TJVS Turkish Journal of Vascular Surgery

Turk J Vasc Surg 2025;34(2):155-63
DOI: 10.9739/tjvs.2025.06.030

Available online at www.turkishjournalofvascularsurgery.org

Original Article

Glycation burden and glycemic variability: Key drivers of chronic venous insufficiency severity and adverse outcomes

Ayhan Muduroglu[1], Hakan Guven[2]

[1]Bursa City Hospital, Department of Cardiovascular Surgery, Bursa, Türkiye
[2]Medical Park Bursa Hospital, Department of Cardiovascular Surgery, Bursa, Türkiye

Received: June 17, 2025 Accepted: July 14, 2025 Published online: July 21, 2025

Abstract

Aim: Advanced glycation end-products (AGEs) have been implicated in vascular pathology, but their role in chronic venous insufficiency (CVI) remains underexplored. This study investigated the association between glycated hemoglobin (HbA1c), a surrogate marker of glycation burden, and CVI severity and outcomes.

Material and Methods: This single-center retrospective cohort study included 612 patients with CVI. Patients were stratified by glycation burden: high (high glycation burden (HGB); HbA1c ≥6.5%, n=247) and low (low glycation burden (LGB); HbA1c <6.5%, n=365). CVI severity was assessed using Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification and Venous Clinical Severity Score (VCSS). Major adverse venous events (MAVEs) were tracked over 36 months.

Results: HGB patients showed higher rates of advanced CVI (CEAP C4-C6: 41.7% vs. 26.0%, p<0.001) and higher VCSS scores (median 9 vs. 7, p<0.001). HbA1c variability (SD) strongly correlated with VCSS (ρ=0.38, p<0.001). In multivariable analysis, HbA1c ≥6.5% (OR 1.52, 95% CI 1.02-2.30), HbA1c SD (OR 2.10, 95% CI 1.45-3.06), and HOMA-IR (OR 1.19, 95% CI 1.07-1.33) independently predicted severe CVI. MAVEs were more frequent in HGB patients (14.2% vs. 8.5%, p=0.021).

Conclusion: Glycation burden and glycemic variability are independently associated with CVI severity and adverse outcomes. These findings suggest that metabolic dysfunction contributes to venous pathology and may represent potential therapeutic targets.

Keywords: Chronic venous insufficiency, glycated hemoglobin, advanced glycation end-products, venous ulcer, glycemic variability

INTRODUCTION

Chronic venous insufficiency (CVI) represents a significant global health burden, affecting approximately 25–40% of adults worldwide and imposing substantial socioeconomic costs through reduced quality of life, work productivity loss, and healthcare expenditures exceeding $3 billion annually in developed nations [1,2]. This prevalent vascular disorder, characterized by impaired venous return, manifests through a pathophysiological cascade involving venous valvular incompetence, sustained ambulatory venous hypertension, endothelial dysfunction, and progressive extracellular matrix (ECM) remodelling [3,4]. The clinical spectrum ranges from cosmetic concerns to debilitating venous ulcers, with the latter affecting 1–3% of the elderly population and demonstrating recurrence rates approaching 70% despite optimal management [5,6]. The molecular mechanisms underlying venous wall deterioration and disease progression in CVI remain incompletely understood, representing a critical knowledge gap in vascular pathophysiology [7].

While traditional paradigms have focused predominantly on hemodynamic factors and inflammatory processes, emerging evidence suggests that biochemical modifications of structural proteins may play a pivotal role in venous wall remodelling [8,9]. Non-enzymatic glycation—a post-translational modification process resulting in advanced glycation end-products (AGEs)—

CITATION
Muduroglu A, Guven H. Glycation burden and glycemic variability: Key drivers of chronic venous insufficiency severity and adverse outcomes. Turk J Vasc Surg. 2025;34(2):155-63.

Corresponding Author: Ayhan Muduroglu, Bursa City Hospital, Department of Cardiovascular Surgery, Bursa, Türkiye
Email: ayhanmuduroglu@gmail.com

has been extensively implicated in arterial pathology and diabetic vasculopathy, yet its contribution to venous disease pathogenesis remains remarkably underexplored [10,11]. AGEs are formed through Maillard reactions between reducing sugars and free amino groups of proteins, lipids, or nucleic acids, particularly affecting long-lived matrix components such as collagen and elastin [11]. Their accumulation in vascular tissue contributes to increased cross-linking of ECM proteins, leading to decreased elasticity, increased stiffness, and progressive loss of compliance in vessel walls [12]. Beyond these structural alterations, AGEs exert potent pro-inflammatory and pro-oxidant effects via interaction with their receptor (RAGE), initiating a cascade of inflammatory responses involving nuclear factor-kappa B (NF-κB) activation, cytokine release, and oxidative stress generation [13,14]. These mechanisms potentially compromise endothelial integrity and contribute to venous remodeling, though the specific pathways in venous pathology remain inadequately characterized [9].

