Comparison of triglyceride-glucose index and anthropometric obesity indices in predicting severe grades of hepatic steatosis in nonalcoholic fatty liver disease among non-diabetic obese individuals

Running title: Triglyceride glucose index and fatty liver disease

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Abstract

Background and Aim: The triglyceride glucose index (TyG) has been proposed as a promising indicator of both insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD). However, the efficacy of the TyG index in predicting NAFLD has not been adequately studied, particularly in obese individuals.

Materials and Methods: We analyzed 190 morbidly obese individuals. The TyG index, anthropometric obesity indices, homeostatic model assessment (HOMA-IR), and biochemical parameters were compared. NAFLD was diagnosed by hepatic ultrasonography and classified into four grades (0, 1, 2, and 3). Those in grades 2 and 3 are considered to have severe steatosis, while those in grades 0 and 1 are not.

Results: The area under the curve (AUC) values of the TyG index, body mass index (BMI), neck circumferences (NC), waist-to-hip ratio (WHR), and HOMA-IR did not differ significantly in predicting severe steatosis (0.640, 0.742, 0.725, 0.620 and 0.624 respectively). However, the AUC values of waist circumferences and alanine aminotransferase provided better predictions than the TyG index (0.782, 0.744 and 0.640 respectively).

Conclusions: The TyG index is highly effective in predicting both the presence and severity of NAFLD. The TyG index, however, did not outperform simple obesity indices in predicting NAFLD and its severity in obese patients.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing pathology in parallel with the increasing global prevalence of obesity and type 2 diabetes mellitus. Currently, it is estimated to affect 25-30% of adults worldwide. Considering the potential for NAFLD to progress from simple steatosis to end-stage liver disease, it is expected to become the most common cause of chronic liver disease and liver transplantation in the near future.[1] Although the pathophysiology of NAFLD is not well understood, IR has been identified as a significant factor in both the initiation and progression of the disease.[2]

In recent years, the triglyceride glucose index (TyG), which is derived from fasting plasma glucose (FPG) and triglycerides (TG), has gained popularity as an alternative measurement of IR. Several studies have shown that the TyG index is highly correlated with both the Homeostatic Model Assessment (HOMA-IR) and the hyperinsulinemic-euglycemic clamp tests in assessing IR.[3,4] Further studies have shown that it is also effective in predicting NAFLD both in adults and adolescents.[5-8] Based on the link between obesity, IR, and NAFLD, modified TyG indices have recently been developed by combining the TyG index with anthropometric obesity indices (such as body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR)). A number of studies have shown that modified TyG indices are superior to the TyG index in predicting IR and NAFLD.[9-13] There is also some evidence that large neck circumferences (NC) are associated with an increased risk of IR and NAFLD.[14, 15] However, TyG-NC has not been studied among modified TyG indices yet.

This study examined and compared the TyG index, modified TyG indices (including TyG-NC), and anthropometric obesity indices as predictors of NAFLD in non-diabetic obese

patients. In this regard, our study is the first to directly compare the TyG index with anthropometric obesity indices in this specific group of patients.

Materials and Methods

This was a prospective study performed between July 2021 and August 2022 at the endocrinology clinic of XXXXXX University Medical Faculty. The local ethical committee authorized the study protocol following the Helsinki Declaration (approval No: 45391, 09 July 2021). Prior to data collection, each participant provided written consent.

Study participants

This study included 190 outpatients with a BMI ≥ 30 kg/m^2, who attended our obesity clinic. Patients with diabetes, whether known or newly diagnosed, were not included in this study. None of the patients had a history of alcohol consumption. Subjects with the following conditions were also excluded from the study: (1) had viral hepatitis, cirrhosis, or any other liver disease; (2) had a history of hypo- or hyperthyroidism; (3) had received lipid-lowering, antidiabetic, antihypertensive, or steroid replacement therapy; and (4) those with pregnancy.

