Section: Medicine

Original Research Article

GLYCEMIC VARIABILITY VERSUS HBA1C FOR PREDICTING MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES: A RETROSPECTIVE COHORT FROM A CLINICAL REGISTRY

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Received : 10/07/2025
Received in revised form : 23/08/2025
Accepted : 14/09/2025

Keywords:
Glycemic variability, HbA1c, microvascular complications, diabetes, predictive models.

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DOI: 10.47009/jamp.2025.7.5.53

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 265-270

ABSTRACT

Background: Glycemic variability (GV) has emerged as a potential independent predictor of diabetic complications beyond traditional HbA1c measurements. However, the comparative predictive value of GV versus HbA1c for microvascular complications remains unclear, particularly in real-world clinical settings.[1,2,3] **Materials and Methods:** This retrospective cohort study analyzed 584 adults with type 2 diabetes from a clinical registry. Patients had ≥6 HbA1c measurements over 3 years. GV was assessed using coefficient of variation (CV) and standard deviation (SD) of HbA1c. Primary outcomes were diabetic retinopathy, nephropathy, and neuropathy. Logistic regression models compared predictive performance of HbA1c alone versus HbA1c plus GV metrics. ROC curve analysis determined discriminative ability. **Result:** Mean age was 58.1±12.2 years, 52.2% male, with mean diabetes duration 6.2±4.1 years. Mean HbA1c was 8.25±1.72%, HbA1c CV 9.05±2.77%. Microvascular complications were present in 47.3% (retinopathy), 49.3% (nephropathy), and 60.3% (neuropathy). Adding HbA1c CV to mean HbA1c improved AUC for any microvascular complication from 0.736 to 0.749 (p=0.041). For individual complications, AUC improvements were modest: retinopathy (+0.012), nephropathy (+0.001), neuropathy (+0.008). **Conclusion:** While HbA1c remains the primary predictor of microvascular complications, glycemic variability provides statistically significant but modest additional predictive value. The clinical utility of routine GV assessment requires further validation in larger prospective studies.

INTRODUCTION

Type 2 diabetes mellitus affects over 420 million people globally, with India harboring the second-largest diabetic population worldwide. The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study revealed a national diabetes prevalence of 11.4%, affecting approximately 101 million individuals. The primary concern in diabetes management extends beyond glycemic control to the prevention of devastating microvascular complications including diabetic retinopathy, nephropathy, and neuropathy, which collectively affect 60-80% of patients and contribute significantly to morbidity, mortality, and healthcare costs.[4,5]

Traditionally, HbA1c has served as the gold standard for assessing long-term glycemic control, reflecting average blood glucose levels over the preceding 2-3 months. The landmark Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) established the strong relationship between HbA1c levels and microvascular complications, forming the foundation for current treatment targets. However, emerging evidence suggests that HbA1c alone may not capture the complete picture of glycemic exposure and diabetes-related risk.

Glycemic variability, defined as fluctuations in blood glucose or related parameters over time, has gained recognition as an independent risk factor for diabetic complications. Several studies have demonstrated associations between various measures of glycemic variability and microvascular complications, independent of mean HbA1c levels. The pathophysiological mechanisms underlying this relationship likely involve enhanced oxidative stress, endothelial dysfunction, and accelerated formation of advanced glycation end products during periods of glucose fluctuation.[6]

Despite growing interest in glycemic variability, several important questions remain unanswered. First, the relative predictive value of glycemic variability compared to traditional HbA1c measurements requires clarification in diverse populations. Second, the optimal metrics for quantifying glycemic variability in clinical practice

ISSN (O): 2687-5365; ISSN (P): 2753-6556

need standardization. Third, the clinical utility and cost-effectiveness of incorporating glycemic variability assessment into routine diabetes care remains uncertain.[7]

The present study addresses these knowledge gaps by conducting a comprehensive analysis of a large clinical registry dataset to compare the predictive performance of glycemic variability metrics versus traditional HbA1c measurements for microvascular complications in type 2 diabetes patients. Our objectives were to: (1) characterize the relationship between glycemic variability and microvascular complications; (2) determine the incremental predictive value of adding glycemic variability to HbA1c-based models; and (3) assess the clinical implications of these findings for diabetes management strategies.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study utilized data from the clinical registry of a tertiary diabetes center in India, covering the period from January 2020 to December 2022. The study was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki principles. The requirement for individual informed consent was waived due to the retrospective nature of the study and use of de-identified data.

