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CORRELATION BETWEEN SERUM BIOMARKERS AND ELECTROCARDIOGRAM CHARACTERISTICS, PULSE WAVE VELOCITY, BLOOD LIPID LEVELS, AND CAROTID ATHEROSCLEROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

KORELACIJA IZMEĐU SERUMSKIH BIOMARKERA I KARAKTERISTIKA ELEKTROKARDIOGRAMA, BRZINE PULSNOG TALASA, NIVOA LIPIDA U KRVI I KAROTIDNE ATEROSKLEROZE KOD PACIJENATA SA DIJABETESOM MELITUS TIP 2

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Summary

Background: Patients with type 2 diabetes mellitus (T2DM) often suffer from atherosclerotic cardiovascular risk. This study evaluated the associations between electrocardiographic (ECG) parameters, pulse wave velocity (PWV), glycaemic indices, lipid profiles, and novel serum biomarkers with CAS in T2DM patients.
Methods: A retrospective study included 201 T2DM patients at Zhongshan Hospital (Xiamen), Fudan University, from January 2024 to December 2025. Patients were allocated to the control group (AG, 91 cases with normal carotid arteries or only intimal thickening) or observation group (BG, 110 cases with carotid plaques). General data, ECG indicators, vascular function indicators, blood glucose, blood lipid levels, low-sensitivity C-reactive protein (CRP-L), and novel serum were collected.
Results: Compared to AG, the BG exhibited significantly longer P-wave duration (PR) and QT interval (both P<0.001), higher left and right PWV (P<0.001), elevated HbA1c and CRP-L (P<0.001), and lower fasting plasma glucose (FPG) and LDL-C (P<0.001). Among novel biomarkers, adiponectin was lower in BG, while leptin, sICAM-1, and IL-6 were higher (all P<0.001). In multi-

Kratak sadržaj

Uvod: Pacijenti sa dijabetesom melitus tipa 2 (T2DM) često imaju povećan rizik od aterosklerotskih kardiovaskularnih bolesti. Ova studija je procenjivala povezanost elektrokardiografskih (EKG) parametara, brzine širenja pulsnog talasa (PWV), glikemijskih pokazatelja, lipidnog profila i novih serumskih biomarkera sa karotidnom aterosklerozom kod pacijenata sa T2DM.
Metode: Retrospektivnom studijom je obuhvaćen je 201 pacijent sa T2DM lečen u bolnici Zhongshan (Sijamen), Univerzitet Fudan, u periodu od januara 2024. do decembra 2025. godine. Pacijenti su podeljeni u kontrolnu grupu (AG, 91 slučaj sa normalnim karotidnim arterijama ili samo zadebljanjem intime) i ispitivanu grupu (BG, 110 slučajeva sa karotidnim plakovima). Prikupljeni su opšti podaci, EKG parametri, pokazatelji vaskularne funkcije, vrednosti glukoze u krvi, lipidni status, niskosenzitivni C-reaktivni protein (CRP-L) i novi serumski biomarkeri.
Rezultati: U poređenju sa AG, BG je pokazala značajno duže trajanje P-talasa (PR interval) i QT intervala (oba P<0,001), više vrednosti PWV levo i desno (P<0,001), povišene vrednosti HbA1c i CRP-L (P<0,001), kao i niže vrednosti glukoze u plazmi natašte (FPG) i LDL-holesterola

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variate logistic regression, independent predictors of carotid plaque presence included prolonged PR interval (OR [95% CI]: 1.02 [1.00–1.04], P=0.024), increased PWV-right (OR: 1.67 [1.02–2.74], P=0.005), higher HbA1c (OR: 1.67 [1.02–4.70], P=0.001), elevated CRP-L (OR: 1.63 [0.92–3.13], P=0.001), and increased IL-6 (OR: 1.34 [1.10–1.62], P=0.003). Lipid associations were not independent predictors after adjustment and are likely confounded by statin therapy.

Conclusion: In T2DM, prolonged atrial conduction, arterial stiffening, poor long-term glycaemic control, and systemic inflammation independently associate with carotid plaque burden. Comprehensive risk stratification should integrate electrophysiological, hemodynamic, and inflammatory markers. Lipid findings require cautious interpretation due to confounding by treatment.

Keywords: type 2 diabetes mellitus, carotid atherosclerosis, pulse wave velocity, electrocardiogram, HbA1c, inflammation, adiponectin

(P<0,001). Od novih biomarkera, adiponektin je bio niži u BG, dok su leptin, sICAM-1 i IL-6 bili viši (sve P<0,001). Multivarijantna logistička regresiona analiza je pokazala da su nezavisni prediktori prisustva karotidnih plakova produžen PR interval (OR [95% CI]: 1,02 [1,00–1,04], P=0,024), povećana PWV desno (OR: 1,67 [1,02–2,74], P=0,005), viši HbA1c (OR: 1,67 [1,02–4,70], P=0,001), povišen CRP-L (OR: 1,63 [0,92–3,13], P=0,001) i poveć an IL-6 (OR: 1,34 [1,10–1,62], P=0,003). Povezanost sa lipidima nije ostala nezavisna nakon prilagođavanja i verovatno je pod uticajem terapije statinima.

