

Evaluation of the Triglyceride Glucose Index as a Marker of Insulin Resistance in Adults with Isolated Impaired Glucose Tolerance

İzole Bozulmuş Glukoz Toleransı Olan Erişkinlerde Bir İnsülin Direnci Belirteci Olarak Trigliserit-Glukoz İndeksinin Değerlendirilmesi

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ÖZ

Giriş: Amacımız uzun dönem laboratuvar verilerini analiz ederek, izole bozulmuş açlık glukoz (BAG)'lu yetişkin popülasyon da TyG ile İnsülin Direncinin Homeostatik Modeli Değerlendirmesi (HOMA-IR) arasındaki ilişkiyi değerlendirmek ve IR'yi ön görmek için popülasyonumuzdaki TyG kesim değerini belirlemektir.

Araçlar ve Yöntem: Bu çalışmada BAG ve sağlıklı toplam 440 erişkin birey retrospektif olarak değerlendirildi. Klinik veriler tıbbi kayıtlardan toplandı. Açlık glukozu, lipid paneli [total kolesterol, trigliserid (TG), düşük dansiteli lipoprotein (LDL), yüksek dansiteli lipoprotein (HDL)] ve insülin düzeyleri ticari reaktifler kullanılarak ölçüldü. (Roche Cobas C701, Roche Diagnostic, Germany). Hemoglobın A1c (HbA1c) ise yüksek performanslı likit kromatografi (HPLC) (Lifotronic H9, Lifotrophic Technology, China) ile ölçüldü. TyG, HOMA-IR ve TG/HDL-kolesterol hesaplandı. HOMA-IR ≥ 2.5 olanlar IR olarak tanımlandı.

Bulgular: Çalışmamıza 230'u kontrol, 210'u BAG olan hasta dahil edildi. Kontrol hastaları için ortalama yaş 42.5 ± 12.0 yıl ve BAG'li hasta grubu için 44.7 ± 10.7 yıl idi. Glukoz, total kolesterol, HbA1c, TG, LDL-kolesterol, insülin, TG/HDL-kolesterol, HOMA-IR ve TyG indeksi BAG hasta grubunda anlamlı olarak yüksek bulundu ($p < 0.001$). HOMA-IR ile TyG indeksi arasında zayıf fakat anlamlı bir korelasyon vardı ($r = 0.210$, $p = 0.009$). ROC analizine göre HOMA-IR için AUC 0.867 (%95 Güven Aralığı (GA), 0.833-0.900, $p < 0.001$) ve TyG indeksi için AUC 0.708 (%95 GA, 0.659-0.758, $p < 0.001$) bulundu.

Sonuç: Çalışmamıza göre, TyG indeksi, BAG'li hastalarda IR'nin değerlendirilmesi için nispeten doğru, basit, kolay erişilebilir ve düşük maliyetli bir belirteç olarak önerilmektedir. Ancak popülasyonumuz için daha yüksek hasta katılımı olan popülasyon temelli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: bozulmuş açlık glukozu; bozulmuş glukoz toleransı; HOMA-IR; insülin direnci; TG/HDL-C; TyG indeksi

ABSTRACT

Purpose: By analyzing long-term laboratory data, we aim to evaluate the relationship between the TyG and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in the adult population with isolated impaired fasting glucose (IFG), and also to determine the cut off value of The triglyceride (TG) to glucose index (TyG) to estimate the IR in our population.

Materials and Methods: In this study, data were evaluated retrospectively from medical records. Fasting glucose, lipid panel [Total cholesterol, TG, High-density lipoprotein (HDL), Low-density lipoprotein (LDL)] and insulin levels were analyzed with commercially reagents. (Roche Cobas C701, Roche Diagnostic, Germany). High-Performance Liquid Chromatography (HPLC) method was used for hemoglobın A1c (HbA1c) (Lifotronic H9, Lifotrophic Technology, China). TyG, HOMA-IR, and TG/HDLcholesterol were calculated. IR was defined as HOMA-IR ≥ 2.5 .

Results: A total of 440 subject, (controls: 230 and IFG:210), were included in our study. The average age of the subjects was 42.5 ± 12.0 years and 44.7 ± 10.7 years for IFG and control, respectively. Glucose, total cholesterol, TG, LDL-cholesterol, insulin, HbA1c, TG/HDL-cholesterol, HOMA-IR, and TyG were significantly higher in the IFG group ($p < 0.001$). There was a weak but significant correlation between HOMA-IR and the TyG ($r = 0.210$, $p = 0.009$). In the ROC analysis, the AUC for HOMA-IR and the TyG, respectively was 0.867 (95% CI, 0.833-0.900, $p < 0.001$) and 0.708 (95% CI, 0.659-0.758, $p < 0.001$).

