The Atherogenic Index Log (Triglyceride/HDL-Cholesterol) as a Biomarker to Identify Type 2 Diabetes Patients with Poor Glycemic Control

Abstract

Background: Identifying appropriate biomarkers for predicting type 2 diabetes (T2D) patients with increased HbA1c may prove helpful in preventing increased risk of cardiovascular disease (CVD). The present study was conducted to analyze the diagnostic performance of the atherogenic index log (TG/HDL-C) in T2D patients with increased HbA1c. **Methods:** Patients with T2D were classified into two groups according to having an HbA1c <8% or ≥8%. Atherogenic index was calculated from the logarithmic transformation of TG/HDL-C. Receiver operating characteristic curve was used to evaluate the diagnostic performance of log (TG/HDL-C). Insulin and fasting glucose concentrations were used to determine homeostasis model assessment for insulin resistance (HOMA-IR). **Results:** Compared with the patients with HbA1c <8%, log (TG/HDL-C) was significantly higher in the patients with HbA1c ≥8% ($p = 0.025$). The atherogenic index was a biomarker for the prediction of T2D patients with HbA1c ≥8% versus patients with HbA1c <8%, as shown in the area under the curve (AUC = 0.61, $P = 0.013$). The best cut-off point of log (TG/HDL-C) for the discrimination between patients with HbA1c ≥8% versus patients with HbA1c <8% determined to be 0.44. Atherogenic index was significantly and positively correlated with HOMA-IR in female patients ($r = 0.313$, $P = 0.003$) and in patients with an age ≥5o ($r = 0.253$, $P = 0.021$). **Conclusion:** The log (TG/HDL-C) in addition to its known association with enhanced CVD risk could be considered as a biomarker to predict T2D patients with poor glycemic control. Therefore, the increased ratio may provide a simple and useful way of identifying poor glycemic T2D patients who are possibly to be at elevated risk of CVD.

Keywords: *Biomarker, cardiovascular disease, HbA1c, Log (TG/HDL-C), type 2 diabetes*

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Introduction

Diabetes mellitus is a major threat to public health worldwide and its prevalence is increasing rapidly. These conditions are likely to worsen in the future as a result of increasing lifestyle negative changes, such as obesity. Patients with type 2 diabetes (T2D) often develop dyslipidemia that can lead to the increases risk of cardiovascular disease (CVD).[1,2] Evaluation of dyslipidemia and oxidative stress markers can be useful for the assessment of cardiovascular risk in patients with T2D.[1,3] Atherogenic dyslipidemia including increased triglycerides (TGs) and low levels of high-density lipoprotein (HDL) cholesterol, often with increased apolipoprotein B and non-HDL cholesterol, is common in patients with established CVD, T2D, or metabolic syndrome and contributes vascular residual risk.[4]

Studies in prediabetic subjects have indicated that an atherogenic pattern of risk factors may contribute to the risk of macrovascular outcomes as much as the duration of clinical diabetes itself, therefore in order to reduce the cardiovascular risk in diabetic individuals it may be necessary to intervene before the onset of clinical diabetes.[5] The association of hypertriglyceridemia with impaired glucose tolerance, impaired fasting glucose, insulin resistance, and T2D shows importance of high TG in T2D.[6,7] According to recent studies, risk factors for CVD such as log (TG/HDL-C) and low-density lipoprotein (LDL)/HDL have higher predictive value than individual concentrations of lipid parameters; therefore, it could be an advantage for these atherogenic indices to be an alert to the increased cardiovascular risk.[8]

The longer periods of exposure to HbA1c levels ≥8% were associated with increasing

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cardiovascular complications and mortality risk.[9] The present study thus seeks to answer the question whether the atherogenic index can have the predictive role in T2D patients with poor glycemic control. The importance of the predictor role of log (TG/HDL-C) in these patients becomes more apparent when noting that this index contribute to the prediction of cardiovascular complications in patients with T2D.