Zaključak: Kod pacijenata sa T2DM, produženo atrijalno provođenje, povećana arterijska ukočenost, loša dugoročna glikemijska kontrola i sistemska inflamacija su nezavisno povezani sa opterećenjem karotidnim plakovima. Sveobuhvatna procena rizika treba da uključi elektrofiziološke, hemodinamske i inflamatorne pokazatelje. Nalaze u vezi sa lipidima treba tumačiti oprezno zbog uticaja terapije.

Ključne reči: dijabetes melitus tipa 2, karotidna atero-skleroza, brzina pulsnog talasa, elektrokardiogram, HbA1c, inflamacija, adiponektin

Introduction

Type 2 diabetes mellitus (T2DM) confers a two- to four-fold increased risk of atherosclerotic cardiovascular disease (ASCVD), representing the leading cause of morbidity and mortality in this population (1–5). Among the various manifestations of ASCVD, CAD is considered a window into systemic atherosclerosis due to its ease of non-invasive detection and strong correlation with coronary and cerebral vascular lesions. Carotid intima-media thickness (CIMT) and plaque formation are early signs of subclinical atherosclerosis. However, the occurrence and development of CAS are not isolated processes but are closely related to multiple systemic pathological changes (6–9). ECG abnormalities (such as repolarization abnormalities or conduction blocks) independently predict major adverse cardiac events in T2DM patients, suggesting that ECG may be an early marker of cardiovascular risk associated with CAS (10–12).

Dyslipidemia is extremely common in T2DM patients, characterized by elevated triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C). Total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) levels may be only mildly elevated. Still, changes in particle number, oxidative modification status, and clearance efficiency significantly enhance their pro-inflammatory and pro-atherosclerotic effects. Statin lipid-lowering therapy can effectively delay CIMT growth and reduce the risk of cardiovascular events. Blood lipid profiles are not only direct drivers of atherosclerosis but also important monitoring indicators for intervention effectiveness (13–16).

In addition to traditional risk factors, emerging serum biomarkers have garnered increasing attention for their roles in reflecting subclinical vascular injury, endothelial dysfunction, and systemic inflammation in T2DM. Adipokines such as adiponectin and leptin are involved in insulin sensitivity and vascular inflammation; endothelial dysfunction markers like soluble intercellular adhesion molecule-1 (sICAM-1) reflect early atherogenic changes; inflammatory cytokines, including interleukin-6 (IL-6), are key mediators of chronic low-grade inflammation; and metabolic regulators such as fibroblast growth factor-21 (FGF-21) are associated with glucose and lipid metabolism. These biomarkers may provide complementary information beyond conventional metabolic and inflammatory indicators, enhancing early risk stratification for atherosclerosis in diabetic patients.

However, most prior investigations have evaluated these parameters in isolation, failing to capture the synergistic, multidimensional nature of diabetic vasculopathy. Crucially, the independent and combined associations of electrophysiological, hemodynamic, metabolic, and novel serological markers with CAS in T2DM remain incompletely defined. Furthermore, the influence of background pharmacotherapy – particularly statin use – on these relationships is seldom accounted for in retrospective analyses, potentially confounding the interpretation of traditional lipid parameters.

This study aims to collect standard 12-lead ECG, PWV, blood lipid indicators, and a panel of novel serum biomarkers simultaneously in a group of patients with confirmed T2DM to systematically explore the association between ECG parameters and the severity of CAS, analyse PWV values, and assess the predictive value of blood lipid and serum biomarkers for carotid lesions.

Materials and Methods

Study subjects

A total of 201 patients with T2DM admitted to the inpatient department of Zhongshan Hospital (Xiamen), Fudan University, from January 2024 to December 2025 were retrospectively collected. These patients were allocated to the control group (AG, 91 cases with normal carotid arteries or only intimal thickening) or the observation group (BG, 110 cases with carotid plaques) based on carotid artery condition.

Inclusion criteria: (1) A confirmed diagnosis of T2DM; (2) Complete clinical data available; (3) No acute cardiovascular incidents for the past three months, with relatively stable conditions.

Exclusion criteria: (1) T1DM or other special types of DM; (2) Presence of severe arrhythmias or a history of pacemaker implantation, affecting the interpretation of ECG features; (3) Contraindications to carotid ultrasound examination or poor image quality, making it impossible to measure the CIMT or plaque accurately; (4) Severe hepatic or renal dysfunction.

Carotid ultrasound examination

A colour Doppler ultrasound diagnostic instrument (Shenzhen Mairui Medical Technology Co., Ltd., China) with a 10 MHz probe was used to scan the left and right common carotid arteries (CCAs), external carotid arteries, internal carotid arteries, subclavian arteries, and vertebral arteries. Atherosclerotic plaque formation, degree of lumen stenosis, and changes in CIMT of the CCA were assessed. The subjects were placed in a supine position with their heads slightly tilted backward to ensure a clear acoustic window. Using grayscale imaging mode, the structures of the above-mentioned vascular branches were observed in combination with transverse and longitudinal sections. The CIMT of both CCA was determined, and the smoothness of the vascular wall, the presence of plaque, stenosis, or occlusion was recorded. The criteria were defined as follows: Carotid intima thickening: CIMT≥1.0 mm; Atherosclerotic plaque: Focal CIMT≥1.5 mm at one or more sites.

Observation indicators

1. General information of the participants was collected, including age, gender, and BMI.

2. ECG indicators of the participants were collected, including P wave duration (PR), QT, and corrected QT (QTc).

3. Vascular function indicators of the participants were collected, including ABI-Left, ABI-Right, PWV-Left, and PWV-Right.