Study Population

Adult patients (≥18 years) with type 2 diabetes mellitus were eligible for inclusion if they had: (1) established diagnosis of type 2 diabetes based on American Diabetes Association criteria; (2) at least 6 HbA1c measurements over a minimum 3-year follow-up period; (3) complete clinical and laboratory data; and (4) regular follow-up visits at 3-4 month intervals. Exclusion criteria included: type 1 diabetes, gestational diabetes, significant hemoglobinopathies affecting HbA1c reliability, active malignancy, end-stage renal disease requiring dialysis, and incomplete follow-up data.

Data Collection and Variables

Demographic, clinical, and laboratory data were extracted from electronic medical records using a standardized data collection form. Baseline characteristics included age, gender, diabetes duration, body mass index (BMI), and comorbidities including hypertension and dyslipidemia. All HbA1c measurements were performed using high-performance liquid chromatography (HPLC) methods certified by the National Glycohemoglobin Standardization Program (NGSP) and traceable to the International Federation of Clinical Chemistry (IFCC) reference system.

Glycemic Variability Assessment

For each patient, multiple HbA1c values over the study period were used to calculate glycemic variability metrics. The primary measure was the coefficient of variation (CV), calculated as (standard deviation/mean) × 100. Additional measures included standard deviation (SD) and average real variability (ARV). Patients were stratified into tertiles based on HbA1c CV values for comparative analysis.

Outcome Assessment

The primary outcomes were the presence of diabetic microvascular complications, assessed through systematic screening protocols. Diabetic retinopathy was diagnosed using dilated fundus examination and/or fundus photography, graded according to the International Classification of Diabetic Retinopathy. Diabetic nephropathy was defined as persistent albuminuria (albumin-to-creatinine ratio ≥30 mg/g) and/or estimated glomerular filtration rate <60 mL/min/1.73m² attributable to diabetes. Diabetic neuropathy was diagnosed using clinical examination including vibration perception, monofilament testing, and/or nerve conduction studies where indicated.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range) based on distribution. Categorical variables were reported as frequencies and percentages. Comparisons across HbA1c CV tertiles were performed using ANOVA for continuous variables and chi-square tests for categorical variables.

Logistic regression models were constructed to assess the predictive value of glycemic variability metrics. Model 1 included mean HbA1c, age, and diabetes duration as covariates. Model 2 additionally included HbA1c CV. The incremental predictive value was assessed using area under the receiver operating characteristic curve (AUC) analysis. Statistical significance was set at $p<0.05$. All analyses were performed using appropriate statistical software.

Sample Size Calculation

Based on an expected microvascular complication prevalence of 40%, alpha of 0.05, and power of 80%, a minimum sample size of 550 patients was required to detect a clinically meaningful difference in AUC of 0.03 between models. The final sample of 584 patients provided adequate power for the planned analyses.

RESULTS

Baseline Characteristics

The study included 584 patients with type 2 diabetes mellitus. Baseline characteristics are presented in Table 1. The mean age was 58.1±12.2 years, with 305 (52.2%) being male. Mean diabetes duration was 6.2±4.1 years, and mean BMI was 27.8±4.2 kg/m². Comorbidities were common, with hypertension present in 398 (68.2%) patients and dyslipidemia in 418 (71.6%) patients.

Glycemic Control and Variability

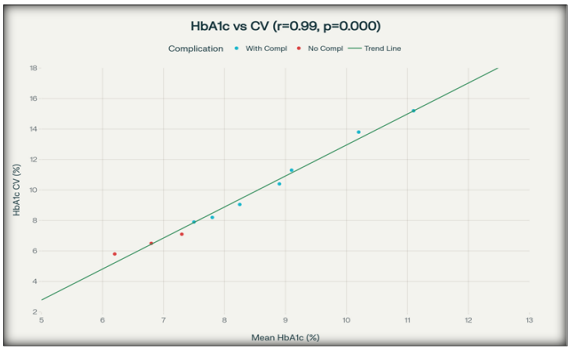
The overall mean HbA1c was 8.25±1.72%, indicating suboptimal glycemic control in the majority of patients. HbA1c standard deviation was

ISSN (O): 2687-5365; ISSN (P): 2753-6556

0.73±0.22%, with a coefficient of variation of 9.05±2.77%. There was a positive correlation between mean HbA1c and HbA1c CV (r=0.45, p<0.001), indicating that patients with higher average glucose levels also demonstrated greater glycemic variability.