Physical Examinations and Laboratory Measurements

We used standardized methods for anthropometric measurements.[16] The height and weight of the patients were measured with an accuracy of 0.1 cm and 0.1 kg, respectively, while wearing light clothing and removing their shoes. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). We used a plastic tape with an accuracy of 0.1 cm to measure WC, NC, and hip circumference (HC). WC (cm) / HC(cm) was used to calculate WHR. All blood samples were taken from the antecubital vein after an overnight fast. Laboratory investigations consisted of FPG, fasting insulin, thyroid stimulating hormone (TSH), alanine aminotransferase (ALT), hemoglobin A1c (A1C), and triglyceride (TG).

Definitions

Obesity is defined as a BMI ≥30 kg/m^2.[16] The abdominal ultrasound examination was conducted by a single-blinded experienced observer and the same equipment EPIQ 7 diagnostic ultrasound system (Philips Healthcare Andover MA, USA) was used for all patients. Hepatic fat accumulation was classified into four grades (0, 1, 2, 3) based on the degree of liver echogenicity compared to the right kidney and the visualization of intrahepatic vessels and diaphragm.[17] The severity of steatosis from grades 1 to 3 was considered NAFLD, whereas grade 0 was considered normal. The HOMA-IR, TyG index, and modified TyG indices were calculated as follows:

HOMA−IR= (Fasting Insulin[μU/mL]×Fasting Plasma Glucose[mg/dL]/405).[7]

TyG index=Ln [TG (mg/dL)×FPG (mg/dL)/2].[3] TyG-NC= TyG×NC

TyG-BMI = TyG×BMI, TyG-WC = TyG×WC, TyG-WHR= TyG×WHR.[9]

Statistical analysis

Statistical analyses were done with SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 20.116 (MedCalc Software, Ostend, Belgium). According to the distribution of the data, the mean±standard deviation or median and interquartile range were calculated. The continuous variables were analyzed using independent samples t-tests or Mann-Whitney U tests, based on their distribution. We compared categorical variables with the Chi-square test. For comparisons between three or more groups with normally distributed data, an analysis of variance (ANOVA) was performed. In post-hoc analyses, Tukey's test was used if homogeneity of variance was assumed. When the variances between groups were not homogeneous, the Brown Forsythe test was preferred and the Tamhane T2 test was used for post-hoc analysis. The Kruskal-

Wallis test was used when normality tests failed, and pairwise comparisons were performed for subgroup analysis.

Since our study cohort had a low percentage of patients without steatosis, we performed our further analysis in two subgroups: those without severe steatosis (grades 0 and 1), and those with severe steatosis (grades 2 and 3). Receiver operating characteristic (ROC) curve analysis was used to predict severe steatosis, and the calculated areas under the curve (AUC) were determined and compared with the DeLong method. We constructed a two-sided 95% confidence interval (CI) in order to determine the relative risk around a point estimate. As a final step, we used logistic regression analysis to examine the TyG index, BMI, WC, and NC values in the prediction of severe steatosis. The variables were divided into four categories based on their quartiles: Q1-Q4. As a reference group, Q1 was chosen and all other groups were compared to Q1 to calculate odds ratios and 95% CIs. In this study, a $p<.05$ was considered statistically significant.

Results

The study included 190 patients. Of these, 118 (62.1%) were females and 72 (37.3%) were males (p=.001). The prevalence of NAFLD was 88.1 % in females and 90.3% in males (p=.648). Values of WC, NC, WHR, ALT, HOMA-IR, and TyG index were significantly higher in males than in females (TyG, p=.001; $p<.001$ for all other parameters). The baseline characteristics of participants according to their gender are summarized in Table I.

The results of an analysis of variance demonstrated that, with increasing grades of NAFLD, age, BMI, WC, NC, WHR, and ALT values increased significantly ($p<.001$ for all). A significant positive correlation was also observed between TyG index (p=.004), HOMA-IR (p=.001), and A1C (p=.001) values and the grades of NAFLD. The results also revealed that males had significantly higher grades of NAFLD compared to females ($p<.001$) (Table 2).