4. Blood glucose indicators of the participants were collected, including fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2h-PPG), and glycated haemoglobin (HbA1c).

5. Blood lipid indicators of the participants were collected.

6. Novel serum biomarkers: Fasting venous blood samples were collected in the morning after an overnight fast of at least 8 hours. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at -80 °C until analysis. The following biomarkers were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions: adiponectin, leptin, soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), and fibroblast growth factor-21 (FGF-21). All assays were performed in duplicate, and the average value was used for analysis.

Statistical methods

Continuous data are presented as mean ± standard deviation (SD). Normality was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using independent-samples t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were compared using the Chi-square (χ^2) test. Multivariate logistic regression was employed to identify independent correlates of carotid atherosclerosis. Predictor variables were selected for inclusion in the initial model based on clinical relevance and a univariate screening threshold of $P<0.10$. Given the exploratory nature of this study and the modest sample size, a backward stepwise elimination procedure (based on the Akaike Information Criterion) was utilized to derive a parsimonious final model. Collinearity diagnostics were inspected, and no variance inflation factor (VIF) exceeded 5. Critical Limitation Regarding Pharmacological Confounding: This study is constrained by the unavailability of comprehensive medication records in the retrospective dataset. Consequently, we were unable to adjust the regression models for statin use, antihypertensive agents, or specific glucose-lowering therapies (e.g., SGLT2 inhibitors or GLP-1 receptor agonists). Therefore, all reported associations – particularly those involving lipid profiles and inflammatory markers – should be regarded as potentially confounded by treatment effects. Statistical significance was defined as a two-tailed P-value <0.05. Analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

General information

A total of 201 T2DM patients were included in this retrospective analysis, comprising 91 patients in the control group (AG) with normal carotid arteries or only intimal thickening, and 110 patients in the observation group (BG) with confirmed carotid plaques. Baseline demographic characteristics are summarized in *Table I*. Patients in the plaque group were significantly older than those in the non-plaque group (61.91±8.24 vs. 51.47±8.15 years, P<0.001), whereas sex distribution and body mass index (BMI) did not differ significantly between the two groups.

Electrocardiographic and vascular function parameters

Electrocardiographic analysis revealed significant differences in cardiac conduction and repolarization parameters between the two groups (*Table II*). As shown in *Figure 1A*, the P wave duration (PR interval) was markedly prolonged in the BG (162.7±22.1 ms) compared to the AG (145.2±18.3 ms) (P<0.001). Similarly, *Figure 1B* demonstrates that the uncorrected QT interval was significantly longer in the BG (402.8±36.7 ms) versus the AG (380.5±32.4 ms) (P<0.001). However, as presented in *Figure 1C*, the corrected QT interval (QTc) showed no significant difference between groups (AG: 425.6±24.8 ms vs. BG: 428.3±27.5 ms, P=0.456). These results suggest that T2DM patients with carotid plaques exhibit distinct alterations in cardiac electrical activity, particularly in atrial conduction and ventricular repolarization, which may reflect underlying myocardial structural or autonomic changes.

Table I Baseline demographic characteristics of the study cohort.

Indicator	AG	BG	χ^2/t	P
Number of cases (cases)	91	110		
Sex (cases)			1.724	0.515
Male	56	68		
Female	35	42		
Age (years)	51.47±8.15	61.91±8.24	8.98	<0.001
BMI	25.19±3.17	23.63±3.87	0.522	0.062

Vascular function parameters

Assessment of vascular function demonstrated significant alterations in arterial stiffness parameters in patients with carotid atherosclerosis. As detailed in *Table II* and illustrated in *Figure 2*, the ankle-brachial index (ABI) values, both left (*Figure 2A*) and right (*Figure 2B*), did not differ significantly between groups (ABI-Left: AG 1.08±0.12 vs. BG 1.06±0.14, P=0.312; ABI-Right: AG 1.07±0.13 vs. BG 1.05±0.15, P=0.289). In contrast, pulse wave velocity (PWV) measurements were substantially elevated in the BG. As clearly depicted in *Figure 3*, PWV-Left increased from 8.42±1.56 m/s in the AG to 10.23±2.14 m/s in the BG (*Figure 3A*; P<0.001), while PWV-Right increased from 8.38±1.61 m/s to 10.17±2.08 m/s (*Figure 3B*; P<0.001). These findings indicate that, while peripheral arterial patency remains preserved, central and large-artery stiffness is significantly increased in T2DM patients with carotid plaques, reflecting advanced vascular remodelling and reduced arterial compliance.

Blood glucose indicators

Analysis of glycaemic control parameters revealed a complex pattern in T2DM patients with carotid atherosclerosis (*Table III*). As illustrated in *Figure 4A*, fasting plasma glucose (FPG) levels were unexpectedly lower in the BG (7.12±1.38 mmol/L) compared to the AG (7.85±1.42 mmol/L; P<0.001). No significant difference was observed in 2-hour postprandial plasma glucose (2h-PPG)

Table II Electrocardiographic and vascular function parameters.

