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Content

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REVIEW ARTICLE

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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 Ln [fasting TG (mg/dL) × 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 occurance 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 adrenocorticotropic 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

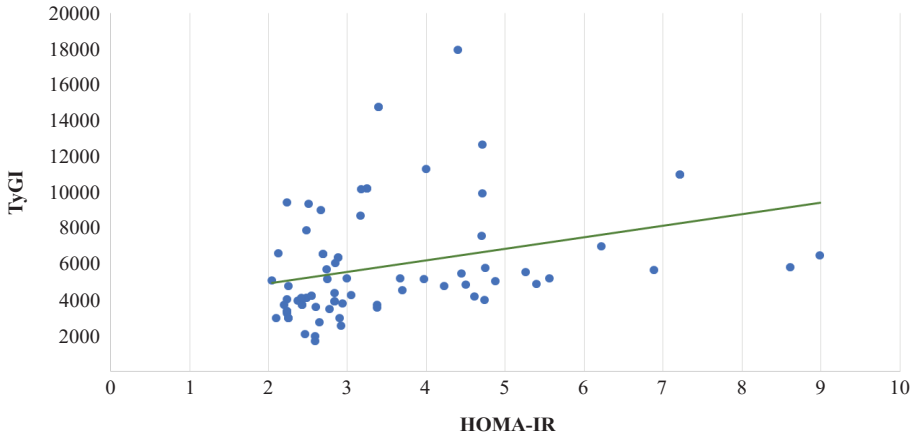

Figure 1. Positive correlation was observed between HOMA-IR and TyGI in PCOS subjects (r=0.117; *p*=0.003).

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)-4α 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)

Conclusion

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

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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

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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 Ln [fasting TG (mg/dL) × 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 occurance 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 adrenocorticotropic 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

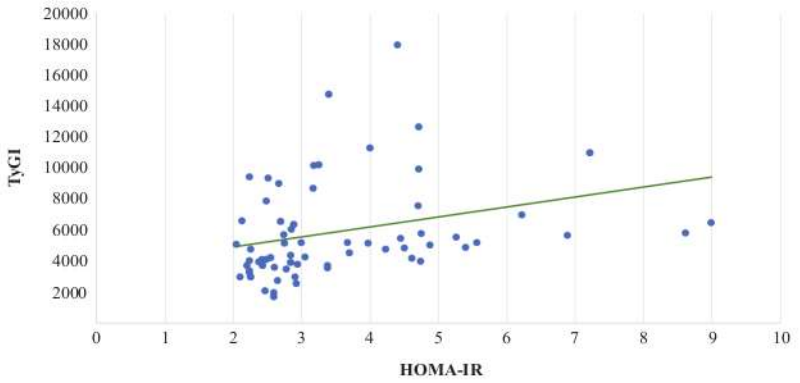

Figure 1. Positive correlation was observed between HOMA-IR and TyGI in PCOS subjects (r=0.117; *p*=0.003).

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)-4α 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)

Conclusion

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

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GENERAL COMMENTS

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UNIVERSITAS TRISAKTI

Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023276 Editor Decision Round 1 - Resubmit for Review

Secretariat of InaBJ <secretariatinabj@gmail.com> Wed, Oct 18, 2023 at 2:27 PM
To: ferry@trisakti.ac.id

Dear Dr. Ferry Sandra,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, manuscript M2023276 entitled "**Triglyceride-glucose Index as A Main Determinant Factor of Insulin Resistance in PCOS Women**".

Our decision is: **Resubmit for Review.**

Find the files attached to see detailed comments from reviewers. Please make sure you read all the comments and revise the manuscript based on the suggestions given. Revise this manuscript thoroughly before **November 1, 2023**.

When you are done, you can upload it in: https://inabj.org/index.php/ibj/author/submissionReview/2639, or simply send us an email of your revised manuscript and response letter.

Please let us know when you have received this email. If you have any questions, do not hesitate to contact us. Thank you for your attention. We wish you a nice day.

Best Regards,
--
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4 attachments

- **Round 1 Reviewer 2 - F09 Manuscript Review Form.pdf** 174K
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Manuscript Review Form

Reviewer	:	Reviewer 1
Manuscript #	:	M2023276
Manuscript Title	:	**Triglyceride-glucose Index as A Main Determinant Factor of Insulin Resistance in PCOS Women**

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?	**v**	
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?	V	
	Notes: A little extra regarding the importance of this study needs to be added, what to look for?		
3	Do the title and abstract reflect the study result/content?	V	
	Notes: Title need more specific: what determinant for in PCOS?		
4.	Is the significance of the study well explained at the Background?	v	
	Notes: The purpose of background research can be further clarified regarding its utilization (potentially in the future).		
5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?	v	
	Notes:		
6.	Are the results, ideas, and data presented in this manuscript important enough for publication?	v	

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	Notes:		
7.	Are all figures and tables necessarily presented?	v	
	Notes:		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?	v	
	Notes: Discussion flow is not very smooth, bridging between paragraphs needs to be added		
9.	Are the conclusions and interpretations valid and supported by the data?	v	
	Notes:		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?		
	Notes:		

Specific Reviewer's Comments and Suggestions:

(These comments may be in addition to or in lieu of reviewer comments inserted into the text of the manuscript. Use as many lines as needed.)

Discussions on this manuscript still raise the question so what?

What is meant by the Triglyceride-glucose index, how to get it and the potential benefits of this marker need to be clarified

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Reviewer's Recommendation (Please tick only one option)	√
Accept Submission (No significant alterations suggested)	
Revisions Required (Suggest changes to the manuscript as specified in this review)	
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	

Further Reviewer's Comments Regarding Disposition of the Manuscript:

Date and Sign:
2023-10-18

Reviewer 1
……..

Triglyceride-glucose Index as A Main Determinant Factor of Insulin Resistance in PCOS Women

Abstract

Background: The metabolic endocrine disorder Polycystic Ovary Syndrome, also known as PCOS affects 5-10% of women of childbearing age worldwide. PCOS involves various potential comorbidities, implicating reproductive and metabolic dysregulation. Insulin Resistance (IR) is one of the metabolic dysregulation in PCOS with a prevalence of 35%-80%. Thus, this study aims to correlate the most significant factor between hormone profile, metabolic-lipid profile, and anthropometric profile with IR in PCOS. Therefore, it is crucial to determine the association between these factors and insulin resistance occurrence in PCOS. Researchers aim to identify one of the factors most strongly associated with the incidence of insulin resistance in PCOS.

Methods: This study was conducted involving 76 PCOS women ranging from 20-35 years old defined by Rotterdam criteria at Yasmin Fertility Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia from July-December 2019. Participants were divided into 2 subgroups: 50 subjects of IR and 26 subjects of non-IR. Physical examination, gynaecological ultrasound examination and blood sampling were carried out on each participant.

Results: Age, weight, waist circumference, BMI, FG, fasting glucose, post-prandial glucose, prolactin, LDL, HDL, LH, FSH, TSH, FTI, TG-HDL ratio, LH-FSH ratio, and cholesterol level showed no significant differences. Contrary to fasting insulin (p = <0.001), SHBG (p = 0.012), and TG (p = <0.001) showed significant differences among non-IR and IR in PCOS subjects. Multivariate analysis showed significant differences in the TG-Glucose Index (p = 0.023).

Conclusion: TG-Glucose index is the most significant factor of IR occurrences in PCOS.

Commented [1]: FG : Fasting Glucose?

