



Diabetic retinopathy

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Diabetic retinopathy is a common and specific microvascular complication of diabetes, and remains the leading cause of preventable blindness in working-aged people. It is identified in a third of people with diabetes and associated with increased risk of life-threatening systemic vascular complications, including stroke, coronary heart disease, and heart failure. Optimum control of blood glucose, blood pressure, and possibly blood lipids remains the foundation for reduction of risk of retinopathy development and progression. Timely laser therapy is effective for preservation of sight in proliferative retinopathy and macular oedema, but its ability to reverse visual loss is poor. Vitrectomy surgery might occasionally be needed for advanced retinopathy. New therapies, such as intraocular injection of steroids and antivascular endothelial growth-factor agents, are less destructive to the retina than are older therapies, and could be useful in patients who respond poorly to conventional therapy. The outlook for future treatment modalities, such as inhibition of other angiogenic factors, regenerative therapy, and topical therapy, is promising.

Introduction

As the worldwide prevalence of diabetes mellitus continues to increase, diabetic retinopathy remains a leading cause of vision loss in many developed countries.^{1,2} Although diabetes affects the eye in many ways (eg, heightened risk of cataract),³ diabetic retinopathy is the most common and serious ocular complication. Of the 246 million people with diabetes,⁴ about a third have signs of diabetic retinopathy, and a third of these might have vision-threatening retinopathy, defined as severe retinopathy or macular oedema.⁵ Apart from its effects on vision, the presence of diabetic retinopathy also signifies a heightened risk of life-threatening systemic vascular complications.⁶

Epidemiological, genetic, and experimental studies have furthered our understanding of the pathophysiology underlying diabetic retinopathy. Moreover, new clinical trials have provided contemporary data for evidence-based treatment strategies for diabetic retinopathy. This Seminar summarises the present state of knowledge of diabetic retinopathy, from epidemiological, pathophysiological, and clinical perspectives.

Epidemiology

Prevalence

In many countries, diabetic retinopathy is the most frequent cause of preventable blindness in working-aged adults (20–74 years).⁷ In the USA, an estimated 40% (8% for vision-threatening retinopathy) of people with type 2 diabetes and 86% (42%) with type 1 diabetes have diabetic retinopathy.^{8,9} Similarly, high prevalence estimates have been reported in other countries (figure 1).¹² The low prevalence rates reported in some developing countries (eg, India^{16,17}) will probably change with increasing numbers (eg, due to changing socio-economic conditions and increased obesity) and lifespans (ie, diabetes duration) of people with diabetes.

However, evidence suggests that the prevalence of diabetic retinopathy might be decreasing in the USA and other developed countries,¹⁸ especially in people with type 1 diabetes.^{19,20} This finding might be a result of improvement in the control of systemic risk factors in

diabetes care.^{21,22} Nevertheless, whether this declining trend will continue is uncertain, with increasing numbers and lifespans of people with diabetes expected.⁵

Despite concern about a potential diabetes epidemic in Asia,²³ epidemiological data for diabetic retinopathy in Asian countries are scarce.²⁴ Results of a study¹³ in rural China showed that diabetic retinopathy is common, with rates of 43% for any retinopathy and 6·3% for vision-threatening retinopathy. These estimates are higher than are those reported in another study¹⁵ of mostly urban Chinese residents, suggesting that preventive efforts should be targeted in rural areas of China. On the basis of these data, an estimated 9·2 million Chinese people living in rural areas have diabetic retinopathy, of whom 1·2 million having vision-threatening retinopathy.¹³ In southeast Asia, data¹⁴ from Singapore showed that 34% of Asian Malay adults with diabetes had signs of retinopathy, and, alarmingly, 10% had vision-threatening retinopathy. These studies confirm the international effect of diabetic retinopathy as a major public health problem, not only in high-income countries but also in Asia.

Incidence

Few population-based studies²⁵ have reported the incidence of diabetic retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)²⁶

Search strategy and selection criteria

We searched the Cochrane Library (1980–2009), Medline (1980–2009), and Embase (1980–2009). We used the search terms “diabetic retinopathy” in combination with the following terms: “prevalence”, “incidence”, “risk factors”, “pathogenesis”, “gene”, “diagnosis”, “screening”, “imaging”, “treatment”, and “therapy”. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and references than this Seminar provides.

in the USA, the overall 10-year incidence of retinopathy was 74%, and in people with retinopathy at baseline, 64% developed more severe retinopathy and 17% progressed to develop proliferative retinopathy.²⁵ About 20% of those with type 1 diabetes and 14–25% with type 2 diabetes developed macular oedema during a 10-year follow-up.²⁷ Data from the 25-year follow-up of the WESDR type 1 diabetes cohort show that almost all patients (97%) developed retinopathy over time, with a third to a half developing vision-threatening disease (43% developed proliferative retinopathy and 29% developed macular oedema).^{20,28} Notably, by contrast with the first 10 years of follow-up when incidence rates were largely constant,^{27,28} the WESDR results have shown a reduction in the yearly incidence and progression of diabetic retinopathy during the past 15 years. Additionally, both the prevalence and incidence of proliferative retinopathy were lowered in people with a recent diagnosis of diabetes. These results suggest the positive effect of improved diabetes management in high-income countries during the past two decades.²⁶

Risk factors

The panel shows several important risk factors for diabetic retinopathy. Ethnic origin differences in the prevalence of diabetic retinopathy have been a focal point of interest in research. Findings from population-based studies suggest that the prevalence and severity of diabetic retinopathy are higher in African Americans, Hispanics, and south Asians than in white people, and are not fully accounted for by differences in the distribution of retinopathy risk factors.^{12,25,29} For example, in the UK Asian Diabetes Study,¹² researchers showed that after controlling for retinopathy risk factors, people with a south Asian ethnic origin were more likely to have diabetic retinopathy than were white people, a finding also supported by a large clinical trial.³⁰ Nevertheless, whether these apparent variations represent sub-population differences associated with medical care or variability in genetic predisposition to microvascular damage is unknown.

Emerging evidence^{31,32} supports a genetic component for diabetic retinopathy. Findings from familial aggregation studies and clinical trials such as the Diabetes Control and Complications Trial (DCCT)³³ show a heritable tendency for diabetic retinopathy, independent of shared risk factors. In the past 5 years, in studies³¹ of populations of other ethnic origins, investigators reported similar heritability for severe diabetic retinopathy that was not fully accounted for by lifestyle or environmental factors. A recent meta-analysis³² identified several genes (eg, aldose reductase gene) associated with diabetic retinopathy.

