

ORIGINAL RESEARCH

Glycemic Burden and Carotid Atherosclerotic Phenotype Across Cerebrovascular Presentations: Associations of HbA1c, Fasting and Postprandial Glucose With Carotid Intima-Media Thickness and Plaque

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ABSTRACT

Background: Glycemia is a continuous vascular risk factor, but it is unclear which routinely measured glycemic marker best reflects carotid atherosclerosis, and whether this relationship differs across cerebrovascular presentations. **Objectives:** To compare the independent associations of glycated hemoglobin (HbA1c), fasting blood glucose (FBS) and postprandial blood glucose (PPBS) with carotid intima-media thickness (cIMT) and carotid plaque, and to compare carotid phenotype across ischemic infarction (INF), transient ischemic attack (TIA) and intracerebral hemorrhage (ICH). **Methods:** This cross-sectional study included 447 patients at a teaching hospital in Kolkata, India (235 INF, 92 TIA, 57 ICH, 38 without cerebrovascular disease and 25 with other presentations). Associations per 1-SD increase in each marker were estimated by multivariable linear and logistic regression adjusted for age, sex, hypertension, systolic blood pressure, smoking, non-HDL cholesterol and estimated glomerular filtration rate, with joint-marker, spline, interaction and discrimination (AUROC) analyses. **Results:** No glycemic marker was independently associated with mean cIMT (per-SD change: HbA1c 0.013 mm, 95% CI -0.012 to 0.037; FBS 0.007 mm; PPBS 0.004 mm; all $P > 0.30$), maximum cIMT or any plaque phenotype (ORs for any plaque 1.02–1.10; all $P > 0.40$), and adding them to a clinical model barely changed plaque discrimination (AUROC 0.664 vs 0.668). Mean cIMT was similar in INF, TIA and ICH ($P = 0.987$), but plaque prevalence differed (61.0%, 39.7% and 53.1%; $P = 0.006$), with higher adjusted odds of plaque in INF than TIA (OR 2.47, 95% CI 1.38–4.40). Presentation and diabetes status did not modify the glycemic associations. **Conclusions:** In this cerebrovascular cohort, single measurements of HbA1c, FBS and PPBS were not independently associated with carotid wall thickness or plaque. Focal plaque, rather than cIMT, distinguished completed infarction from TIA.

Keywords: HbA1c; Blood glucose; Carotid intima-media thickness; Carotid plaque; Stroke; Transient ischemic attack; Intracerebral hemorrhage

INTRODUCTION

Diabetes mellitus and dysglycemia are among the most important modifiable determinants of atherosclerotic cardiovascular disease and stroke. The International Diabetes Federation estimates that hundreds of millions of adults worldwide live with diabetes, and many more have intermediate hyperglycemia or undiagnosed disease [1]. Contemporary guidelines therefore place cardiovascular risk reduction at the center of diabetes care, combining glycemic control with management of blood pressure, atherogenic lipoproteins, smoking, obesity and kidney disease [2]. The vascular effect of glycemia, however, is not captured by the simple presence or absence of diabetes. Large prospective analyses have shown that diabetes substantially increases the risk of ischemic stroke and that vascular risk rises progressively with circulating glucose across the glycemic continuum [3]. HbA1c likewise predicts cardiovascular outcomes even below the diagnostic threshold for diabetes [4]. These observations support the concept of glycemic burden as a continuous vascular exposure and raise a practical question: which routinely available glycemic marker most closely reflects structural atherosclerosis, and does this relationship vary across cerebrovascular presentations?

HbA1c, fasting blood glucose (FBS) and postprandial blood glucose (PPBS) describe related but biologically distinct aspects of glucose homeostasis. HbA1c reflects average glycemic exposure over approximately 2–3 months and is strongly associated with long-term diabetic complications [4,5]. Fasting glucose is determined mainly by basal hepatic glucose output and insulin resistance, whereas postprandial glucose reflects meal-related glucose influx, early insulin secretion, peripheral glucose disposal and transient glycemic excursions. These differences matter clinically, because similar HbA1c values can coexist with very different fasting and postprandial profiles. In the San Luigi Gonzaga Diabetes Study, postprandial glucose predicted cardiovascular events more strongly than fasting glucose in patients with type 2 diabetes [6]. Postprandial hyperglycemia has also been linked mechanistically to oxidative stress, endothelial dysfunction, inflammation, reduced nitric oxide bioavailability and prothrombotic responses, providing a plausible pathway by which intermittent glucose excursions might promote arterial injury beyond the effect of average glycemia [7].

Carotid studies suggest that these glycemic domains are not interchangeable. Postchallenge glucose has been independently associated with increased carotid intima-media thickness (cIMT) in people without diabetes [8]. In type 2 diabetes, post-meal glucose peaks are related to carotid wall thickening [9], and targeted reduction of postprandial hyperglycemia has been associated with regression of cIMT despite similar improvements in HbA1c [10]. In nondiabetic individuals, prediabetes defined by postchallenge glucose identified a subgroup with a less favorable cardiometabolic profile and greater cIMT than prediabetes defined by HbA1c alone [11]. These findings provide a rationale for evaluating HbA1c, FBS and PPBS together, comparing their standardized effect sizes, and testing whether each contributes independent information about carotid atherosclerosis.

Carotid ultrasonography offers a noninvasive view of systemic arterial disease, but it yields more than one measure of atherosclerosis. cIMT is a continuous marker of arterial wall remodeling, whereas focal carotid plaque represents a discrete and more advanced atherosclerotic lesion. The Mannheim consensus standardized the definitions and measurement of both and emphasized the need to distinguish diffuse wall thickening from focal plaque [12]. Increased cIMT is associated with future myocardial infarction and stroke, although its predictive strength varies with the arterial segment and measurement method [13]. Carotid plaque may provide more direct evidence of atherosclerotic burden and, in many settings, stronger risk information than cIMT alone [14]. In the Atherosclerosis Risk in Communities (ARIC) study, adding plaque information to cIMT improved cardiovascular risk classification beyond conventional risk factors [15]. cIMT and plaque should therefore be analyzed as complementary but separate outcomes, together with plaque distribution, bilaterality and internal carotid artery (ICA) involvement.

