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Effect of intensive glycemic control on the changes of diabetic retinopathy in type 2 diabetes: a prospective observational cohort study

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Abstract

Background A large body of evidence supports the long-term benefits of intensive glycemic control for patients with type 2 diabetes mellitus (T2DM). However, the relationship between intensive glycemic control and diabetic retinopathy (DR) progression in T2DM patients in the short-term remains under debate. Therefore, we investigated the effect of intensive glycemic control on DR changes in the short-term.

Methods A total of 254 patients with T2DM, all exhibition hemoglobin A_{1c} (HbA_{1c}) levels above 7% were included in the study. We collected HbA_{1c} values at baseline and after 12-months. HbA_{1c} control classified into two categories: intensive control, targeting an HbA_{1c} of less than 7%, and less intensive control, targeting an HbA_{1c} of 7% or higher at 12-month follow-up. The severity of DR were graded based on seven-field 45° conventional fundus photographs examinations according to the United Kingdom National Diabetic Eye Screening Program guidelines.

Results After a one-year follow-up, 129 participants achieved a target HbA_{1c} of less than 7% and 125 achieved 7% or more. We found no significant difference in DR changes (incidence, progression, or regression) between two groups after adjustments for age and gender. Further adjustments for confounding factors such as body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes duration, insulin use and baseline HbA_{1c}, revealed no association between intensive glycemic control and the DR changes.

Conclusions This prospective cohort study demonstrates that intensive glycemic control did not associated with DR changes in T2DM patients in the short term. Further research is required to ascertain the long-term effects of intensive glycemic control on DR.

Trial registration The trail has been registered at The UK's Clinical Study Registry (https://www.isrctn.com) on 2020/04/13 (ISRCTN15853192).

Keywords Glycemic control, Diabetic retinopathy, Type 2 diabetes

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Introduction

Diabetic retinopathy (DR) is one of the most frequent diabetic complications and is the primary cause of preventable blindness in the working-age population [1]. Epidemiologic studies, including the Diabetes Control and Complication Trial (DCCT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, have demonstrated that poor hemoglobin A1 C (HbA_{1c}) control, a widely adopted biomarker for long-term glycemic control, is a risk factor for DR [2, 3]. Good glycemic control has also been proven to effectively lower the risk of DR progression in long-term [4]. Therefore, keeping blood glucose levels within the normal range is an important goal in DR monitoring. Recently, many studies have highlighted the negative influence of intensive glycemic control in patients with type 1 diabetes mellitus (T1DM), presenting as a risk factor for DR progression [5]. However, the impact of intensive glycemic control on DR progression in patients with type 2 diabetes mellitus (T2DM) in short-term is controversial. Increasing research interest is being towards identifying a small subset of T2DM patients whose DR worsens rapidly due to rapid blood glucose reduction, and to provide them with early ophthalmological examination and intervention [6, 7]. Moreover, most investigations focus on the effect of intensive glycemic control on DR development or DR incidence, there is a paucity of research on the effect of intensive glycemic control on DR regression [6–8].

The Guangzhou Diabetic Eye Study (GDES) is the first large-scale cohort study of T2DM patients in southern China. Therefore, this prospective cohort study aimed to investigate the impacts of intensive glycemic control on DR changes including DR incidence, progression and regression in one-year follow-up period.

Methods

Study participants

The GDES is an ongoing prospective cohort study that enrolled T2DM patients in communities in Guangzhou (ISRCTN15853192). The study protocol was approved by the Zhongshan Ophthalmic Center Ethics Committee (2017 KYPJ094). Written informed consent was obtained from all subjects. Prior to enrollment, the participants were diagnosed with T2DM in comprehensive hospitals and followed up in community health centers.

