The Relationship Between Low-Grade Inflammation and Common Femoral Artery Intima-Media Thickness in Newly Diagnosed Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND: Besides the observed risks in type 2 diabetes mellitus (T2DM), intima-media thickness (IMT) is a surrogate marker for early diagnosing atherosclerosis and assessing the risk of subsequent developing cardiovascular disease. Low-grade inflammation (LGI) plays an important role in the development of intima-media damage of blood vessels in diabetes. Compared with IMT in the carotid artery, thickening IMT in the femoral artery occurs earlier and well reflects atherosclerosis process in diabetes mellitus.

OBJECTIVES: To investigate the relationship between LGI and common femoral artery IMT in patients with newly diagnosed T2DM.

METHODS: A descriptive and cross-sectional study on 332 patients with T2DM diagnosed for the first time administered to Vietnam National Hospital of Endocrinology. LGI is defined as patients with high sensitive C-reactive protein (hs-CRP) from 3 to 10 mg/L. hs-CRP-to-albumin ratio (CAR) was used as a marker for LGI. The position for IMT assessment is 2 cm from the bifurcation of the common femoral artery toward the groin following Pignoli's method by B-mode ultrasound.

RESULTS: Patients with LGI showed higher IMT than those without LGI ($P < .05$). In multivariate linear regression, CAR positively correlated with IMT after adjusting with age, waist-to-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and LDL-C, with a standardized beta of 0.296 and $P < .001$. There were significant differences in CAR among groups stratified by IMT. In the logistic regression model, covariates for gender, BMI, HbA1c, LDL-C, insulin resistance (HOMA-IR), triglyceride, and triglyceride-to-HDL ratio were adjusted. It was determined that the likelihood of an increase in IMT was 3.68 times higher than the baseline (Q1) risk for Q4 and 2.27 times higher for Q2 of CAR. There was a positive correlation between elevated levels of CAR and an increased risk of IMT.

CONCLUSION: In patients with newly diagnosed T2DM, there is a relationship between LGI and common femoral artery IMT. Particularly, IMT positively correlated with CAR.

PLAIN LANGUAGE SUMMARY

The relationship between low-grade inflammation and common femoral artery innermost layers thickness in newly diagnosed type 2 diabetes mellitus

The arterial wall is composed of three layers, namely the inner, the medial, and the outer ones. The thickness of the innermost layers (the inner and medial) of the thigh artery is a surrogate marker for early diagnosis of atherosclerosis and assessing the risk of subsequently developing heart disease in diabetes. Low-level inflammation is important in developing damage to the blood vessels' innermost layers in diabetes. In this study, we aimed to assess the relationship between low inflammation and common femoral artery inner-to-medial thickness in patients with newly diagnosed diabetes. Patients with low inflammation showed greater arterial thickness than the counter group. An increment of low inflammation increases the thickness of the femoral artery's innermost layers. Patients with thicker femoral arterial innermost layers exhibit nearly 2 to 4 times higher risk of developing low inflammation. Besides, multifactorial control, which increases low inflammation, including blood pressure, apart from glycemic control, could enhance the inflammation status and improve the thickness of femoral arteries, reducing heart disease risks in newly diagnosed diabetes.

KEYWORDS: Low-grade inflammation, hs-CRP-to-albumin ratio, common femoral artery, intima-media thickness, newly diagnosed type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide. T2DM increases the risk of cardiovascular disease (CVD) and increases the mortality rate by 2 to 4 fold higher compared with the normoglycemic population.[1] Observed cardiovascular risk factors in patients with T2DM, as well as in metabolic syndrome, include hypertension, obesity, family history of CVD, and age. However, in patients with T2DM with well-controlled risk factors, the process of damage to the vascular system progressively occurs and is attributed to low-grade inflammation.[2]

