Cardiovascular Diabetology

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Association between the GMI/HbA1c ratio and preclinical carotid atherosclerosis in type 1 diabetes: impact of the fast-glycator phenotype across age groups

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Abstract

Background Since the arrival of continuous glucose monitoring (CGM), the relationship between the glucose management indicator (GMI) and HbA1c has been a topic of considerable interest in diabetes research. This study aims to explore the association between the GMI/HbA1c ratio and the presence of preclinical carotid atherosclerosis in type 1 diabetes (T1D).

Methods Individuals with T1D and no prior history of cardiovascular disease were recruited from two centers. Carotid ultrasonography was performed using a standardized protocol and carotid plaques were defined as intima-media thickness ≥ 1.5 mm. CGM-derived data were collected from a 14-day report. A GMI/HbA1c ratio < 0.90 was selected to identify "fast-glycator" phenotype.

Results A total of 584 participants were included (319 women, 54.6%), with a mean age of 48.8 ± 10.7 years and a mean diabetes duration of 27.5 ± 11.4 years. Carotid plaques were present in 231 subjects (39.6%). Approximately 43.7% and 13.4% of participants showed absolute differences of ≥ 0.5 and ≥ 1.0 between 14-day GMI and HbA1c, respectively. Among patients ≥ 48 years, the fast-glycator phenotype was independently associated with presence of plaques (OR 2.27, 95%CI: 1.06–4.87), even after adjusting for non-specific and T1D-specific risk factors and statin treatment. No significant association was observed in younger subjects (p for interaction < 0.05).

Conclusions Fast-glycator phenotype is independently associated with atherosclerosis in T1D individuals aged ≥ 48 years, suggesting an age-related increase in the glycation risk. These findings highlight the potential of the GMI/HbA1c ratio for cardiovascular risk stratification in this population.

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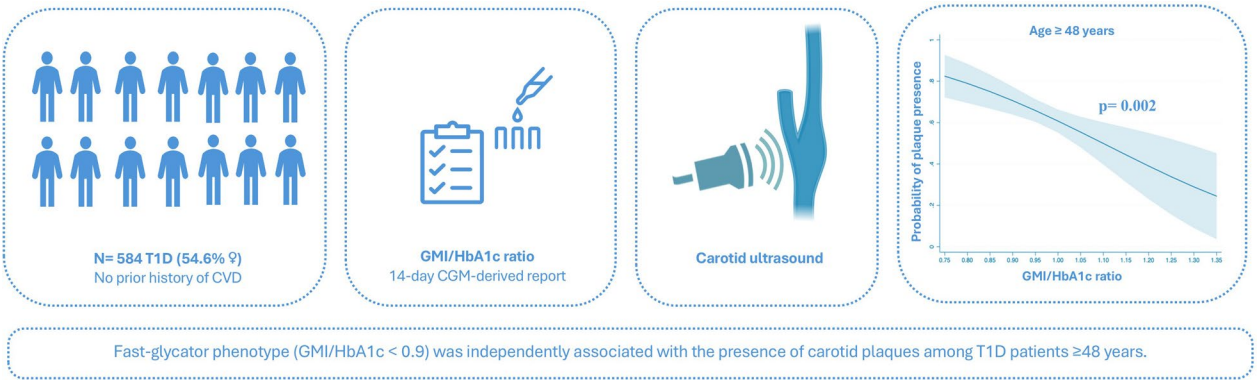
Graphical abstract



Keywords Carotid atherosclerosis, Type 1 diabetes, Glucose Management Indicator, Hemoglobin glycation

Background

Type 1 diabetes (T1D) is a chronic disease associated with an increased cardiovascular risk, making glycemic control essential for preventing both microvascular and macrovascular complications [1, 2]. Glycated hemoglobin (HbA1c), expressed as the percentage of adult hemoglobin that is glycated, reflects the average blood glucose level over the past two to three months [3]. Traditionally, HbA1c has been the gold standard for assessing long-term glycemic control in diabetes, and a wealth of epidemiological evidence supports a good correlation between HbA1c levels and the risk of long-term complications [1, 2, 4]. However, the emergence of continuous glucose monitoring (CGM) has revealed limitations in HbA1c testing. While CGM provides insights into daily fluctuations of glucose, it can also be used to calculate the Glucose Management Indicator (GMI), representing an estimation of HbA1c calculated exclusively from CGM data and being proposed as a substitute for laboratory-measured HbA1c [5].

GMI uses the same scale (% or mmol/mol) as HbA1c but usually is based on short-term (14-days) average glucose values, rather than long-term glucose exposure, making evident that estimated HbA1c and laboratory HbA1c values can differ widely. The GMI/HbA1c ratio provides insight into the discrepancy between observed and expected glycation, potentially revealing interindividual differences in hemoglobin glycation rates [6]. This discrepancy could provide additional insights into cardiovascular risk stratification, especially since evidence suggests that individuals with higher levels of glycation may have increased cardiovascular risk [7–9] and, more particularly, a higher incidence of carotid atherosclerotic disease [10, 11].

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in individuals with T1D [12, 13]. Carotid intima-media thickness (IMT) and the presence of carotid plaques are established markers of subclinical atherosclerosis and important predictors of future cardiovascular events [14]. The use of carotid ultrasound enables the identification of atherosclerosis in its early stages and has proven to be a valuable tool in assessing cardiovascular risk in T1D [15, 16] prompting clinicians to enhance cardioprotective treatments [17]. Therefore, understanding and targeting the pathological processes and early markers of preclinical atherosclerosis in T1D subjects is critical for an early detection.

The present work aims to explore the association between the GMI/HbA1c ratio and the presence of preclinical carotid atherosclerosis in a well-defined cohort of subjects with T1D. By examining the GMI/HbA1c ratio, we aimed to assess whether this marker can improve cardiovascular risk stratification beyond traditional metrics like HbA1c alone.

