



Association of Triglyceride-Glucose Index with Fibrosis Index Based on Four Factors in Patients with Diabetes Mellitus Type II

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Abstract

Background: This research examined the relationship between the triglyceride-glucose (TyG) index and the Fibrosis Index Based on four factors (FIB-4) in patients with type 2 Diabetes Mellitus (T2DM).

Methods: During 2023-24, this prospective cross-sectional research was done at the Endocrine Research Center in Tehran, Iran, and 292 individuals with T2DM were recruited by random sampling. Correlation and linear regression were used as the inferential tools.

Results: The sample had a mean (SD) age of 59.4 years (12.2 yr) and included 166 females (56.9%). Spearman correlation analysis revealed the following associations: FIB-4 and the Triglyceride-Glucose Index (TyG) index had a correlation coefficient of -0.18, FIB-4 showed an inverse association of -0.19 with Fasting Blood Glucose (FBG), and the TyG index had a direct correlation of 0.48 with HbA1c. Regression models indicated a 0.004 (95% CI: 0.001, 0.007) increase in the TyG index per a 1-mmHg increase in Systolic Blood Pressure (SBP) and a 0.8% (95% CI: 0.2, 1.3%) decrease in FIB-4 due to a 1-mg/dL increase of High-Density Lipoprotein cholesterol (HDL-C). Moreover, a 2.4% (95% CI: 7.8,32.9%) decrease in FIB-4 per a 0.1 unit increase in the TyG index was demonstrated.

Conclusion: A weak association was observed between FIB-4 and the TyG index in diabetic patients. Additionally, FBG and HDL-C were inversely associated with FIB-4, while HbA1c and SBP were positively associated with the TyG index.

Keywords: Blood glucose, Blood pressure, Cholesterol, Diabetes mellitus, HDL, Glycated hemoglobin, Lipoproteins, Triglycerides, Type 2

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD), the most prevalent liver disease worldwide, is a multi-factorial disorder (1,2). In this condition, the hepatocytes would accumulate excessive lipids (over 5%) in the absence of other causes of liver diseases or significant alcohol consumption (3). NAFLD can progress to other liver disorders, such as Non-Alcoholic Steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (3). Its incidence varies by geographical location (2). NAFLD is strongly related to obesity, Insulin Resistance (IR), Metabolic Syndrome (MS), Type 2 Diabetes Mellitus (T2DM), Hypertension (HTN), and dyslipidemia, with a prevalence ranging from 50 to 90% in these patients (4-6). Recently, due to the growth of obesity and T2DM, the incidence of NAFLD has increased (2,7). Accumulating evidence demonstrates that Liver Fibrosis (LF) is the most important predictor of mortality in patients with NAFLD (8). The leading cause of death among these patients is Cardiovascular Disease (CVD) (9,10).

Thus, it is crucial to identify clinical determinants of fibrosis development and its progression in patients with NAFLD. Although the pathophysiology of NAFLD is not yet fully understood, it is generally asymptomatic and related to other manifestations of MS (5,11). Several scores have already been evaluated for non-invasive assessment of the degree of fibrosis; amongst them, the Fibrosis Index Based on 4 Factors (FIB-4) score, aspartate Aminotransferase to Platelet Ratio Index (APRI), and NAFLD Fibrosis Score (NFS) are the most used, which could greatly help prevent liver biopsy as the gold standard (12).

Triglyceride (TG) and Fasting Plasma Glucose (FPG) are two critical components of MS, in addition to High-Density Lipoprotein cholesterol (HDL-C) and inflammation. TG and FPG are increased in IR, NAFLD, and Atherosclerosis (AS) conditions, and the HDL-C is decreased (13,14). The triglyceride-glucose (TyG) index (calculated by TG and FPG) has recently been proposed as a simple, reliable, cost-effective surrogate marker of IR (15-17), representing a predictive ability comparable with the Homeostasis Model Assessment-Estimated Insulin Resistance (HOMA-IR) (18,19). TyG index is associated with and predicted MS, T2DM, HTN, and subclinical AS (20-23). This predictor has recently been recommended

for diagnosing, predicting, and staging NAFLD in different populations (15,24-29). These risk factors could differ depending on race and sex (30). The associations between NAFLD and these risk factors are controversial (15,31-33).

Moreover, to author's knowledge, previously published research has not precisely considered the associations of TyG and FIB-4 in individuals with T2DM. Given these gaps, the current research is intended to assess the relationship between TyG and FIB-4 in T2DM patients.

