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Evaluation of Insulin Resistance Measurement Methods in Patients with Polycystic Ovary Syndrome

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ABSTRACT

Aim: This study aims to compare insulin resistance (IR) measurement methods in women with and without polycystic ovary syndrome (PCOS) who have the same body mass index.

Material and Methods: There were 84 women with PCOS and non-PCOS (n=18 normal weight and n=24 overweight/obese in both groups). Triglyceride glucose index (TyG), assessment of insulin resistance with homeostasis model (HOMA-IR), visceral adiposity index (VAI) were calculated using lipid level, glucose level and anthropometric measurements. Mann-Whitney U or Student's t-test was used to compare measurements between the groups. The relationship between HOMA-IR and age was calculated with the Pearson correlation test, and the relationship between HOMA-IR and TyG was calculated with the Spearman correlation test. p<0.05 was considered significant.

Results: Triglyceride levels, insulin, TyG, and HOMA-IR were higher in the PCOS group than in the non-PCOS group (p=0.003, p=0.001, p=0.006, p=0.001, respectively). In the PCOS group, there was a negative correlation between HOMA-IR and age (r=-0.399, p=0.024), and a positive correlation between HOMA-IR and TyG index (r=0.776, p<0.001). TyG index and HOMA-IR were higher in normal weight PCOS women than non-PCOS (p=0.002, p=0.003, respectively), however there was no difference in overweight/obese PCOS women and non-PCOS. In PCOS patients, a TyG index >3.91 (89.5% sensitivity, 76.9% specificity) predicted insulin resistance (IR).

Conclusion: TyG and HOMA-IR levels are higher in women with PCOS than non-PCOS. The TyG index can be used as an alternative method in evaluating insulin resistance among these patients.

Keywords: *Polycystic ovary syndrome, Insulin resistance, TyG, VAI, HOMA-IR*

Polikistik Over Sendromlu Hastalarda İnsülin Direnci Ölçüm Metodlarının Değerlendirilmesi

ÖZ

Amaç: Bu çalışmada polikistik over sendromlu (PKOS) kadınlarda insülin direnci (IR) ölçüm metodlarının, aynı beden kütle indeksine sahip PKOS olmayan kadınlarla karşılaştırılması hedeflenmiştir.

Gereç ve Yöntemler: Çalışmamıza PKOS (n=18 normal kilolu ve n=24 hafif kilolu/obez) ve PKOS olmayan (n=18 normal kilolu ve n=24 hafif kilolu/obez) toplam 84 kadın dahil edildi. Lipit düzeyi, glukoz düzeyi ve antropometrik ölçümler kullanılarak trigliserid glukoz indeksi (TyG), insülin direncinin homeostaz modeliyle değerlendirmesi (HOMA-IR), visseral adipozite indeksi (VAI) hesaplandı. PKOS olan ve olmayan gruplar arasında ölçüm değerlerinin karşılaştırılmasında Mann-Whitney U test ya da Student t-test kullanıldı. HOMA-IR ile yaş arasındaki ilişki Pearson korelasyon testi, HOMA-IR ile TyG arasındaki ilişki Spearman korelasyon testi ile hesaplandı. p<0.05 anlamlı kabul edildi.

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Bulgular: PKOS grubunda PKOS olmayan gruba göre trigliserid düzeyi, insülin, TyG ve HOMA-IR yüksek bulundu (sırasıyla; p= 0.003, p=0.001, p=0.006, p=0.001). PKOS grubunda HOMA-IR ile yaş arasında negatif korelasyon (r=-0.399, p=0.024), HOMA-IR ile TyG indeksi arasında pozitif korelasyon (r=0.776, p< 0.001) tespit edildi. Normal kilolu PKOS'lu kadınlarda PKOS olmayanlara göre TyG indeksi ve HOMA-IR yüksek bulundu. (sırasıyla p=0.002, p=0.003). Ancak hafif kilolu/obez PKOS'lu kadınlarda PKOS olmayanlara göre fark görülmedi. PKOS hastalarında TyG indeksinin >3.91 olması (%89.5 sensivite, %76.9 spesifite) insulin rezistansını (IR) predikte etti.