The inclusion criteria were as follows: (1) patients with type 2 diabetes between the ages of 30 and 85; (2) HbA_{1c} above 7%; (3) intraocular pressure less than 21 mmHg; (4) spherical refraction within ±6.0D and AL ≤26 mm, cylinder degree within ±3.0D; (5) no severe systemic diseases other than diabetes, such as severe cardiovascular diseases, malignancies, and nephritis; (6) no history of glaucoma, no retinal disease other than DR and no history of previous intraocular treatment, a history of systemic surgery, thrombolytic therapy, or renal transplantation including intravitreal injections, retinal laser procedures and intraocular surgery; (7) no history of systemic surgery, thrombolytic therapy, or renal transplantation; (8) no history of ocular diseases, such as glaucoma, amblyopia, or other retinal diseases (rhegmatogenous retinal detachment [RRD], age-related macular degeneration [AMD], or retinal vein occulusion [RVO], etc.); (9) no history of ocular surgery, such as corneal refractive surgery, glaucoma surgery, or cataract surgery. They were referred to Zhongshan Ophthalmic Center and underwent ophthalmic and physical examinations at baseline and at the 12-month follow-up visit. Participants were grouped into intensive or less intensive glycemic control, based on their HbA_{1c} at the 12 month follow-up. According to the most recent blood glucose control guidelines, the American Diabetes Association's (ADA)"Standards of Care in Diabetes" [9], an HbA_{1c} target of less than 7% was considered intensive glycemic control while an HbA_{1c} target of 7% or higher was considered less intensive glycemic control. Statistical analysis was performed using data from the eye with poorer visual acuity.

General information and laboratory measurements

Basic patient information, including age, gender, diabetes duration, pharmacy history, and past medical history, was collected through questionnaire surveys. Body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by experienced nurses. HbA_{1c} was determined by mono S High-Performance Liquid Chromatography (HPLC) ion exchange chromatography (nondiabetic range 3.00–6.00%) at baseline and end point. They were divided into two groups: intensive glycemic control group and less intensive glycemic control group, as described above.

Other laboratory indicators, such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were obtained through laboratory tests.

Fundus photography and stage of diabetic retinopathy

Each patient underwent a comprehensive eye examination. Ophthalmologists conducted a preliminary assessment of the anterior and posterior segments of the patient's eyes under a slit lamp.

Digital fundus photography (Canon CX-1, Tokyo, Japan) was used to capture standard seven-field fundus images of each eye after pupil dilation. Fundus images with artifacts and poor quality, such as blurring, incorrect orientation, or inability to grade, were excluded. Three experienced ophthalmologists graded the fundus photographs of both eyes according to the United Kingdom

National Diabetic Eye Screening Program classification system. The severity of DR was classified as R0, R1, R2, or R3 [10]. DR progression was defined as an increase in severity level by 1 step or more among these patients who had DR of R1 or R2 at baseline [8]. DR regression was defined as a decrease in severity level by 1 step or more among these patients with any DR at baseline. DR incidence was defined as any DR presence at the 12-month follow-up among these patients who did not have DR at baseline.