Puberty and pregnancy are well known risk factors for diabetic retinopathy in people with type 1 diabetes.^{34–36} In the WESDR results, diabetes duration after menarche, a marker of puberty onset, was associated with a 30% excess

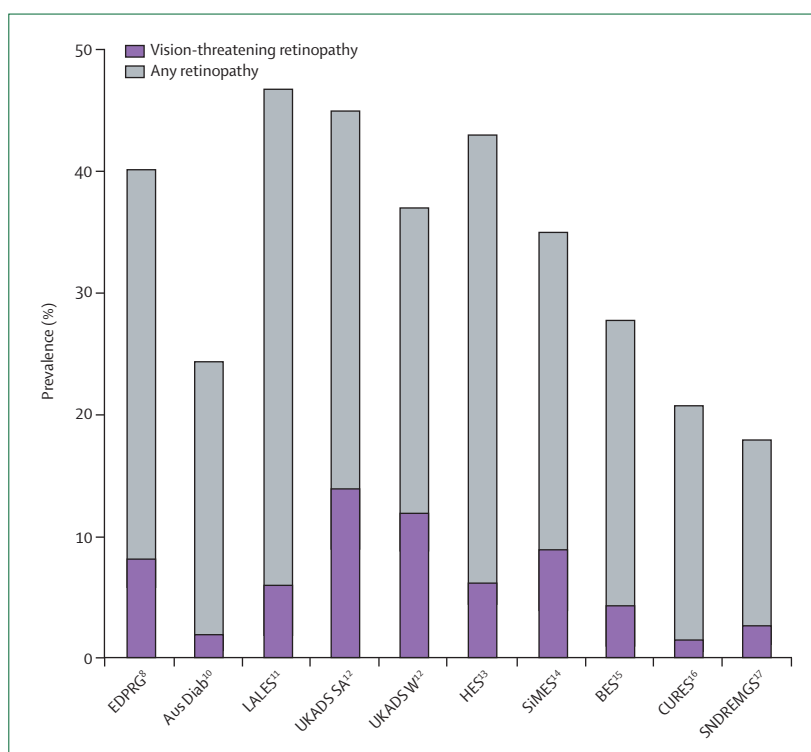


Figure 1: Prevalence of diabetic retinopathy in population-based studies^{8,10–17} with standardised photographic assessment

Vision-threatening diabetic retinopathy defined as presence of severe non-proliferative retinopathy, proliferative diabetic retinopathy, or clinically significant macular oedema. SA=south Asian people. W=European white people.

risk of retinopathy compared with diabetes duration before menarche.³⁴ Similarly, pregnancy is associated with worsening diabetic retinopathy.^{37,38} Thus, planned dilated retinal examination should be considered for patients with type 1 diabetes after puberty and during the course of pregnancy.

Panel: Risk factors for diabetic retinopathy

- Hyperglycaemia
 - 1% decrease in glycated haemoglobin (HbA_{1c}) roughly equates to a decreased risk of retinopathy by 40%, progression to vision-threatening retinopathy by 25%, need for laser therapy by 25%, and blindness by 15% (webappendix pp 1–2)
- Hypertension
 - 10 mm Hg decreased systolic blood pressure roughly equates to a decreased risk of retinopathy progression by 35%, need for laser therapy by 35%, and visual loss by 50% (webappendix pp 1–2)
- Dyslipidaemia
- Diabetes duration
- Ethnic origin (Hispanic, south Asian)
- Pregnancy
- Puberty
- Cataract surgery

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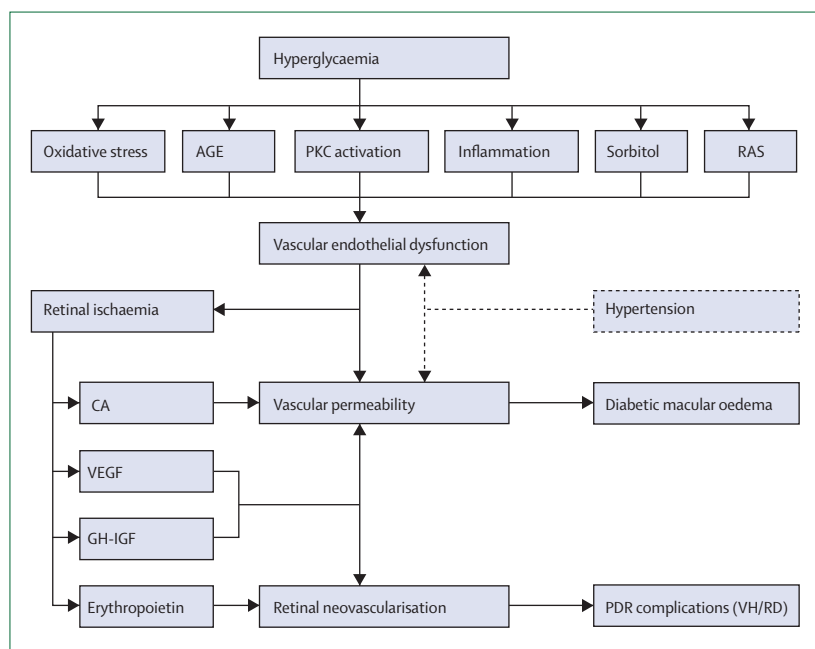


Figure 2: Pathophysiology of diabetic retinopathy

Hyperglycaemia instigates a cascade of events leading to retinal vascular endothelial dysfunction (table 1). Resultant retinal ischaemia and increased vascular permeability, augmented by hypertension, are two key common pathways underlying development of vision-threatening diabetic retinopathy. AGE=advanced glycation end-products. PKC=protein kinase C. RAS=renin-angiotensin system. CA=carbonic anhydrase. VEGF=vascular endothelial growth factor. GH-IGF=growth factor–insulin growth factor. PDR=proliferative diabetic retinopathy. VH=vitreous haemorrhage. RD=retinal detachment.

Results of previous epidemiological studies have also shown that diabetic retinopathy is associated with many other systemic and lifestyle factors, including nephropathy,³⁹ obesity,⁴⁰ alcohol consumption,⁴¹ and haematological markers of anaemia,⁴² hypothyroidism,⁴³ inflammation, and endothelial dysfunction.⁴⁴ However, some of these findings have been inconsistent, and the precise role of such factors in the pathogenesis of diabetic retinopathy is not well defined.

Besides retinopathy risk factors, findings from epidemiological studies⁶ suggest that diabetic retinopathy is a risk marker for systemic vascular complications. Presence of retinopathy, even in its mildest form, is associated with a doubling or tripling of risk of stroke, coronary heart disease, and heart failure, independent of cardiovascular risk factors.^{45–47} These findings suggest that the presence of retinopathy is a sign of widespread end-organ microcirculatory damage in people with diabetes, and that there is the need for improvement in careful cardiovascular monitoring and follow-up for patients with diabetic retinopathy.⁶

Pathophysiology

Our understanding of the pathophysiological mechanisms underlying the development of diabetic retinopathy is constantly evolving with new research.^{48–50} Chronic exposure to hyperglycaemia and other causal risk factors (eg, hypertension) is believed to initiate a

cascade of biochemical and physiological changes that ultimately lead to microvascular damage and retinal dysfunction (figure 2).