Methods

Study population

This cross-sectional study was performed in 2 university hospitals (Hospital Mútua Terrassa and Hospital Clínic de Barcelona), both situated in the north-northeast region of Spain. Inclusion criteria were T1D aged > 18 years confirmed by clinical records, use of CGM, available HbA1c data and absence of known CVD (coronary heart disease, stroke, peripheral artery disease or heart failure). For T1D from Hospital Clinic de Barcelona, additional inclusion criteria were: (a) age ≥ 40 years; (b) presence of any stage of diabetic kidney disease (DKD), irrespective of age or diabetes duration; and/or c) ≥ 10 years of duration of T1DM with at least one additional CVD risk factor (defined as either any of the following: retinopathy, family history of premature CVD in first degree relatives (defined as any CVD occurring < 55 years

in men and < 65 years in women), active smoking habit, hypertension, low high-density lipoprotein cholesterol (HDL-cholesterol; < 40 mg/dL in males, < 45 mg/dL in females), triglycerides > 150 mg/d, the presence of severe hypoglycemia events or hypoglycemia unawareness, and women with a history of preeclampsia/eclampsia in at least one pregnancy). Individuals with concomitant diseases, conditions, or treatments that could affect HbA1c (e.g., anemia) were excluded from the study.

Study visit

All the participants were invited to attend a single visit for physical examination and ascertainment of inclusion criteria. Lifestyle factors, including smoking habit (current, former, or never smoker), T1D duration and type of insulin regimen (multiple daily injection [MDI] or continuous subcutaneous insulin infusion [CSII]) were documented. Additionally, the use of cardiovascular treatments, such as antiplatelet, antihypertensive (Angiotensin Converting Enzyme Inhibitors [ACEI] and Angiotensin Receptor Blockers [ARBs]) or lipid-lowering medications, was also recorded. Hypertension was defined as the use of antihypertensive drugs or repeated clinical systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg [18, 19]. DKD was defined as an albumin-to-creatinine ratio ≥ 30 mg/g (confirmed on at least two of three consecutive determinations) and/or estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73m^2. Diabetic retinopathy was diagnosed by Fundus Oculi and it was always confirmed by an ophthalmologist. Anthropometric measurements were recorded as follows: patients were weighed wearing light clothing and without footwear, using calibrated scales accurate to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm. Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). BP was measured in the supine position with a blood pressure monitor (Omron HEM-7223-E; Hoofddorp, The Netherlands) after a brief period of rest (3-minute seated rest before measurement). BP was measured twice, and the average was used for analyses.

Biochemistry

Information about biochemistry, such as HbA1c, eGFR, creatinine and albuminuric status, was obtained with standardized methods, and collected from electronic records. HbA1c was measured by high-performance liquid chromatography (Tosoh G8 Automated HPLC Analyzer; Tosoh Bioscience, South San Francisco, CA).

Continuous glucose monitoring

The CGM-derived data was collected from ambulatory glucose profile report generated for the 14 days preceding the laboratory analysis. Mean glucose, glucose variability (expressed as coefficient of variation [CV]), GMI, Time Below Range (TBR), Time In Range (TIR), Time Above Range (TAR) and percentage of time in each glucose range (< 54, 54–70, 180–250 and > 250 mg/dL, respectively) were recorded [20]. The majority of the individuals were using FreeStyle Libre 2® (n = 446, 76.4%), with a minority on Dexcom G6 or Guardian 3 (23.6%).

GMI/HbA1c ratio

This ratio was obtained by dividing the 14-day GMI by the actual HbA1c measured in the laboratory. A lower ratio is indicative of a GMI lower than what would be expected based on the HbA1c, suggesting a higher degree of hemoglobin glycation for a given level of glycemic exposure. Following previous studies, a cut-off of < 0.9 was selected for select those patients with higher glycation (i.e., fast-glycation phenotype) [21].

Carotid B-mode ultrasound imaging

A bilateral carotid artery B-mode ultrasound was conducted to assess the presence of plaques during a single visit, adhering to a previously described standardized protocol [22]. The ultrasound systems used were the Acuson X700 (Siemens) and Aplio a450 (Canon) at Hospital Clínic de Barcelona and the Logic P9 (General Electrics) at Hospital Mútua Terrassa. Carotid plaques were identified using both B-mode and color Doppler examinations in both longitudinal and transverse planes to detect circumferential asymmetry. Carotid plaques (in the bulb, internal, or common carotid arteries) were defined as focal wall thickenings that protruded into the arterial lumen by at least 50% of the surrounding IMT value or had a thickness of at least 1.5 mm, measured from the media-adventitia interface to the intima-lumen surface [23].

Statistical analysis

Data are presented as median and 25th and 75th percentiles, mean ± standard deviation (SD) or number (percentage). The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Between-group differences in clinical, laboratory and treatment variables were evaluated using the Chi squared test for categorical variables, the Mann–Whitney test for continuous nonnormally distributed variables, or the unpaired Student's t test for continuous normally distributed variables. Associations between GMI and HbA1c were assessed with Spearman correlation analysis. Logistic regression models were employed to evaluate the independent association between the GMI/HbA1c ratio and the presence of carotid plaque (dependent variable), adjusting for potential confounders. All the models included the GMI/A1c ratio (either continuous [0.1 increase] or using the cut-off of < 0.9 for identifying

fast-glycator phenotype) and the type of CGM [FreeStyle Libre 2 vs. others]. Two models were constructed: Model 1 (age and sex-adjusted model) and Model 2 (fully-adjusted model: Model 1 + center of origin, low-density lipoprotein cholesterol [LDL-cholesterol] and HDL-cholesterol levels, BMI, systolic BP, statin use, smoking status [non-smoker vs. ex-smoker/never smoker], duration of T1D, type of insulin treatment [MDI/CSII] and the presence of microvascular complications).

Based on previous literature [31], we evaluated the interaction between age (as a continuous variable) and the GMI/HbA1c ratio. The interaction was significant ($p = 0.047$), indicating an age-dependent effect. Marginal effect analysis showed that the association became significant from 35 years. However, the predictive margins plot revealed a shift in the association at approximately 45 years (see Supplementary Fig. 1), aligning with the median age of our sample (48 years), which was used as the stratification cut-off. Therefore, models were applied to the entire cohort and separately for those below and above 48 years.

