doi.org/10.36721/PJPS.2026.39.12.341.1

Glycated hemoglobin and retinal microvascular changes in type 2 diabetic retinopathy patients treated with metformin and/or insulin: A retrospective study

Zhongshu Han and Ping Zhu*
Department of Ophthalmology, Affiliated Haining Hospital of Jiaxing University (Haining People's Hospital), Jiaxing, China

Abstract: **Background**: Diabetes retinopathy (DR) is the main blinding complication of type 2 diabetes (T2DM). Glycated hemoglobin (HbA_{1c}) can reflect long-term blood glucose control and optical coherence tomography (OCT) can evaluate retinal microvessels. The effects of metformin and insulin regimens on microvascular structure are not yet clear. **Objectives**: To explore the relationship between HbA_{1c} levels and retinal microvascular changes in T2DM patients receiving metformin and/or insulin and to evaluate the impact of different hypoglycemic regimens on DR progression. **Methods**: This retrospective study included T2DM patients with non-proliferative DR treated between January 2023 and December 2024. After propensity score matching (PSM), 31 patients per group received metformin monotherapy (M), insulin-based therapy (Ins), or combined therapy (M-Ins). HbA_{1c}, HbA_{1c} variability (HbA_{1c}-SD), DR grade, central macular thickness (CMT), retinal nerve fiber layer (RNFL) thickness and superficial/deep capillary plexus (SCP/DCP) density were recorded at baseline, 1- and 2-year follow-up. Multiple linear regression and Cox regression were used. **Results**: After 2 years, HbA_{1c} and HbA_{1c}-SD decreased significantly in all groups ($p<0.05$), with greater reduction in the M-Ins group. DR progression was documented in 23 patients (24.7%), with rates of 16.1%, 38.7% and 19.4% in the M, Ins and M-Ins groups, respectively ($p>0.05$). OCT showed reduced CMT/RNFL and increased SCP/DCP density in all groups ($p<0.05$), with better improvement in M-Ins group ($p<0.05$). HbA_{1c} correlated positively with CMT/RNFL and negatively with SCP/DCP ($p<0.05$). Cox regression indicated that higher HbA_{1c}-SD was an independent risk factor for DR progression (HR = 3.216, 95% CI: 1.011–10.230, p= 0.048), while metformin use was an independent protective factor (HR=0.694, 95% CI: 0.451–0.840, p=0.001). **Conclusion**: Metformin plus insulin was associated with greater HbA_{1c} reduction, decreased glycemic variability and increased retinal vessel density and may thus slow DR progression. Both HbA_{1c}-SD and SCP density were correlated with DR progression risk, supporting the combined use of glycemic variability and OCT parameters for clinical evaluation and treatment guidance.

Keywords: Glycated hemoglobin; Insulin; Metformin; Optical coherence tomography; Retinal microvasculature; Type 2 diabetes retinopathy

Submitted on 12-05-2026 – Revised on 07-06-2026 – Accepted on 30-06-2026 – Available online on 25-08-2026 – Published on 01-12-2026

INTRODUCTION

Diabetes retinopathy (DR) is a serious microvascular complication of type 2 diabetes (T2DM), which involves the progressive injury of retinal capillary endothelial cells, the destruction of blood retinal barrier, vascular leakage, pathological neovascularization and activation of glial cells and ultimately leads to permanent visual impairment (Tuli *et al*., 2026). The pathogenesis of DR involves complex interactions across multiple molecular and cellular pathways. Chronic hyperglycemia initiates and sustains retinal microvascular damage through activation of the polyol and protein kinase C pathways, promotion of advanced glycation end-product deposition, upregulation of the hexosamine pathway and increased oxidative stress. (Tuli *et al*., 2026). Peripheral cell loss, basement membrane thickening, endothelial dysfunction and increased vascular permeability can collectively trigger clinical features of diabetic retinopathy, including microaneurysms, retinal hemorrhage, exudation and neovascularization (Antonetti *et al*., 2021). Research has shown that retinal neurodegeneration characterized by ganglion cell apoptosis and thinning of the nerve fiber layer may occur prior to microvascular abnormalities (Simó et al., 2018) In the management of T2DM patients with DR, hypoglycemic therapy should not only aim to achieve optimal blood glucose control, but also incorporate strategies to regulate systemic inflammation. A reasonable multi-drug regimen is crucial for preventing glucose fluctuations, as glucose fluctuations can exacerbate retinal microvascular damage and hinder vascular repair.

Long-term inadequate blood glucose control is a key risk factor for the development and progression of diabetic retinopathy. Glycated hemoglobin (HbA_{1c}) is closely related to the onset and deterioration of diabetes retinopathy (Rossing, 2023, UK Prospective Diabetes Study (UKPDS) Group, 1998). Recent studies have shown that in addition to average HbA_{1c} levels, blood glucose variability (GV) is also an important risk factor for the progression of diabetic retinopathy. HbA_{1c} variability is typically quantified by the standard

**Corresponding author:* e-mail: 15325739966@189.cn

deviation (HbA_{1c}-SD), which reflects the magnitude of long-term blood glucose fluctuations. And after adjusting for mean HbA_{1c}, it can independently predict DR progression (Monnier et al., 2023, Kim et al., 2021). Excessive glycemic variability may accelerate diabetic retinopathy progression through enhanced oxidative stress, inflammatory activation and endothelial dysfunction. (Ceriello et al., 2022b, Ceriello et al., 2022a). Optical coherence tomography (OCT) and OCT angiography (OCTA) have revolutionized the diagnosis and monitoring of diabetic retinopathy. OCT can achieve non-invasive, high-resolution visualization of retinal layering structure, accurately measuring macular center thickness (CMT), retinal nerve fiber layer (RNFL) thickness and other parameters (Javed *et al*., 2023) In terms of blood flow comparison, OCTA clearly visualizes the superficial capillary plexus (SCP) and deep capillary plexus (DCP) without contrast agents. It can also quantify vessel density (VD) and the area of avascular zone (FAZ) in the fovea centralis, providing a better method for evaluating retinal microvascular structure and function (Chua *et al*., 2024). There is evidence that OCTA can detect the lower VD in SCP and DCP and the increase of FAZ in diabetes patients without obvious clinical DR, which highlights its value for early DR screening and diagnosis (Guo *et al*., 2023) (Guo *et al*., 2023).

