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Original Article

Association of Triglyceride and Glucose Index with Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is significantly linked to obesity, insulin resistance (IR), metabolic syndrome, and type 2 diabetes (T2DM). There isn't a single biomarker used to diagnose NAFLD. **Objectives:** Analyzing the association between triglyceride and glucose index (TyG) with NAFLD in T2DM. **Methods:** This cross-sectional study aimed to assess the efficacy of TyG as a potential NAFLD biomarker. The study was conducted on 103 diabetes outpatient clinics at the Dr. Soetomo General Academic Hospital from August to October 2023. Sixty-seven subjects experienced steatosis, while those who did not experience steatosis were 36. The statistical analysis used in this study is binary logistic regression with p <0.05. **Results:** The receiver operating characteristic curves (ROC) analysis showed a TyG cut-off value of 9.334 (AUC = 0.660). Analysis of the risk of TyG on the incidence of steatosis was carried out using binary logistic regression. The results showed that TyG was a significant risk factor for steatosis. Patients with a TyG value above 9.334 risk developing steatosis 3.567 times greater than patients with a TyG value below 9.334 (OR 95% = 1.373 – 9.270, p = 0.009). **Conclusion:** A significant association between TyG and NAFLD in T2DM patients, which the TyG index may be a more effective, valuable, and uncomplicated measure for detecting and controlling NAFLD.

Keywords: Hepatic steatosis, Insulin resistance, NAFLD, TyG index, Type 2 Diabetes mellitus.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is 30% worldwide and rising, requiring urgent and comprehensive measures to raise awareness and address all facets of the disease at local, regional, and global levels [1]. A study conducted in Indonesia also revealed that 30% of the population has fatty livers [2,3]. NAFLD is defined by the accumulation of pathological ectopic fat in the liver and a low-grade chronic inflammatory state [4]. Non-alcoholic fatty liver disease includes a range of liver diseases, ranging from simple fat accumulation (steatosis) to steatohepatitis, cirrhosis, and hepatocellular cancer [5]. According to previous studies, NAFLD increases the risk of type 2 diabetes mellitus (T2DM), worsens glycemic and lipid control, and contributes to the pathogenesis of major chronic cardiometabolic complications like insulin resistance (IR), dyslipidemia, metabolic syndrome, and cardiovascular disease, especially in people with established T2DM [4,6-8].

Although a liver biopsy is considered the gold standard for diagnosing NAFLD, its routine use is limited due to its invasive nature [9]. Ultrasonography (USG) is the preferred imaging method for diagnosing hepatic steatosis in clinical practice since it is widely accessible and less expensive than other options. Controlled biopsies of non-alcoholic steatohepatitis (NASH) patients demonstrate that responsiveness is diminished in early steatosis, and ultrasonography may miss a significant proportion of patients when it detects 5-20% of fatty liver disease [10]. Transient elastography (TE) is the most well-validated non-invasive approach for fibrosis evaluation (e.g., FibroScan), measures steatosis, and reports the passing of ultrasound signal through the liver parenchyma as a controlled attenuation parameter (CAP) [11]. Several non-invasive markers, such as liver function tests like amino-transferase level, can be used as an alternative. However, a prior study indicated that 79% of patients with NAFLD had normal alanine aminotransferase (ALT) [12].

The triglyceride and glucose index (TyG), calculated as the product of an individual's serum triglyceride (TG) and fasting plasma glucose (FPG), has been proposed as a valid and straightforward surrogate marker for IR [13]. A fatty liver produces excessive amounts of TG and FPG [12]. The triglyceride and glucose index may predict the subsequent occurrence of NAFLD in later life, as triglyceride accumulation and IR are the hallmarks of NAFLD. Research has demonstrated a robust and positive correlation between the risk of NAFLD and TyG in various populations [14]. The severity of liver steatosis and the presence of liver fibrosis, as assessed by transient elastography in patients with NAFLD, were also positively correlated with the TyG index [15].

The high prevalence and inferior prognosis of T2DM patients with NAFLD make early detection of NAFLD crucial for early intervention. However, insufficient evidence exists to assess the TyG among NAFLD patients in Indonesia. This study aims to investigate the role of TyG in identifying NAFLD among patients attending a tertiary care hospital in Indonesia.

