# Association Between Lipid-related Parameters and the Carotid Intima-media Thickness, Relating to Type 2 Diabetes Mellitus

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**Keywords.** association, lipid-related parameters, carotid intima-media thickness, type 2 diabetes mellitus

**Introduction.** Higher carotid intima-media thickness (CIMT), indicates a greater burden of subclinical atherosclerosis (AS) and cardiovascular disease (CVD). The AS is related to insulin resistance and lipid oxidation. Detection of reliable and affordable surrogate markers and metabolic components for assessing the CVD risk is world-shaking. This study aimed to inspect the relationship between lipid-related parameters and CIMT, considering the impact of type 2 diabetes mellitus (T2DM).
**Methods.** This cross-sectional study was conducted on a total of 244 participants (113 men and 131 women), including 118 diagnosed with diabetes (DM) and 126 without diabetes (non-DM). Duplex ultrasonography parameters, demographic, physical, biochemical assessments, and lipid-related parameters were measured. Correlation and linear regression analyses assessed the relationship between the lipid-related parameters and CIMT.
**Results.** The DM patients' levels of triglyceride-glucose (TyG) index were significantly higher than the non-DM ones, however, the two groups demonstrated no statistically significant difference in CIMT levels. CIMT was correlated with low-density lipoprotein ($r = 0.33$, $P = .033$) in the DM group and with age ($r = 0.41$, $P < .001$) in the non-DM group. The multivariate linear regression model demonstrated age, TyG-BMI, and LDL/HDL ratio as the significant associates of CIMT, with age having the largest standardized regression coefficient of 0.311 ($P < .001$).
**Conclusions.** The current study revealed direct associations of CIMT with age, TyG-BMI, and LDL/HDL ratio, taking into account the DM/non-DM binary among the study participants.

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## INTRODUCTION

Atherosclerosis (AS) is a chronic vascular disease characterized by the accumulation of fatty streaks in arterial walls, with possible progression into plaque formation (atheroma), plaque rupture, and eventually thrombotic occlusion of the vessels.[1] Accordingly, this process may cause mortality and morbidity, such as ischemic heart disease, stroke, and peripheral arterial disease, which, in turn, impose significant burdens on the health of

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community members.[2] Thus, it is crucial for the early identification of high-risk people and the timely control of AS progression.[3] It is known that some risk factors, including hypertension (HTN) and diabetes mellitus (DM), can accelerate the progression of AS at different levels,[4] as well as endothelial dysfunction.[5] Hence, HTN and DM are now considered essential parameters in the risk prediction of cardiovascular disease (CVD).[6] In this context, it was also demonstrated that insulin resistance (IR) plays a staple role in the development of DM, HTN, and AS,[1,7] and it is a well-known predictor of a wide range of CVDs.[8] Given these facts, several studies have examined the predictive ability of different insulin resistance markers to achieve an accurate and non-invasive tool for the early detection of AS, particularly in high-risk groups.[9]

In recent years, some reliable and affordable surrogate markers for IR have been introduced, such as the triglyceride glucose (TyG) index, the TyG-modified indices (the TyG-body mass index (TyG-BMI) and TyG-waist circumference (TyG-WC)), triglyceride/ high-density lipoprotein cholesterol (TG/HDL) ratio, total cholesterol/ HDL (TC/HDL) ratio, low-density lipoprotein cholesterol/HDL (LDL/HDL) ratio and TG minus HDL.[10-13] Some of the mentioned parameters could predict IR more accurately than the homeostasis model assessment-estimated insulin resistance (HOMA-IR).[14,15]

Given that both hypertriglyceridemia and impaired glucose metabolism are commonly related to IR and AS,[16] growing attention is now attracted to assessing the association of the TyG index with AS.[11,17] The studies demonstrated that higher TyG-BMI index, TG/HDL, TC/HDL, LDL/HDL ratios, and TG-HDL are associated with increased IR, metabolic dysregulation, and CVD.[11-13]