Methods

Study population

This study conducted on 133 patients with T2D. All patients were diagnosed according to the diagnostic criteria as recommended by the WHO incorporating both fasting glucose and a 2-h oral glucose tolerance test. Based on the recommendations of the American Diabetes Association Standards of Medical Care in Diabetes (2020), HbA1C goals <8% may be appropriate for patients with an advanced microvascular or macrovascular complications.[10] Furthermore, poor glycemic control has been defined as HbA1c values ≥8% in some other studies.[11,12] Therefore, the study patients with T2D were classified according to having an HbA1c <8% (n = 69) or ≥8% (*n* = 64). Information about demographic parameters, medical history, personal habits, and medication use was obtained using a questionnaire. Criteria for exclusion in the study were type 1 diabetes, history of myocardial infarction or stroke, previous history of renal failure, liver diseases, cancer, and pregnancy. The patients were taking medications, including metformin, a sulfonylurea and a statin. The study protocol was planned based on the ethical criteria detailed in the Declaration of Helsinki and was approved by the university local ethics committee. Written informed consent was received from all participants.

Assay of laboratory parameters

Insulin levels were measured using ELISA kit (Diametra Corporation, Milan, Italy). TG, HDL-C, and fasting blood glucose were measured by commercial kits (Greiner Diagnostics GmbH, Bahlingen, Germany). Atherogenic index was calculated from the logarithmic transformation of TG/HDL-C. HbA1c was measured using a commercially available immunoturbidimetric assay kit (Pars Azmoon Co, Tehran, Iran). Insulin and fasting glucose concentrations were used to determine HOMA-IR using the following equation[13]:

$$HOMA\text{-}IR = \text{fasting glucose (mmol/L)} \times \text{fasting insulin (}\mu U/mL)/22.5$$

Statistical analyses

Comparisons between groups were performed using *t*-test for parametric variables and Mann–Whitney *U* test for nonparametric variables. Receiver operating characteristic (ROC) analyses were performed to analyze the predictive performance of atherogenic index in the study groups. The area under the curve (AUC) was determined in order to estimate the overall discriminative capacity of the variables. Pearson correlation coefficient was used to analyze the association between study variables. SPSS (version 16.0) and R (version 3.0.0) software were used for statistical analyses. Two-tailed *P* value less than 0.05 was considered to be significant.

Results

Table 1 shows the comparison of values of the study parameters when HbA1c was categorized as <8% or ≥8%. There also was no statistically significant difference between patients with HbA1c ≥8% and patients with <8% with respect to medications, including metformin, a sulfonylurea and a statin. As shown in Figure 1, compared to the patients with HbA1c <8%, atherogenic index was significantly higher in the patients with HbA1c ≥8% (*p* = 0.025).

As can be seen in Figure 2, log (TG/HDL-C) was an appropriate biomarker for the prediction of T2D patients with HbA1c ≥8% versus patients with HbA1c <8%, as shown in the AUC (AUC = 0.61, *P* = 0.013). The ratio log (TG/HDL-C) remained a significant predictor for patients with HbA1c ≥8% after multivariate adjustment for age, sex, and body mass index. Based on Youden's index, the best cut-off point of log (TG/HDL-C) for the discrimination between patients with HbA1c ≥8% versus patients with HbA1c <8% was 0.44, with a specificity of 48% and a sensitivity of 81%.

As indicated in Figure 3, our findings showed that atherogenic index was significantly and positively correlated with HOMA-IR (*r* = 0.313, *P* = 0.003) in female patients. This index was also found to be positively correlated with HOMA-IR in male patients; however, the correlation was not statistically significant (*r* = 0.146, *P* = 0.375). When patients were classified according to age, atherogenic index was found to be positively correlated with HOMA-IR in both patients with an age <50 and age ≥5o; however,

Table 1: Clinical and biochemical characteristics of patients with type 2 diabetes according to HbA1c

