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Evaluation of the Relationship Between Macrovascular Complications and Hemoglobin Glycation Index (HGI) in Patients with Type 2 Diabetes Mellitus

Tip 2 Diyabetli Hastalarda Makrovasküler Komplikasyonlar ile Hemoglobin Glikasyon İndeksi (HGİ) Arasındaki İlişkinin Değerlendirilmesi

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Abstract: The Hemoglobin Glycation Index (HGI) reflects individual differences in hemoglobin glycation beyond mean blood glucose levels and may provide a more accurate assessment of vascular risk in type 2 diabetes mellitus (T2DM). This retrospective cross-sectional study included 391 adults with T2DM who were treated in the internal medicine outpatient clinic of a tertiary hospital between January and December 2024. Patients were categorized based on the presence of macrovascular complications, including coronary artery disease, ischemic stroke, and peripheral artery disease. HGI was calculated as the difference between measured HbA1c and the HbA1c predicted from fasting plasma glucose using the equation Predicted HbA1c = 0.024 × FPG + 3.1. Patients with macrovascular complications had significantly higher HGI values compared to those without (median (IQR): 1.68 (1.31–2.06) vs. 0.48 (0.11–1.14); $p < 0.001$). Receiver operating characteristic (ROC) curve analysis demonstrated a strong discriminative power of HGI for identifying macrovascular complications (AUC = 0.870, 95% CI: 0.833–0.908; $p < 0.001$), with an optimal cutoff value of 1.13 providing 87.6% sensitivity and 74.2% specificity. In multivariate logistic regression analysis, HGI (OR = 6.75, 95% CI: 4.25–10.71; $p < 0.001$), diabetes duration, and urinary albumin-to-creatinine ratio were independent predictors of macrovascular complications, regardless of HbA1c levels and traditional cardiovascular risk factors. These findings suggest that elevated HGI is closely associated with macrovascular complications and may serve as a simple and reliable marker of glycation-related vascular stress, complementing HbA1c in cardiovascular risk assessment for patients with T2DM.

Keywords: Type 2 Diabetes Mellitus; Hemoglobin glycation index; Macrovascular complications; Cardiovascular risk; Glycation variability

Özet: Hemoglobin Glikasyon İndeksi (HGI), ortalama kan şekeri düzeylerinin ötesinde bireyler arası hemoglobin glikasyon farklılıklarını yansıtır ve tip 2 diyabetes mellitusta (T2DM) vasküler riskin daha doğru değerlendirilmesini sağlayabilir. Bu retrospektif kesitsel çalışmaya, Ocak–Aralık 2024 tarihleri arasında üçüncü basamak bir hastanenin dahiliye polikliniğinde izlenen 391 T2DM'li yetişkin hasta dahil edildi. Hastalar, koroner arter hastalığı, iskemik inme ve periferik arter hastalığı gibi makrovasküler komplikasyonların varlığına göre sınıflandırıldı. HGI, ölçülen HbA1c değeri ile açlık plazma glukozundan (FPG) tahmin edilen HbA1c arasındaki fark olarak hesaplandı (Tahmini HbA1c = 0.024 × FPG + 3.1). Makrovasküler komplikasyonu olan hastalarda HGI değerleri anlamlı olarak daha yüksekti (medyan (IQR): 1.68 (1.31–2.06) vs. 0.48 (0.11–1.14); $p < 0.001$). HGI'nin makrovasküler komplikasyonları öngörmedeki ROC eğrisi altındaki alanı 0.870 (95% GA: 0.833–0.908; $p < 0.001$) olup, 1.13 kesim değeri %87.6 duyarlılık ve %74.2 özgüllük sağladı. Çok değişkenli lojistik regresyon analizinde HGI (OR = 6.75, %95 GA: 4.25–10.71; $p < 0.001$), diyabet süresi ve idrar albümin/kreatinin oranı HbA1c düzeylerinden ve geleneksel kardiyovasküler risk faktörlerinden bağımsız olarak makrovasküler komplikasyonların bağımsız belirleyicileri olarak saptandı. Bu bulgular, yüksek HGI'nin makrovasküler komplikasyonlarla yakından ilişkili olduğunu göstermekte ve HGI'nin, HbA1c'yi tamamlayan, glikasyona bağlı vasküler stresin basit, düşük maliyetli ve klinik olarak anlamlı bir biyobelirteci olabileceğini düşündürmektedir.