Carotid intima-media thickness (CIMT) is a widely used imaging marker for the diagnosis of preclinical carotid AS,[18] which was shown to have predictive value for future cardio/cerebrovascular events as well.[19] Previous studies explored the positive relationship between some of the mentioned parameters and CIMT in different populations from the point of view such as of age, weight, and comorbidities,[20-26] however, some controversial results are present.[17,27]

Moreover, to our knowledge, previously published research has not precisely compared the associations of lipid-related parameters totally and CIMT in individuals with and without diabetes mellitus.[28,29] Consequently, the current research examined the mentioned relationship.

## MATERIALS AND METHODS

### Study Design and Participants

This cross-sectional study was conducted at the Endocrine Research Center, Iran University of Medical Sciences, and Firoozgar General Hospital, Tehran, Iran; from 2019 to 2021. The eligible participants were enrolled via convenience sampling, DM patients from the endocrine clinic, and non-DM patients from the neurologic clinic. The site of sampling was a referral center located in a metropolitan district of the middle socioeconomic status, which to some extent secures the generalizability of the findings.

The inclusion criteria were as follows: (DM group) T2DM, and the age range of 20 to 70 years old for both groups. The exclusion criteria for both groups were: smoking; substance abuse; pregnancy; taking corticosteroids, immunosuppressive medications, omega-3, lipid-lowering agents, and contraceptives; renal transplantation; systemic conditions (autoimmune diseases, chronic renal disease, chronic or acute infection); CV surgery; malignancy; and albuminuria (urine albumin to creatinine ratio > 30 mg/g). Diabetes mellitus was diagnosed according to criteria recommended by the American Diabetes Association (ADA).[19]

The research protocol was approved by the ethics committee of the Iran University of Medical Sciences (No: IR.IUMS.REC.1401.820), and all participants signed and provided written permission.

### Clinical Measurements and Definitions

Data on demographic characteristics, clinical assessments, past medical history, and medications were collected via a standard questionnaire by a trained physician, who conducted a face-to-face interview at the initial appointment.

A calibrated stadiometer & digital scale (Seca GmbH& Co. KG. Germany) were used to measure standing height and weight, respectively. BMI

was demonstrated as the weight (kg) divided by the square of the height ($m^2$). Participants' blood pressures were measured by a mercury sphygmomanometer (Riester, Exacta 1350, Germany) in the standard position (sitting position after a 10-minute rest).

The blood samples were collected in the tubes containing the clot activator after an overnight fast of at least 8 hours. The separated serum was then analyzed for evaluating the biochemistry panel, including fasting blood glucose (FBG), creatinine, and lipid profile. The samples were analyzed using the Enzymatic Calorimeter technique (Biorex).

The TyG index and modified TyG index were calculated using the following formulae:

TyG index: Ln [TG (mg/dl) × FBG (mg/dl) /2][30] and TyG-BMI (TyG index × BMI). In addition, the other lipid-related parameters are as follows: TG/HDL-C ratio (TG divided by HDL-C), TC/HDL-C ratio (TC divided by HDL-C), LDL-C/HDL-C ratio (LDL-C divided by HDL-C), and TG minus HDL-C.

Additionally, e-GFR was determined by applying diet modification in renal disease (MDRD) formula.[31]

### Assessment of Carotid Intima-media Thickness (CIMT)

An expert neurologist with certified neurosonology experience performed the carotid ultrasonography assessments. The mentioned neurologist was blinded to all participants' characteristics and laboratory results.