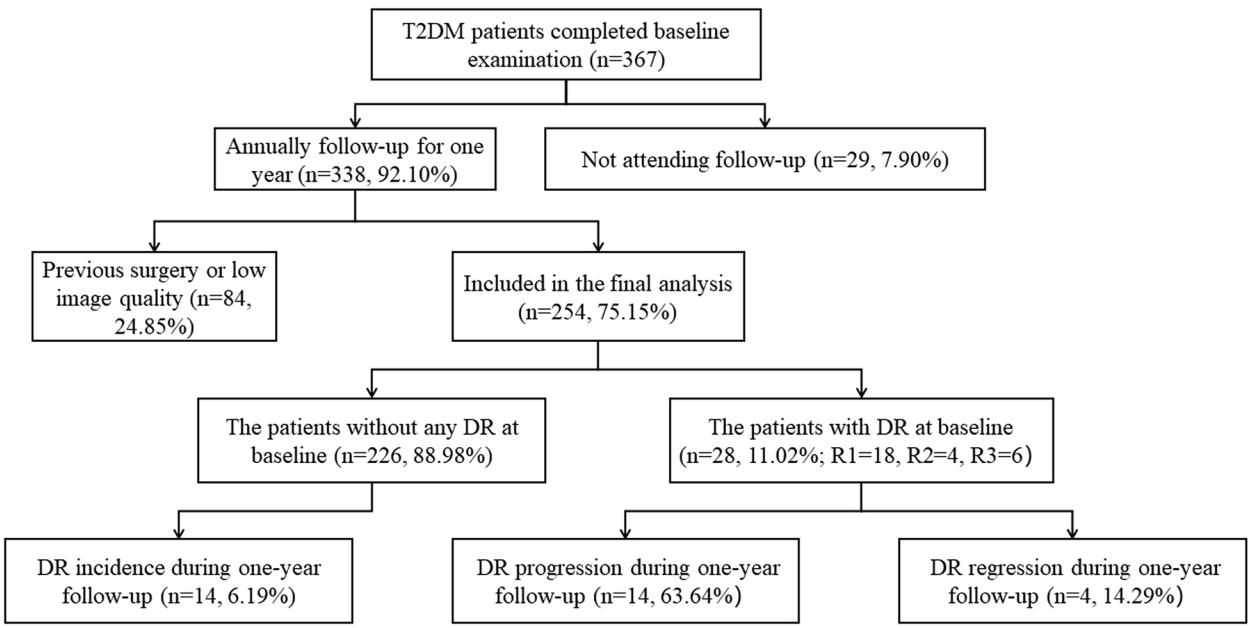
Statistical analyses

In this study, all analyses were performed using Stata 25.0 software (version 26.0, IBM, Armonk, NY). Continuous variables were first tested for normal distribution by the Kolmogorov–Smirnov test. After that, unpaired t-test was conducted for the normal distribution continuous variables analysis and Mann–Whitney U test was conducted for the non-normal continuous variables analysis. Normal continuous variables are presented as mean and standard deviation (SD), while non-normal continuous variables are presented as median (M) and interquartile range (IQR). A chi-square test was used for categorical variable analysis. And the categorical variables are presented as numbers (%). Three logistic regression models were employed to investigate the associations between intensive glycemic control with DR changes (incidence, progression, or regression) at the one-year follow-up. We included a total of 254 diabetic patients, of whom 14 had DR incidence, 14 had DR progression, and 4 had DR regression after one year follow-up. Initially, the associations were adjusted for age and sex in the model 1. Subsequently, adjustments were made for selected risk factors (universally accepted risk factors) in the model 2 and model 3. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A p-value of <0.05 was considered statistically significant.

Results

Demographics and baseline characteristics of the study population

Figure 1 shows the flow process of the participant selection. A total of 367 T2DM patients completed the baseline examination. Finally, 254 subjects were included in the final analysis without previous surgery, low image quality or missing data. Among 254 patients, 226 (88.98%) patients without DR at baseline and 28 (11.02%) patients with DR. Among 226 patients without DR at baseline, 14 (6.19%) patients had newly developed of any DR. Of the 28 patients with DR at baseline, 14 (63.64%) had DR progression ≥ 1 step after one year follow-up. Four patients experienced DR regression out of the 28 patients with DR (Fig. 1). The demographics and baseline characteristics of the intensive glycemic control group



Abbreviations:
HbA1c, hemoglobin A1C; T2DM, type 2 dibetic retinopathy; DR, diabetic retinopathy.

Fig. 1 Flowchart of study patients through one-year follow-up

and less intensive glycemic control group are shown in Table 1. There were no significant differences in age, sex, diabetes duration, BMI, SBP, DBP, the proportion of patients with using of insulin, and the level of HbA_{1c}, TC, TG, LDL and HDL at baseline between the two groups (Table 1).

Association of intensive glycemic control with DR changes

Table 2 shows the association of intensive glycemic control with DR incidence. The results of different logistic regression models adjusted by universally accepted confounding factors are shown in Fig. 2. We did not find any significant association between intensive glycemic control and the DR changes (incidence, progression, or regression) either in the unadjusted model or after progressive adjustments.

Discussion

In this prospective observational cohort study, our results suggested that intensive glycemic control in the short term was not associated with DR changes (incidence, progression, or regression). This is important because most type 2 diabetic mellitus (T2DM) patients had no DR or mild DR in the real world.