Metformin and insulin are basic drugs for the treatment of T2DM. Metformin reduces blood glucose by inhibiting liver glucose production and enhancing peripheral insulin sensitivity (Foretz *et al*., 2023). In addition to blood sugar control, it can also improve blood lipid status, reduce weight and provide cardiovascular protection (Rena *et al*., 2013). Metformin may exert a protective effect on the retina through activation of AMP-activated protein kinase (AMPK), along with reduction of oxidative stress and inflammation and improvement of endothelial function (Fan et al., 2020, Li et al., 2018). Insulin therapy is effective in patients with long-standing disease, declining beta-cell function, inadequate response to oral agents, or advanced complications. (Davies *et al*., 2022). Insulin therapy can effectively reduce HbA_{1c} levels and minimize glucose fluctuations, but it is associated with an increased risk of hypoglycemia and weight gain (Holman *et al*., 2008). However, the impact of insulin therapy on DR remains controversial. There is a research report that suggests early deterioration of diabetic retinopathy (EWDR) after rapid glucose normalization (Holman et al., 2008, UK Prospective Diabetes Study (UKPDS) Group, 1998). The Diabetes Control and Complications Trial (DCCT) reported that early worsening of diabetic retinopathy (EWDR) occurred in 13.1% of patients in the intensive insulin group, versus 7.6% in the conventional group; however, this phenomenon was reversible within 18 months. Long-term intensive treatment was associated with a significantly reduced risk of DR progression (Shah *et al*., 2024). In clinical practice, metformin and insulin are commonly combined to achieve synergistic glycemic control, reduce insulin requirements, lower hypoglycemia risk and provide potential weight benefits. (Alasbily *et al*., 2025). However, the effects of different hypoglycemic strategies on retinal microvascular structure and their relationship with DR progression are still poorly understood. To date, few studies have evaluated the effects of metformin or insulin treatment on retinal microvascular changes in patients with T2DM and DR and most have been cross-sectional or small-sample studies without longitudinal data.

Based on this, the purpose of this study is to conduct a retrospective analysis, investigate the association between HbA_{1c} levels, HbA_{1c} variability and changes in retinal microvascular structure in patients with T2DM and non-proliferative diabetic retinopathy (NPDR) who received metformin or insulin treatment and evaluate the impact of different hypoglycemic regimens on DR progression and to provide evidence-based support for individualized glucose management and DR prevention strategies.

MATERIALS AND METHODS

Study subjects

This study is a retrospective clinical observational investigation, with data collection and analysis conducted independently by researchers not involved in patient treatment. Patients with T2DM and NPDR admitted to the Department of Endocrinology and Ophthalmology of Haining People's Hospital from January 2023 to December 2024 were screened via the electronic medical record system. Based on the glucose-lowering regimens received, patients were divided into three groups: metformin monotherapy (Group M), insulin-based therapy (Group Ins) and metformin plus insulin combination therapy (Group M-Ins). Propensity score matching (PSM) was applied at a 1:1:1 ratio(Austin, 2011, Rosenbaum and Rubin, 1983), ultimately including 31 patients in each group. The detailed selection process is illustrated in Fig. 1.

As the allocation of glucose-lowering regimens was non-randomized, PSM was employed to reduce selection bias by adjusting for baseline differences among the three groups. Treatment allocation—specifically, metformin use and insulin-based therapy as the primary regimen—was defined as the treatment variables. Covariates included age, sex, diabetes duration, baseline HbA_{1c}, body mass index (BMI), blood pressure, estimated glomerular filtration rate (eGFR) and baseline DR grade. Propensity scores were estimated using multivariate logistic regression models. Nearest-neighbor matching (1:1) with a caliper width of 0.2 was applied. After matching, each group comprised 31 patients, with all standardized differences < 0.1, indicating adequate covariate balance across groups.

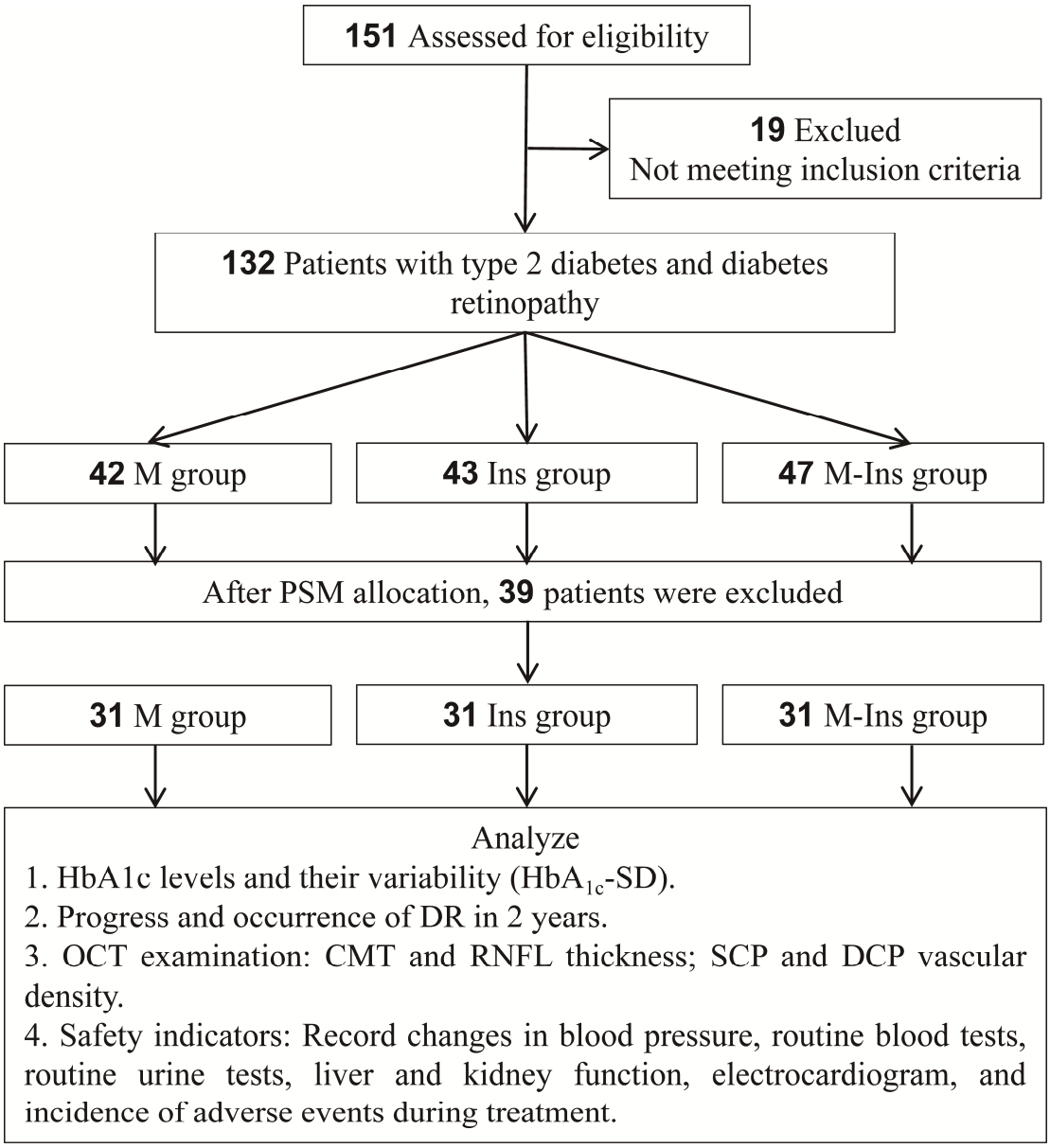

Fig. 1: Research flowchart.