Biochemical changes

Several biochemical mechanisms have been proposed to modulate the pathogenesis of retinopathy through effects on cellular metabolism, signalling, and growth factors.² Implicated pathways include the accumulation of sorbitol and advanced glycation end-products (AGE), oxidative stress, protein kinase C activation, inflammation, and upregulation of the renin-angiotensin system and vascular endothelial growth factor (VEGF; table 1). Recognition of the potential roles for these processes has led to development of new therapeutic agents, several of which have been or are being tested in clinical trials.

Although the relevance of VEGF in the pathogenesis of diabetic retinopathy, especially for proliferative disease, is indisputable,⁶⁴ new VEGF-independent pathways for diabetic retinopathy have been identified.^{51,65} Of these, erythropoietin is a potent ischaemia-induced angiogenic factor that acts independently of VEGF during retinal angiogenesis in proliferative retinopathy.^{55,66} In animals, inhibition of erythropoietin is very effective in suppression of retinal neovascularisation.^{55,67} However, erythropoietin is also expressed in response to stimuli other than retinal ischaemia,⁶⁸ and at the early stage of diabetic retinopathy it might serve to protect the neural retina.^{69,70} Thus, erythropoietin inhibition as a therapeutic approach for diabetic retinopathy needs to be balanced by its potential adverse effects on photoreceptor survival.⁵¹

Another new VEGF-independent pathway was discovered with proteomic analyses. Gao and co-workers⁵⁶ showed that the vitreous concentration of extracellular carbonic anhydrase was greatly raised in eyes of people with diabetic retinopathy. In animals, inhibition of carbonic anhydrase activity reduced retinal vascular permeability.⁵⁶ However, whether topical carbonic anhydrase inhibitors, which are commonly used to lower intraocular pressure in patients with glaucoma, could reduce the risk of diabetic retinopathy is not yet established.⁷¹

There is growing evidence that inflammation plays a prominent part in the pathogenesis of diabetic retinopathy.^{49,72} In response to hyperglycaemia and other stresses (eg, dyslipidaemia), an array of inflammatory mediators are upregulated in diabetes, triggering proinflammatory responses that might cause abnormal leucocyte-endothelial interactions and ultimately retinal microvascular damage. This effect is probably a local occurrence, because studies^{44,73} have shown little evidence for a strong association between markers of systemic inflammation and risk of diabetic retinopathy.

Finally, the traditional notion that diabetic retinopathy is purely a manifestation of microvascular damage is incomplete. Neuroretinal compromise might develop early in the course of diabetic retinopathy, even before the onset of microvascular changes.⁴⁹ This occurrence

	Key points on mechanisms	Evidence
Vascular endothelial growth factor (VEGF)	In response to hypoxia, retinal endothelial cells, pericytes, and pigment epithelial cells express VEGF, stimulating angiogenesis (neovascularisation) and increasing capillary permeability (retinal oedema)	Intraocular VEGF is strongly related to retinal neovascularisation, retinopathy severity, and macular oedema, and decreases with laser photocoagulation; ^{51,52} RCTs*
Inflammation	Diabetes disrupts balance between prosurvival neurotrophins and inflammatory mediators, leading to maladaptive chronic inflammatory response in retinal endothelial and neural cells, resulting in VEGF production and recruitment of inflammatory mediators, causing increased vascular permeability, capillary non-perfusion (apoptosis of endothelial cells), neurodegeneration (apoptosis of neural cells), and neovascularisation\	Intravitreal triamcinolone is effective for treatment of refractory diabetic macular oedema in the short term but not long term; ^{53,54} intravitreal fluocinolone and dexamethasone delivered via a surgical implant to avoid repeated injections might be effective but no long-term follow-up data are available ⁵³
Renin-angiotensin	Intraocular rennin-angiotensin system can be up-regulated in diabetes, and angiotensin II might stimulate VEGF expression in retinal vascular endothelial cells	RCTs†
Erythropoietin	Expressed in response to retinal ischaemia and possibly other intraocular factors (high glucose levels, oxidative stress, inflammation and some cytokines), erythropoietin can have neuroprotective effects and promote VEGF-independent angiogenic activity in retinal vascular endothelial cells	Intraocular erythropoietin is increased in proliferative diabetic retinopathy in human beings, and its inhibition decreases hypoxia-induced retinal neovascularisation in animal studies ⁵⁵
Carbonic anhydrase	Extracellular carbonic anhydrase increases retinal vascular permeability by increasing pH, leading to kallikrein-mediated proteolytic activation of kinin	Intraocular carbonic anhydrase is increased in diabetic retinopathy in human beings, and its inhibition decreases retinal vascular permeability in animal studies ⁵⁶
Oxidative stress	Hyperglycaemia increases production of reactive-oxygen species (free radicals), leading to activation of protein kinase C, formation of advanced glycation end-products (AGE), activation of the polyol pathway, and VEGF production	Normalisation of mitochondrial reactive oxygen species prevents glucose-induced activation of protein kinase C, AGE formation, and sorbitol accumulation; ⁵⁷ in an RCT, ⁵⁸ oral vitamin E did not prevent need for laser therapy for diabetic retinopathy
Protein kinase C	Hyperglycaemia increases activation of retinal cellular protein-kinase C, leading to increased expression of matrix proteins and vasoactive mediators, with adverse structural (pericyte apoptosis, basement membrane thickening) and functional (increased retinal vascular permeability and retinal blood flow) retinal vascular changes	Ruboxistaurin (32 mg per day) decreased risk of vision loss, macular oedema progression, and laser treatment for macular oedema in two RCTs ^{59,60}
Growth hormone and insulin growth factor (IGF)	Growth hormone and IGF modulate the function of retinal endothelial precursor cells and drive retinal angiogenesis in response to hypoxia; IGF-1 can also disrupt the blood-retina barrier and increase retinal vascular permeability	Diabetic retinopathy improved after spontaneous destruction of the pituitary gland or surgical hypophysectomy; ⁶¹ somatostatin is antiangiogenic and neuroprotective for retina; ⁶² in small RCTs subcutaneous octreotide slowed diabetic retinopathy progression, decreased need for laser treatment, and reduced occurrence of vitreous haemorrhage ⁷
Sorbitol	Hyperglycaemia increases glucose flux through the polyol pathway, via which aldose reductase converts glucose into intracellular sorbitol, possibly inducing osmotic damage to retinal endothelial cells and pericytes	The aldose reductase gene had the largest number of polymorphisms associated with diabetic retinopathy; ⁶³ RCTs have not yet shown efficacy ⁷
AGE	Hyperglycaemia induces non-enzymatic glycation of proteins to form AGE, possibly contributing to retinal pericyte loss, microaneurysm formation, and vascular endothelial damage	Patients with type 1 diabetes who were given pimagedine were less likely to develop retinopathy progression than were untreated patients in an RCT (10% vs 16%, p=0.03) ⁶³

RCT=randomised controlled trial. *See webappendix p 4. †See webappendix pp 1–2.

