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RESEARCH ARTICLE

Triglyceride-Glucose Index as A Crucial Marker for Polycystic Ovary Syndrome Women with Insulin Resistance

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Abstract

BACKGROUND: Insulin resistance (IR) is considered as the main driver of polycystic ovary syndrome (PCOS) pathogenesis. In PCOS condition, IR is frequently related to glucose, anthropometric profile, lipid profile, and hormone profile parameters. However, not all PCOS phenotype show IR. Therefore, this study was conducted to determine the association the parameters mentioned above in PCOS subjects with and without IR.

METHODS: Fifty PCOS women with IR and 26 PCOS women without IR were recruited. All subjects underwent physical examination for measurement of weight, waist circumference (WC), and body mass index (BMI). Ferriman Gallwey Score (FGS) was used to evaluate hirsutism. Blood sample was taken from each subject for measurement of fasting glucose, postprandial glucose, fasting insulin, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglyceride (TG), sex hormone binding globulin (SHBG), thyroid-stimulating hormone (TSH),

luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin. Homeostatic model assessment for IR (HOMA-IR), TG-glucose index (TyGI), and free testosterone index (FTI) were then calculated.

RESULTS: From all the parameters examined, only fasting insulin ($p<0.001$), HOMA-IR ($p<0.001$), SHBG ($p=0.012$), TG ($p<0.001$), and TyGI ($p=0.008$) that show significant differences between PCOS subjects with and without IR. After multivariate analysis, TyGI was found to have strong association with IR occurrence in PCOS subjects ($p=0.005$) with an odd ratio of 5.26 (1.65–16.74).

CONCLUSION: TyGI appears to have a significant association with the IR occurrence in PCOS subjects. Hence, it can be suggested that TyGI could be an important marker for PCOS women with IR.

KEYWORDS: insulin resistance, lipid metabolism, polycystic ovary syndrome, triglyceride-glucose index

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Introduction

Polycystic ovarian syndrome (PCOS), also known as metabolic-endocrine disorder syndrome, affects 5-10% of reproductive women worldwide. PCOS was diagnosed according to the Rotterdam criteria if 2 of the following 3

criteria are present: hyperandrogenism, oligo-anovulation, and findings of ≥ 12 follicles measuring 2-9 mm per ovary or 12-20 antral follicles on high-frequency probe ultrasound.(1) PCOS is frequently related to several multiple disorders, specifically insulin resistance (IR) and hyperandrogenism, which are accompanied by enduring long-term consequences such as obesity, type 2 diabetes

mellitus (T2DM), dyslipidemia, cardiovascular disease, and endometrial cancer.(2-4)

IR is one of the most frequent characteristics of PCOS, with a prevalence varying from 35-80%.(5,6) IR is characterized by a reduced receptor response to insulin stimulation, which prevents target tissues from delivering glucose into cells, suppresses lipolysis, stimulates glycogen synthesis, and inhibits hepatic glucose.(7) IR is quite common in women with PCOS, although the prevalence of IR is independent of body mass index (BMI), obesity has been reported to be associated with an increased occurrence of IR in PCOS. Approximately 55-70% of obese PCOS patients experience IR, while non-obese PCOS patients show an incidence of IR of around 38-40%. This condition is in accordance with several publications which state that in PCOS, homeostatic model assessment for IR (HOMA-IR) is positively correlated with waist circumference (WC), triglyceride (TG), chronic low-grade inflammation, free testosterone, and free androgen index and negatively correlated with high-density lipoprotein (HDL) and sex hormone binding globulin (SHBG).(8-10) In addition, genetic and epigenetic factors, as well as prenatal androgen exposure are proven to play a significant role in the occurrence of IR in PCOS women.(11,12) Therefore, early recognition of IR, anthropometric profile, hormone profile, glucose, and lipid profile in PCOS are crucial for optimal screening, prevention, and intervention.(13) However, there is a PCOS phenotype that does not show IR. This may be influenced by other causes such as central gonadotropin hormone dysregulation and hyperandrogenic state.(14,15)

In IR states, non-esterified fatty acids are mobilized from muscle and adipose tissue to the liver, thereby increasing the substrate for TG production. Fasting TG-glucose index (TyGI) is closely associated with IR.(16) It seems that TyGI is a reliable, inexpensive, and at the same time useful marker for detecting changes in lipid profile and glucose metabolism disorders associated with IR, especially in PCOS.(17) Since BMI, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, glucose, lipids, and TyGI are associated with IR, therefore, it is crucial to determine the association between these factors in PCOS subjects with and without IR.

