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ORIGINAL ARTICLE

Triglyceride glucose-waist to height ratio: a novel and effective marker for identifying hepatic steatosis in individuals with type 2 diabetes mellitus

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Abstract

Background The triglyceride-glucose index (TyG), and TyG-driven parameters incorporating TyG and obesity indices have been proposed as reliable indicators of insulin resistance and its related comorbidities. This study evaluated the effectiveness of these indices in identifying hepatic steatosis in individuals with Type 2 diabetes (T2DM).

Methods This was a cross-sectional study consisting of 175 patients with T2DM (122 with and 53 without NAFLD). TyG index, triglyceride glucose-body mass index (TyG-BMI), triglyceride glucose-waist circumference (TyG-WC), and triglyceride glucose-waist-to-height ratio (TyG-WHtR) were determined using standard formulas. Controlled attenuation parameter (CAP) was measured by transient elastography (FibroScan).

Results Among obesity parameters, CAP showed the strongest correlation with WHtR, followed by BMI and WC (all $P < 0.001$). Regression analyses demonstrated TyG-WHtR as a significant predictor of NAFLD with the highest odds ratio, reaching 10.69 (95% CI: 1.68–68.22) for the top quartile (Q4) compared to the first quartile ($P = 0.01$), followed by TyG-BMI (Q4: 6.75; 95% CI: 1.49–30.67) and TyG-WC (Q4: 5.90; 95% CI: 0.99–35.18). Moreover, TyG-WHtR presented the largest AUC for detection of NAFLD (0.783, $P < 0.001$) in ROC analysis, followed by TyG-BMI (AUC: 0.751, $P < 0.001$), TyG-WC (AUC: 0.751, $P < 0.001$), and TyG (AUC: 0.647, $P = 0.002$). TyG-WHtR value of 5.58 (sensitivity: 79%, specificity: 68%, $P < 0.001$) was the best cut-off point to identify hepatic steatosis in this population.

Conclusions This study confirmed that the TyG-related indices comprising TyG and obesity parameters can identify hepatic steatosis more successfully than TyG alone. Furthermore, our results highlighted TyG-WHtR as a simple and effective marker for screening fatty liver in patients with T2DM, which may be used practically in clinical setting.

Keywords TyG · TyG-WC · TyG-BMI · TyG-WHtR · Non-alcoholic fatty liver disease · Diabetes mellitus · Hepatic steatosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common liver disorder characterized by accumulation of excessive fat in hepatocytes in the absence of high alcohol consumption [1]. NAFLD comprises a wide spectrum of histopathologic features from a benign steatosis to non-alcoholic steatohepatitis, fibrosis, and cirrhosis [1].

There is a growing body of evidence demonstrating a bidirectional link between NAFLD and type 2 diabetes mellitus (T2DM) [2]. While, the prevalence of NAFLD is almost 25% in general population, it increases to over 60% for individuals with T2DM [3, 4]. Furthermore, patients with T2DM have an increased risk for developing the more advanced forms of NAFLD [5, 6], leading to higher rates of mortality and morbidity [7]. Of note, NAFLD is typically asymptomatic until the advanced stages [8], highlighting the importance of exploring accurate non-invasive tools for prediction and early diagnosis of fatty liver, particularly in high-risk groups including those with diabetes.

Triglyceride and glucose index (TyG) is a novel biomarker which has been initially proposed as a surrogate

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measure of insulin resistance [9]. Subsequent epidemiological studies, however, confirmed a close relationship between the elevated levels of TyG index and the incidence of T2DM and NAFLD [10, 11]. More recently, emerging evidence indicates that the TyG-related parameters combining TyG and obesity indices may have a higher predictive ability than TyG alone [12–14]. However, despite these findings and the strong evidence linking both T2DM and NAFLD to obesity [15], there is a paucity of data regarding the association of these indices with fatty liver in diabetic patients. Accordingly, the present study aimed to evaluate the predictive power of TyG index and its related parameters (TyG-WC, TyG-BMI, and TyG-WHtR) for detecting hepatic steatosis in individuals with T2DM.