Anahtar Kelimeler: Tip 2 Diyabet; Hemoglobin glikasyon indeksi; Makrovasküler komplikasyonlar; Kardiyovasküler risk; Glikasyon değişkenliği

Ethics Committee Approval: The study was approved by the Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (decision date: 02 May 2025, number: E-80929729-000-275250589).

Informed Consent: The authors declared that it was not considered necessary to obtain informed consent from patients because the study was based on retrospective data analysis.

Authorship Contributions: Concept – Ö.Y.; Design – Ö.Y., O.E.; Data Collection or Processing – Ö.Y., Ş.A.Y., M.A.; Analysis or Interpretation – Ö.Y., O.E.; Literature Search – Ö.Y.; Writing – Ö.Y., O.E.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly growing global health problem, currently affecting more than 460 million people worldwide, and the number is projected to exceed 700 million by 2045, mainly due to aging, obesity, and lifestyle changes (1–3). T2DM substantially increases the risk of both microvascular and macrovascular complications; the latter includes coronary artery disease (CAD), ischemic stroke, and peripheral artery disease (PAD), which remain the leading causes of premature morbidity and mortality (4,5).

Glycemic control, traditionally assessed by glycated hemoglobin (HbA1c), plays a central role in diabetes management. HbA1c reflects average blood sugar levels over the past 8–12 weeks and acts as both a diagnostic and therapeutic marker (6). However, HbA1c values are influenced by factors such as red blood cell lifespan, hemoglobin variants, anemia, inflammation, and oxidative stress, which can cause discrepancies between HbA1c and true glycemic exposure (7–9). HbA1c variations exceeding 1% can lead to misclassification of glycemic status. This underscores the need for complementary indices that more accurately reflect true glycemic burden and vascular risk beyond HbA1c alone (9). To address these limitations, Hempe and colleagues proposed the Hemoglobin Glycation Index (HGI), defined as the difference between measured HbA1c and the HbA1c predicted from fasting plasma glucose (FPG) using a population-derived regression equation (10,11). A positive HGI suggests higher-than-expected glycation relative to glucose levels, whereas a negative HGI indicates lower-than-expected glycation. By considering individual differences in glycation efficiency, HGI offers a more individualized assessment of glycemic response.

Emerging evidence suggests that HGI is associated with adverse cardiovascular outcomes in T2DM. In a retrospective cohort of 918 Chinese patients undergoing percutaneous coronary intervention (PCI), those in the highest HGI tertile had a significantly increased risk of major adverse cardiovascular events (MACE) over three years (12). Similarly, Lin et al. reported a U-shaped relationship between HGI quintiles and cardiovascular events in a study of 11,921 patients with angiographically confirmed CAD, showing that both low and high HGI values were linked to increased risk (13). Supporting this non-linear association, a database analysis of 8,055 critically ill diabetic patients demonstrated a significantly higher risk of myocardial infarction in the highest HGI quartile compared with the lowest (14). Additional studies on PCI and acute coronary syndrome cohorts further showed that both abnormally high and low HGI values were associated with increased all-cause mortality and cardiovascular events (15,16).

Beyond coronary disease, HGI has also been associated with other macrovascular outcomes. A multicenter Chinese registry showed that both low and high HGI values were linked to less favorable outcomes after ischemic stroke (17). Likewise, peripheral artery disease, a frequently underdiagnosed yet clinically important macrovascular complication, has been independently associated with elevated HGI values in population-based studies (18). Moreover, increased HGI has been associated with greater carotid intima-media thickness as well as carotid plaque burden, which are surrogate markers of cerebrovascular disease, reinforcing its potential role in arterial remodeling and endothelial dysfunction (19,20). Collectively, these findings suggest that abnormal glycation patterns carry broad vascular implications, underscoring HGI's potential as a systemic marker for cardiovascular risk.

The underlying mechanisms likely differ across the HGI spectrum. Elevated HGI likely reflects enhanced non-enzymatic glycation, which could contribute to the accumulation of advanced glycation end products (AGEs), which promote oxidative stress, inflammation, and endothelial dysfunction pathways that are central to atherosclerosis (21). Conversely, low HGI may indicate shortened RBC lifespan, anemia, or other hematologic alterations that independently contribute to vascular risk (8).