Parameter	HbA1c <8% (*n*=69)	HbA1c ≥8% (*n*=64)	*P*
Age (year)	52.35±5.99	51.29±6.56	0.334
Women (%)	76.8	60.9	0.059
BMI (kg/m²)	29.95±4.35	30.06±4.94	0.998
Smoking (%)	4.35	7.81	0.466
Triglyceride (mmol/L)	2.03±1.26	2.42±1.34	0.096
HDL-C (mmol/L)	1.21±0.31	1.13±0.27	0.099
HOMA-IR	3.89±3.45	6.59±4.7	<0.001
Medications (%)			
Metformin	71.1	81.2	0.216
Sulfonylurea	14.5	26.6	0.084
Statins	32.8	35.6	0.853

Values are presented as percent or mean±SD.

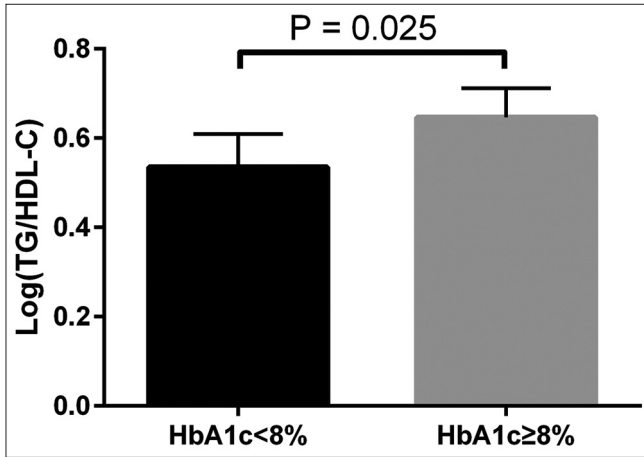only the correlation in the age $\geq 5o$ group was statistically significant ($r = 0.253$, $P = 0.021$).

Figure 1: Comparison of atherogenic index in type 2 diabetes patients with HbA1c ≥8% and patients with HbA1c <8%.
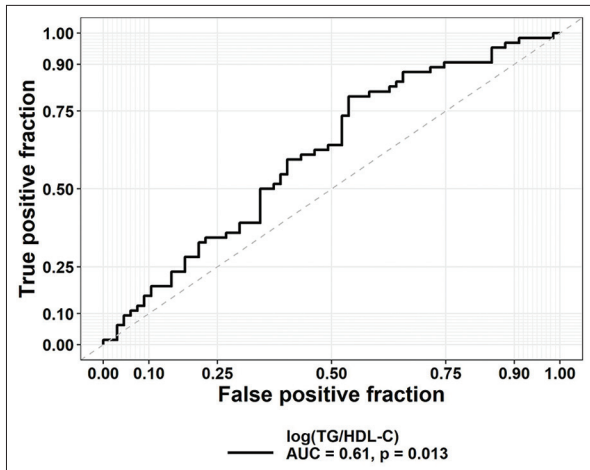

Figure 2: The receiver operating characteristics (ROC) curves for atherogenic index for discriminating patients with HbA1c ≥8% versus patients with HbA1c <8%. The corresponding value of the area under the curve (AUC) and *P* value are reported

Discussion

In the lipid and lipoprotein therapy strategies, after the introduction of statins, clinical priority first focused on LDL cholesterol-lowering, then raising HDL cholesterol, with less focus on lowering TG. However, it has now generated renewed interest in lowering TGs because recent studies are showing that TG levels and TG-rich lipoproteins are in the causal pathway of CVD.[14] According to standards of medical care in diabetes, high serum levels of TG and low HDL cholesterol are associated with pre-diabetes and diabetes in asymptomatic adult subjects.[15] Identifying appropriate biomarkers can help develop therapeutic strategies to improve the survival of patients.[16]