Methods

Subjects and study design

This was a cross-sectional study carried out in the Institute of Diabetes and Metabolism, Iran University of medical sciences. Eligible participants were insulin-naïve adults with T2DM aged 30–65 years. Exclusion criteria were as follows: hepatitis (including viral, drug induced, or autoimmune), hemochromatosis, primary sclerosing cholangitis, primary biliary cirrhosis, cancer, presence of any cystic or solid mass in liver, alcohol consumption more than 20 ml/day, and pregnant or breast feeding women.

Clinical measurements

Weight and height were measured using OMRON BF511 body composition monitor and stadiometer, respectively. Body mass index (BMI) was calculated as weight (kg)/[height(m)]². Waist circumference (WC) was measured midpoint between the lowest ribs and the iliac crest using a non-elastic plastic tape. Controlled attenuation parameter (CAP) was measured by transient elastography (TE) using the FibroScan®, equipped with M and XL probes. The CAP value ≥288 dB/m was used as the cut-off level for diagnosing hepatic steatosis [16].

Laboratory measurements

Venous blood samples were collected after a 10–12 h overnight fast. Plasma and serum samples were then stored at −80 °C until analyses. Enzymatic colorimetric method was used to determine fasting blood glucose level. Enzymatic assays were also performed to measure serum levels of triglyceride, total cholesterol, and high-density lipoprotein (HDL) using standard biochemical kits (Pars Azmun Co., Iran) with between- and within-run coefficient of variations <6.2%. Low-density lipoprotein (LDL) was computed from modified version of Friedewald equation [17]. Roche Diagnostics kits (Roche Cobas 6000 analyzer) were used for serum insulin evaluation with ECLIA method. HOMA-IR was calculated as fasting glucose (mg/dl) × fasting insulin (μU/ml)/405 [18]. TyG index was determined as Ln [TG (mg/dl) × fasting glucose (mg/dl)/2] [9]. TyG was multiplied by WHtR (waist-to-height ratio), BMI, and WC to produce TyG-WHtR, TyG-BMI, and TyG-WC [13, 14], respectively. Hepatic steatosis index (HSI) was calculated as ALT/AST ratio × 8+ BMI (+2 for female; +2 for diabetes mellitus) [19]. Comprehensive index (CI) was calculated by $-0.063 \times \text{weight} + 0.065 \times \text{WC} + 0.315 \times \text{BMI} - 2.165 \times \text{AST/ALT} + 0.935 \times \text{TG} + 0.276 \times \text{FPG} - 11.236$ [20]. The NAFLD liver fat score (NAFLD-FLS) was calculated by 1.18 × metabolic syndrome (1 if yes; 0, if no) + 0.45 × diabetes (2, if yes; 0, if no) + 0.15 × fasting serum insulin (mU/L) + 0.04 × AST (U/L) − 0.94 × AST/ALT − 2.89 [21].

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for windows (Version 22.0 IBM Corp. Released 2013. Armonk, NY). Continuous variables are presented as means ± standard deviation or medians with interquartile range (IQR) for skewed data. The differences between groups with and without NAFLD were examined using χ^2 test, independent sample *t*-test or Mann–Whitney U test, as appropriate. The correlations of CAP score with variables of interest were assessed using Spearman's rank-order correlation coefficients (r_s), after controlling for age and gender. TyG and TyG-related indices were compared across quartiles of CAP score using ANOVA and Kruskal–Wallis tests. Logistic regression analyses were performed to evaluate the association of TyG and TyG-related parameters with NAFLD as a dependent variable. The crude and adjusted odds ratios (95% CI) for NAFLD in quartiles 2–4 of each index were estimated and compared to the first quartile as a reference. The discriminative power of TyG and its related markers were evaluated using the receiver operating characteristic curve (ROC) analysis. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Data were analyzed from 175 diabetic patients (80 men and 95 women), comprising 122 participants with and 53 without NAFLD (Table 1). The mean ages of participants were 49.9 ± 8.7 and 46.7 ± 8.5 years in the NAFLD and control groups, respectively. The two groups of participants were comparable in terms of gender, diabetes duration,

Table 1 Demographic and clinical characteristics of participants by the presence of liver steatosis