To further assess the robustness of our analysis and rule out significant confounders, we performed several sensitivity analyses. These included exploring the relationships between the GMI/HbA1c ratio and atherosclerosis stratified by diabetes duration (median 26.9 years) or type of CGM; further adjusting our regression models for triglyceride levels and treatment with ACEI/ARBs (Model 3); replacing the composite variable "microvascular complications" with eGFR and the presence of retinopathy (Model 4); and incorporating the 5-year mean HbA1c as a forced covariate in the regression models.

As an exploratory analysis, we also examined the independent association between the GMI/HbA1c ratio and both eGFR and the presence of retinopathy (as dependent variables), using the same covariates as in Model 2, with the respective dependent variable excluded accordingly. Additionally, we assessed the independent associations of other glycemic metrics (HbA1c, GMI, and TIR) with clinical outcomes (carotid atherosclerosis, eGFR, and retinopathy) using the same Model 2 covariates, while ensuring that the respective dependent variables were excluded from each analysis.

The two-sided significance level was set as $p < 0.05$. All statistical analyses were performed using the SPSS 20.0 statistical package (Chicago, IL) and STATA 14.0 (College Station, TX).

Results

Baseline clinical characteristics of the study population

The study population comprised a total of 584 participants with T1D, of whom 319 (54.6%) were women. The median age at inclusion was 48 years (mean of 48.8 ± 10.7 years), and the mean duration of diabetes was 27.5 ± 11.4 years. Regarding glycemic-related variables, the mean HbA1c was 7.3 ± 0.9%, and the GMI was 7.1 ± 0.7%, yielding a mean GMI/HbA1c ratio of 0.98 ± 0.09. The mean glucose level was 158 ± 29 mg/dL, with a CV of 36.2 ± 6.1%, and TIR was 63.5 ± 16.0% (Table 1). Additionally, when the sample was divided according to the median age (48 years), the older group had a significantly higher diabetes duration ($p < 0.001$), a lower GMI/A1c ratio (0.97 vs. 0.99, $p = 0.007$) and a significant higher use of CSII (36.8% vs. 28.9%, $p = 0.041$). Furthermore, these individuals exhibited a significantly greater proportion of hypertension and statin and ACEI/ARBs treatment (35.9% vs. 9.6%, 59.5% vs. 23.4%, and 32.9% vs. 11.6%, respectively, $p < 0.001$, for all comparisons; Supplementary Table 1). Finally, baseline characteristics, including sex distribution, duration of diabetes, and HbA1c levels, and GMI/HbA1c ratio were similar across the two recruiting centers (Supplementary Table 2).

Preclinical carotid atherosclerosis

Preclinical atherosclerosis was identified in 231 participants (39.6%). Supplementary Table 3 displays the characteristics of patients grouped by the presence of carotid plaque. Subjects with plaques were predominantly males (52.4% vs. 40.8%), older (55.8 vs. 44.2 years) and had a longer duration of diabetes (31.1 vs. 25.1 years; $p < 0.001$ for all comparisons). These individuals also had significantly higher HbA1c (7.5% vs. 7.1%), and GMI (7.25% vs. 7.0%), whereas GMI/HbA1c ratio was significantly lower (0.97 vs. 0.99; $p < 0.05$ for all). Furthermore, they had higher systolic BP and triglycerides, lower eGFR and a higher prevalence of hypertension and statin and ACEI/ARBs treatment ($p < 0.001$ for all comparisons).

Differences between GMI and HbA1c

In the overall cohort, there was a strong correlation between GMI and HbA1c (unadjusted r_s=0.682, $p < 0.001$), with an absolute difference of 0.51 ± 0.43%. In Fig. 1 is depicted the histogram of the differences in GMI vs. HbA1c in the entire population (A), and in absolute numbers (B). The vast majority of patients fell within a difference range of -2.0 to + 2.0%, with the peak percentage of patients having a difference less than ± 1.0%. Specifically, approximately 29.3% of patients had differences < -0.5% (HbA1c > GMI), while about 13.2% had differences ≥ + 0.5% (GMI > HbA1c). Notably, 43.7% and 13.4% of the subjects showed absolute differences ≥ 0.5% and ≥ 1.0% between the two different methods, respectively. When the sample was divided according to the cut-off of GMI/HbA1c ratio of 0.90, fast glycators ($n = 95$, 16.3%) only showed higher values of HbA1c, lower eGFR and higher proportion of active smokers ($p < 0.05$ for all comparisons); with no differences in the type of CGM system used, age, sex or other cardiovascular risk factors

Table 1 Baseline characteristics of the total study population and according to the fast-glycation phenotype