Conclusions: In our study, the TyG is proposed as a relatively accurate, simple, easily accessible, and low-cost marker for IR evaluation with IFG patients. However, population-based studies with higher patient participation are needed for future studies.

Keywords: impaired fasting glucose; impaired glucose tolerance; HOMA-IR; Insulin resistance; TG/HDL-C; TyG index;

Received: 04.07.2022; Accepted: 19.01.2023

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How to cite: Kirtıl G, Alpdemir M, Alpdemir MF, Şeneş M. Evaluation of the triglyceride glucose index as a marker of insulin resistance in adults with isolated impaired glucose tolerance. Ahi Evran Med J. 2023;7(2):205-211. DOI: 10.46332/aemj.1140228

INTRODUCTION

Insulin resistance (IR) that occurs with a decrease in the insulin's physiological effect of on peripheral tissues causes a metabolic disorder. Because it occurs before the beginning of Type 2 diabetes mellitus (Type 2 DM) and atherosclerotic vascular disease, IR is essential for etiology of both diseases. As a result, early diagnosis of IR appears as a significant implement in the planning of prevention methods for these diseases.¹

The gold standard approach for measuring IR is use of a hyperinsulinemic-euglycemic glucose clamp technique. Unfortunately, this procedure is time consuming, invasive, special equipment and experienced personnel, is expensive, and is only utilized for research purposes, and making clinical applicability difficult.² Therefore, various indexes have been estimated for the starting diagnosis of IR with various formulas using parameters measured in serum or plasma. Among them, the "Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)" index is the most chosen to investigate the IR, which are generated using glucose and insulin concentrations in fasting. However, since serum measurement of insulin levels are costly, it is not routinely measured in every laboratory, which is a disadvantage in calculating this index.²⁻³

According to studies, the triglyceride-glucose index (TyG) may be an possible marker for the evaluation of IR, which is regarded to be simpler and more reliable.⁴ There are fasting triglyceride (TG) and glucose concentrations in constructing this formula.⁵ The TyG index has the advantage of being easy to apply, as tests are routinely measured in most medical laboratories and insulin measurement is not required.⁴⁻⁶

Every day, worldwide prevalence of disorders affecting glucose metabolism, such as prediabetes and after that Type 2 DM, rises on worldwide. One of the primary risk threats for prediabetes people that precede the onset of Type 2 DM is impaired fasting glucose (IFG).⁴ Two pathological factors that is impaired cell function and raised insulin resistance lead to the development of prediabetes and, eventually, diabetes.⁷

Earlier studies have demonstrated that both prediabetes and a high prevalence of diabetes is related with elevated TyG levels. Moreover, ischemic stroke, cardiovascular events, and vascular damage have all been related to the TyG index.⁸⁻¹⁰

Data-based scientific studies in medicine are increasing day by day. With laboratory data gathered from databases, valuable information is obtained for screening, diagnosis, and follow-up of diseases, which contributes significantly to the improvement of the quality of health services. Another advantage is that studies made from this big data cost nothing.¹¹

In addition, laboratory data is a practical method that may be used to create population-specific data in terms of containing information on the findings of many individuals. The performance of the TyG index should be calculated particularly for each community to determine the IR, as each population's dietary and physical activity habits may vary depending on its socio-cultural structure. By evaluating long-term laboratory data, we aim to investigate the relation between HOMA-IR and the TyG index among the Turkish population with isolated IFG adults. Furthermore, it is also to estimate the cut off points of the TyG index in order to determinate the IR.

MATERIALS and METHODS

Study Population

The study was conducted retrospectively by examining the data of patients who requested an oral glucose tolerance test (OGTT) in the Medical Biochemistry Laboratory of the Ankara Training and Research Hospital between January 1, 2019, and January 1, 2021. On these dates, a total of 440 patient results were obtained (210 patients with isolated IFG and 230 healthy control) from patients between 18-65 ages (the average age of the subjects: 43.6±12.0). The study was approved by the SBU Ankara Training and Research Hospital Clinical Research Ethics Committee (Accepted: 22/12/2021, No: 834/2021) according to the principles of the Helsinki Declarations.