Although exposure to high glycemic levels is a well-established risk factor for DR, optimizing glycemic control has always been recommended. However, the velocity and magnitude of the decrease in HbA_{1c} remain a matter of debate [11]. Diabetic patients with vision impairment due to DR are suggested to lower blood glucose levels as soon as possible, as this is anticipated to alleviate diabetes-related complications in the long term [12]. However, intensive glycemic control in the short

Table 1 Demographics and baseline characteristics of the study population

	Less intensive control (125)	Intensive control (129)	*P* value
Age (years), mean (SD)	65.51 ± 1.03	66.96 ± 0.74	0.24
Male, n (%)	55 (44.00)	67 (51.94)	0.21
Diabetes duration (years), Median (IQR)	6.50 (4.00, 13.00)	6.50 (4.00, 17.00)	0.84
HbA_{1c} (%), Median (IQR)	8.15 (7.60, 8.80)	8.00 (7.50, 9.10)	0.48
Reduction of HbA_{1c} (%), Median (IQR)	0.20 (−1.00, 0.60)	3.20 (1.50, 5.43)	< 0.001
BMI (kg/m^2), mean (SD)	24.68 ± 0.38	24.82 ± 0.33	0.93
SBP (mmHg), mean (SD)	132.65 ± 2.15	132.64 ± 1.93	0.37
DBP (mmHg), mean (SD)	67.38 ± 1.09	66.1 ± 1.11	0.58
TC (mg/dL), Median (IQR)	4.18 (3.93, 5.47)	3.80 (3.46, 5.54)	0.64
TG (mg/dL), Median (IQR)	3.09 (1.44, 4.41)	2.60 (1.44, 3. 56)	0.74
LDL-C (mg/dL), Median (IQR)	2.52 (1.95, 3. 52)	2.41 (1.74, 3.72)	0.80
HDL-C (mg/dL), Median (IQR)	1.48 (0.99, 2.22)	1.44 (1.08, 1.90)	0.90
Use of insulin, n (%)	11 (8.80)	11 (8.53)	0.94

Data are presented as mean (SD), Median (IQR) or n (%)

Reduction of HbA_{1c} is calculated as HbA_{1c} value at baseline subtract HbA_{1c} value after 1-year follow-up

Abbreviations: HbA_{1c} hemoglobin A1 C, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SD* standard deviation, *IQR* interquartile range

Table 2 Association between HbA_{1c} control and DR incidence, DR progression and DR regression

HbA_{1c} control	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
DR incidence	1.79(0.58, 5.59)	0.31	1.83(0.58, 5.77)	0.31	0.96(0.19, 4.98)	0.96
DR progression	1.90(0.61, 5.89)	0.27	1.89(0.60, 5.91)	0.27	1.09(0.22, 5.34)	0.92
DR regression	0.96(0.13, 7.29)	0.97	1.11(0.13, 9.51)	0.92	__§	__§

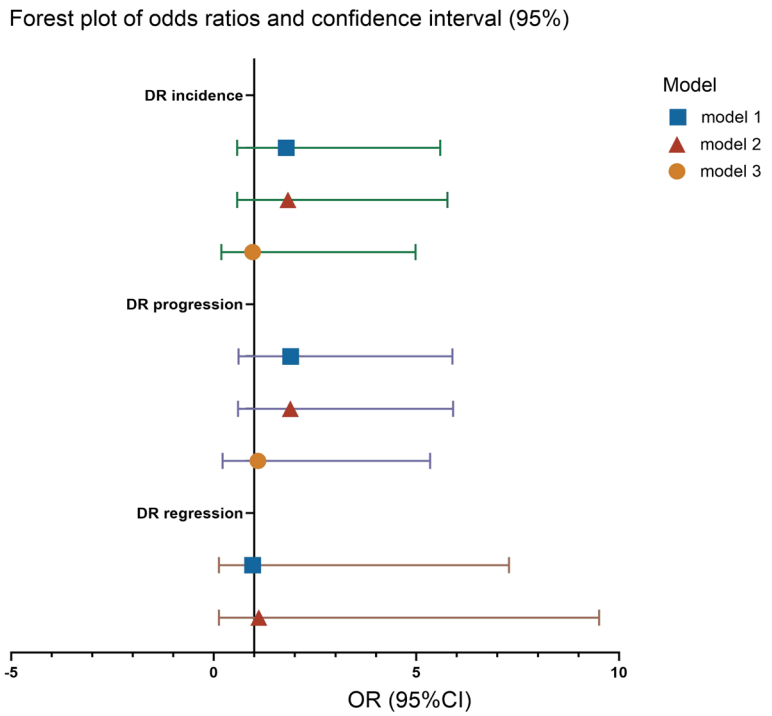
Model 1, adjusted for age and gender

Model 2, further adjusted for BMI, SBP and DBP

Model 3, further adjusted for diabetic duration, use of insulin and baseline HbA_{1c}

Abbreviations: DR diabetic retinopathy, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA_{1c}* hemoglobin A1 C, *OR* odds ratio, *CI* confidence interval

§ The model failed because of the small sample size



Model 1, adjusted for age and gender.

