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Efficacy Of Novel Non-Insulin-Based Indices In Predicting Insulin Resistance In Women With PCOS – An Observational Study

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS) is the most common cause of female infertility globally. Insulin Resistance (IR) is seen in most of the women with PCOS. Recent studies has proposed non-insulin-based indices as the predictors of insulin resistance, which include Visceral Adiposity Index (VAI), Lipid Accumulation Product (LAP), Triglyceride Glucose (TyG) index, Triglyceride to HDL (TG/HDL-C) Ratio and Metabolic score for insulin resistance (METS-IR). But the predictive value of these indices is still debatable.

Aim: To compare the non-insulin-based indices and find out the one with best clinical efficiency in predicting IR

Materials and Methods: Total of 180 women (including 90 Healthy & 90 PCOS patients), aged between 18 to 40 years were included. Fasting Glucose, Triglyceride, Total cholesterol, HDL and Insulin levels were estimated. LAP, VAI, Triglyceride/ HDL-C ratio, TyG Index and METS – IR were calculated and statistical analysis was done.

Results: ROC Curve analysis found that the TyG index had the highest area under the curve of 0.87, with the sensitivity of 90.6% and specificity of 67% in PCOS group, followed by METS-IR having AUC of 0.81 with the sensitivity of 87.5% and specificity of 67%.

Conclusion: TyG index and METS IR were found to be effective indicators (p Value < 0.005), in assessing the IR in PCOS. Both has good predictive capacity in predicting Insulin resistance among the non-insulin-based indices.

Keywords: Non-insulin Based indices, TyG Index, METS – IR, Insulin Resistance, PCOS

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among females of reproductive age and also the common cause for female infertility. The incidence of PCOS and infertility have been increased in recent years. According to WHO, PCOS affects about 8-13% of women in reproductive age worldwide (1). PCOS is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovary morphology along with some metabolic abnormalities. Genetic, Epigenetic, Environmental and Metabolic factors play various role in the pathogenesis of PCOS.

Insulin Resistance (IR) is a pathognomonic feature in people with metabolic syndrome, obesity, type 2 diabetes, polycystic ovarian disease and pre-diabetes. Insulin Resistance (IR) is seen in around 35 to 80 % of the women with PCOS (2). Insulin resistance (IR) is a metabolic state where insulin dependent tissues lose their sensitivity to insulin, leading to metabolic imbalance and hyperinsulinemia. Compensatory

hyperinsulinemia is seen as result of insulin resistance. Hyperinsulinemia, which in turn stimulates proliferation of theca cells and also increases release of pituitary LH leading to abnormal ovarian steroidogenesis. The severity of Metabolic disease increases with Androgen excess.

Early identification of IR will be significant for the prevention of co-morbidities like type 2 DM, metabolic syndrome, and their complications in these women. The hyper- insulinemic euglycemic clamp is considered as gold standard for the determination of IR. However, it is costly and it requires time and trained personnel. Alternatives have been proposed, such as the homeostatic model assessment (HOMA - IR), the quantitative insulin check index (QUICKI), and the Matsuda index for clinical use (3). But these requires fasting Insulin level for evaluating insulin resistance.

Recently, alternative indices have emerged as tools of interest to identify IR because of their efficiency and low cost. Some of the recent studies has proposed Non-insulin based indices as the predictors of insulin resistance, which include Visceral Adiposity Index (VAI), Lipid accumulation product (LAP), Triglyceride Glucose (TyG) index, Triglyceride to HDL (TG/HDL-c) Ratio and Metabolic score for insulin resistance (METS-IR).

Visceral adiposity index (VAI) is a mathematical model that uses anthropometric measurement (waist circumference, BMI) and blood parameters (Triglyceride level and HDL) (4). Lipid accumulation product (LAP) is an index of lipid over accumulation, calculated using waist circumference and fasting triglycerides (5). Triglyceride glucose (TyG) index, which consists of serum triglyceride (TG) level and fasting plasma glucose (FPG) level, also suggested as a marker for assessing IR (6). TG to high-density lipoprotein cholesterol (TG/HDL-C) ratio was another index, significantly associated with IR regardless of anthropometric parameters (7). Metabolic score for insulin resistance (METS-IR) index is a novel index that uses Glucose, Triglyceride, HDL-c and BMI to assess insulin sensitivity (8).

