



## Research Article

# Assessment of relationship between triglyceride/HDL-C ratio and incident type 2 diabetes mellitus risk

Muzaffer Katar<sup>1</sup>, Osman Demir<sup>2</sup>

<sup>1</sup>Department of Medical Biochemistry, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

<sup>2</sup>Department of Biostatistics, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

### Abstract

**Objectives:** The most prevalent endocrine condition in the world today is diabetes mellitus (DM). In addition to the recognized markers for assessing glycemic control and insulin resistance (IR), easily available, accurate, and repeatable markers are required. In order to assess the use of the triglyceride (TG), HDL cholesterol ratio (THR) as a marker for insulin resistance and glycemic management, our study was conducted.

**Methods:** We looked back at the TG, fasting serum glucose (FSG), and Fasting Insulin levels of 953 samples that were concurrently evaluated in our Faculty of Medicine Hospital Laboratory from March 2023 to August 2023. In terms of their homeostasis model assessment-estimated insulin resistance (HOMA-IR) values, the patients were split into two groups: those with good glycemic control and those with poor glycemic control. The THR's capacity to distinguish between good and poor glycemic control was assessed using ROC analysis. The accepted level of statistical significance was  $p < 0.05$ . Additionally, a multivariate logistic regression analysis was conducted.

**Results:** The mean age was  $40.83 \pm 16.78$  years. All the patients had significant differences ( $p < 0.001$ ) in gender, FSG, HOMA-IR, FI, TG, and THR based on glycemic control, except age ( $p = 0.613$ ). In pairwise correlation, THR had moderate negative correlation ( $r = -0.555$ ,  $p < 0.001$ ) with HDL, while strong positive correlation with TG ( $r = 0.959$ ,  $p < 0.001$ ). THR had the high selectivity and positive predictive value (PPV) with a cutoff value of  $\geq 2.64$  (AUC:0.72, Se:65%, Sp:70% ( $p < 0.001$ ; 95% CI:0.66-0.78)). Men are 2.247 times more likely than women to have poor glycemic control ( $p = 0.022$ ). Poor glycemic control risk rised by 1.045 times with age, and by 1.056 times with glucose ( $p = 0.007$ ).

**Conclusion:** Based on the current results, we think that the THR may be a useful marker of glycemic control and IR.

**Keywords:** Diabetes mellitus, glycemic control, HDL-C, insulin resistance, triglyceride

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One of the biggest socioeconomic and health issues is diabetes mellitus. Diabetes mellitus type 2 (T2DM) is becoming more prevalent globally. According to numerous regional and national studies, the overall prevalence of T2DM in Türkiye ranges from 12.7% to 14.7% [1–4]. Additionally, the frequency of early fatalities brought on by macro- and microvascular complications in diabetes is increasing [5]. The pathophysiology of diabetes and metabolic syndrome is significantly influ-

enced by insulin resistance (IR), which is the reduced insulin sensitivity of peripheral tissues. It may manifest one to two decades prior to the official diagnosis of T2DM [6]. IR's value as a predictor of future diabetes or insulin-sensitizing drugs' ability to prevent T2DM lends credence to this notion [7]. Diabetic dyslipidemia is another cardiovascular disease (CVD) risk factor in individuals with T2DM. Increased triglycerides (TG), decreased HDL-C (high-density lipoprotein cholesterol), and

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**Address for correspondence:** Muzaffer Katar, MD. Department of Medical Biochemistry, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

**Phone:** +90 532 575 78 79 **E-mail:** drkatar@hotmail.com **ORCID:** 0000-0002-6296-2390

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postprandial lipemia are its constituents. The atherogenic index of plasma, which measures the ratio of blood triglycerides to high-density lipoprotein cholesterol (THR), is a significant risk factor for cardiovascular disease and metabolic syndrome [8, 9]. There is a correlation between endothelial dysfunction and a higher THR. Additionally, the THR has been suggested as an indicator of IR [10]. This is because lipid metabolism is altered by the metabolic processes that induce IR, and these alterations are mirrored in serum triglyceride and HDL cholesterol levels [11]. THR has also been demonstrated by Quispe et al. [12] to be a measure of glycemic control, particularly in obese individuals with T2DM. A further indicator linked to IR is the triglyceride to glucose (TyG) index. It assists in identifying asymptomatic T2DM patients who are at high risk of CVD [13]. THR and IR in diabetic individuals have been the subject of the majority of research to date [14].