Model 2, further adjusted for BMI, SBP and DBP.

Model 3, further adjusted for diabetic duration, use of insulin and baseline HbA_{1c}.

Abbreviations: DR, diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A1C; OR, odds ratio; CI, confidence interval.

Fig. 2 Forest plot of ORs for DR changes taking into confounding factors and the control of HbA_{1c}

term may also make diabetic retinopathy worse [6]. In one early report, 18 patients with long-term (mean, 14.6 years) poorly controlled diabetes showed that going from a period of poor control to tight control of diabetes was harmful for patients who already had DR. Four patients with moderate-to-severe DR experienced rapid progression of retinopathy within three to six months after initiation of continuous subcutaneous insulin infusion (CSII), while seven patients experienced worsening slightly [13]. Further, it is still difficult to adjust the speed of blood glycemic decline in clinical practice according to a standard protocol, given that patients often respond differently to the same treatment. Therefore, some patients with inappropriate blood glucose fluctuations can always be seen in the clinic. Compared with the standard control protocol, the disadvantages of intensive glucose control with rapid reduction of HbA_{1c} include weight gain, risk of hypoglycemia, and an increased rate of hospitalization [12].

The acceleration of diabetes complications owing to intensive glucose control is not confined to systemic risks. Starting in 1977, 3867 newly diagnosed T2DM patients were enrolled in UKPDS, which was designed to determine whether intensive blood glucose control could reduce the risk of macrovascular or microvascular complications [14]. There have been a few RCTs, retrospective studies, broad cross-sectional studies, and meta-analyses on the relationship between rapid blood glucose control and DR progression [11, 12]. However, the data remain controversial. In UKPDS, the intensive blood glucose control group, with a median HbA_{1c} reduction of 11% in the first 10 years, had a 25% reduced risk of microvascular endpoints, most of which was due to fewer patients requiring photocoagulation [14]. The researchers also found that few intensive blood glucose control patients experienced late-stage DR, such as vitreous hemorrhage or even blindness, which might be due to insufficient follow-up time or the decreased risk of retinal damage and blindness after photocoagulation [14]. The ACCORD study demonstrated a reduced incidence or progression of DR in intensive glycemic control in the long term for T2DM patients [3]. In a follow-on study

(ACCORDION), DR progressed by 5.8% in the intensive glycemic control group versus 12.7% in the standard control group at the trial end (4 years) ($p < 0.0001$). Moreover, although HbA_{1c} levels had become close in both groups by the end of the study, continued reduced DR progression was observed in the prior intensive glycemic control group, even 8 years after randomization and 4 years after the end of the trial [11]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, a broad cross-section of T2DM patients, concluded that there was no evidence that reduced new or worsening DR resulted in retinal photocoagulation in the intensive glucose control group [12]. A retrospective nested case–control study showed that the reduction of HbA_{1c} was not associated with DR progression in T2DM patients with mild or moderate NPDR [15]. Results from a meta-analysis of four trials (UKPDS, ADVANCE, ACCORD, and VADT) in 27,049 patients with T2DM suggested a 13% risk reduction of eye events (a composite of demand for pars plana vitrectomy [PPV] or retinal photocoagulation, development of PDR, or DR progression) in intensive versus conventional glucose control after a five-year follow-up [11]. Interestingly, T2DM patients with the greatest HbA_{1c} reduction who switched to insulin treatment encountered the most severe DR progression, demonstrating that a substantial lowering of blood glucose might be associated with a temporarily increased risk of DR progression [16]. Further, a retrospective, case–control hospital-based study demonstrated that significant DR worsening was associated with significant improvement of poor glycemic control in predominantly minority patients with T2DM, despite similar average HbA_{1c} concentrations in the two groups over a two-year period [10]. The magnitude of the reduction of HbA_{1c} and the presence of preexisting DR were considered the main variables accounting for the DR worsening.

