PERFORMANCE OF SURROGATE MARKERS FOR INSULIN RESISTANCE IN WOMEN WITH PCOS

Meeta, Deepa, Tanvir, Akanshi Madan

Tanvir Hospital

Acknowledgement

- PCOS WOMEN ENROLLED

Staff of Tanvir Hospital

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- Mrs. Jasmineet-Statistics
- Mrs Vijaya-Physiotherapist
- Mr Rahul ,Miss Ishrat-Trainers
- Dr Daljeet -Psychologist

Disclosure

NONE

PCOS India -Ethnicity

Indian women are reported to have a high prevalence of PCOS [1]

Indian patients have higher fasting insulin levels and greater IR, compared with British and Australian white women with PCOS [2]

Increased visceral fat has been observed in Asian Indians, which is not apparent from their BMI.[3]

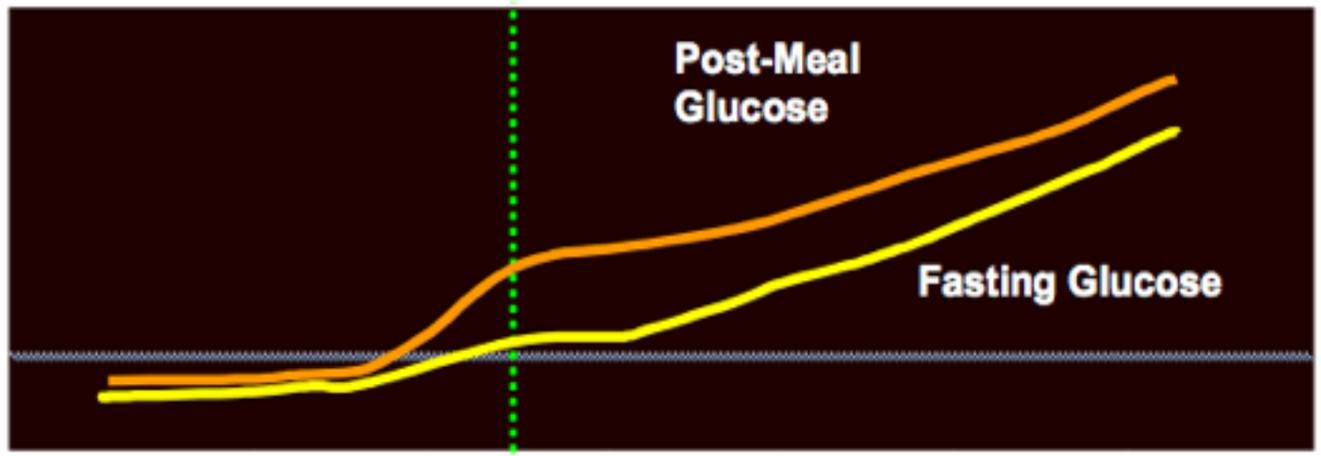
1.Rodin DA, Bano G, Bland JM, Taylor K, Nussey SS. Polycystic ovaries and associated metabolic abnormalities in Indian subcontinent Asian women. Clin Endocrinol 1998;49:91–9 Norman RJ, Mahabeer S, Masters S. Ethnic differences in insulin and glucose response to glucose between white and Indian women with polycystic syndrome. Fertil Steril 1995;63:58–62. 1
Wijeyaratne CN, Balen AH, Barth JH, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference? Clin Endocrinol 2002;57:343–50.1
Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1929-35. 1

2.South Asian immigrants in Britain and Durban have also shown high prevalence of PCOS. Epidemiology of Polycystic Ovary syndrome in Polycystic Ovary syndrome: A guide to clinical management.2

