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Triglyceride to high-density lipoprotein cholesterol ratio as a marker of non-alcoholic fatty liver disease in type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and non-alcoholic liver disease (NAFLD) shared a common feature, insulin resistance (IR), which is marked by a change in the lipoprotein fraction, namely increased triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) levels. Blood lipids are routinely examined in T2DM patients; thus, our study aimed to investigate the performance of TG/HDL-C ratio values to identify hepatic steatosis, the earliest manifestation of nonalcoholic fatty liver disease (NAFLD), in T2DM patients. One hundred adult T2DM patients over 30 years old were recruited from the diabetes outpatient clinic at the Dr. Soetomo General Academic Hospital from August to October 2023. Data regarding sociodemographics, medication, glycosylated hemoglobin (HbA1c), lipid profiles, and FibroScan with controlled attenuation parameter (CAP) were collected from all participants. The group with hepatic steatosis (CAP≥237 dB/m) had a higher body mass index (BMI), higher TG levels, and TG/HDL-C ratio values. The TG/HDL-C ratio was significantly correlated with CAP values. Hepatic steatosis can be identified using the TG/HDL-C ratio with a cut-off value of 2.83 (sensitivity:72.4%; specificity:71.4%). An elevated TG/HDL-C ratio is associated with a higher risk (OR:6.562; $p<0.05$) of having hepatic steatosis. The TG/HDL-C ratio is a potential marker to predict NAFLD in T2DM patients.

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1. INTRODUCTION

Indonesia is one of the top ten countries with the highest prevalence of diabetes, expected to have around 13.7 million cases in 2030 and predicted to increase to 16.6 million in 2045 [1], [2]. Meanwhile, non-alcoholic liver disease (NAFLD) is a chronic liver disease that encompasses simple steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and end-stage liver disease [3]. Type 2 diabetes mellitus and NAFLD have a close correlation, and its prevalence is also increasing. The prevalence of NAFLD in T2DM patients is estimated to be around 55.5% worldwide, according to a recent meta-analysis [4]. There is mounting

evidence that people with T2DM and NAFLD typically have worse glycemic control than people with T2DM alone. Patients with T2DM and NAFLD also have a greater risk of developing microvascular and macrovascular complications, namely retinopathy, chronic kidney disease (CKD), and cardiovascular disease (CVD) [5]–[7].

A liver biopsy is considered the gold standard for the diagnosis of NAFLD; however, due to its invasiveness, it has limited use in daily practice [8]. FibroScan, an advanced transient elastography device, has been considered as an alternative to liver biopsy. Controlled attenuation parameter (CAP) is a novel method to determine the severity of hepatic steatosis using the ultrasonic properties of the radiofrequency and back propagated signals in conjunction with the FibroScan. The CAP has proven a good sensitivity, specificity, and high area under the curve (AUC) for the detection of hepatic steatosis confirmed by liver biopsy, according to a recent meta-analysis [9]. Nevertheless, the number of T2DM patients is vast; thus, routine liver FibroScan screening is expensive, and several facilities still lack FibroScan equipment. Therefore, many studies have aimed for the early identification of patients with NAFLD using a number of serum biomarkers. However, as of today, there is still no acceptable serum biomarker for accurately diagnosing NAFLD [10].

Liver enzymes and blood lipids are serum biochemical indices that are routinely examined in T2DM patients [11]. However, because changes in liver enzyme levels are weakly correlated with the degree of hepatic steatosis, they are unreliable for the screening of NAFLD [12]. The changes in lipid metabolism are pivotal in the development of NAFLD. Increased liver fat content in the pathogenesis of NAFLD is the result of the dysregulation of several pathways: uptake of free fatty acids, enhanced hepatic *de novo* lipogenesis (DNL), impaired beta-oxidation, and altered export of lipoproteins as components of very-low density lipoprotein (VLDL) [13]. As a result, dyslipidemia in patients with NAFLD is characterized by elevated serum triglycerides (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C). Several previous studies reported that lipoprotein ratios, rather than single lipid parameters, are more useful as predictors of NAFLD because they represent the interaction between each lipid component [14].