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Keywords: Insulin Resistance, Lipid Metabolism, Polycystic Ovary Syndrome, Triglyceride-Glucose Index

Introduction

Polycystic Ovarian Syndrome, 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 were 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)

Polycystic ovary syndrome (PCOS) is frequently related to several significant multiple disorders, specifically insulin resistance and hyperandrogenism, which are accompanied by enduring long-term consequences such as obesity, Type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial cancer.(2)

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Insulin Resistance (IR) is one of the most frequent characteristics of PCOS, with a prevalence varying from 35 and 80 percent.(3) IR is characterized by a reduced receptors response to insulin stimulation, which prevents target tissues from delivering glucose into cells, suppresses lipolysis, stimulates glycogen synthesis, and inhibits hepatic glucose.(4) Insulin resistance is quite common in women with PCOS. Although the prevalence of insulin resistance is independent of body mass index, obesity has been reported to be associated with an increased prevalence of insulin resistance in PCOS. Approximately 55-70% of obese PCOS experience insulin resistance, while non-obese PCOS show an incidence of insulin resistance of around 38-40%. This condition is in accordance with several publications which state that in PCOS, HOMA-IR is positively correlated with waist circumference, triglycerides, chronic low-grade inflammation, free testosterone, and free androgen index (FAI) and negatively

correlated with HDL cholesterol and steroid hormone binding globulin (SHBG).(5, 6) In addition, genetic, epigenetic factors, and prenatal androgen exposure are proven to play a significant role in the incidence of insulin resistance in PCOS women.(7, 8)

As a result, early recognition of IR, anthropometric profile, hormone profile, metabolic and lipid profile, in PCOS are crucial for optimal screening, prevention, and intervention. (9) However, there is a PCOS phenotype that does not show insulin resistance. This may be influenced by other causes such as central gonadotropin hormone dysregulation and hyperandrogenic state. (10, 11)

Compared to healthy women, with the same body mass index (BMI), women with polycystic ovary syndrome (PCOS) more often experience lipid metabolism disorders, which are characterized by increased total cholesterol, low-density lipoprotein (LDL), triglycerides, accompanied by low high-density lipoprotein (HDL) levels. In general, women with PCOS have a higher average BMI and waist circumference than those women without PCOS. (12) LH baseline tone and kisspeptin production were shown to be elevated in PCOS compared to the control group, despite the dynamic expression of the LH to FSH ratio. (13)

It has been widely reported that there are discrepancies in the lipid profile, hormone profile, anthropometric profile, and metabolic profile between women with PCOS and the control group concerning the occurrence of hyperandrogenism and insulin resistance. However, few studies of comparable characters have examined the association between the mentioned variables and the incidence of insulin resistance among PCOS subjects. (14)

Therefore, it is crucial to determine the association between these factors and insulin resistance occurrence in PCOS. Researchers aim to identify one of the factors most strongly associated with the incidence of insulin resistance in PCOS.

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Methods

Study Design

An observational cross-sectional study was conducted on 76 women aged 20-35 years old at Yasmin Fertility Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia from July to December 2019. Approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia and Cipto Mangunkusumo General Hospital, indicated through reference number 929/UN2.F1/ETIK/IX/2017. Participants were then asked to complete an informed consent form.

Inclusion and Exclusion Criteria

PCOS condition was diagnosed according to the Rotterdam criteria, if 2 of the following 3 criteria were 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) This study excludes other following etiologies such as gynecological disorders, adrenal gland disease, hypothalamic-pituitary axis alterations, excessive prolactinemia, abnormal uterine bleeding of unknown cause, thromboembolic or cerebrovascular disorders and pregnancy. In addition, participants who are habitual smoker, consume alcohol, or have taken any hormonal prescription are not included in this study.

Research Process

This study included 76 reproductive aged women with PCOS were divided into 2 groups, consisting of 50 PCOS women with insulin resistance and 26 PCOS women without insulin resistance. Prior to this research, all participants were provided with comprehensive information of the study and had provided their informed permission. Anamnesis and physical examination including measurement of waist circumference, body weight, height, and assessment of hirsutism according to the Ferriman-Gallwey Score (FGS) were carried out on participants who met the inclusion criteria.

Each participant fasted for around 8-12 hours beforehand and then collected approximately 10 ml of their venous blood to be stored in several Vacutainers. Two hours after consuming a high-calorie intake, or a carbohydrate intake of 75 g, venous blood was collected to assess 2-hour postprandial glucose status. Samples from venous blood are needed to measure blood glucose, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Prolactin levels, total cholesterol, HDL, LDL, Triglycerides, SHBG, FSH, LH, TSH, testosterone, and Free Testosterone Index (FTI).

Fasting and two hours post-prandial blood glucose were assessed using the ARCHITECT glucose reagent kit (Abbott Diagnostics, Illinois, USA). Plasma insulin was measured using the ARCHITECT insulin reagent kit (Abbott Diagnostics, Illinois, USA). Fasting insulin (IU/ml) multiply by fasting plasma glucose (mg/dL) and divided by 405 was used to calculate HOMA-IR.

ADVIA Centaur Prolactin Kit (Siemens Healthineers Global, New York, United States), Sekisui cholesterol (Siemens Healthineers Global, New York, United States), ADVIA Triglyceride reagent kit (Siemens Healthineers Global, New York, United States) and ADVIA Centaur Immunoassay SHBG Kit (Siemens Healthineers Global, New York, USA) were used to assess cholesterol prolactin total, HDL-C, LDL-C, Triglycerides and SHBG respectively.

ADVIA Chemical TSH Reagent Kit (Siemens Healthineers Global, New York, USA), ADVIA Centaur LH Kit (Siemens Healthineers Global, New York, United States), and ADVIA Centaur FSH Kit (Siemens Healthineers Global, New York, United States) were used for determine the concentrations of TSH, LH and FSH respectively.

Testosterone levels were measured using the Testosterone kit (Roche Diagnostics, Risch-Rotkreuz, Switzerland), and total testosterone (nmol/L) divided by SHBG (nmol/L) multiplied by 100 is the formula used to calculate the Free Testosterone Index (FTI). Excessive

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terminal hair growth in certain areas of the female body that is specific to males, called hirsutism, is measured by the visual instrument Ferriman Gallwey score (FGS).

During the FGS examination, nine androgen sensitive areas were assessed, and each area was assigned a score between 1 and 4 based on the density of hair growth. Areas studied include upper lip, mandible, chest, upper abdomen, lower abdomen, upper arms, upper back and lower back. Hirsutism diagnosis rates vary depending on race and ethnicity. As a final result of FGS, the equal cumulative score of 8 or higher is consistent with hirsutism.

The subjects were classified into 2 groups based on the presence of insulin resistance. Insulin resistance was defined by a high score of HOMA-IR. The cut-off for HOMA-IR in this study was set at 2.69. The primary outcome of this study was the association between anthropometric and lipid profiles with insulin resistance and also factors that contribute to the insulin resistance condition in PCOS women.

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Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17.0, SPSS Inc., Chicago, Illinois, 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 insulin resistance and PCOS without insulin resistance, using an independent T test, and the Mann-Whitney U test involving independent variables include age, body mass index (BMI), weight, height, waist circumference, fasting glucose, 2 hours postprandial glucose, fasting insulin, HOMA-IR, LDL, HDL, triglycerides, SHBG, TSH, LH, FSH, and testosterone. A p value of less than or equal to 0.05 is considered statistically significant and logistic regression analysis is applied to several independent variables that have a p-value of less than 0.25.