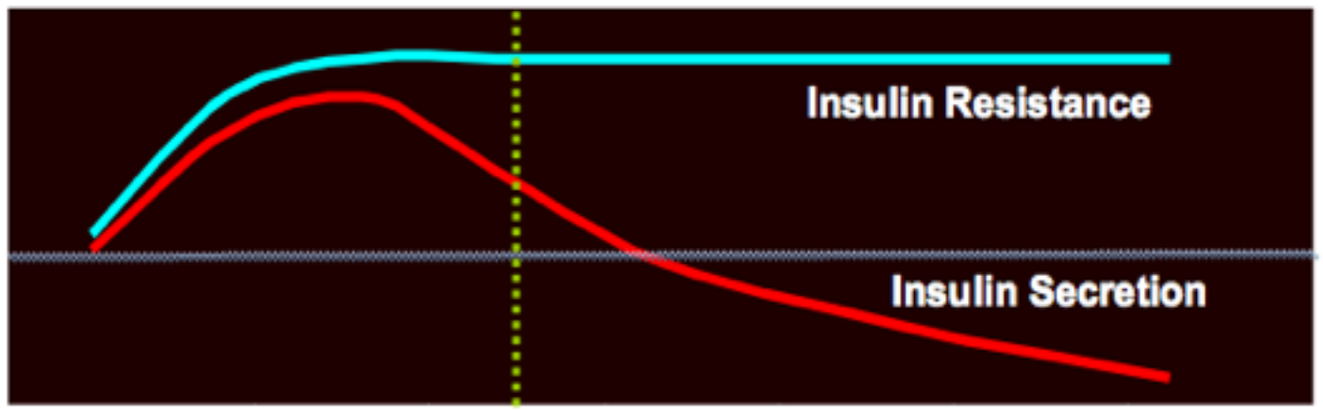
3.Balen AH, Gerard SC, Homburg R, Legro RS (editors). Taylor and Francis: London;2005. p. 23-31.2 Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and Insulin resistance in healthy Asian Indians and Caucasians. J Clin Endocrinol Metab 2001;86:5366-71. 3

Natural History of Type 2 Diabetes

Non obese **Obesity** **IGT*** **Diabetes** **Uncontrolled Hyperglycemia**



IR - A Protective Mechanism,correctable



Guidelines-OST Lipid Profile

Reliable, simple tool- IR

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MI 0.9
RIC5-
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Rt Ovary

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Lt Ovary

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141°/ 26Hz
GYN 1
Har-low
Gn -1
C7 / M4
P3 / E2
SRI II 3

Ov-L
Ov-H
Ov-W

Rt Ov-L 4.21cm
Rt Ov-H 2.12cm
Rt Ov-W 3.26cm
Rt Ov-Vol. 15.235cm³

egum, Mubeen *
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TIb 0.2
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RIC5-9-D
GYN
5.0cm / 0.8
141°/ 26Hz
GYN 1
Har-low
Gn -5
C7 / M4
P3 / E2
SRI II 3

Ut-H
Ut-W

Ut-L 6.09cm
Ut-H 4.04cm
Ut-W 5.27cm
Ut-Vol. 67.890cm³

Gynecologist -PCOS Beyond Reproductive Health

The gynecologist has the opportunity to detect 'at risk' women with PCOS and IR at an early , asymptomatic stage —

THE NEED

A simple, reliable, reproducible, economically viable surrogate marker for clinical utility for measuring IR

Problems In Detecting IR

- Difficulties in measuring insulin in routine practice
- The problems with assay procedures
- Standardisation
- The lack of a well-defined cut point differentiating normal from abnormal
- Availability, cost

IR—Tests

Clinical

Biomarkers to detect insulin resistance

- Tests showing the degree of pancreatic output -"pancreatic stress" - measures beta cell function and insulin sensitivity
- Measurements of lipid hormones such as leptin and adiponectin
- Inflammatory markers-C-reactive protein measurement (CRP) etc
- Measurements that quantify fatty acid metabolism and the fatty acids

IR - Direct Tests

The hyperinsulinemic euglycemic clamp is the gold standard, scientifically sound

IV glucose tolerance tests: "minimal model."

time consuming, not practical

primarily used in medical research

IR-Indirect Tests

Fasting insulin	Mc Auley's Index
Fasting plasma glucose	Bennett index
The glucose/insulin (G/I) ratio	Matsuda index
Fasting insulin resistance index (FIRI)	Gutt index
HOMA -IR	Stumvoll index
HOMA β cell	Avignon index
quantitative insulin sensitivity check index (QUICKI)	

Aim of the study

The objective was to compare the performance of surrogate markers for insulin resistance in Indian woman with PCOS

To identify a reliable yet simple, reproducible, economically viable surrogate marker for detection of insulin resistance (IR)

Markers -IR

- Fasting glucose/insulin ratio (FG:FI RATIO) = < 4.5
- HOMA IR: fasting insulin level (mU/l)× (FPG (mmol/l))/ 22.5 = >2.8
- Triglycerides to High-Density Lipoprotein Cholesterol Ratio (TG/HDL-C) = > 2.5
- TyG index ln [FPG(mg/dL) × TG (mg/dL)]/2 = 4.4

References

Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemichyperinsulinemic clamp. J ClinEndocrinolMetab. 2010; 95:3347–3351.

Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and tri- glycerides as surrogate for identifying insulin resistance in apparently healthy subjects. MetabSyndrRe- latDisord. 2008; 6:299–304. PMID: 19067533

Maria ar´ıa Claudia Espinel-Bermu´dez, MSc,* Jose´ Antonio Robles-Cervantes, PhD,* Insulin Resistance in Adult Primary Care Patients With a Surrogate Index, Guadalajara, Mexico, 2012 Journal of Investigative Medicine & Volume 63, Number 2, February 2015

Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indi- cators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovascular Diabetology. 2014; 13:146.146–155. PMID: 25326814

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Lee SH, Han K, Yang HK, Kim MK, Yoon KH, Kwon HS, et al. Identifying subgroups of obesity using the product of triglycerides and glucose: the Korea National Health and Nutrition Examination Survey, 2008–2010. ClinEndocrinol (Oxf). 2014; 82:213–20.

Lee DY, Lee ES, Kim JH, Park SE, Park C- Y, Oh K-W, et al. (2016) Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. PLoS ONE 11(9): e0163465. doi:10.1371/ journal.pone.0163465

Materials and Methodology

Research Design: Prospective Cross Sectional Study (Jan 2012- Jan 2016)

Sampling Design: Simple Random Technique

Sample Size: 283 Samples (calculated using PS- power calculator)

Sampling Area: Urban, Specialty Hospital,Hyderabad

Statistical analysis: Scientific Package for Social Sciences (SPSS) version 18.1

Approved by Independent Institutional Ethics Committee

Informed consent from the participants taken

Inclusion criteria

- Women diagnosed with PCOS Rotterdam criteria based on

(i) hyperandrogenism, (ii) oligo-ovulation, and iii) specific criteria for PCOS in an ultrasound scan (iv) the exclusion of related disorders

- *Age* : 16-35yrs old

Most of the women presented either with symptoms of hyperandrogenism, menstrual irregularities OR fertility issues

Exclusion Criteria

- Girls three yrs pre menarche
- >35 years
- Known diabetes, hypothyroidism, liver, kidney, or heart failure, neoplasia or any medical problem
- On steroid hormones
- On drugs known to have effects on lipid metabolism during the past 2 years
- OCP for the past three months

Methods-Clinical

History : General, gynaec, medical, lifestyle

Family history of type 2 diabetes, hypertension or cardiovascular disease, history of glucose intolerance or gestational diabetes, diagnosis of hypertension, elevated triglycerides/low HDL-cholesterol, or cardiovascular disease, acanthosis nigrican and polycystic ovary syndrome

Blood Pressure was measured after 10 minutes of rest

Height was measured by using a stadiometer after deep inhalation.

Weight was measured by using an electronic digital scale calibrated in kilograms.

BMI was calculated as weight (kg) divided by height (m) squared.