Although the association between dyslipidemia and NAFLD is well documented, the data regarding the relationship between lipid ratios, especially TG to HDL-C (TG/HDL-C), and NAFLD in T2DM patients in Indonesia are scarce. Early detection of NAFLD in T2DM patients is important for early intervention due to the high prevalence and poorer prognosis of T2DM patients with NAFLD. Therefore, our present study aimed to explore the association between TG/HDL-C ratio and hepatic steatosis and the performance of TG/HDL-C ratio to identify hepatic steatosis in T2DM patients.

2. METHOD

2.1. Research ethics clearance

Approval for this study was granted by the ethical committee at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, under the reference number 0723/KEPK/VII/2023. First, the researchers gave a comprehensive briefing regarding the research procedure to all eligible participants. After which, the participants who agreed were requested to provide written informed consent.

2.2. Design, subjects, and research variables

This study was a cross-sectional design study conducted in the Endocrinology and Diabetes outpatient clinic at the Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, from August to October 2023. The sampling process was done using consecutive method following the inclusion and exclusion criteria. All adult T2DM patients over 30 years of age were included. Subjects who were pregnant, diagnosed with chronic viral hepatitis infection, autoimmune hepatitis, alcoholics, using steatogenic drugs (amiodarone, corticosteroid, methotrexate, or tamoxifene), or diagnosed with severe congestive heart failure were excluded from this study. The dependent variable was the severity of hepatic steatosis measured by CAP of the FibroScan, and the independent variable was the TG/HDL-C ratio.

2.3. Data collection

Comprehensive history-taking, physical examination, and FibroScan examination were performed on all subjects. The laboratory data regarding glycosylated hemoglobin (HbA1c) levels and lipid profiles (total cholesterol (TC), low-density lipoprotein (LDL) cholesterol (LDL-C), HDL-C, and TG) were retrieved from the most recent examination within three months from the medical record. If there was no recent laboratory data, we collected a venous blood sample under fasting conditions and sent it to the laboratory of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, for biochemical analysis. The TG/HDL ratio was calculated by dividing the absolute value of serum TG levels by HDL-C levels.

2.4. Measurement of hepatic steatosis

The severity of hepatic steatosis was measured using the CAP of the FibroScan by ECHOSENS FibroScan type 502 touch (Delrus Europe, Budapest), and it was reported in decibels/meter (dB/m). The CAP value ranges indicated the degree of hepatic steatosis, starting from S0 (no steatosis) to S3 (severe steatosis). They were between 237.0-259.0 dB/m for S1, 259.0-291.0 dB/m for S2, and 291.0-400 dB/m for S3 [15]. The measurement was performed by experienced gastroentero-hepatologists who have performed the examination using FibroScan multiple times.

2.5. Statistical analysis

SPSS version 23.0 for Windows (IBM Corporation, New York, USA) was used to analyze the data. The normality of the data was determined using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as frequency distribution and mean with standard deviation for normally distributed data or median with minimum and maximum values if the data were not normally distributed. We used an independent t-test or Mann-Whitney U-test to detect differences in TG/HDL-C ratio values between groups with and without hepatic steatosis. The correlation between the TG/HDL-C ratio and CAP values was assessed through either the Pearson or Spearman correlation test. Receiver operating characteristic curves (ROC) analysis was performed to determine the TG/HDL-C ratio's cut-off value, sensitivity, and specificity for identifying hepatic steatosis. Finally, risk prediction of the TG/HDL-C ratio against hepatic steatosis in T2DM was estimated using bivariate logistic regression analysis. Statistical significance was determined with a threshold of $p<0.05$, and a 95% confidence interval (CI) was applied.

3. RESULTS AND DISCUSSION

3.1. Results

3.1.1. Characteristics of the participants

A total of 100 T2DM patients were enrolled, matching the inclusion criteria. The sociodemographic characteristics (age and sex) were not significantly different between the group with and without steatosis. The group with hepatic steatosis had a longer duration (≥5 years) of diabetes and a significantly higher body mass index (BMI) compared to the group without hepatic steatosis. The laboratory parameters of the group with and without hepatic steatosis were not significantly different apart from the TG levels, HDL-C levels, and the TG/HDL-C ratio values. The comparison of the characteristics between the two groups is described in Table 1.