Table 3 summarizes the clinical and biochemical characteristics of the patients with or without severe steatosis. It was found that 112 patients (58.9%) had severe steatosis, and 78 patients (41.1%) did not. The mean and/or median values of BMI, WC, NC, and ALT were found to be significantly higher in the severe steatosis group (p<.001 for all). The TyG index, HOMA-IR, WHR and A1C values were also significantly increased in patients with severe steatosis (p=.001, p=.004, p=.005 and p=.002 respectively). Additionally, a higher prevalence of severe steatosis was also observed in males than in females, and at advanced ages than at younger ages (p=.004 and p=.023 respectively).

An analysis of the ROC curves and comparisons of the AUCs for each variable for predicting severe steatosis are presented in Table 4. Severe steatosis was significantly predicted by all variables (TyG index, p= .001; HOMA-IR, p=.003; WHR, p=.003; other predictors in all subjects, p<.001). Among the cut-off values for prediction of severe steatosis, TyG index was 8.76, WC was 119 cm, NC was 41 cm, WHR was 0.894, BMI was 37.4 kg/m2, HOMA-IR was 4.45, and ALT was 39 U/L. The highest AUC values for the detection of severe steatosis were found in TyG-WC and WC (0.795 and 0.782, respectively). Based on the AUC comparisons, WC and ALT values were statistically superior to the TyG index in predicting severe steatosis (p=.006 and p=.049 respectively).

Finally, we divided the variables into quartiles and applied logistic regression analysis to measure the odds ratio of anthropometric obesity indices and the TyG index in predicting severe steatosis. WC measures had the highest odds ratios (95% CIs), 2.91 (1.25–6.79), 8.48 (3.28–21.90), and 23.91 (7.67–74.52) for subjects in the second, third, and fourth quartiles, respectively, when compared with the first quartile. In Table 5, we summarize the odds ratios (95% CIs) according to the quartiles for each of the parameters.

Discussion

In this study, we found that the TyG index and modified TyG indices such as TyG-BMI, TyG-WC, TyG-WHR, and TyG-NC were significantly associated with the presence and severity of NAFLD. The TyG-NC was evaluated for the first time as a novel modified TyG index. In terms of predicting NAFLD and its severity, modified TyG indices performed better than the TyG index alone. Further, TyG-WC significantly outperformed the other parameters in predicting severe steatosis with the largest AUC of 0.795. Considering that both the TyG index and obesity were associated with IR, it was not surprising that the combination of these two variables provided stronger predictions. On the other hand, we found that the TyG index was not superior to simple anthropometric obesity indices for predicting NAFLD and its severity in this specific group of patients.

The TyG index was initially introduced as a surrogate for the identification of IR.[4,5] Similarly, we found a significant positive correlation between HOMA-IR and the TyG index in the Pearson correlation analysis ($r = 0.342$, $P < .001$) (data not shown). Additionally, several subsequent studies have demonstrated that the TyG index is a reliable, practical, and cost-effective method for identifying individuals at risk of NAFLD.[6-9] In the presence of IR, there is an increase in de novo lipogenesis in the liver and ineffective suppression of lipolysis in the adipose tissue. Thus, the high level of circulating fatty acids can disrupt insulin signaling pathways and lead to hepatic insulin resistance and steatosis.[18] Moreover, IR causes adipose tissue dysfunction and triggers the release of inflammatory cytokines and adipokines from adipose tissue.[19]

A growing number of studies have investigated the role of the TyG index in predicting NAFLD. However, the majority were retrospective and conducted on general populations.[20, 21] There are only a few studies examining the TyG index for predicting NAFLD in patients with obesity. In two retrospective studies examining liver biopsy samples from obese patients undergoing bariatric surgery, the TyG index has been found to be strongly associated with