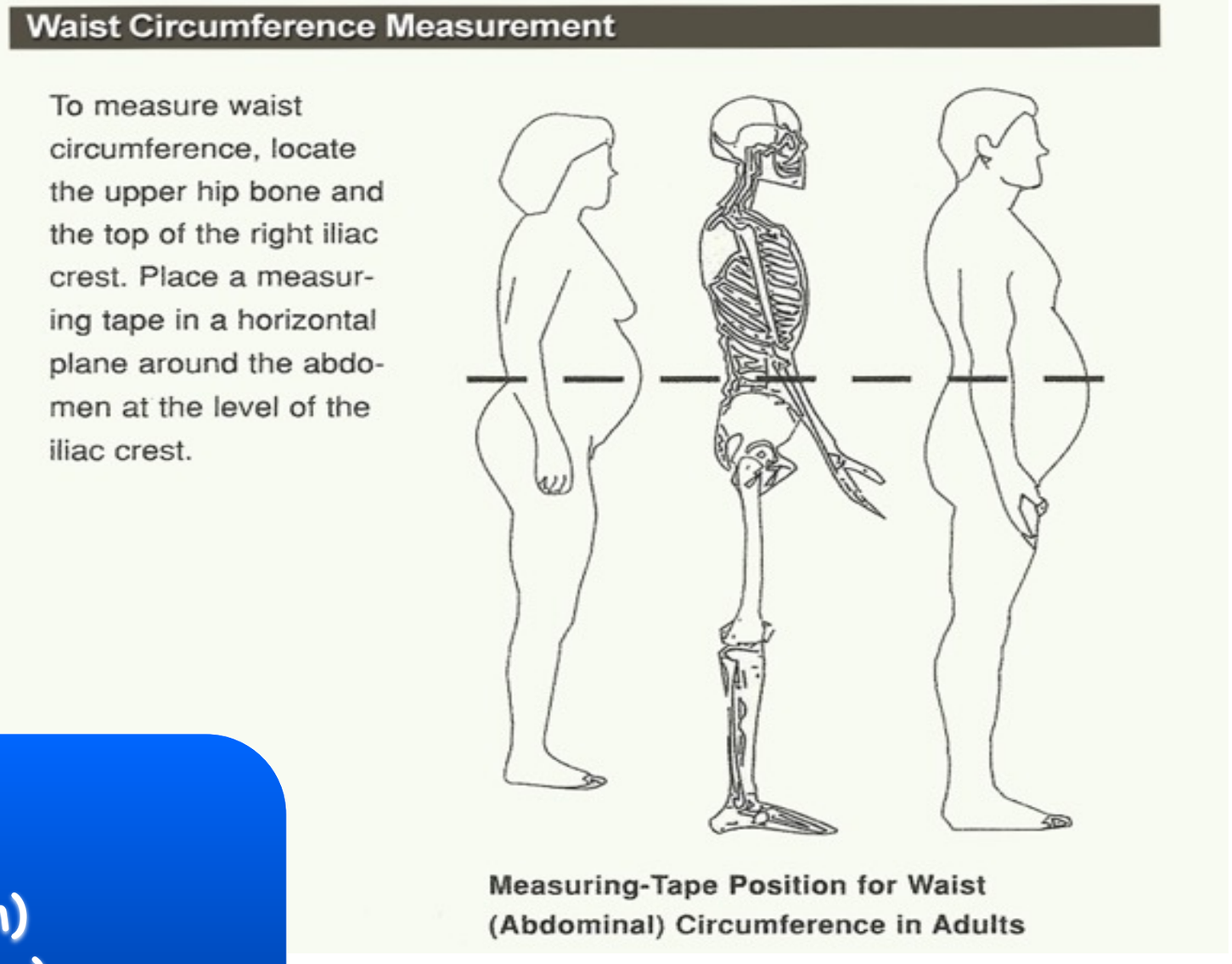
The Body Mass Index as defined by WHO weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm.

Measuring Waist Circumference

Overweight (BMI >23 kg/m^2) and central obesity (waist circumference >80 cm) were defined by Asian criteria

Snehalatha C, Vishwanathan V, Ramachandran A. Cut off values for normal anthropometric variables in Asian Indians. Diabetes Care 2003;26:1380

High Risk
Men: >40" (<102 cm)
Women: >35" (>88 cm)
Asian Men: >35" (>90 cm)
Asian Women: >31" (>80 cm)



Methods

- In all women with PCOS and in normal controls, a blood sample was obtained after 10 hrs of fasting between 8:00 and 9:00 AM for measurements of insulin, glucose and a lipid profile .
- Ten normal women were selected on the basis of having normal body weight, an absence of hirsutism or signs of androgenization, and normal ovulatory menstrual cycles, with no history of medical problems and not on any medication
- All biochemical analytes were mea sured using an autoanalyzer (Bayer RA-XT, Tarrytown, NY). Hormones were measured by RIA (serum T and insulin; Diagnostic Products Corporation, Los Angeles, CA;

Results

Methods (n-283)	NON- IR	IR	Chi Square Value
HOMA IR	137	146	314.07**
TG/HDL Ratio	135	148	
FG/FI	209	74	
TyG Index (>4.4)	51	232	

P<0.01

TyG Index could identify more than 75% of the studied population to have Insulin Resistance in comparison to HOMA IR and TGL/HDL Ratio could identify only 50%.