A high-resolution duplex ultrasound system (B-Mode) with an 8-Hz linear probe (Sonosite M Turbo, Fuji Film, Japan) measured CIMT. The CIMT was estimated by measuring the thickness of the innermost two layers of intima-media 10 mm before the bifurcation of the common carotid artery (CCA), where no atherosclerotic plaque was present. The left and right CIMT average was calculated and used in all analyses. Mean CIMT over the 75th percentile for age, race, and gender was considered a CV events risk factor, according to the American Echocardiographic Association criteria.[32]

### Statistical Analysis

Demographic and clinical characteristics of participants in the study groups are described as proportions, means (standard deviation (SD)), or medians (interquartile range (IQR)). Between-group comparisons were conducted using an independent sample t-test and Mann-Whitney test for data with and without normal distribution. Categorical variables were compared using the $\chi^2$ test. A Spearman's correlation analysis was performed to examine the correlations of CIMT with different clinical parameters.

Moreover, the associations of CIMT with lipid-related parameters were explored using univariate and multivariate linear regression analyses. The significance level was set at .05. The statistical analyses were performed using the statistical software Stata (ver. 13).

## RESULTS

Data included 244 participants (113 men and 131 women) with a mean (SD) of age equal to 46.4 (10.4) years, consisting of 126 individuals without and 118 with T2DM (median (IQR) duration of DM = 7 (5 to 10) years). As presented in Table 1, the two groups of participants were comparable in terms of gender, BMI, serum TG, and HDL-C. Also, there was no significant difference between CIMT evaluated in the two groups. However, individuals with T2DM were older and had significantly higher BP, FBG, and TyG indexes and lower e-GFR, TC, LDL-C, LDL/HDL, and TC/HDL than those without diabetes (all $P$ values < .05).

Next, the Spearman correlations were computed between CIMT and the variables assessed in Table 1, stratified for the diabetes status, and applying the Bonferroni multiple testing adjustment. Accordingly, in the DM group, LDL showed an association of 0.33 ($P$ value = .033), and in the non-DM group, age, SBP, and TyG-BMI owned correlations of 0.41, 0.30, and 0.30 ($P$ values of < .001, .085, .076; respectively).

Furthermore, considering the variables of $P$ values lower than .1 in Table 1 and the Spearman correlations of $P$ values lower than .1, the univariate regression models were fitted on CIMT as the response variable and adjusted for the diabetes status. The covariates included age, SBP, DBP, FBG, Total cholesterol, LDL-C, TyG, TyG-BMI, LDL/HDL, TC/HDL, and e-GFR. The findings reported in Table 2 indicated all covariates to be significantly

**Table 1.** Characteristics of the Study Participants, Compared in Terms of Diabetes Status

| | Non-diabetic group (n = 126) | Diabetic group (n = 118) | *P* |
|---|---|---|---|
| Age, y (mean (SD)) | 42.7 (9.8) | 50.3 (9.6) | < .001[a] |
| Gender (female, n (%)) | 69 (54.8%) | 62 (52.5%) | .730[b] |
| BMI, kg/m$^2$ (mean (SD)) | 26.2 (4.3) | 26.6 (3.9) | .459[a] |
| SBP, mmHg (median (IQR)) | 120 (110 to 120) | 120 (120 to 130) | < .001[c] |
| DBP, mmHg ( (median (IQR)) | 80 (70 to 80) | 80 (70 to 80) | .004[c] |
| FBG, mmol/l (median (IQR)) | 96 (92 to 103) | 115 (103 to 138) | < .001[c] |
| TG, mmol/l (median (IQR)) | 95 (75 to 148) | 105 (89 to 124) | .288[c] |
| TC, mmol/l (median (IQR)) | 149 (123 to 182) | 132 (122 to 146) | .001[c] |
| LDL-C, mmol/l (median (IQR)) | 95 (80 to 118) | 70 (58 to 83) | < .001[c] |
| HDL-C, mmol/l (median (IQR)) | 43 (41 to 48) | 44 (41 to 48) | .567[c] |
| TyG, median (IQR) | 8.4 (8.2 to 8.9) | 8.8 (8.5 to 9) | < .001[c] |
| TG/HDL, median (IQR) | 2.3 (1.8 to 3.5) | 2.4 (2 to 2.9) | .616[c] |
| TG-HDL, median (IQR) | 51.5 (32 to 106) | 60 (44 to 82) | .396[c] |
| TyG-BMI, median (IQR) | 223.2 (196.4 to 250.6) | 230.1 (211.8 to 254) | .069[c] |
| LDL/HDL, median (IQR) | 2.3 (1.7 to 2.8) | 1.5 (1.3 to 1.9) | < .001[c] |
| TC/HDL, median (IQR) | 3.5 (2.8 to 4.3) | 3 (2.7 to 3.4) | < .001[c] |
| e-GFR, mL/min/ 1.73m$^2$ (median (IQR)) | 103.5 (82.9 to 130) | 88.5 (74.4 to 106.3) | .001[c] |
| CIMT, mm (mean (SD)) | 0.41 (0.11) | 0.40 (0.13) | .506[a] |