The importance of carotid phenotype becomes clearer when cerebrovascular disease is viewed as a spectrum of pathophysiologically distinct presentations rather than a single entity. Atherosclerotic burden would be expected to relate more directly to ischemic events than to primary intracerebral hemorrhage (ICH), yet even within ischemic disease the relationship is heterogeneous. In the China Kadoorie Biobank, carotid plaque burden was more strongly associated with probable large-artery ischemic stroke than with lacunar stroke and was not similarly associated with probable cardioembolic stroke [16]. In the SMART study, cIMT was greater in large-vessel than in small-vessel ischemic stroke after adjustment for major vascular risk factors [17]. Comparisons of ischemic stroke and ICH have also reported differences in common carotid IMT, suggesting that carotid wall phenotype may help to distinguish atherosclerotic from hemorrhagic cerebrovascular processes [18].

Transient ischemic attack (TIA) is a further clinically important phenotype. It shares many mechanisms with completed infarction but may reflect a different burden, distribution or instability of vascular disease. High-resolution plaque imaging has shown greater wall burden and more vulnerable plaque features in patients with ischemic stroke than in those with TIA [19]. Few studies, however, have examined whether chronic, fasting and postprandial glycemia relate differently to carotid structure across infarction, TIA and ICH within the same cohort. Indian data have linked HbA1c with carotid atherosclerosis in ischemic stroke [20], but studies confined to a single presentation or a single marker cannot determine whether the association is specific to ischemic disease, whether it differs between TIA and completed infarction, or whether HbA1c outperforms FBS and PPBS when all three are compared on the same scale.

We therefore examined HbA1c as the principal marker of chronic glycemc exposure, with FBS and PPBS as complementary fasting and postprandial measures, in relation to cIMT and plaque phenotypes across INF, TIA and ICH. We hypothesized that greater glycemc burden would be independently associated with thicker cIMT and a higher probability of carotid plaque, and that these associations would be strongest in ischemic presentations.

MATERIALS AND METHODS

Study design and participants

This cross-sectional observational study included 447 patients evaluated at Jagannath Gupta Institute of Medical Sciences and Hospital, Budge Budge, Kolkata, India, between 2023 November and 2025 November, with data collected retrospectively from hospital records. The study was approved by the Institutional Ethics Committee of the institute (approval number IEC/JGIMSH/2025/02), and the requirement for informed consent was waived because of the retrospective design. Patients were classified by cerebrovascular presentation as ischemic infarction (INF; n = 235), transient ischemic attack (TIA; n = 92) or intracerebral hemorrhage (ICH; n = 57). A further 38 patients had no recorded cerebrovascular disease, and 25 had other or unrecorded presentations. INF and ICH were diagnosed clinically and confirmed by computed tomography or magnetic resonance imaging of the brain, and TIA was defined as a transient episode of focal neurological dysfunction without acute infarction on imaging. The principal between-presentation comparison was restricted to the 384 patients classified as INF, TIA or ICH; analyses of glycemc markers and carotid measures used all patients with available data.

Clinical and laboratory variables

Age, sex, hypertension, diabetes mellitus, current smoking and systolic blood pressure were recorded. HbA1c, FBS, PPBS, lipid profile and serum creatinine were measured, and non-HDL cholesterol and estimated glomerular filtration rate (eGFR) were calculated. Hypertension and diabetes were defined as a previous diagnosis, current treatment, or values meeting standard diagnostic criteria, and current smoking. Blood samples were collected within 1 hour of admission; FBS was measured after an overnight fast of at least 8 hours and PPBS 2 hours after a meal. HbA1c was measured by method, e.g., NGSP-certified high-performance liquid chromatography, and eGFR was calculated with the CKD-EPI 2021 equation.

Carotid ultrasonography

Carotid arteries were examined by B-mode ultrasonography. Mean and maximum cIMT were recorded, together with the presence of any carotid plaque, bilateral plaque and ICA plaque. Examinations were performed with ultrasound system using a linear-array transducer by an operator blinded to clinical and laboratory data. cIMT was measured on the far wall of the distal 1 cm of the common carotid artery on both sides; mean cIMT was the average of the left and right measurements, and maximum cIMT the greatest single value. Plaque was defined according to the Mannheim consensus as a focal structure encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT, or with a thickness greater than 1.5 mm measured from the media–adventitia interface to the intima–lumen interface [12]. Plaque phenotypes were analyzed as any plaque, bilateral plaque (plaque in both carotid systems) and ICA plaque.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range), and categorical variables as number (percentage). INF, TIA and ICH were compared using Welch analysis of variance or the Kruskal–Wallis test for continuous variables, and the chi-square or Fisher’s exact test for proportions. Pairwise comparisons of plaque prevalence used Fisher’s exact test with Holm adjustment for multiple comparisons.

Correlations between glycemc markers and cIMT were assessed with Pearson and Spearman coefficients. The associations of each glycemc marker with mean and maximum cIMT were estimated by multivariable linear regression, and with any, bilateral and ICA plaque by multivariable logistic regression. Effects were expressed per 1-SD increase in the marker, as regression coefficients (β , mm) or odds ratios (ORs) with 95% confidence intervals (CIs). All models were

adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and eGFR. The independent contribution of each marker was examined in a joint model containing all three markers. Possible non-linearity between HbA1c and mean cIMT was assessed with restricted cubic splines with HbA1c distribution.