All these indices do not require insulin measurement, which is a costly investigation and has been proposed to predict IR. But the predictive value of these indices is still debatable. With this background, in this study we aimed to compare the Non-insulin based indices (LAP, VAI, TyG Index, TG/HDL Ratio and METS-IR) with the HOMA -IR model, which is the gold standard method in predicting the insulin resistance in PCOS patients.

Objectives:

1. To compare the non-insulin-based indices with the HOMA -IR model in PCOS patients.
2. To find the index with best clinical efficiency among the non-insulin-based indices in predicting Insulin resistance in PCOS patients
3. To determine the cut-off values for the non-insulin-based indices in predicting Insulin resistance in PCOS women.

Materials And Methods

This study was conducted in our Medical College, after getting clearance from Institutional Research Committee and Institutional Ethical Committee. Total of 180 women, including 90 PCOS patients & 90 Healthy, aged between 18 to 40 years were included in the study. The sample size was calculated based on a similar study by *Katuzna et al* (9). The formula used for calculation was

$n \geq (Z_{1-\alpha/2})^2 \; P(1-P)/d^2$

where p is the expected proportion

d is the absolute precision

The level of significance was taken as 5%.

Inclusion criteria:

Group 1: PCOS subjects were selected randomly from OB&G OPD using revised Rotterdam criteria which states Women may be diagnosed as PCOS if any two of the following are present: clinical or biochemical hyperandrogenism, oligo / anovulation, polycystic appearance of ovarian morphology on ultrasound, with exclusion of other relevant disorders.

Group 2: Healthy group include Non diabetic and Non PCOS women.

Exclusion criteria: Women already diagnosed as Diabetic, Pregnant women, Women having menstrual irregularities due to etiologies other than PCOS were excluded from the study.

Demographic characteristic details were noted and a detailed clinical history was collected from all the subjects using a self-adjusted questionnaire, which

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include the Menstrual history, presence or absence of any other illness, drug history etc.

Height, Weight & Waist circumference were measured and BMI was calculated. 5ml of venous blood was collected after 8-10 hrs of fasting, serum was separated. Fasting Glucose, Triglyceride, Cholesterol and HDL levels were measured using fully automated Biochemistry analyser (Mindray BS-480). All the parameter reports were taken after both levels of QC pass the quality checks. Fasting Insulin level was measured by CLIA method.

Other parameters were calculated using the formulas:

LAP: (WC-58) × TG (mmol/L)

VAI: {WC/ [36.58 + (1.89 × BMI)]} × (TG/0.81) × (1.52/HDL)

TyG Index = Ln [TG (mg/dL) x FG (mg/dL)/2]

Triglyceride-/HDL-C ratio= TG (mg/dl)/HDL-C (mg/dl)

METS-IR was calculated as ln [2 X Glucose(mg/dl) + TG (mg/dl)] X BMI (kg/m2) / ln [HDL-C(mg/dl)].

HOMA-IR was calculated using the formula, fasting insulin (microU/L) x Fasting glucose (nmol/L)/22.5.

Results

All the data were analyzed using SPSS Software version 29. Data distribution was assessed using Kolmogrov smirnov test and was found to be of normal. Continuous variables were expressed as the Mean +/- Standard deviation. Independent t Test was used for comparison of various parameters among the groups and the p value < 0.05 was taken as statistically significant.

Comparison of variables between the PCOS and Non-PCOS shows that HOMA-IR and all non-insulin-based indices (VAI, LAP, TyG Index, TG/HDL ratio and METS IR) were found to be statistically significant. Other parameters like weight, BMI, waist circumference, fasting glucose, triglyceride and cholesterol levels were also statistically significant among both groups. Age, Height and HDL levels were not significant between PCOS and Non-PCOS group (Table 1).