IR-PCOS-Indian Studies

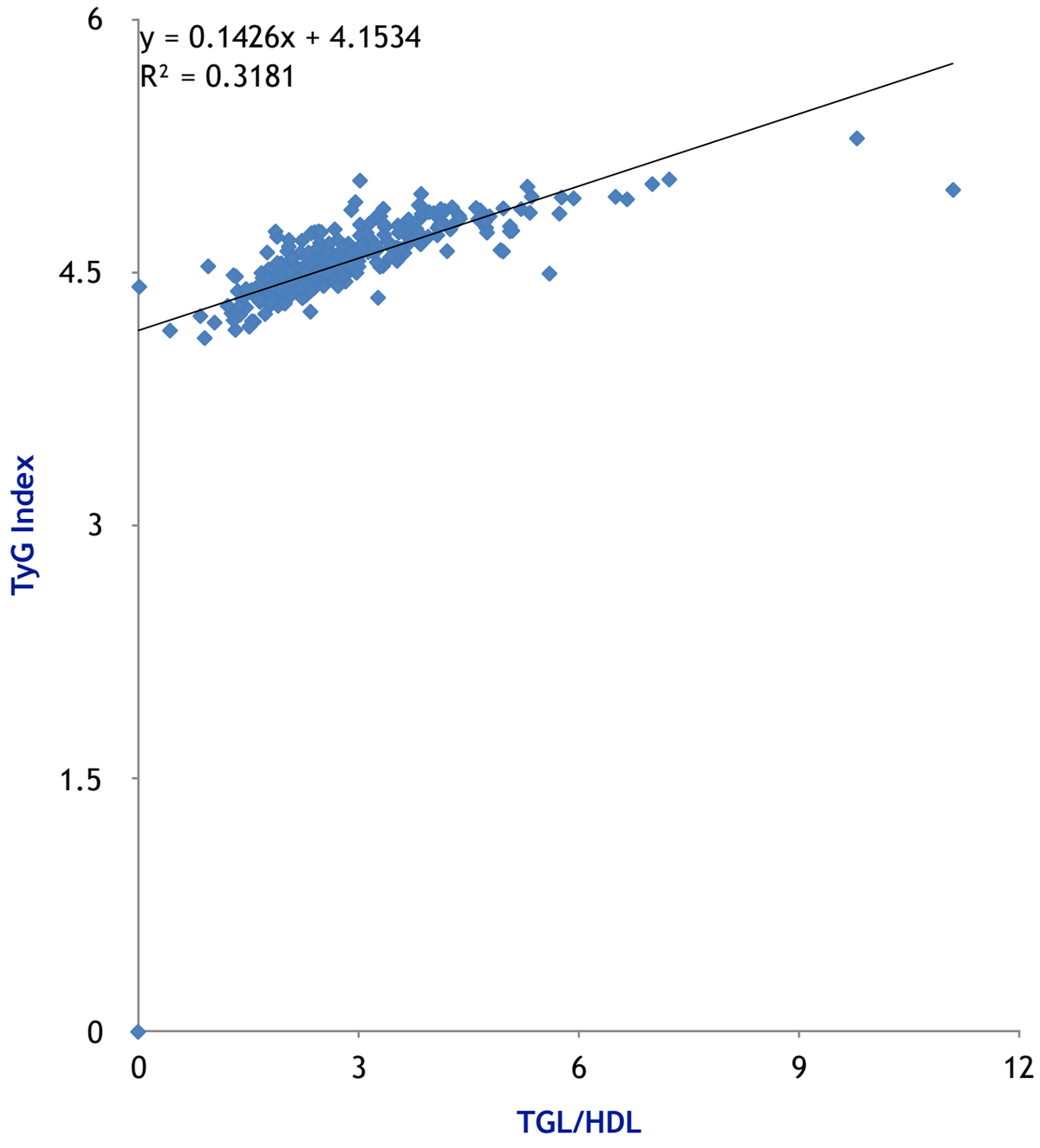
Study	Age Group	Obese	Lean	Total	N	Method
Vaidya	Adolescent	75%	25%	45.5%	36/79	FG/FI
Joshi	Adolescent			19.2%		Fasting Insulin
Ganie,Ashraf	Adolescent +Adult			44%	74/168	HOMA-IR
Karla	Aolescent +Adult			77%	50/65	FG/FI
Shahikala	Aolescent +Adult	28%	26%	54%	27/50	Fasting Insulin
Karr	Aolescent +Adult	25.6%	3.25%	28.7%	118/410	HOMA-IR
Meeta	Aolescent +Adult	79.5% 87%	20.5% 13%	51% 26%	284	HOMA IR FG/FI

