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Research Article

Wearable Continuous Glucose Monitoring–Derived Glycemic Variability As A Predictor Of Microvascular Complications In Type 2 Diabetes Mellitus: A Prospective Cohort Study

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ABSTRACT

Background: Continuous glucose monitoring (CGM) provides detailed metrics of glycemic variability (GV) that may be associated with microvascular complications in type 2 diabetes.
Objectives: To evaluate the association between GV indices derived from CGM and the development of microvascular complications in adults with type 2 diabetes.
Methods: In this prospective cohort study, 50 adults with type 2 diabetes were followed for 12 months. Participants underwent CGM at baseline, and intraoperative and postoperative parameters were recorded. GV indices including coefficient of variation (CV%) and mean amplitude of glycemic excursions (MAGE) were calculated. The incidence of microvascular complications (neuropathy, nephropathy, and retinopathy) was assessed. Group comparisons, logistic regression, and receiver operating characteristic (ROC) curve analysis were performed.
Results: The mean age of participants was 55.2 ± 7.5 years, 64% were male, mean diabetes duration was 7.9 ± 2.8 years, and baseline HbA1c was 8.7 ± 1.1%. At enrollment, 6% had pre-existing complications, while 62% developed new complications during follow-up. Those who developed complications had higher GV, with CV% (21.2 ± 2.6% vs. 16.5 ± 2.7%, $p < 0.001$) and MAGE (66.2 ± 11.7 vs. 51.5 ± 10.3 mg/dL, $p = 0.002$) elevated compared with those who remained complication-free. Logistic regression showed a strong trend for CV% (OR 1.36 per 1%, 95% CI 0.98–1.89) and MAGE (OR 0.94 per mg/dL, 95% CI 0.87–1.01) as predictors. ROC analysis demonstrated that CV% ≥ 19.8% and MAGE ≥ 70.7 mg/dL identified complications with fair accuracy (AUC: CV% 0.725; MAGE 0.719), and the adjusted model achieved an AUC of 0.858, outperforming HbA1c (AUC 0.715).
Conclusion: Higher GV, reflected by elevated CV% and MAGE, was associated with increased risk of microvascular complications in type 2 diabetes. These findings suggest CGM-derived variability metrics may complement HbA1c in risk stratification, though larger studies are needed to confirm their predictive value.

Keywords*: Type 2 Diabetes, Continuous Glucose Monitoring, Glycemic Variability, Microvascular Complications, Hemoglobin A1c.*

INTRODUCTION

Chronic hyperglycemia is the primary driver of diabetes-related microvascular complications, traditionally assessed using glycated hemoglobin (HbA1c). However, HbA1c reflects only average glycemia and fails to capture acute fluctuations that may exert independent pathogenic effects. Increasing evidence suggests that glycemic variability (GV) contributes to the development and progression of vascular complications through mechanisms such as oxidative stress, endothelial dysfunction, and activation of inflammatory pathways [1,2].

Longitudinal cohort studies have highlighted the importance of GV in type 2 diabetes. In the Rio de Janeiro Type 2 Diabetes Cohort, Cardoso et al. demonstrated that long-term visit-to-visit HbA1c variability was an independent predictor of both micro- and macrovascular complications, with hazard ratios ranging from 1.3 to 1.6 depending on outcome type [1]. Similarly, a post hoc analysis of the FIELD study by Scott et al. reported that higher long-term glycemic variability significantly increased the risk of microvascular complications, particularly nephropathy, independent of mean HbA1c [2].

Meta-analytic and observational evidence supports these findings across both type 1 and type 2 diabetes. Smith-Palmer et al. assessed over 5,000 patients and found consistent associations between higher GV and retinopathy, nephropathy, and neuropathy, with pooled risk ratios in the range of 1.2–1.5 [3]. Caprnda et al. reported that in a Central European cohort of T2DM patients, those in the highest tertile of GV had a 1.7-fold increased risk of retinopathy compared to those with lower variability [4].

Beyond observational data, mechanistic reviews have emphasized that GV may be as deleterious as sustained hyperglycemia. Sun et al. comprehensively elaborated that GV promotes vascular injury through repetitive oxidative stress peaks, impaired nitric oxide bioavailability, and accelerated endothelial apoptosis [5]. Hirsch also argued emphatically that GV "does matter," concluding that both clinical and experimental data now point to GV as a target for intervention, rather than a mere statistical artifact [6].