Results

Seventy-six women with PCOS were recruited into this study, which were then divided into 2 groups; 24 PCOS with insulin resistance and 52 PCOS without insulin resistance. The median age of the subjects was 28 (23-35) years, with the BMI mostly classified as overweight (according to the Asia Pacific World Health Organization classification), and indicating central obesity (81.57%). Average fasting glucose level of subjects was 89.33 ± 7.77 mg/dL, while average postprandial glucose level was 112.5 (56-237) mg/dL. As for the lipid profile of subjects, the median LDL was 128.5 (59-239) mg/dL, the average HDL was 42.51±6.59 mg/dL, and the median triglyceride was 109.5 (45-390) mg/dL. A total of 65.8% of participants had insulin resistance in this study. Participant characteristics are shown in Table I.

Using bivariate analysis, significant differences between insulin resistance and some variables such as fasting insulin level ($p < 0.001$), triglyceride level ($p = 0.001$), SHBG level ($p = 0.032$), TSHs level ($p = 0.041$), and triglyceride/HDL level ($p = 0.003$). The result of the bivariate analysis in this study can be found in Table II.

Multivariate analysis was carried out using logistic regression, involving 13 variables with a p-value of less than 0.25. Among these variables, body mass index and triglyceride were found to be important determinants of insulin resistance conditions in PCOS participants. The result of the multivariate analysis in this study can be found in Table III.

Based on correlation analysis, there was no association between insulin levels and SHBG production in PCOS women with and without insulin resistance. The result of the correlation analysis in this study can be found in Table IV.

Based on correlation analysis we observed a weak positive correlation between the TG-glucose index and HOMA-IR with ($p = 0.003$) and ($r = 0.117$). The result of the correlation analysis in this study can be found in Figure 1.

Discussion

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This research was conducted to determine the various factors impacting insulin resistance conditions in PCOS subjects. Insulin resistance is characterized by a decrease in insulin sensitivity and an increase in insulin necessity for metabolism. Indirectly, insulin resistance was determined by multiplying fasting insulin by fasting glucose and dividing the result by 405. This study applied a cut-off of 2.69 for insulin resistance, which matches studies conducted on Chinese PCOS subjects (15). In this study, the insulin resistance of 76 PCOS participants was evaluated. Fifty (65.8%) of the individuals were determined to have insulin resistance with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values of 2.69 or greater (15).

Attributing to insulin resistance, the HOMA-IR cut-off value determined in this study is consistent with the HOMA-IR results obtained from the Asian PCOS subjects (7). HOMA-IR appears to be equally prevalent in European populations. This is likely due to the similarity between HOMA-IR examination methods. However, the Croatian PCOS population was reported to have a higher HOMA-IR value, which may correlate with the participant's Body Mass Index (BMI). (16)

Insulin resistance and hyperinsulinemia are known to have a negative impact on metabolic effects of the adipose tissue i.e. decreased glucose uptake, increased lipid accumulation, and decreased lipid decomposition; decreased insulin sensitivity in skeletal muscle; decreased glycogen synthesis, decreased Sex Hormone-Binding Globulin (SHBG) secretion, and increased Insulin-Like Growth Factor-1 (IGF-1) in the liver. In addition, high insulin levels in women with insulin resistance have a negative impact on reproductive function, specifically an increased Luteinizing Hormone (LH) production by the Anterior Pituitary as a result of an increased Gonadotropin-Releasing Hormone (GnRH) pulsatile release in the Hypothalamus. (8) Hyperinsulinemia condition can also disrupt the balance between the Hypothalamic Pituitary Ovary (HPO) Axis and the Hypothalamic Pituitary

Adrenal (HPA), this is due to an increased Adrenocorticotropic Hormone (ACTH) by the adrenal glands. (8)

In our study, PCOS subjects with insulin resistance had lower SHBG levels than PCOS subjects without insulin resistance. This finding is consistent with findings from numerous studies addressing the decreased production of SHBG in PCOS women with insulin resistance. This condition correlates with insulin resistance which will lead to increased delivery of monosaccharides to the liver; increased lipolysis of adipose tissue, which produces non-esterified fatty acids (NEFA), which stimulate gluconeogenesis and lipogenesis; increase in the proinflammatory cytokine TNF-alpha; as well as an increase in De Novo Lipogenesis (DNL) followed by a decrease in HNF-4 alpha production and ends with a decrease in SHBG production. (17)

In this study, the PCOS group with insulin resistance had lesser LDL levels, whereas there was no difference in HDL levels between the two groups. Furthermore, the PCOS group with insulin resistance had higher triglycerides (TG) levels, and TG to HDL ratios compared to PCOS groups without insulin resistance. (18) Multivariate analysis showed a significant association between the TG-Glucose index and insulin resistance in PCOS.

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Dyslipidemia is a common metabolic complication affecting up to 70% of PCOS-affected women. Multiple factors are known to contribute to the disruption of lipid metabolism and dyslipidemia. Insulin Resistance performs a crucial role by predominantly stimulating lipolysis and altering the expression of lipoprotein lipase and hepatic lipase. Under conditions of insulin resistance, non-esterified fatty acids are transported from muscle and adipose tissue to the liver, thereby augmenting the substrate for TG biosynthesis. (18, 19)

In this study, the PCOS group with insulin resistance had higher triglyceride levels than the PCOS group without insulin resistance, but the ratio of triglyceride to HDL and fasting triglyceride-glucose index did not differ between the two groups. In contrast, multivariate

analysis revealed a substantial association between the fasting triglyceride-glucose index and the occurrence of IR in PCOS.

In China, Peru, India, and Taiwan, researchers found a significant correlation between TG/HDL and the incidence of insulin resistance in polycystic ovary syndrome (PCOS). (5, 20) However, our findings are consistent with the study conducted on African-American populations (21, 22), which indicates that the Triglyceride to HDL ratio is unreliable for determining insulin resistance.

In addition, as an IR marker for PCOS, the fasting triglyceride-glucose index is a practical and inexpensive test with a high degree of reliability, in accordance with the findings of our study which are validated by studies conducted in Iran, Iraq and China. (5, 23, 24)

Weight reduction of about 5-10% is recommended for overweight and obese women, in an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day) applied. Weight loss will result in a significant reduction in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and fasting insulin. (25, 26) This has shown a significant improvement in secondary reproductive outcomes such as a decrease in free androgen index (FAI), testosterone (T), hirsutism (Ferriman-Gallwey score), and increasement in sex hormone-binding globulin (SHBG). In addition, a weight reduction of more than five percent can significantly improve menstrual periods, increase fertilization, increase live births, follicular development and reduce ovarian volume. (25, 26)

Research has shown that dietary patterns have a significant role in the management of polycystic ovary syndrome (PCOS). It is recommended that subjects with PCOS uphold specific diet namely low-fat, high-protein, low-glycemic index (GI) to glycemic load (GL) ratio, and enriched with monounsaturated fatty acid (MUFA). (25). A study revealed that adopting a nutritious diet that includes adequate amounts of fruits, vegetables, whole grains, seeds, nuts, legumes, and low-fat dairy, whereas mostly consisting of carbohydrates with a low

glycemic index, is the optimal approach for decreasing insulin resistance. In addition, a vegetarian diet showed a decrease in inflammatory markers (CRP, resistin, and adiponectin) when compared with a meat-based diet. According to the international evidence-based guideline for the assessment and management of PCOS (2018), individuals are recommended to engage in 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity each week to avoid weight gain. For weight reduction and prevention of weight regain, a higher level of physical activity is advised, particularly 250 minutes of moderate physical activity or 150 minutes of vigorous physical activity exercise per week. (27) In addition, there were significant negative correlations between the suggested intake of several micronutrients (vitamin C, B6, niacin, and iron) and the FAI development in PCOS women. (28)

The study's sample size is constrained and certain exclusion criteria obtained solely from anamnesis and physical examination such as moderate adrenal gland disease, thromboembolic disorder, alcohol intake, and frequent smoking, all of which may impact the statistical power of this study.