Histopathological investigations in varicose veins have demonstrated AGE accumulation within the vein wall, particularly in collagen-rich regions, alongside alterations in collagen I/III ratios and fragmentation of elastic fibers—hallmarks of degenerative ECM remodelling [15,16]. Moreover, AGE-induced endothelial dysfunction has been associated with increased leukocyte adhesion and impaired nitric oxide bioavailability, further propagating local inflammation and tissue hypoxia [17]. However, the clinical relevance of these findings and their relationship with disease severity and outcomes have not been comprehensively evaluated in CVI populations [3].

Glycated hemoglobin (HbA1c), a widely utilized marker of long-term glycemic exposure, correlates with systemic AGE burden and has been proposed as an indirect surrogate for chronic glycation exposure even in non-diabetic populations [18]. Nevertheless, its relationship with venous disease severity and CVI-associated clinical outcomes remains largely unexplored, representing a significant translational research gap [8]. Furthermore, the potential contribution of glycemic variability—increasingly recognized as an independent risk factor for vascular complications—to venous pathology has not been previously investigated [19].This study aims to address these critical knowledge gaps by investigating the association between HbA1c levels, glycemic variability, and CVI severity, as measured by Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification and the Venous Clinical Severity Score (VCSS), as well as the incidence of major adverse venous events (MAVEs). By elucidating the potential mechanistic and prognostic role of glycation in the pathogenesis and progression of CVI, we seek to establish a novel pathophysiological framework that may inform risk stratification strategies and therapeutic interventions targeting the AGE-RAGE axis in venous disease.

MATERIAL AND METHODS

Study Design and Population

This study was designed as a retrospective, observational, single-center cohort analysis conducted at local hospital with data collected between January 2015 and December 2024. The study protocol was approved by the Mudanya University Ethics Committee (Approval No: 2025-2/10, Date: 22.05.2025) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective and anonymized nature of data collection. The study population included adult patients aged ≥18 years with a confirmed diagnosis of CVI, defined by a CEAP clinical classification of C2 or higher, representing at least the presence of visible varicose veins. After applying inclusion and exclusion criteria, a total of 612 patients were included in the final analysis. Based on their glycation burden, patients were stratified into two groups: a high glycation burden group (HGB; HbA1c ≥6.5%, n=247) and a low glycation burden group (LGB; HbA1c <6.5%, n=365). Inclusion criteria additionally required the availability of glycated hemoglobin (HbA1c) measurements within six months before or after the CVI diagnosis and a completed lower extremity venous Doppler ultrasonography assessing venous reflux. Patients were excluded if they had a history of active malignancy or chemotherapy within the past 12 months, chronic autoimmune or inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus), solid organ transplantation, chronic infectious diseases (e.g., HIV, tuberculosis), or incomplete clinical or laboratory records.

Data Collection

All clinical data, including baseline characteristics, laboratory parameters, and longitudinal follow-up events, were systematically extracted from the hospital's centralized electronic health record (EHR) system for the period between January 2015 and December 2024. In addition to standard baseline demographic and clinical variables (age, sex, BMI, smoking status, hypertension, dyslipidemia, coronary artery disease, and diabetes), extended glycemic and metabolic parameters were collected to minimize residual confounding in interpreting HbA1c:

- Diabetes duration (in years) was recorded from electronic medical records or self-report validated against diagnosis dates.
- Glycemic variability was estimated using longitudinal HbA1c data obtained from laboratory databases over the prior 24 months. Metrics included HbA1c standard deviation (SD), coefficient of variation (CV%), and interquartile fluctuation (ΔIQR). We acknowledge that while these metrics provide a better assessment of glycemic instability than a single

HbA1c measurement, they remain limited in capturing short-term, daily, and intra-day glucose fluctuations compared to continuous glucose monitoring (CGM) data, which was not available for this retrospective cohort.

- Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), calculated as: HOMA-IR = [Fasting insulin (μIU/mL) × Fasting glucose (mg/dL)] / 405.
- Laboratory parameters included HbA1c (%) measured using standardized high-performance liquid chromatography (HPLC), fasting plasma glucose (mg/dL), serum insulin (μIU/mL), LDL-cholesterol (mg/dL), serum albumin (g/dL), and high-sensitivity C-reactive protein (hs-CRP, mg/L). HbA1c was used as a validated surrogate marker of chronic glycation exposure in the absence of direct AGE measurement, recognizing its correlation with non-enzymatic glycation and endothelial dysfunction.

Venous Doppler ultrasonography was performed by certified vascular sonographers according to standardized protocols as described in international consensus statements [20]. Examinations included assessments in the standing position with calf compression maneuvers to evaluate reflux in both superficial and deep venous systems. CVI severity was classified according to CEAP criteria and quantified using the VCSS. These values were extracted from clinical records, where they had been contemporaneously documented by board-certified vascular specialists.

MAVEs were defined as a composite endpoint including: (1) presence of active venous ulcers, (2) requirement for surgical venous intervention, or (3) occurrence of venous limb-threatening complications. Follow-up data regarding MAVEs were tracked over a median period of 36 months by systematically reviewing patients' electronic health records for documented outcomes.