Table 1: Biochemical pathways underlying diabetic retinopathy

has been linked to the theory that diabetes might reduce insulin receptor signalling in the retina, leading to neurodegeneration. Results of experimental studies suggest that diabetes adversely affects the entire neurosensory retina, with accelerated neuronal apoptosis and activation or altered metabolism of neuroretinal supporting cells.⁴⁹ These findings suggest that diabetic retinopathy could be a sensory neuropathy that affects the retinal parenchyma, similar to peripheral diabetic neuropathy. Although the interplay between the neural and vascular elements of retinopathy pathogenesis remains to be clarified, understanding how diabetes affects the neural retina could eventually lead to development of neuroprotective agents as new potential treatment modalities.¹¹

Retinal vascular changes

Structural and functional changes in the retinal vasculature are closely related to diabetes and diabetic retinopathy.⁴⁸ Advances in computer-based retinal image analysis have allowed quantitative assessment of the

retinal vasculature to study these changes in greater detail. For example, widened retinal arteriolar calibre has been associated with the development of retinopathy in both type 1 and type 2 diabetes.^{10,74,75} Retinal arteriolar dilatation might be an early physiological indicator of microvascular dysfunction,⁷⁶ signifying impaired arteriolar autoregulation. Retinal arteriolar dilatation has been further postulated,⁷⁵ according to the laws of Starling and Laplace, to increase retinal capillary pressure, leading to capillary wall dilatation (microaneurysms), leakage (oedema and hard exudates), and rupture (haemorrhages). By contrast, widened retinal venular calibre is independently associated with prevalence and progression of diabetic retinopathy,^{77–81} and predicts risk of proliferative retinopathy.⁷⁷ Proposed mechanisms underlying this association are multifactorial (eg, retinal hypoxia, inflammation, and endothelial dysfunction).^{82–85} Together, these findings suggest that retinal arteriolar dilatation could be an early subclinical marker of microvascular dysfunction preceding development of non-proliferative diabetic

	Defining features	Clinical implications	Frequency of examination
No retinopathy	No microvascular lesions	Low risk of progression to vision-threatening retinopathy	Once every 1–2 years
Mild non-proliferative diabetic retinopathy (NPDR)	Microaneurysms only	5% (within 1 year) and 14% (within 3 years) progress to proliferative diabetic retinopathy ⁸⁹	Yearly
Moderate NPDR	Microaneurysms and other microvascular lesions, but not severe NPDR	12–26% (within 1 year) and 30–48% (within 3 years) progress to proliferative diabetic retinopathy ⁸⁹	Every 3–6 months
Severe NPDR	More than 20 intraretinal haemorrhages in four quadrants or venous beading in two or more quadrants, or intraretinal microvascular abnormalities in one or more quadrant but not proliferative diabetic retinopathy	52% (within 1 year) and 71% (within 3 years) progress to proliferative diabetic retinopathy ⁸⁹	Every 3–6 months
Proliferative diabetic retinopathy	Neovascularisation of optic disc (NVD) or elsewhere (NVE), preretinal haemorrhage, or vitreous haemorrhage; high-risk characteristics are mild NVD with vitreous haemorrhage, moderate-to-severe NVD with or without vitreous haemorrhage; moderate NVE with vitreous haemorrhage	Indication for panretinal photocoagulation; ⁹⁰ urgent if high-risk characteristics are present ⁹¹	Variable
Clinically significant macular oedema	Retinal thickening within 500 µm from centre of macula; hard exudates within 500 µm from centre of macula with adjacent retinal thickening; retinal thickening of more than one optic disc area within one optic disc diameter from centre of macula	Can develop at any stage of diabetic retinopathy; indication for macular laser ⁹²	Variable

Table 2: Classification of diabetic retinopathy by severity⁸⁷

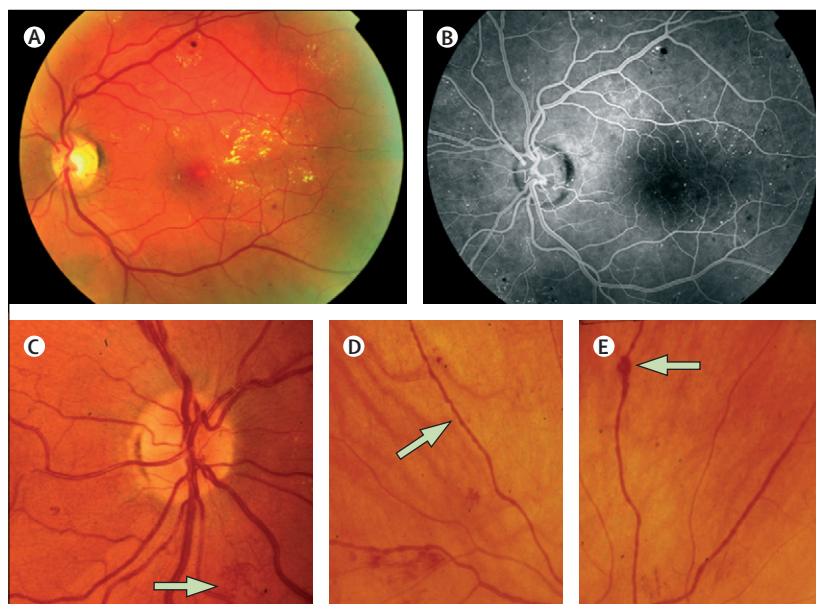


Figure 3: Non-proliferative diabetic retinopathy
Cardinal signs are retinal microaneurysms, haemorrhages, and hard exudates (A and B); and intraretinal microvascular abnormalities (C, arrow); venous beading (D, arrow); and venous loop formation (E, arrow).

retinopathy, whereas retinal venular dilatation might be a marker of progression to more advanced diseases such as proliferative retinopathy.

Fractal analysis has been used to assess the overall geometry of the retinal vascular network in diabetes.⁸⁶ Retinal fractal dimension, a measure of the density of the vascular branching pattern, is associated with early diabetic retinopathy in type 1 diabetes.⁸⁷ Furthermore, researchers^{84,88} investigating new dynamic retinal vascular changes have shown that eyes with diabetic retinopathy have reduced retinal vasodilation after flicker-light stimulation, a measure of endothelial dysfunction. These evolving retinal vascular imaging

techniques might offer a new means of assessing diabetic retinopathy risk.

Clinical assessment

Clinical features and classifications

Clinically, diabetic retinopathy is defined as the presence of typical retinal microvascular signs in an individual with diabetes mellitus. Vision loss develops from the sequelae of maculopathy (macular oedema and ischaemia) and neovascularisation of the retina (vitreous haemorrhage and retinal detachment) and iris (neovascular glaucoma). Clinical assessment should therefore aim to detect these serious ocular manifestations, and in their absence assess the risk of progression to vision-threatening disease (table 2).