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

Characteristics	Hepatic steatosis present (CAP≥237 dB/m) n=58	Hepatic steatosis absent (CAP<237 dB/m) n=42	p
Age (years), (mean±SD)	54.6±8.0	57.7±9.4	0.078
Sex (n, %)			0.168
Male	21 (50.0%)	21 (50.0%)	
Female	37 (63.8%)	21 (36.2%)	
Duration of diabetes (n, %)			0.038*
<5 years	21 (46.7%)	24 (53.3%)	
≥5 years	37 (67.3%)	18 (32.7)	
Hypertension (n, %)			0.224
Yes	32 (64.0%)	18 (36.0%)	
No	26 (52.0%)	24 (48.0%)	
Use of statins and/or fibrates (n, %)			0.970
Yes	44 (57.9%)	32 (42.1%)	
No	14 (58.3%)	10 (41.7%)	
BMI (kg/m2) (mean±SD)	28.8±4.3	23.8±3.4	0.000*
HbA1c (%), median (min–max)	8.6 (5.7-12.7)	8.0 (5.4-12.5)	0.505
Serum creatinine (mg/dL), median (min-max)	0.9 (0.4-2)	1.1 (0.5-4.3)	0.297
SGOT (IU/L), median (min–max)	21 (13-71)	19 (12-31)	0.111
SGPT (IU/L), median (min–max)	20 (8-78)	19 (6-71)	0.476
Total cholesterol (mg/dL), (mean±SD)	182.1±37.6	189.4±44.1	0.379
Triglyceride (mg/dL), median (min-max)	162 (55-654)	106 (33-266)	0.000*
HDL-C (mg/dL), median (min-max)	42.5 (27-85)	47 (29-102)	0.019*
LDL-C (mg/dL) (mean±SD)	104.9±30.5	113.9±34.7	0.170
TG/HDL-C, median (min-max)	3.7 (0.9-17.7)	2.1 (0.5-5.6)	0.000*

CAP: controlled attenuation parameter; BMI: body mass index, HbA1c: glycosylated hemoglobin, SGOT: serum Glutamic Oxaloacetic Transaminase, SGPT: serum glutamic pyruvic transaminase, HDL-C: high-density lipoprotein, LDL-C: low-density lipoprotein, TG: triglyceride; *significant ($p<0.05$)

3.1.2. Correlation of the TG/HDL-C ratio with the CAP

There was no significant correlation between HbA1c levels, liver enzyme levels, total cholesterol, LDL-C levels, and CAP values. The TG levels were positively correlated with CAP values with strong relationship (p=0.477). The HDL-C levels were not correlated with CAP values; however, when combined with TG levels as a TG/HDL-C ratio, they strongly correlated with CAP values (p=0.440). The correlation is presented in Table 2.

Table 2. Correlation of glycemic control, liver enzymes, lipid profile, and triglyceride to HDL cholesterol ratio with the severity of hepatic steatosis using controlled attenuation parameter

Parameter	*r*	ρ	p
HbA1c (%)		0.065	0.518
SGOT (IU/L)		0.190	0.058
SGPT (IU/L)		0.145	0.149
Total cholesterol (mg/dL)	-0.048		0.634
Triglyceride (mg/dL)		0.477	0.000*
HDL-C (mg/dL)		-0.182	0.070
LDL-C (mg/dL)	-0.193		0.054
TG/HDL-C		0.440	0.000*

HbA1c: glycosylated hemoglobin, SGOT: serum Glutamic Oxaloacetic Transaminase, SGPT: serum glutamic pyruvic transaminase, HDL-C: high-density lipoprotein, LDL-C: low-density lipoprotein, TC: total cholesterol, TG: triglyceride; *r*: Pearson correlation coefficient; ρ: Spearman correlation coefficient; *significant (p<0.05)

3.1.3. Diagnostic performance of the TG/HDL-C ratio for NAFLD in type 2 DM patients

The ROC analysis for TG/HDL-C ratio and other single lipid parameters for hepatic steatosis as an outcome is presented in Figure 1. Only the TG levels as a single lipid parameter can be used (AUC>0.7) to predict the presence of hepatic steatosis with a cut-off value of 134.5 (sensitivity: 67.2% and specificity: 73.8%). The TG/HDL-C ratio however, had better sensitivity (72.4%) to detect hepatic steatosis compared to TG levels alone. The diagnostic performance of lipid profiles and TG/HDL-C ratio are described in Table 3.