Besides the observed risks, intima-media thickness (IMT) is a surrogate marker for early diagnosing atherosclerosis and assessing the risk of subsequent developing cardiovascular disease.[3] Moreover, intima-media lesions appear early in patients with T2DM.[4] Low-grade inflammation (LGI) plays an important role in the development of intima-media damage of blood vessels in diabetes.[5] Unlike high-grade inflammation with high-sensitive C-Reactive protein (hs-CRP) >10 mg/L, low-grade inflammation plays an important role in the pathogenesis of insulin resistance and vascular damage formation. The inflammatory process causes changes in the function of vascular endothelial cells, causing migration and adhesion of leukocytes to the vessel wall.[6] This activates the process of atherosclerosis and damage to the vessel wall, starting from the endothelium and invading the media of the vessel wall. In clinical practice, there are many indicators used to assess low-grade inflammation, including those based on blood cells and those based on hs-CRP, albumin, and HDL-C. Among them, the indicators based on hs-CRP are more stable and better predictive for all-cause mortality than the remaining indicators.[7,8]

Clinically, IMT is evaluated in the carotid and femoral arteries. Compared with IMT in the carotid artery, thickening IMT in the femoral artery occurs earlier and well reflects atherosclerosis process in diabetes mellitus.[9,10] Additionally, a previous study of patients with type 2 diabetes who were diagnosed and treated revealed that the changes in femoral artery IMT were associated with indicators of chronic inflammation.[11]

However, to the best of our knowledge, there are not many reports on the association between femoral IMT and LGI in patients with newly diagnosed T2DM, which not affected by treatment methods. We conducted this study with the goal to investigate the relationship between LGI and common femoral artery IMT in patients with newly diagnosed T2DM.

Subjects and Methods

Study design

A descriptive and cross-sectional study on 332 patients with T2DM diagnosed for the first time administered at Vietnam National Hospital of Endocrinology from January 2015 to May 2018.

In addition, the patients suffered no comorbidities such as hypertension, severe acute illness (namely infection, shock, stroke, myocardial infarction, and hs-CRP > 10 mg/L), or severe liver and kidney dysfunction.

Method

Clinical examination

Patients were asked about typical clinical symptoms of hyperglycemia and examined to rule out diseases as in the exclusion criteria section. Patients' height, body weight, waist and hip circumferences, body mass index (BMI), waist-to-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured.

Laboratory tests

Patients were asked to fast for at least 8 hours on the morning of admission. On the day of admission, fasting venous blood was aspirated for tests, including fasting plasma glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipid profiles (total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)), hs-CRP, HbA1c, insulin and creatinine. Those parameters were measured by using a hexokinase assay (BeckmanAU680, USA) for FPG, and by the high-performance liquid chromatography method (Adams A1C, Japan) for HbA1c, and by the enzyme colorimetric method (Beckman AU680, USA) for the other parameters. Twenty-four hour urine samples were collected for microalbuminuria (24h-MAU) measurements by auto-analyzed and immunoturbidimetric method (Beckman AU680, USA).

Low-grade inflammation is assessed through the following indicators[12-14]:

Triglyceride-to-HDL-C (TrH) = Triglyceride (mmol/L)/HDL-C (mg/dL),
hs-CRP-to-HDL-C (CH) = hs-CRP (mg/L)/HDL-C (mg/dL),
hs-CRP-to-albumin (CAR) = hs-CRP (mg/L)/Albumin (g/L),
and hs-CRP.

Low-grade inflammation was defined as patients with hs-CRP from 3 to 10 mg/L.[15]

IMT measurement

The patient lay in the supine position and underwent bilateral femoral artery ultrasound using the B-mode. The position for IMT assessment is 2 cm from the bifurcation of the common femoral artery toward the groin following Pignoli et al's method.[16] The sonographer was blinded to the study information. Each patient's IMT values was the maximum IMT of the left and right common femoral arteries. IMT was divided into normal (<1.0 mm), thick (1.0 ⩽ IMT < 1.5 mm), and atherosclerosis (⩾1.5 mm) groups.[17]

Data analysis and statistical analysis

Data were expressed in mean (standard deviation) or median (interquartile range) forms for normally or non-normally distributed continuous variables in the above order. Qualitative variables are expressed as percentages. Independent *t*-student and Mann-Whitney *U* tests (or Kruskal-Wallis with Dunn post hoc test) were employed to compare 2 or more means and medians, respectively. Univariate and multivariate linear regression was employed to evaluate the correlation between IMT and other independent variables. Logistic regression models were performed on IMT to assess the association of CAR with IMT. The model adjusted covariates for gender, BMI, HbA1c, LDL-C, homeostatic model assessment for insulin resistance (HOMA-IR), triglyceride, and triglyceride-to-HDL ratio. A $P < .05$ was considered significant. Data were analyzed with SPSS 24.0 (Microsoft Inc Co).