Despite growing research interest, important gaps still exist. Most prior studies have been conducted in PCI registries, intensive care cohorts, or large prospective databases, although evidence in stable outpatient populations remains scarce. Furthermore, there is no consensus on the optimal approach to categorize HGI, with some studies using tertiles or quintiles and others analyzing it as a continuous variable, which complicates comparability across studies and limits clinical translation (11).

This study aimed to investigate the association between the HGI and macrovascular complications in individuals with T2DM, independent of HbA1c and traditional cardiovascular risk factors such as

age, hypertension, dyslipidemia, and diabetes duration. In addition, HGI was evaluated as a continuous variable in an outpatient setting to clarify its potential role as a complementary biomarker for individualized cardiovascular risk stratification.

2. Materials and Methods

2.1. Study Design and Setting

This single-center, retrospective, cross-sectional study was conducted in the internal medicine outpatient clinic of a tertiary care hospital, which functions as a regional referral center for endocrine and metabolic diseases, providing advanced diagnostic and therapeutic services and receiving referrals from surrounding primary and secondary care facilities, and included patients who presented between January 1, 2024, and December 31, 2024. Clinical and laboratory data of adult patients diagnosed with T2DM were retrospectively retrieved from the hospital's electronic medical record system. All personal identifiers were anonymized prior to analysis to ensure patient confidentiality. All procedures complied with the Declaration of Helsinki. The study was approved by the Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (decision date: 02 May 2025, number: E-80929729-000-275250589). As this was a retrospective analysis of anonymized data, the requirement for informed consent was waived by the ethics committee.

2.2. Study Population

The initial cohort comprised 842 adult patients (≥18 years) with a confirmed diagnosis of T2DM based on the 2024 diagnostic criteria of the American Diabetes Association (ADA) (22). After applying predefined inclusion and exclusion criteria, 522 patients were excluded due to missing essential laboratory data, major comorbidities or incomplete clinical documentation. The final analytic sample included 391 patients with complete laboratory data, enabling calculation of the HGI from both FPG and HbA1c values.

Patients were stratified into two groups according to the presence or absence of macrovascular complications. The first group consisted of patients with at least one documented macrovascular event: (i) coronary artery disease, defined as prior myocardial infarction, angiographically confirmed stenosis ≥50%, or a history of percutaneous coronary intervention/coronary artery bypass grafting; (ii) ischemic stroke, diagnosed through neurological assessment and confirmed by neuroimaging; or (iii) peripheral artery disease, diagnosed by an ankle–brachial index <0.9, vascular imaging, or prior limb revascularization. Diagnoses were verified by retrospective review of hospital records, including physician notes, discharge summaries, imaging reports, and procedural documentation. The second group consisted of patients with T2DM but no documented macrovascular complications during the study period. Their disease-free status was confirmed through detailed review of follow-up records and diagnostic test results.

2.3. Exclusion Criteria

Patients with type 1 diabetes, gestational diabetes, pregnancy, hemoglobinopathies, advanced chronic kidney disease (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², calculated using the MDRD equation) (23), chronic liver disease, active malignancy, or hematologic disorders were excluded. Individuals receiving medications known to affect HbA1c (e.g., corticosteroids, chemotherapy, erythropoiesis-stimulating agents) were also excluded. In addition, patients with acute illness, active infection, or hospitalization within the past three months, as well as those with missing or inaccessible essential clinical or laboratory data, were not included in the final analysis.

2.4. Data Collection and Biochemical Measurements

All clinical and laboratory data were retrospectively retrieved from the hospital's electronic medical records. Demographic characteristics, including age, sex, and diabetes duration were recorded. Anthropometric data, such as height and weight, were used to calculate the body mass index (BMI) using the standard formula (weight (kg) / height (m)²). Blood pressure values were obtained from the most recent outpatient visit.

2.5. Calculation of the Hemoglobin Glycation Index

HGI was calculated as the difference between the observed HbA1c and the HbA1c predicted from FPG. Predicted HbA1c values were obtained using a previously validated regression equation reported in the literature (Predicted HbA1c = 0.024 × FPG (mg/dL) + 3.1) (11). Accordingly, HGI was defined as: HGI = Measured HbA1c – Predicted HbA1c (11). This method has been widely applied in clinical studies and provides a standardized approach to quantify interindividual variation in glycation tendency beyond glycemia, thereby enabling its evaluation as a potential predictor of macrovascular complications.

2.6. Outcomes

The primary objective of this study was to determine whether the HGI is independently associated with macrovascular complications in individuals with T2DM. The study also evaluated whether HGI could provide additional value in identifying patients at increased cardiovascular risk despite similar glycemic control levels among a stable outpatient group with T2DM.