ROC curve analysis : Receiver operator characteristic (ROC) curve analysis was done in comparison with HOMA-IR, among both groups, in order to find the index with good predictive capacity for insulin resistance.

ROC curve of non-insulin based indices with reference to HOMA-IR in PCOS group is shown in Figure 1, while ROC curve of non- insulin based indices with reference to HOMA-IR in Non PCOS group (Healthy Group) shown in Figure 2. ROC analysis shows that the TyG index, LAP, TG/HDL-c and the METS -IR were found to be effective indicators, in assessing the Insulin Resistance in women with PCOS (p Value < 0.05). TG/HDL-C ratio and METS-IR have significance in assessing the Insulin Resistance among the Non-PCOS group (Table 2).

In PCOS group, among the non-insulin-based indices, TyG index had the highest area under the curve (AUC) of 0.87, with the sensitivity of 90.6% and specificity of 67%, while METS-IR has AUC of 0.81 with the sensitivity of 87.5% and specificity of 67%. TG/HDL-C ratio has AUC of 0.74 with sensitivity of 75 % and specificity of 67%. LAP has AUC of 0.77 with sensitivity of 71.9% and specificity of 67%. The cut-off value of these indices in PCOS group was found to be 43.49, 8.55, 2.15 and 39.64 for LAP, TyG index, TG/HDL-c ratio and METS-IR index respectively.

In Non-PCOS group, METS-IR has the highest AUC of 0.86 with the sensitivity of 95.7% and specificity of 60%.TG/HDL-C ratio has AUC of 0.69 with sensitivity of 95.7% and specificity of 40%.

Discussion

PCOS is often associated with various disorders like obesity, dyslipidemia and metabolic syndrome. HAIR-AN syndrome is a sub phenotype of PCOS characterized by Hyperandrogenism (HA), Insulin Resistance (IR) and Acanthosis Nigricans (AN), associated with mutation in insulin receptor gene and also a risk of endometrial carcinoma (10).

Prevalence of PCOS is increasing in the past few decades mainly due to changes in the life style and diet habits. About 70% of affected women remain undiagnosed (1). It not only affects the reproductive system but also contributes to diseases like cardiovascular disorder, Diabetes mellitus, metabolic syndrome, depression and anxiety (11).

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Tables And Figures

Table 1: Comparison of different parameter between groups

Parameters	Group	Mean	SD	t value	p value
Age (yrs)	1	26.34	5.64	-0.279	0.391
	2	26.68	5.04		
Height(cm)	1	153.55	5.13	-2.156	0.017
	2	156.00	4.76		
Weight(kg)	1	68.68	5.28	5.219	<0.001*
	2	60.72	7.79		
BMI	1	29.20	2.58	6.876	<0.001*
	2	24.96	2.79		
WC (cm)	1	96.62	4.98	6.509	<0.001*
	2	87.74	6.78		
F Glucose (mg/dl)	1	96.51	8.10	5.045	<0.001*
	2	88.61	5.26		
TG (mg/dl)	1	112.13	13.64	9.987	<0.001*
	2	83.01	11.71		
HDL (mg/dl)	1	49.12	4.26	-3.212	0.001
	2	53.09	6.33		
LAP	1	49.11	10.18	10.512	<0.001*
	2	27.90	7.16		
VAI	1	2.00	0.33	8.906	<0.001*
	2	1.37	0.28		
TyG Index	1	8.59	0.16	11.132	<0.001*
	2	8.20	0.15		
TG/HDL ratio	1	2.30	0.35	9.266	<0.001*
	2	1.59	0.31		
METS -IR	1	42.93	3.96	8.060	<0.001*
	2	35.08	4.51		
F Insulin	1	14.65	3.90	6.695	<0.001*
	2	9.94	1.89		
HOMA IR	1	3.50	1.02	7.306	<0.001*
	2	2.18	0.45		