Exposure Stratification and Definitions

Participants were stratified into two glycation burden categories:

- High glycation burden: HbA1c≥6.5%,
- Low glycation burden: HbA1c<6.5% Severe CVI was defined as the presence of CEAP class C4–C6 and/or VCSS score ≥9.

Statistical Analysis

All statistical analyses were conducted using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean±SD or median with interquartile range (IQR) based on distribution normality. Categorical variables were presented as frequencies and percentages. Between-group comparisons (high vs. low glycation) were assessed using independent samples t-tests or Mann–Whitney U tests for continuous variables and Chi-square or Fisher's exact tests for categorical data. Spearman's rank correlation was used to assess associations between HbA1c (and its variability indices) and CVI severity markers (CEAP class and VCSS).

Multivariable logistic regression models were constructed to identify independent predictors of severe CVI. The models included covariates such as age, sex, BMI, smoking status, diabetes duration, LDL-cholesterol, hs-CRP, HOMA-IR, and HbA1c variability (SD or CV%). Variables with $p<0.10$ in univariate analysis were entered into multivariable models to account for residual confounding. For the analysis of MAVEs, we conducted between-group comparisons of event rates using Chi-square tests. Kaplan-Meier analysis with log-rank testing was performed to compare venous ulcer-free survival between glycation burden groups. It should be noted that multivariable time-to-event analysis (Cox proportional hazards regression) for the composite MAVE endpoint was not performed in this study due to limitations in capturing precise event timing for all components of the composite endpoint in our retrospective dataset. This represents a limitation of our analysis that is addressed in the discussion section.

Model discrimination was assessed by receiver operating characteristic (ROC) curves, with area under the curve (AUC) and 95% confidence intervals reported. Predictive enhancement by HbA1c was evaluated using Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) statistics.

Sample Size Estimation

A priori power analysis assumed a 20% prevalence of severe CVI in the low glycation group and a 30% prevalence in the high glycation group. Using $\alpha=0.05$ and 80% power, the minimum required sample size was calculated as 456 patients (228 per group). To allow for exclusions due to missing data or eligibility failure, a 30% oversampling strategy was employed, targeting an initial cohort size of approximately 600 participants. Post-hoc power analysis confirmed that the final sample size of 612 patients provided 87% power to detect the observed difference in severe CVI prevalence between groups.

RESULTS

Baseline Characteristics

Of the 612 patients enrolled, 247 (40.4%) were classified into the high glycation burden (HGB) group (HbA1c ≥6.5%), and 365 (59.6%) were classified into the low glycation burden (LGB) group (HbA1c <6.5%). Baseline demographic, clinical, and laboratory characteristics are summarized in Table 1.

Table 1. Baseline characteristics and glycemic parameters of the study population (N=612)

Characteristic	LGB (HbA1c<6.5%) (n=365)	HGB (HbA1c≥6.5%) (n=247)	p-value
Demographics			
Age, years (mean±SD)	62.8±10.2	67.1±9.4	<0.001
Male sex, n (%)	216 (59.2)	149 (60.3)	0.781
BMI, kg/m² (mean±SD)	27.1±3.8	29.4±4.2	<0.001
Comorbidities			
Hypertension, n (%)	197 (54.0)	174 (70.4)	<0.001
Dyslipidemia, n (%)	201 (55.1)	169 (68.4)	0.002
Coronary artery disease, n (%)	83 (22.7)	79 (32.0)	0.010
Diabetes mellitus, n (%)	98 (26.8)	247 (100.0)	<0.001
Diabetes duration, years (mean±SD)	3.1±2.7	9.2±6.1	<0.001
Smoking history, n (%)	142 (38.9)	95 (38.5)	0.921
Laboratory parameters			
HbA1c, % (mean±SD)	5.7±0.4	7.4±0.9	<0.001
HbA1c SD (median [IQR])	0.31 [0.24–0.43]	0.52 [0.40–0.66]	<0.001
HbA1c CV% (median [IQR])	4.4 [3.5–5.8]	7.1 [5.6–8.9]	<0.001
Fasting glucose, mg/dL (mean±SD)	102.4±12.6	143.7±31.5	<0.001
HOMA-IR (mean±SD)	2.7±1.4	4.9±2.1	<0.001
LDL-cholesterol, mg/dL (mean±SD)	118.3±34.2	124.6±38.7	0.042
Serum albumin, g/dL (mean±SD)	4.2±0.4	4.0±0.5	<0.001
hs-CRP, mg/L (median [IQR])	2.1 [1.2–3.5]	3.4 [2.0–5.6]	<0.001

LGB: low glycation burden, HGB: high glycation burden; BMI: body mass index, SD: standard deviation; CV%: coefficient of variation; HOMA-IR: homeostatic model assessment of insulin resistance, hs-CRP: high-sensitivity C-reactive protein, IQR: interquartile range; p-values derived from Student's t-test, Mann–Whitney U test, or chi-square test, as appropriate

Clinically, patients with a high glycation burden were significantly older (mean 67.1 vs. 62.8 years), had a higher body mass index (BMI; mean 29.4 vs. 27.1 kg/m²), and a longer duration of diabetes (mean 9.2 vs. 3.1 years) compared to the LGB group (p<0.001 for all). Furthermore, cardiovascular risk factors, including hypertension, dyslipidemia, and coronary artery disease, were significantly more prevalent in the HGB group (p<0.001, p=0.002, and p=0.010, respectively). No significant differences were observed in sex distribution or smoking history.