Subjects Data Analysis

Based on OGTT results, those with fasting glucose 100-125 mg/dL and HbA1c <6.5% were defined as having isolated IFG patient and those with fasting glucose <100 mg/dL and HbA1c ≤5.6% were included as having control group.¹² Patient results were retrieved from the database. At the same time, patients with fasting glucose, insulin, total cholesterol, HDL-C, LDL-C, TG and HbA1c results were included in the study. The subjects were screened in the Laboratory and Hospital information management System (LIS and HIS) for clinical diagnosis and medication information. Tests such as liver function tests, kidney function tests and thyroid function tests of these patients that would primarily affect glucose metabolism were questioned. Subjects with pathological results were not included in the study. None of the individuals had chronic diseases such as Type 2 DM, liver disorder, thyroid dysfunction, hypertension, cardiovascular disease, dyslipidemia, patients using lipid-reducing drugs (statin and fibrate), patients with chronic inflammatory diseases and cancer were not included from this study.

Methods of Biochemical Tests

Serum glucose, lipid panel levels were analyzed with commercially reagents (Roche Cobas C701, Roche Diagnostic, Germany). High-Performance Liquid Chromatography (HPLC) method was used for HbA1c (Lifotronic H9, Lifotrophic Technology, Shenzhen, China). Insulin was measured by the electrochemiluminescent immunoassay (Roche Cobas e801, Roche Diagnostic, Germany). The analytical performance of all tests is presented in Table 1. The LDL-C was estimated by the Friedewald formula (LDL-C: Total cholesterol – HDL – TG/5).

Insulin Resistance Estimation

The estimation formulas for the HOMA-IR and TyG indexes are as follows.

HOMA-IR: [fasting glucose (mg/dL) × fasting insulin (mIU/L) / 405].²

TyG: Ln [(fasting triglyceride (mg/dL) × fasting glucose (mg/dL)] / 2.⁵

Statistical Analysis

The data was expressed as percentiles (%) and the mean±standard deviation (SD) or median [(inter quartile range (IQR)]. The normality of data was evaluated using the Kolmogorov-Smirnov test. Differences between the groups were statistically analyzed with the independent samples T-test to compare among parametric data, and with the Mann-Whitney U test to compare among non-parametric data. Additionally, correlations between parameters were evaluated with Pearson or Spearman correlation analysis. Box-plot graphs are used in statistical analysis. Based on HOMA-IR results, the patients were categorized into two groups: IR (≥2.5) and insulin sensitivity (IS) (<2.5). ROC (Receiver operating characteristic) analysis was performed for detecting IR. In addition, diagnostic performance characteristics [positive/negative predictive value (PPV/ NPV), likelihood ratio negative/positive (LR-/LR+), sensitivity/specificity, and accuracy] of the biochemical parameters were determined. The data values were evaluated using IBM SPSS Statistics version 26 (IBM Corp, NY, USA).

RESULTS

A total of 440 patients, (controls: 230 and IFG:210) were selected for present study. The average age of the subjects was 42.5±12.0 years for the control and 44.7±10.7 years for IFG. Women and men were 73% and 27% of the control group, were 76% and 24% of the IFG group. Table 1 shows the biochemical parameters and demographic features of the control and patient groups. Glucose, total cholesterol, TG, LDL-C, TG/HDL-C, insulin, HbA1c, HOMA-IR, and TyG index were defined to be statistically significant higher in the IFG patients (p<0.001). As presented Figure 1, there are no statistically significant difference to compare of HOMA-IR and the TyG between females and males (p=0.897, p=0.816, respectively). In our study, both control and patients were separated into two groups (IS and IR), according to the HOMA-IR (cut off: 2.5) results. HOMA-IR, TyG index, glucose, TG, and TG/HDL-C were statistically significant higher in control subjects with the IR than IS (Table 2). There was only a statistically significant difference in total cholesterol, TG/HDL-C, insulin, and HOMA-IR between IR and IS groups in the IFG group (Table 2). A

statistically significant but weak correlation was found between HOMA-IR and TyG index. ($r=0.210$, $p=0.009$) (Table 3). In our study, the cut-off value for TyG index was determined as 4.44 after analyzing our data. Table 4 is presented the diagnostic performance of the HOMA-IR and TyG index. According to our ROC analysis, the AUC for HOMA-IR was 0.867 (95% CI, 0.833-0.900, $p<0.001$), the AUC for the TyG index was 0.708 (95% CI, 0.659-0.758, $p<0.001$), the AUC for TG/HDL-C was 0.620 (95% CI, 0.568-0.724, $p<0.001$), the AUC for insulin was 0.793 (95% CI, 0.752-0.834, $p<0.001$), and the AUC for the TG was 0,613 (95% CI, 0.560-0.666, $p<0.001$) (Figure 2).