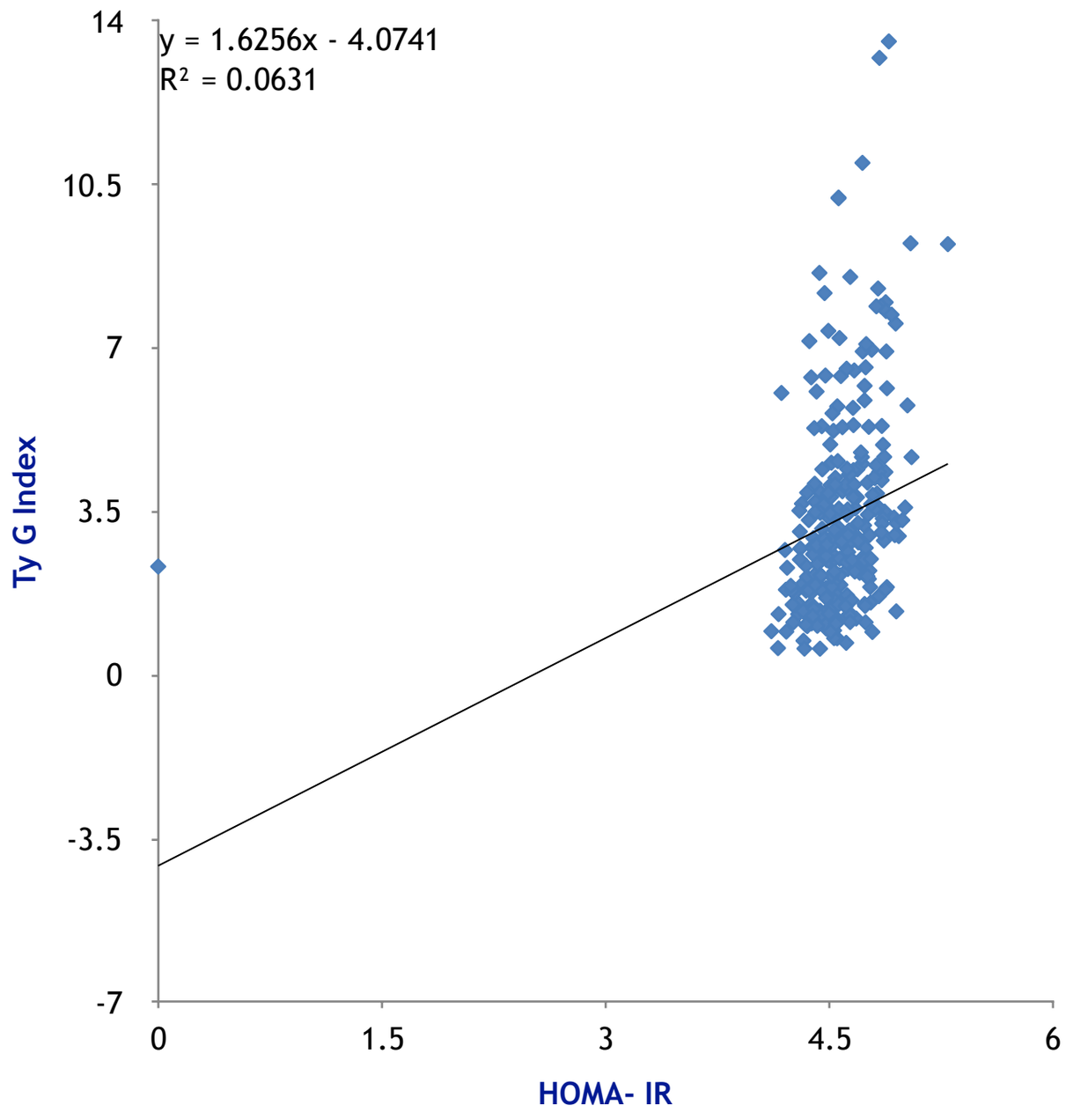
Results

Methods	Sensitivity (95% C.I)	Specificity (95% C.I)	IR Prevalence%
HOMA IR	99.32%	99.28 %	51.58%
TG/HDL Ratio	99.33%	99.26 %	52.28%
FG/FI	97.37%	**99.52 %**	26.57%
TyG Index (>4.4)	**99.57%**	96.23 %	**81.47%**

TyG Index was the most sensitive tool (99.57%) among the four tools and it identified insulin resistance in almost 81.47% population as evident from the above table.