From a metabolic standpoint, patients in the HGB group exhibited significantly greater glycemic variability (HbA1c SD and CV%) and more pronounced insulin resistance (HOMA-IR) (p<0.001 for all). This indicates that metabolic control was not only chronically poor but also more unstable in this cohort. Additionally, lower serum albumin and higher hs-CRP levels in the HGB group (p<0.001 for both) suggest the presence of systemic inflammation and potentially a poorer overall health status.

Severity of Chronic Venous Insufficiency (CVI) and Clinical Outcomes

A high glycation burden was directly associated with more severe manifestations of chronic venous disease (Table 2, Figure 1). Advanced-stage CVI (CEAP class C4-C6) was identified in 41.7% of HGB patients compared to 26.0% in the LGB group (p<0.001), suggesting that poor glycemic control plays a significant role in the progression to more severe forms of the disease. Similarly, the VCSS and the prevalence of active venous ulcers were significantly higher in the HGB group (p<0.001 and p=0.032, respectively).

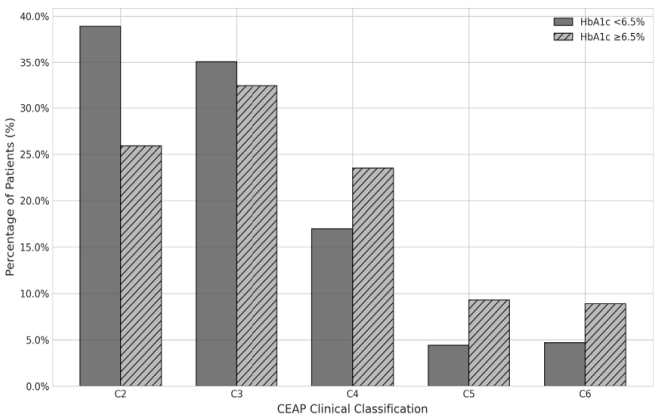

Figure 1. Distribution of patients according to CEAP clinical classification

Table 2. CVI severity measures by glycation burden

Severity measure	LGB (HbA1c<6.5%) (n=365)	HGB (HbA1c≥6.5%) (n=247)	p-value
CEAP clinical classification			<0.001
C2, n (%)	142 (38.9)	64 (25.9)	
C3, n (%)	128 (35.1)	80 (32.4)	
C4, n (%)	62 (17.0)	58 (23.5)	
C5, n (%)	16 (4.4)	23 (9.3)	
C6, n (%)	17 (4.7)	22 (8.9)	
Advanced CVI (C4-C6), n (%)	95 (26.0)	103 (41.7)	<0.001
VCSS score, median [IQR]	7 [5–9]	9 [7–11]	<0.001
Active venous ulcer, n (%)	17 (4.7)	22 (8.9)	0.032

CEAP: clinical-etiological-anatomical-pathophysiological classification, VCSS: venous clinical severity score, IQR: interquartile range

Correlation analysis confirmed that increasing HbA1c levels were positively associated with both disease stage (CEAP) and severity (VCSS) (ρ=0.32 and ρ=0.35, respectively; p<0.001). More importantly, HbA1c variability (HbA1c SD), which reflects fluctuations in glycemic control, demonstrated an even stronger correlation with venous disease severity (VCSS; ρ=0.38, p<0.001) (Table 3). This finding suggests that glycemic instability, beyond mean glucose levels, may be a key contributor to venous endothelial damage.

Table 3. Relationship between glycemic variability and venous disease severity

Parameter	VCSS score correlation	p-value	CEAP class correlation	p-value
HbA1c (%)	ρ=0.35	<0.001	ρ=0.32	<0.001
HbA1c SD	ρ=0.38	<0.001	ρ=0.29	<0.001
HbA1c CV%	ρ=0.31	<0.001	ρ=0.25	0.002
HOMA-IR	ρ=0.33	<0.001	ρ=0.28	<0.001
Diabetes duration (years)	ρ=0.27	<0.001	ρ=0.24	0.003

VCSS: venous clinical severity score; CEAP: clinical-etiological-anatomical-pathophysiological classification; SD: standard deviation; CV%: coefficient of variation; HOMA-IR: homeostatic model assessment of insulin resistance; ρ: Spearman's rank correlation coefficient; All correlations adjusted for age, sex, and body mass index (BMI)

Independent Predictors of Severe CVI

Multivariable logistic regression analysis was performed to identify factors independently associated with severe CVI (Figure 2). The analysis revealed that the strongest independent predictor was HbA1c variability (SD), which more than doubled the odds of severe CVI (adjusted OR 2.10; 95% CI 1.45–3.06; p<0.001). This implies that instability in glucose levels may be a more critical risk factor for venous disease progression than chronic hyperglycemia alone.

