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Triglyceride–Glucose Index And Nonalcoholic Fatty Liver Disease In Children With Type 1 Diabetes Mellitus: A Cross-Sectional Study.

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) in children has no specific clinical manifestations. So, it is difficult to diagnose early .This study aimed to explore the diagnostic value of the triglyceride-glucose (TyG) index for an early prediction of NAFLD in children with T1DM. Methods: Total 103 T1DM children and adolescence were included in this study (43male, 60 female); with age range from 6 to 18 years. Thirty-eight children were with NAFLD and 65 were without NAFLD. NAFLD was diagnosed by abdominal ultrasonography. We analyzed the lipid profile, and liver enzymes, HbA1c%, fasting blood glucose (FBG). The TyG index was calculated, and the correlations between the TyG index and clinical, biochemical and other modalities were evaluated. A receiver operating characteristics curve analysis and area under the curve (AUC) were used to evaluate diagnostic accuracy. Results: The NAFLD group had significantly higher levels of TyG index. There was a statistically significant difference between the TyG index and grades of steatosis and fibroscan in T1DM children with NAFLD. Glucose Index was significantly positively correlated with NAFLD, Triglyceride ,liver stiffness, liver span, grades of steatosis and visceral fat thickness with P value [.000, . 004,000,.014 ,.000,.028 respectively] . Predictability of the TyG index was superior to BMI, WC and VFT, in predicting NAFLD among T1DM children .The cut-off value of the TyG index for incident NAFLD was 8.02 (sensitivity = 0.971, specificity= 0.897). Conclusion: According to these findings, it is reasonable to use the TyG index to predict NAFLD in children and adolescence with T1DM.

Keywords: Triglyceride-glucose index; type 1 diabetes mellitus (T1DM) ; non-alcoholic fatty liver disease and visceral fat thickness

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INTRODUCTION

Glucose and lipid metabolism abnormalities are associated with nonalcoholic fatty liver disease (NAFLD). Glucotoxicity and Lipotoxicity, which begin in hepatocyte exposure to high glucose and lipid levels, play vital roles in the development and progression of NAFLD [1, 2]. Thus, the recently developed triglyceride–glucose (TyG) index has been recommended as a simple and reliable indicator to identify individuals at risk for NAFLD [3, 4].

Previous studies have evaluated the occurrence of NAFLD spectrum in children with type 1 diabetes mellitus (T1DM) [5-8]. However, studies on the association between the TyG index and NAFLD and glycemic parameters for NAFLD risk, in patients with T1DM, are lacking. The recently developed triglyceride–glucose (TyG) index is easily calculated using fasting blood glucose (FBG) and triglyceride (TG) levels [9]. Thus, if the TyG-index can be used to predict the early identification of an individual's risk of NAFLD so it will be important for not only the prevention of liver related morbidity and mortality, but also the prevention of diseases such as chronic kidney disease (CKD), and cardiovascular disease.

Therefore, our study aimed to investigate whether the TyG-index can be used to predict incident NAFLD in children with T1DM and to evaluate the relationship between TyG index, lipid parameters, and glycemic parameters.

MATERIAL AND METHODS

A cross-sectional study including: 103 children with type 1 diabetes mellitus (T1DM). The age range was (6–18) years. They were referred to the Pediatric Clinic in the Centre of Excellence in the National Research Centre between January 2018 and December 2019. The study protocol was approved by the Human Ethics Committee of National Research Centre Approval no. (16-334), and written informed consents were obtained from all parents/legal guardians of the children.

Exclusion criteria were as follows: children with secondary DM and any chronic-related diseases like hypothyroidism or hypo-adrenalism; also, children with any previous hepatic involvement, especially viral hepatitis, were excluded from the study. Complete history taking and thorough clinical examination including anthropometric measurements (height and weight) were done following the International Biological Program (IBP) [10]. BMI was calculated as usual (kg/m^2).

Laboratory Measurements

Ten millimeters of venous blood were withdrawn under complete aseptic precautions from fasting subjects (12 - 14 hrs). Samples were labeled and left to clot at room temperature for 15 min then centrifuged, sera were collected and aliquated for evaluation of the following parameters:

Fasting blood glucose was assessed using Hitachi 912 chemistry analyzer (Roche Diagnostics GmbH, D-68298 Mannheim, Germany) by colorimetric techniques.

Pertinent laboratory investigations were performed for all patients including glycosylated hemoglobin (HbA1C) levels, lipid profile (cholesterol, triglyceride, HDL and LDL and liver enzymes including AST and ALT, using an Olympus AU 400 autoanalyser supplied from Olympus Life and Material Science (Europe GmbH, Wendenstraße, Hamburg, Germany).