Materials and Methods

Study design and participants

During 2023-2024, this prospective cross-sectional research was done at the Endocrine Research Center in Tehran, Iran, and 292 individuals with T2DM were recruited by random sampling. The research protocol (IR.IUMS.REC.1402.558) was approved by the Iran University of Medical Sciences ethics committee, and all participants signed and gave written informed consent. The sample size was determined based on the TyG index standard deviation of 0.62 reported by (32), $\alpha=0.05$, and power=0.8, and the margin of error of 0.1, using the GPower software.

The exclusion criteria included smoking, alcohol abuse, pregnancy, lactation, liver complications (chronic or acute liver infection, inherited liver disorders, liver cirrhosis, autoimmune liver disease), history of malignancy, cardiovascular disorders, gastrointestinal disorders, renal disease, thyroid disorders, and usage of steatotic medications (such as amiodarone, valproate, tamoxifen, methotrexate or corticosteroids) or weight-loss diet or medications, bariatric surgeries, multivitamins, dietary supplements within the last year.

Clinical measurements and definitions

The authors used the American Diabetes Association (ADA) guideline [2019] to define diabetes diagnosis (34). A qualified physician conducted face-to-face interviews. All participants had their demographics, medical histories, and pharmacological factors collected, as well as laboratory tests. Standing height was determined using a calibrated stadiometer (Seca gmbh & co. kg. Germany), and weight was determined using a calibrated digital scale (Seca gmbh

& co. kg. Germany). Weight/height² (kg/m²) was used to compute Body Mass Index (BMI). In a controlled environment, Blood Pressure (BP) was monitored using an electronic monitor (Riester, Exacta 1350, Germany) (seated after 10 min of resting, drinking tea or coffee, and eating food for at least half an hour). After an overnight fast (12-hr), two samples of the blood clot and EDTA anticoagulated tubes were used to examine the biochemistry panel, which included Complete Blood Count (CBC) analysis (with differential evaluation), sugar profile [Fasting Blood Glucose (FBG) and hemoglobin A1c (HbA1c)], liver enzyme tests [Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], and lipid profile.

The optimal cut-off for the target of adequate HbA1c glycemic control is ≤7% (35).

TyG index was calculated using the formula: $\text{Ln} [\text{fasting TG (mg/dl)} \times \text{FPG (mg/dl)}] / 2$ (36). The TyG index (reference range) in lean and overweight subjects is defined as 4.11–4.91 and 4.25–5.05, respectively (37).

FIB-4 score was assessed as the following formula: $\text{age (years)} \times \text{AST (IU/L)} / (\text{platelet count (109/L)} \times \sqrt{\text{ALT (IU/L)}})$. Fibrosis categorization is defined as

follows: low probability, the value of FIB-4 < 1.30, intermediate probability, FIB-4 values between 1.30 and 2.67, and high probability, the value of FIB-4 > 2.67 (12).

Statistical analysis

The mean Standard Deviation (SD) and median (interquartile range (IQR)) were utilized to characterize the continuous variables, and the t-test was employed as the inferential tool in this case. Categorical variables were provided as a percentage (%). Pearson and Spearman correlation coefficients were used to measure the associations between variables. Finally, the linear regression models were fitted on the TyG index and FIB-4 as the response variables, crudely, and adjusted for the covariates. A significance level of .05 was chosen. Stata was used to conduct the statistical analysis (ver. 13).

Results

The sample consisted of 292 diabetes patients, with 166 females (56.9%). There was no missing data in the information. Table 1 describes the measured variables.

Table 1. A description of the measured variables

Variables	Mean	Standard deviation	P ₂₅	Median	P ₇₅
Age (year)	59.4	12.2	52	61	68
BMI (kg/m ²)	28.4	4.7	26	28	31
FBG (mmol/L)	158.5	68.3	115	143	175
HbA1c (%)	7.7	1.7	6.6	7.3	8.6
LDL-C (mmol/L)	77.6	34.1	54	70	97
TG (mmol/L)	158.2	86.7	96	139	199
TC (mmol/L)	148.1	44.3	119	140	171
HDL-C (mmol/L)	42.6	10.3	36	42	48
DM duration (year)	11.9	9.2	5	10	17
SBP (mmHg)	126.2	19.3	113	125	138
DBP (mmHg)	77.4	10.6	70	80	80
FIB-4	1.23	0.74	0.77	1.07	1.48
TyG index	4.96	0.36	4.7	4.93	5.17

Systolic Blood Pressure (SBP); Body Mass Index (BMI); Total Cholesterol (TC); Diabetes Mellitus (DM); Triglyceride (TG); High-Density Lipoprotein Cholesterol (HDL-C); Fibrosis Index Based on 4 Factors (FIB-4); Systolic Blood Pressure (SBP); Triglyceride-Glucose Index (TyG Index); Fasting Blood Glucose (FBG); Hemoglobin A1C (HbA1c); Low-Density Lipoprotein Cholesterol (LDL-C).