Parameter	Control Group (AG)	Observation Group (BG)	P-value
Electrocardiographic Parameters			
PR interval (ms)	145.2±18.3	162.7±22.1	<0.001
QT interval (ms)	380.5±32.4	402.8±36.7	<0.001
QTc interval (ms)	425.6±24.8	428.3±27.5	0.456
Vascular Function Parameters			
ABI-Left	1.08±0.12	1.06±0.14	0.312
ABI-Right	1.07±0.13	1.05±0.15	0.289
PWV-Left (m/s)	8.42±1.56	10.23±2.14	<0.001
PWV-Right (m/s)	8.38±1.61	10.17±2.08	<0.001

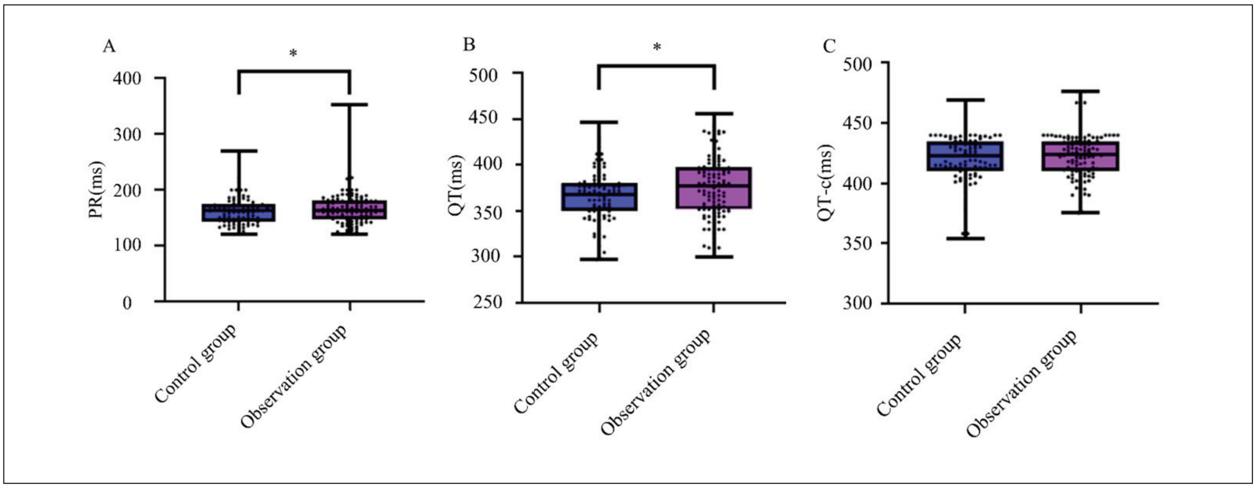

Figure 1 PR, QT, and QTc indicators.
Note: A: PR; B: QT; C: QTc; * in contrast to the AG, $P<0.05$