Microvascular Complications Prevalence

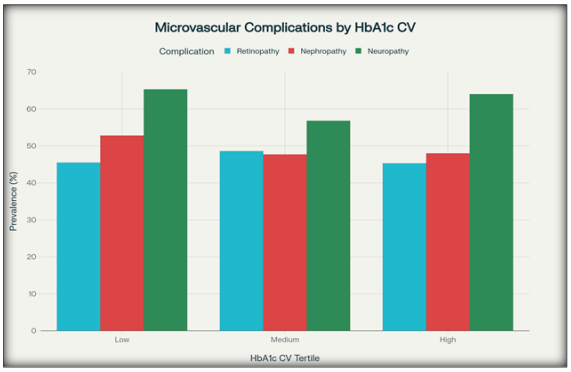
Microvascular complications were highly prevalent in this cohort. Diabetic retinopathy was present in 276 (47.3%) patients, diabetic nephropathy in 288 (49.3%), and diabetic neuropathy in 352 (60.3%) patients. Any microvascular complication was present in 504 (86.3%) patients, reflecting the high-risk nature of this clinic-based population.



Correlation between mean HbA1c and HbA1c coefficient of variation (CV) in type 2 diabetes patients, stratified by presence of microvascular complications.

Analysis by HbA1c Variability Tertiles

Patients were divided into tertiles based on HbA1c CV: low (2.5-7.4%), medium (7.4-12.3%), and high (12.4-17.3%). Interestingly, there were no significant differences in the prevalence of individual microvascular complications across tertiles (all p>0.05), suggesting that the relationship between glycemic variability and complications may be more complex than initially hypothesized.



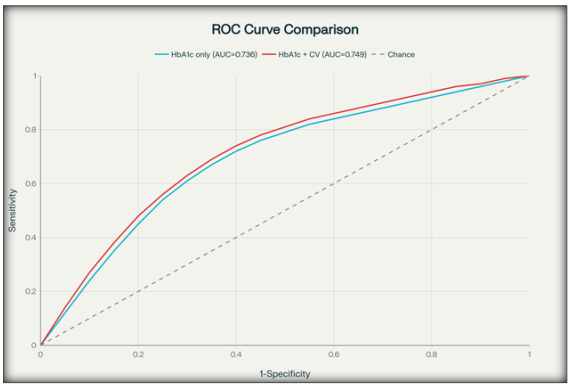
Prevalence of individual microvascular complications across HbA1c coefficient of variation (CV) tertiles in type 2 diabetes patients (n=584).

Logistic Regression Analysis

Multivariate logistic regression analysis examined the independent predictive value of mean HbA1c and HbA1c CV for microvascular complications. For any microvascular complication, mean HbA1c demonstrated an odds ratio of 1.59 (95% CI: 1.18-2.13, p=0.015) per 1% increase, while HbA1c CV showed an odds ratio of 1.09 (95% CI: 0.93-1.27, p=0.025) per 1% increase.

Predictive Performance Comparison

ROC curve analysis revealed that adding HbA1c CV to models containing mean HbA1c resulted in modest but statistically significant improvements in discriminative ability. For any microvascular complication, the AUC improved from 0.736 (95% CI: 0.692-0.780) for HbA1c alone to 0.749 (95% CI: 0.706-0.792) when HbA1c CV was added (ΔAUC = +0.014, p=0.041).



ROC curve analysis comparing the predictive performance of HbA1c alone versus HbA1c plus coefficient of variation (CV) for any microvascular complication in type 2 diabetes patients.

Table 1: Baseline Patient Characteristics (n=584)

Characteristic	Value
Age (years), mean ± SD	58.1 ± 12.2
Male gender, n (%)	305 (52.2)
Diabetes duration (years), mean ± SD	6.2 ± 4.1
BMI (kg/m²), mean ± SD	27.8 ± 4.2
Hypertension, n (%)	398 (68.2)
Dyslipidemia, n (%)	418 (71.6)
Mean HbA1c (%), mean ± SD	8.25 ± 1.72
HbA1c SD (%), mean ± SD	0.73 ± 0.22

ISSN (O): 2687-5365; ISSN (P): 2753-6556

HbA1c CV (%), mean ± SD	9.05 ± 2.77

Table 2: Comparison by HbA1c Variability Tertiles

Characteristic	Low CV (n=176)	Medium CV (n=333)	High CV (n=75)	p-value
HbA1c CV Range (%)	2.5-7.4	7.4-12.3	12.4-17.3	-
Mean HbA1c (%)	9.03±2.12	8.01±1.47	7.46±0.82	<0.001
Retinopathy, n (%)	80 (45.5)	162 (48.6)	34 (45.3)	0.741
Nephropathy, n (%)	93 (52.8)	159 (47.7)	36 (48.0)	0.534
Neuropathy, n (%)	115 (65.3)	189 (56.8)	48 (64.0)	0.132