In order to evaluate insulin sensitivity, the medical profession has therefore looked for substitute, indirect biomarkers. Strong predictive ability, high specificity, and sensitivity make Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Fasting Insulin (FI) popular surrogate markers for IR assessment. However, although being more practical than the hyperinsulinemic-euglycemic clamp technique, they are still difficult to use in day-to-day situations [11, 15]. Since insulin is not measured in every hospital, and due to transportation problems of blood samples from small family medicine offices to the hospital laboratories or HOMA-IR measurement handicaps, the quest for easier biomarkers to incorporate into a routine test is ongoing. Because measurement of triglyceride, HDL, and glucose levels is common and reasonably priced, THR can be calculated more frequently in clinical practice [16]. Over the past 20 years, efforts have been made to define the precise predictive power, constraints, and idiosyncrasies of THR, because of the unquestionable ease of use and accessibility of these two biomarkers.

Studies that sought to evaluate the relationship between glycemic control and the THR are scarce in our country, nevertheless. Thus, this study's objective was to assess the relationship between our population's THR and incident T2DM risk.

## Materials and Methods

After taking approval from the ethical committee of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (Date 26/10/2023, No: 23-KAEK-252), this cross-sectional retrospective study was conducted in Tokat Gaziosmanpaşa University. The study was designed in accordance with the Helsinki Declaration. All 953 participants aged between 18–75 years old, had blood tests for fasting serum glucose (FSG), HOMA-IR, FI, and TG levels between March and August 2023 were included in the study. THR was calculated according to following formula “serum triglyceride(mg/dL)/serum HDL(mg/dL)” [17] and HOMA-IR was derived (FSG): (mg/dL) / 405 [18]. We excluded participants under 18 years, having chronic thyroid disease, liver diseases, chronic kidney disease, hematological disorders or malignancies, systemic inflamma-

tory or infectious diseases, a history of metabolic or bariatric surgery and use of anti-inflammatory or steroid therapy.

All the information of the patients was collected retrospectively from our hospital data system (ENLIL HBYS Co. Türkiye). Cobas c501 (Roche Diagnostics, GmbH, Mannheim, Germany) instrument was used to estimate FSG, TG, levels. Serum FI estimation was performed on Cobas e411 (Roche Diagnostics, GmbH, Mannheim, Germany).

## Statistical analysis

Participants were grouped on the basis of HOMA-IR values and evaluated according to their cutoff value as 2.5 [19]. After evaluating the qualitative variables, we looked at the distributions of the quantitative variables.

The relationship between the significant variables and THR was evaluated for HOMA-IR group. We defined the cutoff values and The Receiver Operating Characteristic (ROC) curves of THR for HOMA-IR group. Then, we performed logistic regression analysis of the selected variables based on our study group.

To learn more about the overall traits of the research group, descriptive analyses were carried out. Continuous variable data are displayed as mean±standard deviation, whereas categorical variable data are displayed as n (%). Independent sample t test was used to compare the normally distributed age, FSG, HDL variables between two groups and Mann-Whitney U Test was used to compare the non-normally distributed HOMA-IR, FI, TG, THR variables between two groups. To find performance metrics for predicting THR variable, ROC analysis was employed. In examining the relationships among the variables THR and age, FSG, HOMA-IR, HDL, FI, and TG, Spearman correlation coefficient was used. A multivariate logistic regression model was implemented to determine relation among selected variables and HOMA-IR. If a P value was less than 0.05, it was deemed statistically significant. For the computations, pre-made statistical software (SPSS 22.0 Chicago, IL, USA) was utilized.