METHODS

Design, subjects, and research variables

This study is an analytical observational study with a cross-sectional approach. The sample for this study was T2DM patients at the diabetes outpatient

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clinics at the Dr. Soetomo General Academic Hospital from August to October 2023. Subjects were carried out using a consecutive sampling technique, which meets the inclusion and exclusion criteria. The subject inclusion criteria were T2DM patients over 30 years old who were willing to participate in the research and sign informed consent forms. Meanwhile, the subject exclusion criteria include pregnant women, chronic hepatitis virus infection, history of autoimmune hepatitis, alcoholism, history of use of steatogenic drugs, severe heart failure, infectious conditions, chronic kidney disease, undergoing renal replacement therapy (dialysis or transplantation), chronic inflammatory disease, and history of malignancy. The number of subjects in this study was 103 patients with T2DM.

Data collection

Data in this study include age, gender, history of hypertension, duration of diabetes, anti-diabetic drugs (metformin), statins and/or fibrates, insulin, body mass index, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), TyG, FPG, and glycosylated hemoglobin (HbA1c). The main aim of this research is to see the effect of TyG on the incidence of steatosis, so the dependent variable used is NAFLD. In contrast, the independent variable is the TyG.

Measurement of hepatic steatosis and TyG

The degree of fatty liver is obtained using the controlled attenuation parameter (CAP) parameter. The controlled attenuation parameter value indicates a fatty liver with a score ≥237.0 dB/m. The triglyceride and glucose index (TyG) of each study subject was calculated using the following formula:

$$TyG = Ln[fasting\ triglyceride(mg/dl) \times fasting\ glucose(mg/dl)/2]$$ [16].

Statistical analysis

The analysis was carried out using descriptive analysis to see the frequency distribution, average value and standard deviation, or median with minimum and maximum values of the characteristics of the study subjects. A normality test was carried out on data with an interval scale using the Kolmogorov-Smirnov test. Next, the analysis was carried out using Receiver operating characteristic curves (ROC) analysis to determine the cut-off value of TyG. Then, a binary logistic regression analysis was carried out to determine the risk of TyG in the incidence of fatty liver or steatosis. All analyses were carried out using SPSS 27 software. Statistical significance was determined with a threshold of p <0.05, and a 95% confidence interval (CI) was applied.

RESULTS

Characteristics of Subjects

In terms of patient characteristics, it was found that age, body mass index, triglycerides, HDL, and TyG had a significant association with the incidence of steatosis. Meanwhile, gender, history of hypertension, duration of diabetes, anti-diabetic drugs (metformin), statins and/or fibrates, LDL levels, total cholesterol, SGOT, SGPT, and FPG, HbA1c did not significantly influence the steatosis incidence. Patients who do not experience steatosis are older than patients who experience steatosis.

The average body mass index of patients who experienced steatosis was 27.79 kg/m^2, higher than that of patients who did not experience steatosis, 24.08 kg/m^2. Based on Triglycerides, patients who experience steatosis have higher triglyceride levels with a median of 146 mg/dL. The HDL value of patients who do not experience steatosis is higher than patients who experience steatosis, namely 49. Based on the TyG value, patients who do not experience steatosis have an average of 8.90, while patients who experience steatosis have an average of TyG of 9.31 (Tables 1 and 2).

Effect of Triglyceride and Glucose Index on NAFLD

ROC analysis on the effect of TyG on the incidence of steatosis. The single effect of TyG is quite good at predicting the incidence of steatosis, as shown by an area under the curve (AUC) value of 0.660 (AUC >0.5) with a cut-off value of 9.334 (Fig. 1). Patients were then categorized into two categories based on the cut-off value: patients with TyG values below 9.334 and patients with TyG values above 9.334 (Table 3). The effect of TyG on the incidence of steatosis can be analyzed using logistic regression. The analysis results showed that TyG was a significant risk factor for steatosis. Patients with TyG values above 9.334 risk developing steatosis 3.567 times greater than those with TyG values below 9.334 (OR 95% = 1.373 – 9.270, p = 0.009; Table 4).

Table 1. Comparison of demographic and clinical characteristics between groups with and without hepatic steatosis based on distribution.