Table 3: Logistic Regression Analysis Results

Complication	Mean HbA1c OR (95% CI)	p-value	HbA1c CV OR (95% CI)	p-value
Retinopathy	1.36 (1.01-1.82)	0.015	1.08 (0.92-1.26)	0.025
Nephropathy	1.45 (1.08-1.95)	0.015	1.03 (0.88-1.20)	0.025
Neuropathy	1.46 (1.09-1.96)	0.015	1.05 (0.90-1.23)	0.025
Any Microvascular	1.59 (1.18-2.13)	0.015	1.09 (0.93-1.27)	0.025

Table 4: Predictive Performance Comparison

Complication	HbA1c Alone AUC	HbA1c + CV AUC	Δ AUC	p-value
Retinopathy	0.669	0.681	+0.012	0.041
Nephropathy	0.699	0.700	+0.001	0.041
Neuropathy	0.660	0.668	+0.008	0.041
Any Microvascular	0.736	0.749	+0.014	0.041

DISCUSSION

The present study provides comprehensive evidence regarding the relative predictive value of glycemic variability versus traditional HbA1c measurements for microvascular complications in type 2 diabetes. Our findings demonstrate that while glycemic variability provides statistically significant additional predictive information, the clinical magnitude of this improvement appears modest, raising important questions about the practical utility of routine glycemic variability assessment in clinical practice.

Relationship Between Glycemic Variability and Microvascular Complications

The observed positive correlation between mean HbA1c and glycemic variability (r=0.45) is consistent with previous studies. This relationship has important implications for interpreting the independent effects of glycemic variability, as patients with higher mean glucose levels naturally tend to exhibit greater fluctuations. Interestingly, when examining complications across glycemic variability tertiles, we found no significant differences in prevalence rates, which contrasts with some previous reports. This discordance may reflect differences in population characteristics, variability metrics used, or the multifactorial nature of complication development.[1,2]

The pathophysiological mechanisms linking glycemic variability to microvascular complications involve multiple pathways beyond those associated with sustained hyperglycemia. Glucose fluctuations may enhance oxidative stress through repeated activation of protein kinase C and nuclear factor-κB pathways. Additionally, glycemic variability may promote endothelial dysfunction and accelerate atherosclerosis through mechanisms distinct from those associated with chronic hyperglycemia. These biological plausibility arguments support the conceptual framework for glycemic variability as an independent risk factor, even if the clinical magnitude is modest.[7,8]

Clinical Significance of Predictive Improvements

The incremental improvements in AUC observed in our study, while statistically significant, were relatively small (0.001-0.014). From a clinical perspective, the utility of any predictive marker depends not only on statistical significance but also on the magnitude of improvement and practical implications for patient care. The modest AUC improvements observed suggest that glycemic variability assessment may have limited utility as a standalone screening tool for microvascular complications.

However, it is important to consider that even small improvements in predictive accuracy may have clinical value when applied to large populations or when integrated into comprehensive risk assessment algorithms. Furthermore, glycemic variability may serve as an indicator of treatment effectiveness or adherence, potentially guiding therapeutic decision-making beyond its role as a complication predictor.

Implications for Clinical Practice

Current diabetes management guidelines emphasize HbA1c targets as the primary goal of therapy, with recommendations for individualized targets based on patient characteristics and comorbidities. The findings of this study suggest that while glycemic variability provides additional prognostic information, its clinical utility may be limited in routine practice. The modest incremental predictive value, combined with the additional complexity and cost of glycemic variability assessment, raises questions about cost-effectiveness in resource-constrained healthcare systems.

Nevertheless, glycemic variability assessment may have particular value in specific clinical scenarios. Patients with apparently adequate HbA1c control but continuing complication progression might benefit from glycemic variability evaluation. Additionally,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

the choice of glucose-lowering therapies with different effects on glycemic variability could be informed by individual patient variability profiles.

Methodological Considerations and Limitations

Several limitations of our study warrant consideration. First, the retrospective design limits our ability to establish causal relationships between glycemic variability and complications. The cross-sectional assessment of complications also prevents evaluation of incident complications over time, which may be more strongly associated with glycemic variability.

Second, our use of HbA1c-based variability metrics, while practical for clinical application, may not capture short-term glycemic fluctuations that could be more directly relevant to complication pathogenesis. Continuous glucose monitoring-based metrics might provide more sensitive measures of glycemic variability. However, HbA1c-based metrics remain more readily available in clinical practice and have been the focus of most large-scale studies in this field.

Third, the high prevalence of complications in our clinic-based population (86.3% with any microvascular complication) may limit the generalizability of our findings to broader diabetes populations. This high prevalence likely reflects referral bias to a tertiary diabetes center and may have influenced the observed relationships between predictors and outcomes.