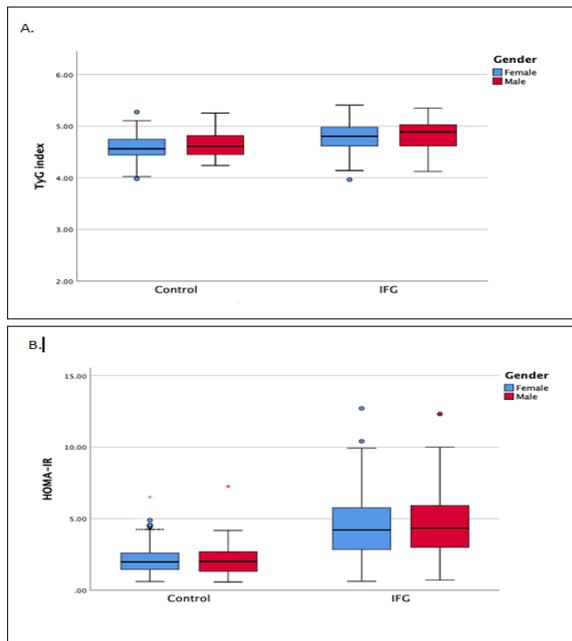


Figure 1. Box-Plot graphs of HOMA-IR and TyG indexes according to the groups.

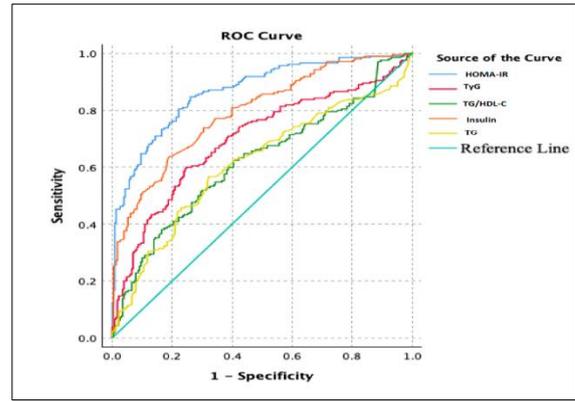


Figure 2. ROC analysis of biochemical parameters in detection of the IFG.

Table 1. Demographic and biochemical characteristics of the control and patient groups.

Variables	Control n= 230	IFG n=210	p-value
Age (year)	42.5±12.0	44.7±10.7	<0.001
Gender, n (%)			
Female	169 (73)	160 (76)	<0.001
Male	51 (27)	50 8(24)	
Glucose, mg/dL	91 (9.0)	110 (9.0)	<0.001
Cholesterol, mg/dL	187 ±58	200 ±41	<0.001*
Triglyceride, mg/dL	107 (69)	138 (84)	<0.001
HDL-C, mg/dL	53.6 (13)	48 (13)	<0.001
LDL-C, mg/dL	110 ±54	121±36	<0.001*
HbA1C, %	5.3 (0.4)	6.0 (0.5)	<0.001
Insulin, mIU/L	8.73 (5.53)	14.80(10.8)	<0.001
TG/HDL-C	2.03 (1.96)	2.90 (3.41)	<0.001
HOMA-IR	2.13 (1.2)	4.3 (2.96)	<0.001
TyG	4.60±0.24	4.78 ±0.30	<0.001*

Data are presented as mean±SD, median (IQR), and number (percentage). *: Independent samples t-test, others: Mann-Whitney U test.

Table 2. Demographic and biochemical variables according to IS and IR group discrimination.

Variables	Control		p-value	IFG		p-value
	IS n= 170	IR n= 60		IS n= 33	IR n=177	
Age	42.1 (13.3)	43.4(18.0)	0.549	50 (11.5)	45 (18.0)	0.008
Gender, (n)						
Female	125	44	<0.001	26	134	<0.001
male	45	16		7	43	
Glucose, mg/dL	91.0(9.0)	93.0 (6.0)	<0.001	108 (10)	110 (9.0)	0.261
Cholesterol, mg/dL	190±43	194±44	0.492*	212 ±42	197±40	0.041*
Triglyceride, mg/dL	100 (62)	130 (100)	<0.001	124 (86)	138(108)	0.377
HDL-C, mg/dL	55 (17)	49 (13)	0.001	53 (14.5)	44 (16)	0.004
LDL-C, mg/dL	112±38	114±38	0.756*	130±35	118±36	0.091*
HbA1C, %	5.36 (0.40)	5.44 (0.30)	0.048	6.1(0.5)	6.0 (0.5)	0.082
Insulin, mIU/L	7.58 (3.78)	14.87(3.75)	<0.001	7.5(1.9)	16.4 (9.45)	<0.001
TG/HDL-C	1.81 (1.50)	2.68 (2.39)	<0.001	2.58 (2.34)	3.69 (3.74)	0.026
HOMA-IR	1.65±0.51	3.47±0.88	<0.001*	1.91±0.46	5.10±2.03	<0.001
TyG	4.55±0.23	4.73±0.25	<0.001*	4.74±0.29	4.79±0.30	0.379*