Inclusion criteria

(1) Age ≥ 18 years; (2) Diagnosis of T2DM according to the World Health Organization (WHO) diagnostic criteria (American Diabetes Association Professional Practice Committee, 2025), with disease duration ≥ 1 year; (3) Confirmed NPDR by fundus examination and fundus fluorescein angiography (FFA); (4) Complete clinical data available, including HbA_{1c} measurements and OCT examinations at baseline and during follow-up; (5) Follow-up duration ≥ 2 years.

Exclusion criteria

(1) Type 1 diabetes mellitus or other specific types of diabetes; (2) Presence of proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), or a history of retinal laser photocoagulation, intravitreal injection, or vitrectomy; (3) Coexisting ocular disorders such as age-related macular degeneration, retinal vein occlusion, or glaucoma; (4) Severe hepatic or renal dysfunction (Child–Pugh class C or eGFR < 30 mL/min/1.73 m²); (5) Pregnancy or lactation; (6) Active malignancy or life expectancy < 2 years; (7) Incomplete clinical data or loss to follow-up.

Ethical statement

This study was conducted in strict accordance with the principles of the Declaration of Helsinki(Wen *et al*., 2025) and was approved by the Institutional Ethics Committee of Haining People's Hospital (Approval No. 2025-104). Written informed consent was retrospectively obtained from all participants in accordance with the Institutional Ethics Committee's requirements. All participants were

informed of the study purpose, treatment regimens and potential risks and provided written informed consent. All study data were anonymized to ensure patient privacy.

Sample size estimation

Sample size estimation was performed using G*Power 3.1 software (Kim *et al*., 2017). Based on previously reported differences in DR progression rates among the three treatment groups (Li et al., 2018, Fan et al., 2020), a medium effect size (Cohen's w = 0.30) was assumed. With a significance level of α = 0.05 and a statistical power of 0.80, the required sample size was calculated to be at least 29 patients per group (total n = 87). Following propensity score matching, 31 patients were included in each group, which met the pre-specified sample size requirements.

Treatment methods

All treatment regimens were retrospectively collected from patients' medical records, without any experimental intervention by the investigators.

M group: According to medical records, patients in this group were treated with metformin hydrochloride tablets at a dose of 500 mg twice daily, taken orally with meals. The dose was adjusted by the treating physician based on fasting blood glucose, 2-hour postprandial blood glucose and HbA_{1c} levels, with a maximum documented dose of 2000 mg/d.

Ins group: Based on medical records, patients received basal insulin therapy selected by their physicians according to pancreatic islet function and glycemic profiles. The following basal insulin formulations were documented: (1) insulin glargine injection, initiated at 0.2 U/(kg·day) subcutaneously once daily at bedtime; (2) insulin detemir injection, initiated at 0.2 U/(kg·day) subcutaneously once daily at bedtime or before breakfast; (3) insulin degludec injection, initiated at 0.16 U/(kg·day) subcutaneously once daily, with timing independent of meals. Insulin doses were titrated by the treating physician every 3 days based on fasting blood glucose levels: an increase of 2–4 U was applied if fasting glucose was >7.0 mmol/L, a reduction of 2–4 U if fasting glucose was <4.4 mmol/L, targeting a fasting glucose range of 4.4–7.0 mmol/L. The distribution of specific insulin types among the 31 patients could not be reliably extracted from medical records; therefore, subgroup analysis by insulin type was not performed.

M-Ins group: Medical records indicated that patients in this group received the same metformin regimen as the M group, along with basal insulin therapy as described for the Ins group.

Throughout the treatment period, all patients were provided with standardized diabetes education, which included guidance on diet, physical activity, blood glucose self-monitoring and hypoglycemia prevention. Regular follow-up assessments (every 3 months) were conducted to monitor blood glucose, HbA_{1c} and hepatic and renal function. Treatment regimens were adjusted accordingly based on the results of these evaluations.

Observation indicators

HbA_{1c} and HbA_{1c} variability

HbA_{1c} levels were collected at baseline (T0), one year after treatment (T1) and two years after treatment (T2). The following indices were calculated:

(1) Mean HbA_{1c};

(2) HbA_{1c}-SD, serving as an indicator of long-term glycemic variability, with adjustment for the number of measurements using the factor n/(n−1)(Lee *et al*., 2021)。

DR grading and progression assessment

Diabetic retinopathy grading was performed by trained ophthalmologists in accordance with the International Clinical Diabetic Retinopathy Severity Scale (Early Treatment Diabetic Retinopathy Study Research Group, 1991, Attiku et al., 2023) (mild, moderate and severe non-proliferative DR, as well as proliferative DR). In cases of disagreement, a senior attending ophthalmologist made the final determination. DR progression was defined as a worsening of at least one grade from baseline within two years or progression from NPDR to PDR. The observation period was calculated from baseline to the time of first documented progression (in months) or to the end of follow-up.

OCT examination

All patients underwent OCT/OCTA examinations using the same device (DREAM OCT), with image acquisition performed by a designated technician.

(1) *Central macular thickness (CMT)*: Measured as the retinal thickness (μm) within a 1 mm diameter circle centered on the fovea;

(2) *Retinal nerve fiber layer (RNFL) thickness*: Measured via a 3.4 mm diameter circular scan centered on the optic disc, with the average peripapillary RNFL thickness (μm) recorded;

(3) *OCTA parameters*: Macular scans of 3 × 3 mm or 6 × 6 mm were obtained. The superficial capillary plexus (SCP) and deep capillary plexus (DCP) were automatically segmented and vessel density (%) was recorded for both layers. Images with a quality score < 7 or significant motion artifacts were excluded from analysis (Chen *et al*., 2023).

