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Research Article

A Prospective Observational Study to Determine the Efficacy of 2 Hours Post 75 Grams Glucose Serum Insulin Levels Versus HOMA-IR–for Diagnosing Insulin Resistance in Women with Polycystic Ovarian Syndrome

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Abstract

The overall prevalence of insulin resistance among women with PCOS is between 50%-75%. Measurement of 2 hours post 75 grams glucose, serum insulin levels has been shown to correlate with presence of insulin resistance better then HOMA-IR as it is a dynamic test and gives better interpretation of hepatic and peripheral insulin resistance.

Subject and Methods: A Prospective, Single Centre, Observational Study carried for a period of 1 year from January 2023 to December 2023 which included 140 patients. Fasting serum glucose and serum insulin levels and 2 hours post 75 grams glucose, serum glucose and insulin levels were checked in 140 PCOS women in reproductive age group (20-35 years). Correlation between HOMA-IR index and serum insulin levels was done.

Results: In 79% patients, result of post glucose insulin correlated with HOMA-IR. In 17% cases there were raised post glucose insulin levels but normal HOMA-IR.

Conclusion: 2 hours post 75 grams glucose, serum insulin levels can be considered a better parameter to determine presence of insulin resistance as it is a dynamic test and requires only single blood sample. Using this method will help us detect and treat those 17% women which were likely to be missed by doing HOMA-IR.

Keywords: HOMA-IR; Fasting Insulin; Blood Sugar Levels; 2 Hours Post 75 Grams Glucose Serum Insulin; Insulin Resistance; PCOS

Abbreviations

HI: Hyperinsulinemia; IR: Insulin Resistance; PCOS: Polycystic Ovarian Syndrome; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; DM: Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test; FBS: Fasting Blood Glucose; F: Fasting Insulin Levels; PPBS: 2 Hours Post 75 Grams Glucose Blood Glucose; PP: 2 Hours Post 75 Grams Glucose Insulin Levels

Introduction

Irving F. Stein and Michael L. Leventhal first described symptoms suggestive of anovulation in 1935. PCOS affects 3.7% - 22.5% of reproductive age women [1]. Hyperinsulinemia (HI) occurs as a compensatory effect by the pancreatic beta cells for insulin resistance (IR). The importance of IR, HI and insulin action in the pathogenesis of PCOS was 1st suggested by a study conducted in 1980, demonstrating significant correlations between basal levels of plasma insulin, androstenedione, testosterone and between insulin and testosterone levels after an oral glucose load. The overall prevalence of IR ranges between 50-75%. Insulin sensitivity is decreased by an average 35-40% in women with PCOS compared to normal women. Up to 35% of women with PCOS exhibit impaired glucose tolerance and 7-10% meet criteria for type 2 DM [2]. Insulin resistance predisposes to wide range of problems including anovulatory infertility, type 2 diabetes mellitus, dyslipidaemia, metabolic syndrome and cardiovascular disease [3,4].

An index of IR can be defined as a quantitative measurement of the biological effect of endogenous or exogenous insulin in relation to the ambient blood glucose level [5]. The Hyperinsulinemic Euglycaemic Clamp (HEC) and the Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) are considered gold standard tests for determining Insulin Resistance. But they are cumbersome to perform and are widely accepted as an epidemiological test. The relatively simpler, cost effective and practical tests include Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). HOMA requires only fasting state glucose and insulin levels. The Oral Glucose Tolerance Test (OGTT) gives an idea about physiological insulin response to oral glucose load and is performed by taking fasting, 1 hour and 2 hour blood samples after administration of 75 grams glucose and comparing corresponding glucose and insulin levels with pre-determined standards. OGTT-derived indices have an upper hand to fasting indices as it can detect subtle changes in development of IR because an individual can have fasting euglycemia but may become hyperinsulinemic and hyperglycemic when exposed to glucose challenge. Borai., *et al*. in their article have tried to highlight these problems about the various methods available and the pros and cons associated with each method which makes choosing a suitable method a question amongst all the investigators [5].

Aims

To determine effectiveness of 2 hours post 75 grams glucose, serum insulin levels in determining presence of insulin resistance in PCOS women in reproductive age group.

Objectives

To compare the effectiveness of serum insulin levels, post 2 hours of 75 grams glucose with HOMA-IR index in determining Insulin Resistance in PCOS women.

Material and Methods

This is a Prospective, Single Centre, Observational Study carried out in a private Fertility Centre in Mumbai, India. The following women were included in the study.

Inclusion criteria

PCOS patients (Revised Rotterdam criteria) between 20-35 years of age.