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Table 2: ROC curve analysis of non-insulin based indices with HOMA-IR in Both groups

Variables	Group 1: PCOS group					Group 2: Non PCOS group				
	AUC	p value	Cut off	Sensitivity	Specificity	AUC	p value	Cut off	Sensitivity	Specificity
LAP	0.776	0.006*	43.49	71.90	67.00	0.620	0.242	26.93	73.90	46.70
VAI	0.693	0.110	1.70	90.60	50.00	0.633	0.186	1.07	87.00	40.00
TyG	0.870	0.000*	8.55	90.60	67.00	0.661	0.099	8.17	73.90	46.70
TG/HDL	0.742	0.023*	2.15	75.00	67.00	0.694	0.030*	1.27	95.70	40.00
METS-IR	0.818	0.000*	39.64	87.50	67.00	0.862	0.000*	32.15	95.70	60.00

*Statistically significant (p value < 0.05)

Fig 1: ROC Curve for PCOS Group

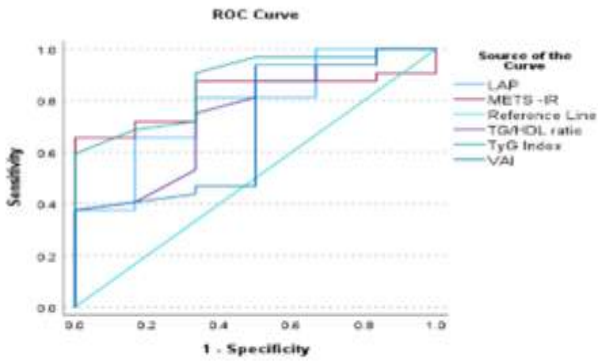
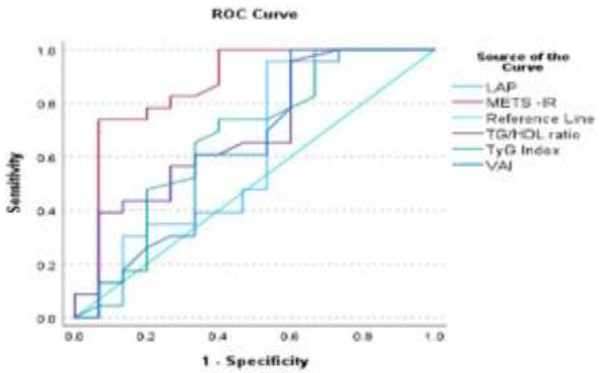


Fig 2: ROC Curve for Non PCOS Group



Since, irregular menstrual cycle within 2-3 years of menarche is physiological, PCOS was not considered as a serious issue by most of the females during their adolescent age. PCOS patients usually seeks medical help only, when they suffer from dysmenorrhea or infertility. By that time, Insulin resistance is well established and they are at the risk of associated co-morbidities.

In women with PCOS, Increased androgen levels promotes inflammation by activating nuclear factor kappa B (NF-κB). This affects intracellular enzyme pathways related with insulin receptors (12,13). Hyperandrogenaemia also affect the phosphorylation of protein kinase C which is activated by insulin, leading to a decrease in GLUT-4 receptors in subcutaneous adipose tissue and a decrease in serine phosphorylation of GSK3. Defects in either insulin receptor binding or phosphorylation leads to Insulin Resistance in Adipose tissue (14,15).

Insulin receptors found in stroma and follicular cells of ovaries. Insulin has a direct effect on ovaries and steroid production (16,17). HI promotes intrathecal steroid production and causes impaired follicular maturation. Hyperinsulinemia further increases hyperandrogenaemia, resulting in a vicious cycle that affects the metabolic function (18,19). So, Early diagnosis and intervention for Insulin resistance might be helpful in preventing co-morbidities like Type 2 DM and Metabolic syndrome in PCOS patients.