Other significant independent predictors included high glycation burden (HbA1c≥6.5%), insulin resistance (HOMA-IR), advanced age, higher BMI, and elevated hs-CRP levels. Conversely, higher serum albumin was found to be a protective factor (adjusted OR 0.72; p=0.023). Factors such as diabetes duration and LDL-cholesterol were not independently associated with severe CVI in this model.

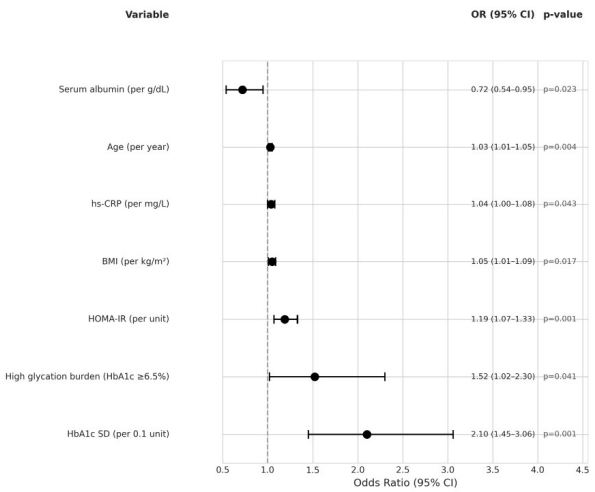

Figure 2. Independent predictors of severe CVI (CEAP C4-C6 or VCSS ≥9)

Predictive Performance and Model Improvement

The predictive power of HbA1c alone for severe CVI was modest (AUC 0.68). However, when metabolic markers—specifically HbA1c variability (SD) and HOMA-IR—were added to a base model of clinical risk factors, the model's accuracy in predicting severe CVI improved significantly (AUC increased to 0.73, p=0.003 for IDI) (Figure 3). This result indicates that incorporating measures of glycemic variability and insulin resistance into risk assessments, alongside traditional factors, could enhance clinical decision-making for identifying high-risk patients.

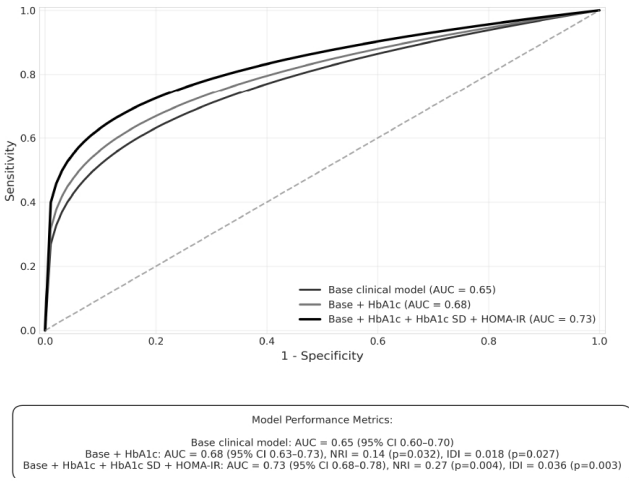

Figure 3. ROC curves for prediction of severe CVI

Major Adverse Venous Events (MAVEs)

Over a median follow-up of 36 months, the incidence of major adverse venous events (MAVEs) was significantly higher in the HGB group (14.2% vs. 8.5%; p=0.021). Specifically, the HGB cohort experienced a higher frequency of new or persistent venous ulcers (8.5% vs. 3.6%), need for surgical interventions (6.9% vs. 2.5%), and limb-threatening complications (2.8% vs. 0.8%) (Table 4). Kaplan-Meier analysis further confirmed that patients in the HGB group had a consistently higher risk of developing venous ulcers throughout the follow-up period (Log-rank p=0.015) (Figure 4). These findings demonstrate that poor glycemic control not only exacerbates disease severity but also leads to worse long-term clinical outcomes.

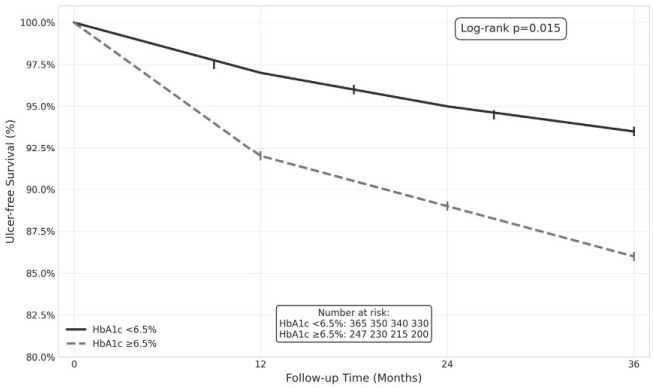

Figure 4. Kaplan-Meier curve for venous ulcer development

Table 4. Major adverse venous events by glycation burden

Event	LGB (HbA1c <6.5%) (n=365)	HGB (HbA1c ≥6.5%) (n=247)	p-value
Composite MAVE, n (%)	31 (8.5)	35 (14.2)	0.021
New or persistent venous ulcers, n (%)	13 (3.6)	21 (8.5)	0.015
Surgical interventions, n (%)	9 (2.5)	17 (6.9)	0.009
Limb-threatening complications, n (%)	3 (0.8)	7 (2.8)	0.047