Viral Markers (HB s Ag, HCV Ab, and HIV Ab) were done to exclude viral hepatitis in our cases using the PRECHECK Kit (USA).

Imaging Modalities

Abdominal ultrasonography was performed, by the same expert, for liver size and echogenicity. Normal liver parenchyma has a homogeneous echo texture with echogenicity equal to or slightly greater than

that of the renal cortex and spleen. The liver reveals echogenicity more than the kidney and spleen due to fatty infiltration [11]. Various (0-3) grades of steatosis have been proposed based on analysis of the intensity of the echogenicity [12]. Also VFT was also measured. The model of ultrasound apparatus is SA –R3 (No S06YM3 HDC00012F) SAMSUNG MEDISON Company –South Korea.

Acoustic radiation force impulse elastography (ARFI): Acoustic radiation force impulse elastography was performed for all subjects with a Siemens Acuson S3000 Virtual Touch ultrasound system (Siemens AG, Erlangen, Germany) with a 6CI transducer [13].

The triglyceride and glucose index (TyG) of each study subject's was calculated by the following formula [14].

$$TyG = Ln\ [\text{fasting triglyceride(mg/dl)} \times \text{fasting glucose(mg/dl)}/2]$$

The T1DM subjects were divided into two subgroups: subgroup patients with NAFLD and subgroup patients without NAFLD according to ultrasographic (0-3) grades of steatosis based on analysis of the intensity of the echogenicity [12].

Statistical Analysis

Analysis of our results was carried out using the standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 17.0 (SPSS Inc., USA). All numerical variables were expressed mean ± standard deviation (SD). The intergroup comparisons were performed by using an independent-sample t test and a one-way analysis of variance and chi-square tests for categorical variables. Pearson's and Spearman's correlation tests (r = correlation coefficient) were used for the correlation of normal and nonparametric variables, respectively.

Multiple Linear regression analysis was used to evaluate the independent predictor of NAFLD in these subjects. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of the triglyceride - Glucose Index, ALT, liver stiffness, liver span, visceral Fat for incident NAFLD. The cut-off point, sensitivity, and specificity were obtained for the triglyceride - Glucose Index. For all tests, a $p < 0.05$ was considered significant and $p < 0.01$ was considered highly significant.

RESULTS

Total 103T1DM subjects were included in this study. Among them 65 were without NAFLD patients and 38 were with NAFLD. The mean age was 13.70±4.10 years in NAFLD group and 12.16 ±3.34 years in group without NAFLD. Difference of mean age between the groups was statistically significant ($p = .045$).Table 1 shows the comparative demographic, clinical characteristics and the laboratory in T1DM children with or without NAFLD

Among total study population female were more frequent than male (60 subjects and 43 respectively), although the gender differences were not statistically significant ($p = 0.053$). Fig1, 2) show the Triglyceride-glucose index in male and female T1DM children without and with NAFLD.

Participants in the NAFLD group were older and had a higher BMI, higher mean systolic and diastolic BP, longer diabetes duration, more metabolic profile (Fasting plasma sugar, AST, ALT ,cholesterol, triglyceride and LDL), lower HDL-C level and AST/ALT ratio, and higher TyG index .The NAFLD group had significantly higher mean levels of WC, VFT and stiffness (Table 1).

Comparing ultrasonography results between our T1DM children with or without NAFLD, there was a highly significant difference in liver span, $P = 0.000$. Also echogenicity grades difference in T1DM cases without NAFLD was normal echogenicity in 65cases (95.6%), while grade I was in 2cases (3%) and grade2 was in one case (1.4%). While grade I was in 16 NAFLD cases (45.7 %), in addition grade II in cases with NAFLD was 29 cases (54.3%) FIG3

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Also, Fibroscan level in T1DM cases without NAFLD: grade 1 was in 66 (97.1%) cases, while grade 2 in 2 (2.9%) cases without NAFLD. In cases with NAFLD there was 27(77.1%) cases in grade1 and 2 (5.7%), in cases with NAFLD, in addition grade 3was in 6 (17.2%) NAFLD cases (Fig4).