Only one eye per patient (the eye with the higher baseline DR grade, or the right eye if both eyes were equally affected) was included in the analysis to avoid statistical bias from inter-eye correlation. All OCT/OCTA examinations were performed by a single trained technician using the same DREAM OCT device. The

built-in automated segmentation algorithm was used to delineate the superficial capillary plexus (from the internal limiting membrane to the inner plexiform layer) and the deep capillary plexus (from the inner plexiform layer to the outer plexiform layer). Vessel density was defined as the percentage area occupied by flowing blood vessels (vessels with detectable decorrelation signal) within the 3×3 mm or 6×6 mm macular scan region. Only scans with a quality score ≥ 7 (on a 10-point scale) and absence of significant motion artifacts or blink artifacts were included. Inter-observer reproducibility was not formally assessed, as this was a retrospective study; nevertheless, a single masked reader performed all analyses to ensure consistency.

Safety indicators

Record changes in blood pressure, routine blood tests, routine urine tests, liver and kidney function and electrocardiogram during the treatment period. Use the MedDRA system to record adverse events (ARs) (Brown *et al*., 1999).

Statistical analysis

Data were analyzed using SPSS 25.0. Normality was assessed with the Kolmogorov-Smirnov test and Q-Q plots and homogeneity of variance by Levene's test. Normally distributed continuous data are expressed as mean ± SD, with comparisons among three groups performed via one-way ANOVA; repeated-measures ANOVA was applied for within-group comparisons across time. Non-normally distributed data are presented as median (IQR) and intergroup differences were evaluated using the Kruskal-Wallis H test. Categorical data were expressed as cases (percentage, n %) and analyzed using the chi-square test.

Given the exploratory nature of this study, no adjustment for multiple comparisons (Bonferroni correction) was applied. For repeated-measures ANOVA, Mauchly's test of sphericity was performed; if violated, the Greenhouse–Geisser correction was used. The group × time interaction term was included in the model. When the interaction was significant, a one-way ANOVA at each time point, followed by Tukey's HSD post hoc correction, was applied for between-group comparisons. Unstandardized coefficients (B) with 95% confidence intervals are reported for linear regression models and hazard ratios (HR) with 95% confidence intervals are reported for Cox proportional hazards regression models.

RESULTS

Baseline characteristics

After PSM, there were no statistically significant differences in baseline characteristics ($p>0.05$), indicating good balance and comparability of baseline characteristics (Table 1).

HbA_{1c} levels and variability changes

During the 2-year follow-up, HbA_{1c} levels decreased significantly from baseline across all three groups (time main effect: $p < 0.001$; Table 2). At T1 and T2, HbA_{1c} values in the M-Ins group were significantly lower than those in the M and Ins groups ($p < 0.05$ for between-group comparisons), which suggests that combination therapy with metformin and insulin may be associated with greater and more sustained reductions in HbA_{1c}. Furthermore, HbA_{1c}-SD was significantly lower in the M and M-Ins groups than in the Ins group ($p = 0.020$).

DR progress status

During the 2-year follow-up, DR progression was observed in 23 patients (24.7%). As shown in Table 3, the progression rates in the M (5/31, 16.1%), Ins (12/31, 38.7%) and M-Ins (6/31, 19.4%) groups did not differ significantly ($p > 0.05$).

Changes in OCT parameters over time

At the end of the two-year follow-up period (Table 4), all three groups showed varying degrees of reduction in CMT compared to baseline, suggesting either alleviation of mild macular edema or potential structural remodeling. A mild to moderate decrease in RNFL thickness was observed across groups. This reduction may partly reflect either alleviation of subclinical macular edema or ongoing neurodegeneration. Therefore, the decline in RNFL should be interpreted with caution, as it does not necessarily indicate improved neural health. Notably, the magnitude of increase in both SCP and DCP vessel density was significantly greater in the M-Ins group compared to the other two groups ($p < 0.05$). The increase in SCP and DCP vessel density was significantly greater in the M-Ins group compared to the other two groups ($p < 0.05$).

The correlation between HbA_{1c} and OCT parameters

Multivariate linear regression was conducted to determine factors related to OCT parameters at T2, including CMT, RNFL thickness and VD in SCP and DCP. Independent variables included mean HbA_{1c} levels (averaged over T0, T1 and T2) and overall HbA_{1c}-SD over the two-year period. Baseline covariates such as age and OCT parameters at T0 and T1 were adjusted as potential confounders. The results demonstrated that HbA_{1c} level was significantly positively associated with CMT ($B = 9.872$, 95% CI: 7.509–12.235, $p<0.001$) and RNFL thickness ($B=6.032$, 95% CI: 4.600–7.465, $p<0.001$). Conversely, HbA_{1c} level was significantly negatively associated with vessel density in both the SCP ($B=–2.821$, 95% CI: –3.930 to –1.712, $p<0.001$) and DCP ($B=–3.910$, 95% CI: –5.038 to –2.782, $p<0.001$). All VIF values were below 2, indicating no significant multicollinearity among the independent variables in any of the models (Table 5).

Table 1: Baseline characteristics [mean±SD, n (%)].

Variables	M group (n=31)	Ins group (n=31)	M-Ins group (n=31)	F/χ^2	p
Age (years)	56.2±8.3	57.0±7.9	55.8±8.1	0.370	0.692
Gender					
Male	13 (41.9)	14 (45.2)	12 (38.7)		
Female	18 (58.1)	17 (54.8)	19 (61.3)	0.265	0.876
Diabetes duration (years)	8.4±2.1	8.9±2.5	8.7±2.3	0.302	0.740
BMI (kg/m²)	25.6±3.3	25.9±3.1	25.4±3.2	0.131	0.878
SBP (mmHg)	134.5±12.8	136.2±13.1	135.1±12.4	0.137	0.872
DBP (mmHg)	82.6±4.2	81.4±4.9	82.2±4.1	0.690	0.504
eGFR (mL·min^{-1}·1.73m^{-2})	88.5±15.2	86.9±16.0	89.3±14.8	0.194	0.824
LDL-C (mmol/L)	2.7±0.7	2.7±0.7	2.7±0.8	0.204	0.816
Hypertension	19 (61.3)	18 (58.1)	20 (64.5)	0.272	0.873
HbA_{1c} (%)	9.0±1.1	9.2±1.0	9.2±0.8	0.374	0.689
DR grading					
Mild NPDR	13 (41.9)	12 (38.7)	12 (38.7)	0.141	0.998
Moderate NPDR	11 (35.5)	11 (35.5)	11 (35.5)		
Severe NPDR	7 (22.6)	8 (25.8)	8 (25.8)		

Note: BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: Estimated Glomerular Filtration Rate; LDL-C: Low-Density Lipoprotein Cholesterol; HbA_{1c}: Hemoglobin A_{1c} (Glycated Hemoglobin); DR: Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy. The same below. F-test was used for continuous variables (age, BMI, SBP, DBP, eGFR, LDL-C, HbA_{1c}); Chi-square test was used for categorical variables (gender, hypertension, DR grading). The standardized differences (SMD) of each covariate in the three groups are all<0.1.