Methods

Study Design and Subjects Recruitment

An observational cross-sectional study was conducted. Female subjects with PCOS, aged 20-35 years old, visiting

Yasmin Fertility Clinic, Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia in July to December 2019, were recruited. PCOS condition was diagnosed according to the Rotterdam criteria.(1) Pregnant subjects or subjects with medical records of gynecological disorders, adrenal gland disease, hypothalamic-pituitary axis alterations, excessive prolactinemia, abnormal uterine bleeding of unknown cause, and thromboembolic or cerebrovascular disorders, were excluded. Subjects having hormonal medication, smoking, and alcohol consuming habits were also excluded. This study protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo National Central General Hospital (No. 929/UN2.F1/ETIK/IX/2017). All subjects were provided with comprehensive information of the study. Subjects signed informed consent prior to the study enrollment.

Demographic and Anthropometric Profile Measurement

Anamnesis and physical examination were performed for measurement of body weight, WC, and BMI. In addition, subjects were evaluated for hirsutism as well with Ferriman Gallwey Score (FGS). Subjects were scored on a scale of 0-4 for terminal hair growth on eleven different body areas.

Glucose Profiling

For each glucose profile, about 5 mL of venous blood was collected from each subject. For fasting glucose, the blood collection was performed after 8-12 hours of fasting, while for the postprandial glucose, the blood collection was performed at 2 hours after 75 g carbohydrate intake. Despite fasting glucose and postprandial glucose, collected blood was processed to measure plasma insulin using the ARCHITECT Colorimetric Assay kit (Abbott Diagnostics, Lake Forest, IL, USA). HOMA-IR was calculated by multiplying fasting insulin and fasting glucose, and then dividing it by 405. A high score of HOMA-IR defined IR. The cut-off for HOMA-IR in this study was set at 2.69. (18) Meanwhile, the TyGI value was determined using the formula $\text{Ln} [\text{fasting TG (mg/dL)} \times \text{fasting plasma glucose (mg/dL)}^2]$.

Lipid Profiling

Each subject fasted for 10 hours prior to the collection of 5 mL venous blood. The collected blood was processed to measure low-density lipoprotein (LDL), HDL, total cholesterol, and TG, using ADVIA Centaur Immunoassay System (Siemens Healthineers, Erlangen, Germany).

Hormone Profiling

About 5 mL of venous blood was collected from each subject. The collected blood was processed to measure SHBG, follicle stimulating hormone (TSH), LH, FSH, and prolactin using the ADVIA Centaur XPT Immunoassay System. Testosterone was measured using Elecsys Testosterone II (Roche, Basel, Switzerland) with electrochemiluminescence immunoassay method, using Cobas e 402/e 801 (Roche). Free testosterone index (FTI) was defined by dividing total testosterone level by SHBG level and then multiplying the result by 100.

Statistical Analysis

Statistical analysis was performed using the SPSS version 17.0 (IBM Corporation, Armonk, NY, USA). The mean, median, and standard deviation were obtained through univariate analysis, which was then followed by bivariate analysis to assess differences between the 2 groups, namely PCOS with IR and PCOS without IR. A p -value of <0.05 was considered statistically significant.

Results

Seventy-six women with PCOS were recruited into this study, which were then divided into 2 groups; 50 PCOS subjects with IR and 26 PCOS subjects without IR. The median age was 28 years old, the median BMI was 27.78 kg/m², and the median of FGS was 3, meanwhile, the mean weight was 71.87 kg, and the mean WC was 92.01 cm (Table 1).

Glucose Profiles of PCOS Subjects

A normal range of fasting glucose level was observed both in PCOS subjects with and without IR (Table 2). The median postprandial glucose level of PCOS subjects with IR was 127 (61-237) mg/dL, whereas 30% of the postprandial glucose level of the PCOS subjects with IR was >140 mg/dL. The fasting insulin level of PCOS subjects with IR was confirmed significantly higher than PCOS subjects without IR ($p<0001$).

Lipid Profiles of PCOS Subjects

There was no significant difference level of LDL, HDL, and total cholesterol between PCOS subjects with and without IR (Table 2). PCOS subjects with IR had significantly higher TG level ($p<0.001$) than the ones without IR. PCOS subjects with IR had significantly higher TyGI ($p=0.008$) than the ones without IR as well.

Hormone Profiles of PCOS Subjects

PCOS subjects with IR had significantly lower SHBG level ($p=0.012$) than the ones without IR (Table 2). There was no significant difference level of TSH, LH, FSH, and prolactin between PCOS subjects with and without IR (Table 2).

Multivariate Analysis Results

Multivariate analysis was carried out using binary logistic regression, involving variables with $p<0.25$. However, variables which in principle, did not influence the incidence of IR (TG to HDL ratio, prolactin and FSH) were excluded. TyGI showed a strong relationship with the IR occurrence in PCOS women after multivariate analysis using logistic

Table 1. Baseline characteristics of the study subjects.