## Results

Participants in the study included 953 patients, whose mean age was 40.83±16.78. Research groups had significant differences ( $p<0.001$ ) in FSG, HOMA-IR, FI, TG, and THR parameters, based on HOMA-IR cut off value of 2.5 (Table 1). In research groups, THR had a moderate negative correlation with HDL ( $r=-0.555$ ,  $p<0.001$ ), while strong positive correlation with TG ( $r=0.959$ ,  $p<0.001$ ) in pairwise correlation (Table 2). For HOMA-IR, THR had the highest selectivity and positive predictive value (PPV) with a cut off value of  $\geq 2.64$  (AUC:0.72, Se:65%, Sp:70% ( $p<0.001$ : 95% CI:0.66–0.78)) and ROC analysis results for THR are shown in Table 3. THR had the value of Area Under Curve (AUC) of 0.72 for HOMA-IR group in Receiver Operating Characteristic (ROC) analysis (Fig. 1). According to multivariate logistic regression analysis, men are 2.247 times more likely than women to have poor glycemic control and this difference is statistically significant ( $p=0.022$ ). The risk of having poor glycemic control rises by 1.045 times with each unit of age, and this difference is statisti-

**Table 1. Distribution of quantitative variables**

Variables	Total (n=953) Mean±SD	HOMA-IR group		p
		<2.5 (n=379) Mean±SD	≥2.5 (n=574) Mean±SD	
Age (Year)	40.83±16.78	41.42±16.6	40.5±16.89	0.130
FSG (mg/dL)	115.28±59.91	99.88±34.48	123.77±68.67	<0.001
HDL-C (mg/dL)	50.97±12.51	56.62±13.93	47.94±10.53	<0.001
HOMA-IR	3.2 [2.08–5.22]	1.82 [1.34–2.24]	4.64 [3.47–7.13]	<0.001*
FI (mIU/mL)	12.63 [8.14–19.36]	7.78 [5.32–9.36]	17.7 [13.79–25.12]	<0.001*
TG (mg/dL)	127 [93.3–179]	109 [77–141.95]	145.1 [107–204]	<0.001*
THR	2.65 [1.54–4.07]	1.74 [1.2–2.89]	3.26 [1.96–5.12]	<0.001*

Data are shown as mean±standard deviation or median [Quartile 1–Quartile 3]. Independent Samples t test was used. \*: Mann Whitney U test was used. HOMA-IR: Homeostasis model assessment-estimated insulin resistance; SD: Standard deviation; FSG: Fasting serum glucose; HDL-C: High-density lipoprotein cholesterol; FI: Fasting insulin; TG: Triglycerides; THR: Triglyceride/HDL-C ratio

**Table 2. Pairwise correlation between variables**

Variables	Total THR	HOMA-IR <2.5 THR	HOMA-IR ≥2.5 THR
Age (year)			
r	0.069	0.268*	0.111
p	0.258	0.005	0.165
FSG (mg/dL)			
r	0.276*	0.399*	0.219*
p	<0.001	<0.001	0.006
HOMA-IR			
r	0.372*	0.239*	0.292*
p	<0.001	0.012	<0.001
HDL (mg/dL)			
r	-0.555*	-0.613*	-0.549*
p	<0.001	<0.001	<0.001
FI (mIU/mL)			
r	0.254*	0.087	0.146
p	<0.001	0.364	0.066
TG (mg/dL)			
r	0.959*	0.924*	0.962*
p	<0.001	<0.001	<0.001

Spearman correlation coefficient was used. \*: Statistically significant positive correlations. HOMA-IR: Homeostasis model assessment-estimated insulin resistance; THR: Triglyceride/HDL-C ratio; FSG: Fasting serum glucose; HDL: High-density lipoprotein; FI: Fasting insulin; TG: Triglycerides.

cally significant ( $p=0.007$ ). The likelihood of having poor glycemic control rises by 1.056 times for every unit of FSG, and this increase is statistically significant ( $p=0.001$ ) (Table 4).