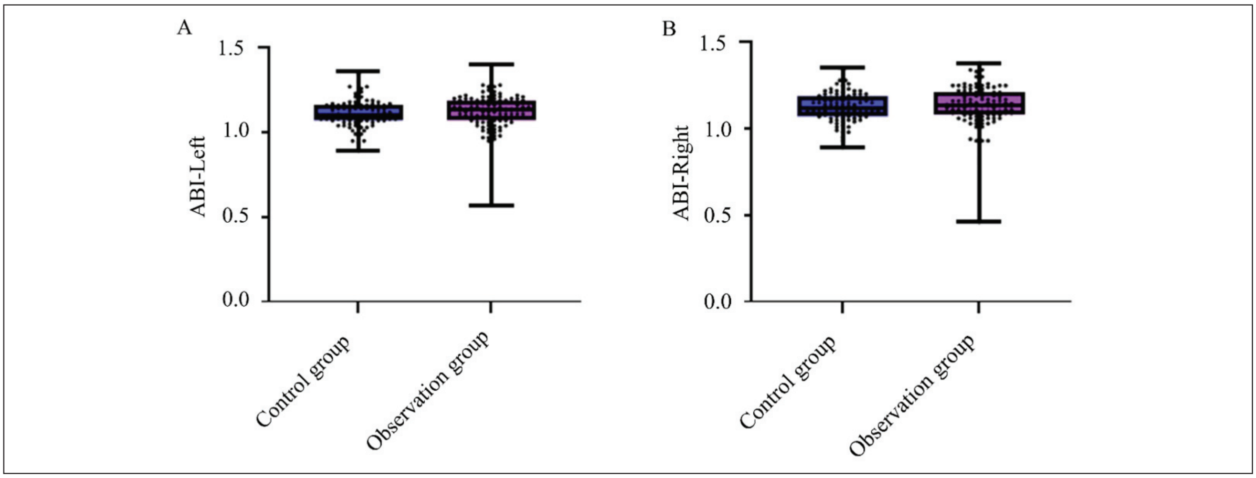

Figure 2 ABI indicators.
Note: A: ABI-Left; B: ABI-Right

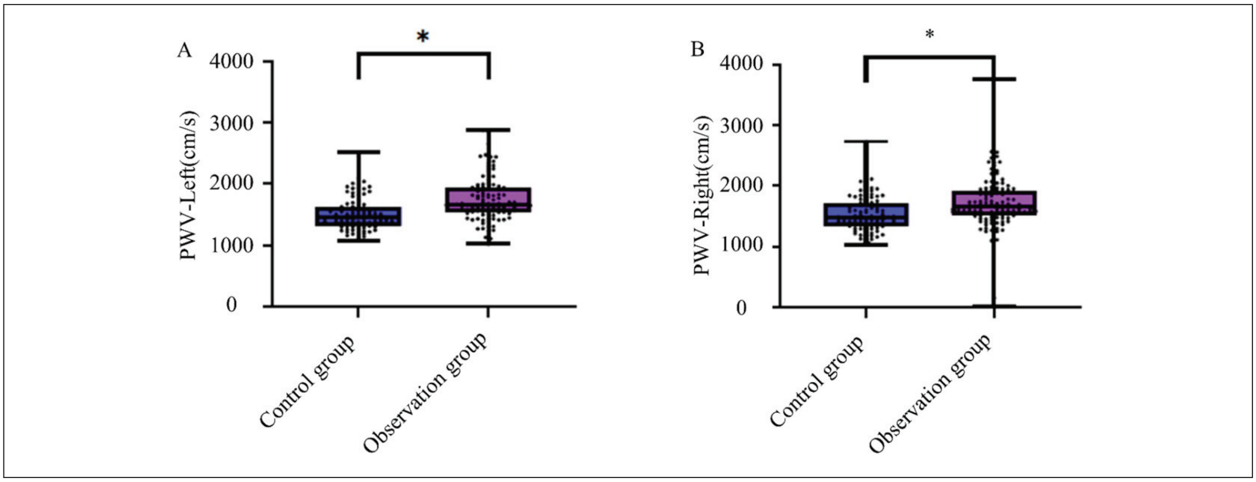

Figure 3 PWV indicators.
Note: A represents PWV-Left; B represents PWV-Right; *in contrast to the AG, $P<0.05$

Table III Glycaemic and traditional lipid/inflammatory marker profiles.

Parameter	Control Group (AG)	Observation Group (BG)	P-value
Glycaemic Parameters			
FPG (mmol/L)	7.85±1.42	7.12±1.38	<0.001
2h-PPG (mmol/L)	11.24±2.67	11.58±3.02	0.418
HbA1c (%)	7.12±0.89	8.67±1.24	<0.001
Lipid and Inflammatory Markers			
TG (mmol/L)	2.34±0.87	1.89±0.76	<0.001
TC (mmol/L)	4.78±1.02	4.21±0.94	<0.001
HDL-C (mmol/L)	1.12±0.28	1.08±0.31	0.356
LDL-C (mmol/L)	2.89±0.76	2.45±0.68	<0.001
CRP-L (mg/L)	2.14±0.89	4.67±1.58	<0.001
IL-6 (pg/mL)	3.45±1.23	6.78±2.45	<0.001

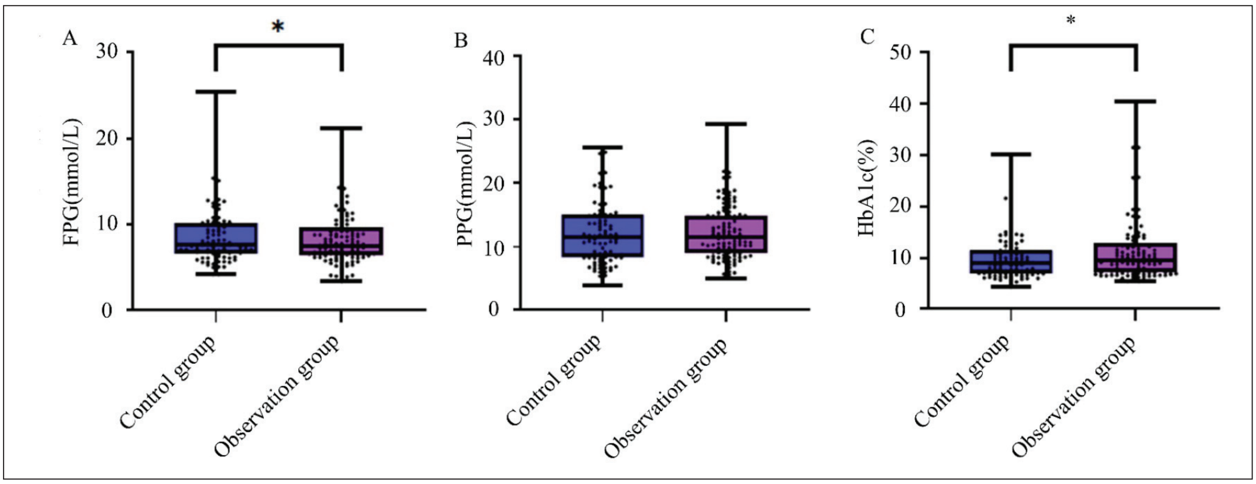

Figure 4 Blood glucose indicators.

Note: A: FPG; B: PPG; C: HbA1c; * in contrast to the AG, $P<0.05$

between groups (*Figure 4B*; AG: 11.24±2.67 mmol/L vs. BG: 11.58±3.02 mmol/L; P=0.418). Most notably, as shown in *Figure 4C*, glycated haemoglobin (HbA1c) levels were substantially elevated in the BG (8.67±1.24%) compared to the AG (7.12±0.89%; P<0.001). This discordance between acute (FPG) and chronic (HbA1c) glycaemic markers suggests that long-term glucose exposure and glycaemic variability, rather than isolated fasting hyperglycaemia, may be more closely associated with the progression of carotid atherosclerosis in T2DM patients.

