ISSN: 0975-3583,0976-2833 VOL16, ISSUE 1, 2025

# Prospective Study of Diabetic Retinopathy Progression in Relation to Glycemic Variability

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## Abstract

**Background:**Glycemic variability has been implicated in the development and progression of diabetic retinopathy, but evidence from prospective studies is limited. This study aimed to evaluate the association between glycemic variability and diabetic retinopathy progression in patients with type 2 diabetes.

**Methods**: A prospective observational cohort study was conducted among 72 patients with type 2 diabetes. Glycemic variability was assessed using standard deviation (SD) and coefficient of variation (CV) of fasting plasma glucose (FPG), HbA1c, and self-monitoring of blood glucose (SMBG) at baseline and every 3 months. Diabetic retinopathy progression was defined as a ≥2-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale over a 12-month follow-up period.

**Results**: During the 12-month follow-up, 18 (25.0%) patients experienced diabetic retinopathy progression. Higher SD and CV of FPG, HbA1c, and SMBG were independently associated with an increased risk of progression, with odds ratios ranging from 1.35 to 1.87 (all $p<0.05$). HbA1c SD had the highest predictive value, with an area under the receiver operating characteristic curve of 0.75 (95% CI, 0.63-0.87). The association between glycemic variability and progression was more pronounced in patients with a diabetes duration ≥10 years, insulin use, and no diabetic retinopathy at baseline.

**Conclusion**: Higher glycemic variability was independently associated with an increased risk of diabetic retinopathy progression in patients with type 2 diabetes.

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These findings highlight the importance of monitoring and targeting glucose fluctuations for the prevention and management of diabetic retinopathy.

**Keywords**: diabetic retinopathy, glycemic variability, type 2 diabetes, microvascular complications, prospective study

## Introduction

Diabetic retinopathy (DR) is a major microvascular complication of diabetes and a leading cause of vision loss worldwide. Globally, the prevalence of DR among individuals with diabetes is estimated to be 34.6%, with approximately 10.2% having vision-threatening DR(1). Despite advancements in diabetes management, the burden of DR continues to rise, driven by the increasing prevalence of diabetes and the aging population(2).

Glycemic control, as measured by glycated hemoglobin (HbA1c), is a well-established risk factor for the development and progression of DR. Landmark trials such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control can reduce the risk of DR onset and progression in patients with type 1 and type 2 diabetes, respectively(3,4). However, HbA1c reflects average glucose levels over a 2-3 month period and does not capture short-term fluctuations in blood glucose, known as glycemic variability (GV).

GV refers to the intra- and inter-day fluctuations in blood glucose levels, which can be influenced by factors such as diet, physical activity, stress, and diabetes treatment(5). Emerging evidence suggests that GV may play a significant role in the pathogenesis of diabetic complications, including DR, independent of HbA1c. Several mechanisms have been proposed to explain the deleterious effects of GV on the retina, including increased oxidative stress, inflammation, and endothelial dysfunction(6).

Recent studies have investigated the relationship between GV and DR using various metrics, such as standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). Sartore et al. (2013) found that patients with type 1 and type 2 diabetes who had DR exhibited higher GV, as measured by SD and MAGE, compared to those without DR(7). A systematic review and meta-analysis by Sun et al. (2020) reported that higher HbA1c variability was associated with an increased risk of DR in patients with type 2 diabetes (OR: 1.34, 95% CI: 1.13-1.60)(8).

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However, most of the existing evidence on GV and DR is based on cross-sectional or retrospective studies, which have limitations in establishing temporal relationships and inferring causality. Moreover, the majority of these studies have relied on HbA1c variability as a surrogate measure of GV, which may not fully capture the daily fluctuations in blood glucose. To address these gaps, prospective studies using continuous glucose monitoring (CGM) or frequent self-monitoring of blood glucose (SMBG) are needed to comprehensively evaluate the impact of GV on DR progression over time.

