Title: Worsening diabetic retinopathy with rapid improvement in systemic glucose control: a review

Running title: Early worsening diabetic retinopathy and glucose control

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Abstract

Worsening of diabetic retinopathy (DR) is associated with the initiation of effective treatment of glycemia in some patients with diabetes. It has been associated with risk factors such as poor blood-glucose control and hypertension, and manifests prior to the long-term benefits of optimizing glycaemic control. The majority of evidence supports an association of large and rapid reductions in blood-glucose levels with early worsening of DR. Despite a general awareness of early worsening within the diabetes community, mechanisms to explain the phenomenon remain speculative. We provide an overview of early worsening of DR and its pathophysiology based on current data. We describe the phenomenon in various settings, including in patients receiving insulin or non-insulin-based treatments, those undergoing bariatric surgery, and pregnant women. We discuss various mechanisms and theories suggested to explain this paradoxical phenomenon, and summarize implications of these in clinical practice.

The early worsening phenomenon in diabetic retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes affecting the vasculature in the eye and occurring in approximately one-third of patients with diabetes.[1,2] It is the leading cause of vision loss in the working-age and elderly population.[3] Its progression and development is associated with a number of risk factors, including long diabetes duration, poor glycaemic control, and poorly controlled hypertension.[2,3] Deterioration of DR, upon initiation of stringent diabetes treatment, is referred to as 'early worsening'. In this context, the term 'early' refers to the establishment of good glycaemic control, and not a short duration of diabetes. This seemingly paradoxical outcome was first described in the 1980s in patients with type 1 diabetes, treated intensively with continuous subcutaneous insulin infusion (CSII) versus conventional treatment (i.e. short- or intermediate-acting insulin).[4-6] In one early report, 18 patients with long-term (mean, 14.6 years) poorly controlled diabetes showed that changing from a period of poor- to tightly-controlled diabetes was detrimental for patients with existing DR. In this study, 7 patients had worsening DR, while 4 patients with existing moderate-to-severe DR had rapid progression of retinopathy within 3 to 6 months of CSII.[4]

The timescale over which early worsening has been reported ranges from 3 months up to 3 years after treatment initiation.[7-11] In the Oslo study, early worsening developed after 3 months of treatment in half of the patients treated with CSII (n=7/15) or multiple insulin injections (n=8/15) compared with none in the conventional treatment group.[7] Similarly, in the Kroc collaborative study, almost half of the patients receiving CSII (47%) developed early worsening by month 8 of treatment (versus 27% in the conventional treatment group).[8] In these trials early worsening was defined in various ways, including by progression on the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale – a standardized scale of disease severity derived from grading of retinal fundus photographs, which characterizes DR stages (also known as the diabetic retinopathy severity scale [DRSS]) [12] – and by fluorescein angiograms.[7-9]

While the existence of early worsening is not in doubt, the pathophysiology of this phenomenon is not well understood. Furthermore, the circumstances under which it appears remain to be fully elucidated. Since its discovery, early worsening has been described in patients with type 1 and type 2 diabetes, including those on various diabetic therapies, who have had bariatric surgery, and in pregnant women.[13] Here we review the current understanding of the pathophysiology of early worsening and possible underlying mechanisms. We explore the literature related to early worsening of DR in various different settings, the microvascular changes that occur, and existing theories that explain early worsening.

Methodology on literature search strategy and selection criteria

A literature search was conducted using BIOSIS Previews®, Current Contents® Search, EMBASE®, and MEDLINE® databases to identify DR-related publications. Search terms used are shown in **Table 1**. Searches covered publication dates from 1 January 2012 to 31 December 2017. A total of 167 primary and secondary articles and 41 reviews were retrieved and assessed for suitability of inclusion. Clinically relevant publications, as decided by authors, were also included.

Articles were considered suitable for inclusion if they covered specific topics, such as factors impacting DR progression, the relationship between glycaemic control and long-term diabetes outcomes, and the relationship between glycaemic improvement and early or transient worsening of DR. Landmark trials for both type 1 and type 2 diabetes were also included.

Staging of diabetic retinopathy

DR is a progressive disease comprising several stages including: 1) no DR, in which there are no abnormalities; 2) mild non-proliferative DR, in which there are microaneurysms only; 3) moderate non-proliferative DR, in which there may be microaneurysms, retinal dot-and-blot haemorrhages, hard exudates or cotton wool spots, but no signs of severe non-proliferative DR; 4) severe non-proliferative DR, in which there may be intraretinal haemorrhages, definite

venous beading, or intraretinal microvascular abnormalities, but no signs of proliferative DR; and 5) proliferative DR with neovascularization and/or vitreous or preretinal haemorrhages.[3] This five-stage DR severity score is the standard for measuring DR disease and reflects changes in the eye following eye examinations or fundus photography.[12] In severe non-proliferative DR, abnormal new blood vessels grow in response to the hypoxic environment caused by capillary occlusion, which worsens ischemia. In proliferative DR the main pathogenic factor is retinal hypoxia, which stimulates vascular endothelial growth factor (VEGF) production, resulting in retinal neovascularization.[3]

Evidence suggests that retinal neurodegeneration is an early process that precedes the microvascular complications of the eye.[14] This has been reflected in the guidelines from the American Diabetes Association, where DR is referred to as a highly specific neurovascular complication of diabetes.[15]

The pathophysiology of early worsening – mechanism of action

The definition of early worsening of DR varies across trials, ranging from changes in severity to specific morphological changes or clinically significant progression. The definition of "worsening" has been recorded as cotton-wool spots/soft exudates, haemorrhages (including dot-and-blot haemorrhages), 'red spots' or microaneurysms, intraretinal microvascular abnormalities (IRMA) and capillary-free areas.[6,9,16-18] Cotton-wool spots are lesions caused by microvascular perfusion abnormalities and secondary axoplasmic stasis.[19] The relationship between cotton-wool spots and glycaemic change is unclear. One theory suggests that a decrease in retinal blood flow may cause cotton-wool exudates to appear. This leads to an insufficient blood supply on the downstream side of arteriosclerotic arterioles. Impaired autoregulation may also be involved.[9]