Sonuç: PKOS'lu kadınlarda PKOS olmayanlara göre TyG ve HOMA-IR düzeyleri yüksektir. Bu hastalarda insulin rezistansı değerlendirilmesinde TyG indeksi alternatif bir metod olarak kullanılabilir.

Anahtar Sözcükler: *Polikistik over sendromu, İnsülin direnci, TyG, VAİ, HOMA-IR*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and ovulatory dysfunction, accompanied by prevalent endocrine and metabolic abnormalities (1). PCOS is one of the most common causes of infertility in women of reproductive age, with a prevalence ranging from 5%-10% (1). Hyperinsulinemia is associated with clinical findings in PCOS patients and plays a vital role in its pathogenesis (2).

As reported in previous studies, hyperinsulinemia induces the development of insulin resistance (IR), type 2 diabetes, and cardiovascular diseases in women with PCOS (3,4), and thus it is crucial to detect IR and related metabolic dysfunction earlier. Homeostasis model assessment of insulin resistance (HOMA-IR) is widely used to detect IR, where euglycemic/hyperinsulinemic clamp is accepted as the gold standard testing method (5-7).

Recently novel models have been suggested to work as effective as previous tests in detecting IR (6,7). Triglyceride and glucose (TyG) index is one such method and is closely associated with cardiovascular diseases, notably atherosclerosis (8-10).

Consequently, the visceral adiposity index (VAI) is considered an anthropometric indicator that indirectly predicts the risk of cardiometabolic complications (11). VAI is a reliable marker of adipose tissue dysfunction in patients with PCOS (12). This study aimed to compare insulin resistance measurement methods in women with PCOS and investigate the association between these models and PCOS.

MATERIAL and METHODS

The participant group was selected sequentially among the patients admitted to the Department of Endocrinology and Metabolic Diseases of Farabi Hospital, Karadeniz Technical University Faculty of Medicine between June 2021- November 2021.

The PCOS diagnosis was based on the presence of at least two out of three of the following criteria: chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovary detection during ultrasound imaging. (13).

Patients below 18 years and above 35 years; patients with a body mass index (BMI) of <18.50 kg/m^{2}and of >34.99 kg/m^2; patients with hypothyroidism, diabetes mellitus, and other chronic diseases; pregnant women; patients under treatment with drugs such as metformin, pioglitazone, and patients using oral contraceptives in the last one year were excluded from the PCOS group.

The non-PCOS group was selected sequentially from healthy volunteers who visited our medical outpatient clinic for the general examination. Volunteer inclusion criteria were as follows: having regular menstrual cycles, no chronic diseases and under treatment with drugs, no clinical findings of Cushing's syndrome etc., and no evidence of clinical hyperandrogenemia.

Patients with BMI ≥35 kg/m^2 were not included in the study because of the low reliability of waist circumference measurement. Height, weight, BMI, waist circumference (WC), hip circumference (HC), body fat ratio, and amount of body fat of participants were recorded by endocrinology specialists and physicians (BC-418 total body composition analyzer). Waist circumference was measured from the midpoint between the lower rib edge and the top of the iliac crest at the end of the exhalation, whereas the HC was measured from the greater trochanter level. The waist-to-hip ratio was calculated as waist circumference divided by the HC. BMI of 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, and 30-35.0 kg/m^2 were classified, as normal-weight, overweight and obese, respectively (14).

Blood pressure was measured using a mercury sphygmomanometer in the sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were recorded (15), and mean arterial pressure was calculated based on the following formula: 1/3*SBP + 2/3*DBP. Patients with PCOS were grouped and divided as hyperandrogenic polycystic ovary syndrome (HA-PCOS) and normoandrogenic polycystic ovary syndrome (NA-PCOS) based on the total testosterone level (total testosterone level ≥75 ng/dl and <75 ng/dl, respectively).