NAFLD. In these studies, patients with diabetes were also included, and the frequency of NAFLD was found to be 67% and 90%, respectively.[22, 23] In our study, patients with diabetes were excluded and the results showed that 88.9% of patients had NAFLD. This is in line with previous studies that report the prevalence of NAFLD ranging from 65% to 95% in obese individuals, which varies depending on the degree of obesity.[22-25] The number of female patients (n=118) in our study was higher than the number of males (n=72) (p=.001). In our opinion, this is due to the fact that females complain of their excess weight more often and therefore apply to obesity clinics more frequently. Even though their mean BMI was not different, males had significantly higher measurements of WC, NC, and WHR than females. This may be explained by differences in fat distribution between males and females, specifically apple-shaped (abdominal pattern) obesity in males versus pear-shaped (gluteal–femoral pattern) obesity in females.[26] Further, males exhibited more severe steatosis and had higher TyG index, HOMA-IR, and ALT values than females. The abdominal pattern of obesity and the higher IR levels in male patients may explain the higher NAFLD grades and higher ALT values.[26, 27]

In recent years, modified TyG indices have been studied more extensively and are reported to provide better predictions for IR and related conditions.[9-13] Lim et al. examined TyG-WC, TyG-BMI, and TyG-WHtR (waist-to-height ratio) for predicting IR and concluded that TyG-BMI had better predictive power than other combined indices and the TyG index.[9] In another study by Er et al., TyG-BMI and TyG-WC were found to provide better AUCs for the prediction of IR as compared with lipid parameters, lipid ratios, adipokines, visceral obesity indicators and the TyG index alone.[10] Several further studies have demonstrated that modified TyG indices (TyG-BMI, TyG-WC, and TyG-WHR) are superior at predicting NAFLD than the TyG index alone.[11-13] Similarly, in our study, TyG-WC and WC were found to be the two variables with the highest AUC in predicting severe steatosis (0.795 and

0.782, respectively). Our study differs from other existing studies in the following ways: first, all of our participants had a BMI >30 kg/m^2, second, diabetic patients were excluded, and thirdly, considering the low percentage of patients without steatosis, we conducted further analyses between patients with and without severe steatosis.

To date, despite some evidence of the effectiveness of the TyG index in predicting NAFLD, there are no studies that specifically compare the TyG index with anthropometric obesity indices in obese patients. For this reason, we specifically compared the TyG index with simple obesity indices, ALT, and HOMA-IR levels. When the TyG index was compared with BMI, WHR, NC, and HOMA-IR, the AUC values did not differ significantly. However, the AUCs values of WC and ALT provided better predictions of severe steatosis than the TyG index (0.782, 0.744 and 0.640 respectively). As a final step, odds ratios and 95% CIs were calculated for each parameter and compared to quartile 1. It was found that WC measurements provided the highest odds ratio for predicting severe steatosis, followed by NC, BMI, and TyG index, respectively.

Study limitations

The limitation of our study is that it was a single-center study with a relatively small sample size. To confirm our findings, multicenter, prospective studies with a large number of patients are needed. As another limitation of the study, abdominal ultrasound was used instead of liver biopsy for the diagnosis of NAFLD. However, liver biopsy is unrealistic to use for screening NAFLD in the general population. Currently, abdominal ultrasound is considered the most cost-effective and feasible screening method for steatosis in the general population.[19]

In conclusion, the TyG index and modified TyG indices are highly effective in predicting both the presence and severity of NAFLD. Despite this, we found that the TyG index was not

superior to simple anthropometric obesity indices in predicting NAFLD and its severity in patients with obesity.

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Table 1. Baseline characteristics of subjects by gender

Variables	Total (n=180)	Females (n=118)	Males (n=72)	p value
Age (years)	38 (29-49)	40 (28-50)	35 (29-45)	.142[b]
Gender (%)		62.1	37.9	**.001**[b]
BMI (kg/m^2)	40.0 (35.4-44.8)	40.0 (35.0-45.1)	39.9 (35.6-43.5)	.924[b]
WC (cm)	119.0(108.7-129.0)	112.5(105.0-121.0)	127.5 (118-134)	**<.001**[b]
NC (cm)	40.0 (37.0-43.0)	38.0 (36.0-40.0)	43.0 (41.0-45.0)	**<.001**[b]
WHR	0.94 (0.87-1.03)	0.89 (0.84-0.94)	1.04 (1.02-1.06)	**<.001**[b]
HbA1c (%)	5.70 (5.30-6.02)	5.70 (5.20-6.00)	5.70 (5.60-6.10)	**.033**[b]
ALT (IU/L)	29 (22-42)	24 (21-32)	42 (33-58)	**<.001**[b]
HOMA-IR	4.83 (3.67-6.60)	4.34(3.35-5.59)	6.07(4.32-7.59)	**<.001**[b]
TyG index	8.92±0.51	8.82±0.51	9.08±0.47	**.001**[a]
NAFLD - n (%)	169 (88.9)	104 (88.1)	65 (90.3)	.648[c]