	Control group ($n = 53$)	NAFLD group ($n = 122$)	*P*-value
Age (year)	46.72 ± 8.53	49.89 ± 8.65	0.027
Female (%)	24 (45.3%)	71 (58.2%)	0.115
BMI (kg/m^2)	27.93 ± 3.90	31.18 ± 4.15	<0.001
WC (cm)	98.32 ± 9.06	106.68 ± 10.28	<0.001
WHR	0.96 (0.91–0.99)	1.00 (0.95–1.05)	<0.001
WHtR	0.59 ± 0.06	0.65 ± 0.07	<0.001
SBP (mmHg)	115.96 ± 12.56	118.02 ± 12.68	0.325
DBP(mmHg)	73.75 ± 9.48	73.39 ± 9.78	0.817
Glucose (mg/dl)	128.00 (106.00–159.00)	151.00 (127.75–183.00)	0.003
A1C (%)	7.40 (6.40–8.50)	8.05 (7.30–8.90)	0.017
Total cholesterol (mg/dl)	134.00 (119.50–163.50)	151.00 (126.00–171.00)	0.061
Triglyceride (mg/dl)	130.00 (89.50–181.00)	158.00 (115.50–226.50)	0.012
HDL.chol (mg/dl)	45.11 ± 11.22	45.26 ± 9.46	0.929
LDL.chol (mg/dl)	75.30 ± 27.42	83.73 ± 25.43	0.052
Insulin (μIU/ml)	8.40 (6.69–12.33)	13.78 (10.54–19.35)	<0.001
HOMA-IR	2.82 (2.03–4.88)	5.07	<0.001
ALT (IU/l)	19.00 (12.00–27.00)	22.00 (15.00–35.25)	0.089
AST (IU/l)	20.00 (17.00–25.00)	21.00 (15.75–30.50)	0.321
CAP (dB/m)	265.00 (250.00–280.00)	322.50 (310.00–369.40)	<0.001
HSI	38.99 ± 5.45	43.09 ± 5.04	<0.001
CI	164.80 (113.71–202.59)	190.39 (144.44–259.74)	0.005
NAFLD-FLS	−0.05 (−0.88,0.96)	1.11 (−0.004, 2.07)	<0.001
TyG index	9.04 (8.60–9.45)	9.32 (8.97–9.90)	0.002
TyG-BMI	249.81 (220.75–281.61)	284.00 (262.50–318.35)	<0.001
TyG-WC	893.86 ± 112.68	1008.69 ± 125.46	<0.001
TyG-WHtR	5.37 ± 0.66	6.16 ± 0.77	<0.001
Smoking, *n* (%)	13 (24.5%)	16 (13.1%)	0.06
Diabetes duration (y)	6.00 (4.00–10.00)	6.00 (3.00–10.00)	0.667
Physical activity (MET-min/week)	834.0 (369.0–2958.0)	1518.0 (636.0–3054.5)	0.156

Continuous data are presented as means ± SD or medians with interquartile range (IQR) for skewed data; categorical data are presented as number (%); between-group comparisons were performed using χ^2 test, independent sample *t*-test or non-parametric tests, as appropriate

WHR waist to hip ratio, *WHtR* waist to height ratio, *CAP* controlled attenuation parameter, *NAFLD-FLS* NAFLD-liver fat score, *HSI* hepatic steatosis index, *CI* comprehensive index

systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, HDL-chol, AST, ALT, and physical activity levels. However, diabetic patients with NAFLD had significantly higher BMI, waist circumference (WC), waist to height ratio (WHtR), fasting glucose, triglyceride (TG), HbA1C, CAP score, TyG, TyG-BMI, TyG-WC, and TyG-WHtR than those without NAFLD (all *P* values <0.05).

In correlation analyses, CAP score was significantly associated with WC ($r_s = 0.437$, $P < 0.001$), WHtR ($r_s = 0.482$, $P < 0.001$), BMI ($r_s = 0.478$, $P < 0.001$), FPG ($r_s = 0.219$, $P = 0.004$), TG ($r_s = 0.216$, $P = 0.005$), AST ($r_s = 0.194$, $P = 0.011$), and ALT ($r_s = 0.243$, $P = 0.001$), after controlling for age and gender.