MAVE: major adverse venous events

DISCUSSION

This single-center retrospective study demonstrates a statistically and biologically significant association between glycation burden—indirectly assessed through glycated hemoglobin (HbA1c) levels—and both the clinical severity of CVI and the incidence of major adverse venous events (MAVEs). Our findings reveal that patients with elevated HbA1c (≥6.5%) exhibited significantly higher rates of advanced disease (CEAP C4–C6: 41.7% vs. 26.0%; p<0.001) and venous ulceration (8.9% vs. 4.7%; p=0.032) compared to those with lower glycation burden. Importantly, we identified that increased glycemic variability (HbA1c SD), insulin resistance (homeostatic model assessment of insulin resistance [HOMA-IR]), and longer diabetes duration were independently associated with more severe venous disease and worse clinical outcomes, suggesting that beyond chronic hyperglycemia, dynamic glycemic instability and metabolic dysregulation play crucial roles in venous disease pathogenesis [10].

These observations align with our initial hypothesis that non-enzymatic glycation contributes to venous wall deterioration and disease progression [19]. The robust association between HbA1c variability and severe CVI (adjusted odds ratio [OR] 2.10; 95% confidence interval [CI] 1.45–3.06; p<0.001) represents a novel finding that extends beyond the established paradigm of average glycemic control. This relationship remained significant after adjustment for multiple confounders, including age,

body mass index, comorbidities, and inflammatory markers, suggesting an independent pathophysiological mechanism. The stronger predictive value of glycemic variability compared to absolute HbA1c levels parallels emerging evidence in diabetic macrovascular and microvascular complications, where glycemic fluctuations have been shown to induce more pronounced oxidative stress and endothelial dysfunction than sustained hyperglycemia [21]. It is important to acknowledge that our assessment of glycemic variability using HbA1c SD and coefficient of variation (CV%) from longitudinal measurements over 24 months, while more informative than a single HbA1c value, has limitations in capturing short-term, daily, and intra-day glucose fluctuations [22]. Whether HGB occurs before the development of CVI or worsens existing CVI cannot be determined from retrospective data. Prospective studies are needed to clarify the temporal relationship of HbA1c and AGE accumulation to the onset and progression of CVI. CGM data would provide more granular information on glycemic excursions and could potentially reveal stronger associations with venous pathology by capturing the "dynamic glycemic instability" that may directly impact venous wall integrity [22]. Future studies incorporating CGM technology could further elucidate the temporal relationship between acute glycemic fluctuations and venous wall stress [3].

The pathophysiological mechanisms underlying these associations likely involve both structural and functional alterations in the venous wall [12]. AGE-induced cross-linking of collagen and elastin fibers reduces vessel wall compliance and elasticity, potentially compromising venous valve function and exacerbating ambulatory venous hypertension [13,14]. Concurrently, AGE-RAGE interaction activates pro-inflammatory signaling cascades, including NF-κB-mediated upregulation of adhesion molecules, cytokines, and matrix metalloproteinases, which further contribute to venous remodeling and valvular incompetence [13]. Our findings of higher high-sensitivity C-reactive protein (hs-CRP) levels in the high glycation group (3.4 [2.0–5.6] vs. 2.1 [1.2–3.5] mg/L; $p<0.001$) support this inflammatory component, consistent with previous histopathological studies demonstrating increased inflammatory cell infiltration in glycated venous tissue. We acknowledge that our study did not measure key inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), reactive oxygen species (ROS) markers, or soluble RAGE (sRAGE), which would have provided more direct evidence of AGE-RAGE axis activation and downstream inflammatory pathways [9]. The absence of these specific biomarkers limits our ability to definitively establish the proposed mechanisms (AGE-RAGE interaction, inflammation, oxidative stress) as the direct causes underlying our findings. The mechanistic framework presented should therefore be considered hypothetical, requiring validation in future studies that incorporate these specific biomarkers to more directly link glycation with venous wall inflammation and remodeling [23].

Insulin resistance emerged as an independent predictor of severe CVI (adjusted OR 1.19 per unit increase; $p=0.001$), suggesting a potential synergistic effect with glycation in venous pathology [23]. This observation extends the concept of "insulin resistance syndrome" to venous disease, paralleling its established role in arterial pathology [17]. Insulin resistance promotes endothelial dysfunction through multiple mechanisms, including reduced nitric oxide bioavailability, increased endothelin-1 production, and enhanced oxidative stress [24]. Additionally, hyperinsulinemia stimulates smooth muscle cell proliferation and migration, potentially contributing to venous wall hypertrophy and remodelling [7]. The integration of insulin resistance into venous pathophysiology represents a paradigm shift that merges metabolic and hemodynamic factors in CVI progression.