Effect modification by cerebrovascular presentation, diabetes status and overall cerebrovascular disease status was tested with multiplicative interaction terms. A secondary logistic model compared ischemic presentations (INF and TIA combined) with ICH. The incremental value of glycemic markers for identifying carotid plaque was assessed by comparing the area under the receiver operating characteristic curve (AUROC) of a clinical model with that of models including glycemic markers, in a common complete-case dataset, with bootstrap 95% CIs. Analyses were performed on complete cases; the number of patients included in each analysis is reported. Two-sided P values below 0.05 were considered statistically significant.

RESULTS

Study population and comparison of cerebrovascular presentations

Of the 447 patients, 235 had INF, 92 TIA, 57 ICH, 38 no recorded cerebrovascular disease, and 25 other or unrecorded presentations (Figure 1). The comparison of cerebrovascular presentations included the 384 patients with INF, TIA or ICH. The three groups were similar in age, sex, prevalence of hypertension, diabetes and smoking, and in HbA1c, FBS and PPBS (Table 1). Mean cIMT was also comparable ($P = 0.987$; Figure 2), but the prevalence of any plaque (61.0%, 39.7% and 53.1% in INF, TIA and ICH, respectively; $P = 0.006$) and of ICA plaque ($P = 0.026$) differed significantly (Table 1; Figure 3). Plaque data were available for 327 of the 384 patients (85.2%).

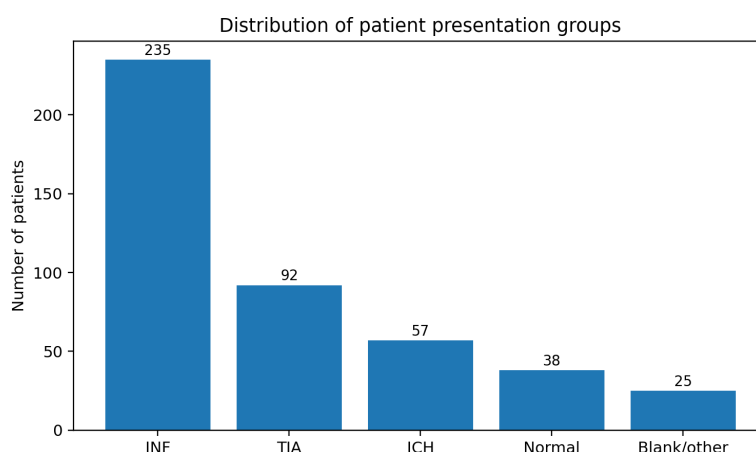


Figure 1. Distribution of patients by cerebrovascular presentation ($n = 447$). INF, ischemic infarction; TIA, transient ischemic attack; ICH, intracerebral hemorrhage.

Table 1. Clinical, glycemic and carotid characteristics of patients with INF, TIA and ICH

Variable	INF (n = 235)	TIA (n = 92)	ICH (n = 57)	P value
Age, years	65.2 ± 12.7	65.8 ± 13.9	65.9 ± 12.6	0.902
Male sex	126/235 (53.6)	47/92 (51.1)	24/57 (42.1)	0.296
Hypertension	169/235 (71.9)	66/92 (71.7)	44/57 (77.2)	0.707
Diabetes mellitus	105/234 (44.9)	35/92 (38.0)	21/57 (36.8)	0.367
Current smoking	51/234 (21.8)	23/92 (25.0)	11/57 (19.3)	0.698
HbA1c, %	6.78 ± 0.87	6.67 ± 0.82	6.65 ± 0.87	0.461
FBS, mg/dL	115.0 (98.0–160.0)	105.5 (90.0–136.0)	111.0 (98.0–145.0)	0.079
PPBS, mg/dL	140.0 (112.0–218.0)	122.5 (110.0–192.5)	124.0 (114.0–202.0)	0.239
Mean cIMT, mm	1.114 ± 0.221	1.115 ± 0.233	1.120 ± 0.257	0.987

Variable	INF (n = 235)	TIA (n = 92)	ICH (n = 57)	P value
Maximum cIMT, mm	1.184 ± 0.267	1.192 ± 0.292	1.186 ± 0.282	0.974
Any carotid plaque	122/200 (61.0)	31/78 (39.7)	26/49 (53.1)	0.006
Bilateral plaque	44/200 (22.0)	12/78 (15.4)	13/49 (26.5)	0.287
ICA plaque	97/200 (48.5)	24/78 (30.8)	20/49 (40.8)	0.026

Values are mean ± SD, median (interquartile range) or n/N (%). cIMT, carotid intima-media thickness; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; ICA, internal carotid artery; ICH, intracerebral hemorrhage; INF, ischemic infarction; PPBS, postprandial blood glucose; SD, standard deviation; TIA, transient ischemic attack.

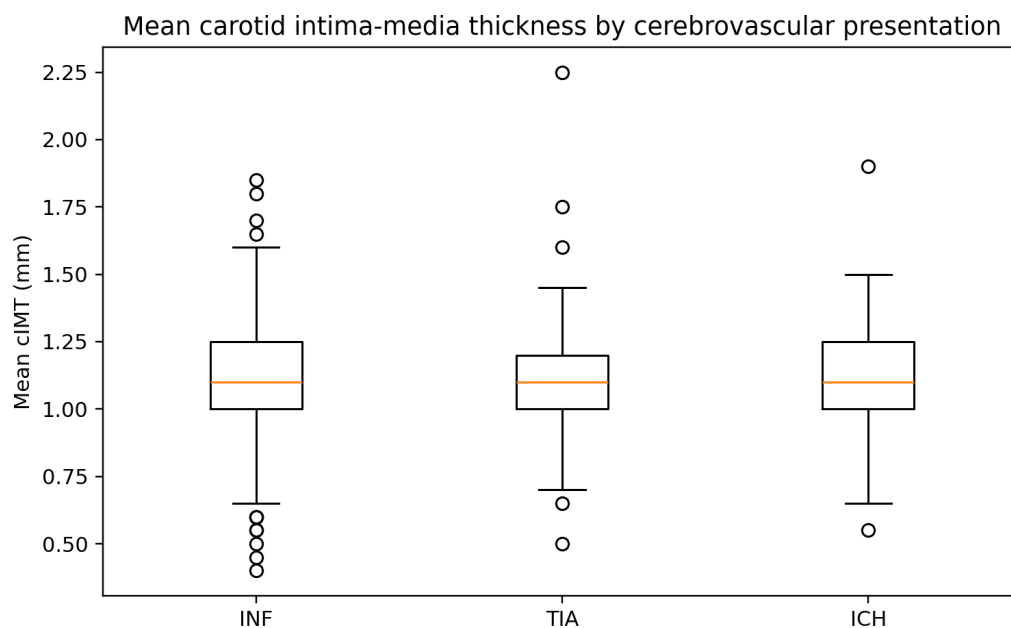


Figure 2. Distribution of mean carotid intima-media thickness (cIMT) in patients with INF, TIA and ICH.