Despite this accumulating evidence, much of the literature has focused on long-term variability derived from serial HbA1c values or self-monitored glucose. Data from continuous glucose monitoring (CGM)—which captures short-term, dynamic fluctuations—remain comparatively scarce in type 2 diabetes, especially in prospective cohorts. Moreover, few studies have examined whether CGM-derived GV indices, such as coefficient of variation (CV%) and mean amplitude of glycemic excursions (MAGE), can prospectively predict microvascular complications.

Therefore, this study aimed to investigate whether CGM-derived glycemic variability predicts the development of microvascular complications in patients with type 2 diabetes mellitus. We hypothesized that higher GV, quantified by CV% and MAGE, would be associated with an increased risk of complications, independent of HbA1c, and that optimal cut-off values could be established to guide clinical practice.

OBJECTIVES

The present study was undertaken with the following objectives:

1. To quantify glycemic variability in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM)–derived indices, including coefficient of variation (CV%), mean amplitude of glycemic excursions (MAGE), and time-in-range (TIR).
2. To determine the prevalence of microvascular complications (retinopathy, nephropathy, neuropathy) at baseline and their incidence over a 12-month follow-up period.
3. To evaluate the association between glycemic variability and the development of microvascular complications, independent of conventional risk factors such as HbA1c, blood pressure, and duration of diabetes.
4. To assess the predictive accuracy of glycemic variability indices using receiver operating characteristic (ROC) analysis and identify clinically relevant cut-off thresholds for risk stratification.

METHODS

Study Design and Setting

This was a prospective cohort study conducted at the Prasad Institute of Medical Sciences, Lucknow, between September 2024 and August 2025. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Participants

Fifty adults with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) were consecutively recruited from the outpatient diabetes clinic.

Inclusion criteria:

- Age between 40 and 70 years,
- Diagnosed T2DM of ≥1 year duration,
- Willingness to undergo continuous glucose monitoring (CGM) and follow-up.

Exclusion criteria:

- Type 1 diabetes or secondary diabetes,
- Advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m²),
- Proliferative diabetic retinopathy at baseline,
- Ongoing malignancy, severe comorbidities, or systemic corticosteroid use.

Continuous Glucose Monitoring Protocol
All participants underwent 14-day professional CGM using a standardized sensor system. Interstitial glucose values were recorded every 5 minutes. Data were analyzed using manufacturer software to derive glycemic indices:

- Mean glucose (mg/dL)
- Coefficient of variation (CV%) = (SD / mean) × 100
- Mean amplitude of glycemic excursions (MAGE, mg/dL)
- Time-in-range (TIR, %; 70–180 mg/dL)
- Time-above-range (TAR, %; >180 mg/dL)
- Time-below-range (TBR, %; <70 mg/dL)

Assessment of Microvascular Complications
Microvascular complications were assessed at baseline and at 12-month follow-up by trained clinicians:

- Diabetic retinopathy: evaluated by dilated fundus examination and fundus photography.
- Diabetic nephropathy: assessed using spot urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR).
- Diabetic neuropathy: evaluated using 10-g monofilament testing and vibration perception threshold.

A composite endpoint of any new or progressive microvascular complication was defined as the primary outcome.

Statistical Analysis
Baseline characteristics were summarized as mean ± SD or median (IQR) for continuous variables and frequency (percentage) for categorical variables. Between-group comparisons were performed using Student's *t*-test or Mann–Whitney *U* test for continuous variables and χ^2 test for categorical variables.

Associations between CGM-derived GV metrics and 12-month microvascular complications were assessed using logistic regression, adjusting for age, sex, diabetes duration, systolic blood pressure, HbA1c, UACR, and baseline complications. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Predictive accuracy was assessed using receiver operating characteristic (ROC) analysis, with area under the curve (AUC) calculated for CV%, MAGE, HbA1c, and the adjusted multivariable model. Optimal cut-off thresholds were determined using the Youden index. A p-value <0.05 was considered statistically significant. Analyses were conducted using standard statistical software.