Revised 2003 Rotterdam ESHRE/ASRM criteria [6]

- Biochemical Hyperandrogenism- Elevated free or total testosterone or calculated indices of free testosterone index.
- Clinical Hyperandrogenism- A modified Ferriman-Gallwey score of >/=4 and >/= 8.
- Oligo-Anovulation- Oligo-Amenorrhea (Cycles >35 days apart or <8 menses a year)

Exclusion criteria

- Patients with diabetes mellitus type I and Type II.
- Patients on medications known to affect baseline sugar levels e.g. - steroids.
- Patients with known endocrine disorders. e.g. - Cushing's syndrome.

Sample size

In a time duration of 1 year between January 2023 to December 2023, we included 140 women with PCOS after taking informed consents and considering all inclusion and exclusion criteria.

Design

In all women with PCOS, height, weight and BMI were calculated. Blood was collected for fasting blood glucose (FBS) and fasting insulin levels (F) after which the women were asked to consume 75 grams glucose and samples were collected 2 hours after glucose consumption for blood glucose (PPBS) and insulin levels (PP). In between, the women were asked not to eat or drink anything except water. Reference values for fasting blood glucose was taken as (n=</=100 mg/dl), Fasting blood insulin levels as (n=</=27 mIU/ml), 2 hours post 75 grams glucose, sugar levels as (n=</= 140 m/dl), 2 hours post 75 grams glucose insulin levels as (n=</=82 mIU/ml). HOMA-IR index was calculated as fasting glucose (mg/dl) x fasting insulin (mIU/ml) / 405 (n </= 2.5) [7]. The Architect/Alinity Insulin Assay kit (Abbott Pharmaceuticals) was used to determine serum insulin levels using an *in vitro* chemiluminescent microparticle immunoassay (CMIA) in the same laboratory for all patients. The sensitivity of the Architect Insulin Assay is 0.4 U/ mL and the specificity is ≤ 10%.

Results

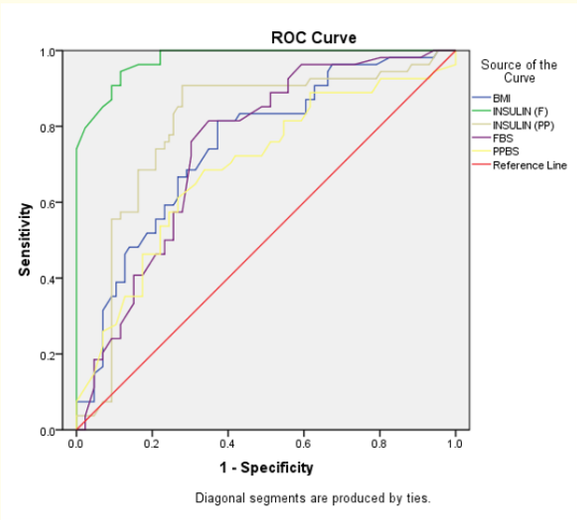

Figure 1: Outcome Measure(s): The precision of 2 hours post 75 grams glucose, serum insulin level was determined using the area under the curve (AUC) in a receiver operating characteristic analysis. Various parameters were compared with HOMA-IR using Chi square test.

Table 1: Distribution of Study Subjects according to the HOMA-IR (N = 140).

HOMA-IR	No.	Percentage (%)
Normal	86	61.4
Elevated	54	38.6

61% women had normal HOMA-IR index while 39% had raised HOMA-IR index.

Table 2: Correlation Coefficient between HOMA-IR and other Parameters in the Study (N = 140).

	Correlation Coefficient	P Value
BMI	0.401	<0.001*
Insulin (F)	0.977	<0.001*
Insulin (PP)	0.409	<0.001*
FBS	0.354	<0.001*
PPBS	0.368	<0.001*

Statistically significant correlation exists between HOMA-IR and individual parameters measured during the study.

Table 3: Comparison of BMI, Insulin and Sugar Levels with HOMA-IR (N = 140).

	HOMA-IR Normal Mean (SD)	HOMA-IR Elevated Mean (SD)	P Value
BMI	25.96 (4.54)	30.27 (6.11)	<0.001*
Insulin (F)	9.46 (2.43)	16.81 (4.31)	<0.001*
Insulin (PP)	76.88 (55.17)	122.21 (52.05)	<0.001*
FBS	82.83 (7.15)	88.86 (6.17)	<0.001*
PPBS	106.35 (15.15)	117.07 (16.65)	<0.001*

As HOMA-IR values increased, the mean values of other variables also showed a rise which was statistically significant.