Variable	Study population (*N* = 584)	Non-fast glycators (*n* = 489)	Fast glycators (*n* = 95)	*p*-value*
Age (years)	48.8 ± 10.7	48.6 ± 10.7	49.9 ± 10.8	0.249
Sex (women)	319 (54.6%)	263 (53.8%)	56 (58.9%)	0.355
Diabetes Duration (years)	27.5 ± 11.4	27.5 ± 11.3	27.7 ± 12.00	0.894
Current smoker	122/581 (21.0%)	94/486 (19.2%)	28 (29.5%)	0.027
Hypertension	132/581 (22.7%)	104/486 (21.4%)	28 (29.5%)	0.086
Microvascular complications				
Retinopathy	206/572 (36.0%)	165/479 (34.4%)	41/93 (44.1%)	0.076
DKD	42/578 (7.3%)	35/484 (7.2%)	7/94 (7.4%)	0.941
BMI (kg/m^2)	26.0 ± 4.5	26.1 ± 4.5	25.8 ± 4.5	0.556
Systolic BP (mmHg)	127 ± 15	126 ± 15	128 ± 154	0.320
HbA1c (%)	7.3 ± 0.9	7.1 ± 0.8	8.2 ± 0.9	< 0.001
Creatinine (mg/dl)	0.87 ± 0.19	0.86 ± 0.17	0.92 ± 0.27	0.013
eGFR (mL/min/1.73m^2)	91.0 ± 15.5	91.9 ± 14.7	86.6 ± 18.3	0.003
Fasting glucose (mg/dl)	150 ± 59	148 ± 58	158 ± 62	0.131
Total cholesterol (mg/dl)	181 ± 32	181 ± 32	181 ± 31	0.984
LDL-cholesterol (mg/dl)	104 ± 27	104 ± 27	101 ± 26	0.258
HDL-cholesterol (mg/dl)	62 ± 15	61 ± 15	63 ± 16	0.299
Triglycerides (mg/dL)	70 (58–91)	70 (57–90)	73 (60–100)	0.194
Albumin-to-creatinine ratio (mg/g)	14.2 ± 98.7	9.9 ± 29.8	36.3 ± 234.6	0.018
CGM related variables				
GMI (%)	7.1 ± 0.7	7.1 ± 0.7	7.0 ± 0.7	0.205
Mean Glucose (mg/dl)	158 ± 29	159 ± 29	156 ± 28	0.386
Coefficient of Variation (%)	36.2 ± 6.1	36.1 ± 6.1	36.9 ± 6.3	0.236
Time < 54 mg/dL (%)	0.7 ± 1.3	0.7 ± 1.2	1.0 ± 1.8	0.042
Time 54–70 mg/dL (%)	3.8 ± 3.5	3.7 ± 3.3	4.3 ± 4.2	0.183
TIR (%)	63.5 ± 16.0	63.2 ± 16.2	64.7 ± 14.9	0.394
Time 180–250 mg/dL (%)	22.3 ± 9.3	22.5 ± 9.3	21.2 ± 9.3	0.215
Time > 250 mg/dL (%)	9.3 ± 10.3	9.4 ± 10.6	8.5 ± 9.1	0.416
GMI/HbA1c Ratio	0.98 ± 0.09	1.01 ± 0.07	0.86 ± 0.04	< 0.001
Statin use	240/580 (41.4%)	195/485 (40.2%)	45 (47.4%)	0.195
ACEI/ARBs use	130 (22.3%)	105 (21.5%)	25 (26.3%)	0.299
CSII	190/579 (32.8%)	159/484 (32.9%)	31 (32.6%)	0.967
FSL2 users	446 (76.0%)	371 (75.9%)	75 (78.9%)	0.518
Presence of carotid plaques (yes)	231 (39.6%)	186 (38.0%)	45 (47.7%)	0.089

Results are expressed in mean ± standard deviation or median (25th -75th percentile) for continuous variables, and n (%) or n/N (%) in case of missing data for categorical variables. *p value between non-fast glycators and fast glycators. ACEI: Angiotensin Converting Enzyme Inhibitors. ARBs: Angiotensin Receptor Blockers. BMI: Body Mass Index. BP: Blood Pressure. CGM: Continuous Glucose Monitoring. CSII: Continuous Subcutaneous Insulin Infusion. DKD: Diabetic Kidney Disease. eGFR: estimated Glomerular Filtration Rate. GMI: Glucose Management Indicator. HbA1c: glycated hemoglobin. HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein. TIR: Time In Range

(Table 1). Specifically, GMI/HbA1c ratio and the absolute differences between these two variables were similar between FreeStyle Libre users vs. users of other CGM systems (0.98 ± 0.09 vs. 0.99 ± 0.08, $p = 0.374$; and 0.53 ± 0.44 vs. 0.46 ± 0.37, $p = 0.087$; respectively), and between CSII vs. MDI (0.98 ± 0.08 vs. 0.98 ± 0.09; $p = 0.510$; and 0.51 ± 0.40 vs. 0.52 ± 0.44, $p = 0.788$; respectively).

Association between GMI/HbA1c ratio and preclinical carotid atherosclerosis

In the entire cohort, individuals harboring carotid plaques showed a lower non-adjusted GMI/HbA1c ratio (0.97 ± 0.09 vs. 0.99 ± 0.08; $p = 0.030$; Supplementary Table 3). However, in fully-adjusted models, when confounders were taken into account (logistic regression analysis), these relationships were blunted (OR 0.85 [0.65–1.1], $p = 0.208$ and 1.44 (0.91–2.55), $p = 0.210$; for 0.1 increase in the ratio (Supplementary Table 4) and fast-glycation phenotype (Table 2), respectively. Although no significant interaction was observed with sex ($p = 0.075$), a significant interaction was found with age ($p < 0.05$). Whereas the probability of harboring plaques was not significantly associated with GMI/HbA1c ratio in those < 48 years ($p = 0.065$), there was a significant association in those ≥ 48 years ($p = 0.002$; Fig. 2), even after accounting for potential confounders. Similarly, only older patients (≥ 48 years) showed a significant association between GMI/HbA1c ratio and carotid plaque, either in age and sex-adjusted models (OR 0.61 [0.44–0.83]) and in fully-adjusted models (OR 0.59 [0.42–0.83]) for 0.1 increase in the ratio (Supplementary Table 4); $p < 0.05$ for all the comparisons. This association was also significant for fast-glycation phenotype in sex-adjusted (OR 2.04 [1.03–4.05]) and in fully-adjusted models (OR 2.27 [1.06–4.87]) (Table 2); $p < 0.05$ for all the comparisons. Further adjustment for ACEI/ARBs treatment and triglyceride levels (Model 3), as well as replacing "microvascular complications" with eGFR and retinopathy (Model 4), yielded consistent results (OR 2.21 [1.02–4.77] and 2.20 [1.01–4.79], respectively; $p < 0.05$ for both; Supplementary Table 5).