## Discussion

Patients in our study who had uncontrolled T2DM had elevated THR levels as well. Additionally, there was a negative association between THR and HDL levels, while there was a sig-

nificant high positive association with TG, and a low positive association with FSG and HOMA-IR. These findings imply that THR can be considered independently as a major predictor to determine the increased risk of acquiring incident T2DM.

IR and reduced  $\beta$ -cell activity are characteristics of incident T2DM [20]. The presence of IR causes hyperglycemia and hyperlipidemia in a variety of tissues, including muscle, liver, adipose, and pancreatic  $\beta$ -cells [21]. Triglycerides reduce glucokinase activity and glucose-stimulated insulin release in islets during hypertriglyceridemia [22]. Hyperglycemia results in ongoing oxidative stress on islet cells, even if the cells themselves have a lower antioxidant capacity [23]. Therefore, lipotoxicity and glucose toxicity may have an effect on  $\beta$ -cell failure [21].

Considering its critical role in T2DM and metabolic syndrome, IR assessment is important. In epidemiological studies and clinical practice, HOMA is a widely used and proven technique to measure IR from FSG and insulin [24]. In 28 studies, HOMA-IR was the most commonly used technique to measure IR [18]. In our study, HOMA-IR was significantly increased in poor glycemic control group and it was positively and significantly associated with THR, which was consistent with the existing research results.

Baneu et al. [25] stated in their review that ROC curve analysis for the assessment of IR was used in 17 studies with an AUC greater than 0.7, indicating a reasonable predictive power. In line with this result, we found an AUC of 0.72 in our study, indicating a moderate predictive power of THR.

FI is a measurement that assesses insulin levels in the blood following an overnight fast. Despite its simplicity, it does not provide a complete picture of insulin sensitivity, which limits its usefulness [26, 27]. FI was significantly increased in poor glycemic control group and it had a positive significant association with THR in our study.

The hyperinsulinemic-euglycemic clamp technique is the gold standard for determining insulin sensitivity and resistance. This approach is labor-intensive, expensive, and re-

**Table 3. ROC analysis results for THR**

Variable	Cut-off	AUC (95% CI)	Se	Sp	PPV	NPV	p
THR	≥2.64	0.72 (0.66–0.78)	0.65	0.70	0.76	0.58	<0.001

ROC: Receiver operating characteristic; THR: Triglyceride/HDL-C ratio; AUC: Area under curve, CI: Confidence interval; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

**Table 4. Logistic regression analysis of selected variables**

Model	Univariate				Multivariate			
	p	Odds ratio	95% CI for odds ratio		p	Odds ratio	95% CI for odds ratio	
			Lower	Upper			Lower	Upper
Gender (F/M)	0.026	1.382	1.040	1.835	<b>0.022</b>	2.247	1.051	4.504
Age (year)	0.130	1.007	0.986	1.002	<b>0.001</b>	1.056	1.033	1.081
FSG (mg/dL)	<0.001	1.016	1.010	1.021	0.007	1.045	1.012	1.079
HDL_cholesterol	<0.001	1.066	0.918	0.958	<b>0.032</b>	1.053	1.004	1.103
TG (mg/dL)	<0.001	1.009	1.006	1.012	0.884	1.002	0.979	1.025
THR	<0.001	1.534	1.295	1.818	0.991	0.996	0.487	2.034

Reference category: Women for Gender. CI: Confidence interval; FSG: Fasting serum glucose; HDL: High-density lipoprotein; TG: Triglycerides; THR: Triglyceride/HDL-C ratio.

quires extensive knowledge [28, 29]. We could not evaluate this technique in our cross-sectional study.