Characteristics	Hepatic steatosis absent (n=36)	Hepatic steatosis present (n=67)	p
Sex; n (%)			
Male	16 (37.2)	27 (62.8)	0.684
Female	20 (33.3)	40 (66.7)	
Hypertension; n (%)			
No	12 (41.4)	17 (58.6)	0.392
Yes	24 (32.4%)	50 (67.6)	
Duration of diabetes; n (%)			
<10 years	21 (30.4)	48 (69.6)	0.171
≥10 years	15 (44.1)	19 (55.9)	
Metformin; n (%)			
No	21 (32.8)	43 (67.2)	0.560
Yes	15 (38.5)	24 (61.5)	
Statin and/or Fibrates; n (%)			
No	10 (43.5)	13 (56.5)	0.330
Yes	26 (32.5)	54 (67.5)	
Statin; n (%)			
No	10 (40.0)	15 (60.0)	0.543
Yes	26 (33.3)	52 (66.7)	
Insulin; n (%)			
No	14 (32.6)	29 (67.4)	0.666
Yes	22 (36.7)	38 (63.3)	

Table 2. Comparison of demographic and clinical characteristics between groups with and without hepatic steatosis based on frequency.

Characteristics	Hepatic steatosis absent (n=36)	Hepatic steatosis present (n=67)	p
Age	59.53 ± 9.15	54.97 ± 8.19	0.011*
BMI	24.08 ± 3.17	27.79 ± 4.84	<0.0010**
Triglycerides	112 (33 – 315)	146 (45 – 654)	0.011*
HDL	49 (29 – 102)	43 (27 – 78)	0.009
LDL	117.08 ± 34.36	104.66 ± 32.76	0.074
Total Cholesterol	195.03 ± 45.18	182.42 ± 42.11	0.161
SGOT	19.5 (12 – 31)	20 (11 – 71)	0.330
SGPT	19 (6 – 71)	19 (7 – 78)	0.482
TyG	8.90 ± 0.67	9.31 ± 0.74	0.006*
FPG	120 (72 – 309)	142 (64 – 381)	0.139
HbA1c	7.55 (5.50 – 12.50)	8.70 (5.70 – 14.90)	0.058

Note: BMI = body mass index; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SGOT = serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; TyG: triglyceride and glucose index; *significant <0.05; **significant <0.001.

Table 3. Cut-off Value of TyG index for the best prediction of NAFLD.

Parameter	AUC	95% CI	Cut-off Value	Sensitivity	Specificity	p
TyG	0.660	0.551 – 0.768	9.334	0.816	0.806	0.008

Table 4. Binary logistic regression analysis model of TyG for having hepatic steatosis in type 2 diabetes mellitus.

Parameter	β	OR	95% CI	p
Triglyceride and Glucose Indeks (TyG)	1.272	3.567	1.373 – 9.270	0.009
Constant	-1.056	0.348		

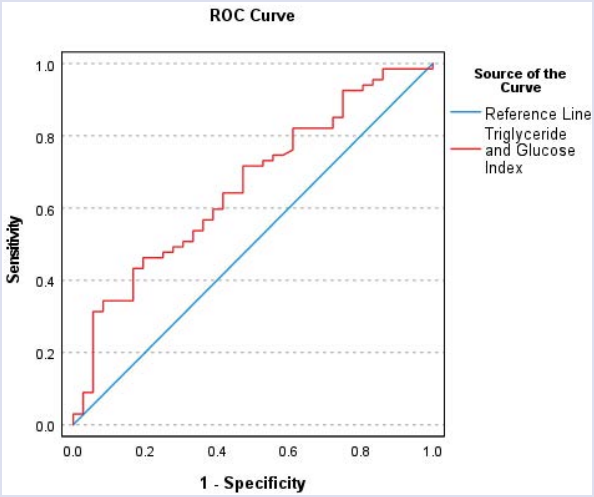

Figure 1. Receiver operating characteristic (ROC) curve of TyG index for the best prediction of NAFLD.

DISCUSSION

In this cross-sectional study, we found the incidence of NAFLD was 67/103 (65%) among the T2DM patients at the diabetes outpatient clinics at the Dr. Soetomo General Academic Hospital. This was higher than the previous study in Indonesia, which demonstrated that the proportion of NAFLD in diabetes patients is as high as 45.2% [2]. This could be attributed to transient elastography with CAP parameters in this investigation, which has higher sensitivity and specificity than prior studies that employed ultrasonography to detect NAFLD [17]. In our current investigation, we also established the threshold value of the TyG for detecting hepatic steatosis. This finding could potentially aid in the early detection of non-alcoholic NAFLD in patients with T2DM. After adjusting for potential confounders, this cross-sectional study revealed a robust and positive correlation between the TyG index and the risk of NAFLD. NAFLD was also correlated with age, BMI, TG, HDL-C, and TG.