Data are presented as mean±SD, median (IQR), and number (percentage). *: Independent samples T-test, Others: Mann-Whitney U test. IR: insulin resistance, IS: insulin sensitivity

Table 3. Correlation coefficients among HOMA-IR, TyG and other parameters of patient groups.

Variables	HOMA-IR		TyG	
	r	p-value	r	p-value
Age	0.274	<0.001	0.052	0.043
Glucose, mg/dL	0.186	0.007	0.152	0.028
Cholesterol, mg/dL	0.202	0.003	0.246	<0.001
Triglyceride, mg/dL	0.168	<0.001	0.994	<0.001
HDL-C, mg/dL	-0.291	<0.001	-0.41	<0.001
LDL-C, mg/dL	0.19	0.006	0.06	0.365
HbA1C, %	0.063	0.361	0.205	<0.001
TG/HDL-c	0.227	0.001	0.606	<0.001
HOMA-IR	-	-	0.21	0.009
TyG index	0.21	0.009	-	-

*: Spearman rank correlation analysis. r: correlation coefficient.

Table 4. Diagnostic performance of the HOMA-IR and TyG index.

Variables	Sensitivity 95% CI	Specificity 95% CI	PPV	NPV	LR (+)	LR (-)	Accuracy 95% CI
HOMA-IR	0.85 (0.78-0.88)	0.73 (0.67-0.79)	0.75	0.83	3.14	0.2	0.79 (0.74-0.82)
TyG	0.78 (0.71-0.82)	0.54 (0.48-0.60)	0.6	0.73	1.69	0.41	0.66 (0.62-0.72)

PPV: Positive predictive value, NPV: Negative predictive value, LR (+): Likely hood ratio (positive), LR (-) Likely hood ratio (negative)

DISCUSSION

The importance of the TyG index in predicting IR was investigated in individuals with IFG. The control and IFG subjects had important difference for TyG index in our study. Furthermore, there was a significant correlation between HOMA-IR and TyG in the groups, but this correlation was weak. Diagnostic performance was seen between the HOMA-IR and the TyG. In this respect, it was concluded that the TyG index may be beneficial in determining IR as a readily available marker in individuals with IFG.

IR is a metabolic condition that occurs because of the insufficient response of fat, muscle, and liver cells to the insulin hormone. This causes to the development of IFG, which is the early stage of type 2 DM. Ethnic differences, socio-economic status, and diet-related lifestyles have been shown to cause differences in IR.¹³ Simenta Mendia et al.⁵ suggested that the TyG index is a practical and accessible marker for IR determination. In many studies conducted in recently years, the TyG index in determination of IR has also been investigated as a diagnostic biomarker in diabetes, hypertension, and atherosclerosis.⁸⁻¹⁰⁻¹⁴ In addition to these, studies have been carried out for different populations in determining IR. According to Mazidi et al.,¹⁵ they determined the TyG as a pre-indicator of IR in US adults in their research. Navarro-González et al.,¹⁶ showed in their epidemiological study for the white European population that the TyG index is helpful for the early diagnosis of people that have risk of

type 2 DM. Similarly, Lee et al.¹⁷ recommended it as a screening biomarker to detect IR in middle-aged Korean individuals with high-risk type 2 DM. According to our knowledge, there is no research showing the relationship between TyG and IR prediction in Turkish population. Based on our findings, the TyG values can be candidate for recognizing IR in the subjects with IFG.

The persons with IR and dyslipidemia have essential risk factors for prediabetes. Wen et al.¹⁸ showed in their study that the useability of the TyG index to detected IR is higher than not included insulin IR indexes such as TG, HDL-C, and TG/HDL-C. Huang et al.¹⁹ determined a significant correlation among HOMA-IR, TyG and TG/HDL-C in their study, and results like ours were obtained. In our study, HOMA-IR, TyG, and TG/HDL-C values had a significant positive correlation.