PP Insulin	No. (n)	HOMA-IR Normal	HOMA-IR Elevated
Normal	67	62	5
Raised	73	24	49
Chi-Square Test, P Value <0.001, Significant			

Table 4: Association between PP Insulin and HOMA-IR (N = 140).

62 women with normal HOMA-IR had normal PP insulin levels but 24 women with normal HOMA-IR had raised PP insulin.

Discussion

Insulin is secreted by the beta cells of the pancreas in response to the glucose which enters the pancreas after a meal. This insulin reaches liver, out of which 60-70% gets degraded while 30-40% reaches peripheral tissues. In patients with insulin resistance, the insulin receptors undergo serine phosphorylation instead of tyrosine phosphorylation because of which the peripheral tissues become resistant to insulin action leading to compensatory HI [2].

It has been found in literature that most young women with Insulin resistance and PCOS are able to produce compensatory hyperinsulinemia in response to glucose load to maintain normal glucose homeostasis. Hence 2 hours OGTT is recommended in all PCOS women to determine impaired glucose tolerance. Incidence of patients with impaired glucose tolerance is up to 35% [2]. IR in PCOS is because of improper functioning of insulin receptors present on various tissues. This causes increased insulin secretion thus causing hyperinsulinemia when exposed to glucose load. HI caused by tissue IR is central to PCOS pathology [8].

In our study, we found that all parameters showed increasing trend with rise in HOMA-IR, including 2 hours post 75 grams glucose Insulin levels which is statistically significant. In 111 (79%) subjects HOMA-IR and Post glucose serum insulin values corresponded, i.e., high HOMA-IR showed raised Post glucose insulin levels and normal HOMA-IR showed normal post glucose insulin levels. However, it was found that in 24 (17%) women, the serum insulin levels post glucose, were raised in spite of HOMA-IR values being in normal range. Our study points out to this cohort of subjects in whom HOMA-IR levels are normal but HI is seen when given a glucose load thus missing out on subjects with underlying insulin resistance.

HOMA-IR has been found to have large coefficient of variation up to 10% as per studies conducted by DiNicolantonio JJ., *et al*. Fasting insulin concentrations also have coefficient of variation ranging from 25-50% and requires repeated sampling in order to determine exact value after taking an average. Since hyperinsulinemia generally results from a postprandial state, it remains unknown whether fasting measures such as HOMA-IR are sufficiently accurate to predict postprandial hyperinsulinemia. Dynamic tests after an oral glucose load can more accurately determine occult IR and Diabetes [9].

HOMA-IR which has been traditionally used to determine IR has been found to have variations with ethnicity and populations due to different cut off of insulin values. Lewandowski KC and associates state that there is no universal acceptance of cut off points for various Insulin resistance indices and to determine cut off for a particular population, the ethnic variation of values needs to be considered. Hence, arbitrary application of a pre-defined cut off point without considering population and ethnic characteristics cannot be validated and considered as a reference [10].

The ethnic variation in cut off values of HOMA-IR can be seen from the fact that an Indian study conducted by Jayashree S., *et al*. has taken HOMA-IR cut off as > 2.5 whereas a study conducted by Jamil AS in Iran has taken HOMA-IR value cut off as >/=3.8 [7,11]. Chen F and colleagues state that HOMA-IR is currently the best and most widely validated marker, but the cut-off point for the diagnosis of PCOS-IR is still not universally accepted [12].

Our proposal of using post 75 grams glucose serum insulin levels as a method of determining IR helps those PCOS women who are not detected due to normal fasting values but may have deranged values on giving glucose load. Using only post glucose values, also prevents excessive resource use, as it is a single prick test unlike OGTT. This was also found in correlation with study conducted by Borai., *et al*. which stated that physiological response of pancreas can be determined only after a dynamic test and that a dynamic

test can tell us about hepatic and peripheral IR unlike fasting test which can only tell us about presence of hepatic IR [5].

Conclusion

According to our study using fasting parameters for determining IR might not detect IR in women in whom the there is no fasting HI but a compensatory HI following glucose load. While OGTT might be found cumbersome for some women due to multiple sample collections and it might be difficult to conduct OGTT in low resource settings, use of single prick post glucose insulin levels helps prevent resource overconsumption as well as detects IR in additional small group of women too.

Limitations

Smaller sample size in a single centre setup. Larger studies should be done in order to overcome the variations associated with variable glucose absorption rates and a suitable cut off should be determined after comparing the test with gold standard tests like Hyperinsulinemic Euglycemic Clamp technique.

Conflict of Interest

The authors do not have any conflict of interest.

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