Results

Patients with LGI showed significantly higher age, SBP, and DBP compared with the non-LGI group. Regarding LGI, CAR and CH were significantly higher in the LGI group than the non-LGI group (0.13 vs 0.03, $P < .001$ for CAR and 4.57 vs 0.96, $P < .001$ for CH). Patients with LGI showed higher common femoral artery IMT than those without LGI (1.15 vs 1.00 mm, $P < .05$; Table 1).

There were no significant differences in atherosclerotic risks between LGI and non-LGI groups (Table 2).

In univariate linear regression, there were positive correlations between common femoral artery IMT and age ($r = .44$; $P < .001$), WHR ($r = .133$; $P = .016$), SBP ($r = .275$; $P < .001$), DBP ($r = .156$; $P = .005$), 24h-MAU ($r = .230$; $P = .001$), and CAR ($r = .278$, $P < .001$). In multivariate linear regression, CAR positively correlated with common femoral artery IMT after adjusting with age, WHR, SBP, DBP, LDL-C, and 24h-MAU (Table 3).

There were significant differences in CAR and TrH among groups stratified by common femoral artery IMT. Particularly, patients with normal IMT showed lower CAR and TrH compared with those with thick IMT and atherosclerosis (Figure 1).

Table 1. Comparison of clinical and laboratory test findings between low-grade inflammation and non-low-grade inflammation type 2 diabetes mellitus.

PARAMETERS	LGI (n = 182)	NON-LGI (n = 150)	*P*
Age, years	55.34 ± 10.34	52.40 ± 10.18	.010*
BMI, kg/m^2	22.74 ± 3.13	22.37 ± 2.80	.262
SBP, mmHg	131.10 ± 18.26	124.09±15.20	<.001*
DBP, mmHg	79.13 ± 10.53	75.51 ± 9.69	.001*
FPG, mmol/L	12.36 ± 4.64	11.52 ± 4.36	.091
HbA1C, %	9.93 ± 2.54	9.55 ± 2.52	.180
HDL-C, mmol/L	1.26 ± 0.34	1.32 ± 0.60	.257
LDL-C, mmol/L	3.28 ± 1.05	3.15 ± 1.12	.283
CAR	0.13 (0.09; 0.23)	0.03 (0.02; 0.04)	<.001$
TrH	1.77 (1.22; 3.02)	1.79 (1.00; 2.76)	.107
CH	4.57 (2.90; 8.90)	0.96 (0.58; 1.47)	<.001$
IMT, mm	1.15 ± 0.54	1.00 ± 0.47	.014*

Abbreviations: BMI, body mass index; CAR, hs-CRP-to-Albumin ratio; CH, hs-CRP-to-HDL-C ratio; DBP, diastolic blood pressure; FPG, fasting plasma glucose; hs-CRP, high sensitive C-reactive protein; IMT, intima-media thickness; LGI, low-grade inflammation; SBP, systolic blood pressure; TrH, triglyceride-to-HDL-C ratio.
*Independent *t*-test; $Mann-Whitney *U* test.

Table 2. Comparison of atherosclerotic risk factors between low-grade inflammation and non-low-grade inflammation type 2 diabetes mellitus.