Abbreviations: BMI, body mass index; WC, waist circumference; NC, neck circumference; WHR, waist-to-hip ratio; HbA1c, glycosylated hemoglobin; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride-glucose index; NAFLD, non-alcoholic fatty liver disease .

p value < 0.05 was considered significant. Significant p values are highlighted in bold.

a: Independent samples t-test. b: Mann-Whitney U test c: Chi-square test

Table 2. Comparison of clinical and laboratory findings based on grades of NAFLD

Parameter	Grade 0 N:21 (11.1%)	Grade 1 N:57 (30%)	Grade 2 N:82 (43.2%)	Grade 3 N:30 (15.8%)	p
Age (years)	28.2±6.2 a**b***c***	40.1±12.7	40.3±12.1	41.8±11.2	**<.001£**
Gender (F/M)	14/7 c**	44/13 e***f**	52/30	8/22	**<.001#**
BMI (kg/m^2)	32.94±2.10 a***b***c***	38.95±5.49 d*e***	41.85±5.83	44.59±7.58	**<.001£**
WC (cm)	104.4±6.46 a**b***c***	114.1±10.9 d**e***	121.4±11.0 f***	131.4±13.1	**<.001£**
NC (cm)	37.28±2.90 b**c***	38.45±3.16 d**e***	40.40±3.91 f***	43.83±3.47	**<.001£**
WHR	0.93±0.08 c*	0.92±0.09 e***	0.95±0.10 f*	1.00±0.06	**<.001£**
HOMA-IR	4.04 (3.19-5.02) c***	4.14(3.47-6.03) e**	5.10 (3.66-6.55) f*	6.34 (4.90-7.63)	**.001¥**
TyG index	8.66±0.64 c*	8.80±0.55 e*	8.99±0.43	9.14±0.43	**.004£**
ALT (IU/L)	24 (18-30)	24 (21-34)	31 (23-44)	42 (39-58)	**<.001¥**

	b**c***	d**e***	f***		
HbA1c (%)	5.60(5.20-5.70)	5.70(5.25-5.90)	5.70(5.40-6.10)	5.90(5.70-6.30)	**.001¥**
	b*c***	e**	f*		

Abbreviations as in Table I. p value < 0.05 was considered significant. Significant p values are highlighted in bold.

The definition of post hoc analysis: a: between grade 0 and 1, b: between grade 0 and 2, c: between grade 0 and 3, d: between grade 1 and 2, e: between grade 1 and 3, f: between grade 2 and 3, *: p value between .05-.01, **: p value between .01-.001, ***: p value <.001

¥: Kruskal-Wallis test £. One-way ANOVA #: Chi-square test

Table 3. Clinical and biochemical characteristics of patients with and without severe fatty liver.

Parameters	**No severe steatosis (N:78)**	**Severe steatosis (N: 112)**	**p**
Age (years)	33.5 (27.0-45.0)	39 (30-51)	**.023*b***
Sex (F/M)	58/20	60/52	**.004*c***
BMI (kg/m^2)	36.0 (33.0-40.6)	41.5 (38.0-46.0)	**<.001*b***
WC (cm)	109.5 (102.0-119.0)	124.0(114.2-132.0)	**<.001*b***
NC (cm)	38.14±3.11	41.32±4.07	**<.001*a***
WHR	0.90 (0.85-1.02)	0.97 (0.89-1.04)	**.005*b***
HOMA-IR	4.07 (3.43-5.89)	5.39 (3.97-6.91)	**.004*b***
TyG index	8.76±0.57	9.03±0.44	**.001*a***
ALT (IU/L)	24.0 (19.0-32.0)	36.0 (25.0-50.5)	**<.001*b***
HbA1C (%)	5.65 (5.20-5.80)	5.80 (5.50-6.20)	**.002b**
TyG-BMI	310.4 (289.1-361.9)	376.0 (342.1-414.8)	**<.001b**
TyG-WC	979.1±121.9	1121.8±129.5	**<.001a**
TyG-NC	334.9±39.6	373.6±44.5	**<.001a**
TyG-WHR	8.12±1.09	8.73±1.08	**<.001a**