Characteristic	Value
Demographic and Anthropometric Profile	
Age (year)	28 (23–35)
Weight (kg)	71.87±13.15
WC (cm)	92.01±9.80
BMI (kg/m ²)	27.78 (20.75–39.77)
FGS	3 (1–11)
Metabolic and Lipid Profile	
Fasting glucose (mg/dL)	89.33±7.77
Postprandial glucose (mg/dL)	112.5 (56–237)
Fasting insulin (μIU/mL)	14 (9–37)
LDL (mg/dL)	128.5 (59–239)
HDL (mg/dL)	42.51 (30–62)
Total cholesterol (mg/dL)	204.72 (121.80–316.30)
TG (mg/dL)	109.5 (45–390)
TyGI	4925.5 (1680–17940)
TG to HDL ratio	2.59 (0.85–10)
LDL to HDL ratio	3.25±0.77
TG to BMI ratio	3.695 (1.49–16.53)
HOMA-IR	2.89 (2.05–8.99)
Hormone Profile	
SHBG (nmol/L)	21.5 (7–66)
TSH (μIU/mL)	2 (0–9)
LH (μIU/mL)	10.68±4.48
FSH (μIU/mL)	6 (2–10)
Prolactin (ng/mL)	9 (4–32)
FTI (ng/dL)	5 (1–31)
LH to FSH ratio	1.76±0.84

Numerical variables with normal data distribution: mean±SD, while numerical variables with non-normal data distribution: median (min–max). WC: Waist Circumference; BMI: Body Mass Index; FGS: Ferriman Gallwey Score; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TG: Triglyceride; TyGI: Triglyceride Glucose Index; SHBG: Sex Hormone-Binding Globulin; TSH: Thyroid Stimulating Hormone; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; FTI: Free Testosterone Index.

Table 2. Characteristic comparison of PCOS subjects with and without IR.

Characteristic	Non-IR (n=26)	IR (n=50)	p-value
Demographic and Anthropometric Profile			
Age (years)	28.05±2.86	28.28±3.46	0.708
Weight (kg)	68.05±13.23	73.23±12.98	0.131
WC (cm)	89.08±8.67	93.54±10.07	0.731
BMI (kg/m ²)	26.95 (20.75–34.10)	29.49 (21.91–39.77)	0.204
FGS	2 (1–9)	3 (1–11)	0.298
Metabolic and Lipid Profile			
Fasting glucose (mg/dL)	87.3±6.7	90.3±8.1	0.198
Postprandial glucose (mg/dL)	109 (56–155)	127 (61–237)	0.128
Fasting insulin (μIU/mL)	10 (9–13)	18 (12–37)	<0.001*
LDL (mg/dL)	136.23±23.15	125.5 (101–239)	0.387
HDL (mg/dL)	43.03±5.87	43.61±7.29	0.620
Total cholesterol (mg/dL)	206.79±21.20	203.98±39.98	0.696
TG (mg/dL)	85 (45–236)	123 (65–390)	<0.001*
TyGI	4248 (1680–9393)	6687 (2503–17940)	0.008*
TG to HDL ratio	2.4 (0.85–6.50)	3.6 (1.17–10)	0.078
LDL to HDL ratio	3.29±0.48	3.23±0.86	0.736
HOMA-IR	2.36±0.16	3.31 (2.69–8.62)	<0.001*
Hormone Profile			
SHBG (nmol/L)	29 (10–50)	21.8 (10–50)	0.012*
TSH (μIU/mL)	2.2 (1–9)	2.0 (1–6)	0.426
LH (μIU/mL)	10.10±4.48	10.89±4.50	0.500
FSH (μIU/mL)	6 (3–8)	7 (2–10)	0.078
Prolactin (ng/mL)	9 (5–26)	9.5 (4–32)	0.831
FTI (ng/dL)	4 (2–31)	6 (1–18)	0.108
LH to FSH ratio	1.90±1.13	1.71±0.72	0.489

Numerical variables with normal data distribution: mean±SD, were analyzed using an independent T-test. Numerical variables with non-normal data distribution: median (min–max), were analyzed using the Mann-Whitney test. WC: Waist Circumference; BMI: Body Mass Index; FGS: Ferriman Gallwey Score; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TG: Triglyceride; TyGI: Triglyceride Glucose Index; SHBG: Sex Hormone-Binding Globulin; TSH: Thyroid Stimulating Hormone; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; FTI: Free Testosterone Index.

regression and the 5-stage backward Wald method. This relationship was found to have a *p*-value of 0.005 and an odds ratio of 5.26 with 95% CI (1.65–16.74). Based on correlation analysis carried out with the Spearman test, we observed a weak positive correlation between the TyGI and HOMA-IR with *p*=0.003 and (*r*=0.117) (Figure 1).