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In this present study, all non – insulin-based indices are found to be statistically significant on comparison between PCOS and Non-PCOS. It also shows that the TyG index, LAP, TG/HDL-c and the METS -IR are effective indicators of insulin resistance among women with PCOS. Among those non -insulin based indices, TyG index have high sensitivity of 90.6% and specificity of 67% in PCOS group, followed by METS-IR having AUC of 0.81 with the sensitivity of 87.5% and specificity of 67%.

Visceral adiposity index considered as a reliable indicator of visceral fat function associated with cardiometabolic risk and metabolic syndrome (20,21). Chan *et al* suggests Lipid Accumulation Product as a Simple and Accurate Index for Predicting Metabolic Syndrome (22). Khan *et al* suggested that Triglyceride glucose (TyG) index can be been considered a surrogate marker for assessing IR (6). Kim et al suggested that TG/HDLC ratio was significantly associated with IR in general population (23). METS-IR index has been suggested as a good diagnostic performance to assess insulin sensitivity (8,24). A cross-sectional study by Kałuzna *et al* suggests that LAP, TG/HDL-C, VAI and WHtR as superior markers to identify MS in PCOS (9). Similar study by Haiyan Wang *et al* states LAP and VAI as Predictors of Insulin Resistance and Hyperandrogenaemia in Obesity/Overweight Women with Polycystic Ovary Syndrome (25). Jog *et al* compared these indices with HOMA-IR in Metabolic Syndrome in South Indian Population and proposed cut off for LAP, TyG and TG/HDL-C indices (26). An Another study by Naghshband *et al* suggested VAI and LAP as significant determinants of MetS in south Indian women with PCOS (27).

Our study has certain limitations with relatively small sample size, did not assess the risk of development of metabolic syndrome and CVD as future outcomes in PCOS women. It would have been more, if we included estimation and correlation of androgen levels and these indices along with insulin resistance. Thus, prospective follow-up studies are required to evaluate the role of lipid and obesity indices in estimating risk.

Conclusion

Based on our study, TyG index and METS- IR can be used as predictor to determine for Insulin Resistance in PCOS. We highly emphasize investigation for insulin resistance in women with PCOS, using this non-insulin- based indices (avoiding costly investigations) on a regular basis in order to prevent the co-morbidities and associated complications.

References

1. https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome
2. Amisi CA. Markers of insulin resistance in Polycystic ovary syndrome women: An update. World J Diabetes 2022; 13(3): 129-149
3. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocr Metab 2015; 19:160-4.
4. Amato MC, Giordano C, Pitrone M. et al. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis. 2011; 10: 183
5. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005; 5:26.
6. Khan SH, Sobia F, Niazi NK, et al. Metabolic clustering of risk factors: evaluation of Triglyceride-glucose index (TyG index) for evaluation of insulin resistance. Diabetol Metab Syndr 2018; 10: 74.
7. Chauhan A, Singhal A, Goyal P. TG/HDL Ratio: A marker for insulin resistance and atherosclerosis in prediabetics or not? J Family Med Prim Care.2021Oct;10(10):3700-3705.
8. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and ident type 2 diabetes. Eur J Endocrinol 2018; 178: 533–544.
9. Kałużna M, Czlapka-Matyasik M, Kompf P, Moczko J, Wachowiak-Ochmańska K, Janicki A, Samarzewska K, Ruchała M, Ziemnicka K. Lipid ratios and obesity indices are effective predictors of metabolic syndrome in women with polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2022 Jan 10; 13:20420188211066699.
10. Cuenca D, Ventura-Gallegos JL, Almeda-Valdes P, Tusié-Luna MT, Reza-Albarran A, Ventura-Ayala L, Ordoñez-Sánchez ML, Segura-Kato Y, Gomez-Perez FJ, Conte MP, Gonzalez LR,