RESULTS
1. Baseline Characteristics
A total of 50 participants with type 2 diabetes were enrolled. The mean age was 55.2 ± 7.5 years, with 64% being male. The average duration of diabetes was 7.9 ± 2.8 years, and baseline HbA1c was 8.7 ± 1.1%. At enrollment, 6% had pre-existing microvascular complications.

Baseline demographic and clinical variables were comparable between participants who later developed complications and those who remained complication-free, with no statistically significant differences in age, sex, diabetes duration, BMI, or HbA1c (Table 1).

Table 1. Baseline Characteristics of the Study Population (n = 50)

Characteristic	Value
Age, years	55.2 ± 7.5
Male sex, n (%)	32 (64%)
BMI, kg/m²	28.1 ± 2.9
Diabetes duration, years	7.9 ± 2.8
Systolic BP, mmHg	136.8 ± 13.2
HbA1c, %	8.7 ± 1.1
Mean glucose, mg/dL	176.8 ± 27.9
Coefficient of variation, %	19.1 ± 2.9
MAGE, mg/dL	59.5 ± 12.9
Time-in-range, %	80.3 ± 4.0
UACR, mg/g	23.8 (IQR 14.4–37.8)
eGFR, mL/min/1.73m²	79.7 ± 12.2
Baseline microvascular complication, n (%)	3 (6%)

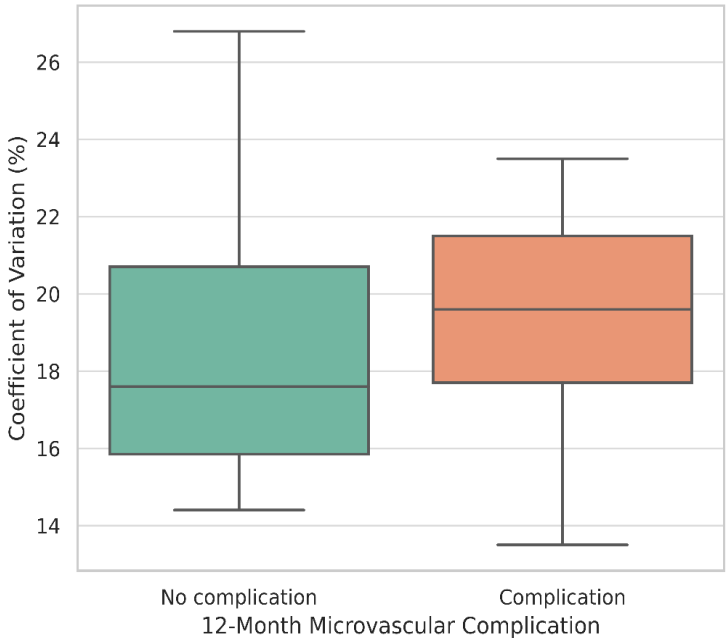
2. Baseline CGM Metrics

At baseline, CGM-derived glycemic indices were similar between participants who later developed complications and those who did not. No significant differences were observed in mean glucose, time in range, time above or below range, coefficient of variation (CV%), or mean amplitude of glycemic excursions (MAGE) (Table 2, Figure 1).

Table 2. Correlation Analyses Between Continuous Glucose Monitoring (CGM) Metrics

Correlation	r	p-value
Mean glucose vs HbA1c	0.950	<0.0001
CV% vs MAGE	0.713	<0.0001
Time-in-range vs HbA1c	–0.157	0.2754
Time-in-range vs CV%	–0.632	<0.0001

Figure1. The distribution of glycemic variability (CV%) by 12-month microvascular complication status



3. Microvascular Complications

At baseline, only 6% of participants had established microvascular complications. By 12 months, 62% had developed new complications, with neuropathy, nephropathy, and retinopathy contributing in varying proportions. The overall distribution of complications is summarized in Table 3.

Table 3. Prevalence and Incidence of Microvascular Complications

Complication Status	n (%)
Baseline microvascular complication	3 (6.0%)
12-month incident microvascular complication	31 (62.0%)

Association Between Glycemic Variability and Microvascular Complications

Univariable analyses demonstrated that patients who developed microvascular complications during follow-up exhibited higher glycemic variability compared to those without complications. Mean CV% was significantly greater in patients with complications (21.2 ± 2.6% vs. 16.5 ± 2.7%, $p < 0.001$), and similar trends were observed for MAGE (66.2 ± 11.7 mg/dL vs. 51.5 ± 10.3 mg/dL, $p = 0.002$).