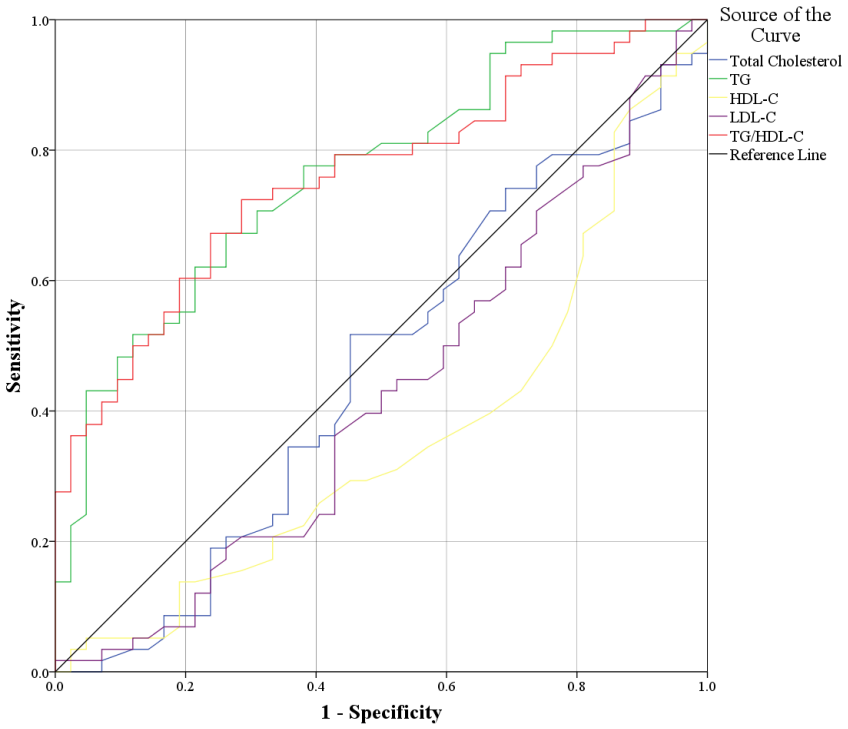

Figure 1. Receiver operator characteristics curve analysis of lipid profile and triglyceride to HDL cholesterol ratio as a predictor of hepatic steatosis in type 2 diabetes mellitus

Table 3. Characteristics of lipid profile and triglyceride to HDL cholesterol ratio using the optimal cut-off value to detect the presence of hepatic steatosis in type 2 diabetes mellitus

Parameter	AUC	95% CI	Cut-off value	Sensitivity	Specificity	p
Total cholesterol (mg/dL)	0.464	0.347-0.581	180.5	51.7%	54.8%	0.060
Triglyceride (mg/dL)	0.763	0.671-0.856	134.5	67.2%	73.8%	0.047*
HDL-C (mg/dL)	0.362	0.251-0.473	77	34.0%	97.6%	0.057
LDL-C (mg/dL)	0.424	0.309-0.540	56	98.3%	4.8%	0.059
TG/HDL-C	0.759	0.666-0.851	2.83	72.4%	71.4%	0.047*

AUC: area under the curve, CI: confidence interval; HDL-C: high-density lipoprotein, LDL-C: low-density lipoprotein, TG: triglyceride; *significant ($p<0.05$)

3.1.4. Risk analysis model of the TG/HDL-C ratio as predictor for NAFLD in type 2 DM patients

The TG/HDL-C ratio with a cut-off value of 2.83 was used to determine the presence of hepatic steatosis. An elevated TG/HDL-C ratio was defined by a value greater than or equal to 2.83; otherwise, the TG/HDL-C ratio was considered normal. An elevated TG/HDL-C ratio value has proven to be a risk factor significantly associated with hepatic steatosis in T2DM patients, according to bivariate logistic regression (OR:6.562; p=0.000). Even after adjusting for sex, use of statins and/or fibrates, duration of diabetes, presence of hypertension, obesity, and glycemic control, the association remained significant. The binary logistic regression analysis model is described in Table 4.