The formulas used for calculating the ratio of total cholesterol to high-density lipoprotein cholesterol (Total-C/HDL-C), triglyceride to high-density lipoprotein cholesterol (triglyceride/HDL-C), TyG index, HOMA-IR, and VAI are given below (16-18).

Total-C/HDL-C: Total-C (mg/dL) / HDL-C (mg/dL)

Triglyceride/HDL-C: Triglyceride (mg/dL) / HDL-C (mg/dL)

TyG index: Ln (Triglycerides (mg/dL) × Fasting plasma glucose (mg/dL)/2)

HOMA-IR = Fasting glucose (mIU/L) × Insulin (mg/dl)/405

VAI: [WC (cm) / (36.58 + (1.89 x BMI)] × [Triglycerides (mmol/L) / 0.81] × [1.52 / HDL-c (mmol/L)]

Conversion factor: 1 mg/dL = 0.0555 mmol/L

HOMA-IR levels of >2.5 was considered IR (19, 20)

Biochemical Analysis

Blood samples were collected in the morning after 12 hours of fasting. Glucose, Lipid parameters (Total-c, HDL-c, low-density lipoprotein (LDL-c) and triglyceride levels), alanine aminotransferase (ALT) were measured using the enzymatic colorimetric method with a Beckman Coulter AU5800 (Shizuoka, Japan) autoanalyzer with the manufacturer's original kits. Insulin levels were determined by the chemiluminescent immunometric method using an Immulite Insulin kit (Siemens, Munich, Germany). Normal ranges for glucose, creatinine, Total-c, HDL-c, LDL-c, triglyceride, ALT, thyroid-stimulating hormone (TSH) level, total testosterone were defined as 70-100 mg/dl, 0.51-0.95 mg/dl, 120-200 mg/dl, 45-65 mg/dl, <160 mg/dl and 50-150 mg/dl, 0-45 U/L, 0.41-6.80 mIU/L, 10-75 ng/dl respectively.

Statistical Analysis

All statistical analyses were performed with the SPSS 23.0 software package (SPSS, Inc., Chicago, Illinois). Descriptive statistics for the continuous variables were expressed as mean ± SD or median (IQR), and categorical variables were noted as numerics and percent (%). The normal distribution of the variables was checked by the Shapiro-Wilk test. Student T-test was used to compare independent groups with normal distribution, and Mann Whitney U (MWU) test was used for those that are not normally distributed. Pearson correlation analysis was used to analyze correlations between normally distributed variables, and Spearman correlation analysis was used to analyze non-normally distributed variables. Receiver operating characteristics curve analysis was used to investigate the ability of the TyG index to predict IR. In evaluation of the area under the curve, cases with Type-1 error level below 5% was interpreted as the diagnostic value of the test was statistically significant. $p<0.05$ was considered statistically significant.

At the beginning of the study, the sample size was calculated using the OpenEpi version 3.01 program. Unger et al.'s (21) research was taken as reference. In this study, TyG index was compared in patients with and without metabolic syndrome, and found that the mean TyG index of the metabolic syndrome group was 9.6% higher than the control group. Accordingly, the minimum sample size required for the planned study was 16 participants, with 95% confidence interval and 80% power. A post hoc power analysis using OpenEpi version 3.01 was used to determine the power of the present study. With α of 0.05 and a sample size of 42 per group, a power of 0.89 was achieved.

RESULTS

A total of 84 participants divided into the PCOS (n = 42) and non-PCOS (n = 42) groups were included in the study. The PCOS and non-PCOS groups had similar age and BMI characteristics ($p = 0.296$ and $p = 0.464$, respectively).