Table 2: Changes of HbA_{1c} and HbA_{1c}-SD Over 2 Years [mean±SD, M (Q1, Q3)].

Index	Time	M group (n=31)	Ins group (n=31)	M-Ins group (n=31)	F	p*group	p*time
HbA_{1c} (%)	T0	9.0±1.1	9.2±1.0	9.2±0.8	0.374	0.689	
	T1	7.9±0.7	7.9±0.8	7.5±0.6	3.715	0.028	
	T2	6.9±0.4	7.1±0.7	6.6±0.4	7.222	0.001	<0.001
HbA_{1c}-SD		0.5±0.2	0.7±0.3	0.6±0.2	4.114	0.020	-

Note: HbA_{1c} levels: within-group comparisons across time points were analyzed by repeated-measures ANOVA; between-group comparisons at each time point were analyzed by one-way ANOVA. HbA_{1c}-SD (non-normal): between-group comparisons were analyzed by Kruskal-Wallis H test. Compared with T0, HbA_{1c} levels were significantly reduced in all three groups at T1 and T2 time points (all p<0.001); The HbA_{1c} of M-Ins group was lower than that of M group and Ins group at T1 and T2 (p<0.05 for pairwise comparison).

Table 3: Comparison of dr progression among the three groups.

	M group (n=31)	Ins group (n=31)	M-Ins group (n=31)	χ^2	p
Number of DR progress cases (n)	5	12	6		
DR Progress Rate (%)	16.1	38.7	19.4	4.968	0.083

Note: Chi-square test was used for DR progression rates (categorical).

Cox proportional hazards regression analysis of DR progression

A multivariate Cox proportional hazards regression model was constructed with DR progression as the dependent variable, with adjustment for baseline covariates including age (Table 6). The results revealed that higher HbA_{1c}-SD was an independent risk factor for DR progression (HR = 3.216, 95% CI: 1.011–10.230, p = 0.048). Conversely, sustained metformin use emerged as an independent protective factor against DR progression (HR = 0.694, 95% CI: 0.451–0.840, p = 0.001).

Safety analysis

Retrospective analysis of the occurrence of ARs showed that overall (Table 7), there was no significant difference in the occurrence of ARs between the two groups of patients (χ^2=1.205, p=0.547). The most common ARs are hypoglycemia. The incidence of hypoglycemia was 3.2% (1/31) in the M group, 12.9% (4/31) in the Ins group and 9.7% (3/31) in the M-Ins group. All hypoglycemic events were mild and were managed with dietary intake or dose adjustment. No serious hypoglycemic events have occurred.

Table 4: Changes in OCT/OCTA parameters at baseline and 2 years [mean±SD].

Index	Time	M group (n=31)	Ins group (n=31)	M-Ins group (n=31)	F	p*group	p*time
CMT (μm)	T0	292.4±14.6	294.1±15.2	295.6±16.0	0.340	0.713	
	T1	279.3±8.7	279.5±8.9	273.3±11.4	3.424	0.037	
	T2	268.7±8.8	270.2±7.1	263.9±8.0	5.211	0.007	<0.001
RNFL (μm)	T0	106.8±5.8	103.7±8.2	105.1±7.0	1.487	0.232	
	T1	98.8±5.1	96.9±5.3	94.6±3.6	5.951	0.004	
	T2	92.5±5.8	92.5±5.5	89.1±2.8	4.909	0.010	<0.001
SCP (%)	T0	41.4±2.9	41.1±2.7	41.3±3.3	0.090	0.914	
	T1	44.9±1.7	44.6±2.0	46.3±2.6	5.786	0.003	
	T2	48.1±2.6	48.1±3.4	50.3±3.3	4.869	0.010	<0.001
DCP (%)	T0	43.5±2.2	43.2±1.8	43.3±1.9	0.137	0.873	
	T1	46.6±2.4	46.5±2.3	48.5±3.4	5.216	0.007	
	T2	49.7±3.2	49.6±3.2	52.9±4.0	9.148	<0.001	<0.001

Note: For CMT, RNFL, SCP and DCP (continuous, normally distributed): Within-group comparisons across T0, T1 and T2 were analyzed using repeated-measures ANOVA (main effect of time). Within-group comparisons showed statistically significant changes over time ($p<0.05$) for all parameters in all three groups. Between-group comparisons at each time point (T0, T1, T2) were analyzed using one-way ANOVA (F-test).

Table 5: Multiple linear regression analysis of OCT parameters.

Dependent variable	Independent variable	β	t	p	95% CI for B		VIF	Adjusted R^2
					Lower limits	Upper limits		
CMT	HbA_{1c} mean	9.872	8.316	<0.001	7.509	12.235	1.359	0.552
RNFL	HbA_{1c} mean	6.032	8.386	<0.001	4.600	7.465	1.345	0.541
SCP	HbA_{1c} mean	-2.821	-5.063	<0.001	-3.930	-1.712	1.348	0.338
DCP	HbA_{1c} mean	-3.910	-6.901	<0.001	-5.038	-2.782	1.337	0.489

Table 6: Multivariate Cox regression analysis of DR progress.

	B	SE	Wald χ^2	p	HR	95.0% CI	
						Lower limits	upper limits
Insulin used	1.200	0.815	2.169	0.141	3.320	0.672	16.393
Metformin used	-0.365	0.091	0.135	0.001	0.694	0.451	0.840
Age	0.036	0.032	1.265	0.261	1.037	0.974	1.104
Gender	-0.488	0.547	0.794	0.373	0.614	0.210	1.795
Disease duration	-0.069	0.104	0.438	0.508	0.933	0.761	1.145
BMI	0.083	0.090	0.843	0.359	1.087	0.91	1.297
SBP	-0.018	0.020	0.754	0.385	0.983	0.944	1.022
DBP	-0.046	0.064	0.511	0.475	0.955	0.843	1.083
eGFR	-0.003	0.010	0.086	0.770	0.997	0.979	1.016
LDL-C	-0.286	0.382	0.559	0.455	0.751	0.355	1.589
Hypertension	-0.207	0.517	0.160	0.689	0.813	0.295	2.238
DR grading	-0.092	0.601	0.023	0.879	0.912	0.281	2.962
HbA_{1c}-SD	1.168	0.590	3.914	0.048	3.216	1.011	10.230
mean-HbA_{1c}	-0.006	0.774	0.001	0.994	0.994	0.218	4.534

Note: χ^2=49.614, df=14, p<0.001

DISCUSSION

This study showed that all three glucose-lowering regimens significantly reduced HbA_{1c} levels, with the M-Ins group exhibiting the most pronounced decrease and the highest rate of glycemic control. This hypoglycemic regimen is designed to increase insulin sensitivity, reduce liver glucose output and provide exogenous insulin, thereby more effectively controlling blood sugar. (Kim *et al*., 2021). UKPDS research shows that strengthening blood glucose control significantly reduces the risk of DR progression (UK Prospective Diabetes Study (UKPDS) Group, 1998). In this study, the M-Ins group had the lowest HbA_{1c} levels.