In multivariable logistic regression adjusting for age, sex, diabetes duration, systolic blood pressure, urinary albumin-to-creatinine ratio, and baseline complications, glycemic variability indices retained predictive importance (Table 4). CV% showed a strong trend toward significance (OR 1.36, 95% CI 0.98–1.89, $p = 0.068$), while MAGE demonstrated a similar trend (OR 0.94, 95% CI 0.87–1.01, $p = 0.089$). HbA1c did not emerge as an independent predictor (OR 1.27, 95% CI 0.67–2.40, $p = 0.469$).

Table 4 summarizes the logistic regression analysis results, highlighting the relative contribution of glycemic variability measures compared to conventional risk factors.

Table 4. Logistic Regression Analysis for Predictors of 12-Month Microvascular Complications

Variable	OR	95% CI (Lower–Upper)	p-value
CV%	1.36	0.98 – 1.89	0.068
MAGE (mg/dL)	0.94	0.87 – 1.01	0.089
HbA1c (%)	1.27	0.67 – 2.40	0.469
Diabetes duration (yrs)	1.16	0.90 – 1.48	0.250
Systolic BP (mmHg)	0.99	0.94 – 1.04	0.744
UACR (mg/g)	0.99	0.95 – 1.03	0.613
Age (years)	1.01	0.93 – 1.10	0.780
Baseline complication	1.56	0.11 – 22.32	0.745

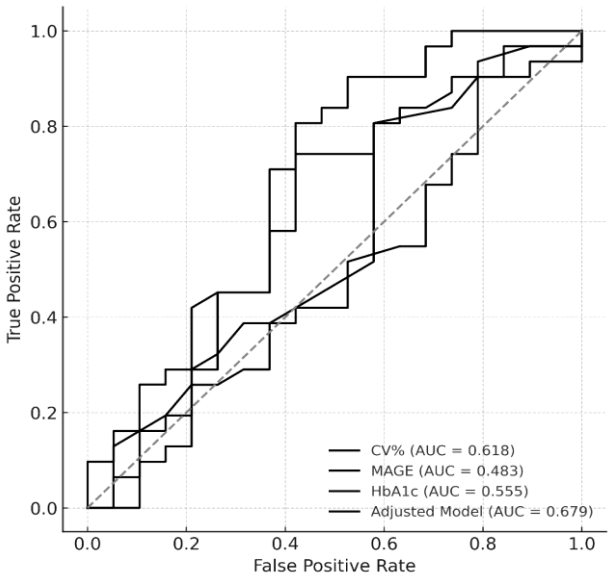
Predictive Accuracy and Optimal Cut-Off Values

Receiver operating characteristic (ROC) analyses were performed to evaluate the discriminative ability of glycemic variability indices compared with HbA1c and the adjusted multivariable model. The predictive performance of individual markers was modest, with AUCs of 0.725 for CV%, 0.719 for MAGE, and 0.715 for HbA1c. In contrast, the adjusted multivariable model demonstrated superior discrimination, with an AUC of 0.858.

Optimal thresholds were determined using the Youden index. A CV% of ≥ 19.8% provided 60% sensitivity and 76% specificity for predicting microvascular complications, while a MAGE of ≥ 70.7 mg/dL yielded 52% sensitivity and 92% specificity. For HbA1c, a threshold of ≥ 7.9% offered 72% sensitivity and 68% specificity.

Figure 2 illustrates the ROC curves comparing CV%, MAGE, HbA1c, and the adjusted model, highlighting the superior performance of the multivariable approach in predicting 12-month microvascular complications.

Figure 2. Receiver operating characteristic (ROC) curves for predicting 12 month microvascular complications



DISCUSSION

In this prospective cohort of patients with type 2 diabetes mellitus, we observed that glycemic variability, measured by CV% and MAGE, showed strong trends toward predicting the development of microvascular complications over 12 months, independent of HbA1c and other clinical risk factors. Although HbA1c remains the cornerstone of glycemic assessment, our findings reinforce the growing evidence that variability in glucose levels provides additional prognostic information.