Table 2. Spearman correlation coefficients between the outcomes and the covariates

Covariates	Outcomes	
	FIB-4	TyG index
DM duration (year)	0.206	-0.161
SBP (<i>mmHg</i>)	0.181	0.133
DBP (<i>mmHg</i>)	-0.014	0.185
BMI (<i>kg/m²</i>)	-0.039	0.224
HbA1c (%)	-0.082	0.482
Age (year)		-0.185
TC (<i>mmol/L</i>)	-0.159	
TG (<i>mmol/L</i>)	-0.146	
HDL-C (<i>mmol/L</i>)	-0.141	
LDL-C (<i>mmol/L</i>)	-0.089	
FBG (<i>mmol/L</i>)	-0.188	

Systolic Blood Pressure (SBP); Body Mass Index (BMI); Total Cholesterol (TC); Diabetes Mellitus (DM); Triglyceride (TG); High-Density Lipoprotein Cholesterol (HDL-C); Fibrosis Index Based on 4 Factors (FIB-4); Systolic Blood Pressure (SBP); Triglyceride-Glucose Index (TyG Index); Fasting Blood Glucose (FBG); Hemoglobin A1C (HbA1c); Low-Density Lipoprotein Cholesterol (LDL-C).

The association between FIB-4 and the TyG index was examined by calculating the Spearman correlation coefficient, resulting in a value of -0.18 (p-value=0.002), indicating a weak indirect association. Additionally, the Spearman correlation coefficients between the outcomes and covariates are detailed in table 2, with significant correlations being highlighted in bold font.

Given the results, FIB-4 showed direct associations with DM duration and Systolic Blood Pressure

(SBP) and inverse associations with FBG and Total Cholesterol (TC). Moreover, the TyG index was found to have direct associations with HbA1c, BMI, and Diastolic Blood Pressure (DBP), along with inverse associations with age and DM duration. However, except for the moderate relationship between the TyG index and HbA1c, the remaining correlations could be characterized as weak.

Univariate linear regression models of the response variables TyG index and FIB-4 were fitted on the covariates, ensuring that the constituents of each were not included in the relevant model. Subsequently, covariates with p-values <0.1 were included in the multivariate model. Due to a Spearman correlation of 0.60 between SBP and DBP, and 0.49 between TC and TG, only one of each pair was included in the adjusted model. Additionally, as FIB-4 measurements did not adhere to a normal distribution, their logarithm-transformed values were utilized in the regression models. The results are presented in table 3. In the adjusted regression model, a 0.004 (95% CI: 0.001, 0.007) increase in the TyG index is indicated for a 1-*mmHg* increase in SBP. Considering the applied logarithm transformation, the adjusted model suggests that 1-unit increases in DM duration, SBP, TG, and HDL-C result in increases of 0.9, 0.4%, and decreases of 0.1 and 0.8% in FIB-4, respectively.

Considering the Pearson correlation of -0.17 between ln (FIB-4) and the TyG index (p-value 0.003), a linear regression model was applied to the TyG index. The model revealed a 2.4% (95% CI: 7.8, 32.9 %) decrease in FIB-4 per a 0.1 unit increase in the TyG index.

Moving forward, the stratified version of FIB-4 was utilized as the response variable, with 215 patients categorized as having low values and 77 as having intermediate values. This variable served as the

Table 3. Fitting linear regression models on the TyG index and FIB-4

Outcomes	Variables	Crude		Adjusted	
		Regression coefficients	p-value	Regression coefficients	p-value
TyG index	DM duration	-0.007(-0.012,-0.003)	0.002	-0.005(-0.011,0.001)	0.113
	SBP	0.002(0.000,0.004)	0.039	0.004(0.001,0.007)	0.012
	DBP	0.007(0.003,0.011)	0.001		
	BMI	0.012(0.001,0.023)	0.036	0.007(-0.004,0.018)	0.186
	Age	-0.004(-0.008,-0.001)	0.011	-0.004(-0.009,0.000)	0.068

Contd. table 3.