Conclusion

This study is conducted to determine the association of lipid profile, hormone profile, anthropometric profile, and metabolic profile among PCOS subjects with insulin resistance. In this study, triglyceride was found higher in PCOS with insulin resistance compared to PCOS without insulin resistance. The results of the bivariate analysis showed no difference in the triglyceride-glucose index between PCOS with insulin resistance and PCOS without insulin resistance. The triglyceride-glucose index appears to have a significant association with the occurrence of insulin resistance in PCOS, based on the results of the multivariate analysis. It is recommended to continue the study by expanding the PCOS subjects with varying BMI and matched controls.

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Figures/Tables

Table I. Characteristics of the Study Population

Characteristic	Value (n = 76)
Demographic and Anthropometric Profile	
Age	28 (23 – 35) years
Weight	71.87 ± 13.15 kg
Waist Circumference	92.01 ± 9.80 cm
Body Mass Index	27.78 (20.75 – 39.77) kg/m^2
Ferriman-Gallwey Score	3 (1 – 11)
Metabolic and Lipid Profile	
Fasting Glucose	89.33 ± 7.77 mg/dL
Postprandial Glucose	112.5 (56 – 237) mg/dL
Fasting Insulin	14 (9 – 37) µIU/mL
LDL	128.5 (59 – 239) mg/dL
HDL	42.51 ± 6.59 mg/dL
Triglyceride	109.5 (45 – 390) mg/dL
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)
Hormone Profile	
LH to FSH Ratio	1.76 ± 0.84 µIU/mL
SHBG	21.5 (7 – 66) nmol/l
TSH	2 (0 – 9) µIU/mL
LH	10.68 ± 4.48 µIU/mL
FSH	6 (2 – 10) µIU/mL
Prolactin	9 (4 – 32) ng/mL
FTI	5 (1 – 31) ng/dL

Note: Numerical variables with normal data distribution are presented as mean ± standard deviation, while numerical variables with abnormal data distribution are presented as median (minimum–maximum value).

Abbreviations: HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein, TG = Triglyceride, BMI = Body Mass Index, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone, SHBG = Sex Hormone-Binding Globulin, TSH = Thyroid Stimulating Hormone, FTI = Free Testosterone Index.

Table II. Characteristic Comparison of Insulin Resistance and Non-Insulin Resistance among PCOS Women

Characteristic	Group		*p* value
	Non-Insulin Resistance	Insulin Resistance	
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
Waist Circumference (cm)	89.08 ± 8.67	93.54 ± 10.07	0.731
Body Mass Index (kg/m^2)	26.95 (20.75 – 34.10)	29.49 (21.91 – 39.77)	0.204
Ferriman-Gallwey Score	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
Triglyceride (mg/dL)	85 (45 – 236)	123 (65 – 390)	<0,001
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
TG Glucose Index	4248 (1680 – 9393)	6687 (2503 – 17.940)	0.238
Total Cholesterol (mg/dL)	206.79 ±21.20	203.98 ± 39.98	0.696
Hormone Profile			
Prolactin (ng/ml)	9 (5 – 26)	9.5 (4 – 32)	0.831
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
FTI	4 (2 – 31)	6 (1 – 18)	0.108
LH to FSH Ratio	1.90 ± 1.13	1.71 ± 0.72	0.489

Note*:* Numerical variables with normal data distribution were analyzed using an independent T-test and are presented as mean ± standard deviation, while numerical variables with abnormal data distribution were analyzed using the Mann-Whitney test and are presented as median (minimum–maximum value).

Abbreviations: HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein, TG = Triglyceride, BMI = Body Mass Index, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone, SHBG = Sex Hormone-Binding Globulin, TSH = Thyroid Stimulating Hormone, FTI = Free Testosterone Index.

Table III. Multivariate Regression Analysis.

Biochemical Parameter	Odds Ratio	95% Confidence Interval	*p Value*
Triglyceride Glucose Index	5.625	1.668 – 18.971	0.005

Abbreviations: OR = Odds Ratio, CI = Confidence Interval.

Table IV. Correlation between SHBG and Insulin among PCOS Subjects with Insulin Resistance and without Insulin Resistance.

Variables	SHBG PCOS Non-IR	SHBG PCOS IR
Insulin PCOS Non-IR	r: -0.278 p: 0.169	
Insulin PCOS IR		r: -0.168 p: 0.239

Abbreviations: IR = Insulin Resistance, p = p value, PCOS = Polycystic Ovary Syndrome, r = Coefficient Correlation, SHBG = Sex Hormone-Binding Globulin.

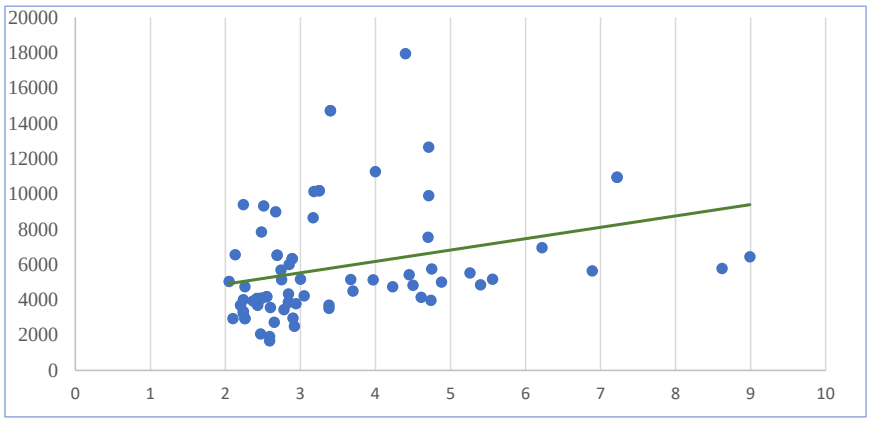

Figure 1. Triglyceride-Glucose Index

Note: The Correlation Curve between HOMA-IR and Triglyceride Glucose Index (r = 0.117; p=0.003)

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Reviewer	:	Reviewer 2
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Manuscript Title	:	M2023276 – Triglyceride-glucose Index and Insulin Resistance in PCOS

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?		
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?		
	Notes:		
3	Do the title and abstract reflect the study result/content?		
	Notes:		
4.	Is the significance of the study well explained at the Background?		
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	enough for publication?		
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7.	Are all figures and tables necessarily presented?		
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	Notes:		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?		
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Specific Reviewer's Comments and Suggestions:

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Sorry for not completing the review. It is necessary to clarify basic matters regarding the proportion of samples in the 2 groups.

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Reviewer 2

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Triglyceride-glucose Index as A Main Determinant Factor of Insulin Resistance in PCOS Women

Abstract

Background: The metabolic endocrine disorder Polycystic Ovary Syndrome, also known as PCOS affects 5-10% of women of childbearing age worldwide. PCOS involves various potential comorbidities, implicating reproductive and metabolic dysregulation. Insulin Resistance (IR) is one of the metabolic dysregulation in PCOS with a prevalence of 35%-80%. Thus, this study aims to correlate the most significant factor between hormone profile, metabolic-lipid profile, and anthropometric profile with IR in PCOS. Therefore, it is crucial to determine the association between these factors and insulin resistance occurrence in PCOS. Researchers aim to identify one of the factors most strongly associated with the incidence of insulin resistance in PCOS.

Methods: This study was conducted involving 76 PCOS women ranging from 20-35 years old defined by Rotterdam criteria at Yasmin Fertility Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia from July-December 2019. Participants were divided into 2 subgroups: 50 subjects of IR and 26 subjects of non-IR. Physical examination, gynaecological ultrasound examination and blood sampling were carried out on each participant.