In the Kroc Collaboration study subjects in the intensively treated group were characterized by increased numbers of soft exudates (cotton-wool spots) and IRMA, compared with those in the conventionally treated group, after 8 months. However, at 2 years, the number of soft exudates and IRMA were similar in both treatment groups.[20] In the STENO study early

worsening events were characterized by soft exudates, microaneurysms, and haemorrhages at 1 year. In this study, retinal morphology had improved at 2 years.[5,9] In the Oslo study, at 3 months, only subjects in the intensively treated group had significantly more microaneurysms and haemorrhages versus baseline.[6] However, at 2 years, those in the conventionally treated group had significantly more microaneurysms and haemorrhages versus baseline and versus the intensively treated group.[6] In the landmark Diabetic Control and Complications Trial (DCCT), at 4 years compared with baseline, there was more significant progression of DR in those with soft exudates and IRMA versus those without. Furthermore, early worsening of DR was higher in the intensively versus conventionally treated group and in patients who previously had early worsening than those who had not. In the DCCT, the most important factors for early worsening were a higher HbA_{1c} level at screening and reduction of this level during the first 6 months of treatment.[17] This effect was also seen in a study of patients who underwent successful pancreas transplantations. The group of patients who experienced early worsening had, among other characteristics, a poor pre-transplant glycaemic control and a large difference in HbA_{1c} between the pre- and post-transplant periods.[21]

Early worsening of DR, from treatment with insulin and other agents including GLP-1RAs, suggests a glycaemia-related mechanism of action. However, other possible mechanisms should be considered to explain early worsening in patients with diabetes.

Other potential mechanisms of early worsening

The role of blood pressure (BP) control in early worsening remains to be clarified. The UK Prospective Diabetes Study (UKPDS) reported the effect of BP control on DR progression, suggesting that tight BP control may reduce the risk of DR complications. After 1.5 years the relative risk of two-step or worse deterioration on the ETDRS scale in those randomized to tight BP control was lower versus those with less tight BP control (RR, 0.88; 95% CI, 0.60 to 1.29).[22] At 4.5 years after randomization, there was a significant difference in microaneurysms between the tight BP control versus less-tight BP control group (23.3% versus 33.5%, RR 0.7, p=0.003). This effect continued to 7.5 years. In addition, although cotton-wool spots increased

in both groups, there were fewer in the tight BP control group. Fewer patients in the tight BP control group, versus less-tight BP control group, had 2-step or more deterioration on the ETDRS scale at 4.5 years (RR, 0.75, p=0.02).[23] Conversely, in the ADVANCE study, BP lowering (or intensive glucose control) did not significantly reduce the incidence and progression of clinically significant DR.[24] In the ACCORD BP study, in which 1,263 subjects with type 2 diabetes were randomized to intensive versus standard antihypertensive therapy, BP control had no effect on the rate of progression of DR (adjusted odds ratio, 1.23; 95% CI, 0.84 to 1.79; p=0.29).[25] There was also no reported effect of BP on DR complications in the SUSTAIN 6 trial.[26]

It has also been suggested that a rapid drop in HbA_{1c} with intensive versus conventional treatment lowers intravascular osmotic pressure, creating an osmotic gradient between extracelluar and intracellular compartments. This causes water to move from high to low osmotic pressure levels, with vessels, such as small vessels in the eye, being low-pressure areas that are particularly sensitive. However, this hypothesis is tentative and requires further investigation.[27]

Early worsening in type 1 diabetes

A well-known report of early worsening of DR in type 1 diabetes is from the DCCT (**Figure 1**).[17] This landmark trial documented the frequency, importance of, and risk factors for early worsening of DR using intensive insulin treatment versus conventional treatment in patients with type 1 diabetes who had no-to-moderate non-proliferative DR. At the 6- and/or 12-month visit early worsening was observed in significantly more patients assigned to receive intensive (13.1%) versus conventional (7.6%) treatment (p<0.001). DR regression, that is improvement of DR, subsequently occurred at the 18-month visit in 51% and 55% of patients, respectively. The risk of 3-step (≥3 steps of the ETDRS final scale) or greater progression of DR versus baseline was higher in patients with early worsening versus those without (**Table 2**).[17] Characteristically, subjects with early worsening had a higher HbA_{1c} at baseline and experienced greater reductions in HbA_{1c} during the first 6-months of treatment versus those

without. However, despite this initial deterioration in DR, intensively treated subjects had similar or more favourable outcomes compared with conventionally treated subjects without early worsening. Furthermore, after 10 years, once HbA_{1c} levels had become comparable between the two treatment groups, the risk of DR progression was still significantly lower in subjects that had been treated intensively compared with conventionally treated patients, and a beneficial effect persisted for up to 18 years (**Table 2**).[28,29]

The effects on DR of rapid reductions in HbA_{1c} were further shown in a retrospective 24-month case–control study, in which people with diabetes and progression of retinopathy (case) were compared with people with diabetes and no progression of retinopathy (control). In the case group, HbA_{1c} values decreased rapidly approximately 10 to 9 months before the progression of retinopathy, whereas the control group HbA_{1c} values did not change during the entire follow-up period. The relative risk for DR progression with a 1, 2 or 3% decrease in HbA_{1c} for approximately 6 months were 1.7, 2.8 and 4.7, respectively **(Table 2)**.[30]

The effect of intensive versus conventional glycaemic targets on long-term complications in patients with type 1 diabetes was assessed in a Cochrane-based review.[31] This review was comprised of 12 trials, a total of 2,230 patients, and a mean follow-up across trials ranging between one and 6.5 years. Findings showed that intensive versus conventional treatment was highly effective in reducing the risk for developing microvascular diabetes complications such as DR (6.2% versus 23.2%, relative risk 0.27, 95% CI 0.18 to 0.42; $p<0.00001$). Furthermore, early worsening of DR was evident after only one year of intensive versus conventional glucose control (34.7% versus 14.9%; relative risk 2.32; 95% CI 1.16 to 4.63; $p<0.02$).[31]

Early worsening in type 2 diabetes

The evidence for early worsening in subjects with type 2 diabetes is limited because many large randomized controlled trials, for example the ADVANCE and ACCORD trials, only

evaluated the effect of intensive versus conventional therapy on DR progression, assessed as retinal change at trial end, rather than as an early outcome.[10,24,25,32]

In UKPDS, which was conducted in patients with new-onset type 2 diabetes, and used regular in-trial graded photography for retinal assessment the risk of two-step progression of DR during the first 3 years was 15.8% with intensive therapy versus 15.3% with conventional therapy in newly diagnosed patients with type 2 diabetes treated with either insulin or a sulphonylurea, and by 9 years there was a sustained significant protective effect of improved control.[10] The long-term risk reduction of DR progression was significantly better in the intensively (23.0%) versus conventionally (27.8%) treated patients after 6 years' follow-up (p=0.017).[10]