2.7. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). As this was a retrospective observational study, no a priori sample size calculation was performed. Nevertheless, a post-hoc power analysis demonstrated that the final cohort of 391 patients provided adequate statistical power (>80% at $\alpha = 0.05$) to detect significant associations between the HGI and macrovascular complications. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were reported as median with interquartile range (IQR). Between-group comparisons were conducted using the independent samples t-test or the Mann–Whitney U test for continuous variables and the chi-square (χ^2) test for categorical variables. Logistic regression analysis was performed to examine the independent association between HGI and macrovascular complications. Candidate variables were included in the multivariable model if they reached statistical significance in univariate analysis ($p < 0.05$) or were considered clinically relevant. Multicollinearity was assessed using variance inflation factor (VIF) and tolerance values, and variables with VIF > 10 or tolerance < 0.1 were excluded. The final model was constructed using a forward stepwise (conditional) approach to minimize overfitting and address collinearity. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), and a p-value < 0.05 was considered statistically significant.

3. Results

A total of 391 patients with T2DM were included, comprising 221 patients without macrovascular complications and 170 patients with macrovascular complications. The overall study population consisted of 60.9% females and 39.1% males. Patients with macrovascular complications were significantly older ($p = 0.026$) and had a longer duration of diabetes ($p < 0.001$) compared with those without complications. The proportion of patients with hyperlipidemia was significantly higher in the macrovascular (+) group ($p = 0.008$). The use of oral antidiabetic drugs was significantly lower in this group ($p = 0.030$), whereas the use of antihypertensive ($p < 0.001$) and lipid-lowering medications ($p < 0.001$) was significantly higher. The demographic and clinical characteristics of the study groups are summarized in Table 1.

Table 1. Comparison of demographic, anthropometric, and clinical characteristics between patients with and without macrovascular complications.

Parameters	Macrovascular (–) (*n* = 221)	Macrovascular (+) (*n* = 170)	*p*
Age, years	58.1 ± 9.9	60.2 ± 8.7	0.026
Sex, n (%)			
Female	116 (52.5)	79 (46.5)	0.28
Male	105 (47.5)	91 (53.5)	
BMI, (kg/m²)	29.06 ± 4.1	28.85 ± 3.8	0.613
SBP, (mmHg)	132 ± 15	131 ± 14	0.662
DBP, (mmHg)	82 ± 10	83 ±11	0.221
Duration of diabetes (years)	10 (7-15)	15 (12-18)	<0.001
HT, n (%)	126 (57.0)	112 (65.9)	0.075
HL, n (%)	119 (53.8)	114 (67.1)	0.008
Smoking, n (%)			
Never	136 (61.5)	99 (58.2)	
Former smoker / Quit	33 (14.9)	23 (13.5)	0.566
-Current	52 (23.5)	48 (28.2)	
CAD, n (%)	-	154 (90.6)	
CVE, n (%)	-	37 (21.8)	
DFD, n (%)	-	9 (5.3)	
Medication, n (%)			
OAD	146 (66.1)	94 (55.3)	0.030
Insulin	27 (12.2)	26 (15.3)	0.378
OAD + Insulin	46 (20.8)	44 (25.9)	0.238

Antihypertensive	112 (50.7)	116 (68.2)	<0.001
Lipid-lowering therapy	93 (42.1)	117 (68.8)	<0.001

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary Artery Disease, CVE: Cerebrovascular Event, DFD: Diabetic Foot Disease, OAD: Oral Antidiabetic Drug. Values are expressed as median (IQR) or n (%). p-values were calculated using the Mann–Whitney U test for continuous variables and chi-square (χ2) test for categorical variables.

Significant differences were observed in glycemic and lipid parameters between the groups. HbA1c levels were higher in patients with macrovascular complications ($p < 0.001$), whereas estimated HbA1c (eHbA1c) and fasting plasma glucose were lower (both $p < 0.001$). Low-density lipoprotein cholesterol (LDL-C) levels were higher in the macrovascular (+) group ($p = 0.038$). Renal parameters, including BUN, creatinine, eGFR, and urinary albumin-to-creatinine ratio (UACR), showed no statistically significant differences between the groups (all $p > 0.05$). The biochemical and other laboratory characteristics of the study groups are summarized in Table 2.