The comparisons of TyG and TyG-related parameters across the quartiles of CAP showed significant between-quartile differences as well as significant upward trends for all indices ($P < 0.001$) (Table 2). Subsequent logistic regression analyses highlighted TyG-WHtR as a significant predictor of NAFLD with the highest odds ratio (OR) both before and after adjustment, reaching 10.69 (95% CI: 1.68–68.22) for the top quartile (Q4) compared to the first quartile ($P = 0.01$), followed by TyG-BMI (Q4, OR: 6.75; 95% CI: 1.49–30.67), TyG-WC (Q4, OR: 5.90; 95% CI: 0.99–35.18) and TyG (OR, Q4: 2.83; 95% CI: 0.45–17.95) (Table 3).

The results of ROC curve analyses of TyG index and related parameters for predicting NAFLD are summarized

Table 2 TyG and related parameters in total participants by CAP score quartiles

	Q1 [193–280 dB/m] ($n = 44$)	Q2 [280–310 dB/m] ($n = 44$)	Q3 [310–335 dB/m] ($n = 44$)	Q4 [335–400 dB/m] ($n = 43$)	P-value† between group	P-value‡ for trend
TyG index	9.00 (8.55–9.37)	9.25 (8.92–9.66)	9.38 (9.02–9.92)	9.50 (8.97–10.16)	0.002	<0.001
TyG-BMI	242.05 (217.62–277.15)	273.26 (255.12–296.54)	280.45 (258.97–302.19)	305.38 (276.95–361.01)	<0.001	<0.001
TyG-WC	875.65 (794.18–954.11)	941.65 (860.91–1040.49)	1000.27 (929.23–1044.52)	1078.80 (937.42–1163.77)	<0.001	<0.001
TyG-WHtR	5.31 ± 0.68	5.93 ± 0.75	6.06 ± 0.64	6.40 ± 0.83	<0.001	<0.001

Continuous variables are expressed as mean ± SD or as median (IQR) for skewed data

†P-value from ANOVA test and Kruskal–Wallis test for normally distributed and skewed variables, respectively

‡P-value from ANOVA test and Jonckheere–Terpstra test for normally distributed and skewed variables

in Table 4. In line with the regression analyses, TyG-WHtR presented the largest area under the ROC curve (AUC) for detection of hepatic steatosis (0.783, 95% CI: 0.714–0.842), followed by TyG-BMI (0.751, 95% CI: 0.670–0.833), TyG-WC (0.751, 95% CI: 0.671–0.832), and TyG (0.647, 95% CI: 0.557–0.737). Using ROC analysis, TyG-WHtR value of 5.58 (sensitivity: 79%, specificity: 68%, $P < 0.001$) was the best cut-off point to identify hepatic steatosis in individuals with T2DM.

Discussion

In the present study, we evaluated the predictive ability of TyG and three TyG-derived indices of TyG-BMI, TyG-WC, and TyG-WHtR to identify hepatic steatosis in individuals with T2DM. Following introducing TyG index as a reliable surrogate marker for insulin resistance [22], growing attentions have been attracted to examine its association with NAFLD and T2DM as the main consequences of insulin resistance [10, 23, 24]. In this context, a cross-sectional study conducted on a large cohort of Chinese people showed that TyG index was successful in detecting individuals at risk of NAFLD with a high sensitivity and specificity [10]. TyG index was also reported to have a better performance in predicting hepatic steatosis compared to HOMA-IR (homeostasis model assessment of insulin resistance) [25], alanine transaminase (ALT) [10], fatty liver index (FLI), algorithm test, Nash Test and Steato Test [26]. Meanwhile, longitudinal studies on different non-diabetic populations highlighted TyG index as a meaningful indicator of the risk for future diabetes [23, 27], with a predictive power stronger that HOMA-IR [23]. The predictive ability of TyG index can be explained by the known association between its two components (TG and FPG) and insulin resistance [22, 28, 29], which in turn promotes the progression of both fatty liver and T2DM [24]. Other probable explanation could involve glucotoxicity and lipotoxicity pathways, playing key roles in the pathogenesis of NAFLD particularly in individual with type 2 diabetes mellitus [25, 30–32].