Early worsening was also demonstrated in a retrospective case-controlled study in 68 public hospital patients with type 2 diabetes, predominantly from ethnic minorities (Latino/other). These patients had annual retinal imaging either as part of a case management programme or as standard diabetes care.[33] An 'intensive' group of patients (n=34) with an HbA_{1c} decrease of >1.5% was compared with randomly chosen (control) patients (n=34) with minimal HbA_{1c} changes over 2 years. In this study, the intensive group had a larger reduction in HbA_{1c} over 2 years versus the control group (4.0±0.41% versus 0.2±0.11%). Patients in the intensive group showed a 22.6% worsening in retinopathy grade progression (p=0.015), while there was minimal change from baseline in the control group (p=NS). Change in retinopathy grade was significantly different between groups (p=0.02). Furthermore, in the intensive group more eyes worsened by ≥1 retinal grade (p=0.0025) and developed sight-threatening retinopathy (p=0.003) versus the control group. [33] This study supports DCCT findings that DR is significantly worsened in poorly controlled type 2 diabetes after early intensification of glycaemic control and a dramatic change in HbA_{1c}.[17,33]

As is the case for patients with type 1 diabetes, there is a large body of evidence supporting a beneficial effect of tight glycaemic control in the long term for patients with type 2 diabetes; the ACCORD eye study, for example, demonstrated reduced incidence or progression of DR.

This study investigated whether intensive glycaemic control, combination therapy for dyslipidaemia, and intensive blood-pressure control could limit DR in patients with type 2 diabetes.[25] Participants (N=10,251) were randomly assigned to receive either intensive (target HbA_{1c} <6.0%/<42 mmol/mol) or conventional (target HbA_{1c} 7.0–7.9%/ 53–63 mmol/mol) treatment for glycemia, dyslipidaemia and BP. At 4 years, rates of progression of DR were 7.3% with intensive glycaemic control versus 10.4% with standard control.[25] A follow-on study (ACCORDION), 4 years after trial end showed that DR progressed in 5.8% with intensive glycaemic control versus 12.7% with standard control (adjusted odds ratio 0.42, 95% CI 0.28 to 0.63; p<0.0001). Thus, prior intensive glycaemic control continued to reduce DR progression, even after study-end when HbA_{1c} levels had become similar in both groups, 8 years after randomization and approximately 4 years after trial end.[34]

Results from a meta-analysis of the ACCORD, UKPDS, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Administration Diabetes Trial (VADT), in patients with type 2 diabetes, suggest that intensive versus conventional glucose control was associated with a 13% risk reduction (HR, 0.87, 95% CI 0.76 to 100; p=0·04) in eye events (a composite of requirement for pan-retinal photocoagulation therapy or pars plana vitrectomy, development of proliferative retinopathy, or progression of DR) after 5 years follow-up.[35]

Early worsening with insulin

Early worsening of DR has historically been associated with the use of insulin therapy. This was based on the observed increase in risk of DR progression (defined as an increase of ≥3 steps on the ETDRS severity scale) in a 6-month phase 3 trial with insulin glargine versus human neutral protamine Hagedorn (NPH) insulin. In this study, 7.0% versus 2.7% of patients in the insulin glargine versus NPH insulin group had DR progression.[36,37] Subsequently, an *in vitro* study showed insulin glargine to have greater binding affinity for the insulin-like growth factor 1 (IGF-1) receptor compared with NPH insulin. [38] It was hypothesized that this might lead to the increased risk of DR progression with insulin glargine. However, this was disputed

by the results of a 5-year trial investigating DR with insulin glargine versus NPH, which showed no difference in the rate of DR progression.[37] Subsequently, the ORIGIN study found that there was no significant difference between insulin glargine and standard of care groups for the occurrence of microvascular events.[39]

Early worsening with non-insulin therapies

The evidence for early worsening of DR with non-insulin therapies continues to grow. Glucagon-like peptide-one receptor agonists (GLP-1RAs), like exenatide, liraglutide and semaglutide, exemplify a non-insulin-therapy drug class associated with increased rates of DR complication events, including early worsening of DR;[11,26,40-42] although, not all increases were significant compared with placebo.[41]

In a retrospective cohort study in patients with type 2 diabetes, >6 months' treatment with exenatide resulted in 29.7% (n=49/165) of patients having progression of DR (of which new onset was in 16 patients and worsening of pre-existing DR in 33 patients), while in 19.4%, DR improved ($p<0.005$). The proportion of patients with progression of DR was higher with greater reductions in HbA_{1c}.[43] Follow-up data from this study showed that sustained treatment with exenatide resulted in 80% of patients having improved (62%) or stable (18%) DR status after a mean 439 days (1.2 years) from the phase-1 screening (initial DR screening was done 234 days [8 months] from baseline).[40] In the LEADER trial, DR complications, defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage, or the onset of diabetes-related blindness, was evaluated in patients with type 2 diabetes and high cardiovascular risk. In this study the incidence of DR complications was non-significantly higher in patients receiving liraglutide versus placebo (0.6 versus 0.5 events per 100 patient-years; HR, 1.15 [95% CI, 0.87 to 1.52]; p=0.33).[41] Similarly, semaglutide was associated with an increased rate of DR complications in SUSTAIN 6, a preapproval trial to evaluate cardiovascular and other long-term outcomes in patients with type 2 diabetes.[11] DR complications were significantly higher in SUSTAIN 6 with semaglutide versus placebo (HR, 1.76; 95% CI, 1.11 to 2.78; p=0.02).[11]

It is important to emphasize that both the LEADER and SUSTAIN 6 trials had similar methodologic limitations with regards to the design of the DR complications endpoint. Neither was designed to assess DR, and based on the DR collection methods used (as part of the general evaluation of investigator-reported AEs), it is not possible to draw definitive conclusions relating to the increased risk of DR from these trials. For example, standardized retinal fundus photography was not included in the LEADER and SUSTAIN 6 study protocols. A subsequent SUSTAIN 6 *post hoc* analysis suggests that the increased risk of DR with semaglutide may not be an agent-specific effect, but rather attributable to the rapidity and magnitude of HbA_{1c} reduction during the first 16 weeks of treatment in patients with pre-existing DR, poor glycaemic control at baseline, and treated with insulin (**Table 2**).[26] Furthermore, it has been hypothesized that the worsening of DR in SUSTAIN 6 may be partially accounted for by the inclusion of patients with advanced non-proliferative or proliferative DR, in whom semaglutide may have triggered neovascularization. However, there is no information available from either *in vitro* or *in vivo* studies on the angiogenic effect of GLP-1RA in the retina, and further investigation is required.[42]