Eye examination by direct ophthalmoscopy permits an adequate assessment of diabetic retinopathy signs, but this assessment is enhanced by slit-lamp biomicroscopy with a condensing lens. Although visual acuity is a crucial measurement, severe diabetic retinopathy can be present without symptomatic visual impairment. Additionally, examination of the peripheral fundus is important, especially in patients with type 1 diabetes, to avoid overlooking peripheral retinal ischaemia and neovascularisation. A comprehensive and systemic examination by clinicians is also advisable for patients with newly diagnosed diabetic retinopathy.⁶

The classic retinal microvascular signs of non-proliferative diabetic retinopathy are microaneurysms, haemorrhages, hard exudates (lipid deposits), cotton-wool spots (accumulations of axoplasmic debris within adjacent bundles of ganglion cell axons⁹³), venous dilation and beading, and intraretinal microvascular abnormalities (dilated pre-existing capillaries; figure 3). Table 2 shows the standard clinical classifications of diabetic retinopathy.⁹⁴ Diabetic macular oedema is an important sign that is assessed separately from the

stages of retinopathy (figure 4), because it can run an independent course.

The appearance of retinal neovascularisation heralds a critical change in the progression of diabetic retinopathy (figure 5). Fibrovascular proliferation is a characteristic of advanced proliferative disease, and visual loss can take place suddenly because of vitreous haemorrhage from new vessels or tractional retinal detachment from progressive fibrosis.

Investigations

Ophthalmic imaging modalities are increasingly important in screening, diagnosis, and monitoring of diabetic retinopathy. Retinal photography serves as a useful screening method for diabetic retinopathy, especially when access to ophthalmologists is difficult. Studies have shown that retinal photography interpreted by trained readers has a high sensitivity (61–90%) and specificity (85–97%) for detection of retinopathy signs,⁹⁵ and can guide appropriate ophthalmic referral.⁹⁶

For several decades, fluorescein angiography has aided clinical assessment of diabetic retinopathy (figures 3 and 5). Microaneurysms and increased capillary permeability are the earliest detectable changes. Focal areas of capillary non-perfusion represent retinal ischaemia, whereas enlargement of the foveal avascular zone signifies macular ischaemia. Retinal neovascularisation is identified as dye leakage into the vitreous. Diabetic macular oedema generally has two main angiographic patterns: focal (from leaking microaneurysms) and diffuse (generalised breakdown of blood-retinal barrier) types.

Optical coherence tomography has emerged as a useful imaging modality. It functions as an optical biopsy of the retina, offering high-resolution, three-dimensional or cross-sectional images that closely approximate the histology of the retina.⁹⁷ This technique allows precise and reproducible measurements of retinal thickness, which are crucial for monitoring progression and treatment response for diabetic macular oedema (figure 4). It is also useful to detect structural changes (eg, vitreomacular traction or epiretinal membranes) that might suggest a need for surgical intervention.

Screening

Regular dilated eye examinations are effective for detection and monitoring of asymptomatic vision-threatening diabetic retinopathy. In the WESDR findings, 14% of people with type 1 and 33% with type 2 diabetes developed diabetic retinopathy within 5 years of a diagnosis of diabetes. Almost all cases of retinopathy in those with type 1 diabetes were mild, whereas in participants older than age 30 years with type 2 diabetes, 2% had proliferative retinopathy and 3% had clinically significant macular oedema.²⁵ These data suggest that diabetic retinopathy screening should be done at diagnosis of diabetes and either yearly or every second year thereafter in people with

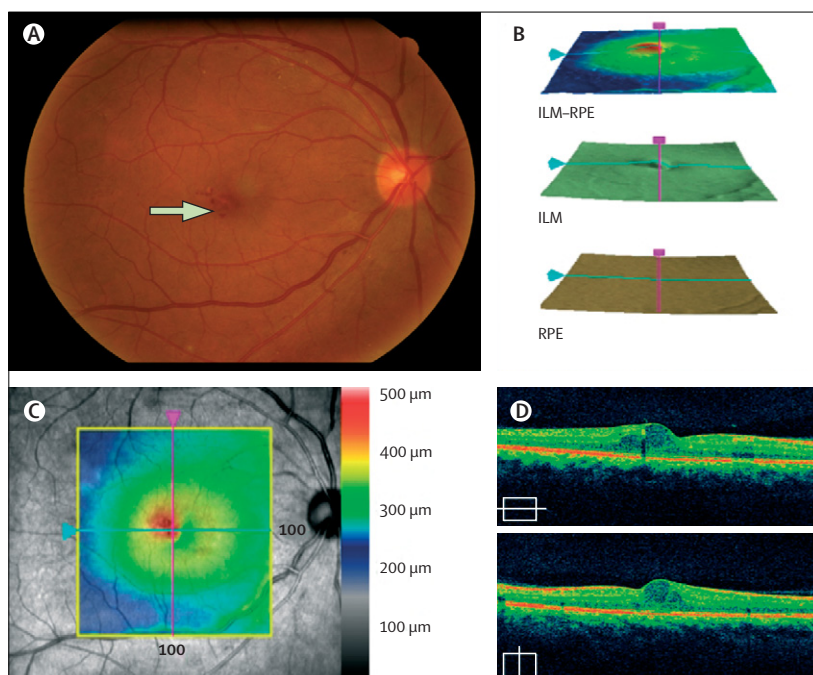


Figure 4: Diabetic macular oedema

Clinical diagnosis of diabetic macular oedema based on stereoscopic examination of the macula (A, arrow) can be supplemented by optical coherence tomography (OCT); three-dimensional topographic maps of the macula from OCT allow visualisation of macular oedema in relation to internal limiting membrane (ILM) or retinal pigment epithelium (RPE; B); overall topographic image (C), and horizontal (upper image, D) and vertical (lower image, D) cross-sectional images of the macula from OCT allow quantitative and qualitative assessment of macular oedema.

type 2 diabetes. Baseline examinations could be extended to 5 years after a diagnosis of type 1 diabetes. Incidence data from the Liverpool Diabetic Eye Study⁹⁸ of a large cohort of people with type 2 diabetes suggested that a 3-year screening interval could be safe for patients without evidence of retinopathy, although yearly or more frequent examination is recommended for patients with any retinopathy signs.

In practice, timing and frequency of eye examinations in people with diabetes are often individualised. In high-risk patients (eg, those with long-term diabetes or poor systemic risk-factor control), even in the absence of retinopathy, examination at least once per year is recommended.⁷ For children with prepubertal diabetes, beginning retinopathy screening at puberty might be appropriate.^{34–36} Furthermore, a comprehensive eye examination might be warranted for pregnant women with non-gestational diabetes during the first trimester, with follow-up throughout pregnancy in the presence of retinopathy.⁹⁹ Finally, regular eye examinations might also be appropriate for their positive psychosocial effects on the care of patients with diabetes (eg, education about risk factors and compliance).²

Systemic therapy

Treatment considerations

Present guidelines for the optimum eye care of patients with diabetes are tight glycaemic and blood pressure

control in conjunction with timely laser therapy as needed.⁷ However, several key questions remain. For example, what are the target glycaemia and blood pressure levels for effective prevention of retinopathy development and progression? Are some hypoglycaemic and blood pressure-lowering agents more effective than are others for retinopathy? What is the role of lipid-lowering agents? Several important studies have made significant contributions to addressing these questions (webappendix pp 1–2).