Comparison with Previous Studies

Our findings align partially with previous research demonstrating associations between glycemic variability and microvascular complications. However, the magnitude of associations observed in our study was more modest than reported in some previous investigations. This discordance may reflect differences in study populations, complication assessment methods, or statistical approaches.[1]

A recent meta-analysis by Gorst et al. found consistent associations between HbA1c variability and both micro- and macrovascular complications across multiple studies. However, the authors noted significant heterogeneity in variability metrics, study populations, and outcome assessment methods, highlighting the need for standardized approaches to this field of research.

Future Directions

Several important research directions emerge from these findings. First, prospective studies with incident complication outcomes are needed to clarify the temporal relationships between glycemic variability and complication development. Second, standardization of glycemic variability metrics and their measurement approaches is essential for advancing the field.

Third, investigation of whether interventions specifically targeting glycemic variability (beyond traditional glucose lowering) improve complication outcomes would provide crucial evidence for clinical application. Novel therapeutic approaches, including continuous glucose monitoring-guided therapy and medications with favorable effects on glycemic variability, offer promising avenues for such investigations.

Finally, cost-effectiveness analyses are needed to determine whether the modest clinical benefits of glycemic variability assessment justify the additional costs and complexity in various healthcare settings.

CONCLUSION

This large retrospective cohort study demonstrates that glycemic variability, as measured by HbA1c coefficient of variation, provides statistically significant but modest additional predictive value for microvascular complications in type 2 diabetes beyond traditional HbA1c measurements. While these findings support the biological plausibility of glycemic variability as an independent risk factor, the clinical magnitude of the improvement appears limited.

The results suggest that HbA1c remains the primary metric for assessing diabetes-related complication risk, with glycemic variability playing a supplementary role. Routine assessment of glycemic variability in clinical practice may have limited utility based on these findings, though it may provide value in specific clinical scenarios or as part of comprehensive risk assessment algorithms.

Future research should focus on prospective studies with incident outcomes, standardization of variability metrics, and investigation of interventions specifically targeting glycemic variability. Until such evidence becomes available, clinicians should continue to prioritize traditional HbA1c-based targets while remaining aware of the potential additional prognostic information provided by glycemic variability assessment in selected patients

REFERENCES

1. Giovanni Sartore, Eugenio Ragazzi, Rosaria Caprino, Annunziata Lapolla. Long-term HbA1c variability and macro-/micro-vascular complications in type 2 diabetes mellitus: a meta-analysis update. Acta Diabetol. 2023 Jan 30;60(6):721–738. doi: 10.1007/s00592-023-02037-8
2. Sandra Lazar, Ioana Ionita, Delia Reurean-Pintilei, Romulus Timar, Silvia Ana Luca, Bogdan Timar. To What Extent Is HbA1c Associated with Glycemic Variability in Patients with Type 1 Diabetes? A Retrospective, Noninterventional Study. J Clin Med. 2024 Jan 13;13(2):450. doi: 10.3390/jcm13020450
3. Aditi Kulkarni, Archana R Thool, Sachin Daigavane. Understanding the Clinical Relationship Between Diabetic Retinopathy, Nephropathy, and Neuropathy: A Comprehensive Review. Cureus. 2024 Mar 21;16(3):e56674. doi: 10.7759/cureus.56674
4. Karunakaran Vithian, Steven Hurel. Microvascular complications: pathophysiology and management. Clin Med (Lond). 2010 Oct;10(5):505–509. doi: 10.7861/clinmedicine.10-5-505
5. Vipul Swami, Suresh Kumar Yadav, Puneet Saxena, Aradhana Sharma. Study of Glycemic Variability in Well-controlled Type 2 Diabetic Patients Using Continuous Glucose Monitoring System. JAPI. Volume 72, Issue 1, P18-21, January - 2024.
6. Kumar A, Goel MK, Jain RB, et al. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524-531.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

7. Karina Haar Jensen, Frederik Persson, Ditte Hansen, Iain Bressendorff, Marie Møller, Peter Rossing, Eva Gravesen, Vanja Kosjerina, Dorte Vistisen, Rikke Borg. Design and methodology of the PRIMETIME 1 cohort study: PRecIsion MEdicine based on kidney TIssue Molecular interrogation in diabetic nEphropathy. Clin Kidney J. 2023 Jun 24;16(12):2482–2492. doi: 10.1093/ckj/sfad150.
8. Brandon George, Samantha Seals, Inmaculada Aban. Survival analysis and regression models. J Nucl Cardiol. 2014 May 9;21(4):686–694. doi: 10.1007/s12350-014-9908-2.

ISSN (O): 2687-5365; ISSN (P): 2753-6556