Table 1: Comparative demographic, clinical characteristics and the laboratory Tests in Non- NAFLD and NAFLD T1DM cases

Items	Without NAFLD (no 65)	With NAFLD (no 38)	Sig. (2-tailed)
Age Years	12.16 ±3.34	13.70±4.10	.045
BMI (kg/m2)	18.98± 4.24	23.47±5.48	.000
Duration of T1DM (years)	4.67±3.12	5.61±3.42	.165
F/M	33/32	27/11	.052
SBP mm Hg	103.61±9.82	107.85±10.13	.070
DBP mm Hg	67.96±7.17	68.92±7.85	.577
Waist circumference [cm]	68.05±9.54	77.80±13.71	.000
LIVER span [cm]	12.51±1.26	14.58±1.70	.000
Visceral Fat Thickness [cm]	.926 ±.34	1.40 ±.55	.000
Subcutaneous Fat Thickness [cm]	2.74±.92	3.51±1.08	.001
Liver Stiffness	1.06±.15	1.18±.29	.012
Fasting plasma sugar [mg/dl]	141.84 ±43.78	169.38 ±40.16	.000
HbA1C%	7.97± .85	8.21 ± .86	.191
Cholesterol [mg/dl]	156.75±17.23	159.48±22.70	.948
Triglyceride [mg/dl]	61.79 ±18.17	71.54 ±30.94	.035
HDLP [mg/dl]	38.86 ±6.60	37.86 ±6.60	.219
LDL [mg/dl]	58.25±6.85	62.89±8.67	.007
ALT U/l	17.42 ±4.15	19.2 ±4.19	.032
AST U/l	16.23± 2.77	19.25 ± 4.19	.000
Ratio of AST to ALT values	0.96	0.92	0.171
The Triglyceride - Glucose Index	8.15 ± .22	8.54 ± .40	.000

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; ALT: alanine transferase; AST: aspartate transferase;

There was a highly statistically significant difference between the TyG index with grades of steatosis and fibroscan in T1DM children with or without NAFLD (Table2).

Regarding gender, the TyG index mean level in male was 8.32 while in female was 8.23 with no statistical significant difference (P=.181).

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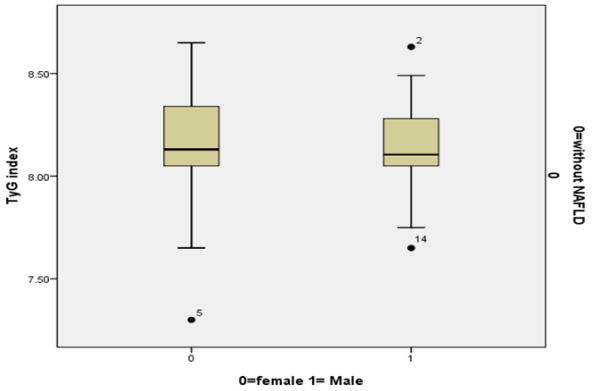