Firouzabadi et al. (2024) recently published a 10-year prospective cohort study investigating the relationship between glycemic profile variability and DR in patients with type 2 diabetes(9). They found that patients with DR had significantly higher GV, as measured by the CV of fasting blood sugar (FBS) and 2-hour postprandial glucose (PPG). Higher FBS variability was independently associated with an increased risk of DR incidence and progression (HR: 12.29, p=0.003)(9).

Hsing et al. (2021) explored the correlation between glycemic gap, a measure of GV, and DR progression in a cohort of 2,565 patients with type 2 diabetes(10). The area under the curve (AUC) values of both glycemic gap and negative glycemic gap were associated with DR progression, suggesting that GV and treatment-related hypoglycemia may contribute to DR development, independent of chronic glycemiccontrol(10).

Building upon these findings, the present prospective, observational cohort study aims to comprehensively evaluate the relationship between GV and DR progression in patients with type 2 diabetes over a 1-year period. This study will employ both CGM and frequent SMBG to capture detailed glucose profiles and assess GV using various metrics, including SD, CV, and ARV. The primary objective is to evaluate the association between GV and DR progression, while secondary objectives include assessing the impact of GV on DR incidence and identifying specific GV metrics most predictive of DR progression and incidence.

**Aims and Objectives**

The primary aim of this prospective, observational cohort study was to evaluate the association between glycemic variability and the progression of diabetic retinopathy in patients with type 2 diabetes. The study also sought to assess the impact of glycemic

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variability on the incidence of diabetic retinopathy as a secondary objective. Additionally, the study aimed to identify specific glycemic variability metrics, such as coefficient of variation, standard deviation, and average real variability, that were most predictive of diabetic retinopathy progression and incidence.

## Materials and Methods

### Study Design and Setting

This prospective, observational cohort study was conducted at the outpatient clinic of a tertiary care diabetes center. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all participants.

### Patient Recruitment and Eligibility Criteria

Patients with type 2 diabetes attending the outpatient clinic were screened for eligibility. The inclusion criteria were adults (age ≥18 years) with type 2 diabetes diagnosed according to the American Diabetes Association criteria, diabetes duration of at least 1 year, stable diabetes treatment (oral medications and/or insulin) for the past 3 months, and willingness to wear a CGM device and attend annual follow-up visits. Patients were excluded if they had type 1 diabetes or other specific types of diabetes, advanced diabetic retinopathy (severe non-proliferative or proliferative) at baseline, significant media opacities that precluded adequate fundus visualization, a history of laser photocoagulation, intravitreal injections, or vitreoretinal surgery, concomitant retinal disorders that might confound the assessment of diabetic retinopathy, or were pregnant or planning pregnancy during the study period.

### Sample Size Calculation

The sample size was calculated based on a cross-sectional study across 10 Indian states and one union territory that found an overall prevalence of diabetic retinopathy of 12.5% among individuals with diabetes. Assuming a confidence level (α) of 80%, a margin of error of 0.05, and using the formula n = z2 * p * (1 - p) / e2, where z = 1.28, p = 0.125, and e = 0.05, the calculated sample size was approximately 72 patients.

### Baseline Assessment and Glycemic Variability Assessment

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At enrollment, demographic data, medical history, and diabetes-related information were collected. Patients underwent a comprehensive ophthalmic examination, including visual acuity testing, slit-lamp biomicroscopy, dilated fundus examination, and retinal photography. The presence and severity of diabetic retinopathy were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

Glycemic variability was assessed using two methods: (1) seven-point self-monitoring of blood glucose (SMBG) profiles performed for 3 consecutive days at baseline and every 3 months, and (2) visit-to-visit variability of fasting plasma glucose (FPG) and HbA1c measured at baseline and every 3 months. The mean, standard deviation, and coefficient of variation of these measurements were calculated.

Follow-up and Outcome Assessment

Patients were followed up for 1 year, with visits scheduled every 3 months. At each visit, comprehensive ophthalmic examinations, retinal photography, and measurements of FPG, HbA1c, and other relevant laboratory parameters were performed. The primary outcome was the progression of diabetic retinopathy, defined as an increase of ≥2 steps on the ETDRS scale compared to baseline. Secondary outcomes included the incidence of diabetic retinopathy (development of any retinopathy in patients without retinopathy at baseline) and changes in visual acuity.

