# Diabetic eye disease

***Diabetes mellitus affects at least 2% of the UK population and complications include blindness. Control of risk factors and laser treatment prevent visual loss. A National Screening Programme will identify at-risk patients. Treatments currently in clinical trial include antipermeability agents.***

Diabetic retinopathy is the most frequent cause of new blindness in working age adults. Loss of vision is usually associated with proliferative diabetic retinopathy (PDR) in type 1 diabetes and with maculopathy in type 2 diabetes. Owing to the higher prevalence of type 2 diabetes maculopathy causes 90% of blindness secondary to diabetes. There are conflicting reports regarding the incidence and prevalence of visual impairment (Williams et al, 2004), but the Wisconsin Epidemiologic Study of Diabetic Retinopathy (Klein et al, 1984) reported a frequency of any visual impairment in people with diabetes of 7.8% and an estimated annual incidence of blindness caused by diabetes of 3.3 per 100 000 total population in southern Wisconsin, USA. The prevalence of diabetes in the UK was estimated to be approximately 2.2% in 1997, and the number of patients affected has been projected to more than double by 2010 (Amos et al, 1997). As the prevalence of diabetes increases, the demand for ophthalmic health care is likely to rise. Moderate to severe visual loss from diabetes is preventable (Aiello, 2003), and a screening protocol has the potential to identify most patients with vision-threatening retinopathy (Bresnick et al, 2000).

## The National Screening Programme for sight-threatening diabetic retinopathy

In 1989 the UK agreed, along with other European nations, to set a priority to reduce blindness from diabetic retinopathy by one third or more as part of the St. Vincent Declaration. In 2003, a National Service Framework (NSF) was launched to standardize diabetic care across the UK (Department of Health, 2003), including a priorities and planning framework to prevent blindness (www.nscretinopathy.org.uk). Diabetic retinal screening programmes have been running successfully in many parts of the UK for many years but service provision has been very patchy with large geographical areas having no provision.

The Diabetes NSF led to the introduction of a National Screening Programme for the early detection of sight-threatening diabetic retinopathy. By March 2006 it is aimed to offer a minimum of 80% of people with diabetes (excluding children under the age of 12 years) screening for the early detection of diabetic retinopathy. This target is due to increase to 100% of at-risk diabetics by December 2007. All patients detected as screen positive will be offered appropriate treatment under the care of ophthalmologists except those deemed unfit to undergo treatment because of other medical problems.

The National Institute for Health and Clinical Excellence (2005) and the National Screening Committee recommended digital retinal photography as the preferred method of retinal screening. The retinal images will be assessed by an accredited grader, with overall responsibility provided by a diabetologist or ophthalmologist with an interest in retinopathy.

The UK National Screening Committee assists strategic health authorities and primary care trusts with the implementation of the programme. The National Screening Committee provides standards for quality assurance, training and education packages, and a framework for the purchase of digital cameras and related equipment. Locations for screening include fixed and mobile units and optometry-based services.

## Pathophysiology of diabetic eye disease

Before any clinical findings of diabetic retinopathy are detected, a breakdown of the blood–retinal barrier allows leakage of small molecules into the retina, and an increased retinal circulation in response to hypoxia. Vascular endothelial growth factor (VEGF) is secreted by the hypoxic retina and promotes capillary hyperpermeability and neovascularization.

Histological changes include degeneration of pericytes, capillary basement membrane thickening and endothelial cell loss. Gradually, focal areas of capillary closure, microaneurysms and haemorrhages appear on ophthalmoscopy. These are the earliest clinical signs of retinopathy.

Small arteriolar occlusions give rise to areas of focal nerve fibre layer ischaemia known as 'cotton wool spots'. As the retinopathy progresses, changes in the calibre of larger vessels become evident, including dilatation, 'beading' and looping, and intraretinal microvascular abnormalities (IRMAs) may be detected.