Table 7: Comparison of ARs [n (%)].

	M group (n=31)	Ins group (n=31)	M-Ins group (n=31)	χ^2	p
Hypoglycemia	1 (3.2)	4 (12.9)	3 (9.7)		
Gastrointestinal reactions	5 (16.1)	2 (6.5)	4 (12.9)		
Nausea	3 (9.7)	1 (3.2)	2 (6.5)		
Diarrhea	2 (6.5)	0 (0)	1 (3.2)		
Abdominal distension	2 (6.5)	1 (3.2)	2 (6.5)		
Abnormal liver and kidney function	0 (0)	1 (3.2)	0 (0)		
Serious ARs	0 (0)	0 (0)	0 (0)		
Overall	13 (41.9)	9 (29.0)	12 (38.7)	1.205	0.547

Note: Between-group comparisons for each adverse event and for the overall event rate were analyzed using the chi-square test.

HbA_{1c}-SD was significantly lower in the M-Ins group than in the M and Ins groups, indicating that combination therapy not only improves glycemic control but also reduces glycemic variability. Blood glucose variability can reflect the amplitude and frequency of glucose fluctuations (Hirsch and Brownlee, 2010) (Hsu *et al*., 2012). Multiple linear regression analysis showed that HbA_{1c}-SD was positively correlated with CMT and RNFL thickness and negatively correlated with SCP and DCP vessel density, emphasizing the role of blood glucose variability in the pathogenesis of diabetic retinopathy. The lowest blood glucose variability in the M-Ins group indicates its smoother hypoglycemic effect. Metformin can improve insulin sensitivity and reduce postprandial blood glucose fluctuations, while basal insulin provides stable background insulin levels. The combination of the two can achieve more stable blood glucose control (Yapanis *et al*., 2022).

The application of OCT and OCTA technologies provides strong support for the diagnosis and monitoring of DR. After treatment, CMT and RNFL thickness decreased significantly from baseline across all three groups, while SCP and DCP vessel density increased significantly, suggesting that glucose-lowering therapy may be associated with improvements in retinal microvascular structure and a potential amelioration of neurodegenerative changes. Good blood sugar control can alleviate retinal edema, improve retinal blood perfusion and delay the progression of diabetic retinopathy (Ismail-Beigi *et al*., 2010). Compared with the M and Ins groups, the M-Ins group showed a more significant improvement in retinal microvascular structure. A decrease in CMT indicates a reduction in macular edema, a decrease in RNFL thickness is associated with improved ganglion cell function and an increase in SCP and DCP vessel density indicates enhanced retinal capillary perfusion (Horii *et al*., 2012). SCP and DCP are key components of retinal microcirculation. SCP is mainly supplied by the central retinal artery, located in the nerve fiber layer and ganglion cell layer. DCP is located in the inner and outer reticular layers and receives blood supply from the choroid and retinal blood vessels (Campbell *et al*., 2017). Research has shown that in early DR, DCP is the first to be affected, showing a decrease in vessel density, while SCP becomes increasingly damaged as the disease progresses (Waheed *et al*., 2023). In this study, SCP and DCP vessel density increased significantly across all three groups, with the M-Ins group exhibiting the greatest increase. This indicates that the combined treatment effectively enhances microcirculation in both the superficial and deep retinal capillary plexuses, which has important clinical implications for the prevention and management of diabetic retinopathy.

Interpretation of the observed RNFL thickness changes warrants caution. Over the 2-year follow-up, RNFL thickness decreased across all three groups. This reduction may reflect either regression of subclinical optic disc edema or progressive retinal neurodegeneration—a known component of diabetic retinopathy that is not necessarily vascular in origin. Therefore, the reduction in RNFL thickness may not necessarily reflect therapeutic benefits. The continuous improvement of SCP/DCP vessel density and the reduction of CMT are more reliable indicators of microvascular recovery. In the future, it is necessary to combine electrophysiological testing research to elucidate the neural effects of different hypoglycemic regimens.

During the 2-year follow-up period, 23 patients experienced DR progression, with an overall progression rate of 24.7%: 5/31 (16.1%) in the M group, 12/31 (38.7%) in the Ins group and 6/31 (19.4%) in the M-Ins group. Although the Ins group showed a higher progression rate than the other two groups, the difference did not reach statistical significance ($p > 0.05$; Table 3), likely due to the limited sample size and relatively low event rate. These findings suggest that insulin monotherapy may not be the best choice for DR management and the combination of metformin can alleviate some adverse reactions. The relatively higher DR progression rate in the insulin group may be due to: (1) Insulin promotes the synthesis of insulin-like growth

factor-1 (IGF-1), which promotes angiogenesis and may accelerate the progression of DR (Yagasaki *et al*., 2024); (2) Insulin therapy is usually accompanied by weight gain; (3) The risk of hypoglycemia is higher during insulin therapy, as hypoglycemia can trigger oxidative stress and inflammatory reactions, leading to endothelial dysfunction (Cryer, 2007). Hypoglycemia incidence did not differ significantly between the Ins and M-Ins groups ($p > 0.05$), suggesting that the addition of metformin to insulin therapy was not associated with an increased risk of hypoglycemia (Salpeter *et al*., 2010). The protective effect of metformin on the retina may involve multiple mechanisms: (1) AMPK pathway is activated, cellular energy metabolism is enhanced and oxidative stress is reduced (Katila *et al*., 2021); (2) Inhibiting inflammatory response by reducing levels of inflammatory cytokines (Kristófi and Eriksson, 2021); (3) Improving endothelial function by increasing the synthesis of nitric oxide and enhancing vascular dilation (Liu *et al*., 2022); (4) Inhibiting the formation of late glycation products to alleviate glycation damage (Wang *et al*., 2022); (5) Directly inhibit the proliferation of retinal endothelial cells and neovascularization (Han *et al*., 2018).