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride glucose index; e-GFR, estimated glomerular filtration rate; CIMT, carotid intima-media thickness.
a, t-test; b, $\chi^2$ test; c, Mann-Whitney test.

**Table 2.** Univariate Regression Analyses of Carotid Intima-media Thickness

| Variables | Coefficients | 95% CI | *P* | Standardized Coefficients |
|---|---|---|---|---|
| Age, y | 0.0039 | 0.0025, 0.0052 | < .001 | 0.333 |
| SBP, mmHg | 0.0010 | -0.0002, 0.0022 | .101 | 0.108 |
| DBP, mmHg | -0.0002 | -0.0016, 0.0013 | .839 | -0.014 |
| FBG, mmol/L | 0.0010 | 0.0003, 0.0017 | .005 | 0.208 |
| TC, mmol/L | 0.0007 | 0.0003, 0.0011 | .002 | 0.207 |
| LDL-C, mmol/L | 0.0013 | 0.0008, 0.0018 | < .001 | 0.320 |
| TyG | 0.0518 | 0.0248, 0.0788 | < .001 | 0.216 |
| TyG-BMI | 0.0007 | 0.0003, 0.0011 | < .001 | 0.229 |
| LDL/HDL | 0.0443 | 0.0223, 0.0664 | < .001 | 0.272 |
| TC/HDL | 0.0215 | 0.0055, 0.0374 | .009 | 0.168 |
| e-GFR, mL/min/ 1.73m$^2$ | -0.0005 | -0.0009, 0.0000 | .063 | -0.126 |

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride glucose index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate.

**Table 3.** Multivariate Regression Analyses of Carotid Intima-media Thickness

| Variables | Coefficients | 95% CI | *P* | Standardized Coefficients |
|---|---|---|---|---|
| Age, y | 0.0036 | 0.0023, 0.0049 | < .001 | 0.311 |
| TyG-BMI | 0.0005 | 0.0002, 0.0009 | .005 | 0.172 |
| LDL/HDL | 0.0466 | 0.0215, 0.0716 | < .001 | 0.285 |
| TC/HDL | -0.0069 | -0.0261, 0.0123 | .478 | -0.054 |

Abbreviations: TyG, triglyceride glucose index; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

associated with CIMT, except for SBP, DBP, and e-GFR. Moreover, age and LDL-C had the highest standardized regression coefficients. Regarding the significant covariates and the interrelations between them, the multivariate regression model was fitted, including the covariates of age, TyG-BMI, LDL/HDL, and TC/HDL, leading to the findings reported in Table 3. In this model, age,

TyG-BMI, and LDL/HDL remained significant correlates of CIMT and the largest standardized coefficient belonged to age.

## DISCUSSION

This study examined the association of the lipid-related parameters totally with CIMT as an accepted marker for AS in a sample of the Iranian population with T2DM compared to that in non-diabetic people.

Our results highlighted a direct correlation between CIMT and age, TyG-BMI, and LDL/HDL ratio, evaluated in the diabetic and non-diabetic groups.