Eventually new vessels proliferate, originating from the optic disc and retina. These new vessels are fragile and form abnormal networks. Most often, they grow using the posterior face of degenerating vitreous gel as a scaffold, and are liable to bleed, causing vitreous haemorrhage. The development of new vessels is accompanied by a fibroglial response (preretinal fibrosis) which may exert traction on the retina, causing tractional retinal detachment in severe cases.

Diabetic maculopathy occurs as a result of a combination of macular oedema and ischaemia. Macular oedema occurs secondary to vascular wall damage causing leakage of fluid, lipid and protein deposits in the retina and may be focal or diffuse. Macular ischaemia occurs when there is capillary closure in the perifoveal capillary plexus caused by the same ischaemic process as described above. This process can have a devastating effect on visual acuity and is not amenable to laser treatment. Occasionally, cystic spaces appear at the fovea. This is known as cystoid macular oedema.

Poorly controlled diabetic patients may have intermittent visual blurring as a result of osmotic effects on the crystalline lens composition with fluctuations in the serum glucose levels. Diabetic patients have a propensity to develop cataracts which may be a result of the accumulation of byproducts of metabolic pathways induced by fluctuating glucose levels.

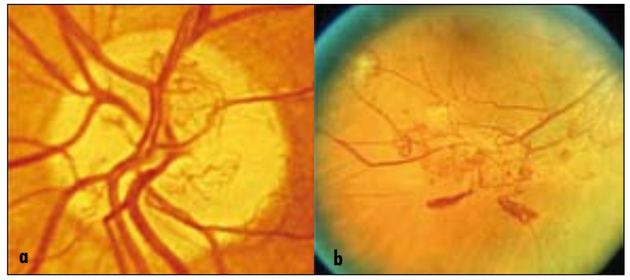



***Figure 1. a. New vessels on the disc and (b) new vessels elsewhere.***

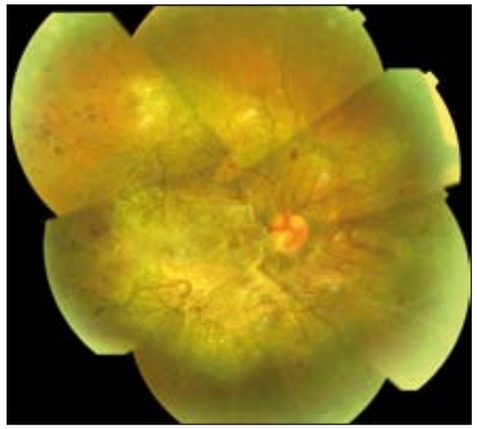


***Figure 2. Advanced diabetic eye disease showing new vessel formation and tractional retinal detachment.***

## Grading of diabetic retinopathy

The NSF uses a simplified grading scheme based on similar parameters to those used in large epidemiological and treatment studies such as the Early Treatment of Diabetic Retinopathy Study (ETDRS; Early Treatment of Diabetic Retinopathy Study Research Group, 1985). Background retinopathy (mild or nonproliferative, R1) is detected by the presence of microaneurysms and retinal haemorrhages. Preproliferative or severe non-proliferative diabetic retinopathy (R2) includes venous beading, loops or reduplication, IRMAs and multiple deep, round or blot haemorrhages. Proliferative diabetic retinopathy (PDR) and iris neovascularization are classified as R3; features may include new vessels on the disc (NVD) and new vessels elsewhere (NVE) (*Figure 1*), pre-retinal or vitreous haemorrhage and pre-retinal fibrosis with or without a tractional retinal detachment (advanced diabetic eye disease) (*Figure 2*).

The minimum screening standard stipulates that 70% of patients with R2 are seen by an ophthalmologist within 13 weeks, and 70% of patients with R3 are seen within 2 weeks.

The ophthalmologist judges whether laser treatment is indicated. Characteristics known to be associated with high likelihood of progression to visual loss are known as high-risk characteristics and include NVD greater than one third of disc area, any NVD in the presence of pre-retinal or vitreous haemorrhage and NVE greater than half of disc area associated with pre-retinal or vitreous haemorrhage. These findings indicate a need for urgent treatment. Non-high risk PDR is typically treated within 6 weeks provided an opportunity exists to treat any co-existent macular oedema beforehand in accordance with ETDRS guidelines.