The mean age of menarche in patients was 12.93±1.45 years, and the mean level of total testosterone was 70.70±25.09 ng/dl.

The triglyceride and insulin levels were significantly higher in the PCOS group compared with the non-PCOS group ($p = 0.003$ and $p = 0.001$, respectively). There were no differences in other anthropometric measurements and biochemical results between the two groups (Table 1). TyG index and HOMA-IR levels were significantly higher in the PCOS group compared with the non-PCOS group ($p = 0.006$ and $p = 0.001$, respectively). There was no significant difference between the two groups in VAI, Total-C/HDL-C, and triglyceride/HDL-C (Table 1).

There was a negative correlation between HOMA-IR and age in the PCOS group ($r = -0.399$, $p = 0.024$) and a positive correlation between HOMA-IR and TyG index ($r = 0.776$, $p < 0.001$). No correlation was found between other insulin resistance methods and variables. ($p > 0.05$). A comparison between participants in the PCOS group (n = 18) with normal BMI and the non-PCOS group (n = 18) indicated that the TyG index and HOMA-IR were significantly higher in the PCOS group ($p = 0.002$ and $p = 0.003$, respectively), while there was no significant difference in other parameters. There was no significant difference in the indexes between participants in the PCOS group (n = 24) with overweight/obese BMI and the non-PCOS group (n = 24) (Table 2).

Table 1: Clinical and biochemical parameters of the polycystic ovary syndrome and non-PCOS group.

Parameters	PCOS (n= 42)	Non-PCOS (n= 42)	*p*
Age (years) [a]	24.65 ± 4.17	25.71 ± 4.46	0.296 [c]
BMI (kg/m²) [a]	27.28 ± 5.58	26.37 ± 4.52	0.464 [c]
TANITA [a]			
Body fat (%)	31.16 ± 10.81	32.23 ± 7.83	0.644 [c]
Body fat mass (kg)	23.66 ± 12.30	23.54 ± 9.28	0.961 [c]
Trunk fat (%)	27.35 ± 13.34	29.76 ± 8.71	0.387 [c]
Trunk fat mass (kg)	11.38 ± 6.97	11.70 ± 4.75	0.826 [c]
Waist circumference (cm) [a]	85.65 ± 13.04	86.89 ± 12.52	0.467 [c]
Hip circumference (cm) [a]	104.90 ± 11.15	104.60 ± 9.97	0.906 [c]
Waist-to-hip ratio (%) [a]	80.61 ± 8.07	82.94 ± 7.53	0.218 [c]
Systolic pressure (mmHg) [a]	114.53 ± 10.87	113.15 ± 10.16	0.554 [c]
Diastolic pressure (mmHg) [a]	75.46 ± 8.83	73.02 ± 8.18	0.261 [c]
MAP (mmhg) [a]	88.48 ± 8.81	86.40 ± 7.99	0.303 [c]
Glucose (mg/dl) [a]	92.75 ± 9.07	90.36 ± 8.77	0.269 [c]
Creatinine (mg/dl) [a]	0.65 ± 0.09	0.66 ± 0.07	0.863 [c]
ALT (U/L) [a]	19.28 ± 13.29	16.57 ± 8.52	0.308 [c]
Total-c (mg/dl) [a]	201.37 ± 34.13	187.47 ± 38.83	0.120 [c]
Triglyceride (mg/dl) [a]	105.15 ± 56.85	79.57 ± 49.32	**0.003** [c]
LDL-c (mg/dl) [a]	120.75 ± 31.19	116.34 ± 31.78	0.562 [c]
HDL-c (mg/dl) [a]	59.43 ± 13.43	55.13 ± 11.48	0.153 [c]
Insulin (mIU/L) [a]	14.37 ± 9.56	8.19 ± 3.61	**0.001** [c]
TSH (mIU/L) [a]	2.39 ± 0.99	2.35 ± 1.18	0.881 [c]
TyG index [a]	3.97 ± 0.12	3.89 ± 0.11	**0.006** [c]
HOMA-IR [b]	2.57 (1.48)	1.77 (1.37)	**0.001** [d]
VAI [b]	2.51 (2.32)	2.16 (1.97)	0.220 [d]
Total-c / HDL-c [a]	3.52 ± 0.90	3.47 ± 0.73	0.779 [c]
Triglyceride / HDL-c [a]	1.94 ± 1.36	1.54 ± 1.10	0.076 [c]