The difference between groups was not significant (Welch ANOVA, $P = 0.987$).

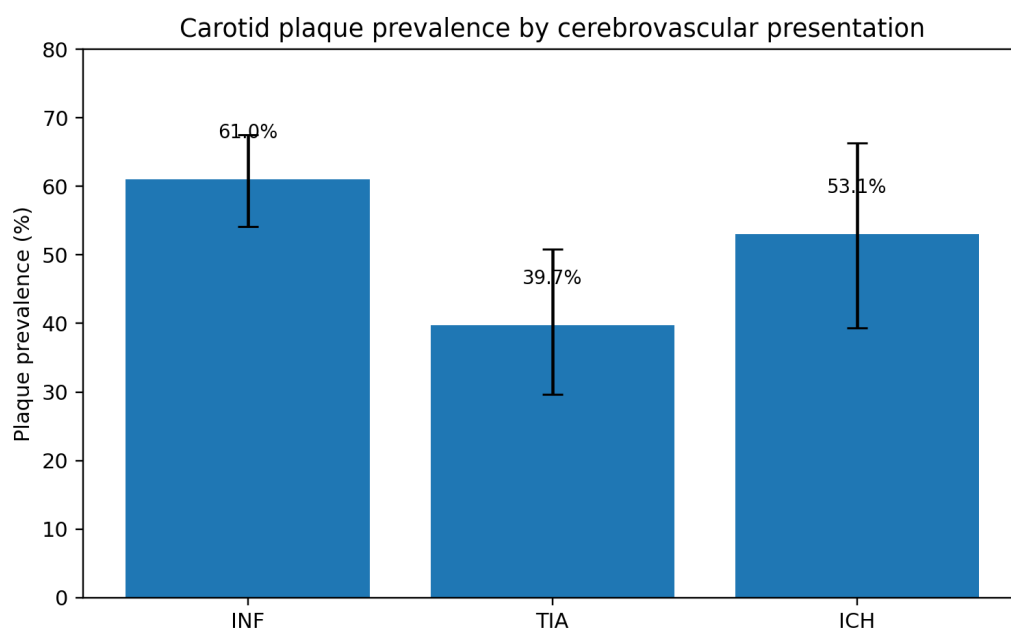


Figure 3. Prevalence of carotid plaque in patients with INF, TIA and ICH

95% Wilson confidence intervals (overall $P = 0.006$).

Glycemic markers and carotid atherosclerotic burden

Correlations between the glycemic markers and mean cIMT were weak and non-significant (Table 2). After adjustment, a 1-SD increase in HbA1c was associated with a 0.013-mm increase in mean cIMT (95% CI -0.012 to 0.037; $P = 0.314$), compared with 0.007 mm for FBS ($P = 0.544$) and 0.004 mm for PPBS ($P = 0.776$) (Figure 4). None of the markers was associated with maximum cIMT. In the joint model containing all three markers ($n = 434$), none was independently associated with mean cIMT, and the model explained little of the variation in cIMT (adjusted $R^2 = 0.068$; Table 3).

All three markers were entered simultaneously; β is per 1-SD increase. Adjusted $R^2 = 0.068$. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; cIMT, carotid intima-media thickness; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; PPBS, postprandial blood glucose.

None of the glycemic markers was associated with carotid plaque (Table 4). The adjusted ORs per 1-SD increase for any plaque were 1.02 for HbA1c, 1.02 for FBS and 1.10 for PPBS, all non-significant.

ORs are per 1-SD increase in the glycemic marker. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; ICA, internal carotid artery; OR, odds ratio; PPBS, postprandial blood glucose.

Table 2. Correlation and adjusted linear regression of glycemic markers with carotid intima-media thickness

Marker	N	Pearson r (P)	Spearman ρ (P)	Adjusted β , mean cIMT (95% CI)	P	Adjusted β , max cIMT (95% CI)	P
HbA1c	439	0.045 (0.351)	0.007 (0.883)	0.013 (-0.012 to 0.037)	0.314	0.018 (-0.010 to 0.047)	0.210
FBS	439	0.031 (0.524)	0.020 (0.680)	0.007 (-0.016 to 0.031)	0.544	0.006 (-0.019 to 0.032)	0.631
PPBS	438	0.017 (0.731)	0.023 (0.630)	0.004 (-0.022 to 0.029)	0.776	0.007 (-0.021 to 0.035)	0.640

β is the change in cIMT (mm) per 1-SD increase in the glycemic marker. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; cIMT, carotid intima-media thickness; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; PPBS, postprandial blood glucose.