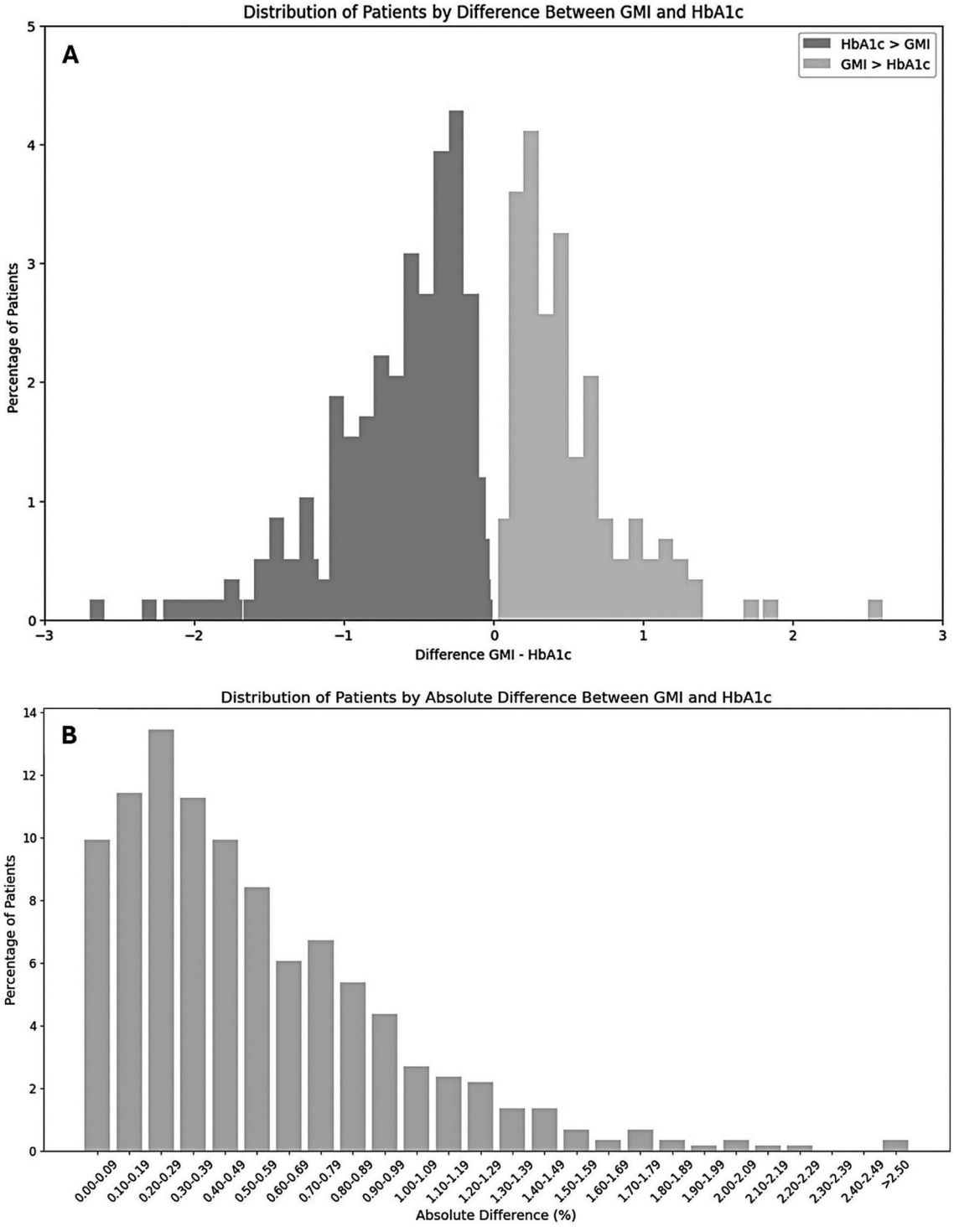


Fig. 1 Distribution of patients by difference and absolute difference between GMI and HbA1c values (%). **A**: The figure illustrates the distribution of patients based on the difference between their 14-day GMI and HbA1c levels. The x-axis represents the difference between GMI and HbA1c. The y-axis shows the percentage of patients in the overall cohort within each difference category. Bars on the left represent patients with HbA1c values greater than GMI (HbA1c > GMI), while bars on the right represent those with GMI values greater than HbA1c (GMI > HbA1c). Patients with the same HbA1c and GMI values have been excluded. **B**: The graph is a visual representation of the distribution of patients based on the absolute difference between GMI and HbA1c values (%). GMI: Glucose Management Indicator. HbA1c: glycated hemoglobin

Table 2 Association between glycation phenotypes and the presence of carotid plaques. Logistic regression models comparing age groups and the whole sample

	GMI/HbA1c ratio	Presence of plaques (n/N (%))	Age and sex-adjusted model		Fully-adjusted model	
			OR (95%CI)	p-value	OR (95%CI)	p-value
Whole sample ($n=584$)	Non-fast glycators	186/489 (38)	1 (Ref)	---	1 (Ref)	---
	Fast glycators	45/95 (47.4)	1.37 (0.81–2.33)	0.244	1.44 (0.91–2.55)	0.210
< 48 years ($n=292$)	Non-fast glycators	43/249 (17.3)	1 (Ref)	---	1 (Ref)	---
	Fast glycators	7/43 (16.3)	0.95 (0.39–2.32)	0.907	0.81 (0.30–2.23)	0.689
≥ 48 years ($n=292$)	Non-fast glycators	143/240 (59.6)	1 (Ref)	---	1 (Ref)	---
	Fast glycators	38/52 (73.1)	2.04 (1.03–4.05)	0.041	2.27 (1.06–4.87)	0.036

Odds ratio (OR) and 95% confidence intervals (CI) are reported

All the models were adjusted for the type of continuous monitoring system used (FreeStyle Libre 2 vs. others)

Fully adjusted model: age, sex, center of origin, LDL-cholesterol, HDL-cholesterol levels, BMI, systolic BP, statin use, smoking status [non-smoker vs. ex-smoker/never smoker], duration of T1D, type of insulin treatment [MDI/CSII] and the presence of microvascular complications. BMI: Body Mass Index. BP: Blood Pressure. CSII: Continuous Subcutaneous Insulin Infusion. GMI: Glucose Management Indicator. HbA1c: glycated hemoglobin. HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein. MDI: Multiple Daily Injection