Table 2. Comparison of biochemical and glycemic parameters between patients with and without macrovascular complications.

Parameters	**Macrovascular (–) (*n* = 221)**	**Macrovascular (+) (*n* = 170)**	***p***
WBC, 10^9/L	8.5 (7-10)	8 (6-9)	0.241
Hemoglobin, g/dL	13.6 ± 1.8	13.7 ± 1.6	0.832
Platelet count, 10^9/L	274 (223-315)	278 (234-314)	0.644
FPG, mg/dL	191 (157-234)	177 (148-195)	<0.001
HOMA-IR	5.8 (3.2-8.5)	5.2 (2.4-8.4)	0.515
HbA1c, %	8.3 (7.2-9.2)	8.9 (8.4-9.6)	<0.001
eHbA1c, %	7.6 (6.8-8.7)	7.3 (6.6-7.8)	<0.001
BUN, mg/dL	31 (25-40)	34 (26-40)	0.165
Creatinine, mg/dL	0.85 (0.71-1)	0.85 (0.69-0.98)	0.439
eGFR, mL/min/1.73 m²	87.80 ± 19	89.49 ± 18	0.384
Uric acid, mg/dL	4.7 (4-6.4)	4.7 (3.7-5.6)	0.100
Total cholesterol, mg/dL	190 (163-211)	196 (160-236)	0.198
Triglyceride, mg/dL	187 (148-224)	182 (133-235)	0.628
HDL-C, mg/dL	44 (36-50)	44 (38-52)	0.394
LDL-C, mg/dL	111 ± 35	120 ± 46	0.038
AST, U/L	17 (14-22)	16 (14-18)	0.019
ALT, U/L	18 (14-24)	16 (13-21)	0.043
CRP, mg/L	3.5 (1.7-6.7)	2.4 (1.3-6.3)	0.111
UACR, mg/g	62.8 (32.1-150)	79.6 (32.5-835)	0.052
HGI	0.48 (0.11-1.14)	1.68 (1.31-2.06)	<0.001

WBC: White Blood Cell count, FGP: Fasting Plasma Glucose, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, HbA1C: Glycated Hemoglobin, BUN: Blood Urea Nitrogen, GFR: Estimated Glomerular Filtration Rate, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, AST: Aspartate Aminotransferase, ALT : Alanine Aminotransferase, CRP: C-Reactive Protein, UACR: Urinary Albumin-to-Creatinine Ratio, HGI: Hemoglobin Glycation Index.Values are expressed as median (IQR). p values were calculated using the Mann–Whitney U test.

In the comparison of HGI values between the groups, the median HGI was 0.48 in patients without macrovascular complications and 1.68 in those with macrovascular complications. A statistically significant difference was detected between the groups ($p < 0.001$). The distribution of HGI values according to the presence of macrovascular complications is shown in Figure 1.

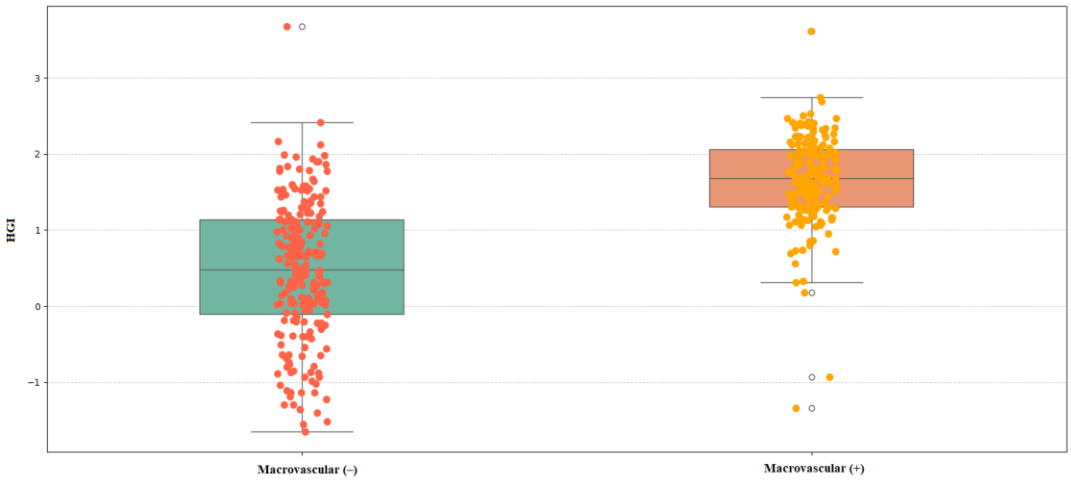

Figure 1. Distribution of HGI values between patients with and without macrovascular complications. Box plots display the median (bold line), interquartile range (box), minimum and maximum values (bars), and outliers. Each individual value is also shown as a color-coded dot.