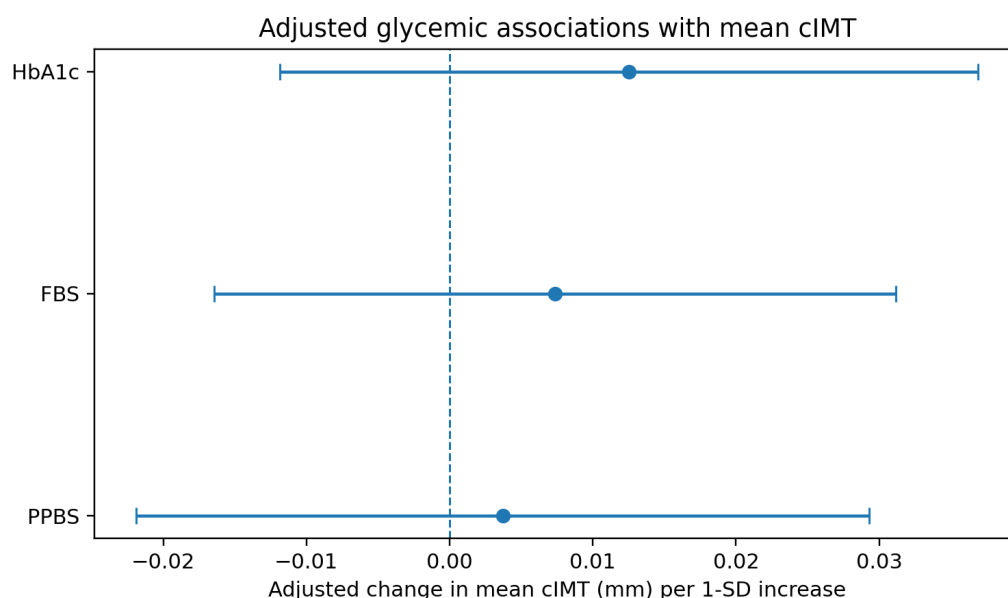


Figure 4. Adjusted associations of HbA1c, fasting blood glucose (FBS) and postprandial blood glucose (PPBS) with mean carotid intima-media thickness (cIMT),

Expressed as change in cIMT per 1-SD increase in each marker, with 95% confidence intervals.

Table 3. Joint multivariable model including HbA1c, FBS and PPBS simultaneously

Glycemic marker	N	Adjusted β , mean cIMT (95% CI)	P value
HbA1c	434	0.023 (−0.014 to 0.060)	0.226
FBS	434	0.013 (−0.028 to 0.054)	0.528
PPBS	434	−0.026 (−0.072 to 0.020)	0.272

All three markers were entered simultaneously; β is per 1-SD increase. Adjusted $R^2 = 0.068$. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; cIMT, carotid intima-media thickness; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; PPBS, postprandial blood glucose.

Table 4. Adjusted associations of glycemic markers with carotid plaque phenotypes

Marker	Any plaque, OR (95% CI)	P	Bilateral plaque, OR (95% CI)	P	ICA plaque, OR (95% CI)	P
HbA1c	1.02 (0.81–1.28)	0.887	1.09 (0.83–1.41)	0.538	0.95 (0.76–1.19)	0.645
FBS	1.02 (0.82–1.27)	0.833	1.12 (0.87–1.43)	0.372	1.02 (0.82–1.27)	0.850
PPBS	1.10 (0.87–1.38)	0.434	1.17 (0.91–1.51)	0.213	0.99 (0.79–1.24)	0.905

ORs are per 1-SD increase in the glycemic marker. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; ICA, internal carotid artery; OR, odds ratio; PPBS, postprandial blood glucose.

Carotid plaque across cerebrovascular presentations

Plaque prevalence was highest in INF and lowest in TIA (Table 1; Figure 3). On pairwise comparison, INF differed significantly from TIA for any plaque (OR 2.37; Holm-adjusted $P = 0.006$) and for ICA plaque (OR 2.12; Holm-adjusted $P = 0.031$), whereas ICH did not differ significantly from either group (Table 5). After covariate adjustment, patients with INF had higher odds of any plaque than those with TIA (OR 2.47, 95% CI 1.38–4.40; $P = 0.002$).

Table 5. Pairwise and adjusted comparisons of plaque phenotype across cerebrovascular presentations

Comparison	OR (95% CI)	Unadjusted P	Holm-adjusted or adjusted P
Any plaque: INF vs TIA	2.37	0.002	0.006
Any plaque: INF vs ICH	1.38	0.333	0.333
Any plaque: TIA vs ICH	0.58	0.149	0.297
ICA plaque: INF vs TIA	2.12	0.010	0.031
ICA plaque: INF vs ICH	1.37	0.344	0.515
ICA plaque: TIA vs ICH	0.64	0.257	0.515
Adjusted, any plaque: INF vs TIA	2.47 (1.38–4.40)	–	0.002
Adjusted, any plaque: ICH vs TIA	1.61 (0.77–3.39)	–	0.208

Unadjusted pairwise comparisons used Fisher's exact test with Holm correction; adjusted ORs are from multivariable logistic regression. Adjusted for age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. CI, confidence interval; ICA, internal carotid artery; ICH, intracerebral hemorrhage; INF, ischemic infarction; OR, odds ratio; TIA, transient ischemic attack.

Plaque phenotypes, non-linearity and discrimination

Neither bilateral nor ICA plaque was associated with any glycemic marker (Table 4). The restricted cubic spline for HbA1c and mean cIMT showed no significant departure from linearity ($P = 0.404$; Figure 5).