Across the rest of the SUSTAIN phase 3a clinical development programme (SUSTAIN 1 to 5 and Japan-based trials) and in SUSTAIN 7, in which patients with sight-threatening DR were excluded, there was no increase in DR adverse events in patients treated with semaglutide versus comparators.[26,44] Furthermore, an assessment using the Food and Drug Administration Adverse Event Reporting System has shown no evidence that GLP-1RAs are associated with adverse events suggestive of DR progression.[45] A meta-analysis assessing the effects of GLP-1RAs on DR showed that treatment with GLP-1RAs was not associated with a significant increase in the incidence of retinopathy (Mantel–Haenszel odds ratio [95% CI] 0.92 [0.74 to 1.16]; p=0.49). However, this analysis did not evaluate early worsening of DR.[46]

In experimental animal models with early-stage DR, systemically and locally administered GLP-1RAs prevented neurodegeneration of the retina and protected from diabetes-related changes to the retina.[47-49] Similarly, DPP4 inhibitors had a protective effect on retinal

microvasculature and prevented neurodegeneration and vascular leakage in the diabetic retina.[50,51] This evidence for a direct beneficial effect of GLP-1RAs on the retina supports the hypothesis that early worsening of DR in SUSTAIN 6 may be attributed to rapid improvement in glucose control in insulin-treated patients with pre-existing retinopathy, rather than by direct retinal toxicity of GLP-1RAs.[45,47-49]

Early worsening following bariatric surgery

The effect of bariatric surgery on DR and early worsening remains debatable. Existing data support positive, neutral and negative effects of bariatric surgery on DR.[52] The potential risk factors for DR progression following bariatric surgery may include DR severity pre-operation, magnitude in HbA_{1c} reduction post-surgery and, in some cases, gender and ethnicity.[53,54]

Uncontrolled studies suggest that bariatric surgery may contribute to the worsening of pre-existing DR post surgery.[53,55] A meta-analysis of four non-randomized case studies (N=148), showed that in patients with DR preoperatively (n=68), 57.4 ± 18.5% patients had no change, 23.5 ± 18.7% had progression and 19.2% ± 2.9% had an improvement in DR. In patients with no preoperative DR (n=80) an average of 92.5 ± 7.4% remained DR free, while 7.5 ± 7.4% progressed to DR. The odds ratio for DR progression in patients with versus without preoperative DR was 2.77 (95% CI, 1.10 to 6.9, p=0.03).[55] However, data such as the time points after bariatric surgery when percentage of no change occurred, progression or improvements in DR occurred, or how improved DR rate was assessed are important considerations when interpreting findings. In a retrospective observational study of patients with type 2 diabetes (N=102) to assess whether bariatric surgery prevented DR progression, the overall incidence of new retinopathy was 24%. In this study, young male patients with pre-existing DR and poor preoperative glycaemic control, and who did not have significantly improved HbA_{1c} levels post-operatively, were at most risk of DR progression.[53] A pilot study in patients with type 2 diabetes and morbid obesity showed moderate background DR, or worse, increased the risk of DR progression, while minimal or no DR resulted in a low incidence of new DR and DR progression in patients.[56] Findings from a retrospective, observational study

in patients with type 2 diabetes showed that the probability of DR progression (to moderate or higher severity) after bariatric surgery was associated with magnitude of HbA_{1c} reduction from pre-surgery levels, short postoperative retinal screening duration, severe preoperative DR, male gender, and ethnicity.[54]

In other studies bariatric surgery has been shown to have no effect on DR deterioration. For example, a survey of the Scandinavian Obesity Surgery Registry showed that in 117 patients with type 2 diabetes, majority of patients had no DR deterioration post-surgery (mean 16 months after surgery; method for evaluating DR was not specified). Furthermore, no association between preoperative body mass index (BMI), HbA_{1c} or reduction in HbA_{1c} and worsening of DR progression was reported.[57]

Conversely, some studies have shown an improvement in DR progression following bariatric surgery. For example, a meta-analysis of seven controlled studies indicated that bariatric surgery prevented new incident cases of retinopathy. However, there were insufficient data to support reduced progression or regression of DR.[58] Similarly, in a retrospective observational cohort study (N=4,683; 40% racial/ethnic minority [Hispanic, non-Hispanic black or other]) patients who had type 2 diabetes remission after bariatric surgery had a 29% lower risk of microvascular complications, including first occurrence of retinopathy. Furthermore, in patients who eventually relapsed, for every year they remained in remission, they experienced a 19% risk reduction of microvascular disease versus patients who did not go into remission.[59]

Early worsening in pregnancy

Pregnancy is a risk factor for DR progression and is associated with increased DR prevalence and severity versus non-pregnant women with diabetes. The highest risk of DR worsening occurs in the second trimester and can persist for up to 12 months postpartum. Factors associated with DR progression in pregnancy include diabetes duration, DR severity at conception, hyperglycaemic control, anaemia and coexisting hypertension.[60] These risk factors have been confirmed in a Japan-based study (N=93; of which type 1 diabetes, n=68 and type 2 diabetes, n=25) in which progression of DR occurred in 17% of patients. In this

study, patients with DR progression had significantly longer diabetes duration ($p<0.00001$), presence of DR pre-pregnancy ($p<0.00001$), and higher BP in the second trimester ($p<0.05$) versus patients who did not have DR progression.[61]

Rapid implementation of tight glycaemic control has also been associated with worsening of retinopathy in pregnant women with type 1 diabetes.[62] Guidelines recommend that pregnant women with pre-existing diabetes be offered retinal assessment by examination and fundus retinal imaging. In addition they suggest that DR should not be considered a contraindication to rapid glycaemic control in women with a high HbA_{1c} in early pregnancy, but rather that retinal assessment is essential in such individuals.[63]

Theories for the paradoxical early worsening of DR

Several theories exist to explain the paradoxical worsening of DR, evident in patients with diabetes, following rapid and large reductions in blood glucose. However, as there are currently no suitable animal models of DR, there are significant limitations associated with such theories.