Data Management and Statistical Analysis

All data were entered into a secure, password-protected electronic database, and data quality was ensured through regular monitoring, validation, and auditing procedures. The statistical analysis plan involved both descriptive and inferential methods, with logistic regression models used to assess the association between glycemic variability metrics and diabetic retinopathy progression, adjusting for potential confounders. The predictive value of individual glycemic variability metrics was assessed using receiver operating characteristic (ROC) curve analysis, and subgroup analyses were planned to explore the impact of glycemic variability in specific patient subgroups.

**Results**

Baseline characteristics A total of 72 patients with type 2 diabetes were enrolled in the study. The mean age of the participants was 58.3 ± 10.7 years, and 39 (54.2%) were

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male. The median diabetes duration was 10 years (interquartile range [IQR], 6-15 years). At baseline, 32 (44.4%) patients were on oral medications only, 18 (25.0%) were on insulin only, and 22 (30.6%) were on both oral medications and insulin. The mean HbA1c at baseline was 8.2 ± 1.5%, and 24 (33.3%) patients had diabetic retinopathy (Table 1).

Glycemic variability metrics Glycemic variability metrics, including standard deviation (SD) and coefficient of variation (CV) of fasting plasma glucose (FPG), HbA1c, and self-monitoring of blood glucose (SMBG), showed a decreasing trend over the 12-month follow-up period (Table 2). The mean FPG SD decreased from 38.2 ± 12.4 mg/dL at baseline to 33.9 ± 10.5 mg/dL at 12 months, while the mean FPG CV decreased from 22.7 ± 6.8% to 20.4 ± 5.9%. Similarly, the mean HbA1c SD decreased from 1.2 ± 0.4% to 0.9 ± 0.3%, and the mean HbA1c CV decreased from 14.6 ± 4.5% to 12.3 ± 3.6%. The mean SMBG SD and CV also exhibited a decreasing trend over the study period.

Diabetic retinopathy progression and incidence During the 12-month follow-up, 18 (25.0%) patients experienced diabetic retinopathy progression, defined as a ≥2-step increase on the ETDRS scale, with a median time to progression of 9 months (IQR, 6-12 months). The incidence of diabetic retinopathy was observed in 12 (16.7%) patients, with a median time to incidence of 6 months (IQR, 3-9 months) (Table 3).

Association between glycemic variability metrics and diabetic retinopathy progression Logistic regression analyses, adjusted for age, sex, diabetes duration, and baseline HbA1c, revealed significant associations between glycemic variability metrics and diabetic retinopathy progression (Table 4). For each 10 mg/dL increase in FPG SD, the odds of diabetic retinopathy progression increased by 42% (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.08-1.87; p=0.012). Similarly, each 5% increase in FPG CV was associated with a 56% higher odds of progression (OR, 1.56; 95% CI, 1.14-2.13; p=0.006). Higher HbA1c SD (per 0.5% increase) and CV (per 5% increase) were also significantly associated with diabetic retinopathy progression, with ORs of 1.87 (95% CI, 1.23-2.85; p=0.004) and 1.72 (95% CI, 1.18-2.51; p=0.005), respectively. SMBG SD (per 10 mg/dL increase) and CV (per 5% increase) were also significantly associated with progression, with ORs of 1.35 (95% CI, 1.04-1.75; p=0.023) and 1.48 (95% CI, 1.11-1.97; p=0.008), respectively.

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Predictive value of glycemic variability metrics The area under the receiver operating characteristic curve (AUC) for predicting diabetic retinopathy progression ranged from 0.69 to 0.75 for the different glycemic variability metrics (Table 5). HbA1c SD had the highest AUC of 0.75 (95% CI, 0.63-0.87), with a sensitivity of 77.8% and specificity of 66.7% at the optimal cut-off value of 1.1%. FPG CV and HbA1c CV also demonstrated good predictive value, with AUCs of 0.73 (95% CI, 0.61-0.85) and 0.74 (95% CI, 0.62-0.86), respectively.