Traditional lipid and inflammatory markers

In the comparison of traditional lipid and inflammatory markers (*Table III*), a notable pattern emerged. As depicted in *Figure 5* (panels A, B, and D), triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were significantly lower in the BG compared to the AG (all P<0.001). As shown in *Figure 5C*, high-density lipoprotein cholesterol (HDL-C) did not show a significant between-group difference (P=0.356). In stark contrast, *Figure 5E* demonstrates that C-reactive protein (CRP-L) was markedly higher in the BG (4.67±1.58 mg/L vs. 2.14±0.89

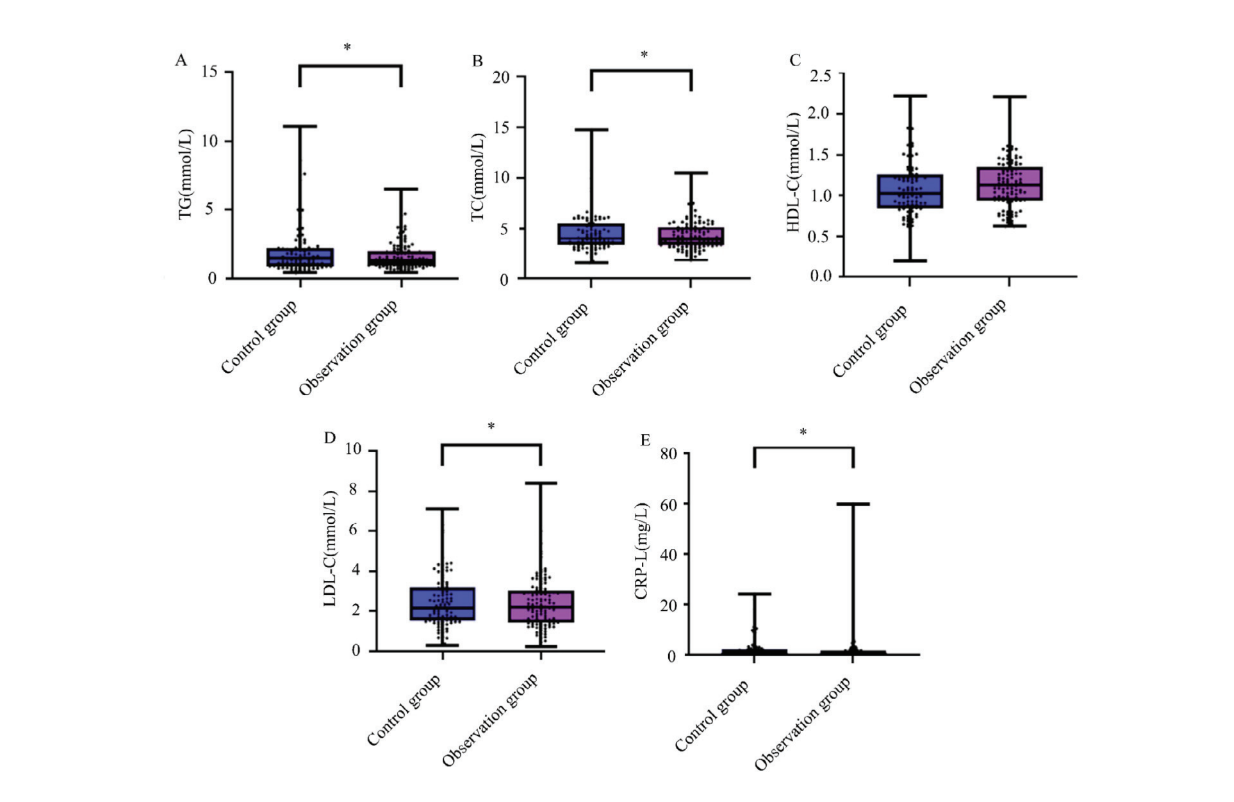

Figure 5 Blood lipid indicators.
Note: A: TG; B: TC; C: HDL-C; D: LDL-C; E: CRP-L; *in contrast to the AG, $P<0.05$

Table IV Comparison of novel serum biomarkers between groups.

Biomarker	Control Group (AG)	Observation Group (BG)	P-value
Adiponectin (mg/mL)	8.67±2.34	5.89±1.98	<0.001
Leptin (ng/mL)	12.45±4.23	18.76±5.67	<0.001
sICAM-1 (ng/mL)	245.6±67.8	356.4±89.2	<0.001
FGF-21 (pg/mL)	125.4±45.6	130.2±48.9	0.478

mg/L; P<0.001), suggesting greater systemic inflammatory activity in patients with established carotid plaques. Because medication exposure, particularly lipid-lowering treatment, could not be reliably ascertained in this retrospective dataset, the observed lipid profile differences should be interpreted with substantial caution. These findings should not be regarded as evidence that lower lipid levels are biologically protective; rather, they are likely confounded by treatment and should be considered hypothesis-generating.

Novel serum biomarkers

Analysis of novel serum biomarkers revealed significant alterations in adipokine profiles, endothelial function markers, and inflammatory cytokines in patients with carotid plaques (*Table IV*). Adiponectin levels were substantially reduced in the BG (5.89±1.98 μg/mL) compared to the AG (8.67±2.34 μg/mL; P<0.001). Conversely, leptin levels were significantly higher in the BG (18.76±5.67 ng/mL) than in the AG (12.45±4.23 ng/mL; P<0.001). The endothelial dysfunction marker soluble intercellular adhesion molecule-1 (sICAM-1) was markedly increased in the BG

Table V Multivariate logistic regression analysis of factors associated with carotid atherosclerosis in T2DM patients.