Glycaemic control

Hyperglycaemia instigates the cascade of events that eventually leads to development of diabetic retinopathy (figure 2). Two landmark trials, the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS), provided strong evidence that tight control of glycaemia (glycated haemoglobin [HbA_{1c}] 7%) reduces the risk of development and progression of diabetic retinopathy in both type 1 and type 2 diabetes (webappendix pp 1–2).⁷ Although a small risk of initial worsening of retinopathy at the onset of therapy exists, the long-term benefits outweigh this risk.¹⁰⁰ Every percent reduction in HbA_{1c} (eg, from 9% to 8%) lowers risk of retinopathy by 30–40% and the effect appear longlasting (metabolic memory).¹⁰¹ Nonetheless, to avoid this beneficial effect waning over time, HbA_{1c} should be maintained at target values for as long as possible.¹⁰²

A recent meta-analysis¹⁰³ of three large population-based studies of diabetic retinopathy showed a graded relation between the level of glycaemia and frequency of retinopathy signs, even below the diagnostic criterion for diabetes (fasting plasma glucose of 7·0 mmol/L). These

findings suggest that further reduction in glycemic levels might have additional benefits for retinopathy in people with diabetes. However, in the Action in Diabetes and Vascular Disease (ADVANCE) trial,¹⁰⁴ aggressive glycaemic control (HbA_{1c}<6·5%) did not substantially affect development or progression of retinopathy in type 2 diabetes.¹⁰⁴ Furthermore, findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)¹⁰⁵ trial showed that such aggressive glycaemic control could be associated with increased mortality, although the cause of unexpected excess deaths remains unclear.¹⁰⁶

Data from the Veterans Affairs Diabetes Trial (VADT)¹⁰⁷ showed that after 5 years of follow-up, there were no significant benefits of intensive glycaemic control (HbA_{1c} 6·9%, similar to targets achieved in DCCT and UKPDS) on retinopathy outcomes. Although these findings contrast with those from the UKPDS, they could be related to population differences (97% men in VADT), length of follow-up (shorter in VADT), and timing of therapy (later in VADT). Notably, the rate of retinopathy progression in the VADT was modestly lower in the intervention group than in the control group (17% vs 22%, $p=0\cdot07$), so that a delayed benefit of intensive glycaemic control, as reported in previous studies,^{108,109} cannot be excluded.

Blood pressure control

Hypertension exacerbates diabetic retinopathy through increased blood flow and mechanical damage (stretching) of vascular endothelial cells, stimulating release of VEGF.^{25,110} Epidemiological studies and clinical trials strongly support hypertension as an important modifiable risk factor for diabetic retinopathy.⁷ Every 10 mm Hg increase in systolic blood pressure is associated with roughly 10% excess risk of early diabetic retinopathy and a 15% excess risk of proliferative retinopathy.^{20,111} In the UKPDS study, tight blood pressure control reduced the risks of retinopathy progression by about a third, visual loss by half, and the need for laser treatment by a third in people with type 2 diabetes (webappendix pp 1–2).⁷ However, these benefits were not sustainable without continuing and long-term maintenance of blood pressure control.¹¹²

Some blood-pressure-lowering drugs, such as renin-angiotensin inhibitors, could have benefits beyond their blood-pressure-lowering effects. Researchers of The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) study¹¹³ showed that lisinopril reduced the risk of retinopathy progression by 50% and proliferative retinopathy by 80%. Limitations of this study, however, were that treatment groups had differing baseline glycaemias and that the follow-up was only 2 years. Since EUCLID, three new clinical trials have reported their findings (webappendix pp 1–2). Although findings from the ADVANCE trial, which used a combination of perindopril and indapamide, did not show any effects on retinopathy outcomes,¹¹⁴ this result could be related

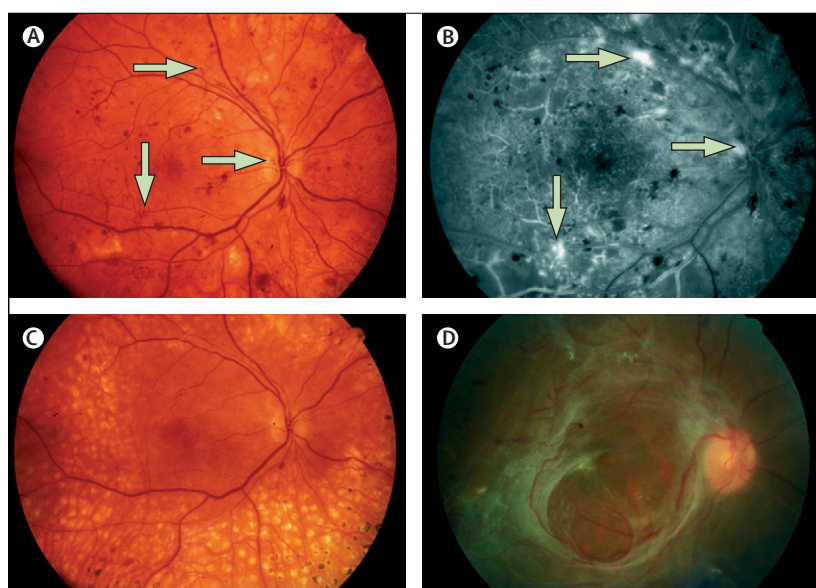


Figure 5: Proliferative diabetic retinopathy

Neovascularisation, a hallmark of proliferative diabetic retinopathy (A, arrows), which can be identified on fluorescein retinal angiogram (B, arrows); resolution of retinopathy with panretinal photocoagulation (C); progression of retinopathy without treatment to fibroproliferative disease (D).

to the absence of detailed photographic assessment. However, in the Diabetic Retinopathy Candesartan Trials (DIRECT), candesartan reduced risk of retinopathy development by 18–35% in type 1 diabetes, and increased regression of retinopathy by 34% in type 2 diabetes.^{115–117} In the Renin-Angiotensin System Study (RASS), enalapril reduced the risk of retinopathy progression by 65% and losartan by 70% in type 1 diabetes, independent of changes in blood pressure during the trial.¹¹⁸ These data suggest that drugs targeting the renin-angiotensin system might be better than are other blood-pressure-lowering drugs for reduction of retinopathy risk.

