Threshold BMI to predict Non-Insulin-resistance in PCOS

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Abstract

Objectives: To suggest a threshold BMI at which IR becomes significant**.**

Methods: This is a cross sectional study conducted at Gandhi Hospital, a tertiary care centre, teaching hospital at Hyderabad, India. The study includes 167patients diagnosed as PCOS by revised Rotterdam criteria in the age-group of 18-30 years attending the gynaecology O.P between January 2013 to August2013. All were subjected to a uniform questionnaire, medical examination, investigations, inclusion and exclusion criteria.

Results: 40% of 167 PCOS patients studied had IR. 87.88% of 66 IR PCOS patients had a BMI >25 kg/m² (Sensitivity- 87.88%). 60.39% of 101 non-IR PCOS patients had BMI <25kg/m² (Specificity-60.39%). Among the 98 PCOS patients with BMI >25 kg/m²,58 (59.18%) had IR. Hence the predictive value of positive test is 59.18%. Among 69 PCOS patients with BMI <25,61(88.4%) had no IR. Hence the predictive value of negative test is 88.4%. Correlation coefficient (r- value) between the two data sets of BMI and IR was 0.842. This shows that increasing BMI and IR are strongly correlated.

Conclusion: IR strongly correlates with BMI. Hence BMI is a simple and easy tool to predict Non-IR among PCOS patients. BMI<25kg/m² is highly predictive of Non-IR and may be used as a threshold to demarcate between IR and non-IR patients.

Key Words: Threshold BMI, Predictive value, Non- Insulin-resistance, PCOS, HOMA-IR

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Introduction

PCOS is the most common endocrine disorder seen in gynaecologic practice and affects 4-6% of women of reproductive age[1]. The National Institute of Health(NIH) in 1990 defined PCOS and gave the NIH criteria.[2] Another expert conference was held in Rotterdam in 2003[3]. The Androgen Excess Society suggested that the original NIH criteria should be accepted with some modifications including the Rotterdam recommendation of ultrasound evidence of polycystic ovaries and PCOS was defined as "androgen excess syndrome".[4]

50–70% of women with PCOS have been found to have hyperinsulinemic insulin-resistance, which may play a major pathological role in the development of the PCOS[5,6]. Moreover, insulin resistance plays a major role in the development of the metabolic syndrome[5,7], with severe endocrine and metabolic disturbances leading to several complications later in life[8,9] PCOS patients thus have an increased risk for these complications later in life. Lean and obese hyperandrogenic women in particular may have completely different metabolic risk profiles and may need different treatment approaches in relation to several complications that may develop later in life.

Insulin resistance(IR) is a physiological condition where the natural hormone insulin becomes less effective at lowering blood sugars. This leads to beta-cells in the pancreas to secrete more insulin and a state of hyperinsulinemia develops with the consequent effects listed below. Insulin-resistance in muscle and fat cells reduces glucose uptake and so lowers local storage of glucose as glycogen and triglycerides respectively. In liver cells Insulin-resistance results in reduced glycogen synthesis and storage leading to glucose release in blood. Further insulin-resistance has an effect on fat cells causing reduced uptake of circulatory lipids and increased hydrolysis of stored triglycerides leading to increased free fatty acids in blood plasma.

PCOS patients have the following risk factors which develop due to hyperinsulinemia consequent to insulin-resistance:

1. increased risk of atherosclerosis, dyslipidemia, hypertension, ischemic heart disease and type-2 diabetes (prevalence of diabetes in women with PCOS is approximately-11%)
2. Endometrial & Breast cancer: Insulin has a powerful mitogenic influence on various tissues like endometrium and breast epithelium and this may contribute to the appearance of oncogenes and transformation of benign to malignant tissue.

Material and Methods

This is a cross sectional study conducted at Gandhi Hospital, a tertiary care centre and a teaching hospital for graduation and post-graduation in medicine at Hyderabad, Telangana, India.

The study includes 167 PCOS patients diagnosed with PCOS by revised Rotterdam criteria in the age-group of 18-30 years attending the infertility office of

the gynaecology O.P between January 2013 to August 2013. The sample size was calculated based on a previous study[10] published in the European Journal of endocrinology-2008.