According to diabetic medical care guidelines, asymptomatic adult patients with high blood levels of TG and low HDL cholesterol are at risk for developing pre-diabetes and diabetes [30]. Finding relevant biomarkers like THR for T2DM can aid in the follow-up and development of new treatment plans to increase patient survival [31].

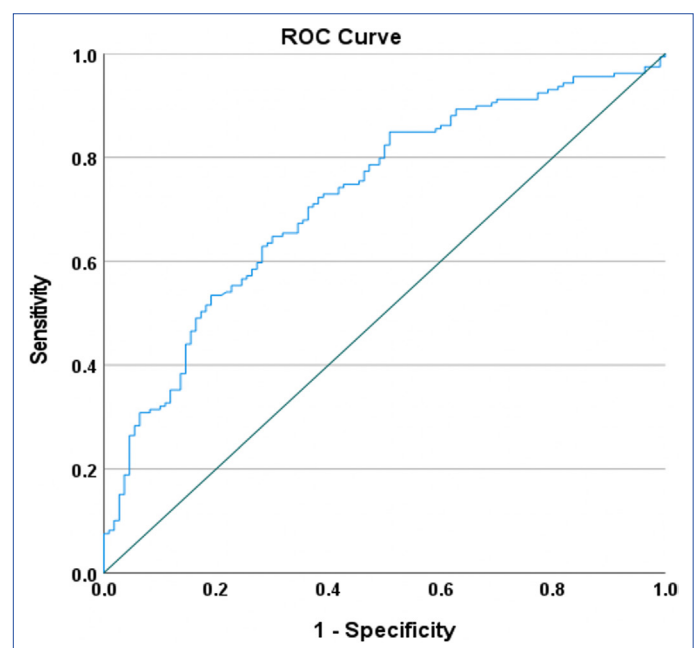
In the study by Jabeen et al. [17], THR levels were found to be increased in patients with uncontrolled T2DM in line with our results. In the study by Gedikli et al. [32], increased FSG levels were positively associated with THR in Chinese T2DM patients, which was consistent with our findings. THR was significantly increased in poor glycemic control group.

Cutoff levels for THR are an important consideration in clinical practice. In 50% of research, authors provided particular cut-off values, whereas the rest treated the THR as a continuous variable. When exact ratios were provided, they were either generic for the entire group or based on race or gender, with many cutoffs proposed. According to three research studies conducted between 2005 and 2008 [33–35], the highest score was 3.5 for both genders. The median cutoff value for women was 2.53, while men's was 2.8. Li et al. [36] addressed the ethnicity question in 2008 and found no significant difference in Odds Ratio (OR) in 3 separate subpopulations of their study, non-Hispanic whites, non-Hispanic blacks, and Mexican Americans, respectively; using ethnicity-specific cutoff points, the THR was 3.0 for Caucasians and Mexican Americans and 2.0 for African Americans. In our study, the THR cut-off value was determined as 2.64 with a moderate predictive value. In addition, men were 2.2 times more likely than wom-

en to have poor glycemic control. Poor glycemic control risk risen by 1.045 times with age and by 1.1 times with FSG levels.

### Strengths of the study

It includes a large community-based sample size across a wide age range, high participation rates, standardized high-quality clinical and laboratory procedures, and adjustment for numerous potential confounding factors.

**Figure 1.** ROC curve of THR.

ROC: Receiver operating characteristic; THR: Triglyceride/HDL-C ratio.



## Limitations of our study

The main limitations are that the study was a retrospective cross-sectional study and its relationship with T2DM complications was not assessed, the progression of diabetes was not followed and any causal relationship between our findings was not inferred. Although the results appear significant, they should be confirmed by the euglycemic clamp method.

## Conclusion

Our results raise the prospect of using THR for diabetes risk assessment in actual clinical settings or extensive epidemiologic research because it is simple to compute from standard laboratory data.

**Ethics Committee Approval:** The study was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (no: 23-KAEK-252, date: 26/10/2023).

**Informed Consent:** Informed consent was obtained from all participants.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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