It is increasingly clear that uncontrolled diabetes is an important prognostic factor in the progression of CVI through metabolic dysfunction characterized not only by chronically high HbA1c levels but also by glycemic variability. The fact that these parameters, which have been shown to be associated with vascular complications in the literature [19], were also found to be significantly associated with more advanced CVI and venous ulcer development in our study suggests that glycemic control should be considered as a therapeutic target in the management of CVI. Approaches that specifically target the AGE-RAGE axis or treatments aimed at reducing glycemic fluctuations have the potential to slow the progression of venous disease [25]. In this context, a multidisciplinary approach that includes endocrinologists along with vascular physicians in the follow-up of patients with CVI is critical for reducing disease severity and preventing complications. The prognostic implications of our findings are underscored by the significantly higher incidence of MAVEs in patients with elevated glycation burden during the 36-month follow-up period (14.2% vs. 8.5%; $p=0.021$). The Kaplan-Meier analysis for venous ulcer development demonstrated early divergence between glycation groups, suggesting that glycation-related venous deterioration begins well before clinical manifestation. This temporal relationship supports the potential utility of glycemic parameters in risk stratification models for CVI progression. It is also critical to address the potential confounding effect of body mass index (BMI), a known risk factor for both CVI and metabolic dysfunction. In our multivariable analysis, we adjusted for BMI, and the association between high glycation burden and severe CVI remained statistically significant. This suggests that while BMI is an independent predictor, glycation burden contributes to CVI severity through mechanisms that extend beyond its association with obesity. Indeed, incorporating HbA1c variability and HOMA-IR into prediction models significantly improved discriminative performance (AUC increase from 0.65

to 0.73; NRI 0.27; p=0.004), highlighting the clinical relevance of these metabolic parameters beyond traditional risk factors. We recognize that while the improvement in model performance (AUC 0.73) is statistically significant, it represents only moderate discriminative ability in clinical terms. This level of predictive performance, though better than the baseline model, would require further refinement and external validation in diverse cohorts before implementation in clinical decision-making. The NRI and IDI values, while statistically significant, also indicate modest improvements in reclassification and discrimination. Future studies should focus on enhancing model performance through the inclusion of additional biomarkers and clinical parameters, as well as validating these models in prospective, multicenter cohorts to establish their generalizability and clinical utility.

A limitation of our MAVE analysis is the absence of multivariable time-to-event analysis (Cox proportional hazards regression) for the composite endpoint. While we performed Kaplan-Meier analysis with log-rank testing for venous ulcer development, a comprehensive survival analysis adjusting for potential confounders would have provided stronger evidence for the independent prognostic value of glycation burden. This limitation was due to challenges in precisely capturing event timing for all components of the composite endpoint in our retrospective dataset. Future prospective studies with systematic follow-up protocols would be better positioned to perform such analyses and establish the adjusted risk ratios for MAVEs associated with glycation burden and glycemic variability.

The inverse association between serum albumin levels and severe CVI (adjusted OR 0.72; p=0.023) merits particular attention. Hypoalbuminemia may reflect both systemic inflammation and protein glycation, as albumin is a primary target for early glycation reactions [26]. This relationship is likely bidirectional: reduced albumin levels may compromise oncotic pressure and tissue perfusion, potentially exacerbating venous stasis and tissue hypoxia, while venous disease itself may contribute to hypoalbuminemia through chronic inflammation and increased vascular permeability [26]. Furthermore, glycated albumin exhibits altered binding properties and reduced antioxidant capacity, potentially amplifying oxidative stress in the venous microenvironment [26]. This finding suggests that protein glycation extends beyond structural components to affect functional plasma proteins, representing another mechanism through which glycation may influence venous pathophysiology [26]. Further research specifically examining albumin glycation levels and their direct effects on venous microcirculation would be valuable in elucidating this relationship more precisely.

Several additional limitations of our study warrant consideration. First, the retrospective design precludes causal inferences, and observed associations should be interpreted as correlational. Furthermore, the cross-sectional nature of the initial assessment makes it impossible to establish the precise temporal sequence between the onset of high glycation burden and the development or progression of CVI. It remains unclear whether elevated glycation is a causative factor, an exacerbating factor for pre-existing disease, or simply a concurrent finding. Second, HbA1c was used as an indirect surrogate of glycation burden, without direct AGE measurements (e.g., skin autofluorescence, plasma AGEs, or histopathology) to validate this assumption [11]. Third, we did not measure key inflammatory mediators such as IL-6, TNF-α, ROS markers, or sRAGE, limiting mechanistic insights into the AGE-RAGE axis in venous pathology [13]. Fourth, our data was sourced from electronic health records, which did not systematically capture information on other established CVI risk factors such as pregnancy history, occupational standing time, or chronic heat exposure. The absence of these variables may introduce residual confounding, and their influence could not be assessed in our models. Additionally, as this was a retrospective analysis of real-world data, treatment protocols for both CVI and diabetes were not standardized and were administered at the discretion of the treating physicians. Variations in treatment could represent a confounding factor influencing the outcomes, which we could not control for in our analysis. Fifth, while we assessed glycemic variability using HbA1c SD, continuous glucose monitoring data would provide more granular information on glycemic excursions. Finally, although our cohort captured detailed clinical information, it originated from a single center, potentially limiting external generalizability.