[a] mean± standard deviation, [b] median (IQR), [c] Student T-test, [d] Mann-Whitney U test, **BMI:** Body mass index, **MAP:** Mean arterial pressure, **ALT:** Alanine aminotransferase, **Total-c:** Total cholesterol, **LDL-c:** Low-density lipoprotein cholesterol, **HDL-c:** High-density lipoprotein cholesterol, **TSH:** Thyroid-stimulating hormone, **TyG:** Triglyceride glucose index, **HOMA-IR:** Homeostasis model assessment of insulin resistance, **VAI:** Visceral adiposity index, p-values in bold are significant values.

There was no significant difference in TyG index, HOMA-IR, VAI, total-C/HDL-C values, and triglyceride/HDL-C values between patients with HA-PCOS (n = 22) and NA-PCOS (n = 20) classified based on elevated levels of biochemical androgen (Table 3). TyG indexes >3.91% (89.5% sensitivity, 76.9% specificity) in patients with PCOS (n = 42) predicted IR (area under the curve [AUC] = 0.889, IR = HOMA-IR > 2.5, p< 0.001) (Figure 1).

DISCUSSION

Approximately 50%-75% of women with PCOS having IR was reported (22). It was suggested that IR and compensatory hyperinsulinemia induced hyperandrogenism and chronic oligo-anovulation (23,24). Patients with PCOS are suspected of increased risk of metabolic syndrome, obesity, type 2 diabetes mellitus, and cardiovascular disease (25, 26).

Nevertheless, there is also increased in visceral fat in non-obese patients with PCOS (27). Visceral fat is associated with elevated triglycerides and hypertension (12). In the present study, patients with PCOS had higher triglycerides, insulin, TyG index, and HOMA-IR compared with women in the non-PCOS group with similar age and BMI. Furthermore, there was a strong positive correlation between the TyG index and HOMA-IR. IR's alteration in lipoprotein

Table 2: Comparison of insulin resistance (IR) measurement methods by body mass index.

Parameters		PCOS (n=18)	Non-PCOS (n=18)	*p*
Normal weight	**TyG index** [a]	3.95 ± 0.09	3.83 ± 0.10	**0.002** [c]
	HOMA-IR [a]	3.18 ± 1.83	1.32 ± 0.75	**0.003** [c]
	VAI [b]	2.23 (0.84)	1.77 (1.00)	0.224 [d]
	Total-c /HDL-c [a]	3.15 ± 0.59	3.37 ± 0.75	0.400 [c]
	Triglyceride/HDL-c [b]	1.26 (0.47)	0.98 (0.56)	0.110 [d]
		PCOS (n=24)	**Non-PCOS (n=24)**	***p***
Overweight / Obese	**TyG index** [a]	3.98 ± 0.15	3.93 ± 0.09	0.223 [c]
	HOMA-IR [a]	3.47 ± 2.82	2.25 ± 0.79	0.092 [c]
	VAI [a]	4.04 ± 2.23	3.08 ± 1.45	0.128 [c]
	Total-c /HDL-c [a]	3.81 ± 1.01	3.54 ± 0.72	0.333 [c]
	Triglyceride/HDL-c [a]	2.21 ± 1.17	1.65 ± 0.08	0.081 [c]

[a] mean± standard deviation, [b] median (IQR), [c] Student T-test, [d] Mann-Whitney U test , **BMI:** Body mass index, **TyG:** Triglyceride glucose index, **HOMA-IR:** Homeostasis model assessment of insulin resistance, **VAI:** Visceral adiposity index, **Total-c:** Total cholesterol, **HDL-c:** High-density lipoprotein cholesterol, p-values in bold are significant values.