Additional analyses were performed to assess whether the observed association between the GMI/HbA1c ratio and carotid atherosclerosis was primarily influenced by age or diabetes duration. Importantly, diabetes duration was not independently associated with carotid atherosclerosis in the fully adjusted models ($p>0.280$ across all analyses). To further investigate this aspect, the analysis was stratified by the median diabetes duration (26.9 years) and median age (48 years). As shown in Supplementary Table 6, the results confirmed that the association between the GMI/HbA1c ratio and carotid plaque presence was significant only in participants aged ≥ 48 years, regardless of diabetes duration (OR 0.47 [0.25–0.90] and 0.64 [0.44–0.93]; for diabetes duration < 26.9 and ≥ 26.9 years, respectively; $p<0.05$ for both). Additionally, the results were not affected by the type of CGM used (p for interaction = 0.653). When the analysis was restricted to Freestyle Libre 2® users ($n=446$), the association with the fast-glycation phenotype lost significance, likely due to the reduced sample size. Nonetheless, the GMI/HbA1c ratio remained inversely associated with carotid atherosclerosis in participants aged ≥ 48 years (OR 0.61 [0.42–0.88], $p=0.008$ in fully adjusted models; Supplementary Tables 7 and 8).

A final analysis included the adjustment for the mean 5-years HbA1c (as a proxy of diabetes exposure) in a subset of $n=517$ participants. Given the strong correlations of this variable with HbA1c, GMI, and the GMI/HbA1c ratio (rs = 0.764, rs = 0.525, and rs=-0.43, respectively), its inclusion in the multivariate models attenuated most associations. However, the inverse association between the GMI/HbA1c ratio and carotid atherosclerosis remained significant only in individuals aged ≥ 48 years (0.68 [0.46–0.99], $p=0.048$; Supplementary Tables 9 and 10).

Association of glycemic metrics with clinical outcomes

In the fully adjusted models, GMI/HbA1c ratio was independently associated with eGFR (β = 0.078; $p=0.037$), but not with diabetic retinopathy (OR 0.20 [0.02–2.71], $p=0.228$). We further examined the associations of HbA1c, GMI, and TIR with key clinical outcomes, including retinopathy, eGFR, and carotid atherosclerosis, stratified by age groups (< 48 years and ≥ 48 years). The results showed significant associations between all three glycemic metrics and retinopathy: a direct association with HbA1c and GMI (OR 1.83 [1.43–2.34] and 2.30 [1.64–3.23], respectively) and an inverse association with TIR (OR 0.97 [0.96–0.98]), with no significant differences by age group. Regarding carotid plaque presence, significant associations were observed only with HbA1c and GMI, particularly in older individuals (≥ 48 years; OR 2.19 [1.49–3.23] and 1.68 [1.06–2.67], respectively). No significant associations were found between any glycemic metrics and eGFR. These findings are detailed in Supplementary Table 11.

Discussion

In our cohort of patients with T1D at primary prevention, we found an independent association between the GMI/HbA1c ratio and preclinical carotid atherosclerosis, even after adjusting for classical and T1D-specific CVD risk factors and statin treatment. Specifically, this association was only observed in those individuals over 48 years, suggesting an age-dependent association between this glycation proxy and atherosclerosis among this population. To the best of our knowledge, this is the first study to evaluate the association between the GMI/HbA1c ratio (as a marker of glycation index) and the presence of preclinical carotid atherosclerosis (a proxy of future CVD events) in individuals with T1D.

Our study brings attention to important discrepancies in glycemic control as assessed by GMI and HbA1c. A substantial proportion of the study population exhibited