CONCLUSION

In conclusion, despite the inherent limitations of its retrospective design, this study provides compelling evidence that glycation burden and glycemic variability are independently associated with the severity and adverse outcomes of chronic venous insufficiency. These findings shift the paradigm of CVI pathophysiology from a purely hemodynamic and inflammatory model to one that incorporates metabolic dysregulation. While these correlational findings require validation in prospective longitudinal studies, they highlight the AGE-RAGE axis and glycemic control as potentially crucial therapeutic targets for preventing the progression of venous disease.

Ethics Committee Approval: The study protocol was approved by the Mudanya University Ethics Committee (Approval No: 2025-2/10, Date: 22.05.2025) and was conducted in accordance with the Declaration of Helsinki.

Patient Consent for Publication: Not necessary for this manuscript.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014;130:333-46.
2. Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ. 2014;17:347-56.
3. Raffetto JD, Mannello F. Pathophysiology of chronic venous disease. Int Angiol. 2014;33:212-21.
4. Diaz JA, Gianesini S, Khalil RA. Glycocalyx disruption, endothelial dysfunction and vascular remodeling as underlying mechanisms and treatment targets of chronic venous disease. Int Angiol. 2024;43:563-90.
5. Santler B, Goerge T. Chronic venous insufficiency—a review of pathophysiology, diagnosis, and treatment. J Dtsch Dermatol Ges. 2017;15:538-56.
6. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol. 2002;46:381-6.
7. Nicolaides AN; Cardiovascular Disease Educational and Research Trust; European Society of Vascular Surgery; ,The International Angiology Scientific Activity Congress Organization; International Union of Angiology; Union Internationale de Phlebologie at the Abbaye des Vaux de Cernay. Investigation of chronic venous insufficiency: a consensus statement (France, March 5-9, 1997). Circulation. 2000;102:E126-63.
8. Molnár AÁ, Nádasy GL, Dörnyei G, Patai BB, Delfavero J, Fülöp GÁ, et al. The aging venous system: from varicosities to vascular cognitive impairment. Geroscience. 2021;43:2761-84.
9. Abrashev H, Abrasheva D, Nikolov N, Ananiev J, Georgieva E. A systematic review of endothelial dysfunction in chronic venous disease—inflammation, oxidative stress, and shear stress. Int J Mol Sci. 2025;26:3660.
10. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813-20.
11. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia. 2001;44:129-46. Erratum in: Diabetologia. 2002;45:293.
12. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res. 2004;63:582-92.
13. Dong H, Zhang Y, Huang Y, Deng H. Pathophysiology of RAGE in inflammatory diseases. Front Immunol. 2022;13:931473.
14. Muthyalaiah YS, Jonnalagadda B, John CM, Arockiasamy S. Impact of advanced glycation end products (AGEs) and its receptor (RAGE) on cancer metabolic signaling pathways and its progression. Glycoconj J. 2021;38:717-34.
15. Elsharawy MA, Naim MM, Abdelmaguid EM, Al-Mulhim AA. Role of saphenous vein wall in the pathogenesis of primary varicose veins. Interact Cardiovasc Thorac Surg. 2007;6:219-24.
16. Fonseca C, Taatjes DJ, Callas P, Ittleman F, Bovill EG. The effects of aging on the intimal region of the human saphenous vein: insights from multimodal microscopy and quantitative image analysis. Histochem Cell Biol. 2012;138:435-45.
17. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al. Inflammatory mechanisms contributing to endothelial dysfunction. Biomedicines. 2021;9:781.
18. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362:800-11.
19. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol. 2019;7:221-30.
20. Cavezzi A, Labropoulos N, Partsch H, Ricci S, Caggiati A, Myers K, Nicolaides A, Smith PC. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs--UIP consensus document. Part II. Anatomy. Eur J Vasc Endovasc Surg. 2006;31:288-99.
21. Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it?. J Diabetes Sci Technol. 2008;2:1094-100.
22. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42:1593-603.
23. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord. 2013;14:5-12.
24. Vallurupalli S, Mehta JL. Vascular remodeling in diabetes mellitus. In: Mechanisms of vascular defects in diabetes mellitus. Springer; 2017. p. 73-93.
25. Yamagishi S, Matsui T, Nakamura K. Blockade of the advanced glycation end products (AGEs) and their receptor (RAGE) system is a possible mechanism for sustained beneficial effects of multifactorial intervention on mortality in type 2 diabetes. Med Hypotheses. 2008;71:749-51.
26. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Serum albumin and health in older people: review and meta-analysis. Maturitas. 2015;81:17-27.