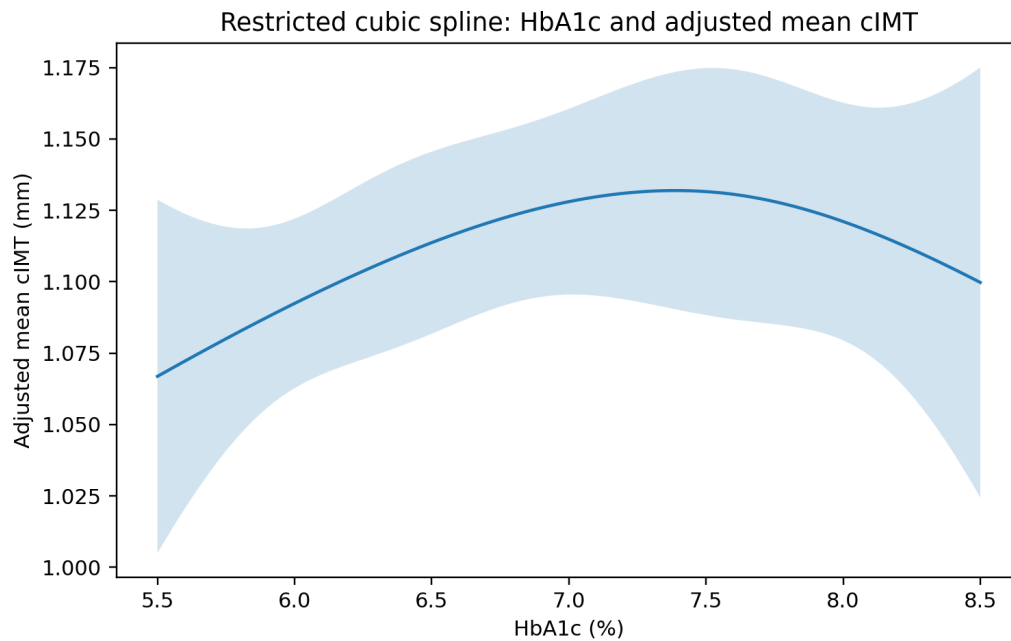


Figure 5. Restricted cubic spline of the adjusted relationship between HbA1c and mean carotid intima-media thickness (cIMT)
95% confidence band (P for non-linearity = 0.404).

In the common complete-case dataset ($n = 372$), the clinical model alone had an AUROC of 0.664 for carotid plaque. Adding HbA1c, FBS or PPBS individually did not improve discrimination, and adding all three increased the AUROC only to 0.668 ($\Delta\text{AUROC} +0.004$; bootstrap 95% CI -0.001 to $+0.045$) (Table 6; Figure 6).

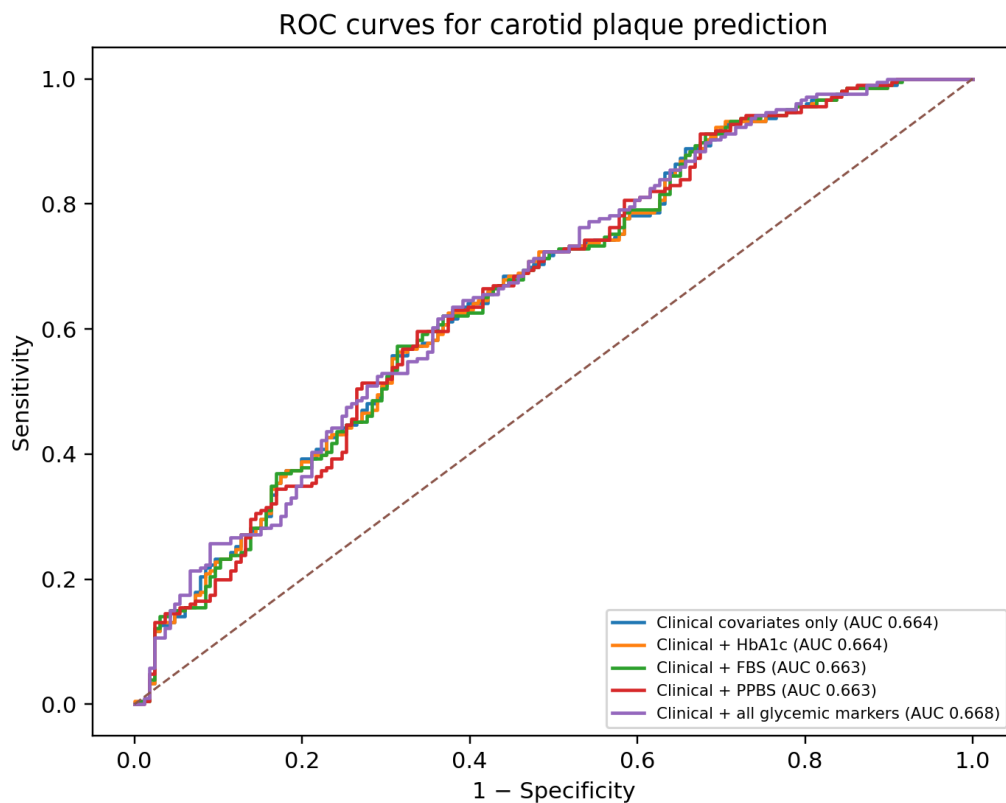


Figure 6. Receiver operating characteristic curves for identifying carotid plaque with the clinical model alone and after addition of glycemic markers.

Table 6. Discrimination of carotid plaque by clinical and glycemic models in the common complete-case dataset (n = 372)

Model	AUROC (bootstrap 95% CI)	Δ AUROC vs clinical model (bootstrap 95% CI)
Clinical covariates only	0.664 (0.623–0.730)	Reference
Clinical + HbA1c	0.664 (0.627–0.733)	0.000 (–0.003 to +0.019)
Clinical + FBS	0.663 (0.629–0.732)	–0.001 (–0.003 to +0.013)
Clinical + PPBS	0.663 (0.629–0.732)	–0.001 (–0.003 to +0.021)
Clinical + all glycemic markers	0.668 (0.640–0.742)	+0.004 (–0.001 to +0.045)

Clinical covariates: age, sex, hypertension, systolic blood pressure, current smoking, non-HDL cholesterol and estimated glomerular filtration rate. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; PPBS, postprandial blood glucose.

Effect modification and sensitivity analyses

None of the formal interaction tests was significant (Table 7). The association between HbA1c and mean cIMT was not significantly modified by cerebrovascular presentation ($P = 0.109$) or diabetes status ($P = 0.469$), and the HbA1c–plaque association was not modified by presentation ($P = 0.261$) or diabetes status ($P = 0.177$). Within the ICH subgroup, HbA1c was positively associated with mean cIMT (0.076 mm per SD; $P = 0.009$). Because the overall interaction was not significant, this subgroup finding should be considered exploratory.