Results: Age, weight, waist circumference, BMI, FG, fasting glucose, post-prandial glucose, prolactin, LDL, HDL, LH, FSH, TSH, FTI, TG-HDL ratio, LH-FSH ratio, and cholesterol level showed no significant differences. Contrary to fasting insulin ($p = <0.001$), SHBG ($p = 0.012$), and TG ($p = <0.001$) showed significant differences among non-IR and IR in PCOS subjects. Multivariate analysis showed significant differences in the TG-Glucose Index ($p = 0.023$).

Conclusion: TG-Glucose index is the most significant factor of IR occurrences in PCOS.

Commented [YL1]: Which hormone?

Commented [YL2]: Description of triglyceride-glucose index?

Keywords: Insulin Resistance, Lipid Metabolism, Polycystic Ovary Syndrome, Triglyceride-Glucose Index

Introduction

Polycystic Ovarian Syndrome, 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 were 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)

Polycystic ovary syndrome (PCOS) is frequently related to several significant multiple disorders, specifically insulin resistance and hyperandrogenism, which are accompanied by enduring long-term consequences such as obesity, Type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial cancer.(2)

Insulin Resistance (IR) is one of the most frequent characteristics of PCOS, with a prevalence varying from 35 and 80 percent.(3) IR is characterized by a reduced receptors response to insulin stimulation, which prevents target tissues from delivering glucose into cells, suppresses lipolysis, stimulates glycogen synthesis, and inhibits hepatic glucose.(4) Insulin resistance is quite common in women with PCOS. Although the prevalence of insulin resistance is independent of body mass index, obesity has been reported to be associated with an increased prevalence of insulin resistance in PCOS. Approximately 55-70% of obese PCOS experience insulin resistance, while non-obese PCOS show an incidence of insulin resistance of around 38-40%. This condition is in accordance with several publications which state that in PCOS, HOMA-IR is positively correlated with waist circumference, triglycerides, chronic low-grade inflammation, free testosterone, and free androgen index (FAI) and negatively

correlated with HDL cholesterol and steroid hormone binding globulin (SHBG).(5, 6) In addition, genetic, epigenetic factors, and prenatal androgen exposure are proven to play a significant role in the incidence of insulin resistance in PCOS women.(7, 8)

As a result, early recognition of IR, anthropometric profile, hormone profile, metabolic and lipid profile, in PCOS are crucial for optimal screening, prevention, and intervention. (9) However, there is a PCOS phenotype that does not show insulin resistance. This may be influenced by other causes such as central gonadotropin hormone dysregulation and hyperandrogenic state. (10, 11)

Compared to healthy women, with the same body mass index (BMI), women with polycystic ovary syndrome (PCOS) more often experience lipid metabolism disorders, which are characterized by increased total cholesterol, low-density lipoprotein (LDL), triglycerides, accompanied by low high-density lipoprotein (HDL) levels. In general, women with PCOS have a higher average BMI and waist circumference than those women without PCOS. (12) LH baseline tone and kisspeptin production were shown to be elevated in PCOS compared to the control group, despite the dynamic expression of the LH to FSH ratio. (13)

It has been widely reported that there are discrepancies in the lipid profile, hormone profile, anthropometric profile, and metabolic profile between women with PCOS and the control group concerning the occurrence of hyperandrogenism and insulin resistance. However, few studies of comparable characters have examined the association between the mentioned variables and the incidence of insulin resistance among PCOS subjects. (14)

Therefore, it is crucial to determine the association between these factors and insulin resistance occurrence in PCOS. Researchers aim to identify one of the factors most strongly associated with the incidence of insulin resistance in PCOS.

Commented [YL3]: There is a need for a sharper description of which variables are primary outcomes, as well as which variables are secondary outcomes

Methods

Study Design

An observational cross-sectional study was conducted on 76 women aged 20-35 years old at Yasmin Fertility Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia from July to December 2019. Approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia and Cipto Mangunkusumo General Hospital, indicated through reference number 929/UN2.F1/ETIK/IX/2017. Participants were then asked to complete an informed consent form.

Inclusion and Exclusion Criteria

PCOS condition was diagnosed according to the Rotterdam criteria, if 2 of the following 3 criteria were 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) This study excludes other following etiologies such as gynecological disorders, adrenal gland disease, hypothalamic-pituitary axis alterations, excessive prolactinemia, abnormal uterine bleeding of unknown cause, thromboembolic or cerebrovascular disorders and pregnancy. In addition, participants who are habitual smoker, consume alcohol, or have taken any hormonal prescription are not included in this study.

Commented [YL4]: How?

Research Process

Commented [YL5]: Description of triglyceride-glucose index?

This study included 76 reproductive aged women with PCOS were divided into 2 groups, consisting of 50 PCOS women with insulin resistance and 26 PCOS women without insulin resistance. Prior to this research, all participants were provided with comprehensive information of the study and had provided their informed permission. Anamnesis and physical examination including measurement of waist circumference, body weight, height, and assessment of hirsutism according to the Ferriman-Gallwey Score (FGS) were carried out on participants who met the inclusion criteria.

Commented [YL6]: 50 IR, 26 non IR

Each participant fasted for around 8-12 hours beforehand and then collected approximately 10 ml of their venous blood to be stored in several Vacutainers. Two hours after consuming a high-calorie intake, or a carbohydrate intake of 75 g, venous blood was collected to assess 2-hour postprandial glucose status. Samples from venous blood are needed to measure blood glucose, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Prolactin levels, total cholesterol, HDL, LDL, Triglycerides, SHBG, FSH, LH, TSH, testosterone, and Free Testosterone Index (FTI).

Commented [YL7]: For what purposed in this current study?

Fasting and two hours post-prandial blood glucose were assessed using the ARCHITECT glucose reagent kit (Abbott Diagnostics, Illinois, USA). Plasma insulin was measured using the ARCHITECT insulin reagent kit (Abbott Diagnostics, Illinois, USA). Fasting insulin (IU/ml) multiply by fasting plasma glucose (mg/dL) and divided by 405 was used to calculate HOMA-IR.

ADVIA Centaur Prolactin Kit (Siemens Healthineers Global, New York, United States), Sekisui cholesterol (Siemens Healthineers Global, New York, United States), ADVIA Triglyceride reagent kit (Siemens Healthineers Global, New York, United States) and ADVIA Centaur Immunoassay SHBG Kit (Siemens Healthineers Global, New York, USA) were used to assess cholesterol prolactin total, HDL-C, LDL-C, Triglycerides and SHBG respectively.

ADVIA Chemical TSH Reagent Kit (Siemens Healthineers Global, New York, USA), ADVIA Centaur LH Kit (Siemens Healthineers Global, New York, United States), and ADVIA Centaur FSH Kit (Siemens Healthineers Global, New York, United States) were used for determine the concentrations of TSH, LH and FSH respectively.

Testosterone levels were measured using the Testosterone kit (Roche Diagnostics, Risch-Rotkreuz, Switzerland), and total testosterone (nmol/L) divided by SHBG (nmol/L) multiplied by 100 is the formula used to calculate the Free Testosterone Index (FTI). Excessive

terminal hair growth in certain areas of the female body that is specific to males, called hirsutism, is measured by the visual instrument Ferriman Gallwey score (FGS).

During the FGS examination, nine androgen sensitive areas were assessed, and each area was assigned a score between 1 and 4 based on the density of hair growth. Areas studied include upper lip, mandible, chest, upper abdomen, lower abdomen, upper arms, upper back and lower back. Hirsutism diagnosis rates vary depending on race and ethnicity. As a final result of FGS, the equal cumulative score of 8 or higher is consistent with hirsutism.