It is known that IR can accelerate AS progression through metabolic abnormalities, such as hyperglycemia and dyslipidemia.[33] Given both abnormalities,[16] growing attention is now attracted to assessing the association of the TyG index with AS.[11,17] Recently, the TyG-modified indices, TG/HDL, TC/HDL, LDL/HDL ratios, and TG minus HDL[10-13] have been highlighted as reliable surrogate markers for IR, and their high values are associated with increased IR, metabolic dysregulation, and CVD.[11-13]

In addition, existing evidence confirms the positive association of the mentioned parameters with obesity and atherogenic dyslipidemia[14] and other CVD risk factors such as T2DM, HTN, and metabolic syndrome.[34-40] TG/HDL ratio and TyG index are defined as a useful predictor of glycemic control in normal-weight and overweight patients with T2DM respectively.[41] Furthermore, the TyG index, modified TyG indices and TG/HDL ratio have been suggested as reliable markers for predicting each aspect of CVD in different populations.[12,13,42-44] The TC/HDL ratio is considered a probable biomarker for screening early peripheral arterial disease.[45] To some extent, controversies are present, a J-shaped relationship was detected between baseline TG/HDL and T2DM risk in Japanese.[34]

CIMT as a predictive marker for the diagnosis of preclinical carotid AS and cardio/cerebrovascular events,[18,19] is positively related to the TyG index;[17] however, some controversial results are presented. For instance, it was revealed that a higher TyG index is linked to carotid AS measured by CIMT in patients with ischemic stroke,[3] this association is consistent with the role of IR in promoting AS and CVD. In another study on 2560 Korean subjects without a previous coronary artery disease and stroke history, the TyG index was associated with CIMT and arterial stiffness.[46] Furthermore, Lu *et al.* detected a direct association between the TyG index and abnormal CIMT in non-diabetic females after adjustment for AS traditional risk factors.[7]

Also, Jia *et al.* detected a U-shaped relationship between the TyG index and elevated CIMT in non-obese Chinese people.[17] However, the TyG index was not significantly correlated with a high CIMT in another study conducted on the Chinese population.[27]

Liu; demonstrated a direct association between TyG-WC and CIMT, reflecting a higher burden of subclinical carotid AS especially in middle-aged and older adults with normal weight.[21]

In addition, the other studies described positive associations between TG/HDL, TC/HDL, and LDL/HDL ratios with CIMT, AS, and carotid plaques in different populations,[22-26] and also these correlations are confirmed in the diabetes population complicated by chronic kidney disease on peritoneal dialysis.[20]

No previous published study has examined the relationship between lipid-related parameters and CIMT in individuals with T2DM compared to non-DM people. However, our findings partially align with the results of only one available preliminary report investigating the predictive ability of TyG concerning carotid atherosclerosis in individuals with T2DM without any control group.[47] Similarly, in another study by Gothwal *et al.*, the TyG index significantly correlated with CIMT in non-DM people.[48]

The mechanism by which the mentioned parameters contribute to the development of AS is not fully demonstrated; however, it has been proposed that at the onset of IR, an increase of fatty acids in the liver, activates the pro-inflammatory pathways and consequently causes AS development and also increase the risk of coronary heart disease.[49-51] In addition, the elevated levels of fatty acids in pancreatic islets alter the metabolism of glucose and damage the beta cells.[52] Another

suggested mechanism is that high glucose levels, which increase reactive oxygen radicals, exert injury to beta cells[25,53] and cause endothelial dysfunction.[20]

Our data also confirmed the direct effects of dyslipidemia and FBG on CIMT reported in previous studies.[54,55] No correlation between BP and CIMT was detected from our data, possibly due to the aggressive hypertension treatment consistent with Oguntola et. al.[24]

In the present manuscript, the references listed are based on studies of the Asian population (e.g., Chinese and Korean). In contrast, the results collected and presented here are based on results collected from the Iranian people, who are genetically closer to the Caucasian population. The differences between results may be due to the differences in the diet and lifestyles of the different populations.