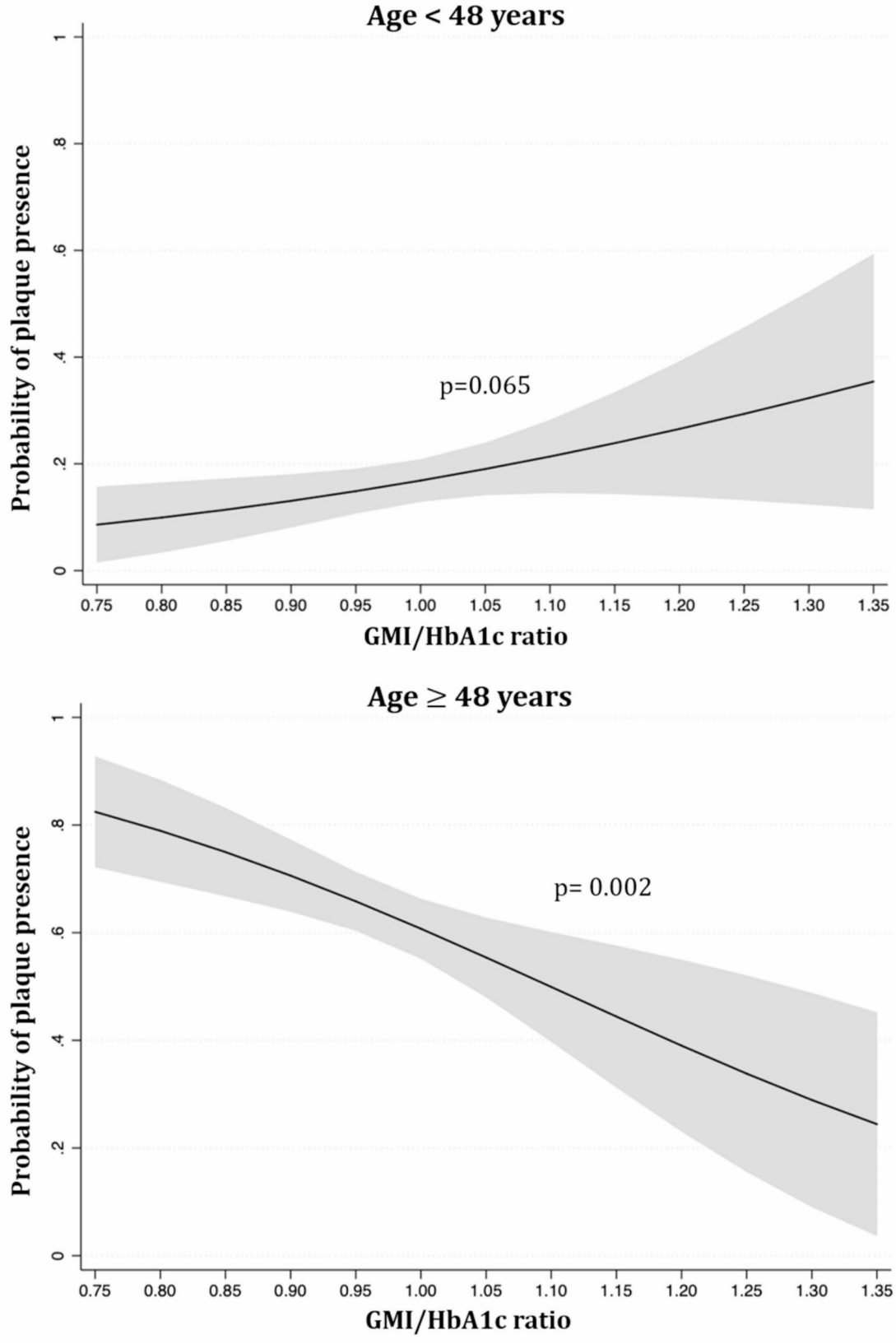


Fig. 2 (See legend on next page.)

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Fig. 2 Probability of plaque presence according to GMI/HbA1c ratio and stratifying for age. Model was adjusted for center, gender, LDL- and HDL-cholesterol, BMI, systolic BP, statin treatment, smoking status, duration of diabetes, type of insulin treatment, CGM system, and the presence of microvascular complications (retinopathy and DKD). Dark line: mean probability; Grey area: 95% confidential interval. BMI: Body Mass Index. BP: Blood Pressure. CGM: Continuous Glucose Monitoring. DKD: Diabetic Kidney Disease. GMI: Glucose Management Indicator. HbA1c: glycated hemoglobin. HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein

significant differences between these two metrics, with roughly one out of two of the individuals showing a discrepancy ≥ 0.5%. Other authors have reported similar discrepancies in real-world studies including T1D subjects [24–26]. Perlman et al. concluded that chronic kidney disease (CKD) was the only comorbidity to have a significant effect on this discordance [24]. This finding was confirmed in a recent study conducted specifically on patients with diabetes, the majority of whom with T1D, both with and without CKD, reporting a significantly more pronounced differences in the CKD group [27]. This aspect has not been specifically explored in our study, given that the majority of our patients had a normal kidney function, and only a minority had DKD. However, consistent with these previous studies and others [28], one of the few variables that showed differences based on fast-glycation phenotype was kidney function, with lower eGFR values observed in patients with a lower ratio (Table 1). Additionally, it seems that discrepancies between GMI and HbA1c can vary significantly depending on the type of CGM sensor used, with GMI-HbA1c differences being higher in users of intermittent scanning comparted with real time CGM [25]. Nonetheless, in our sample, no differences were observed in the GMI/HbA1c ratio or the absolute differences between these two variables based on the CGM system used, nor the type of insulin delivery method (CSII vs. MDI).

Although blood glucose concentration is the primary determinant of HbA1c, it is an indirect measure of hyperglycemia. The discrepancy between HbA1c and GMI may be influenced by various nonglycemic factors, such as differences in red blood cell turnover, hemoglobin variants, and short-term variations in glucose exposure [29]. Higher glycemic variability, however, also does not seem to entirely explain this difference, since GMI does not accurately estimate HbA1c in healthy individuals without diabetes, who would be expected to have lower glycemic variability [30]. Similarly, in individuals with a fast-glycation phenotype, we did not find any differences in CV either. Furthermore, previous studies have reported that the likelihood of having a higher HbA1c than estimated HbA1c (i.e., GMI) increases with age and female gender [31]. Although there were no between-sex differences in our cohort, the GMI/HbA1c ratio was significantly lower (i.e., showing a higher glycation index) in individuals older than 48 years.

In our cohort, we identified a significant age-dependent relationship between the glycation index (GMI/HbA1c ratio) and preclinical carotid atherosclerosis, but found no association with microvascular complications. While this dichotomy between classical microvascular and macrovascular diabetic complications may seem surprising, these relationships are far from being firmly established. For instance, although a small cross-sectional study ($n = 52$) reported that individuals with T1D whose HbA1c levels were higher than their estimated HbA1c (i.e., a lower GMI/HbA1c ratio) had an increased risk of microvascular complications [32], larger studies, such as the Diabetes Control and Complications Trial cohort, did not confirm these findings [33]. Moreover, a study involving 2,721 adults with T1D from the United Kingdom also found no association between this ratio and proliferative diabetic retinopathy [34]. Similarly, our findings align with a recent small cross-sectional study ($n = 135$) in which the association between a fast-glycation phenotype and microvascular complications disappeared after adjusting for potential confounding factors, leaving only a direct link with a composite of macrovascular manifestations (e.g., history of myocardial infarction, stroke, transient ischemic attack, or symptomatic peripheral arterial disease; revascularization of coronary, cerebral, or peripheral arteries; coronary stenosis > 50%, carotid atherosclerotic plaques, or an ankle-brachial index < 0.9) [21]. Therefore, more studies, including the present one, are needed to clarify the relationship between the GMI/HbA1c ratio and chronic diabetic complications in T1D, and to determine whether a true discrepancy exists between microvascular and macrovascular complications in this population.

A possible explanation for our findings is a greater exposure to glucose-induced vascular damage. Hyperglycemia can result in the glycation of various proteins, which undergo a series of reactions that ultimately lead to the formation of advanced glycation end products (AGEs). In this context, the fast-glycator phenotype has also been previously associated with higher levels of AGEs [21]. AGEs are involved in several stages of atheromatous plaque formation, including the promotion of monocyte migration, glycation of lipoproteins that enhances their recognition by macrophages, and the increased production of inflammatory cytokines, among others [35]. Thus, the level of skin AGEs has been shown to predict the risk of 10-year progression of diabetic retinopathy and nephropathy in T1D [36] and have been independently associated with macrovascular complications among T1D individuals [21]. However, the

age-dependent disparity observed in our study is particularly significant, highlighting the crucial role that age may play in the pathophysiological processes linking glycation to vascular damage. This could be due to an age-dependent decline in antioxidant capacity, combined with the cumulative exposure to hyperglycemia over time, leading to greater vascular damage in older individuals with T1D [37].