The subjects were classified into 2 groups based on the presence of insulin resistance. Insulin resistance was defined by a high score of HOMA-IR. The cut-off for HOMA-IR in this study was set at 2.69. The primary outcome of this study was the association between anthropometric and lipid profiles with insulin resistance and also factors that contribute to the insulin resistance condition in PCOS women.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17.0, SPSS Inc., Chicago, Illinois, 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 insulin resistance and PCOS without insulin resistance, using an independent T test, and the Mann-Whitney U test involving independent variables include age, body mass index (BMI), weight, height, waist circumference, fasting glucose, 2 hours postprandial glucose, fasting insulin, HOMA-IR, LDL, HDL, triglycerides, SHBG, TSH, LH, FSH, and testosterone. A p value of less than or equal to 0.05 is considered statistically significant and logistic regression analysis is applied to several independent variables that have a p-value of less than 0.25.

Results

Seventy-six women with PCOS were recruited into this study, which were then divided into 2 groups; 24 PCOS with insulin resistance and 52 PCOS without insulin resistance. The median age of the subjects was 28 (23-35) years, with the BMI mostly classified as overweight (according to the Asia Pacific World Health Organization classification), and indicating central obesity (81.57%). Average fasting glucose level of subjects was 89.33 ± 7.77 mg/dL, while average postprandial glucose level was 112.5 (56-237) mg/dL. As for the lipid profile of subjects, the median LDL was 128.5 (59-239) mg/dL, the average HDL was 42.51±6.59 mg/dL, and the median triglyceride was 109.5 (45-390) mg/dL. A total of 65.8% of participants had insulin resistance in this study. Participant characteristics are shown in Table I.

Commented [YL8]: Amounts that differ from those listed on page 4

Using bivariate analysis, significant differences between insulin resistance and some variables such as fasting insulin level ($p < 0.001$), triglyceride level ($p = 0.001$), SHBG level ($p = 0.032$), TSHs level ($p = 0.041$), and triglyceride/HDL level ($p = 0.003$). The result of the bivariate analysis in this study can be found in Table II.

Multivariate analysis was carried out using logistic regression, involving 13 variables with a p-value of less than 0.25. Among these variables, body mass index and triglyceride were found to be important determinants of insulin resistance conditions in PCOS participants. The result of the multivariate analysis in this study can be found in Table III.

Based on correlation analysis, there was no association between insulin levels and SHBG production in PCOS women with and without insulin resistance. The result of the correlation analysis in this study can be found in Table IV.

Based on correlation analysis we observed a weak positive correlation between the TG-glucose index and HOMA-IR with ($p = 0.003$) and ($r = 0.117$). The result of the correlation analysis in this study can be found in Figure 1.

Discussion

This research was conducted to determine the various factors impacting insulin resistance conditions in PCOS subjects. Insulin resistance is characterized by a decrease in insulin sensitivity and an increase in insulin necessity for metabolism. Indirectly, insulin resistance was determined by multiplying fasting insulin by fasting glucose and dividing the result by 405. This study applied a cut-off of 2.69 for insulin resistance, which matches studies conducted on Chinese PCOS subjects (15). In this study, the insulin resistance of 76 PCOS participants was evaluated. Fifty (65.8%) of the individuals were determined to have insulin resistance with Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values of 2.69 or greater (15).

Attributing to insulin resistance, the HOMA-IR cut-off value determined in this study is consistent with the HOMA-IR results obtained from the Asian PCOS subjects (7). HOMA-IR appears to be equally prevalent in European populations. This is likely due to the similarity between HOMA-IR examination methods. However, the Croatian PCOS population was reported to have a higher HOMA-IR value, which may correlate with the participant's Body Mass Index (BMI). (16)

Insulin resistance and hyperinsulinemia are known to have a negative impact on metabolic effects of the adipose tissue i.e. decreased glucose uptake, increased lipid accumulation, and decreased lipid decomposition; decreased insulin sensitivity in skeletal muscle; decreased glycogen synthesis, decreased Sex Hormone-Binding Globulin (SHBG) secretion, and increased Insulin-Like Growth Factor-1 (IGF-1) in the liver. In addition, high insulin levels in women with insulin resistance have a negative impact on reproductive function, specifically an increased Luteinizing Hormone (LH) production by the Anterior Pituitary as a result of an increased Gonadotropin-Releasing Hormone (GnRH) pulsatile release in the Hypothalamus. (8) Hyperinsulinemia condition can also disrupt the balance between the Hypothalamic Pituitary Ovary (HPO) Axis and the Hypothalamic Pituitary

Adrenal (HPA), this is due to an increased Adrenocorticotropic Hormone (ACTH) by the adrenal glands. (8)

In our study, PCOS subjects with insulin resistance had lower SHBG levels than PCOS subjects without insulin resistance. This finding is consistent with findings from numerous studies addressing the decreased production of SHBG in PCOS women with insulin resistance. This condition correlates with insulin resistance which will lead to increased delivery of monosaccharides to the liver; increased lipolysis of adipose tissue, which produces non-esterified fatty acids (NEFA), which stimulate gluconeogenesis and lipogenesis; increase in the proinflammatory cytokine TNF-alpha; as well as an increase in De Novo Lipogenesis (DNL) followed by a decrease in HNF-4 alpha production and ends with a decrease in SHBG production. (17)

In this study, the PCOS group with insulin resistance had lesser LDL levels, whereas there was no difference in HDL levels between the two groups. Furthermore, the PCOS group with insulin resistance had higher triglycerides (TG) levels, and TG to HDL ratios compared to PCOS groups without insulin resistance. (18) Multivariate analysis showed a significant association between the TG-Glucose index and insulin resistance in PCOS.

Dyslipidemia is a common metabolic complication affecting up to 70% of PCOS-affected women. Multiple factors are known to contribute to the disruption of lipid metabolism and dyslipidemia. Insulin Resistance performs a crucial role by predominantly stimulating lipolysis and altering the expression of lipoprotein lipase and hepatic lipase. Under conditions of insulin resistance, non-esterified fatty acids are transported from muscle and adipose tissue to the liver, thereby augmenting the substrate for TG biosynthesis. (18, 19)

In this study, the PCOS group with insulin resistance had higher triglyceride levels than the PCOS group without insulin resistance, but the ratio of triglyceride to HDL and fasting triglyceride-glucose index did not differ between the two groups. In contrast, multivariate

analysis revealed a substantial association between the fasting triglyceride-glucose index and the occurrence of IR in PCOS.

In China, Peru, India, and Taiwan, researchers found a significant correlation between TG/HDL and the incidence of insulin resistance in polycystic ovary syndrome (PCOS). (5, 20) However, our findings are consistent with the study conducted on African-American populations (21, 22), which indicates that the Triglyceride to HDL ratio is unreliable for determining insulin resistance.