Osmotic force theory

Glucose is an osmotically active molecule and can influence water movements. Thus, changes in blood glucose concentrations can alter osmotic pressure, which in turn affects water retention. Earlier, we described how rapid reductions in blood glucose affect osmotic pressure and the extracellular and intravascular areas.[27] Although evidence for this theory is limited, transient refractive error is associated with tight glycaemic control, relating to the rate of reduction in plasma blood glucose. In a study of 14 patients with diabetes (plasma glucose ≥400 mg/dL [22.2 mmol/L]; HbA_{1c} ≥12.0% [108 mmol/mol]) transient hyperopic change occurred in patients who improved control after hyperglycaemia. There was a positive correlation between the magnitude of maximum hyperopic change and daily rate of plasma glucose reduction over the first 7 days of treatment ($p<0.001$), the number of days required for hyperopia to reach its peak ($p<0.001$), and the number of days required for the

development and resolution of hyperopic changes ($p<0.0001$).[64] This correlation alone, however, is insufficient evidence for causation.

Synergistic hypothesis

The synergistic hypothesis postulates that early worsening is caused by the synergistic action of insulin and VEGF on the blood vessels in the retina, triggering vascular proliferation and therefore worsening DR.[27] In an *in vitro* study, insulin was found to increase reactive oxygen species (ROS) in bovine retinal endothelial cells. This increased insulin-induced ROS production and VEGF expression, in the presence of high glucose, may explain early worsening DR (**Table 3**).[65]

Blood-retinal barrier

Another mechanism suggested to explain transient worsening of DR is that involving a breakdown of the blood–brain barrier following intensive insulin therapy. An *in vitro* study demonstrated an increase in VEGF mRNA and protein levels in the retinas of diabetic rats following acute intensive insulin therapy. Retinal nuclear extracts from insulin-treated rats had high levels of hypoxia-inducible factor-1α (HIF-1α). Thus, acute intensive insulin therapy led to blood–retinal barrier breakdown via HIF-1α-mediated increase in retinal VEGF expression, resulting in transient DR (**Table 3**).[66]

VEGF hypothesis

Tight glycaemic control in a hypoxic environment may lead to VEGF upregulation. In a series of *in vitro* experiments in human and bovine retinal cells, lack of both oxygen and glucose led to significant upregulation of VEGF production, whereas lack of oxygen but excess glucose led to downregulation of VEGF. Sufficient oxygen with excess glucose had no effect on VEGF production.[67] In rat cells, transient ischaemia followed by retinal reperfusion led to a significant increase in VEGF. VEGF expression was linked to vascular permeability.[68]

In addition, a study of 26 patients newly diagnosed with type 1 or type 2 diabetes showed that in those who experienced blurred vision after starting insulin therapy, this was followed by a

transient increase in macular volume and thickness, which is associated with a decrease in the circulating soluble VEGF receptor, sFlt-1 (**Table 3**).[69]

Other potential effects of tight glycaemic control

Although changes in retinal blood flow and haemodynamics are associated with early worsening of DR,[70,71] the exact nature of these changes is controversial. For example, in bovine aortic endothelial cells, mitochondrial ROS (mtROS) production was increased in hypoglycaemic conditions as a result of increased fatty acid oxidation. Furthermore, there was an increase in pathological retinal neovascularization in recurrent hypoglycaemic conditions in streptozotocin (STZ)-induced diabetic control mice versus eMnSOD-Tg (STZ-Tg) mice. Blocking fatty acid oxidation led to reduced ROS production, inhibiting disease progression and suggesting that hypoglycaemia-induced mtROS production may contribute to early worsening of DR (**Table 3**).[70] In another study using human retinal epithelial cells, the rapid achievement of good glycaemic control did not trigger an immediate effect on retinal DNA methylation-hydroxymethylation machinery associated with DR progression. In this study, good glycaemic control for a longer duration, and/or direct targeting of DNA methylation improved mitochondrial damage, and could therefore potentially slow DR progression (**Table 3**).[71] The relationship between hypoglycaemia and ischaemic retinopathy was investigated in an *in vivo* study using Wistar rats. In this study, reduced blood glucose levels or hypoglycaemia caused a significant ($p<0.001$) reduction in vitreous glucose concentration, thereby exacerbating ischaemic retinal injury **(Table 3)**.[72]

The role of epigenetic modifications in early worsening of DR, following tight glycaemic control, remains to be fully investigated.

Conclusions

Early worsening of DR is a well-described phenomenon evident in patients with type 1 and type 2 diabetes, those who have undergone bariatric surgery, or in pregnant women.[13] It does

not appear to be agent-specific as it has been described in patients receiving treatments ranging from intensive insulin therapy, sulphonylureas, thiazolidinediones to GLP-1RAs.[4-6,10,11,26,40,41]

Morphological retinal changes that occur in early worsening include cotton wool spots/soft exudates, IRMA, retinal haemorrhages, and progression to severe non-proliferative or proliferative forms of DR.[3,6,9,16,17] While the mechanism leading to early worsening remains unclear, most evidence suggests an association with glycaemic control. The most important factors that are linked with early worsening of DR following rapid improvement of hyperglycaemia, are a large reduction in HbA_{1c} (<2%) and the severity of pre-existing DR at baseline.[17,30,33]

Consequently, insulin labels carry a warning of the risk of early worsening of DR with large and rapid reductions in HbA_{1c} in patients with diabetes.[73] Although a gradual improvement in HbA_{1c} is possible with insulin, this may not be possible with treatments such as GLP-1RAs, where the improvement in glycaemic control can be rapid and profound. Poorly controlled hypertension is another potential risk factor associated with early worsening.[3]

Various hypotheses have been proposed to explain early worsening of DR, but all are tentative or inconclusive. There are knowledge gaps consequent on the lack of adequate baseline and follow-up retinal imaging data in several large-scale studies. Non-clinical studies might help address gaps and generate more robust theories, but suitable animal models are limited.

Early worsening has implications in clinical practice. The American Diabetes Association guidelines suggest at least annual eye examinations for patients with DR, while the Royal College of Ophthalmologists guidelines recommend annual eye examinations for mild–moderate DR and every 4–6 months for moderately severe–very severe DR. Guideline revisions may be required for patients with DR and poor glycaemic control prior to initiation of

highly efficacious antidiabetic medications.[15,63] Rigorous methodology for DR assessment in future studies evaluating diabetes agents are required.