Our study had some limitations that should be considered when interpreting our findings. First, the cross-sectional design limits our ability to infer causality. While our results indicate significant associations, larger longitudinal studies are needed to confirm these relationships and explore potential causal mechanisms. Furthermore, factors such as sensor signal drifts or motion artifacts, which were not directly assessed, may have influenced the GMI/HbA1c ratio. Second, the study population was drawn from two specific centers and with a population primarily caucasian, which may limit the generalizability of the findings, and future research should aim to validate these findings in larger, more diverse populations. Furthermore, the use of different inclusion criteria for participants from the two recruiting centers may also have introduced heterogeneity that could influence the generalizability of our findings. Third, we used CGM data from the 14 days preceding the laboratory analysis, instead of a 90-day report. Although a 90-day CGM report would better reflect the glycemic period corresponding to the HbA1c measurement, we opted to use the 14-day data as it is the standard practice in daily clinical routines and has demonstrated to be sufficient for an HbA1c estimation [20, 38]. Furthermore, the strength of our data is supported by the fact that many of the factors previously associated with a greater discrepancy between GMI and HbA1c, such as kidney function and age [24, 27, 31, 39], were also identified in our study. Fourth, in our study we utilized the GMI, a linear transformation of mean glucose, as the key CGM metric for comparing to laboratory HbA1c. However, it is important to acknowledge that some experts have raised concerns about the reliability of GMI as a substitute for HbA1c, suggesting that clinical practice should increasingly rely on direct CGM metrics, such as mean glucose and TIR, rather than on GMI [40]. Finally, we lacked reliable data on the presence of diabetic neuropathy, despite its relevance as a prognostic marker of CVD, particularly in the case of cardiovascular autonomic dysfunction [41, 42]. Possible strengths should also be mentioned, since our study stands as one of the most extensive evaluations of the relationship between CGM metrics and HbA1c in a "real-life" cohort of T1D subjects, enhancing the relevance and applicability of our findings to everyday clinical settings. Furthermore, the robustness of our results also lies in the assessment of carotid plaque, an independent predictor of CVD events [43], and the inclusion of major confounders in multivariate analyses.

Conclusions

In conclusion, our study demonstrates an independent association between a lower GMI/HbA1c ratio (indicative of higher glycation relative to glucose levels) and the presence of preclinical carotid atherosclerosis, particularly in T1D patients over 48 years. These discrepancies align with recent studies [44], highlighting the importance of assessing both GMI and HbA1c together in clinical practice to determine whether a patient is a 'high glycator' or 'low glycator'. Consequently, incorporating the GMI/HbA1c ratio into routine assessments could provide a more nuanced understanding of a patient's glycation profile, especially in individuals with longstanding T1D, where such discrepancies may be more pronounced [31]. Our findings support the hypothesis that 'high glycators' are at an increased risk of atherosclerotic disease, reinforcing the potential value of the GMI/HbA1c ratio as an additional tool for identifying patients at higher risk, beyond traditional markers such as HbA1c alone. However, further prospective studies are needed to clarify the clinical relevance of these findings and to confirm these age-dependent associations.

Abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitors
AGEs	Advanced Glycation End-products
ARBs	Angiotensin Receptor Blockers
BMI	Body Mass Index
BP	Blood Pressure
CGM	Continuous Glucose Monitoring
CKD	Chronic Kidney Disease
CV	Coefficient of Variation
CVD	Cardiovascular Disease
CSII	Continuous Subcutaneous Insulin Infusion
DKD	Diabetic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
GMI	Glucose Management Indicator
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
IMT	Intima-Media Thickness
LDL	Low-Density Lipoprotein
MDI	Multiple Daily Injection
OR	Odds Ratio
SD	Standard Deviation
T1D	Type 1 Diabetes
TAR	Time Above Range
TBR	Time Below Range
TIR	Time In Range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02637-4.

Supplementary Material 1: Supplemental Material corresponding to "Association between the GMI/HbA1c ratio and preclinical carotid atherosclerosis in type 1 diabetes: impact of the fast-glycator phenotype across age groups." Description: This file contains 11 supplementary tables. The tables provide detailed characteristics of the study population based on age group, center of origin, and presence of carotid plaques. Several logistic

regression models assess the relationship between the GMI/HbA1c ratio and carotid atherosclerosis, considering various factors such as the use of continuous glucose monitoring systems or microvascular complications. Additionally, sensitivity analyses were performed to explore the impact of diabetes duration, as well as the relationship between glycemic metrics (HbA1c, GMI, and TIR) and key clinical outcomes such as eGFR, retinopathy, and carotid atherosclerosis. Furthermore, additional logistic regression models include the mean 5-year HbA1c to evaluate its influence on the association between glycation phenotypes and carotid plaque presence, with analyses stratified by age groups. The supplementary figure illustrates the probability of plaque presence as a function of age and GMI/HbA1c ratio.

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Author contributions
All authors have discussed the results and commented on the final version of the manuscript. AM, MGi, MGr, BB, CV, CQ, TS-N, VP, IV, IC and AJA acquired and processed all clinical data; AJA, CV and VP performed the US measurements; CP-J, VP and AJA contributed to data analysis and interpretation, wrote, reviewed and edited the manuscript. CP-J, AJA and VP contributed to the study concept and design. MGi, VP, J-A-B-C, IV, IC and AJA supervised the study and participated in data analysis and interpretation. CP-J, VP and AJA wrote the manuscript, designed the figures and had final responsibility for the decision to submit for publication. VP and AJA are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was conducted according to the principles of the Declaration of Helsinki and approved by hospital Research Ethics Committee (HCB/2017/0977 and HCB/2022/0473). All the participants signed written informed consent forms.

Competing interests
The authors declare no competing interests.

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