In addition, as an IR marker for PCOS, the fasting triglyceride-glucose index is a practical and inexpensive test with a high degree of reliability, in accordance with the findings of our study which are validated by studies conducted in Iran, Iraq and China. (5, 23, 24)

Weight reduction of about 5-10% is recommended for overweight and obese women, in an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day) applied. Weight loss will result in a significant reduction in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and fasting insulin. (25, 26) This has shown a significant improvement in secondary reproductive outcomes such as a decrease in free androgen index (FAI), testosterone (T), hirsutism (Ferriman-Gallwey score), and increasement in sex hormone-binding globulin (SHBG). In addition, a weight reduction of more than five percent can significantly improve menstrual periods, increase fertilization, increase live births, follicular development and reduce ovarian volume. (25, 26)

Research has shown that dietary patterns have a significant role in the management of polycystic ovary syndrome (PCOS). It is recommended that subjects with PCOS uphold specific diet namely low-fat, high-protein, low-glycemic index (GI) to glycemic load (GL) ratio, and enriched with monounsaturated fatty acid (MUFA). (25). A study revealed that adopting a nutritious diet that includes adequate amounts of fruits, vegetables, whole grains, seeds, nuts, legumes, and low-fat dairy, whereas mostly consisting of carbohydrates with a low

glycemic index, is the optimal approach for decreasing insulin resistance. In addition, a vegetarian diet showed a decrease in inflammatory markers (CRP, resistin, and adiponectin) when compared with a meat-based diet. According to the international evidence-based guideline for the assessment and management of PCOS (2018), individuals are recommended to engage in 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity each week to avoid weight gain. For weight reduction and prevention of weight regain, a higher level of physical activity is advised, particularly 250 minutes of moderate physical activity or 150 minutes of vigorous physical activity exercise per week. (27) In addition, there were significant negative correlations between the suggested intake of several micronutrients (vitamin C, B6, niacin, and iron) and the FAI development in PCOS women. (28)

The study's sample size is constrained and certain exclusion criteria obtained solely from anamnesis and physical examination such as moderate adrenal gland disease, thromboembolic disorder, alcohol intake, and frequent smoking, all of which may impact the statistical power of this study.

Conclusion

This study is conducted to determine the association of lipid profile, hormone profile, anthropometric profile, and metabolic profile among PCOS subjects with insulin resistance. In this study, triglyceride was found higher in PCOS with insulin resistance compared to PCOS without insulin resistance. The results of the bivariate analysis showed no difference in the triglyceride-glucose index between PCOS with insulin resistance and PCOS without insulin resistance. The triglyceride-glucose index appears to have a significant association with the occurrence of insulin resistance in PCOS, based on the results of the multivariate analysis. It is recommended to continue the study by expanding the PCOS subjects with varying BMI and matched controls.

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Figures/Tables

Table I. Characteristics of the Study Population

Characteristic	Value (n = 76)
Demographic and Anthropometric Profile	
Age	28 (23 – 35) years
Weight	71.87 ± 13.15 kg
Waist Circumference	92.01 ± 9.80 cm
Body Mass Index	27.78 (20.75 – 39.77) kg/m^2
Ferriman-Gallwey Score	3 (1 – 11)
Metabolic and Lipid Profile	
Fasting Glucose	89.33 ± 7.77 mg/dL
Postprandial Glucose	112.5 (56 – 237) mg/dL
Fasting Insulin	14 (9 – 37) µIU/mL
LDL	128.5 (59 – 239) mg/dL
HDL	42.51 ± 6.59 mg/dL
Triglyceride	109.5 (45 – 390) mg/dL
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)
Hormone Profile	
LH to FSH Ratio	1.76 ± 0.84 µIU/mL
SHBG	21.5 (7 – 66) nmol/l
TSH	2 (0 – 9) µIU/mL
LH	10.68 ± 4.48 µIU/mL
FSH	6 (2 – 10) µIU/mL
Prolactin	9 (4 – 32) ng/mL
FTI	5 (1 – 31) ng/dL

Note: Numerical variables with normal data distribution are presented as mean ± standard deviation, while numerical variables with abnormal data distribution are presented as median (minimum–maximum value).

Abbreviations: HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein, TG = Triglyceride, BMI = Body Mass Index, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone, SHBG = Sex Hormone-Binding Globulin, TSH = Thyroid Stimulating Hormone, FTI = Free Testosterone Index.

Table II. Characteristic Comparison of Insulin Resistance and Non-Insulin Resistance among PCOS Women

Characteristic	Group		*p* value
	Non-Insulin Resistance	Insulin Resistance	
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
Waist Circumference (cm)	89.08 ± 8.67	93.54 ± 10.07	0.731
Body Mass Index (kg/m^2)	26.95 (20.75 – 34.10)	29.49 (21.91 – 39.77)	0.204
Ferriman-Gallwey Score	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
Triglyceride (mg/dL)	85 (45 – 236)	123 (65 – 390)	<0,001
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
TG Glucose Index	4248 (1680 – 9393)	6687 (2503 – 17.940)	0.238
Total Cholesterol (mg/dL)	206.79 ±21.20	203.98 ± 39.98	0.696
Hormone Profile			
Prolactin (ng/ml)	9 (5 – 26)	9.5 (4 – 32)	0.831
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
FTI	4 (2 – 31)	6 (1 – 18)	0.108
LH to FSH Ratio	1.90 ± 1.13	1.71 ± 0.72	0.489

Note*:* Numerical variables with normal data distribution were analyzed using an independent T-test and are presented as mean ± standard deviation, while numerical variables with abnormal data distribution were analyzed using the Mann-Whitney test and are presented as median (minimum–maximum value).

Abbreviations: HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein, TG = Triglyceride, BMI = Body Mass Index, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone, SHBG = Sex Hormone-Binding Globulin, TSH = Thyroid Stimulating Hormone, FTI = Free Testosterone Index.

Table III. Multivariate Regression Analysis.

Biochemical Parameter	Odds Ratio	95% Confidence Interval	*p Value*
Triglyceride Glucose Index	5.625	1.668 – 18.971	0.005

Abbreviations: OR = Odds Ratio, CI = Confidence Interval.

Table IV. Correlation between SHBG and Insulin among PCOS Subjects with Insulin Resistance and without Insulin Resistance.

Variables	SHBG PCOS Non-IR	SHBG PCOS IR
Insulin PCOS Non-IR	r: -0.278 p: 0.169	
Insulin PCOS IR		r: -0.168 p: 0.239

Abbreviations: IR = Insulin Resistance, p = p value, PCOS = Polycystic Ovary Syndrome, r = Coefficient Correlation, SHBG = Sex Hormone-Binding Globulin.

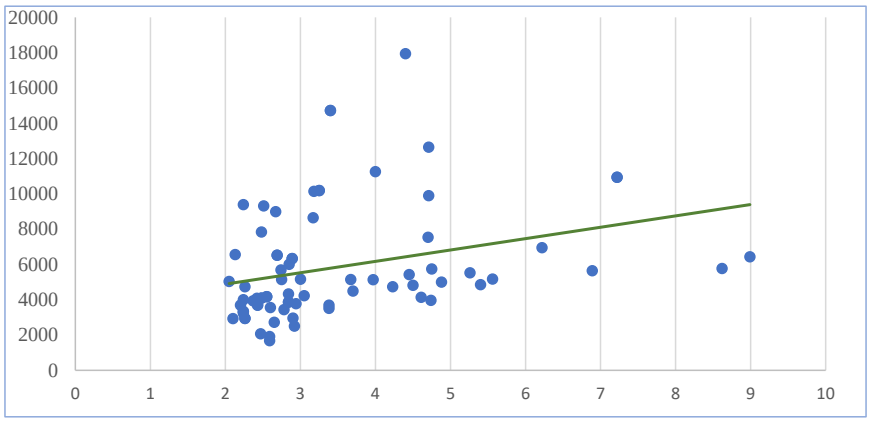

Figure 1. Triglyceride-Glucose Index

Note: The Correlation Curve between HOMA-IR and Triglyceride Glucose Index (r = 0.117; p=0.003)

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[InaBJ] M2023276 Editor Decision Round 1 - Resubmit for Review

Ferry Sandra <ferry@trisakti.ac.id> Mon, Nov 20, 2023 at 10:04 AM
To: Secretariat of InaBJ <secretariatinabj@gmail.com>

Dear Secretariat of The Indonesian Biomedical Journal,

Please find the revised version of the manuscript M2023276 for review round 1. The comments from the reviewers have been revised accordingly.