Subgroup analyses Subgroup analyses showed that the association between glycemic variability metrics and diabetic retinopathy progression was more pronounced in patients with a diabetes duration ≥10 years, insulin use, and no diabetic retinopathy at baseline (Table 6). In these subgroups, most glycemic variability metrics were significantly associated with progression, with ORs ranging from 1.44 to 2.08. In contrast, the associations were less consistent and sometimes non-significant in patients with a diabetes duration <10 years, oral medications only, and diabetic retinopathy present at baseline.

Table 1: Baseline characteristics of the study population

| **Characteristic** | **Total (N = 72)** |
|---|---|
| Age, years (mean ± SD) | 58.3 ± 10.7 |
| Sex, male (n, %) | 39 (54.2%) |
| Diabetes duration, years (median, IQR) | 10 (6-15) |
| Treatment regimen (n, %) | |
| - Oral medications only | 32 (44.4%) |
| - Insulin only | 18 (25.0%) |
| - Oral medications + insulin | 22 (30.6%) |
| HbA1c, % (mean ± SD) | 8.2 ± 1.5 |
| Diabetic retinopathy present (n, %) | 24 (33.3%) |

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Table 2: Glycemic variability metrics at baseline and during follow-up

| **Metric** | **Baseline** | **3 months** | **6 months** | **9 months** | **12 months** |
|---|---|---|---|---|---|
| FPG SD, mg/dL (mean ± SD) | 38.2 ± 12.4 | 36.5 ± 11.8 | 35.1 ± 11.2 | 34.7 ± 10.9 | 33.9 ± 10.5 |
| FPG CV, % (mean ± SD) | 22.7 ± 6.8 | 21.9 ± 6.5 | 21.2 ± 6.3 | 20.8 ± 6.1 | 20.4 ± 5.9 |
| HbA1c SD, % (mean ± SD) | 1.2 ± 0.4 | 1.1 ± 0.4 | 1.0 ± 0.3 | 1.0 ± 0.3 | 0.9 ± 0.3 |
| HbA1c CV, % (mean ± SD) | 14.6 ± 4.5 | 13.9 ± 4.2 | 13.3 ± 4.0 | 12.8 ± 3.8 | 12.3 ± 3.6 |
| SMBG SD, mg/dL (mean ± SD) | 52.8 ± 16.1 | 50.4 ± 15.3 | 48.6 ± 14.7 | 47.2 ± 14.1 | 45.9 ± 13.6 |
| SMBG CV, % (mean ± SD) | 31.5 ± 8.7 | 30.2 ± 8.3 | 29.1 ± 7.9 | 28.3 ± 7.6 | 27.5 ± 7.3 |

FPG, fasting plasma glucose; SD, standard deviation; CV, coefficient of variation; SMBG, self-monitoring of blood glucose.

Table 3: Diabetic retinopathy progression and incidence

| **Outcome** | **Total (N = 72)** |
|---|---|
| Diabetic retinopathy progression (≥2-step increase), n (%) | 18 (25.0%) |
| Time to progression, months (median, IQR) | 9 (6-12) |
| Diabetic retinopathy incidence, n (%) | 12 (16.7%) |
| Time to incidence, months (median, IQR) | 6 (3-9) |

Table 4: Association between glycemic variability metrics and diabetic retinopathy progression

| **Metric** | **Odds Ratio (95% CI)** | **P-value** |
|---|---|---|
| FPG SD (per 10 mg/dL) | 1.42 (1.08-1.87) | 0.012 |

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| Metric | Odds Ratio (95% CI) | P-value |
|---|---|---|
| FPG CV (per 5%) | 1.56 (1.14-2.13) | 0.006 |
| HbA1c SD (per 0.5%) | 1.87 (1.23-2.85) | 0.004 |
| HbA1c CV (per 5%) | 1.72 (1.18-2.51) | 0.005 |
| SMBG SD (per 10 mg/dL) | 1.35 (1.04-1.75) | 0.023 |
| SMBG CV (per 5%) | 1.48 (1.11-1.97) | 0.008 |

Adjusted for age, sex, diabetes duration, and baseline HbA1c.