However, there were several inconsistencies among the trials. First, the types of trials were diverse, including RCTs, retrospective studies, broad cross-sectional studies, and meta-analyses. Second, the discrepancy included differences between the research in terms of the participants' age, diabetes duration, previous retina status, and previous glycemic control status. Third, the clinical significance of the progression was not precise, with the need for PPV or laser treatment, DR development, or deterioration of visual acuity. Fourth, the definition of intensive glycemic control varies among the trials [5, 11, 12, 14]. Current recommendations indicate a target HbA_{1c} level <7% in T2DM to minimize the risk of long term vascular complications [10]. We used this latest standard in our study. With the increase in people's awareness and the development of diabetic mellitus (DM) diagnosis technology, the diagnosis and treatment of DM now occur earlier than before. The sample in our study represents the current situation of the T2DM population in the Guangzhou district of China. Our study is a prospective observational cohort study, most of the participants were T2DM patients with no DR or mild DR, which represents a real-world situation.

Our study has several key strength. First, this is a real-world study based on T2DM patients, the inclusion of individuals who are often excluded from RCTs. Second, according to the American Diabetes Association (ADA) "Standards of Care in Diabetes" [10], which is the latest guideline for blood glucose control standards, intensive glycemic control was defined as an HbA_{1c} target of <7.0% in our study. Third, this research characterized a cohort through the use of standard seven-field fundus photography to confirm DR diagnoses. In these respects, the findings from this cohort may be more generalizable.

Despite its strengths, this study has some limitations. First, we did not statistically analyze the impact of different antidiabetic drug treatments on DR changes. Early worsening of diabetic retinopathy (EWDR) does not appear to be agent-specific. A study revealed no relationship between antidiabetic drugs and EWDR in a real-world population-based sample [17]. Second, the study included only T2DM patients in China, and the findings may not be applicable to other ethnic groups. Therefore, caution should be taken when generalizing the results to other ethnicities and individuals with T1DM. Third, DR is a microvasculopathy, theoretically OCTA is the ideal method for assessing DR. In our forthcoming investigation, we would introduce additional valuable metrics beyond fundus photography for assessing DR. Fourth, due to the relatively good baseline glycemic control (8.15% for the less intensive glycemic control group, 8.00% for the intensive glycemic control group) of the patients we included, the proportion of patients with DR was relatively small. And follow-up period of our study was short, which was also one of the reasons for the small proportion of patients with DR changes. Future research should include more diabetic patients with DR and elongate longer the observational window to further confirm the conclusions.

In summary, this prospective observational cohort study reveals that intensive glycemic control of HbA_{1c} (a targeting HbA_{1c} of <7.0%) in the short term was not associated with DR changes in the real world, with most T2DM patients presenting with no DR or mild DR. Clinicians should not be afraid to optimize glycemic control in a relatively short time in T2DM patients with early stage of DR. However, caution should be exercised in pursuing the strategy for severe stage of DR, in which a careful decrease in HbA_{1c} should be planned.

Abbreviations

DR	Diabetic retinopathy
T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
HbA_{1c}	Hemoglobin A_{1c}
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
GDES	Guangzhou Diabetic Eye Study
RRD	Rhegmatogenous retinal detachment
AMD	Age-related macular degeneration
RVO	Retinal vein occulusion
TC	Total cholesterol
TG	Triglycerides
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
EWDR	Early worsening of diabetic retinopathy
HPLC	High-Performance Liquid Chromatography
CSII	Continuous subcutaneous insulin infusion

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Authors' contributions
X.W., Conceptualization, Formal analysis, Software, Writing-original draft; Y.Y., Investigation Formal analysis, Data curation, Software, Writing-original draft; Y.L., Conceptualization, Project administration; Y.F., Investigation, Data curation; L.L., Project administration; C.T., Methodology, Project administration; K.L., Writing-review & editing; W.H., Supervision, Writing-review & editing; X.L. Project administration, Resources, Supervision, Writing- review & editing; A.H., Supervision, Writing-review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Qelsinki, and approved by the Zhongshan Ophthalmic Center Ethics Committee (2017 KYPJ094). Written informed consent was obtained from all patients after the nature and possible consequences of the study were explained.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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