ROC curve analysis was performed to evaluate the discriminative ability of HGI for the presence of macrovascular complications. The area under the ROC curve (AUC) was 0.870 (95% CI: 0.833–0.908; $p < 0.001$). The optimal cutoff value determined by the Youden index was 1.130, with a sensitivity of 0.876 (87.6%) and a specificity of 0.742 (74.2%). The ROC curve of HGI for identifying macrovascular complications is presented in Figure 2.

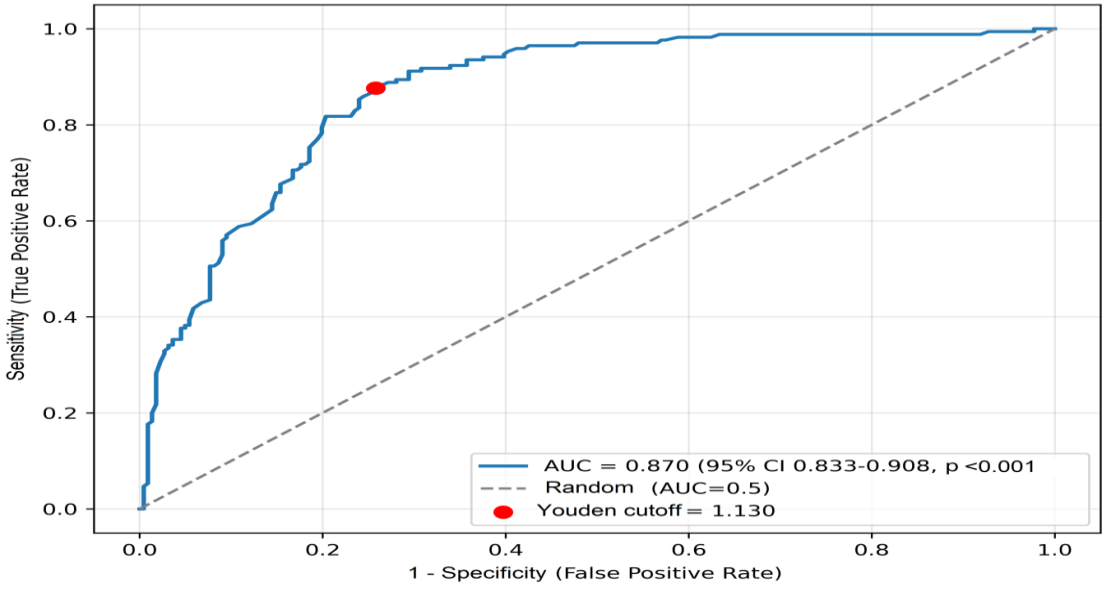

Figure 2. ROC curve of HGI for identifying macrovascular complications in patients with T2DM.

In univariate analysis, age, duration of diabetes, HbA1c, low-density lipoprotein cholesterol (LDL-C), urinary albumin-to-creatinine ratio (UACR) and HGI were significantly associated with the presence of macrovascular complications (all $p < 0.05$), while eHbA1c showed an inverse association ($p < 0.001$). In the multivariate model, duration of diabetes, UACR, and HGI remained significant independent predictors (all $p < 0.001$). Among these, HGI showed the strongest association with macrovascular complications. The results of the logistic regression analyses are summarized in Table 3.

Table 3. Univariate and multivariate logistic regression analyses for factors associated with macrovascular complications.