Lipid-lowering therapy

Dyslipidaemia could have a role in the pathogenesis of diabetic retinopathy.⁷ For example, in the DCCT study, researchers showed that severity of retinopathy was associated with increasing triglycerides and inversely associated with HDL cholesterol.¹¹⁹ In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial,¹²⁰ investigators showed that fenofibrate, a lipid-modifying agent, reduced the need for laser treatment of vision-threatening diabetic retinopathy by 31% in patients with type 2 diabetes. Notably, this finding did not seem to be attributable to measurable changes in lipid profile, suggesting that other as yet unknown mechanisms could contribute to the protective effect of fenofibrate.¹²¹

Multifactorial intervention

The effect of a multifactorial approach was investigated in the Steno-2 study¹²² in patients with type 2 diabetes and microalbuminuria, encompassing treatment goals similar to those recommended in the American Diabetes Association guidelines.¹²² Findings showed that after 8 years of intensified, target-driven intervention that aimed to control several vascular risk factors (webappendix pp 1–2), risk of retinopathy was reduced by 58%. Although significant differences in levels of risk factors between the controlled and intervention groups had gone 5 years later, the beneficial effects on retinopathy remained. This finding lends support to that of metabolic memory as reported in DCCT,¹⁰¹ underscoring the importance of early and meticulous implementation of multifactorial interventions to prevent the long-term development and progression of diabetic retinopathy.

Emerging medical treatments

Several new systemic therapies have been investigated on the basis of their potential pathogenic roles in the development of diabetic retinopathy (table 1). First, hyperglycaemia activates protein kinase C in the retina, a process believed to increase retinal neovascularisation and vascular permeability. Two clinical trials have shown that ruboxistaurin, a well tolerated selective protein kinase C inhibitor, might reduce the risk of progression

and need for laser treatment for diabetic macular oedema,¹²³ and could offer some protection against the vision-damaging effect of long-standing macular oedema.¹²⁴ However, further investigation is needed to verify these findings.

Second, hyperglycaemia is known to increase the accumulation of AGE in the retina, and the AGE levels from skin biopsy samples were shown to predict retinopathy progression in DCCT.¹²⁵ Results from a clinical trial⁶³ in type 1 diabetes suggests that patients given pimagedine, an aminoguanidine that inhibits the formation of AGE, were less likely to have retinopathy progression than were untreated controls. Third, investigators of a recent prospective observational study¹²⁶ reported that rosiglitazone, a frequently used oral insulin-sensitising agent with potential antiangiogenic activity, could delay onset of proliferative retinopathy in type 2 diabetes. However, controversy remains regarding the potential risk of macular oedema associated with use of glitazone drugs.^{127,128} Finally, although an array of other systemic therapeutic strategies have also been assessed (table 1), their effectiveness has not been established.⁷

Ocular therapy

Laser photocoagulation

Laser photocoagulation remains the mainstay of ophthalmic therapy for vision-threatening diabetic retinopathy. However, despite its remarkable efficacy in prevention of visual loss when undertaken in a timely and appropriate manner, the destructive nature of laser is associated with significant ocular side-effects. Additionally, even with adequate laser therapy, reversal of visual loss is uncommon. Therefore, researchers continue to search for new and increasingly effective therapeutic strategies, with an aim to improve vision without tissue destruction.

The two types of laser therapies for diabetic retinopathy are panretinal photocoagulation for proliferative retinopathy (figure 5) and macular (focal or grid) laser photocoagulation for diabetic macular oedema. The goal of panretinal photocoagulation is to place laser burns over the entire retina, sparing the central macula to promote regression and arrest progression of retinal neovascularisation, possibly by a reduction of ischaemia-driven VEGF production.⁵¹ Two landmark clinical trials in ophthalmology, the Diabetic Retinopathy Study (DRS)⁹² and the Early Treatment Diabetic Retinopathy Study (ETDRS),⁹¹ firmly established this therapy as the primary treatment for proliferative retinopathy.

Findings from DRS, in which more than 1758 patients with proliferative disease were included, panretinal photocoagulation reduced the risk of severe visual loss (visual acuity $\leq 5/200$ patients) by 50% over 5 years. In the ETDRS of 3711 patients with less severe diabetic retinopathy than those enrolled in the DRS, early use of this therapy reduced risk of progression to high-risk proliferative retinopathy by half. Findings from both studies have been further reinforced by subsequent clinical trials.⁷ However,

despite the indisputable efficacy in prevention of severe visual loss, panretinal photocoagulation is often associated with substantial ocular side-effects, such as difficulty with light-dark adaptation (25%), a small decrease in visual acuity (10%), and peripheral visual loss (5%), which could impair night vision and affect driving.⁷ Other side-effects include changes in colour vision and worsening of macular oedema.⁷ Notably, results from DRS and ETDRS suggest that less severe stages of diabetic retinopathy might not benefit from laser treatment.

In ETDRS, macular laser reduced the risk of moderate visual loss from clinically significant macular oedema by half.⁷ More recently, the Diabetic Retinopathy Clinical Research Network (DRCR.net) showed that about 30% of patients given macular laser gained better vision (≥ 10 letters) over a 2-year period.¹²⁹ As the DRCR.net included a mixture of patients with focal or diffuse macular oedema, the relative efficacy of laser treatment for specific patterns of macular oedema remains unclear.

Surgical intervention

Vitrectomy has been the mainstay surgical treatment for the two blinding complications of advanced retinopathy—persistent vitreous haemorrhage and tractional retinal detachment. It has both beneficial and harmful effects on the diabetic eye.¹³⁰ It reduces risk of retinal neovascularisation and macular oedema, while increasing risk of iris neovascularisation and cataract formation.¹³⁰ The Diabetic Retinopathy Vitrectomy Study (DRVS)^{131,132} was the largest randomised clinical trial that assessed indications and timing of vitrectomy for management of advanced proliferative retinopathy. In the DRVS, patients with type 1 diabetes with severe vitreous haemorrhage were more likely to achieve desirable visual outcome (visual acuity 20/40) if early vitrectomy was undertaken (within 1–6 months) than were those who had late vitrectomy (at 1 year). However, this benefit was not reported in patients with type 2 diabetes. This finding could have been related to an increased frequency of macular ischaemia in patients with type 2 diabetes. Although data from the DRVS are still valuable for clinical guidance, the threshold for undertaking vitrectomy has lowered because of advances in vitreoretinal surgery, including small gauge instruments and the ability to apply retinal laser during surgery.⁷

Vitrectomy has also been suggested as a treatment option for diabetic macular oedema that is refractory to laser therapy, especially if evidence of macular traction is present (eg, vitreomacular traction, epiretinal membrane, and tractional retinal detachment close to the macula).^{133,134} A few trials⁷ have shown some benefits of vitrectomy combined with peeling of the internal limiting membrane, the innermost layer of the retina, for diffuse or refractory diabetic macular oedema.