Cox proportional hazards regression analysis found that high HbA_{1c}-SD was an independent risk predictor of DR progression, while metformin use and baseline SCP vessel density were protective factors. These findings are of great clinical significance and can provide valuable guidance for the management of T2DM patients with DR. Blood glucose management should simultaneously address the issues of mean HbA_{1c} levels and blood glucose variability. Traditional glycemic targets have centered primarily on mean HbA_{1c} levels; however, the present findings suggest that glycemic variability should be considered an equally important parameter. In clinical practice, continuous glucose monitoring (CGM) should be used to evaluate blood glucose fluctuations in order to optimize treatment plans and minimize blood glucose variability (Battelino *et al*., 2019). For T2DM patients with DR, metformin combined with insulin may be the best treatment strategy. This combination achieves relatively good glycemic control, reduces variability and improves retinal microvascular structure, while delaying DR progression; importantly, this is accomplished without increasing the risk of hypoglycemia. The protective effect of metformin on the retina is not limited to its hypoglycemic properties, but patients treated with metformin have a lower risk of DR progression even under comparable blood glucose control (Li *et al*., 2018). OCT can accurately measure CMT and RNFL thickness and evaluate retinal edema and neurodegeneration. OCTA can provide a non-invasive assessment of retinal microvascular structure and early detection of capillary perfusion abnormalities. Baseline SCP vessel density can serve as a predictive factor for DR progression, enabling risk stratification and personalized management. In addition, patients with moderate to severe NPDR need to strengthen follow-up and intervention. This study suggests that baseline DR grading is an independent risk factor for progression and patients with moderate to severe NPDR face a higher risk of progression. Such patients should undergo more frequent follow-up examinations, receive active glycemic management and consider retinal laser therapy or anti VEGF therapy if necessary.

Study limitations

Firstly, this study did not evaluate the efficacy of other glucose-lowering agents, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Secondly, the quality of OCTA images may be affected by factors such as cataracts or vitreous opacity. Thirdly, this study did not adjust for the effects of ACE inhibitors, angiotensin receptor blockers, or statins on the progression of diabetic retinopathy, so the results of this study should be interpreted with caution. Fourthly, subgroup analyses stratified by insulin type, dosage, or baseline HbA_{1c} levels were not performed owing to the limited sample size. Larger-scale studies are warranted to further investigate these associations.

CONCLUSION

The 2-year follow-up results of T2DM patients with NPDR who received metformin and/or insulin treatment in this study showed that: (1) mean HbA_{1c} levels were correlated with retinal microvascular and neural structural parameters (CMT, RNFL, SCP/DCP density); (2) HbA_{1c}-SD is associated with the progression of DR within 2 years, while the use of metformin is associated with lower risk; (3) Combining HbA_{1c}-SD levels with OCT/OCTA parameters for joint observation may help predict the risk of DR progression. These findings suggest that integrating mean HbA_{1c} and blood glucose variability, along with appropriate use of metformin, may predict DR progression within 2 years, although prospective validation is still needed.

Acknowledgment

None

Author's contributions

Zhongshu Han and Ping Zhu: Provided substantial intellectual input during the drafting and revision of the manuscript. Edited and refined the manuscript with a focus on critical intellectual contributions.

Both authors have read and approved the final manuscript.

Funding
Haining Science and Technology Program Project(Project No.: 2025019)

Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was conducted in strict accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Haining People's Hospital (Approval No. 2025-104). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare that they have no financial conflicts of interest.

Consent to participate
Informed consent was obtained from all participants.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787643718.pdf

REFERENCES

Alasbily H, Ali Fahmi F, Abdulhamid Abdala M, Fouad Asheibi A, Adeil Amhidi A, Abed Elallegy A and A HE (2025). Metformin in diabetic retinopathy: Mechanisms, therapeutic potential and barriers. *Cureus,* **17**(7): e87455.

American Diabetes Association Professional Practice Committee (2025). 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. *Diabetes Care.*

Antonetti DA, Silva PS and Stitt AW (2021). Current understanding of the molecular and cellular pathology of diabetic retinopathy. *Nat. Rev. Endocrinol.,* **17**(4): 195–206.

Attiku Y, Nittala MG, Velaga SB, Ramachandra C, Bhat S, Solanki K, Jayadev C, Choudhry N, Orr SMA, Jiang S, He Y and Sadda SR (2023). Comparison of diabetic retinopathy severity grading on ETDRS 7-field versus ultrawide-field assessment. *Eye (Lond.),* **37**(14): 2946–2949.

Austin PC (2011). An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.,* **46**(3): 399–424.

Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, Devries JH, Donaghue KC, Dovc K, Doyle FJ, 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Norgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA and Phillip M (2019). Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care,* **42**(8): 1593–1603.

Brown EG, Wood L and Wood S (1999). The medical dictionary for regulatory activities (MedDRA). *Drug Saf.,* **20**(2): 109–17.

Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y and Huang D (2017). Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci. Rep.,* **7**: 42201.

Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Franzén S, Svensson AM, Eliasson B and Nicolucci A (2022a). HbA1c variability predicts cardiovascular complications in type 2 diabetes regardless of being at glycemic target. *Cardiovasc. Diabetol.,* **21**(1): 13.

Ceriello A, Rizvi AA and Rizzo M (2022b). Glycemic variability, glycated hemoglobin and cardiovascular complications: Still a dilemma in clinical practice. *Adv. Ther.,* **39**(1): 1–4.

Chen Y, Zhu Z, Cheng W, Bulloch G, Chen Y, Liao H, Li Y, Liang X, Huang W, He M and Wang W (2023). Choriocapillaris flow deficit as a biomarker for diabetic retinopathy and diabetic macular edema: 3-Year longitudinal cohort. *Am. J. Ophthalmol.,* **248**: 76–86.

Chua J, Tan B, Wong D, Garhofer G, Liew XW, Popa-Cherecheanu A, Loong Chin CW, Milea D, Li-Hsian Chen C and Schmetterer L (2024). Optical coherence tomography angiography of the retina and choroid in systemic diseases. *Prog. Retin. Eye Res.,* **103**: 101292.

Cryer PE (2007). Hypoglycemia, functional brain failure and brain death. *J. Clin. Invest.,* **117**(4): 868–70.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A and Buse JB (2022). Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care,* **45**(11): 2753–2786.

Early Treatment Diabetic Retinopathy Study Research Group (1991). Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology,* **98**(5 Suppl): 786–806.

Fan YP, Wu CT, Lin JL, Hsiung CA, Liu HY, Lai JN and Yang CC (2020). Metformin treatment is associated with a decreased risk of nonproliferative diabetic retinopathy in patients with type 2 diabetes mellitus: A

population-based cohort study. *J Diabetes Res,* **2020**: 9161039.