PARAMETERS	LGI (n = 182)	NON-LGI (n = 150)	*P*
Male, n (%)	90 (49.5)	85 (56.7)	.47*
Age > 45	136 (74.7)	127 (84.7)	.25*
Obesity, n (%)	68 (37.4)	68 (45.3)	.31*
Hypertension, n (%)	29 (15.9)	18 (12.0)	.21*
Family history of T2DM, n (%)	31 (17.0)	28 (18.7)	.90*
Exercise > 30 min/day, n (%)	70 (38.5)	69 (46.0)	.36*
Alcohol consumption, n (%)	62 (34.1)	50 (33.3)	.89*
Smoking, n (%)	36 (19.8)	34 (22.7)	.52*
Dyslipidemia, n (%)	20 (11.0)	16 (10.7)	.93*

Abbreviation: T2DM, type 2 diabetes mellitus.
*Chi-square test.

Table 3. Univariate and multivariate linear regression between common femoral artery IMT and low-grade inflammation markers and clinical and laboratory test findings in patients with newly diagnosed type 2 diabetes mellitus.

INDEPENDENT(S)	UNIVARIATE LINEAR REGRESSION		MULTIVARIATE LINEAR REGRESSION	
	r	*P*	STANDARDIZED BETA	*P*
Age, year	.440	<.001	0.305	<.001
BMI, kg/m^2	.059	.288		
WHR	.133	.016	0.052	.460
SBP, mmHg	.275	<.001	0.334	.001
DBP, mmHg	.156	.005	−0.214	.025
HbA1c, %	.012	.827		
FPG, mmol/L	.059	.283		
LDL-C, mmol/L	.074	.195	0.033	.606
HDL-C, mmol/L	−.039	.479		
24h-MAUS, mg/L	.230	.001	0.07	.300
CAR	.278	<.001	0.296	<.001
TrH	.003	.952		
CH	.051	.397		

Abbreviations: 24h-MAUS, 24-hour microalbuminuria secretion; BMI, body mass index; CAR, hs-CRP-to-Albumin ratio; CH, hs-CRP-to-HDL-C ratio; DBP, diastolic blood pressure; FPG, fasting plasma glucose; hs-CRP, high sensitive C-reactive protein; SBP, systolic blood pressure; TrH, Triglyceride-to-HDL-C ratio; WHR, waist-to-hip ratio.

Logistic regression models were performed on common femoral artery IMT to assess the association of CAR with IMT. In the model, covariates were adjusted for gender, BMI, HbA1c, LDL-C, HOMA-IR, triglyceride, and triglyceride-to-HDL ratio. As illustrated in Figure 2, CAR values were divided into quartiles (Q)-1, Q2, Q3 and Q4, respectively. As anticipated, higher CAR were positively correlated with IMT. Particularly, it was determined that the likelihood of an increase in IMT was 3.68 times higher than the baseline (Q1) risk for Q4 and 2.27 times higher for Q2 of CAR. These results indicate a positive correlation between elevated levels of CAR and an increased risk of IMT.

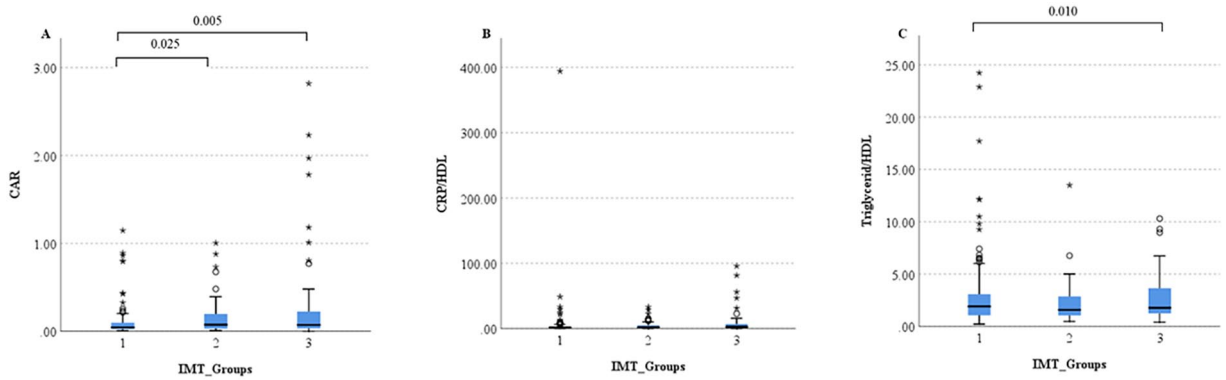

Figure 1. Comparison of low-grade inflammation marker among common femoral artery IMT groups. Comparisons of CAR (A), hs-CRP/HDL-C ratio (B) and Triglyceride/HDL-C ratio (C) among IMT groups. IMT groups: 1: normal IMT, 2: thick IMT, 3: atherosclerosis.