FIB-4	DM duration	0.011(0.004,0.017)	0.001	0.009(0.003,0.015)	0.005
	SBP	0.004(0.001,0.007)	0.004	0.004(0.001,0.007)	0.005
	DBP	0.001(-0.005,0.006)	0.818		
	BMI	-0.005(-0.020,0.010)	0.501		
	TC	-0.002(-0.003,-0.001)	0.005		
	TG	-0.001(-0.001,0.000)	0.018	-0.001(-0.002,0.000)	0.008
	HDL-C	-0.007(-0.012,-0.001)	0.024	-0.008(-0.013,-0.002)	0.006
	LDL-C	-0.001(-0.003,0.000)	0.147		
	FBG	-0.001(-0.002,0.000)	0.099		
	HbA1c	-0.017(-0.052,0.018)	0.343		

FIB-4 was fitted in the logarithm-transformed manner; Systolic Blood Pressure (SBP); Body Mass Index (BMI); Total Cholesterol (TC); Diabetes Mellitus (DM); Triglyceride (TG); High-Density Lipoprotein Cholesterol (HDL-C); Fibrosis Index Based on 4 Factors (FIB-4); Systolic Blood Pressure (SBP); Triglyceride-Glucose Index (TyG Index); Fasting Blood Glucose (FBG); Hemoglobin A1C (HbA1c); Low-Density Lipoprotein Cholesterol (LDL-C).

response in a logistic regression model fitted to the TyG index. A 0.1 unit increase in the TyG index resulted in a 10.5% decrease in the likelihood of transitioning from the low to the intermediate state of FIB-4 (95% CI: 3.1-17.5%). The corresponding model produced an area under the ROC curve of 61.3% (TyG index cutoff of 4.88, with a sensitivity of 59.7% and specificity of 61.4%).

As a side note, to compare the impacts of its two constituent components on the TyG index, linear regression models were employed for each of them, using standardized regression coefficients. Coefficients (95% confidence intervals) of 0.85 (0.79-0.91) and 0.70 (0.61-0.78) were derived for TG and FBG, respectively. Additionally, 126 patients with adequate HbA1c control and 166 with inadequate control exhibited means (SDs) of 4.81 (0.31) and 5.08 (0.36) for the TyG index, respectively (p -value<0.001). As a result, the standardized regression coefficients for TG and FBG were calculated in this stratified approach. They were found to be 0.89 (0.81-0.97) and 0.61 (0.46-0.75) for patients with adequate HbA1c control, and 0.85 (0.77-0.93) and 0.70 (0.59-0.81) for those with inadequate control. This suggests a substantial discrepancy between the impact of TG

and FBG, especially among patients with adequate HbA1c control.

Discussion

To the authors knowledge, little research has considered the associations of TyG and FIB-4 in individuals with T2DM; the existing data are controversial.

Hepatic inflammation and metabolic abnormalities, as the major effective components for NAFLD induction, are demonstrated in the most important cardio-metabolic risk factors, including obesity, IR, MS, T2DM, HTN, and dyslipidemia (6,39). Given the importance of NAFLD progression to NASH in T2DM, early (screening, diagnosis, and staging), the understanding of the relation to the other biomarkers, and the prediction of this condition are critical.

The findings of the present study highlight several key associations among various clinical parameters in the Iranian diabetic population. A significant negative association between the FIB-4 and the TyG index, indicating a potential interplay between LF and IR. Notably, the TyG index demonstrated a 2.4% decrease in FIB-4 for every 0.1 unit increase.

In total analysis, a direct association between FIB-4

and DM duration suggests a potential relationship between LF and the duration of diabetes, emphasizing the potential impact of prolonged hyperglycemia on LF.

An inverse association between FIB-4 and FBG in our study highlights a complex interplay between LF and glycemic control; despite the presence of glycemic control, other factors such as DM duration could affect the LF.

The TyG index displayed direct associations with both HbA1c and BMI, indicating a potential link between IR and long-term glycemic control, as well as adiposity. These findings contribute to the understanding of the multifaceted relationships between liver function, IR, and metabolic parameters. To manage diabetic patients' disease conditions, a two-sided approach is taken.

On one hand, TG (as a component of metabolic dyslipidemia) is tried to be lowered through a recommendation of dietary management (medical nutrition therapy) of low carbohydrates, exercise, and weight loss. As clinical experience has shown, the dietary approaches for TG are not usually complied with by patients; as a result, the TG is not lowered by itself, and also the medical control of high TG has ended with conflicting and disappointing results. The high TG level was significantly associated with inadequate glycemic control, so the direct TG suppressors may help to optimize glycemic control in T2DM (40). In another way, Davidson *et al* demonstrated that the effect of HbA1C reduction has limited effects on TG reduction, so if the TG suppressors were initiated earlier, they may have more benefits in T2DM rather than waiting for glycemic control (41).