Discussion

IR and hyperinsulinemia could be negative impacts of accumulated adipose tissue metabolism, which were related to decreased glycogen synthesis, decreased SHBG secretion, and increased insulin-like growth factor-1 (IGF-1) in the liver. High insulin levels in women with IR will increase

the production of LH by the anterior pituitary following the increased pulsatile release frequency of gonadotropin-releasing hormone (GnRH) in the hypothalamus.(12) Hyperinsulinemia condition can also disrupt the balance between the hypothalamic pituitary ovary (HPO) axis and the hypothalamic pituitary adrenal (HPA), which is related to the increase of adrenocorticotrophic hormone (ACTH) by the adrenal glands.(12)

In our study, PCOS subjects with IR had lower SHBG levels than PCOS subjects without IR. This finding is consistent with the findings of numerous studies addressing the decreased production of SHBG in PCOS women with IR. This condition correlates with IR which will lead to the increase of monosaccharides delivery to the liver and adipose tissue lipolysis, which later induce the production

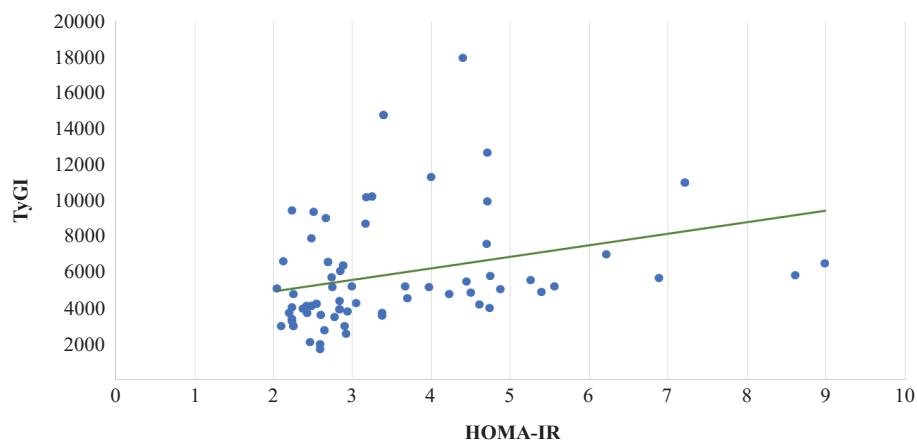


Figure 1. Positive correlation was observed between HOMA-IR and TyGI in PCOS subjects (r=0.117; p=0.003).

of non-esterified fatty acids (NEFA). This will stimulate gluconeogenesis and lipogenesis; and increase the proinflammatory cytokine tumor necrosis factor (TNF)- α as well as *de novo* lipogenesis (DNL) followed by the decrease of hepatocyte nuclear factor (HNF)-4 α and SHBG.(19)

Dyslipidemia is a common metabolic complication affecting up to 70% of women with PCOS. Multiple factors are known to contribute to the disruption of lipid metabolism and dyslipidemia. IR performs a crucial role by predominantly stimulating lipolysis and altering the expression of lipoprotein and hepatic lipases. Under conditions of IR, NEFA is transported from muscle and adipose tissue to the liver, thereby augmenting the substrate for TG biosynthesis.(20,21)

We observed that the PCOS subjects with IR had lesser LDL levels than the ones without IR, whereas there was no difference in HDL levels between the PCOS subjects with and without IR. Furthermore, PCOS subjects with IR had higher TG level and TG to HDL ratio than PCOS subjects without IR. Multivariate analysis showed a significant association between TyGI and IR occurrence in PCOS subjects. Compared to several studies conducted in Iran, Iraq, and China, current study has shown that the TyGI is a practical and inexpensive test with a high degree of reliability for PCOS women with IR.(8,22,23) A positive correlation between the TyGI and the prevalence of metabolic syndrome in women with PCOS has been reported as well. TyGI was found to be independently correlated with hypertension, obesity, central obesity, hyperglycemia, and dyslipidemia in women with PCOS.(24)

but not glucose levels. In addition, TyGI appears to have a significant association with the occurrence of IR in PCOS subjects. Taken together, it can be suggested that TyGI could be an important marker for PCOS women with IR.

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Authors Contribution

AH was involved in the conceptualisation of the study and the data curation. DE, AK, RM, and FS were involved in the investigation and analysis of the data. AK and RM was responsible for the data validation. DE and GP were responsible for the software and project administration. JS designed the visualisation for the manuscript. AH, JS, and GP wrote the original draft of the manuscript. JS and FS substantially and edited the manuscript. AH was involved in the funding acquisition and supervision.

Conclusion

In this study, fasting insulin and TG were found to be higher in PCOS subjects with IR than PCOS subjects without IR,

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