Table 3: Comparison of IR measurement methods by hyperandrogenemia.

IR measurement methods	HA-PCOS (n=22)	NA-PCOS (n=20)	*p*
TyG index [a]	3.96 ± 0.13	3.98 ± 0.13	0.698 [b]
HOMA-IR [a]	3.24 ± 2.50	3.45 ± 2.39	0.812 [b]
VAİ [a]	2.84 ± 1.44	4.25 ± 3.39	0.142 [b]
Total-c / HDL-c [a]	3.26 ± 0.84	3.79 ± 0.91	0.097 [b]
Triglyceride / HDL-c [a]	1.58 ± 0.73	2.29 ± 1.74	0.141 [b]

[a] mean± standard deviation, [b] Student T-test, **HA-PCOS:** Hyperandrogenic polycystic ovary syndrome, **NA-PCOS:** Normoandrogenic polycystic ovary syndrome, **TyG:** Triglyceride glucose index, **HOMA-IR:** Homeostasis model assessment of insulin resistance; **VAI:** Visceral adiposity index, **Total-c:** Total cholesterol, **HDL-c:** High-density lipoprotein cholesterol, p-values in bold are significant values.

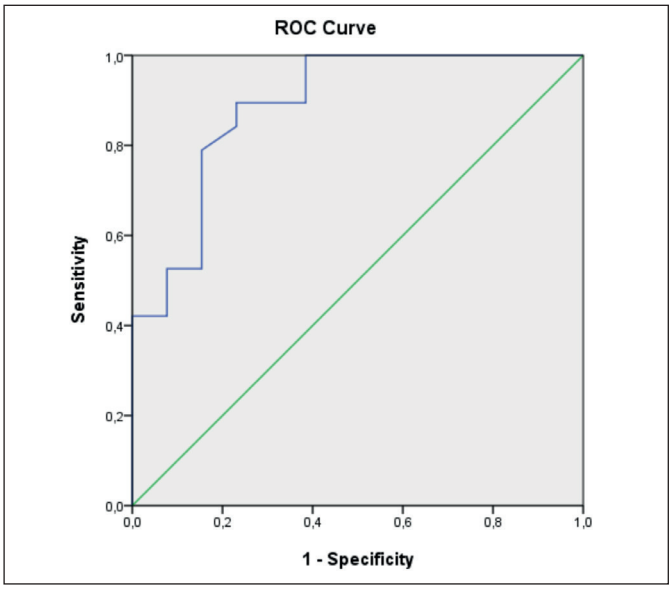

Figure 1: ROC exhibiting TyG index for prediction of IR [(AUC)=0.889, IR=HOMA-IR>2.5, arrow shows cut off of > 3.91, corresponding to sensitivity of 89.5% and specificity of 76.9%)].

lipase and hepatic lipase expression by inducing lipolysis may account for the higher level of triglycerides in women with PCOS (28). The relevant studies in the literature reported that the TyG index approach offered more accurate results than other methods (8-10).

The majority of studies that investigated IR and adiposity indexes in women with PCOS included overweight and obese women (29-31), whereas the present study included normal-weight women with PCOS. In the present study, there were significantly higher TyG index and HOMA-IR levels in normal-weight women with PCOS compared with those in the non-PCOS group, consistent with the relevant studies in the literature (32, 33). There were no similar associations between the overweight/obese groups. The results in the overweight/ obese individuals in the non-PCOS group were similar to those in the PCOS group might be because of the increase in obesity-related IR. HOMA-IR use has limitations, including the fact that insulin levels cannot be measured at every center, and the quality of measurement varies among centers.