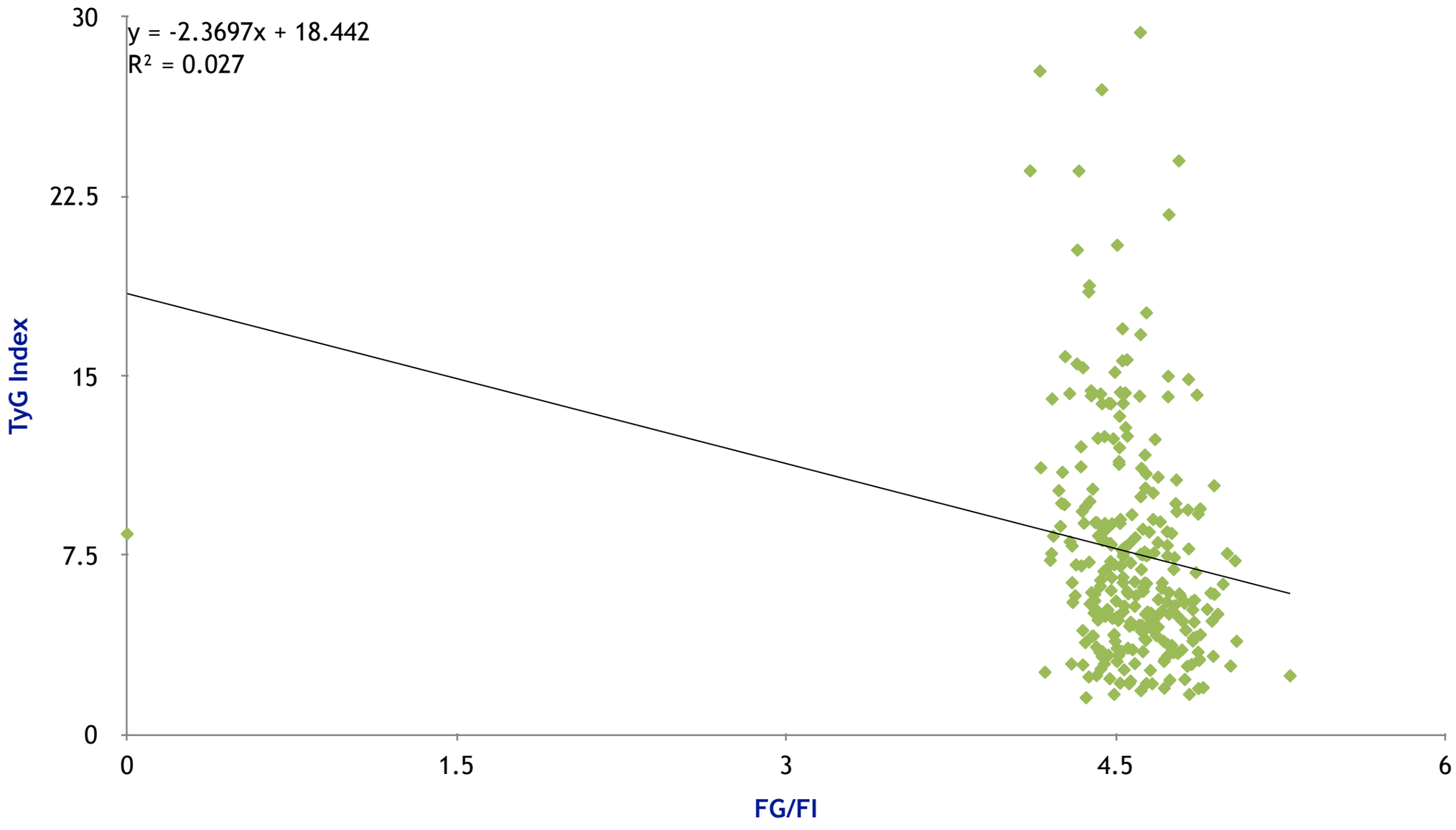
Results





TyG Index had a positive correlation with HOMA –IR and TGL/HDL ratio. There was no statistical seen between the both as seen in the above curves

Results



However, TyG Index had a negative correlation with FG/FI.

Results

Methods (n-283)	Acanthosis		Chi Square Value
	IR	NON- IR	
HOMA IR	83 (57%)	62 (45%)	70.31**
TG/HDL Ratio	84 (57%)	61 (45%)	
FG/FI	48 (65%)	96 (46%)	
TyG Index (>4.4)	119 (51%)	26 (51%)	

