.4±10.7	0.19
2-hour glucose (mg/dL)	84.1±13.3	93.8±15.4	0.02
Fasting insulin level ( $\mu\text{IU}/\text{mL}$ )	6.4±1.8	9.1±4.9	0.03
2-hour insulin level ( $\mu\text{IU}/\text{mL}$ )	18.7±3.1	66.9±40.1	0.00
Area under glucose curve (AUC <sub>g</sub> ) (mg/dL/180 min)	14630.4±2565	16682.2±2420.2	0.008
Area under insulin curve (AUC <sub>i</sub> ) ( $\mu\text{IU}/\text{mL}/180$ min)	5235±620.4	9088±4707.9	<0.001
Insulinogenic index (AUC <sub>i</sub> /AUC <sub>g</sub> )	0.3±0.1	0.6±0.3	0.005
Fasting glucose to insulin ratio	12.2±3.4	11.2±9.6	0.47
2-hour glucose to insulin ratio	4.6±0.8	1.8±0.85	<0.001
Waist/hip ratio	0.84±2.6	0.88±0.07	0.03

Values given are Mean±SD

2-hour insulin, AUC of glucose and insulin, insulinogenic index and 2-hour glucose/insulin ratios were significantly higher in the PCOS patients as compared to the controls.

In the PCOS group, there were 16 lean (BMI<25) and 34 obese (BMI>25) subjects. It was observed that fasting insulin level >25  $\mu\text{U/mL}$  was present in 4 (8%; obese PCOS) and postprandial insulin of >41  $\mu\text{U/mL}$  was present in 44 (88%; 15 lean and 29 obese PCOS) patients, i.e. 88% had IR. All four patients with fasting insulin >25  $\mu\text{U/mL}$  also had higher (>41  $\mu\text{U/mL}$ ) postprandial insulin levels. The hormonal and metabolic profile of lean and obese PCOS patients was comparable. "2-hour post-glucose insulin levels" significantly correlated with AUC of glucose and insulin and insulinogenic index and inversely correlated with 2-hour glucose to insulin ratio ( $r=0.827$ ,  $0.749$  and  $-0.732$ , respectively).

The PCOS group had significantly ( $P<0.05$ ) higher serum triglycerides ( $133.6\pm 37.2$  vs.  $90.16\pm 31.6$  mg/dL) and higher low density lipoprotein (LDL) cholesterol levels ( $113.8\pm 45.6$  vs.  $98\pm 37.1$  mg/dL) but lower high density lipoprotein (HDL) cholesterol levels ( $42.4\pm 27$  vs.  $55.2\pm 31.4$  mg/dL). Total cholesterol levels, however, did not differ between the two groups ( $173.6\pm 45.5$  vs.  $170\pm 43.5$  mg/dL;  $P>0.05$ ).

## DISCUSSION

IR plays a key role in the pathogenesis of PCOS. For detecting IR, a number of techniques such as euglycemic clamp technique,<sup>[6]</sup> insulin tolerance test,<sup>[7]</sup> insulin sensitizing test, i.v./oral glucose tolerance test,<sup>[8]</sup> fasting insulin levels,<sup>[6]</sup> and fasting glucose to insulin ratio have been devised by several investigators. However, all these techniques are time consuming, expensive, stressful to the patients or are applicable to selective group of subjects and are not suitable for wider clinical use. Besides, the high cost and nonavailability of newer technologies is also a hindrance. Recently, "2-hour post-glucose insulin levels" has been recognized as a possible indicator of IR in the PCOS patients.<sup>[9]</sup> In this study, the "2-hour post-glucose insulin levels" in PCOS subjects was observed to correlate well with several parameters of insulin resistance (2 hours glucose/insulin ratio, AUC of glucose and insulin and also with the insulinogenic index), with the latter tests being more tedious, expensive and time consuming. In patients with normal glucose tolerance, values of glucose remain in the normal range due to adequate insulin response. A woman with IR, normal glycemic levels may be noticed after a glucose challenge because the pancreas will have to

secrete excess insulin in order to keep the blood sugar in the normal range.

It was observed that insulin levels were significantly higher 2 hours after 75 g glucose load in PCOS subjects compared to fasting insulin levels and these levels correlated well with other parameters of insulin resistance. Therefore, a single "2-hour post-glucose insulin level" appears to be a reliable indicator of IR in PCOS patients.

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