In our study, patients who do not experience steatosis are older than patients who experience steatosis. Limited research has been conducted on the interaction of BMI and HDL-C, sex, or age in NAFLD. The association between HDL-C, age, and the TyG index could be attributed to the predominance of low HDL-C in the younger population [18]. A previous study found that younger age (<65 years) is linked to increased NAFLD risk when the TyG index is higher [19,20]. In contrast, the mean age of NAFLD patients was 53.11 ± 8.58 years in a study conducted by Lee et al., while the control group had a mean age of 52.29 ± 9.70 years. The average age difference between the two groups in their study was statistically significant ($p < 0.01$) [21]. In a separate trial, there was no statistically significant age disparity between the steatosis and control group [14,22]. The obtained result did not align with the findings of our investigation. The possible cause could be attributed to either a limited sample size or variations in demographic variables.

In the current study, it was noted that the group of NAFLD patients was obese (BMI ≥25 kg/m^2, by Asia Pacific classification) with a BMI mean of 27.79 kg/m^2, while the control subjects were within the overweight or normal body weight range (BMI <25 kg/m^2). The statistical significance of the bodyweight difference between the groups was observed in our study (p = 0.000). The efficacy of TyG in identifying individuals at risk of NAFLD was reported to be significantly influenced by BMI in previous studies, which yielded similar results [12,23].

Our study primarily focused on the association between NAFLD and the TyG index, glycemic parameters, and lipid parameters in a T2DM population. This cross-sectional study observed a robust and positive correlation between the TyG index and the risk of NAFLD, even after adjusting for potential confounding factors. IR is biologically linked to the development of NAFLD. The hyperinsulinemic-euglycemic glucose clamp is the gold standard for measuring IR, although its clinical utility is limited due to time and cost. As an alternative, the homeostasis model assessment insulin resistance (HOMA-IR), a test based on insulin levels and fasting glucose, is most commonly used in clinical practice to evaluate IR. However, HOMA-IR varies significantly depending on the type of insulin assay used, and the range of fasting plasma insulin levels deemed normal. As a result, several surrogate indicators for IR have recently emerged [24]. The TyG index, as expected, was found to be associated with the risk of T2DM.

Furthermore, it is an effective biomarker for identifying NAFLD. Two prospective cohort studies in Chinese and Japanese populations found a connection between NAFLD incidence and the TyG index [14,23]. In Korea, the TyG index outperformed HOMA-IR in predicting NAFLD [21]. Several studies have shown that the TyG index is better than HOMA-IR in predicting diabetes and hypogonadism [25,26].

The triglyceride and glucose index, which uses standard blood tests (FPG and serum triglycerides), is a non-invasive marker of IR and a reliable predictor of NAFLD [12,14]. Studies found a link between hepatic steatosis and TyG levels over 8.5-8.85 [15,24,26-28]. The TyG cut-off value reported in our study is 9.334, higher than the earlier investigations' cut-offs. However, while evaluating our research findings, it is essential to remember that all patients involved were diagnosed with T2DM, which is related to IR and a rising TyG index.

However, this research has several areas for improvement. First, this cross-sectional study cannot identify whether the TyG index causes hepatic steatosis or liver fibrosis in NAFLD. Second, our investigation found the diagnostic gold standard of liver biopsy impossible due to its invasiveness and impracticality. Alternatively, transient elastography was used as a non-invasive diagnostic approach in the current investigation. Finally, no information on nutritional or exercise habits was obtained. These factors may have influenced circulating TG levels.

CONCLUSION

This study showed a strong association between NAFLD and the TyG index in T2DM patients. Thus, the TyG index may be a more effective, valuable, and uncomplicated measure for detecting and controlling NAFLD in individuals with T2DM. The TyG index is simpler to calculate than other IR markers, and the testing costs are low. Furthermore, it appears to be a reliable biomarker for identifying those with NAFLD. In clinical practice, assessing an individual's TyG index is critical. If the TyG index is elevated, lifestyle modifications are required to prevent the development of NAFLD.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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ETHICAL APPROVAL

Approval was obtained from the Institutional Ethical Committee of Dr Soetomo General Academic Hospital, Surabaya, Indonesia, with certificate number 0723/KEPK/VII/2023. Patients were informed and consented to participate in the study, which complied with the Declaration of Helsinki.

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