Figure 1: Triglyceride-glucose index in male and female without NAFLD

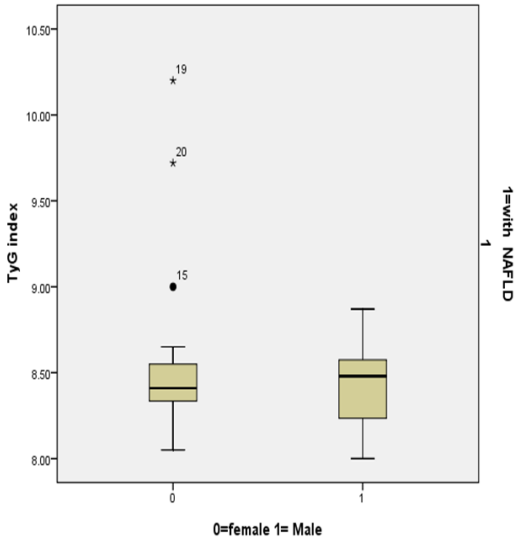

Figure 2: Triglyceride-glucose index in male and female with NAFLD

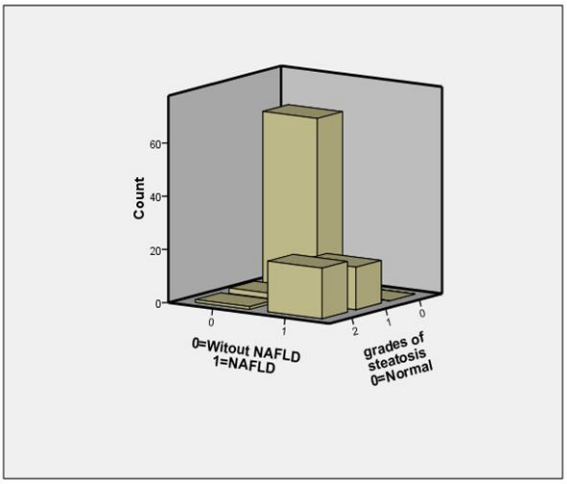

Figure 3: Steatosis evaluation inT1DM children with or without NAFLD

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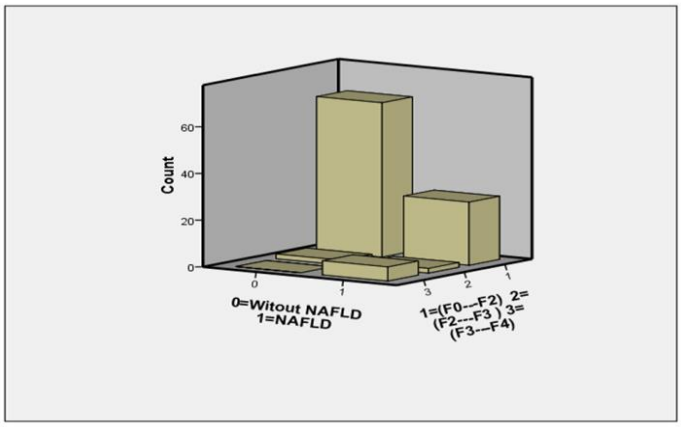

Figure 4: FIBROSCAN evaluation in T1DM children with or without NAFLD

Table 2: Relation between the TyG index with grades of steatosis and fibroscan in T1DM children with or without NAFLD

							ANOVA
	grades of steatosis	N	TyG index Mean	Std. Deviation	Minimum	Maximum	SIG
The Triglyceride and Glucose Index	0=Normal	65	8.1542	.22	7.30	8.65	
	1	18	8.4791	.21	8.00	9.00	.000
	2	20	8.6013	.51	8.05	10.20	
	Total	103	8.2872	.35	7.30	10.20	
fibroscan 1=(F0---F2) 2=(F2---F3) 3=(F3---F4)							
The Triglyceride and Glucose Index	1	93	8.25	.29	8.18	8.31	
	2	4	8.37	.22	8.01	8.74	.000
	3	6	8.78	.70	8.04	9.51	
	Total	103	8.28	.35	8.21	8.35	

The Triglyceride - Glucose Index was significantly positively correlated with NAFLD, Triglyceride., stiffness, liver span, grades of steatosis and visceral fat thickness with P value [.000, . 004,000,.014 ,.000,.028 respectively] (Table 3). No significant correlation was detected between the triglyceride - glucose index and age or sex.

Table 3: Correlations of the Triglyceride - Glucose Index and some studied parameters In T1DM children with or without NAFLD

		NAFLD	Triglyceride	stiffness	LIVER span	grades of steatosis	Visceral Fat Thickness
The Triglyceride - Glucose Index	r	.532**	.279**	.375**	.242*	.532**	.222*
	Sig. (2-tailed)	.000	.004	.000	.014	.000	.028
	N	103	103	97	103	103	98

NAFLD: nonalcoholic fatty liver disease.
* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

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Results of linear multiple regressions, to predict NAFLD showed that the triglyceride - Glucose Index, ALT, stiffness, liver span, visceral Fat were the most independent predictor (P<.000, .003,.776,.000,.020} . Details are included in Table 4 .

Table 4: Result of a multiple linear regression to predict NAFLD in T1DM children

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-5.875	.767		-7.663	.000
	The Triglyceride and Glucose Index	.482	.097	.368	4.949	.000
	ALT	.026	.009	.214	3.063	.003
	Stiffness	-.048	.167	-.022	-.286	.776
	Liver span	.122	.021	.442	5.784	.000
	Visceral Fat Thickness	.181	.076	.185	2.372	.020
a. Dependent Variable: 0=Without NAFLD 1=NAFLD						

The predictive power of the TyG index for NAFLD in T1DM children was analyzed by receiver operating characteristic curve (ROC). Comparison of (ROC) analysis of WC, BMI, VFT and the TyG index for predicting NAFLD in T1DM children was shown in (fig 5). The area under the curve of the TyG index was found as .844 (P = 0.000) while that of BMI was .764 (P = 0.000), WC was .726 (P = 0.000), and VFT was .780 (P = 0.000). Indicating that predictability of the TyG index was superior to BMI, WC and VFT, in predicting NAFLD among T1DM children (Table 5).

The cut-off value of the TyG index for incident NAFLD was 8.02 (sensitivity = 0.971, specificity= 0.897).