The objective of the study was to:

1. To suggest a threshold BMI at which IR becomes significant.
2. To investigate the correlation of increasing body mass index (BMI) with increasing insulin-resistance in patients with PCOS

The PCOD patients enrolled in the study fulfilled the following inclusion and exclusion criteria. The inclusion criteria were the presence of two out of following three criteria (ESHRE/ASRM, 2004): oligo or anovulation, hyperandrogenism (based on F-G score > 7), polycystic ovaries (12 or more follicles of 2-9mm in diameter or ovarian volume > 10cc). The exclusion criteria were: diabetes mellitus, Cushing's syndrome, thyroid disorders, hyperprolactinemia, any drug intake like clomiphene citrate, oral contraceptives, anti-androgens, or drugs to control appetite, adrenal hyperplasia or virilising tumours and pregnancy.

The study was approved by the hospital ethics committee. All of the patients provided written informed consent and completed a uniform medical history questionnaire. All the women underwent a complete screening which included physical examination, weight and height measurement, Ultrasound examination and then BMI was calculated. The study subjects were then advised to be on a standard carbohydrate diet for 3 days and to return after 10-12 hours, fasting overnight, for fasting blood glucose and corresponding insulin levels were determined by RIA method. Besides this baseline investigations like serum prolactin levels, 17-OH-Pg, DHEAS, CT was planned if DHEAS > 16.32 µmol/l to screen for adrenal hyperplasia or adenoma or virilizing androgen secreting neoplasms), 24 hour free urinary cortisol (to exclude Cushing's syndrome) and serum TSH (to screen for thyroid disorders) were done. A transvaginal ultrasound was done using a 7.5 MHz vaginal probe transducer. Both ovaries were measured in the sagittal, transverse, and coronal plane. Ovaries were classified as polycystic based on the presence of 12 or more follicles in each ovary measuring 2–8 mm in diameter, and/or increased ovarian volume (>10ml).

The Homeostatic model for assessment of Insulin resistance(HOMA-IR) was calculated using the formula: Fasting Blood Glucose(mmol / l) × Fasting Insulin(µU/ml) / 22.5

Statistical Analysis

Data analysis was performed using M.S. excel sheet. Numerical variables were presented as mean±SD or number(%) as appropriate.

Epi info for Windows was used for unpaired t test. P value <0.001 was taken as highly significant. The upper and lower limits with Confidence Interval 95% were got using the same software.

Sensitivity, specificity, positive predictive value, negative predictive value for the BMI was calculated from 2 × 2 tables between BMI and IR (Table 1). The threshold value of BMI was taken as 25 kg/m². HOMA-IR of >2 is defined as Insulin resistance.

Correlation coefficient (r) between the two data sets namely BMI and IR was calculated using CORREL function in excel-2013.

Results

Table 1: BMI vs Insulin Resistance

BMI(kg/m²)	IR	Non –IR	Total
>25	58	40	98
<25	8	61	69
Total	66	101	167

Table 1 shows that in the above study 66 (nearly 40%) of the 167 PCOS patients studied were insulin-resistant as compared to 101(nearly 60%) non-insulin resistant PCOS patients.

58 of the 66 insulin-resistant PCOS patients had a BMI of >25 kg/m² **Inference: Sensitivity= 87.88%.**

61 of 101 non-insulin-resistant PCOS patients had a BMI of < 25 kg/m² **Inference: Specificity= 60.39%.**

Only 8 of the 66 insulin-resistant PCOS had a BMI of >25 kg/m² **Inference: False negative percentage = 12.12%.**

40 of the 101 non-insulin-resistant PCOS patients had a BMI of < 25 kg/m² **Inference: False positive percentage = 39.60%.**

58 of the 98 PCOS patients with BMI >25 kg/m² had insulin-resistance **Inference: Predictive value of positive test = 59.18%.**

61 of the 69 PCOS patients with BMI <25, had no insulin-resistance. **Inference: Predictive value of negative test = 88.4%.**

Table 2

Parameter	Percent
Sensitivity	87.88%
Specificity	60.39%
Positive predictive value	59.18%
Negative predictive value	88.4 %

Table 3

	Insulin Resistant	Non-Insulin Resistant	P-value	Confidence Interval-95%	
				Lower Limit	Upper Limit
BMI(Kg/m²)	30.1±2.3	22.3±3.1	<0.001	6.9	8.6
FBS	82.1±5.1	74.4±4.2	<0.001	6.2	9.19
Fasting Insulin	36.05±5.7	8.4 ±1.6	<0.001	26.2	29.08
HOMA IR (>2 defined as IR)	7.3±2.3	1.54±1.1	<0.001	5.15	6.36

Unpaired t-test, P<0.001=highly significant

Table 3 shows that insulin-resistant PCOS patients show a highly significant (P< 0.001) increase in fasting blood sugar, fasting insulin values and also a highly significant(P<0.001) increase in BMI.