Given the cheapness and simplicity of calculation, the TyG-BMI, and LDL/HDL may be regarded as a plausible and available indicator of subclinical carotid atherosclerosis. Although statin therapy is for the reduction of LDL-C level, a residual risk of carotid AS remains, so a combination therapy to control other lipid parameters, in addition to reducing the LDL-C level can be beneficial.[56] Accordingly, lifestyle modification (nutrition and exercise) and medical treatments are recommended for the primary prevention of CVD. So, these associations highlight the importance of assessing both metabolic and anthropometric factors in diabetic individuals for CVD risk stratification and management.

## LIMITATIONS

Some limitations must be taken into account in this investigation. Firstly, recruiting the participants in the study was faced with the challenge of convincing them to go under the color-doppler sonography procedure. Besides, the lack of HbA1C measurements prevented us from achieving a more accurate estimate of the glycemic control status in the diabetic participants. In addition, the lack of medication analysis and categorization, limited us to prove the effect of insulin therapy beyond oral antidiabetic drugs or combination therapy on lipid profile. So the injectable therapies such as insulin could be a confounder variable.

## CONCLUSIONS

In conclusion, the present study revealed direct relationships of carotid intima-media thickness with age, triglyceride glucose-body mass index, and low-density lipoprotein to high-density lipoprotein ratio, based on a sample composed of diabetic and nondiabetic patients. More comprehensive research with larger sample sizes and larger pools of covariates is required to authenticate these findings.

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## DECLARATIONS

### Ethical Approval

This project was accepted by the ethical committee of Iran University of Medical Sciences; ethical code: IR.IUMS.REC.1401.820. The study was conducted after obtaining ethical approval from the ethical committee of the Iran University of Medical Sciences (Ref. No: IR.IUMS.REC.1397.1118). Written informed consent was obtained from all subjects. The authors attest that the participants knew the study's purpose, risks, and benefits. Anonymity was maintained throughout the study period. All activities and methods for the study were carried out considering research ethics guidelines for Iran. All procedures performed in human participant studies followed the institutional and/or national research committee's ethical standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

Date of approval: 08/01/2023

### Conflict of Interest

Atefeh Amouzegar is a member of the editorial board of RJCCN. The author had no involvement in the peer-review or editorial decision-making process for this manuscript.

## Authors' Contributions

LN, AA, AKH, OAGH and ZM did the interventions, reviewed medical aspects, and participated in preparing the manuscript. LN, AA, AKH, OAGH and ZM drafted the manuscript. LN, AKH, OAGH and AA supervised the project and revised the manuscript critically. LN and AKH analyzed the manuscript. All authors read and approved the final version of the manuscript.

## Abbreviations

ADA, American Diabetes Association; AS, Atherosclerosis; BMI, Body Mass Index; BP, Blood Pressure; CCA, Common Carotid Artery; CIMT, Carotid Intima-media Thickness; CV, Cardiovascular; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; e-GFR, Estimated Glomerular Filtration Rate; FBG, Fasting Blood Glucose; FRS, Framingham Risk Score; HbA1C, Hemoglobin A1C; HDL-C, High-density Lipoprotein Cholesterol; HOMA-IR, Homeostasis Model Assessment-estimated Insulin Resistance; HTN, Hypertension; IR, Insulin Resistance; LDL-C, Low-density Lipoprotein Cholesterol; MDRD, Modification of Diet in Renal Disease; SBP, Systolic Blood Pressure; TC, Total Cholestrol; T2DM, Type 2 Diabetes Mellitus; TG, Triglyceride; TyG, Triglyceride Glucose Index

## The place where the study was performed

1. Endocrine Research Center, Institute of Endocrinology & Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran
2. Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran

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