## Grading of maculopathy

The term maculopathy includes macular ischaemia and diabetic macular oedema, and is the most common cause of visual loss in diabetic patients. For screening purposes, maculopathy (M1) can be defined by the presence of exudates within 1DD (disc diameter) of the centre of the fovea, circinate exudates or a groups of exudates within the macula, retinal thickening within 1DD of the centre of the fovea and any microaneurysm or haemorrhage within 1DD of the centre of the fovea only if associated with a best visual acuity of 6/12 or less. The purpose of screening is to detect possible clinically significant macular oedema (CSME) (*Figure 3*). At least 70% of patients with M1 should be seen by an ophthalmologist within 13 weeks.

Slit-lamp biomicroscopy affords the viewer a stereoscopic view of the fundus, allowing the examiner to view CSME directly. CSME is a term used to describe any one of three findings: the presence of retinal thickening within 500 μm of the fovea, hard exudates within 500 μm of the centre of the fovea associated with retinal thickening and retinal thickening greater than 1DD, any part of which is within 1DD of the macula.

Ischaemic change of the macula is common. Fluorescein fundus angiography is commonly used to look for

**Mr Gerry Clare** *is Specialist Registrar in Ophthalmology, Hillingdon Hospital, Uxbridge UB8 3NN,* **Miss Helen Cook** *is Consultant Ophthalmic Surgeon, Hull Royal Infirmary, Hull and* **Mr Philip Hykin** *is Consultant Ophthalmic Surgeon, Medical Retina Service, Moorfields Eye Hospital, London*

*Correspondence to: Mr G Clare*



SYMPOSIUM ON VISUAL LOSS IN THE ELDERLY

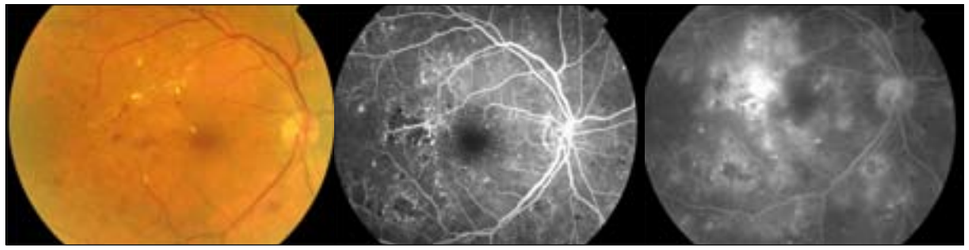


*Figure 3. Fluorescein angiography may be used to demonstrate leakage corresponding to retinal thickening.*

increased perifoveal intercapillary distance, irregular enlargement of the foveal avascular zone (FAZ) and loss of the capillary edge, all signs of macular ischaemia (*Figure 4*). This finding severely limits the visual prognosis of any treatment offered, although mild and moderate ischaemic changes do not preclude laser treatment.

## Disease prevention

There is now a strong body of evidence which shows that strict control of systemic risk factors in diabetes results in a more favourable visual outcome.

The Diabetic Control and Complications Trial showed a 50% reduction in the onset and progression of diabetic retinopathy in type 1 diabetics with intensively controlled blood glucose over a 9-year period (Diabetic Control and Complications Trial Research Group, 1993) (*Figure 5*).

Similar findings for type 2 diabetic patients were demonstrated by the UK Prospective Diabetes Study (UKPDS), in which intensive lowering of glycated haemoglobin ($HbA_{1c}$) from 7.9% to 7.0% reduced the incidence of sight-threatening retinopathy by a fifth (UK Prospective Diabetes Study Group, 1998).

The beneficial effect on vision of tight control of blood pressure among diabetics is well documented (Klein et al, 1998; UK Prospective Diabetes Study Group, 1998). In the UKPDS, blood pressure controlled to less than 150/85 mmHg was associated with a reduction of retinopathy by a third at 12 years. Visual loss was reduced by almost half in the tight blood pressure control arm.