Table 7. Interaction and effect-modification analyses

Analysis	Effect estimate or test	P value
HbA1c slope for mean cIMT, INF	0.007 mm/SD (–0.026 to 0.040)	0.685
HbA1c slope for mean cIMT, TIA	0.012 mm/SD (–0.048 to 0.072)	0.697
HbA1c slope for mean cIMT, ICH	0.076 mm/SD (0.019 to 0.134)	0.009
HbA1c $\times$ presentation, mean cIMT	Joint interaction test	0.109
HbA1c $\times$ presentation, plaque	Joint interaction test	0.261
HbA1c $\times$ diabetes status, mean cIMT	Interaction test	0.469
HbA1c $\times$ diabetes status, plaque	Interaction OR 1.59 (0.81–3.11)	0.177
HbA1c $\times$ cerebrovascular disease status, mean cIMT	Sensitivity interaction test	0.104

Subgroup slopes are exploratory, as the overall presentation interaction was not significant. cIMT, carotid intima-media thickness; HbA1c, glycated hemoglobin; ICH, intracerebral hemorrhage; INF, ischemic infarction; OR, odds ratio; TIA, transient ischemic attack.

In the secondary model comparing ischemic presentations with ICH ($n = 378$), neither HbA1c nor mean cIMT was independently associated with presentation type, and overall discrimination was poor (AUROC 0.575; Table 8). In the sensitivity analysis, patients without cerebrovascular disease had a plaque prevalence similar to that of patients with cerebrovascular disease (48.6% vs 54.9%; $P = 0.584$) and a slightly, but not significantly, lower mean cIMT (1.046 vs 1.115 mm; $P = 0.067$).

Table 8. Secondary model comparing ischemic presentations (INF and TIA) with ICH

Predictor	Adjusted OR for ischemic vs ICH (95% CI)	P value
HbA1c	1.12 (0.83–1.51)	0.448
Mean cIMT	0.96 (0.69–1.33)	0.801
Age	0.96 (0.72–1.28)	0.799
Male sex	1.58 (0.80–3.08)	0.185
Hypertension	0.76 (0.38–1.51)	0.428
Smoking	0.91 (0.39–2.12)	0.832

Ischemic presentations comprise INF and TIA ($n = 378$ in the model); model AUROC 0.575. ORs for HbA1c, mean cIMT and age are per 1-SD increase. cIMT, carotid intima-media thickness; HbA1c, glycated hemoglobin; ICH, intracerebral hemorrhage; INF, ischemic infarction; OR, odds ratio; TIA, transient ischemic attack.

DISCUSSION

This study evaluated the relationship of three routinely measured glycemic indices (HbA1c, FBS and PPBS) with carotid structural disease across major cerebrovascular presentations. The principal finding was that none of the three markers was independently associated with mean or maximum cIMT, any carotid plaque, bilateral plaque or ICA plaque after adjustment for age, sex, hypertension, systolic blood pressure, smoking, non-HDL cholesterol and eGFR. In contrast, carotid plaque phenotype differed significantly among INF, TIA and ICH, despite almost identical mean cIMT. Plaque was present in 61.0% of INF, 39.7% of TIA and 53.1% of ICH patients; the main difference was between INF and TIA, and it persisted after multivariable adjustment. The most consistent signal in these data was therefore not a direct glycemia–cIMT relationship but heterogeneity of focal carotid atherosclerosis across cerebrovascular presentations.

cIMT and plaque should not be regarded as interchangeable. cIMT reflects diffuse arterial wall thickening, which includes age- and pressure-related medial hypertrophy, whereas plaque is a focal atherosclerotic lesion. The Mannheim consensus accordingly recommends that they be assessed separately [12]. Increased cIMT predicts cardiovascular events [13], but focal plaque often provides stronger information about established atherosclerotic burden [14,15]. In a meta-analysis, Inaba et al. found plaque more accurate than cIMT for predicting coronary events [21], and Den Ruijter et al. showed only a small gain in risk prediction from adding common carotid IMT to conventional risk factors [22]. The present finding of nearly identical cIMT but significantly different plaque prevalence across INF, TIA and ICH supports plaque as a distinct and potentially more discriminating phenotype.

A substantial literature links dysglycemia with vascular injury. Diabetes is a major risk factor for atherosclerotic cardiovascular disease and stroke [2,3], and long-term observational data show a graded relationship between glycemic exposure and macrovascular complications [4,5]. Mechanistically, chronic hyperglycemia promotes oxidative stress, formation of advanced glycation end-products, endothelial dysfunction, protein kinase C activation, vascular inflammation and reduced nitric oxide bioavailability [7]. These pathways give strong biological grounds for expecting higher HbA1c to be associated with greater carotid wall disease, and several studies have reported such associations. In Asian Indians with normal glucose tolerance, Venkataraman et al. observed progressively greater cIMT across increasing HbA1c quartiles, with an independent association after adjustment for conventional risk factors [23]. In the Hisayama Study, HbA1c and glycated albumin were associated with carotid atherosclerosis in community-dwelling Japanese adults [24], and Singh et al. reported a relationship between HbA1c and carotid atherosclerosis in Indian patients with ischemic stroke [20].

The present results did not reproduce an independent HbA1c–cIMT association. A 1-SD increase in HbA1c corresponded to only a 0.013-mm adjusted increase in mean cIMT, with a CI spanning zero. FBS and PPBS showed even smaller effects, none of the markers was related to maximum cIMT, and the joint model did not identify a dominant marker. This divergence from earlier positive studies should not be taken to mean that glycemia is unimportant in vascular disease. It suggests instead that, in an older, clinically selected cerebrovascular cohort with a high prevalence of hypertension, diabetes and other competing vascular risk factors, cross-sectional variation in current glycemic indices explains little additional variation in carotid wall thickness once those factors are taken into account. The relatively narrow distribution of HbA1c in this cohort (mean approximately 6.7%) may also have limited the ability to detect an association.