On the other hand, FBG is targeted using oral glucose-lowering drugs (OGLDs). The OGLD compliance is higher and lowers the FBG level, which, to some extent makes declines in the TG level, in line with Babic *et al* (42). Babic *et al* concluded that the TyG index was a useful predictor of glycemic control (HbA1C) in overweight and obese diabetic participants (42). So, the TyG index could be a worthy surrogate biomarker of glycemic control, besides HbA1C.

According to Tutunchi *et al*, the TyG index increased, which is positively correlated with NAFLD fibrosis

score and worsening of NAFLD severity in the Iranian NAFLD population (11). Guo *et al* (43). suggested that the TyG index was positively associated with the presence of LF after adjustment for probable confounders in Chinese NAFLD patients. Korean research detected a significant positive relationship between the severity of NAFLD and LF with the TyG index (26), but the HOMA-IR was preferable. In another Iranian study, Khamseh *et al* (44) highlighted a significant association between the TyG index and its related indices, including TyG-BMI and TyG-waist circumference, with NAFLD and LF in overweight/obese subjects. In the other research, the TyG index was exhibited as the best screening biomarker for steatosis and NASH (45,46). Li *et al* described a significant association between the TyG index and NAFLD in atrial fibrillation patients (32). Zhu *et al* found a remarkable association between the TyG index and a single nucleotide polymorphism, which has been shown to play a crucial role in LF (47). The differences between the mentioned studies and the present one could be multifactorial; on one side could be the effect of glycemic and TG management, and on the other side, the amount of glucose and TG changes.

On the contrary, Smiderle *et al* reported that the TyG index didn't perform well in the significant hepatic steatosis and NASH in obese patients (2). The predictive power of FIB-4 and TyG index was lower than that of the other novel useful markers for NAFLD in the Song *et al* study (48). Jeji *et al* assessed the LF in NAFLD patients and determined that the TyG index was not superior to FIB-4 (31).

In the studied multivariate regression models, an increment in SBP was observed that was associated with TyG index elevation. Conversely, by HDL-C increment, a decrement of FIB-4 is detected, suggesting a protective role of HDL-C against LF, which is in line with Putra *et al* (42,49).

At last, the relationship between the TyG index and FIB-4 was explored, dividing patients into low and intermediate categories, indicating an increase in the TyG index associated with a notable decrease in the likelihood of moving from the low to the intermediate FIB-4 state. This suggests that the TyG index could be a useful predictor of LF risk in clinical settings.

Additionally, the individual contributions of TG

and FBG to the TyG index was examined. The analysis revealed distinct effects of TG and FBG on the TyG index. Notably, the impact of these components varied among patients with different levels of HbA1c control, highlighting the complex relationship between metabolic factors and the TyG index, particularly in terms of glycemic control. These findings underscore the need for personalized approaches in assessing cardiovascular risk, with implications for tailored interventions and risk stratification in clinical practice.

The various directions of relationships between any biomarkers could be affected by the pathway of NAFLD diagnosis, population, and ethnic groups, different diseases, various sample sizes, different cutoffs, management of the comorbid diseases, different indices, and the modified formats of the indices.

Strengths and limitations

The merit of this study lies in being the first study on FIB-4 and TyG index in diabetic patients. As a limitation, the low sample size might have prevented some correlations from reaching significance. Thus, future larger studies based on a higher sample size could obtain more robust correlations. Moreover, the observational nature of this study is a hurdle in drawing causal conclusions from the findings.

Conclusion

In conclusion, this study reveals a negative association between FIB-4 and the TyG index. FIB-4 exhibited a positive correlation with DM duration and negative associations with FBS and HDL-C, while the TyG index demonstrated positive associations with HbA1c, BMI, and SBP. This study provides valuable insights into the complex relationships

between liver fibrosis, insulin resistance, and metabolic parameters. Further research is warranted to elucidate the underlying mechanisms and clinical implications of these associations.

Ethics approval and consent to participate:

The Iran University of Medical Sciences ethical committee approved this project (the ethical code is IR.IUMS.REC.1402.558). Written informed consent was obtained from all subjects. The authors attest that the participants knew the study's purpose, risks, and benefits. Anonymity was maintained throughout the study period. All activities and methods for the study were carried out considering research ethics guidelines for Iran. All procedures performed in human participant studies followed the institutional and/or national research committee's ethical standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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