Eye status should be assessed in patients at increased ocular risk prior to initiating intensive diabetes treatments to achieve glycaemic control and patients should be informed of the risk, and reassured that both the transient loss of visual acuity and possible change in retinal architecture are small compared with the proven long-term benefits of glycaemic control.

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Conflicts of interest

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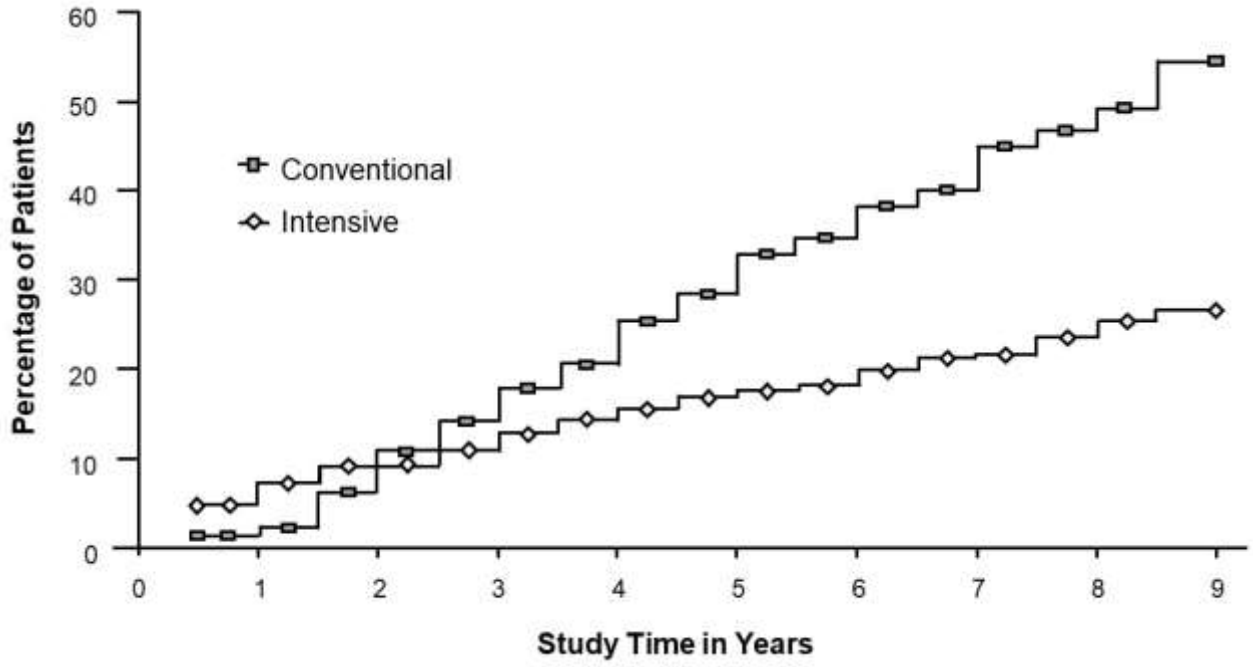
Figures and Tables

Figure 1: Cumulative incidence of DR progression (three-step or greater by ETDRS criteria) in the DCCT primary prevention cohort.



There was little difference in percentage of patients with retinopathy progression between the INT and CON groups over the first 3 years; however, there was a 76% risk reduction for DR progression evident at the conclusion of the DCCT after mean follow-up of 6.5 years [28]. ©2014 by the American Diabetes Association® Diabetes Care 2014 Jan; 37(1):17-23. Reprinted with permission from the American Diabetes Association®.

Table 1: Search terms used for literature searches in BIOSIS Previews®, Current Contents® Search, EMBASE®, and MEDLINE® databases

Set#	Search terms	Results
Primary and secondary articles (NOT reviews)		
S5	S4 NOT (rtype.exact("Review"))	167†
S4	(s1 and s2 and s3) AND pd(20120101-20171231)	184†
S3	ti,ab((glycemic or glycaemic or "blood glucose" or BG) near/3 (control or maintenance or management or improve‡))	120361‡
S2	MESH.EXACT("Disease Progression") OR EMB.EXACT("disease exacerbation") or ti,ab(progression or worsening or exacerbation or aggravat‡)	2055459‡
S1	MJEMB.EXACT("retinopathy") OR MJMESH.EXACT("Diabetic Retinopathy") or ti,ab(diabet* near/3 (retinopathy or retinopathia))	85482‡
Review articles only		
S5	S4 AND (rtype.exact("Review") AND pd(20120101-20171231))	41†
S4	s1 and s2 and s3	586†
S3	ti,ab((glycemic or glycaemic or "blood glucose" or BG) near/3 (control or maintenance or management or improve‡))	120361‡
S2	MESH.EXACT("Disease Progression") OR EMB.EXACT("disease exacerbation") or ti,ab(progression or worsening or exacerbation or aggravat‡)	2055459‡
S1	MJEMB.EXACT("retinopathy") OR MJMESH.EXACT("Diabetic Retinopathy") or ti,ab(diabet‡ near/3 (retinopathy or retinopathia))	85482‡

‡Duplicates were removed from the search, but included in the result count.

†Duplicates were removed from the search and from the result count.

Table 2: Summaries of clinical studies reporting early worsening DR, or associated outcomes

Trial name	Trial type; treatment regimen; duration	Patient population and N	Key findings relating to diabetic r early worsening
Type 1 diabetes			
Diabetes Control and Complications Trial (DCCT)	Multicentre, randomized clinical trial; INT versus CON therapy; Mean follow-up = 6.5 years	• Type 1 diabetes • N=1,441 • INT: n = 728 • CON: n = 711	• INT versus CON therapy reduced the risk of deve • Early worsening was observed at the 6 or 12 mont patients assigned CON versus INT therapy, respe
Epidemiology of Diabetes Intervention and Complications (EDIC)	Observational follow-up of DCCT		• Following DCCT, when HbA_{1c} levels in INT and C 8, INT, 7.98%; CON, 8.07%), the benefit of early ($p<0.0001$) reduction in the risk of further retinopa • A 56% ($p<0.001$) risk reduction in development group • Severe retinal outcomes and procedures to treat in the INT group
18 years follow-up of DCCT/EDIC study	Follow-up of DCCT/EDIC		• 39% versus 56% of INT versus CON therapy progression from DCCT closeout (incidence); 46% 36, 54; $p<0.0001$)