This study showed that the combination of obesity parameters with TyG could predict NAFLD in individuals with T2DM more successfully than TyG alone. Furthermore, we found that TyG-WHtR had a better performance than the other indices, with a higher odds ratio and the largest AUC in the ROC analysis. These results are in part consistent with previous studies comparing the predictive ability of TyG with its related indices in different populations [33–35]. For instance, Zhang et al. reported that TyG-BMI performed better than its components (i.e., TG, FBS, BMI, and TyG index) to detect fatty liver in the non-obese Chinese [33]. The significant association of TyG-BMI with

Table 3 The crude and adjusted odds ratios for liver steatosis in quartiles of TyG and TyG-related indices

Parameters	Model 1			Model 2		
	B	Crude OR (95% CI)	*P*-value	B	AOR (95% CI)	*P*-value
TyG			0.01			0.44
1st Q		1			1	
2nd Q	1.10	3.00 (1.22–7.40)	0.02	0.62	1.86 (0.59–5.92)	0.29
3rd Q	0.98	2.67 (1.10–6.48)	0.03	0.04	1.05 (0.27–4.06)	0.95
4th Q	1.48	4.38 (1.66–11.53)	0.003	1.04	2.83 (0.45–17.95)	0.27
P for trend		0.004			0.35	
TyG-BMI			<0.001			0.006
1st Q		1			1	
2nd Q	1.66	5.25 (2.10–13.15)	<0.001	1.86	6.43 (1.82–22.68)	0.004
3rd Q	2.23	9.25 (3.35–25.52)	<0.001	2.07	7.96 (2.17–29.21)	0.002
4th Q	2.20	9.00 (3.26–24.87)	<0.001	1.91	6.75 (1.49–30.67)	0.01
P for trend		<0.001			0.02	
TyG-WC			<0.001			0.04
1st Q		1			1	
2nd Q	1.13	3.10 (1.30–7.42)	0.01	1.39	4.00 (1.13–14.13)	0.03
3rd Q	1.87	6.50 (2.46–17.21)	<0.001	2.07	7.94 (1.78–35.48)	0.007
4th Q	2.40	10.98 (3.62–33.29)	<0.001	1.78	5.90 (0.99–35.18)	0.05
P for trend		<0.001			0.03	
TyG-WHtR			<0.001			0.003
1st Q		1			1	
2nd Q	2.27	9.64 (3.57–26.07)	<0.001	2.14	8.53 (2.43–30.00)	0.001
3rd Q	1.74	5.71 (2.28–14.31)	<0.001	0.93	2.54 (0.61–10.65)	0.20
4th Q	3.35	28.57 (7.53–108.44)	<0.001	2.37	10.69 (1.68–68.22)	0.01
P for trend		<0.001			0.02	

Each parameter was entered as categorical covariate in a separate analysis; Model 1: With no adjustment; Model 2: Adjusted for age, gender, waist to hip ratio, systolic blood pressure, diastolic blood pressure, serum cholesterol, HDL.chol, LDL.chol, ALT, AST, A1C, HOMA-IR, statin medication, diabetes duration, smoking, and physical activity

Table 4 Results of the receiver operating characteristic (ROC) curve analyses of different predictors of liver steatosis

Parameters	AUC	SE	95% CI	*P*-value
TyG index	0.647	0.046	0.557–0.737	0.002
TyG-BMI	0.751	0.042	0.670–0.833	<0.001
TyG-WC	0.751	0.041	0.671–0.832	<0.001
TyG-WHtR	0.783	0.038	0.708–0.858	<0.001
NAFLD-FLS	0.702	0.043	0.617–0.786	<0.001
Hepatic steatosis index	0.718	0.046	0.629–0.807	<0.001
Comprehensive index	0.632	0.046	0.541–0.723	0.005