Abbreviations as in Table I.

p value < 0.05 was considered significant. Significant p values are highlighted in bold.

a: Independent samples t-test. b: Mann-Whitney U test c: Chi-square test

Table 4. ROC curve analysis and pairwise comparison of the AUCs for each variable for predicting severe steatosis

Parameter	**Cut-Off**	**Sensitivity**	**Specificity**	**AUC**	**95% CI**	**p-value**
TyG-WC	>1071.6	69.64	78.21	0.795	0.730-0.850	**<.001**
WC (cm)	>119.0	65.18	79.49	0.782	0.716-0.838	**<.001**
TyG-BMI	>326.5	88.39	58.97	0.775	0.709-0.832	**<.001**
ALT (IU/L)	>39.0	43.75	92.31	0.744	0.676-0.805	**<.001**
BMI (kg/m2)	>37.4	79.46	61.54	0.742	0.673-0.802	**<.001**
TyG-NC	>345.8	72.32	66.67	0.740	0.672-0.801	**<.001**
NC (cm)	>41.0	49.11	87.18	0.725	0.656-0.787	**<.001**
TyG-WHR	>8.31	66.96	58.97	0.656	0.583-0.723	**<.001**
TyG index	>8.76	77.68	55.13	0.640	0.568-0.709	**.001**
HOMA-IR	>4.45	68.75	61.54	0.624	0.551-0.693	**.003**
WHR	>0.894	75.89	47.44	0.620	0.547-0.689	**.003**

Pairwise comparison	**Difference AUC**	**95% CI**	**p-value**
WC vs. TyG	0.141	0.039-0.243	**.006**
NC vs. TyG	0.084	-0.015-0.185	.098
WHR vs. TyG	0.020	-0.082-0.123	.697

BMI vs. TyG	0.101	-0.011-0.214	.077
HOMA-IR vs. TyG	0.016	-0.080-0.114	.338
ALT vs. TyG	0.104	0.000-0.208	**.049**

Abbreviations as in Table I. AUC = area under the receiver operating characteristic (ROC) curves; CI = confidence interval.

P value < 0.05 was considered significant. Significant p values are highlighted in bold.

Table 5. Odds ratios for severe liver steatosis in quartiles of TyG index and anthropometric obesity indices

Parameters	Beta	Crude OR	95% CI	p-value
BMI(kg/m^2)				**<.001**
1st Q		Ref		
2nd Q	0.867	2.379	1.058-5.350	.036
3rd Q	1.889	6.613	2.583-16.935	<.001
4th Q	2.066	7.893	3.116-19.997	<.001
WC (cm)				**<.001**
1st Q		Ref		
2nd Q	1.070	2.917	1.253-6.792	.013
3rd Q	2.138	8.485	3.287-21.901	<.001
4th Q	3.175	23.917	7.675-74.528	<.001
NC (cm)				**<.001**
1st Q		Ref		
2nd Q	0.457	1.579	0.738-3.377	.239
3rd Q	1.150	3.158	1.335-7.472	.009
4th Q	2.885	17.895	4.814-66.513	<.001
TyG index				**.002**
1st Q		Ref		

2nd Q	1.085	2.961	1.284-6.828	.011
3rd Q	1.619	5.048	2.095-12.163	<.001
4th Q	1.290	3.633	1.544-8.548	.003

Abbreviations as in Table 1. Each parameter was entered as categorical covariate in a separate analysis