			• Overall, fewer former INT group patients continu complications 18 years after DCCT close-out
N/A	Retrospective case–control study	Diabetes with progression of DR (case) and without progression of DR (control) N=76 Case: n=24 Control group 1 (baseline DR): n=23 Control group 2 (no baseline DR): n=29	• HbA_{1c} values decreased rapidly 10 to 9 months b case group. HbA_{1c} remained stable during follow- • The relative risks of a 1, 2 and 3% decrease in Hb to progression of DR were estimated as, respecti
Type 2 diabetes			
Veterans Affairs Diabetes Trial (VADT)	*Post hoc* analysis of VADT prospective study	• Poorly controlled type 2 diabetes completing 7-field stereo fundus photos at baseline and 5 years • N=858	• Odds of DR progression lower by~40% in those w (p=0.007), LDL-C ≥120 mg/dL (p<0.02) or HDL-C versus standard glycaemic treatment • Odds of DR progression lower by ~40–50% wit mg/dL (p<0.0001), of LDL-C of ≥40 mg/dL (p<0.00 (p=0.004) at Year 5 • INT associated with decreased odds of progres retinopathy in those with worse lipid levels at ba lipid levels during the study

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements study (AdRem)	Substudy of ADVANCE, multicentre, randomised clinical trial	• Type 2 diabetes (aged ≥55 years) • N=1,602	• Compared with standard glucose control (n=611 (n=630) did not reduce (p=0.27) the incidence and (OR 0.84; 95% CI 0.61 to 1.15) • Lower, borderline significant risks of microaneu macular oedema observed with intensive glu baseline retinal haemorrhages • BP lowering or intensive glucose control did n incidence and progression of retinopathy
Public hospital study (US)	Retrospective case–control study, retinal imaging	• Type 2 diabetes, minorities • 'Intensive' HbA1c decrease >1.5% (n=34) • Minimal HbA1c changes (n=34)	• Retinopathy grade progressed +0.7 ± 0.25 units fr group (p=0.015), a 22.6% worsening • The control group changed minimally from baselin • More eyes worsened by ≥1 retinal grade (p=0.0 threatening retinopathy (p=0.003) in the intensive • DR significantly worsened in poorly controlled t intensification of glycaemic control and dramatic H
UK Prospective Diabetes Study (UKPDS)	Prospective study; Intensive policy: sulphonylurea (chlorpropamide, glibenclamide, glipizide) or insulin Conventional policy: diet	• Type 2 diabetes (newly diagnosed)	• After 6 years' follow-up, fewer patients in the int group, had a two-step deterioration in retinopathy

Kroc Collaborative Study Group	Randomized study (8 months), 2-year follow-up of DR progression (continuous s.c. insulin infusion [CSII] versus unchanged conventional injection)	• Type 2 diabetes and mild-to-moderate DR • N=64	• In type 2 diabetes patients with mild-to-modera activity associated with tightened control is not sus vasoproliferative deterioration in DR • No lasting damage results from the initial DR fla patients with mild-to-moderate DR after starting C
UKPDS 69	Prospective study	• Type 2 diabetes 19 clinics in UK • N=1,148	• At 1.5 years, in patients with any type of DR at b or worse deterioration on the ETDRS scale in th control was numerically greater versus those witl 1.07; 95% CI, 0.60 to 1.90) • In the long term, reduction in BP was associated
Collaborators on Trials of Lowering Glucose (CONTROL) group	Meta-analysis of microvascular outcomes in ACCORD, ADVANCE, UKPDS and VADT	• Type 2 diabetes • N=27,049	• Compared with less intensive glucose control, mo resulted in an absolute difference of –0·90% (95% HbA_{1c} at completion of follow-up • RR reduced by 13% for eye events (HR: 0·87, 0· • More intensive glucose control over 5 years reduc
N/A	Phase-1 and subsequent follow-up study GLP-1RA therapy;	• Type 2 diabetes • Phase 1: Exenatide treatment n=165 • Follow-up: • N=47	• Phase 1 study: 29.7% (n=49) of patients had prog (n=47) had improvement in HbA_{1c} ○ The proportion of patients with progressi greater HbA_{1c} reduction ○ The degree of worsening of DR was propor

	Follow-up data available from mean 439 days from Phase 1 screening		• Follow-up: 62% (n=24) had an improvement i documented change to DR status
Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)	Multicentre, double-blind, placebo-controlled study; Median follow-up 3.8 years	• Type 2 diabetes • N=9,340 • Liraglutide: • n=4668 • Placebo: • n=4,672	• Incidence of DR events was non-significantly hig placebo group (0.6 versus 0.5 events per 100 pa CI, 0.87 to 1.52; p=0.33)
SUSTAIN 6	Multicentre, double-blind, placebo-controlled study; Median follow-up 2.1 years	• Type 2 diabetes • N=3,297 • Semaglutide: • n=1,648 • Placebo: • n=1,649	• Incidence of DR events was significantly higher placebo group (1.5 versus 0.9 events per 100 pa CI, 1.11 to 2.78; p=0.02)
N/A	Meta-analysis of GLP-1RA RCT microvascular effects	• Type 2 diabetes	• GLP1-RAs not associated with a significant in retinopathy (MH-OR [95% CI] 0.92 [0.74 to 1.16];

		• 37 trials • GLP-1RA (n=21,782) • Comparator (n=17,296)	• In subgroup analyses, GLP1-RAs associated wi versus sulphonylureas • SUSTAIN-6 suggested that treatment with sema with a progression of DR
Type 2 diabetes and bariatric surgery			
Specialist bariatric unit (UK)	Retrospective observational study, following bariatric surgery	• Type 2 diabetes • Post-bariatric surgery • N=102 • 4 years' follow-up	• Preoperatively, 68% of patients had no DR ver retinopathy, 1% pre-proliferative retinopathy and • In the first postoperative visit, 19% of patients dev stable and 11% improved. Proportions did not diff • Bariatric surgery does not prevent progression of • Young male patients with pre-existing DR and p control are most at risk of progression
N/A	Meta-analysis on impact of bariatric surgery on DR	• Type 2 diabetes • DR outcome before and after bariatric surgery • 4 non-randomised case series • N=148	• Patients with no preoperative DR (n=80), follo average of 92.5 ± 7.4% remained disease free, w to DR • Patients with DR preoperatively (n=68), follow average of 57.4 ± 18.5% had no change, 23.5 ± 1 19.2 ± 2.9% had improvement in their disease • Patients with a diagnosis of DR prior to surgery ar disease progression