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Zentella-Dehesa A. A novel nonsense mutation in the insulin receptor gene in a patient with HAIR-AN syndrome and endometrial cancer. Mol Genet Metab Rep. 2023 Mar 13;35: 100965.
11. Zhu S, Zhang B, Jiang X, Li Z, Chen ZJ. Metabolic disturbances in nonobese women with polycystic ovary syndrome: a systematic review and meta-analysis. Fertil Steril. 2019;111(1):168–77.
12. Paulukinas RD, Mesaros CA, Penning TM. Conversion of classical and 11-oxygenated androgens by Insulin-Induced AKR1C3 in a model of human PCOS Adipocytes. Endocrinology. 2022; 7:7.
13. Cassar S, Misso M, Hopkins W, Shaw C, Teede H, Stepto N. Insulin resistance in polycystic ovary syndrome: a systematic review and metaanalysis of euglycaemic-hyperinsulinaemic clamp studies. Hum Reprod (Oxford, England). 2016;31(11):2619–31.
14. Corbould A. Chronic testosterone treatment induces selective insulin resistance in subcutaneous adipocytes of women. J Endocrinol. 2007;192(3):585–94.
15. Jeanes Y, Reeves S. Metabolic consequences of obesity and insulin resistance in polycystic ovary syndrome: diagnostic and methodological challenges. Nutr Res Rev. 2017;30(1):97–105.
16. Li Y, Chen C, Ma Y, Xiao J, Luo G, Li Y, et al. Multi-system reproductive metabolic disorder: significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS). Life Sci. 2019; 228:167–75.
17. Mlinar B, Marc J. New insights into adipose tissue dysfunction in insulin resistance. Clinical Chemistry and Laboratory Medicine (CCLM). 2011;49(12):19251935.
18. Han Zhao, Jiaqi Zhang, Xiangyi Cheng, Xiaozhao Nie and Bing He. Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation and treatment. Journal of Ovarian Research 2023; 16:9
19. Evanthia DK, Andrea D. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012; 6:981–1030.
20. Qing L, Wei R, Chan L. et al. Sensitivity of various body indices and visceral adiposity index in predicting metabolic syndrome among Chinese patients with adult growth hormone deficiency. J Endocrinol Invest. 2017; Feb 23.
21. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920–2.
22. Chan L, Xue H, Xiaoya Z. et al. Lipid Accumulation Product: a Simple and Accurate Index for Predicting Metabolic Syndrome in Patients with Adult Growth Hormone Deficiency. Exp Clin Endocrinol Diabetes. 2016; 124:220-4
23. Kim JS, Kang HT, Shim JY, et al. The association between the triglyceride to high density lipoprotein cholesterol ratio with insulin resistance (HOMA-IR) in the general Korean population: based on the National Health and Nutrition Examination Survey in 2007-2009. Diabetes Res Clin Pract 2012; 97: 132–138.
24. Yoon J, Jung D, Lee Y, Park B. The Metabolic Score for Insulin Resistance (METS-IR) as a Predictor of Incident Ischemic Heart Disease: A Longitudinal Study among Korean without Diabetes. J Pers Med. 2021 Jul 28;11(8):742.
25. Wang H, Cao H, Cao J, Zhang L. The Visceral Adiposity Index (VAI) and Lipid Accumulation Product (LAP) Are Predictors of Insulin Resistance and Hyperandrogenaemia in Obesity/Overweight Women with Polycystic Ovary Syndrome. Biomed Res Int. 2023 Feb 13;2023: 1508675.
26. Jog K S, Eagappan S, Santharam R K, et al. (January 11, 2023) Comparison of Novel Biomarkers of Insulin Resistance with Homeostasis Model Assessment of Insulin Resistance, Its Correlation to Metabolic Syndrome in South Indian Population and Proposition of Population Specific Cutoffs for These Indices. Cureus 15(1): e33653.
27. Naghshband Z, Kumar L, Mandappa S,Niranjana Murthy AS, Malini SS. Visceral adiposity index and lipid accumulation product as diagnostic markers of metabolic syndrome in South Indians with polycystic ovary syndrome. J Hum Reprod Sci 2021; 14:234-43.

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