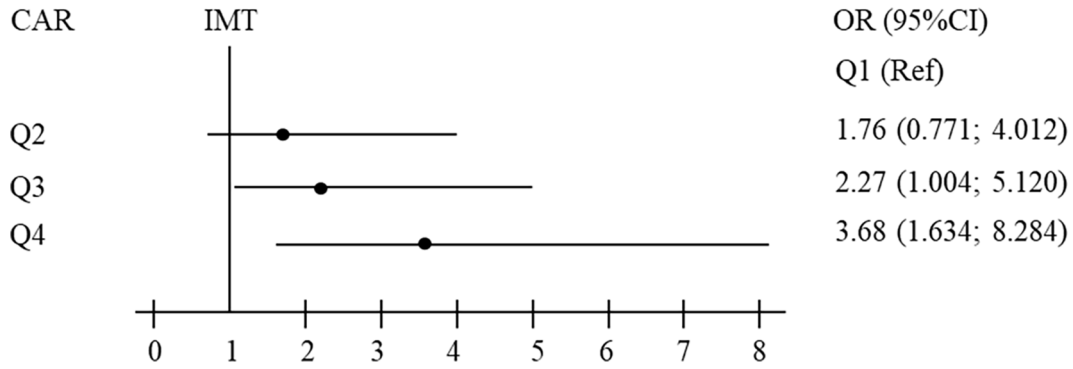

Figure 2. Forest plots illustrating the relationship between CAR and the common femoral artery IMT values. Forest plots displaying the OR for CAR (hs-CRP-to-Albumin ratio) and IMT. The model adjusted covariates for gender, BMI, HbA1c, LDL-C, HOMA-IR, triglyceride, and triglyceride-to-HDL ratio. Black lines illustrate the 95% confidence ranges for OR. Black circles denote OR values. OR, Odd ratios; Q, quartiles.

Discussion

Our study revealed that, in patients with T2DM, patients with LGI show higher common femoral artery IMT than those without LGI.

The relationship between atherosclerosis and the severity of atherosclerotic cardiovascular diseases (ASCVDs) has been widely recognized. Inflammation is a factor that is involved in the progression of atherosclerotic plaques.[18] Inflammation increases IMT in the arteries. In patients with T2DM, LGI plays a vital role in the pathogenesis.[2] LGI increases insulin resistance on the one hand and is a consequence of insulin resistance in tissues, including white adipose tissue.

Previous studies of carotid IMT have shown similar results. In a study by Ayşegül İdil Soylu in 2016 on 150 subjects with an average age of 61.9 (years), a positive correlation was found between low-grade inflammation markers and the degree of carotid artery stenosis. Specifically, the platelet-to-lymphocyte ratio (PLR) positively correlated with the carotid arterial stenosis percentage ($r = 0.250$, $p = 0.002$). Besides, PLR was an independent variable concerning stroke (OR of 1.012, $P = .031$).[19] In Zhang et al's study on 582 elderly subjects, there were positive correlations between neutrophil-to-lymphocyte ratio (NLR), PLR, and systemic inflammation index (SII) with IMT. In the Maximum IMT group, NLR (Q4 vs Q1: OR 3.87, 95% CI 1.81-8.29), PLR (Q4 vs Q1: OR 2.84, 95% CI 1.36-5.95), and SII (Q4 vs Q1: OR 2.64, 95% CI 1.30-5.37).[20] A study of 4596 Chinese patients with T2DM on antihyperglycemic regimens revealed a relationship between femoral artery IMT and indicators of low-grade chronic inflammation. Specifically, the prevalence of femoral plaque in patients with high NLR (OR of 1.93) and high PLR (OR of 1.57) was higher compared with low groups. Higher NLR was significantly related to the prevalence of stenosis in femoral arteries.[11]