In our study, the results obtained from the ROC curve analysis to predict prediabetes were close to the HOMA-IR result. The values obtained in many studies were similar to our study. In the study by Wen et al., one of these studies, It was highlighted that the TyG index should be recognized as a possible and reliable marker for detecting the incidence of prediabetes in clinical situations.¹⁷ Mohd Nor et al.²⁰ identified the TyG index as a possible marker in determining IS in their study population consist of normal, prediabetic, and diabetes patients in the comparison of clamp-measured IS and the TyG.

IR is a critical risk factor associated with prediabetes. In this study, when evaluating the diagnostic performance of the TyG values in the detection of IR, its sensitivity (0.78) and specificity (0.54) were found to be lower than those of the HOMA-IR (0.85-0.74). Similarly, in the study by Simental-Mendia et al., it was presented that the TyG index had higher sensitivity (84%), but lower specificity (45%) compared to the HOMA-IR index in healthy people. Guerrero-Romero et al.²¹ were shown that the TyG index had high sensitivity (96.5%) and specificity (85.0%) according to the euglycemic-hyperinsulinemic clamp in describing IR in identifying individuals with reduced insulin sensitivity. Sanchez-Garcia et al.²² reported to have low-to-moderate quality evidence for the application of the TyG index as a biochemical indicator of the IR in their systematic review. According to their reports, the sensitivity and specificity levels ranged between 73% -90% and 45%-99%, respectively.

It is notable to estimate a validated cut off for clinical application of the TyG index as a surrogate biochemical indicator of IR. Various cut-off values were applied to the studies. In our study, the cut-off value was determined as 4.44 after analyzing both the literature and our data were analyzed. “ $\ln [(fasting\ triglyceride\ (mg/dL) *fasting\ glucose\ (mg/dl)]/2$ ” or “ $\ln [(fasting\ triglyceride\ (mg/dL)*fasting\ glucose\ (mg/dL)/2]$ ” formulas were utilized in several studies. When calculations are performed according to these two formulas, there are differences between the outcomes. This difference in the structure of the formulas results in a substantial variation in the cut-off. For this reason, the researchers who developed the TyG index published a correction letter with the correct formula.⁵ As in our study, a cut-off range between 4,44 and 5,88 was reported in studies using the “ $\ln [(fasting\ triglyceride\ (mg/dL) \times fasting\ glucose\ (mg/dL)]/2$ formula” .^{22,23}

Our research has several limitations. First, our patient population was relatively small. Considering the inclusion criteria, we analyzed the data of patients who underwent OGTT for approximately years; the number of patients with isolated IFG was minimal. For this reason, there is a need for a population-based study with a larger number of participants. Our second limitation is that our

study was conducted retrospectively by reviewing the demographic records of the patients using LIS/HIS data. Each patient included in our study was examined separately based on our study's inclusion/exclusion criteria. However, since there may be a possibility of missing data entry, this may cause a minimal variation in our study. Thirdly, body mass index information could not be included in the study since the height and weight information of the patients were not collected during clinical data entry from LIS/HIS. Our last limitation, IR was compared based on HOMA-IR in this study, but HOMA-IR is not a gold standard method for determining insulin resistance.

As a conclusion, IR is a condition that can be defined as prediabetes, increases the risk of type 2 DM, and has a key act in the complications and pathogenesis of the cardiovascular events. Therefore, it is valuable to regularly screen at the individuals that has high-risk for early diagnosis of type 2 DM. According to our study, the TyG index is proposed as a relatively accurate, simple, easily accessible, and low-cost biochemical parameter for IR evaluation in patients with IFG. However, population-based studies with higher patient participation are needed for our population.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Acknowledgment

Our study was presented as a poster at the TBD International Biochemistry Congress 2021 32nd National Biochemistry Congress 27-30 October 2021.

Ethics Committee Permission

Approval for this study was obtained from the SBU Ankara Training and Research Hospital Clinical Research Ethics Committee (22/12/2021 dated and 834/2021 numbered).

Authors' Contributions

Concept/Design: GK, MA. Data Collection and/or Processing: MFA, MA, GK. Data analysis and interpretation: MA, GK, MŞ. Literature Search: MFA, MA, GK. Drafting manuscript: GK, MFA, MA, MŞ. Critical revision of manuscript: SKMŞ, MA, GK. Supervisor: MŞ.

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