P<0.01

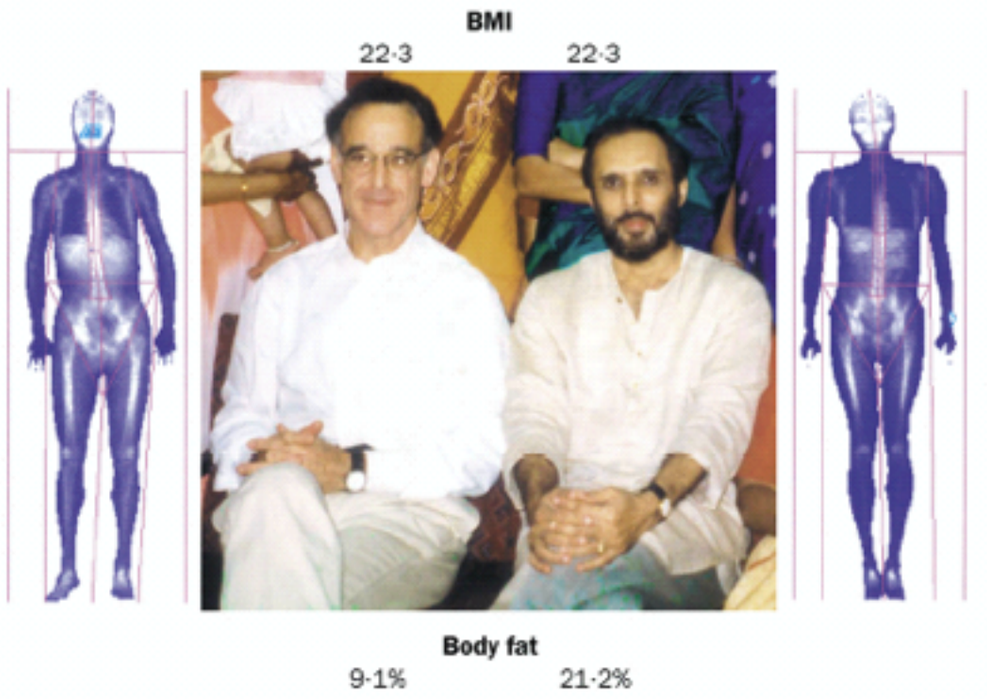
Acanthosis as a Clinical Marker was able to identify only 50% of the studied population to have Insulin Resistance. Hence, it may not be a very reliable tool to identify insulin resistance in women with PCODs.

Results

Demographic Variables	TyG <4.4 (n-51)	TyG> 4.4 (232)	't' Tests
Age	23±5.31	25±5.43	2.39**
BMI	26±5.50	28±6.59	2.01*
WC	84±10.97	89±1.67	6.64***
FBS	81±10.14	87±13.1	3.07*
FI	12±7.9	16±9.5	2.80**
TGL	71±13.52	130±44.89	9.28***
HDL	44±12.85	61±27.5	4.30***

*p<0.05, **p<0.01, ***p<0.001

Waist circumference, TGL and HDL are factors which strongly influence (p<0.001) TyG Index as evident from the above table.



Reported lifestyles: (left) marathon runner, (right) only exercise is running to beat the closing doors of the elevator every morning at work.

Methods	IR			NON IR		
	Obese	Non Obese	Chi Square	Obese	Non Obese	Chi Square
HOMA IR	116 (79.5%)	30 (20.5%)	14.58**	68 (49%)	69 (51%)	2.37**
TG/HDL Ratio	113 (75%)	35 (25%)		74 (55%)	61 (45%)	
FG/FI	65(87%)	9 (13%)		121 (58%)	88 (42%)	
TyG Index (>4.4)	158 (68%)	74 (32%)		29 (57%)	22 (43%)	

**p<0.01

Women with PCODs having Insulin Resistance may not be always obese.
From the above table around 35% of the studied population were lean PCODs with IR.
Likewise, Obese Women with PCODs could be non Insulin Resistance (50-60%) as seen in the above table.

Strengths

To date, no studies have reported on the IR using validated tools in a large group of women with PCOS

Both lean and obese women with PCOS were evaluated

Simple markers using TG,HDL,FG WERE USEDAdvantages

- High sensitivity and specificity

- Less costly

- Measurements of glucose and triglycerides are available in all clinical laboratories

- Insulin measurement not required — expensive test ,less accessible

Limitations

TyG index is not a direct measure of IR

The challenge is whether TyG index can be accurate enough in patients with hypertriglyceridemia.

NEED TO GENERATE CUT OFF VALUES BASED ON GENDER AND AGE IN INDIAN POPULATION

Conclusions / Future Perspectives

The TG,HDL,GLUCOSE BASED mathematical markers correlated well for diagnosing IR.

Good Counseling tool for THERAPEUTIC LIFESTYLE MANAGEMENT

TG/HDL,TyG index could be an accessible and reliable test for estimating insulin resistance in low-income individuals in high-risk groups LIKE PCOS in INDIA

NEED FOR VALIDATION AND GENERATION OFF CUTT OFF POINTS

Thank You