NAFLD was also confirmed in a population-based study on Japanese people [34]. Moreover, it was shown that TyG-WC may be superior to TyG in identifying NAFLD in individuals with overweight and obesity [36]. On the other hand, there is evidence suggesting TyG index, TyG-WC, or TyG-BMI as effective markers for assessment of glycemic control [37], and prediction of some concomitant diabetic complications [38]. Despite these findings and the known association between NAFLD and T2DM, as far as we know, there has been only one preliminary report considering these indices for predicting NAFLD among diabetic patients [39]. In line with our results, they remarked that TyG-BMI had a better discriminative power to identify NAFLD in both diabetic men and women compared to TyG. In this context it should be noted that, to the best of our knowledge, none of the former studies which were conducted on individuals with or without diabetes, evaluated the effectiveness of TyG-WHtR with respect to fatty liver. Accordingly, the present study is the first to introduce this index as an effective indicator of hepatic steatosis, with focus on patients with T2DM.

Of obesity parameters assessed, we found that CAP score showed the strongest correlation with WHtR followed by BMI and WC. There is increasing evidence supporting the close association of fatty liver with obesity, specifically visceral adiposity [40, 41]. However, there is still some controversy regarding the best obesity index to predict

NAFLD. BMI and WC are anthropometric parameters widely used in evaluation of patients with fatty liver [42]. However, given limitations in reflecting body fat distribution, BMI is primarily accepted as a proxy measure of total body fat; [43] and WC, a measure of abdominal obesity, is demonstrated to be associated more strongly with subcutaneous fat rather than visceral adipose tissue [44]. Moreover, it was shown that WC might be less effective to predict cardiovascular risk in individuals who are tall or short [45]. On the other hand, WHtR is another indicator of central obesity taking both WC and height into account, and is supported to outperform BMI and WC in detecting various cardiometabolic disorders and metabolic syndrome, particularly in Asians [46, 47]. In a cross-sectional study, Zheng et al. reported an AUC above 0.87 for the WHtR to predict NAFLD in Chinese people [48]. This result was also evidenced by a population-based study conducted on over 4800 Iranian adults, which showed WHtR as an effective indicator of NAFLD [49]. Similarly, Ghanaei et al. [50] reported that WHtR was superior to BMI and WC for identifying fatty liver in a recent study involving 960 participants. Superiority of WHtR in detecting hepatic steatosis is also supported by the evidence suggesting WHtR as the best anthropometric indicator of both whole body fat percentage and visceral adipose tissue in men and women [51, 52]. Considering these findings, it could be expected that the parameter incorporating TyG and WHtR (TyG-WHtR) would predict NAFLD more effectively than TyG-WC and TyG-BMI.

The main strength of the present study is its novelty to evaluate TyG-WHtR, along with TyG-BMI and TyG-WC as markers for prediction of fatty liver. One limitation of this study is the lack of performing liver biopsy as the gold standard method for evaluating NAFLD status. However, liver steatosis was diagnosed using transient elastography as a more sensitive and specific method compared to ultrasonography [53] which was used commonly in the previous studies in this field [10, 25, 33, 34]. Besides, a relatively small sample size precluded us to examine the associations of TyG and its related indices with liver steatosis by gender, separately. Finally, this study was conducted in patients with T2DM, limiting the generalizability of the findings to non-diabetic populations. Given the paucity of data on this topic, more comprehensive research investigating the association of TyG-WHtR with fatty liver in diabetic/non-diabetic men and women separately, as well as further validation cohort studies would be worthwhile.

Conclusion

The present study supported the notion that the TyG-related parameters comprising both TyG and obesity indices are superior to TyG alone in identifying individuals with hepatic steatosis. Furthermore, our findings highlighted TyG-WHtR as an effective indicator of fatty liver in patients with T2DM. Given the accessibility and simplicity of calculation, these indices could be widely used for screening hepatic steatosis in individuals with T2DM in clinical settings.

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Author contributions M.E.K., M.M., and F.A.S. were involved in the conception and design of the study. S.N. and H.C. were involved in data collection. Data were analyzed and interpreted by F.A.S. who was also involved in drafting the manuscript. All authors have participated in reviewing the manuscript and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval The current study was carried out under Helsinki Declaration and approved by ethics committee of Iran University of Medical Sciences (Approval number: IR.IUMS.REC.1398.1045).

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