Model	Univariate Model			Multivariate Model		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age	1.024	1.002 – 1.047	0.030			
BMI	0.987	0.939 – 1.037	0.612			
Duration of diabetes	1.177	1.125 – 1.231	<0.001	1.158	1.096 – 1.224	<0.001
WBC	0.995	0.931 – 1.064	0.885			
FPG	0.992	0.988 – 0.996	<0.001			
HbA1c	1.607	1.339 – 1.928	<0.001			
eHbA1c	0.723	0.609 – 0.858	<0.001			
Creatinine	0.656	0.285 – 1.506	0.320	0.225	0.066 – 0.771	0.018
Triglyceride	1.000	0.998 – 1.002	0.855			
LDL-C	1.005	1.000 – 1.010	0.039			
CRP	1.001	0.988 – 1.014	0.889			
UACR	1.002	1.001 – 1.002	<0.001	1.002	1.001 – 1.003	<0.001
HGI	8.390	5.405 – 13.025	<0.001	6.751	4.254 – 10.713	<0.001

BMI: Body Mass Index, WBC: White Blood Cell count, FPG: Fasting Plasma Glucose, HbA1C: Glycated Hemoglobin, LDL-C: Low-Density Lipoprotein Cholesterol, CRP: C-Reactive Protein, UACR: Urinary Albumin-to-Creatinine Ratio, HGI: Hemoglobin Glycation Index.

According to Spearman correlation analysis, in patients without macrovascular complications, HGI showed a significant correlation UACR (ρ = –0.216; p = 0.001).

No significant correlations were observed in patients with macrovascular complications. The results of the correlation analyses are presented in Table 4.

Table 4. Spearman correlation analysis between HGI and clinical/laboratory parameters in patients with and without macrovascular complications.

Parameters	**Macrovascular (–) (*n* = 221)**		**Macrovascular (+) (*n* = 170)**	
	ρ	***p***	ρ	***p***
Age	-0.008	0.908	-0.057	0.463
BMI	0.036	0.597	0.093	0.226
Duration of Diabetes	0.068	0.312	-0.053	0.495
SBP	-0.098	0.145	0.039	0.615
DBP	0.027	0.695	0.079	0.307
WBC	-0.047	0.484	-0.008	0.913
Hemoglobin	-0.030	0.655	0.009	0.905
Platelet count	-0.052	0.442	-0.090	0.241
HOMA-IR	-0.117	0.082	-0.035	0.648
BUN	-0.009	0.890	-0.068	0.377
Creatinine	0.045	0.504	-0.013	0.870
eGFR	-0.004	0.954	-0.012	0.880
Uric acid	-0.055	0.413	-0.104	0.178
Total cholesterol	-0.055	0.412	0.052	0.498
Triglyceride	-0.104	0.123	0.000	0.998
HDL-C	-0.044	0.512	-0.053	0.490
LDL-C	-0.071	0.291	0.096	0.211
AST	-0.024	0.721	0.042	0.587
ALT	-0.071	0.291	0.000	0.997
CRP	-0.042	0.532	-0.063	0.412
UACR	**-0.216**	**0.001**	0.125	0.104

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, WBC: White Blood Cell, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, BUN: Blood Urea Nitrogen, GFR: Estimated Glomerular Filtration Rate, HDL-C: High-Density Lipoprotein Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, CRP: C-Reactive Protein, UACR: Urinary Albumin-to-Creatinine Ratio. Correlation analysis was performed using Spearman's rank correlation coefficient. Statistically significant correlations were defined as p < 0.05.

4. Discussion

This study investigated the relationship between the HGI and macrovascular complications in patients with T2DM. HGI levels were significantly higher in patients with macrovascular complications, and this relationship remained robust after multivariate adjustment. ROC analysis supported the discriminative capacity of HGI, suggesting its potential role as an adjunctive vascular risk marker. These findings are consistent with recent studies highlighting the clinical relevance of HGI as an

indicator of interindividual glycation variability. Supporting the clinical relevance of HGI, Bai et al. demonstrated in a recent cohort study that HGI independently predicted the development of diabetes mellitus and prediabetes. These findings indicate that HGI reflects underlying biological variation in glycation propensity rather than being solely a derived numerical index (24). Lin et al. (13) reported a U-shaped relationship between HGI and MACE in patients with T2DM and established coronary artery disease, with a higher risk of MACE and cardiovascular death observed particularly in individuals with low HGI levels, independent of HbA1c. Moreover, Xu et al. (12) demonstrated that higher HGI levels were associated with an increased risk of MACE in patients with T2DM undergoing percutaneous coronary intervention. Zhao et al. (25) reported a U-shaped association between HGI and all-cause as well as cardio-cerebrovascular mortality in a large population with metabolic syndrome.