Correlation coefficient(r-value) between the two data sets of BMI and IR was found to be 0.842. **Inference: Increasing BMI and IR are strongly correlated.**

Discussion

The aim of the study is to evaluate possible association of BMI and Insulin resistance in PCOS patients and to arrive at a threshold value of BMI which can predict insulin resistance or non-resistance. In the study all the women included met the criteria in accordance with the revised Rotterdam criteria.

Insulin-resistance (IR) is known to be a prominent feature in PCOS patients with the risk of metabolic syndrome and development of type-2 diabetes. Hence there is the need for a simple way to predict the possibility of Insulin resistance in PCOS patients. In a study[10] published in the European Journal of Endocrinology-2008, it was found that in general a BMI ≥ 25kg/m² was significantly associated with changes in all of the insulin-sensitivity indices and may therefore serve as a predictive marker of IR in hyperandrogenic women. In the above study it was also found that there is an increase in fasting insulin and glucose values in hyperandrogenic women which was significantly associated and correlated with BMI ≥ 25kg/m². In another study[11] too a correlation between BMI and IR was demonstrated. However it may be difficult to use the cut off points for BMI for diagnosis of IR, although a BMI of 25kg/m² may help identify women who have highest risk for developing IR and thereby diabetes[12]. Recently SHBG was also found to be a predictive marker of IR[13]. In this study SHBG also showed a significant negative correlation with the incidence of hirsutism, amenorrhoea and BMI ≥ 25kg/m².

The importance of diagnosing IR in women with PCOS is that it may help identify individuals for targeted treatment with insulin sensitizers, in order to improve treatment approaches and prevent complications later in life.[14,15]

In a study[16] it was found that higher BMI was associated with higher values for IR (HOMA-IR) and inverse association with β-cell function (HOMA-β) in Korean patients newly presenting with type-2 diabetes. An increase in BMI is known to be contributory for the development of type-2 diabetes. In another study[17] it was shown that BMI was negatively correlated with glucose disposal and positively associated with glucose production in type-2 diabetes mellitus. Another study[18] also reported that BMI was the most important determinant of insulin resistance. Thus in clinical practice, managing body weight may be important in the treatment of PCOS and more importantly prevention of type-2 diabetes in PCOS patients.

The study[19] shows that obesity and insulin resistance are likely to play a role in the development of CVS risk factors. In this study the relationship of BMI and IR with metabolic syndrome which is a clustering of cardiovascular risk factors is demonstrated. In a study[20] which aimed to investigate independent long term predictors of insulin-sensitivity in a large population based sample, BMI was the strongest predictor of insulin-sensitivity. One SD(±2.8) increase in BMI corresponded to a mean 19% decrease in insulin-sensitivity. In this study there were 2 models - the metabolic model and the lifestyle model. In the metabolic model, BMI was the strongest predictor followed by triglycerides, HDL cholesterol, diastolic B.P. and glucose levels. The correlation coefficient (r) for BMI was -0.43 with a P value of 0.0001 whereas in the present study the r-value was found to be 0.842 and P value of < 0.001, and 95% confidence interval between 6.9 to 8.6. In the lifestyle model again BMI was the strongest predictor followed by physical activity, HDL-cholesterol, saturated fat index, socio-economic status (P<0.05).

All studies reviewed have generally concluded that BMI can be a strong indicator for insulin resistance in all subjects. However the present study has concentrated on PCOS patients in order to predict IR using BMI and found that increasing BMI and IR are strongly correlated. Further BMI<25kg/m² can be a good predictor for non-IR (negative predictive value of 88.4% when compared to the positive predictive value which was 59.18%)

The main lacuna in the present study however is BMI value of 25 is taken arbitrarily based on previous studies. There is a scope of getting a closer value of

BMI which can be used as a threshold for the prediction of insulin resistance.

Conclusions

When insulin resistance is measured in PCOS patients using HOMA-IR model, it is found that a significant number of patients(60.47%) are non-insulin-resistant. Insulin resistance strongly correlates with increasing BMI; specifically a BMI<25kg/m² is highly predictive of Non-IR. Hence BMI is a simple and easy tool to predict Non-Insulin resistance among the PCOS patients..

Thus it may be concluded that BMI<25kg/m² is highly predictive of Non-IR and may be used as a threshold to demarcate between insulin-resistant and non-insulin resistant patients. This sub-group of Non-IR PCOS patients have very low risk of developing type-2 diabetes and also cardiovascular risks inherent in metabolic syndrome. Further the Non-IR PCOS patients may not benefit from insulin sensitizers which are commonly used in the management of PCOS.

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