Foretz M, Guigas B and Viollet B (2023). Metformin: Update on mechanisms of action and repurposing potential. *Nat. Rev. Endocrinol.,* **19**(8): 460–476.

Guo X, Chen Y, Bulloch G, Xiong K, Chen Y, Li Y, Liao H, Huang W, Zhu Z and Wang W (2023). Parapapillary choroidal microvasculature predicts diabetic retinopathy progression and diabetic macular edema development: A three-year prospective study. *Am. J. Ophthalmol.,* **245**: 164–173.

Han J, Li Y, Liu X, Zhou T, Sun H, Edwards P, Gao H, Yu FS and Qiao X (2018). Metformin suppresses retinal angiogenesis and inflammation *in-vitro* and *in-vivo*. *PLoS One,* **13**(3): e0193031.

Hirsch IB and Brownlee M (2010). Beyond hemoglobin A1c--need for additional markers of risk for diabetic microvascular complications. *JAMA,* **303**(22): 2291–2.

Holman RR, Paul SK, Bethel MA, Matthews DR and Neil HA (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.,* **359**(15): 1577–89.

Horii T, Murakami T, Nishijima K, Akagi T, Uji A, Arakawa N, Muraoka Y and Yoshimura N (2012). Relationship between fluorescein pooling and optical coherence tomographic reflectivity of cystoid spaces in diabetic macular edema. *Ophthalmology,* **119**(5): 1047–55.

Hsu CC, Chang HY, Huang MC, Hwang SJ, Yang YC, Lee YS, Shin SJ and Tai TY (2012). HbA1c variability is associated with microalbuminuria development in type 2 diabetes: A 7-year prospective cohort study. *Diabetologia,* **55**(12): 3163–72.

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH, Jr., Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D and Hramiak I (2010). Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: An analysis of the ACCORD randomised trial. *Lancet,* **376**(9739): 419–30.

Javed A, Khanna A, Palmer E, Wilde C, Zaman A, Orr G, Kumudhan D, Lakshmanan A and Panos GD (2023). Optical coherence tomography angiography: A review of the current literature. *J. Int. Med. Res.,* **51**(7): 3000605231187933.

Katila N, Bhurtel S, Park PH and Choi DY (2021). Metformin attenuates rotenone-induced oxidative stress and mitochondrial damage via the AKT/Nrf2 pathway. *Neurochem. Int.,* **148**: 105120.

Kim HU, Park SP and Kim YK (2021). Long-term HbA1c variability and the development and progression of diabetic retinopathy in subjects with type 2 diabetes. *Sci. Rep.,* **11**(1): 4731.

Kim N, Fischer AH, Dyring-Andersen B, Rosner B and Okoye GA (2017). Research techniques made simple: Choosing appropriate statistical methods for clinical research. *J. Invest. Dermatol.,* **137**(10): e173–e178.

Kristófi R and Eriksson JW (2021). Metformin as an anti-inflammatory agent: A short review. *J. Endocrinol.,* **251**(2): R11–R22.

Lee S, Liu T, Zhou J, Zhang Q, Wong WT and Tse G (2021). Predictions of diabetes complications and mortality using hba1c variability: A 10-year observational cohort study. *Acta Diabetol.,* **58**(2): 171–180.

Li Y, Ryu C, Munie M, Noorulla S, Rana S, Edwards P, Gao H and Qiao X (2018). Association of metformin treatment with reduced severity of diabetic retinopathy in type 2 diabetic patients. *J Diabetes Res,* **2018**: 2801450.

Liu J, Aylor KW, Chai W, Barrett EJ and Liu Z (2022). Metformin prevents endothelial oxidative stress and microvascular insulin resistance during obesity development in male rats. *Am. J. Physiol. Endocrinol. Metab.,* **322**(3): E293–e306.

Monnier L, Colette C, Bonnet F, Renard E and Owens D (2023). HbA1c variability and diabetes complications: Assessment and implications. *Diabetes Metab.,* **49**(1): 101399.

Rena G, Pearson ER and Sakamoto K (2013). Molecular mechanism of action of metformin: Old or new insights? *Diabetologia,* **56**(9): 1898–906.

Rosenbaum PR and Rubin DB (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika,* **70**(1): 41–55.

Rossing P (2023). HbA1c and beyond. *Nephrol. Dial. Transplant.,* **38**(1): 34–40.

Salpeter SR, Greyber E, Pasternak GA and Salpeter EE (2010). Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst. Rev.,* **2010**(4): Cd002967.

Shah VN, Kanapka LG, Akturk HK, Polsky S, Forlenza GP, Kollman C, Beck RW and Snell-Bergeon JK (2024). Time in range is associated with incident diabetic retinopathy in adults with type 1 diabetes: A longitudinal study. *Diabetes Technol. Ther.,* **26**(4): 246–251.

Simo R, Stitt AW and Gardner TW (2018). Neurodegeneration in diabetic retinopathy: Does it really matter? *Diabetologia,* **61**(9): 1902–1912.

Tuli N, Moroz H, Jaffer A, Kulbay M, Tanya SM, Aslan FS, Ozdemir D, Ali SK and Qian CX (2026). The central role of oxidative stress in diabetic retinopathy: Advances in pathogenesis, diagnosis and therapy. *Diagnostics (Basel),* **16**(3): 392.

Uk Prospective Diabetes Study (Ukpds) Group (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet,* **352**(9131): 837–853.

Waheed NK, Rosen RB, Jia Y, Munk MR, Huang D, Fawzi A, Chong V, Nguyen QD, Sepah Y and Pearce E

(2023). Optical coherence tomography angiography in diabetic retinopathy. *Prog. Retin. Eye Res.,* **97**: 101206.

Wang G, Wang Y, Yang Q, Xu C, Zheng Y, Wang L, Wu J, Zeng M and Luo M (2022). Metformin prevents methylglyoxal-induced apoptosis by suppressing oxidative stress *in-vitro* and *in-vivo*. *Cell Death Dis.,* **13**(1): 29.

Wen B, Zhang G, Zhan C, Chen C and Yi H (2025). The 2024 revision of the Declaration of Helsinki: A modern ethical framework for medical research. *Postgrad. Med. J.,* **101**(1194): 371–382.

Yagasaki R, Morita A, Mori A, Sakamoto K and Nakahara T (2024). The anti-diabetic drug metformin suppresses pathological retinal angiogenesis via blocking the mTORC1 signaling pathway in mice (Metformin Suppresses Pathological Angiogenesis). *Curr. Eye Res.,* **49**(5): 505–512.

Yapanis M, James S, Craig ME, O'neal D and Ekinci EI (2022). Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J. Clin. Endocrinol. Metab.,* **107**(6): e2221–e2236.