Indicator	P	Adjusted OR (95% CI)	Interpretation in Final Model
PR	0.024	1.020 (1.01–1.04)	Significant
QT	0.068	5.229 (1.261–8.341)	Not Significant
PWV-Left	0.008	2.578 (1.078–4.345)	Significant
PWV-Right	0.005	1.671 (1.021–2.741)	Significant
FPG	0.071	5.601 (1.521–8.668)	Not Significant
HbA1c	0.001	1.674 (1.021–4.697)	Significant
TG	0.001	1.746 (0.845–3.247)	Significant
TC	0.036	6.313 (1.898–10.824)	Significant
LDL-C	0.065	5.456 (1.646–8.824)	Not Significant
CRP-L	0.001	1.631 (0.918–3.129)	Significant
Adiponectin	0.011	0.620 (0.428–0.899)	Significant
Leptin	0.004	1.428 (1.119–1.822)	Significant
sICAM-1	0.015	1.002 (1.001–1.004)	Significant
IL-6	0.003	1.335 (1.102–1.618)	Significant

(356.4±89.2 ng/mL) compared to the AG (245.6±67.8 ng/mL; P<0.001). Similarly, the pro-inflammatory cytokine interleukin-6 (IL-6) was significantly higher in the BG (6.78±2.45 pg/mL) than in the AG (3.45±1.23 pg/mL; P<0.001). No significant difference was observed in fibroblast growth factor-21 (FGF-21) levels between groups (AG: 125.4±45.6 pg/mL vs. BG: 130.2±48.9 pg/mL; P=0.478). These findings highlight the multifactorial nature of diabetic atherosclerosis, involving dysregulated adipokine secretion, endothelial activation, and systemic inflammation.

Multivariate logistic regression analysis for CAS predictors

To identify independent predictors of carotid atherosclerosis in T2DM patients, we performed multivariate logistic regression analysis. The final model, presented in *Table V*, revealed several independent correlates of carotid plaque presence. Among ECG parameters, prolonged PR interval remained a significant independent predictor (adjusted OR: 1.020, 95% CI: 1.01–1.04, P=0.024), whereas QT interval did not retain statistical significance in the fully adjusted model (P=0.068). Arterial stiffness indicators, including PWV-Left (adjusted OR: 2.578, 95% CI: 1.078–4.345, P=0.008) and PWV-Right (adjusted OR: 1.671, 95% CI: 1.021–2.741, P=0.005), were strong independent predictors. Among glycaemic parameters, HbA1c emerged as a robust independent risk factor (adjusted OR: 1.674, 95% CI: 1.021–4.697, P=0.001), whereas FPG did not retain significance (P=0.071). Inflammatory markers showed particularly robust associations, with CRP-L (adjusted OR: 1.631, 95% CI: 0.918–3.129, P=0.001) and IL-6 (adjusted OR: 1.335, 95% CI: 1.102–1.618, P=0.003) emerging as independent predictors. Among novel biomarkers, adiponectin demonstrated an independent protective effect (adjusted OR: 0.620, 95% CI: 0.428–0.899, P=0.011). Given the absence of reliable medication data, the adjusted associations reported here – particularly those involving lipid parameters – should be interpreted as exploratory and hypothesis-generating rather than definitive.

Discussion

In this retrospective cohort of patients with type 2 diabetes mellitus, we observed that a combination of prolonged atrial conduction (PR interval), increased arterial stiffness (PWV), and elevated markers of chronic inflammation (CRP-L, IL-6) was independently associated with the presence of carotid atherosclerotic plaques. Notably, the inverse relationship observed between traditional lipid parameters and plaque burden highlights a critical interpretive challenge in observational studies of high-risk populations, namely, the pervasive confounding introduced by unmeasured lipid-lowering pharmacotherapy.

The association between prolonged QT interval on ECG and vascular lesions has also been reported (17–19). Prolonged QTc is significantly associated with the incidence and mortality of cardiovascular disease (CVD) in the general population. Still, no significant association was found in the T2DM population (HR=1.04, 95% CI: 0.96–1.12) (20). This distinction may arise from the fact that DM patients already have a high baseline cardiovascular risk, and the additional effect of prolonged QTc is masked. Given the high prevalence of T2DM in Indian and Asian populations, early and prompt diagnosis and treatment are essential to mitigate mortality and risks (21). QT prolongation is associated with CAD (26.5 ms prolongation, P=0.003) and conduction system disease (26.8 ms prolongation, P=0.033), suggesting that myocardial fibrosis or autonomic dysfunction may simultaneously affect cardiac and vascular structure (22). Although this study did not find differences in QTc, the original QT interval was significantly prolonged, which may reflect myocardial fibrosis or autonomic dysfunction and, by extension, systemic vascular structural remodelling. PWV, a core indicator of arterial stiffness, has been shown in numerous studies to be positively correlated with CIMT and plaques. In patients with CKD stages 3–5, estimated PWV (ePWV) is associated with carotid plaques. This association is influenced by diabetic status, with DM enhancing its robustness, and ePWV mediates 32.9% of the effect of DM on plaque formation (23). In a community cohort, both carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) were significantly associated with carotid plaques. Still, the association of baPWV is non-linear (a positive trend only exists when baPWV<16.85 m/s) (24). PWV>10 m/s (a marker of arterial stiffness) is associated with a higher plaque burden in specific populations. Still, in a certain study population with an average PWV of 9.15 m/s that did not reach this threshold, a correlation with plaque formation was observed (25). This study further supported that PWV can serve as an effective screening tool for subclinical atherosclerosis in DM patients.