Table 4. Binary logistic regression analysis model of triglyceride to HDL cholesterol ratio for having hepatic steatosis in type 2 diabetes mellitus

Parameter	β	OR	95% CI	p
TG/HDL-C	1.881	6.562	2.714-15.869	0.000*
Constant	-0.629	0.533		0.042*

OR: odds ratio, CI: confidence interval; HDL-C: high-density lipoprotein, TG: triglyceride; *significant ($p<0.05$)

3.2. Discussion

To the best of our knowledge, our current study is the first to evaluate the association between the TG/HDL-C ratio and hepatic steatosis in Indonesian T2DM patients. Our present study also determined the cut-off value of the TG/HDL-C ratio to detect hepatic steatosis, which might contribute to the early identification of NAFLD in T2DM patients. The main findings of the present study were: i) the TG/HDL-C ratio was correlated with hepatic steatosis; ii) the TG/HDL-C ratio had good sensitivity and specificity to detect hepatic steatosis; iii) increased TG/HDL-C ratio raised the risk of having hepatic steatosis in T2DM. These results suggest that the TG/HDL-C ratio is independently correlated with the risk of hepatic steatosis in the T2DM population.

In general, our results are consistent with previous studies regarding the association between the TG/HDL-C ratio and NAFLD. Our present study indicated that subjects with hepatic steatosis had significantly higher TG/HDL-C ratio values than those without hepatic steatosis, comparable to the results of prior studies [10], [16]–[19]. The TG/HDL-C ratio is independently correlated with NAFLD, according to two large cross-sectional studies [16], [17]. Another cohort study also reported an independent association between the TG/HDL-C ratio and NAFLD in non-obese subjects [18]. The TG/HDL-C ratio is also effective in detecting NAFLD, as reported by Fan *et al*. [17], Chen *et al*. [18], and and Pérez-Mayorga *et al*. [19], with cut-off values ranging from 0.64 to 3.83, probably related to ethnic differences. However, most of those studies involved apparently healthy individuals who were not diabetic, except for the study by Li *et al*. [10], which involved newly diagnosed T2DM patients. The performance of the TG/HDL-C ratio as a surrogate for NAFLD, especially hepatic steatosis, needs to be explored in the T2DM population since they have different risks and glycemic status.

Our present study indicated that TG/HDL-C ratio is potential as a biomarker of NAFLD in T2DM patients. Insulin resistance is pivotal in the association of TG/HDL-C ratio and hepatic steatosis in T2DM population [20], [21]. Accumulating body of evidence has indicated the strong correlation between TG/HDL-C ratio and IR [22]–[24]. Additionally, T2DM and NAFLD are tightly related to IR early in the disease course. Adipose tissue dysfunction in T2DM is marked by increased lipolysis and fatty acid synthesis, resulting in excess fatty acid flux [25]. Increased levels of fatty acids in the circulation will ultimately accumulate in the liver or fat tissue, resulting in IR [26]. Insulin resistance also induces *de novo* lipogenesis, thereby further increases liver fat content [27]. Lipids are accumulated as TG in the liver, consequently leading to increased assembly and secretion of VLDL [28]. A marked hypertriglyceridemia will enhance cholesterol ester transfer protein (CETP) mediated incorporation of TG into the HDL-C, resulting in

faster clearance of TG-enriched HDL-C from the circulation [29], [30]. Subsequently, secondary low levels of HDL-C will develop, altogether with hypertriglyceridemia, detected as increased TG/HDL-C ratio values.

4. CONCLUSION

The TG/HDL-C ratio is a potential marker that can be used to predict NAFLD in the T2DM population. Type 2 diabetes mellitus patients with NAFLD are likely to have elevated TG/HDL-C ratio values. A health care provider should be aware of the presence of NAFLD in T2DM patients with an elevated TG/HDL-C ratio. However, further large-scale research with a better study design is required prior to applying this value routinely in clinical settings.

Our present study was limited by its cross-sectional design. There are also several limitations to our present study. The golden standard for diagnosing NAFLD is liver biopsy; nevertheless, the CAP of FibroScan is still widely accepted in clinical practice and epidemiological research for its sensitivity and specificity in diagnosing hepatic steatosis. The influence of other factors, especially lipid-lowering medication (statins and fibrates) and oral hypoglycemic agents, namely thiazolidinedione, were not controlled in our present study. Consequently, a bias might affect the association between TG/HDL-C ratio and hepatic steatosis; still, we have the interference of these factors taken into account during statistical analysis.

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