Emerging ophthalmic treatments

As a potent mediator for abnormal retinal vessel growth and leakage, VEGF has long been a therapeutic target

for diabetic retinopathy.⁶⁴ Intraocular VEGF concentrations relate closely to hypoxia and active neovascularisation, and its concentrations fall after successful laser photocoagulation.⁵² Additionally, inhibitors of VEGF activity ameliorate ischaemia-induced retinal neovascularisation in animals.^{52,64} These findings all lend support to the theory that anti-VEGF agents could arrest, or even reverse, proliferative retinopathy and macular oedema. Several agents have been assessed in clinical trials of anti-VEGF therapy (webappendix p 3). These agents are delivered by injection directly into the vitreous of the eye (intravitreal injection), thus theoretically ensuring local efficacy is at a maximum and systemic side-effects are kept to a minimum.

Most trials have shown some benefits with the use of intravitreal anti-VEGF agents for both diabetic macular oedema and proliferative retinopathy (webappendix p 4). Of these trials, a study by the DRCR.net¹³⁵ evaluated the effect of ranibizumab, an anti-VEGF agent used to treat neovascular age-related macular degeneration, on diabetic macular oedema. This randomised trial compared laser therapy plus intravitreal ranibizumab injections versus laser therapy plus sham injections in patients with diabetic macular oedema. Over the first year, there was an approximate one-line extra vision gained over laser therapy from the ranibizumab group. Improvement of vision was twice as frequent in the ranibizumab group (50% for two-line and 30% for three-line or more) as in the laser group (28% and 15%). Importantly, eyes treated with laser and ranibizumab (3–4%) were less likely to have marked visual loss (two-line or more) than were those treated with laser therapy alone (13%). The favourable visual outcome appears to sustain into the second year, although only about 60% of patients had so far been assessed for 2 years. Furthermore, there were no systemic safety concerns demonstrated.

People with diabetes have an increased risk of developing cataracts that need surgery.³ However, in some cases cataract surgery can exacerbate macular oedema and retinopathy progression.^{133,136} Thus, laser treatment for patients with diabetic retinopathy before or promptly after cataract surgery might sometimes be needed. Results of new clinical trials^{137,138} also suggest that intravitreal anti-VEGF agents during cataract surgery might be an effective adjunctive therapy to prevent worsening macular oedema and retinopathy progression after surgery.

Although anti-VEGF therapy has promising clinical applications for management of diabetic retinopathy, its long-term safety in patients with diabetes has not yet been established.⁶⁴ Local adverse events of intravitreal anti-VEGF therapy include cataract formation, retinal detachment, vitreous haemorrhage, infection, and potential loss of neural retinal cells.⁶⁴ Furthermore, a significant portion of anti-VEGF agents injected into the eye could pass into the systemic circulation.^{64,139} Thus, systemic inhibition of

angiogenesis is a potential risk, which could compromise critical vascular responses to ischaemic events in patients with diabetes. Other unwanted systemic side-effects can be hypertension, proteinuria, and impaired wound healing,⁶⁴ which are also of relevant concern for patients with diabetes. Protracted systemic exposure to anti-VEGF agents, because of the lengthy half-life of some agents and the need for repeated administration, are in some cases associated with heightened risks of systemic vascular complications, such as stroke and non-ocular (eg, gastric and renal) haemorrhage.^{139,140} Although clinical trials on the use of intravitreal anti-VEGF therapy for treatment of age-related macular degeneration generally show low (0.6–1.2%) rates of stroke,¹⁴¹ this risk could be increased in patients with diabetic retinopathy because of pre-existing diabetes-related vascular disease.⁶ Thus, both clinicians and patients should recognise and weigh the risks and benefits of these agents when they are used to treat diabetic retinopathy.

Inflammation plays a major part in the pathogenesis of diabetic retinopathy.⁴⁹ Like anti-VEGF agents, intraocular administration of corticosteroids is widely used to treat diabetic macular oedema.^{52,54,129} Results of a systematic review⁵² of seven randomised clinical trials with 632 eyes with diabetic macular oedema suggests that eyes treated with intravitreal triamcinolone, a longacting corticosteroid, modestly improved visual acuity. The few clinical trials on longacting steroid implants (fluocinolone acetonide or dexamethasone) also reported short-term vision improvements.⁵²

The DRCR.net undertook a multicentre randomised clinical trial¹²⁹ in the USA that compared intravitreal triamcinolone with macular laser for treatment of diabetic macular oedema. At 4 months, eyes treated with intravitreal triamcinolone responded better than did eyes treated with laser. However, this difference was not maintained after 1 year, and by 2 years, eyes treated with laser had significantly better vision than did those treated with intravitreal triamcinolone. These findings remained unchanged after 3 years of follow-up.¹⁴² Furthermore, intravitreal triamcinolone was frequently associated with significant ocular adverse events, including ocular hypertension and accelerated cataract progression.^{129,142}

A question not addressed by the DRCR.net was whether intravitreal triamcinolone is useful for eyes that do not respond well to laser (diffuse or refractory diabetic macular oedema). A recent systematic review reported that although intravitreal triamcinolone improves vision in eyes with refractory diabetic macular oedema in the short term (3 months), the benefits are not longlasting.⁵⁴ Nevertheless, intravitreal triamcinolone might have a role as an adjunctive therapy to laser.¹⁴³

Future directions

Despite good control of systemic risk factors, a significant proportion of patients will still progress to develop vision-threatening diabetic retinopathy (either macular oedema or proliferative retinopathy). The

present standard of care for management of these disorders relies mainly on laser therapy, which is inherently destructive, associated with unavoidable side-effects, and not universally effective in reversal of visual loss. Thus, new approaches have also emerged, such as use of intraocular administration of anti-VEGF agents and corticosteroids in selected eyes. However, physicians and ophthalmologists should be aware not only of the apparent benefits but also of the potential risks associated with these new therapies.

As research continues to broaden our pathogenic understanding of diabetic retinopathy, new treatment modalities are expected to emerge. The recent discovery of erythropoietin and carbonic anhydrase represents promising therapeutic targets. Rapid advances in regenerative medicine seed inspiration for further investigation into the potential application of stem-cell therapy for retinal repair in diabetic retinopathy.¹⁴⁴ Finally, most ophthalmic therapies for diabetic retinopathy are relatively invasive. The ability to provide effective topical therapies targeting several pathways underlying retinal neovascularisation and oedema could revolutionise care of diabetic retinopathy.¹⁴⁵ As recent experimental studies show, working towards such a goal is not unrealistic.^{146,147}

Contributors

NC undertook the literature search, data interpretation, formatting of the figures and tables, and writing of the initial and final version of the manuscript. TYW and PM provided the figures and revised the initial and final manuscript.

Conflicts of interest

PM and TYW are on advisory boards for Novartis, Pfizer, and Allergan and have received travel, honoraria, and research support from Novartis, Pfizer, Allergan, and Solvay, but have no stocks, equity, contract of employment, or named position on company board. NC declares that he has no conflicts of interest.

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