It is commonly observed that lipid deposits (exudates) accumulate at the macula as part of diabetic maculopathy. Evidence suggests that dyslipidaemia may contribute to the morbidity of diabetic retinopathy (Chew et al, 1996). The effect of treatment with atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is under investigation (Prisant, 2004).

In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus, treatment of normotensive type 1 diabetic patients with an angiotensin-converting enzyme inhibitor (lisinopril) reduced the progression of retinopathy by 50% at 2 years (Chaturvedi et al, 1998). This suggests that the renin–angiotensin feedback mechanism has a role in the development of retinopathy. A large study is underway to determine whether a similar effect can be achieved by treatment with an angiotensin II blocker (candesartan) (Chaturvedi et al, 2002). The role of aspirin in diabetic retinopathy is not yet clear, but it does not appear to have a significant protective effect (Bergerhoff et al, 2002).

In spite of the evidence that improved glycaemic and hypertensive control reduce the incidence of sight-threatening complications, this is often not achieved. There is a need for greater patient education by all health professionals involved in the care of diabetic patients.

*Figure 4. a. The normal architecture of the foveal avascular zone becomes (b) enlarged and irregular as a result of capillary closure in macular ischaemia (note surrounding laser scars, an example of which is demonstrated by the arrow).*

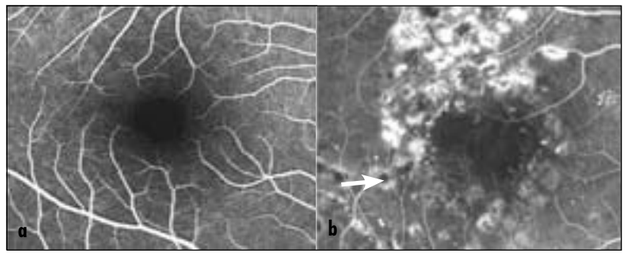
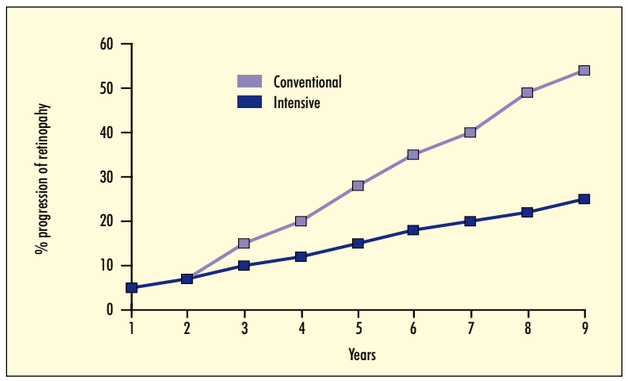



*Figure 5. Tight glycaemic control reduced the progression (and onset, not shown) of retinopathy in the Diabetes Control and Complications Trial (1993).*








## Laser therapy

The mainstay of local treatment for both PDR and CSME is laser photocoagulation. The Diabetic Retinopathy Study showed that pan-retinal laser photocoagulation could halve the risk of severe visual loss over 5 years in PDR (Diabetic Retinopathy Study Research Group, 1981; Lee and Olk, 1991), whereas the ETDRS showed a halving of the risk of moderate visual loss in patients with CSME treated with macular laser (Early Treatment of Diabetic Retinopathy Study Research Group, 1985).

Pan-retinal laser photocoagulation involves the application of laser shots (usually argon) in the retinal mid-periphery (*Figure 6*). A wide-angle contact lens is placed on the cornea to allow visualization of the retina at the slit-lamp. Alternatively a head-mounted indirect ophthalmoscope may be used with a hand-held lens. A laser aiming beam is focussed onto the retina by adjusting the lens position and individual laser pulses are fired using a foot-pedal.