In the present study, patients with T2DM who developed macrovascular complications showed a distinct metabolic profile versus those without complications: higher HbA1c and LDL-C, but lower fasting plasma glucose and estimated HbA1c (eHbA1c). This pattern reflects a marked glycation–glucose mismatch, consistent with the hemoglobin glycation index (HGI), which describes interindividual variability in glycation efficiency independent of mean glycemia. Previous studies have demonstrated a U-shaped association between HGI and adverse cardiovascular outcomes, indicating increased vascular risk at both low and high HGI levels, even when conventional glycemic indices appear comparable (26, 27). Elevated HbA1c and LDL-C levels have also been independently linked to endothelial dysfunction and accelerated atherosclerosis through oxidative and inflammatory mechanisms (28,13). These findings suggest that concurrent dysregulation of glycemic and lipid metabolism may synergistically potentiate macrovascular injury. Conversely, the absence of significant differences in renal indices such as eGFR and UACR in the unadjusted analysis, despite the independent association of UACR in multivariate modeling, indicates that subtle renal endothelial stress may contribute cumulatively to vascular damage (29). Recent evidence also supports an association between HGI and microvascular renal involvement. In a cross-sectional study of patients with T2DM, Xin et al. reported that higher HGI levels were significantly associated with diabetic kidney disease (30).

The discriminative performance of HGI was supported by an AUC of 0.870. While Wu et al. (31) observed that elevated HGI was associated with increased risk of composite cardiovascular events in diabetic cohorts (HR adjusted for conventional risk factors)[1], Xu et al. (12) reported that in CHD patients with T2DM, higher HGI predicted MACE independently. In our cohort, the optimal cutoff of 1.130 yielded sensitivity of 87.6% and specificity of 74.2%, values that are in line with thresholds cited in cardiovascular-glycation studies (32). Together, these observations suggest that HGI, calculated from routine HbA1c and glucose measurements, may serve as a practical adjunct in risk stratification for macrovascular complications.

In the multivariable model, diabetes duration, UACR, and HGI remained independent predictors of macrovascular complications, whereas serum creatinine exhibited an inverse association. The observed association between UACR and macrovascular disease is consistent with evidence suggesting that albuminuria reflects endothelial dysfunction and systemic atherosclerosis (33). The inverse correlation with serum creatinine may reflect confounding by lower muscle mass or medication effects; indeed, declines in muscle mass have been associated with altered creatinine levels and vascular risk (34). Beyond mere statistical associations, these findings support the mechanistic plausibility of HGI as an integrative index of chronic glycation stress and vascular metabolic burden. Elevated HGI implies a discordance between glycemia and HbA1c formation, capturing individual differences in hemoglobin glycation kinetics (35). Experimental and translational evidence further supports that higher HGI is associated with increased accumulation of AGEs, oxidative stress, and endothelial inflammation, key mediators of vascular injury and atherogenesis (36). Taken together, our results suggest that HGI may more accurately reflect glycation-related vascular stress than simple glycemic measures, thereby explaining its strong and independent association with macrovascular complications in our cohort.

Spearman correlation analyses further confirmed the role of HGI as a marker of glycation variability. Lin et al. (13) demonstrated that HGI was correlated with HbA1c and reported a U-shaped association between HGI and cardiovascular outcomes in patients with diabetes and established coronary artery disease. The negative HGI–UACR correlation observed only in patients without macrovascular disease may indicate stage-dependent differences in glycation-related vascular stress. Similar vascular

patterns have been reported in studies linking higher HGI to arterial stiffness and subclinical myocardial injury (37,38). Collectively, these findings support HGI as an integrated index of glycation-driven vascular burden.

This study has certain limitations that should be acknowledged. Because of its cross-sectional design, the findings do not allow for causal inferences between HGI and macrovascular complications. The single-center nature of the study may also limit the generalizability of the results to broader or more diverse populations. Although potential confounders such as medication use, dietary habits, and temporal glycemic variability were not fully controlled, their influence cannot be completely excluded. Furthermore, HGI was derived from single measurements of fasting glucose and HbA1c, which may not entirely reflect long-term glycation dynamics. Despite these limitations, the relatively large sample size and rigorous methodology enhance the reliability of our findings.

5. Conclusion

This study demonstrated that higher HGI levels are closely associated with macrovascular complications in individuals with T2DM. These findings suggest that HGI may serve as a practical and clinically meaningful marker of glycation-related vascular stress, complementing HbA1c in cardiovascular risk assessment. Incorporating HGI into future predictive models may improve early identification of high-risk patients and enhance individualized diabetes management. Further prospective multicenter studies are warranted to confirm these observations and clarify their prognostic implications.

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