The discordance between FPG and HbA1c observed in our plaque group underscores the importance of long-term glycaemic exposure, rather than isolated fasting values, in driving vascular complications. Hyperglycaemia promotes the formation of advanced glycation end-products (AGEs), which activate pro-inflammatory cascades and contribute directly to arterial stiffening independent of concomitant dyslipidaemia (26–28).

In this study, the significant elevation of CRP-L in the BG, which remained an independent risk factor, confirmed the central role of inflammation in diabetic vascular complications. Similarly, elevated IL-6 and sICAM-1 levels further underscore the involvement of systemic inflammation and endothelial activation in plaque development. This study found that conventional lipid parameters were lower in BG than in AG, which seems to contradict the traditional lipid plaque theory but, in fact, reveals the complexity of diabetic lipid metabolism. On the one hand, some patients may already have received statin or fibrate therapy, resulting in artificially lowered lipid levels at detection; on the other hand, HbA1c emerged as one of the strongest correlated factors, suggesting that long-term blood glucose exposure may be the more fundamental mechanism driving plaque formation. Studies have confirmed that elevated high-sensitivity C-reactive protein (hs-CRP) levels are significantly associated with the risk of CAS (RR=2.29–3.04) and plaque formation (RR=2.15–2.63). This association remains after adjusting for confounding factors, supporting the central role of inflammation in diabetic vascular lesions (29). hs-CRP is independently associated with LDL-C and, in men, with thyroid-stimulating hormone; in women, it is associated with age, suggesting that inflammatory mechanisms may promote atherosclerosis through multiple pathways (30). In some patients, hs-CRP is positively correlated with blood glucose parameters, suggesting that the lipid triad characteristic of DM is not fully captured by routine lipid testing, whereas inflammation (hs-CRP) is more sensitive in reflecting the risk of atherosclerosis (31). In patients with acute myocardial infarction and T2DM, hs-CRP and HbA1c levels are significantly correlated, and both indicators can serve as predictors of mortality within six months. HbA1c is positively correlated with hs-CRP and can serve as an independent marker of risk for adverse outcomes in these patients. These findings emphasize the importance of managing blood glucose control and inflammation in DM patients with acute coronary syndrome.

In addition to traditional inflammatory markers, our study highlights the potential of novel serum biomarkers in risk stratification. Reduced adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, was independently associated with increased CAS risk, consistent with its known protective role in vascular health. Conversely, elevated leptin and IL-6 reflect adipocyte dysfunction and systemic inflammation, both of which are implicated in endothelial injury and atherogenesis. sICAM-1, a marker of endothelial activation, further supports the role of endothelial dysfunction in diabetic atherosclerosis. The integration of these biomarkers with functional and imaging parameters may enhance early detection of subclinical vascular disease.

A particularly important interpretive issue in the present study is treatment-related confounding. The observation that several conventional lipid parameters were lower in the plaque group is biologically counterintuitive. It should not be interpreted at face value as indicating a lower atherogenic burden. A more plausible explanation is that patients with more advanced vascular disease were more likely to have received lipid-lowering therapy, resulting in lower measured TG, TC, and LDL-C values at the time of assessment. Because medication exposure could not be reliably retrieved and incorporated into the analytic model, any associations involving traditional lipid parameters remain vulnerable to substantial residual confounding. For this reason, the lipid findings in this study should be regarded as hypothesis-generating. They should be re-examined in prospective studies with systematic treatment tracking.

From a clinical perspective, these findings support a shift away from reliance on isolated lipid measurements toward a more integrated surveillance strategy in T2DM. Readily available tools such as standard 12-lead ECG (specifically PR interval prolongation) and non-invasive PWV assessment may help refine risk stratification in diabetic patients, particularly when interpreted alongside markers of long-term glycaemic control (HbA1c) and systemic inflammation. The independent association of IL-6 with plaque presence further underscores the potential utility of inflammatory profiling in identifying residual vascular risk.

Conclusion

In patients with T2DM, carotid plaque presence was associated with greater arterial stiffness, poorer long-term glycaemic control, higher inflammatory activity, and an adverse profile of selected novel serum biomarkers. Among the findings reported here, associations involving PWV, HbA1c, CRP-L, IL-6, and sICAM-1 appeared more robust and biologically coherent. By contrast, the observed patterns in traditional lipid parameters should be interpreted with caution, as medication exposure, particularly lipid-lowering therapy, could not be reliably assessed or adjusted for in this retrospective study. Therefore, lipid-related findings should be regarded as hypothesis-generating rather than definitive. Prospective studies with systematic medication tracking are needed to clarify the independent contributions of lipid parameters and biomarker profiles to carotid atherosclerosis in T2DM. This pattern is clinically interpretable only with caution because treatment exposure was unavailable.

Authors' contribution

Chunmei Wang and Anjie Xie are the first coauthors of the paper. All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Daohui Yang and Yicheng Wu. The first draft of the manuscript was written by Huixin Wang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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