Our study revealed that common femoral artery IMT positively correlated with CAR after adjusting for factors affecting IMT. CAR is a ratio between CRP and albumin levels. CAR has emerged as a potential marker for LGI.[21] Albumin is essential in the plasma because of its multiple biological functions and antithrombotic effects. Low serum albumin concentrations are associated with an increased risk of ASCVDs and carotid atherosclerosis.[22] In patients with T2DM, serum albumin concentrations are inversely associated with BMI and insulin resistance.[23] Furthermore, the antioxidant and anti-inflammatory properties of albumin in the process of atherosclerosis have been recognized. Therefore, in patients with T2DM, a decrease in albumin concentrations may explain the increased risk of ASCVDs.[24] The association between hs-CRP

and the risk of ASCVDs has been widely recognized.[25] High levels of hs-CRP are associated with decreased nitric oxide (NO) levels, leading to endothelial cell dysfunction.[26] However, the underlying mechanism remains unclear. Increased hs-CRP production in the atherosclerotic plaque region of lower extremities arteries increases the risk of peripheral artery disease in patients with T2DM.[27] Interestingly, studies involving Secreted Frizzled-Related Protein-5 (SFRP-5) have shown an association between its anti-inflammatory role and a reduced risk of ASCVDs.[28] SFRP-5 is an anti-inflammatory adipokine in adipose tissue that contributes to the modulation of insulin resistance. Low SFPR5 levels lead to increased hs-CRP in patients with T2DM.[29] In our study, LGI correlated with IMT thickness in the common femoral artery. In the high IMT group, CAR was significantly higher than in the other groups. Increased CAR increased IMT thickness after adjustment for age, BMI, blood pressure, lipid profiles, and microalbuminuria. In this study, we selected patients with a first-time diabetes diagnosis, thus reducing confounding factors due to treatment effects such as angiotensinogen-converting enzyme (ACE) inhibitors, antiplatelet drugs, or lipid-lowering drugs.

Our study has limitations. First, our study did not have a control group, which reduced the ability to extrapolate our results. Second, the cross-sectional study cannot confirm the causal relationship between low-grade inflammation and IMT. Thirdly, the study did not conduct ultrasound examinations for carotid IMT as a gold standard for classify IMT levels. Finally, power analysis for sample size calculation was not done.

Conclusion

In patients with newly diagnosed T2DM, common femoral artery IMT positively correlated with CAR. This study suggests a significant association between low-grade inflammation and common femoral artery IMT increment in newly diagnosed T2DM. The results of our study denote that multi-factorial control which positively correlates with low-grade inflammation including blood pressure, and proteinuria apart from glycemic control could enhance the inflammation status and, therefore improve the thickness of femoral arteries, reducing cardiovascular risks in newly diagnosed T2DM.

Declarations

Ethical approval and consent to participate

All participants were provided with written informed consent, and the protocol was approved by the Ethical Review Committee of Vietnam Military Medical University (Reference No.168/2014/IRB-VMMU). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Consent for publication

No private information on the participants was employed in the manuscript. All participants consented to allowing the authors to use their clinical findings and laboratory tests for publication.

Author contributions

Son Tien Nguyen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing; Tuan Dinh Le: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing; Hoa Trung Dinh: Data curation, Formal analysis, Methodology, Software, Writing—original draft; Trinh Hien Vu: Data curation, Formal analysis, Methodology, Software, Writing—original draft; Hoang Duong Huy: Data curation, Formal analysis, Methodology, Software, Writing - original draft; Thuc Luong Cong: Methodology, Software, Writing—original draft; Toan Duy Nguyen: Conceptualization, Formal analysis, Validation, Visualization, Writing - original draft, Writing—review & editing; Thong Huy Nguyen: Formal analysis, Methodology, Software, Visualization, Writing—original draft, Writing - review & editing; Binh Van Nguyen: Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing—review & editing; Huy Quang Nguyen: Methodology, Software, Visualization, Writing—original draft, Writing—review & editing; Ba Van Nguyen: Formal Analysis, Methodology, Writing—original draft, Writing—review & editing; Thuy Dinh Thi Thanh: Formal Analysis, Investigation, Methodology; Software, Writing - original draft; Lan Ho Thi Nguyen: Conceptualization, Data curation, Formal analysis, methodology, Software, Supervision, Writing—original draft; Giang Thi Nguyen: Data curation, Formal analysis, methodology, Software, Supervision, Writing—original draft. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; hs-CRP, high sensitive