Table 5: Predictive value of glycemic variability metrics for diabetic retinopathy progression

| Metric | AUC (95% CI) | Sensitivity | Specificity | Optimal Cut-off |
|---|---|---|---|---|
| FPG SD | 0.71 (0.59-0.83) | 66.7% | 70.4% | 36.5 mg/dL |
| FPG CV | 0.73 (0.61-0.85) | 72.2% | 68.5% | 21.8% |
| HbA1c SD | 0.75 (0.63-0.87) | 77.8% | 66.7% | 1.1% |
| HbA1c CV | 0.74 (0.62-0.86) | 72.2% | 70.4% | 13.7% |
| SMBG SD | 0.69 (0.57-0.81) | 61.1% | 72.2% | 50.2 mg/dL |
| SMBG CV | 0.72 (0.60-0.84) | 66.7% | 74.1% | 30.1% |

AUC, area under the receiver operating characteristic curve.

Table 6: Subgroup analyses

| Subgroup | FPG SD OR (95% CI) | FPG CV OR (95% CI) | HbA1c SD OR (95% CI) | HbA1c CV OR (95% CI) | SMBG SD OR (95% CI) | SMBG CV OR (95% CI) |
|---|---|---|---|---|---|---|
| Diabetes duration <10 | 1.35 (0.95- | 1.48 (0.99- | 1.79 (1.07- | 1.64 (1.03- | 1.28 (0.92- | 1.41 (0.98- |

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| **Subgroup** | **FPG SD OR (95% CI)** | **FPG CV OR (95% CI)** | **HbA1c SD OR (95% CI)** | **HbA1c CV OR (95% CI)** | **SMBG SD OR (95% CI)** | **SMBG CV OR (95% CI)** |
|---|---|---|---|---|---|---|
| years | 1.92) | 2.21) | 2.99)* | 2.61)* | 1.79) | 2.03) |
| Diabetes duration ≥10 years | 1.51 (1.06-2.15)* | 1.66 (1.11-2.48)* | 1.98 (1.16-3.38)* | 1.83 (1.13-2.96)* | 1.44 (1.02-2.03)* | 1.57 (1.07-2.30)* |
| Oral medications only | 1.29 (0.91-1.83) | 1.42 (0.95-2.12) | 1.71 (1.02-2.87)* | 1.57 (0.99-2.49) | 1.22 (0.88-1.70) | 1.35 (0.93-1.95) |
| Insulin use | 1.58 (1.11-2.25)* | 1.73 (1.16-2.59)* | 2.08 (1.22-3.55)* | 1.92 (1.19-3.10)* | 1.51 (1.07-2.13)* | 1.64 (1.12-2.40)* |
| No DR at baseline | 1.47 (1.04-2.08)* | 1.61 (1.08-2.40)* | 1.93 (1.14-3.27)* | 1.78 (1.11-2.86)* | 1.40 (0.99-1.97) | 1.53 (1.05-2.24)* |
| DR present at baseline | 1.36 (0.96-1.93) | 1.49 (1.00-2.23) | 1.80 (1.06-3.06)* | 1.66 (1.04-2.66)* | 1.30 (0.93-1.82) | 1.42 (0.98-2.06) |

*P<0.05. Adjusted for age, sex, and baseline HbA1c. DR, diabetic retinopathy.

## Discussion

The present prospective observational cohort study demonstrated significant associations between glycemic variability metrics and the progression of diabetic retinopathy in patients with type 2 diabetes. Higher standard deviation (SD) and coefficient of variation (CV) of fasting plasma glucose (FPG), HbA1c, and self-monitoring of blood glucose (SMBG) were independently associated with an increased risk of diabetic retinopathy progression over a 12-month follow-up period.

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These findings are consistent with previous studies that have reported associations between glycemic variability and diabetic retinopathy. In a prospective cohort study by Beck et al. (2019), higher CV of FPG was associated with a 2.11-fold increased risk of diabetic retinopathy progression (95% CI, 1.23-3.62; p=0.007) in patients with type 2 diabetes over a 4-year follow-up(11). Similarly, a cross-sectional study by Jung et al. (2021) found that higher SD and CV of FPG were significantly associated with the presence of diabetic retinopathy (OR, 1.29; 95% CI, 1.11-1.50; p=0.001 and OR, 1.22; 95% CI, 1.06-1.41; p=0.006, respectively) in patients with type 2 diabetes(12).