Scandinavian Obesity Surgery Registry (SOReg)	Registry survey on DR outcomes before and after GBP	• Type 2 diabetes and bariatric surgery • N=117	• Occurrence of DR before GBP: no DR 62%, mild 2 0% and proliferative DR 2% • No significant changes in occurrence of DR after • No association between preoperative BMI, HbA_{1c} worsening of DR
N/A	Retrospective pilot analysis of electronic hospital records	• Morbid obesity and type 2 diabetes • N=40 pre- and post- surgery DR screening	• Of those without DR pre surgery, 1.5% (n=26) pr post-surgery • Those with minimum BDR (n=9) pre surgery rev 55.6% (n=5) showing evidence of regression • Risk of progression of DR in those with moderate
N/A	Retrospective observational study	• Type 2 diabetes and bariatric surgery • N=318	• 68.6% had no DR pre-operatively versus 18.9% grade of minimal, mild or moderate and higher, re • First post-operative retinal screening results sho had no change in their DR grade, 11% regressed
N/A	Meta-analysis of bariatric surgery and DR	• Obese type 2 diabetes • 7 studies	• Incident cases of DR were fewer with bariatric treatment • Change of DR score (three studies) was not diffe were available on numbers of patients showing p retinopathy

			• Bariatric surgery seems to prevent new cases of D not sufficient to support progression or regressior
N/A	Retrospective observational cohort study (US) of microvascular disease (DR, neuropathy and/or nephropathy)	• Type 2 diabetes and bariatric surgery • N=4,683	• The rate of incident microvascular disease was p DR, which occurred at a rate of 8.0%, 18.2%, 28 and 7 years, post-surgery • For every additional year of time spent in remissi of microvascular disease was reduced by 19% 0.99]) versus patients who never remitted • Remission of type 2 diabetes after bariatric surg of incident microvascular disease even if patien relapse of their type 2 diabetes

BDR, background diabetic retinopathy; BMI, body mass index; BP, blood pressure; CI, confidence interval; CSII, continuous subcutaneo CON, conventional; ETDR, Early Treatment of Diabetic Retinopathy Study; GBP, gastric bypass surgery; GLP-1RA, glucagon-like pept intensive; LDL-C. low-density lipoprotein cholesterol; MH-OR, Mantel-Haenszel Odds Ratio; N/A, not available; NS, not specified; OR, odd relative risk; s.c., subcutaneous; TC, total cholesterol; TG, triglycerides. ***Table 3: Summaries of preclinical studies reporti outcomes***

Title	Study population	Key findings relating to DR and/or early worsening

Topical Administration of GLP-1RAs Prevents Retinal Neurodegeneration in Experimental Diabetes	Human and *db/db* mice retinas	• Abundant expression of GLP-1R in the human retina and retinas from db/db mice • Systemic administration of liraglutide prevented retinal neurodegeneration (glial a apoptosis, and electroretinographical abnormalities) • A similar neuroprotective effect was found using topical administration of na liraglutide, lixisenatide, and exenatide. ○ No reduction in blood glucose levels was observed suggesting that GI prevents retinal neurodegeneration
Different effects of low- and high-dose insulin on ROS production and VEGF expression in bovine retinal microvascular endothelial cells (BRECs) in the presence of high glucose	BRECs	• High-dose insulin-induced ROS production and VEGF expression in BRECs in the glucose might be one of the reasons for the transient worsening of DR during treatment
Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier (BRB) breakdown via hypoxia-inducible factor-1α and VEGF	Diabetic rats	• VEGF mRNA and protein levels are increased in retina of diabetic rats intensi insulin through hypoxia-inducible factor-1α-mediated increases in retinal VEGF ex to BRB breakdown • This mechanism explains the transient worsening of DR, specifically BRB breakd the institution of intensive insulin therapy
The influence of glucose concentration and hypoxia on VEGF secretion by cultured retinal cells	Human and bovine retinal cells	• Lack of both oxygen and glucose led to significant upregulation of VEGF productio of oxygen but excess glucose led to downregulation of VEGF • Sufficient oxygen with excess glucose had no effect on VEGF production

		• "Early worsening" of DR may result when diabetic patients with minimal to mode whose retinal circulation and, hence, retinal oxygen supply is compromised, are p glucose control regimen and their major remaining retinal energy source is redu upregulation as a compensatory mechanism
Effects of Ischemic Preconditioning and Bevacizumab on Apoptosis and Vascular Permeability Following Retinal Ischemia–Reperfusion Injury	Rats	• Transient ischaemia followed by retinal reperfusion led to a significant increase in • VEGF expression was linked to vascular permeability • IR provides an acute model of ischaemic retinopathy including neurodegenera dependent vascular permeability
Effect of intensive insulin therapy on macular biometrics, plasma VEGF and its soluble receptor, in newly diagnosed diabetic patients	Human	• Newly diagnosed patients with blurred vision starting insulin therapy presented increase in macular volume and thickness and decrease in circulating soluble VE
Hypoglycaemia-induced retinal neurodegeneration is associated with mitochondrial ROS (mtROS) production caused by fatty acid oxidation	Bovine aortic endothelia cells	• mtROS production is increased in hypoglycaemic conditions as a result of incr oxidation • Recurrent hypoglycaemia increased ROS production and enhanced pat neovascularization • Hypoglycaemia-induced mtROS production may contribute to early worsening of
The Role of DNA Methylation in the Metabolic Memory Phenomenon Associated With the Continued Progression of DR	Human retinal epithelial cells, diabetic rat retinas	• Retinal DNA methylation-hydroxymethylation machinery does not benefit immediat of hyperglycaemia

		• Maintenance of good glycaemic control for longer duration, and/or direct targeting ameliorates continuous mitochondrial damage, and could retard/halt DR progress
Hypoglycaemia exacerbates ischaemic retinal injury in rats	Rats and rat retinas	• Reduced blood glucose levels or hypoglycaemia caused a significant reduction in concentration, exacerbating ischaemic retinal injury

BRB, blood–retinal barrier; BREC, bovine retinal microvascular endothelial cells; DR, diabetic retinopathy; GLP-1RA, glucagon-like peptide-one rece
factor; mtROS, mitochondrial reactive oxygen species; ROS, reactive oxygen species.