Our results indicated that the log (TG/HDL-C) in addition to its known link to enhanced CVD risk is a significant predictor of T2D patients with poor glycemic control. In other words, the elevated ratio may provide a simple and useful approach to identify poor glycemic T2D patients who are possibly to be at increased risk of CVD. The following studies support the present results. The ratio of TG/HDL-C was found to be the predictor of insulin resistance and LDL particle diameter.[17] Log (TG)/HDL-C was a predictor of progression speed of islet beta cell dysfunction in Chinese T2D patients.[18] Intriguingly, in a recent community-based Korean cohort over 12 years, Lim *et al*.[19] found that high TG/HDL-C ratio at baseline may be a useful indicator of future incident T2D. The importance of the predictor role of log (TG/HDL-C) in T2D patients becomes more apparent when noting that this atherogenic index may be a warning for the increased cardiovascular risk in individuals who do not yet have extremely altered lipid levels.[20] Therefore, the log (TG/HDL-C) may be considered as an important biomarker in the monitoring of cardiovascular complications in T2D.

In our findings, the TG/HDL-C ratio as an atherogenic index was positively associated with HOMA-IR which is consistent with previous studies.[21] However, when the
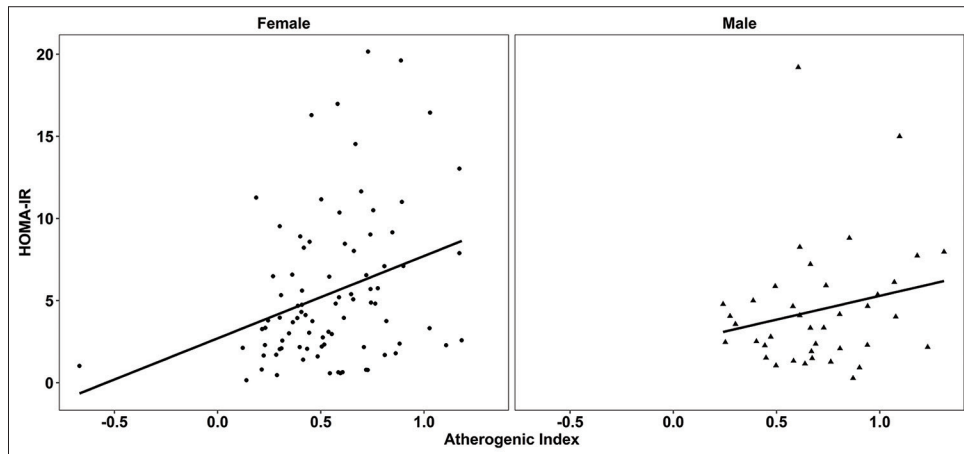

Figure 3: Associations between atherogenic index and HOMA-IR in patients with type 2 diabetes according to gender ($r = 0.313$, $P = 0.003$ for females and $r = 0.146$, $P = 0.375$ for males). HOMA-IR (homeostasis model assessment for insulin resistance)

analyses were performed with regard to gender and age, there were significant correlations between the atherogenic index and HOMA-IR only in the female patients with T2D as well as patients with an age ≥50. This shows that in this group of patients, the higher the insulin resistance, the greater the likelihood of atherogenicity. In other words, it appears that these patients will need more medical care.

Noteworthy, antidiabetic drugs, which are also able to reduce the atherogenic ratios in addition to reducing blood glucose, will likely have positive effects on cardiovascular complications in patients with T2D. In this context, Tan *et al*.[22] showed that pioglitazone monotherapy or in combination therapy with a sulfonylurea, metformin, or insulin reduced the atherogenic ratio log (TG/HDL-C). In addition, fibrates, niacin, and omega-3 fatty acids that are more efficacious in reducing TGs and/or increasing HDL cholesterol should be considered in combinations with statins in order to reducing cardiovascular risk in patients with T2D or metabolic syndrome.[1]

Conclusions

The log (TG/HDL-C) in addition to its known association with enhanced CVD risk could be considered as a biomarker to predict T2D patients with poor glycemic control. Therefore, the increased ratio may provide a simple and useful way of identifying poor glycemic T2D patients who are possibly to be at elevated risk of CVD. The association between log (TG/HDL-C) and insulin resistance differs according to gender and age.

Acknowledgments

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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