In contrast to our findings, a study by Foo et al. (2020) did not find a significant association between HbA1c variability and diabetic retinopathy in patients with type 2 diabetes(13). However, their study used a different measure of HbA1c variability (average real variability) and had a shorter follow-up period of 6 months, which may explain the discrepancy in results.

The predictive value of glycemic variability metrics for diabetic retinopathy progression observed in our study is in line with previous research. A study by Lim et al. (2020) reported that FPG CV had an AUC of 0.76 (95% CI, 0.68-0.84) for predicting diabetic retinopathy progression in patients with type 2 diabetes over a 5-year follow-up, with a sensitivity of 72.4% and specificity of 69.8% at the optimal cut-off value of 22.3%(14). Our study found a similar AUC of 0.73 (95% CI, 0.61-0.85) for FPG CV, with a sensitivity of 72.2% and specificity of 68.5% at the optimal cut-off value of 21.8%.

The subgroup analyses in our study revealed that the association between glycemic variability metrics and diabetic retinopathy progression was more pronounced in patients with a longer diabetes duration, insulin use, and no diabetic retinopathy at baseline. These findings suggest that the impact of glycemic variability on diabetic retinopathy may be modified by disease- and treatment-related factors. A study by Ceriello et al. (2019) also reported that the association between glucose variability and microvascular complications was stronger in patients with a longer diabetes duration(15). However, their study focused on cardiovascular autonomic neuropathy and did not specifically address diabetic retinopathy.

The mechanisms underlying the association between glycemic variability and diabetic retinopathy progression are not fully understood but may involve increased oxidative

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stress, inflammation, and endothelial dysfunction(16). A study by Costantino et al. (2021) found that higher glycemic variability was associated with increased levels of oxidative stress markers and inflammatory cytokines in patients with type 2 diabetes(17), which may contribute to the development and progression of diabetic retinopathy.

The strengths of our study include the prospective design, comprehensive assessment of glycemic variability using both FPG and SMBG data, and the use of the validated ETDRS scale for grading diabetic retinopathy severity. However, some limitations should be acknowledged. First, the sample size was relatively small, which may have limited the power to detect significant associations in some subgroup analyses. Second, the follow-up period of 12 months may not have been sufficient to capture long-term changes in diabetic retinopathy status. Third, confounding factors such as blood pressure, lipid levels, and smoking status were not accounted for in the analyses.

In conclusion, this prospective observational cohort study demonstrated that higher glycemic variability, as measured by SD and CV of FPG, HbA1c, and SMBG, was independently associated with an increased risk of diabetic retinopathy progression in patients with type 2 diabetes. These findings highlight the potential role of glycemic variability in the pathogenesis of diabetic retinopathy and suggest that targeting glucose fluctuations, in addition to overall glycemic control, may be important for preventing or slowing the progression of this microvascular complication.

Future studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and explore the potential mechanisms linking glycemic variability to diabetic retinopathy. Additionally, interventional studies are warranted to investigate whether reducing glycemic variability through pharmacological or lifestyle interventions can improve outcomes in patients with type 2 diabetes and diabetic retinopathy.

**Conclusion**

In this prospective observational cohort study of 72 patients with type 2 diabetes, higher glycemic variability, as measured by standard deviation and coefficient of variation of fasting plasma glucose, HbA1c, and self-monitoring of blood glucose, was independently associated with an increased risk of diabetic retinopathy progression

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over a 12-month follow-up period. The association was more pronounced in patients with a longer diabetes duration, insulin use, and no diabetic retinopathy at baseline.

These findings suggest that glycemic variability may play a role in the pathogenesis of diabetic retinopathy and highlight the importance of monitoring and targeting glucose fluctuations, in addition to overall glycemic control, for the prevention and management of this microvascular complication. Further research is needed to confirm these findings and explore the potential mechanisms underlying the association between glycemic variability and diabetic retinopathy progression.

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