Thank you.

Regards,
Ferry Sandra
[Quoted text hidden]
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Ferry Sandra, D.D.S., Ph.D.
Head of Medical Research Center
Universitas Trisakti

Round 1 Revised - M2023276 Manuscript.docx
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Triglyceride-Glucose Index as A Crucial Marker for Polycystic Ovary Syndrome Women with Insulin Resistance

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

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, Inclusion and Exclusion Criteria, Ethical Approval

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). The subjects were scored on a scale of 0–4 for terminal hair growth on eleven different body areas.

Glucose Profiling

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 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)

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 Statistical Package for the Social Sciences (SPSS), version 17.0 (SPSS Inc., Chicago, IL, 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 with IR and 26 PCOS without IR. The median age was 28 years old, the median BMI was 27.78 kg/m^2, 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 with and without IR

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 with and without IR

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 with and without IR

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-value of <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 occurance in PCOS women after multivariate analysis using logistic 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 adrenocorticotropic 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 of non-esterified fatty acids (NEFA). This will stimulate gluconeogenesis and lipogenesis; and increase the proinflammatory cytokine TNF-alpha as well as *de novo* lipogenesis (DNL) followed by the decrease of Hepatocyte nuclear factor alpha (HNF-4α) 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, the 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 the TyGI and IR occurrence in PCOS subjects. According to the reports of several studies conducted in Iran, Iraq, and China (8,22,23), the current study has shown that the TyGI

is a practical and inexpensive test with a high degree of reliability for PCOS women with IR. A positive correlation between the TyGI and the prevalence of metabolic syndrome in women with PCOS has been reported as well.(24) The TyGI was found to be independently correlated with hypertension, obesity, central obesity, hyperglycemia, and dyslipidemia in women with PCOS.(24)

Conclusion

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

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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; 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 Insulin Resistance

Characteristic	Non-Insulin Resistance (n=26)	Insulin Resistance (n=50)	*p*
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
Ferriman-Gallwey Score	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 – 17.940)	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; 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.

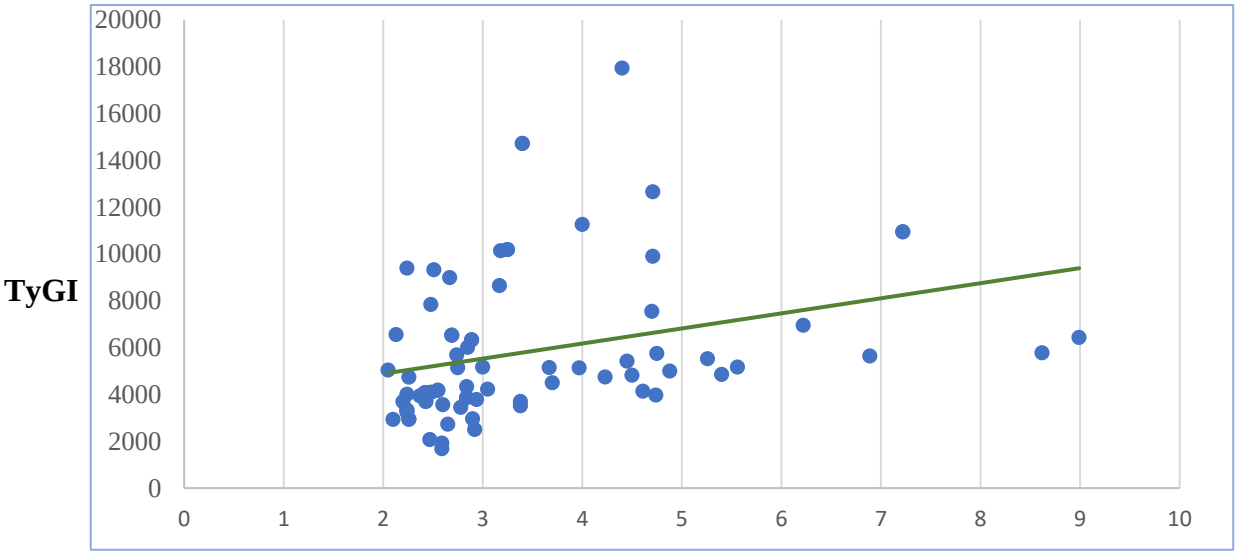

Figure 1. Positive correlation was observed between HOMA-IR and TyGI in PCOS subjects (r=0.117; p=0.003)

UNIVERSITAS TRISAKTI

Ferry Sandra <ferry@trisakti.ac.id>

[InaBJ] M2023276 Editor Decision - Manuscript Accepted

Secretariat of InaBJ <secretariatinabj@gmail.com> Fri, Feb 16, 2024 at 10:46 AM
To: ferry@trisakti.ac.id

Dear Dr. Ferry Sandra,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Triglyceride-Glucose Index as A Crucial Marker for Polycystic Ovary Syndrome Women with Insulin Resistance**."

Our decision is to: **Accept Manuscript.**

Your manuscript has been reviewed, and our reviewers have agreed to accept your manuscript with minor revision. Please find the manuscript review form attached.

Your manuscript will be sent to our publisher for typesetting and you should receive the proofreading in due course.

Congratulations on your interesting research, and thank you for allowing us to publish this valuable material. Please let us know once you have read this email. We wish you a nice day.

Best Regards,
--
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Manuscript Review Form

Reviewer	:	Reviewer 3
Manuscript #	:	M2023276
Manuscript Title	:	Triglyceride-Glucose Index as A Crucial Marker for Polycystic Ovary Syndrome Women with Insulin Resistance

No.	Manuscript Components	Yes	No
1.	Does this manuscript present new ideas or results that have not been previously published?	√	
	Notes:		
2.	Are the title and abstract of the manuscript appropriate?	√	
	Notes:		
3	Do the title and abstract reflect the study result/content?	√	
	Notes:		
4.	Is the significance of the study well explained at the Background?	√	
	Notes:		
5.	Are the research study methods technically correct, accurate, and complete enough to be reproduced/cited by other scientists?	√	
	Notes: A little suggestions, maybe the sub-section title of “Study Design, Inclusion and Exclusion Criteria, Ethical Approval’ can be simplified.		

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6.	Are the results, ideas, and data presented in this manuscript important enough for publication?	√	
	Notes:		
7.	Are all figures and tables necessarily presented?	√	
	Notes:		
8.	Is there a logical flow of argument in the Discussion which elucidate all the presented/obtained data?	√	
	Notes:		
9.	Are the conclusions and interpretations valid and supported by the data?	√	
	Notes:		
10.	Is the manuscript clear, comprehensible, and written in a good English structure?	√	
	Notes:		

Specific Reviewer's Comments and Suggestions:

(These comments may be in addition to or in lieu of reviewer comments inserted into the text of the manuscript. Use as many lines as needed.)

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Reviewer's Recommendation (Please tick only one option)	√
Accept Submission (No significant alterations suggested)	√
Revisions Required (Suggest changes to the manuscript as specified in this review)	
Resubmit for Review (Major revisions should be made and suggestions as specified in this review must be addressed. Revised manuscript should be resubmitted to the reviewer for further review)	
Decline Submission (Do not encourage a rewrite, manuscript is totally rejected)	

Further Reviewer's Comments Regarding Disposition of the Manuscript:

Manuscript is good enough, only a little suggestion in the Methods section.

Date and Sign:
February 15, 2024

Reviewer 3
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