Consequently, triglyceride measurement is more readily accessible and is widely used, giving it an advantage. The TyG index can be an excellent alternative to HOMA-IR, especially in normal-weight women with PCOS. TyG indexes >3.91 in patients with PCOS strongly predicted IR. There was no significant difference between the PCOS and non-PCOS groups in VAI. In other words, there was no difference in VAI in women with PCOS compared with healthy women with a similar phenotype since VAI is predominantly based on anthropometric measurements (11).

Women with PCOS had higher intraperitoneal fat deposits than patients with a similar amount of abdominal fat (34). It has been observed that visceral adiposity induces metabolic and endocrine pathways that play a role in PCOS progression (12, 35). Therefore, it is crucial to know the amount of visceral fat in women with PCOS, regardless of general obesity. Visceral obesity is measured using magnetic resonance imaging or computed tomography. However, the above methods are not accessible due to higher costs and exposure to radiation (36).

Bioelectric impedance analysis measurement is simple and widely used. In this study, using the Tanita scale, we sought an alternative marker for visceral obesity to determine the body fat ratio. Nevertheless, no difference was observed between patients and the non-PCOS group. In conclusion, the body fat ratio measurements did not reflect the amount of intraperitoneal fat deposit. We believe this might be because bioelectric impedance analysis indicates lower body fat (37).

Generally, women with hyperandrogenic PCOS have a poor cardiometabolic profile compared with women with non-hyperandrogenic PCOS (38). In our study, no correlation between total testosterone level and the methods of IR measurement was observed. Further, there was no significant difference between the HA-PCOS and NA-PCOS groups by the methods of IR measurement. Bil et al. reported a higher HOMA-IR in the HA-PCOS phenotype than in NA-PCOS (39). Abruzzese et al. reported that the high metabolic risk in patients with PCOS was independent of an androgenic state (31). These different results may be due to different methods for the measuring IR and that the PCOS patients were not separated in terms of phenotype. In our study, there was an inverse correlation between age and HOMA-IR, i.e., IR decreased as the age increased. Another relevant study found that IR was higher in younger patients with PCOS, regardless of phenotype (31).

The main limitation of this study is that the methods of IR measurement in patients with PCOS were not compared with euglycemic clamp, which is the gold standard method to measure hyperinsulinemia. The second limitation is that the study was designed as a single-centered research.

In conclusion, triglycerides, HOMA-IR, and TyG indexes are higher in women with PCOS than non-PCOS women. The TyG index appears to be an active marker in normal-weight patients with PCOS. TyG indexes >3.91 in patients with PCOS predict IR. There is an inverse correlation between age and HOMA-IR. Multicenter studies with a wider population are required to support the validity of this information.

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Author Contributions

Idea/Concept: **Muhammet Cuneyt Bilginer,** Design: **Muhammet Cuneyt Bilginer, Damla Tufekci, Yasemin Emur Gunay**, **Oguzer Usta,** Control/Supervision: **Mustafa Kocak, Irfan Nuhoglu, Hulya Coskun, Ozge Ucuncu,** Data Collection and/or Processing: **Muhammet Cuneyt Bilginer, Damla Tufekci, Yasemin Emur Gunay, Oguzer Usta,** Analysis and/or Interpretation: **Muhammet Cuneyt Bilginer,** Literature Review: **Muhammet Cuneyt Bilginer,** Writing: **Muhammet Cuneyt Bilginer,** Critical Review: **Muhammet Cuneyt Bilginer,** References and Fundings: **Muhammet Cuneyt Bilginer,** Materials: **Muhammet Cuneyt Bilginer, Damla Tufekci, Yasemin Emur Gunay, Oguzer Usta.**

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Ethical Approval

This study has been approved by The Clinical Researches Ethical Committee of Karadeniz Technical University (Number 2021/232). Declaration of Helsinki was followed in this study design and report.

Peer Review Process

Extremely peer-reviewed and accepted.

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