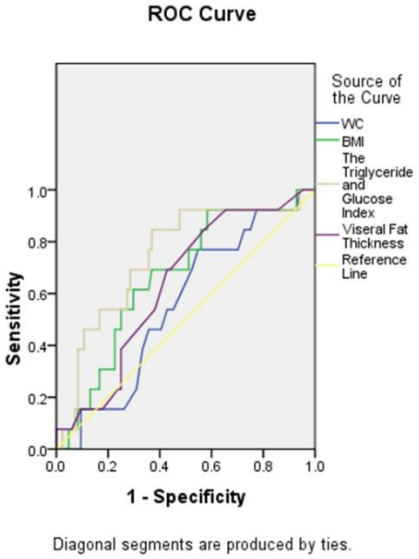

Figure 5: Comparison of receiver-operating characteristics (ROC) analysis of WC, BMI, The triglyceride - glucose index and visceral fat thickness for predicting NAFLD in T1DM children

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Table 5: Area under the curve of WC, BMI, visceral fat thickness, and the triglyceride and glucose index and for predicting NAFLD in T1DM children

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Waist Circumference	.726	.057	.000	.614	.839
Body Mass Index	.764	.054	.000	.659	.869
Visceral Fat Thickness	.780	.050	.000	.682	.878
The Triglyceride and Glucose Index	.844	.044	.000	.759	.930
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

DISCUSSION

In pediatrics age group non-alcoholic fatty liver disease (NAFLD) is a growing disease spectrum, ranging from simple steatosis, through nonalcoholic steatohepatitis (NASH) and culminating in fibrosis and liver cirrhosis [15]. There are available non-invasive biomarkers for hepatic affection in children with T1DM [5]. Recently, a newly noninvasive index (TyG Index) could be used for the identification of NAFLD [14]. Few researches evaluated the TyG index among children and adolescents [16, 17]. The authors reported the cutoff point of 7.88 may be used in this population for insulin resistance risk screening with no difference between the genders. , but authors did not evaluate the TyG Index for diagnosis of NAFLD in children (16). However, few studies have investigated the clinical implications of the TyG index [18-20]. This study evaluated the diagnostic value the TyG index for NAFLD in T1DM children.

In the present study we demonstrated that T1DM children with NAFLD had significantly higher level of TyG index. NAFLD T1DM children had significantly higher BMI, FPG and triglycerides levels than those without NAFLD. So, it is reasonable to use TyG index, a product of triglycerides and FPG, as an effective diagnostic predictor for NAFLD. A recent study by Xiaolin et al, showed that the TyG index is a novel noninvasive marker to Diagnose NAFLD in children [18]. They suggested that it may indicate hepatocyte injury and defect in purine metabolism in children and adolescence with NAFLD [18].

ALT is recommended in several NAFLD diagnostic and treatment guidelines and has been used as a marker for the inflammatory reaction and oxidative stress [22, 23]. Various studies reported that NAFLD could occur in individuals with normal ALT values [24-25]. Our study results revealed that serum ALT level was significantly increased T1DM children with NAFLD.

The TyG index was positively correlated with triglyceride, stiffness, liver span, grades of steatosis and visceral fat thickness which is consistent with previous reports [26].

A multiple linear regression to predict NAFLD in T1DM children showed that the triglyceride - glucose index, ALT, liver span, visceral Fat were the most independent predictor of NAFLD.

Similar results were reported in previous studies [5, 28-30].

Finally, the diagnostic efficacy of the TyG index, WC, BMI and visceral fat thickness for predicting NAFLD in T1DM children were analyzed using a ROC curve. Sensitivity, specificity, AUC and the optimal cut-off of the TyG index for diagnosing NAFLD were done. The optimal cut-off point of TyG for NAFLD was 8 .02 (sensitivity = 0.971, specificity= 0.897). The area under the curve (AUC) for predicting the patients with NAFLD was 0.844 (.614 - .839).

Previous studies reported that Area under the curve (AUC) of the TyG index for predicting the patients with NAFLD was 0.760 (0.646-0.806) in children [18].

Zhang et al. reported that the (AUC) of the TyG index for predicting the patients with NAFLD in adults was 0.782 (0.773 - 0.793) [21]. Comparison of (ROC) analysis of WC, BMI, VFT and the TyG index for predicting NAFLD in T1DM children showed that the TyG index is the best predictor for NAFLD in T1DM children. Similar result was reported in previous studies [18, 26-28]. According to these findings, it is reasonable to use the TyG index to predict NAFLD in children with T1DM.

A limitation of this study

It was a cross-sectional study, with small sample size. The gold standard for diagnosis of NAFLD (liver biopsy) was not done. Therefore, subsequent work with a large sample size is recommended.

CONCLUSION

This study demonstrated that measurement of the TyG index is effective to identify individuals at risk for NAFLD in children with T1DM. Our finding is of great significance considering the avoidance of invasiveness of liver biopsy and to limit application of imaging examinations in children to a certain extent. Also, it could be used in follow up in T1DM. It is the first study to evaluate the TyG index to identify NAFLD in children with T1DM in Egypt, larger multicenter studies are recommended.

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