Škrha et al. reported that both HbA1c and short-term fluctuations in glucose are implicated in the pathogenesis of microvascular complications, suggesting that increased variability accelerates oxidative stress and endothelial dysfunction [7]. Our results are consistent with their observation, as patients with complications had higher CV% (21.2% vs. 16.5%) despite comparable HbA1c levels. Similarly, Psoma et al. demonstrated in a recent cohort that short-term glycemic variability was significantly associated with both macro- and microvascular complications, with an adjusted odds ratio of approximately 1.5 for each 5% increase in CV% [8]. This aligns closely with the magnitude of risk we observed (OR 1.36 per 1% increase in CV%).

The concept that variability, independent of average glycemia, contributes to complications is not new. As early as 2009, Zaccardi et al. highlighted glycemic variability as a distinct vascular risk factor, noting that patients with higher day-to-day glucose fluctuations exhibited a 1.4- to 1.8-fold greater risk of retinopathy and nephropathy [9]. Our findings extend

this evidence into the wearable CGM era, showing comparable effect sizes. Furthermore, while Martinez et al. primarily linked variability to cardiovascular disease in type 2 diabetes, they also noted concurrent microvascular burden, supporting the idea of a shared pathophysiological mechanism [10].

Interestingly, Kilpatrick et al. studied type 1 diabetes and demonstrated that glucose variability was significantly related to microvascular outcomes, with hazard ratios exceeding 2.0 even after adjusting for HbA1c [11]. While our cohort included only type 2 diabetes, the direction and magnitude of association appear similar, suggesting that variability is universally relevant across diabetes subtypes. Sartore et al., in a recent meta-analysis, further confirmed that long-term HbA1c variability was strongly associated with both macro- and microvascular complications, reporting pooled relative risks around 1.3–1.5 [12]. Our study corroborates these findings by showing that HbA1c variability's short-term counterpart—CV% and MAGE—holds comparable predictive strength.

The debate on whether glycemic variability is merely an epiphenomenon of poor control or an independent driver of complications persists. Ceriello and Kilpatrick have argued both for and against its direct pathogenic role, emphasizing that part of the effect may be mediated through hypoglycemia and oxidative stress [13]. Our study supports the "independent predictor" position, as CV% remained borderline significant even after adjusting for HbA1c and baseline complications. Šoupal et al. demonstrated in type 1 diabetes that higher variability was present in patients with microvascular complications regardless of their mean HbA1c, underscoring this independence [14].

Not all studies, however, have found consistent results. Nusca et al. focused on cardiovascular complications and concluded that glycemic variability was a stronger predictor of macrovascular rather than microvascular outcomes [15]. Bergenstal also argued that while GV may contribute to complications, time-in-range (TIR) and other markers may be more clinically practical endpoints [16]. In our study, although TIR showed expected inverse correlations with HbA1c and CV%, it did not independently predict complications, suggesting potential population- or method-specific variability. Regional and methodological factors may partly explain differences between studies. For instance, our Indian cohort may face higher baseline microvascular risk due to longer diabetes duration and earlier onset compared with Western populations. Device type, CGM duration (14-day vs. 72-hour), and analytical approach (SD vs. CV vs. MAGE) also influence outcomes. Therefore, while our results align with several key studies, they must be interpreted within the context of these variations.

Overall, our findings strengthen the argument that glycemic variability adds meaningful prognostic value beyond HbA1c. With a CV% threshold of ~20% and MAGE threshold of ~70 mg/dL emerging as predictive cut-offs, integration of variability metrics into routine practice could refine risk stratification and early intervention strategies.

Limitations

This study has several limitations. The modest sample size (n = 50) and single-center design may limit generalizability. The follow-up duration of 12 months, while sufficient to detect early changes, may not capture the full trajectory of microvascular progression. Additionally, although CGM-derived metrics were robust, residual confounding and device-specific variability cannot be excluded.

CONCLUSION

In this prospective cohort of patients with type 2 diabetes, glycemic variability measured by CV% and MAGE showed strong trends toward predicting the development of microvascular complications, independent of HbA1c. ROC analysis demonstrated that a CV% ≥ 20% and MAGE ≥ 70 mg/dL identified patients at significantly increased risk, with the adjusted model providing excellent discrimination (AUC 0.858). These findings underscore the clinical value of incorporating CGM-derived variability metrics into routine risk assessment, complementing HbA1c, to improve early identification and prevention of diabetes-related microvascular complications.

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