C-reactive protein; CAR, hs-CRP-to-Albumin ratio; TrH, Triglyceride-to-HDL-C ratio; CH, hs-CRP-to-HDL-C ratio; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; FDG, fasting plasma glucose; LGI, low-grade inflammation; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; IMT, intima-media thickness; HOMA-IR, insulin resistance; LDL-C, low density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio; 24h-MAUS, 24-hour microalbuminuria secretion.

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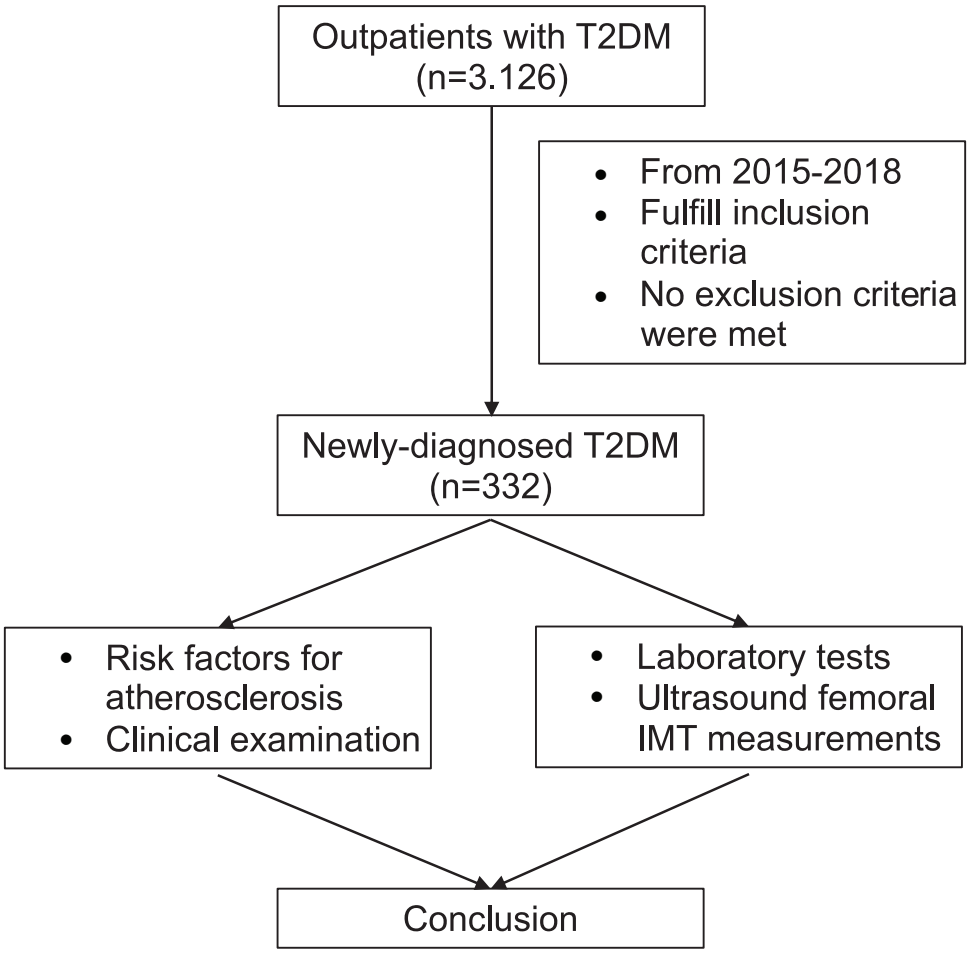

Algorithm 1. Study protocol. T2DM, Type 2 diabetes mellitus; IMT, intima-media thickness.