The clearest positive finding was the difference in plaque prevalence across presentations. Patients with INF had more than twice the odds of plaque compared with those with TIA, an association that remained significant after adjustment (OR 2.47, 95% CI 1.38–4.40), and ICA plaque showed a similar pattern. This is consistent with the concept that completed infarction is associated with greater or more advanced carotid atherosclerosis than transient ischemia, although carotid disease is only one of several possible mechanisms of cerebral ischemia. The finding agrees with high-resolution imaging data: Lu et al., studying symptomatic carotid plaques in 270 patients, found greater wall area, wall thickness and normalized wall index, and a larger lipid-rich necrotic core, in patients with stroke than in those with TIA [19]. Their results suggest that the distinction between TIA and completed infarction reflects not only the duration of neurological symptoms but also differences in plaque burden and vulnerability. Our ultrasound-based study could not assess the necrotic core, fibrous cap, ulceration or intraplaque hemorrhage, but the higher prevalence of overall and ICA plaque in INF is directionally consistent with those observations. Plaque composition may matter at least as much as stenosis: in the

prospective PARISK study, intraplaque hemorrhage and total plaque volume predicted recurrent ipsilateral ischemic stroke or TIA and improved discrimination beyond a conventional clinical score [25]. These data support moving from simple plaque presence toward quantitative and vulnerability-focused plaque phenotyping.

A notable observation was the dissociation between plaque and cIMT. Mean cIMT was essentially identical in INF, TIA and ICH (approximately 1.11–1.12 mm), and maximum cIMT also did not differ, yet the prevalence of any plaque and ICA plaque differed significantly. This pattern suggests that diffuse wall thickening in this older, high-risk cohort reflects a shared background of vascular aging and hypertension, whereas focal plaque captures a more disease-specific atherosclerotic phenotype. The SMART study showed that cIMT can discriminate between ischemic stroke mechanisms, particularly large- versus small-vessel disease, when stroke is classified etiologically [17]. When broad clinical categories such as INF, TIA and ICH are used, each containing heterogeneous mechanisms, the discriminatory capacity of cIMT is likely to be reduced.

The AUROC analysis adds a perspective beyond statistical significance. The clinical model had a modest AUROC of 0.664 for carotid plaque. Adding the glycemic markers individually produced no improvement, and adding all three increased the AUROC only to 0.668, with a bootstrap CI that included zero. The absence of a glycemic association was therefore not merely a matter of P-value thresholds: the markers also failed to add meaningful discrimination. This is consistent with the general principle that a risk factor may be biologically important at the population level yet contribute little incremental predictive information once correlated vascular variables are included in a model.

Formal interaction testing did not show convincing modification of the HbA1c–cIMT or HbA1c–plaque associations by cerebrovascular presentation, diabetes status or overall cerebrovascular disease status. This distinction is important, because a significant result within one subgroup does not establish a significant difference between subgroups. HbA1c was positively associated with mean cIMT within the ICH group (0.076 mm per SD; $P = 0.009$), but the overall interaction was not significant ($P = 0.109$). This result should therefore be regarded as hypothesis-generating; it may reflect chance, the small subgroup size, residual confounding, or a true association that the study lacked power to confirm.

Several limitations should be considered. First, the cross-sectional design precludes causal inference and cannot capture cumulative glycemic exposure; each marker was measured once. Second, FBS and PPBS measured during or soon after an acute cerebrovascular event may be raised by stress hyperglycemia [26], which would weaken their relationship with chronic atherosclerosis; HbA1c is less affected. Third, cerebrovascular presentation was classified clinically rather than by etiological subtype (e.g., TOAST) [27], so large-artery, small-vessel and cardioembolic mechanisms were combined. Fourth, plaque data were unavailable for 57 of the 384 patients with INF, TIA or ICH (14.8%), and analyses were restricted to complete cases, which could introduce bias if data were not missing at random. Fifth, glucose-lowering and lipid-lowering treatments, which may influence both glycemic indices and carotid structure, were not included as covariates. Finally, the single-centre setting, the small ICH and non-cerebrovascular groups and the absence of an a priori sample size calculation limit statistical power and generalizability.

In summary, HbA1c, FBS and PPBS did not independently explain cIMT or plaque burden once conventional vascular risk factors were considered, and no glycemic marker emerged as superior. This contrasts with several community-based and early-dysglycemia studies reporting positive glycemia–cIMT associations [8,23,24,28], and may reflect the smaller incremental contribution of current glycemic measurements in older patients with established vascular disease and multiple competing risk factors. The clearest finding was the higher prevalence of focal carotid plaque, particularly ICA plaque, in completed infarction than in TIA, consistent with advanced imaging studies showing greater plaque burden and vulnerability in stroke [19,25].

CONCLUSION

In this cross-sectional cerebrovascular cohort, HbA1c, FBS and PPBS were not independently associated with mean or maximum cIMT or with carotid plaque after adjustment for major vascular risk factors, and none improved the identification of plaque beyond clinical variables. Carotid plaque, particularly ICA plaque, differed significantly across cerebrovascular presentations and was most frequent in ischemic infarction compared with TIA, whereas mean cIMT did

not distinguish between INF, TIA and ICH. Diffuse wall thickening and focal plaque therefore appear to represent distinct vascular phenotypes, and carotid plaque characterization may offer greater clinical discrimination than a single glycemic measurement in established cerebrovascular disease. Prospective studies using longitudinal glycemic indices, etiological stroke classification and advanced plaque imaging are warranted.

DECLARATIONS

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: De-identified data may be made available by the corresponding author upon reasonable request, subject to institutional and ethical approval.

AI transparency statement: The artificial intelligence system evaluated in this study was used for acoustic voice classification. No generative AI system was used to generate or modify the study data.

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