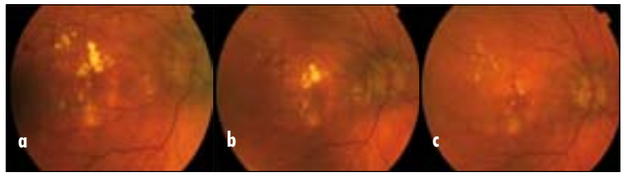
The aim is to apply 1600–2000 retinal laser burns to the retinal mid-periphery usually over several sessions. The response to laser may be reviewed 4–8 weeks later and the treatment repeated until the new vessels show evidence of regression. Signs of regression include evidence of fibrosis of new vessels and reduced venous congestion. Patients have to be warned that they will lose their peripheral and night vision as a result of the treatment and that this may affect their eligibility to drive. In some patients, pan-retinal laser photocoagulation can sometimes precipitate CSME and cause central visual loss. Therefore the ophthalmologist will carefully assess the macula for signs of concurrent maculopathy and either treat the maculopathy first or at the same time as the neovascularization.

Macular laser is a precise treatment whereby small light retinal laser burns are applied carefully to areas of thickening in the macula. Usually between 10 and 100 burns are applied away from the FAZ. Fluorescein angiograms are usually obtained before treatment to more accurately define areas of leakage and vascular landmarks to help identify the edge of the FAZ (*Figures 7* and *8*). The laser treatment may be repeated after 4–6 months until the CSME has resolved. Before treatment, patients are warned that rarely, laser scarring to the central macula can result in visual loss.

Projection of the fundus angiogram next to the patient during treatment is useful to accurately target treatment while avoiding lasering the centre of the FAZ (*Figure 8*).

Treatment is performed according to ETDRS guidelines, i.e. focal laser to focal leaks and grid laser to areas of non-perfusion and diffuse leakage at each session. Treatment is only performed within 200 μm of the edge of the FAZ if it can be done without compromising the perifoveal capillaries. Indications for cessation of therapy include macular ischaemia, maximal prior laser therapy and longstanding cystic changes at the fovea with poor visual acuity. Serial colour photographs and optical coherence tomography imaging may be used to monitor the response to laser therapy.

*Figure 7. Resolution of macular oedema (a) 4, (b) 8 and (c) 16 months after laser treatment. Note the reduction in macular exudates with time as the retinal fluid resolves.*




## Indications for vitrectomy

Several complications of diabetic eye disease can be treated surgically via pars plana incisions under a microscopic viewing system (*Figure 9*). Vitreous surgery is often carried out under a local anaesthetic, particularly useful when diabetic patients have contraindications to general anaesthesia.

Vitrectomy and endolaser (*Figure 10*) is indicated immediately for dense vitreous haemorrhage in type 1

*Figure 6. Panretinal photocoagulation scars. Some scars are heavily pigmented whereas others are atrophic and white.*

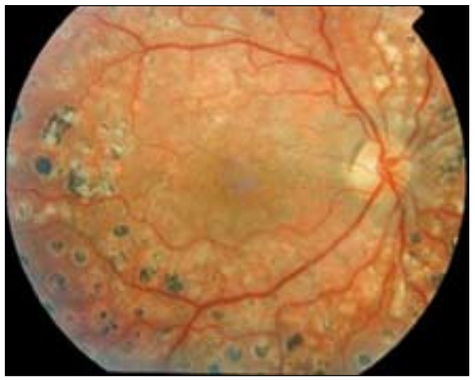
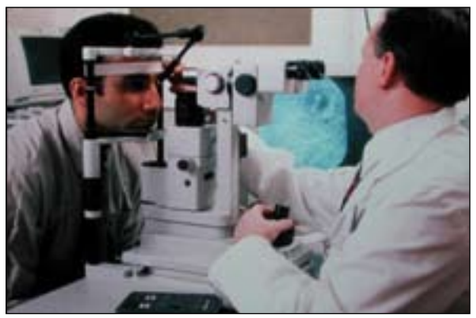


*Figure 8. Fluorescein angiography can be used to guide clinicians planning laser treatment.*



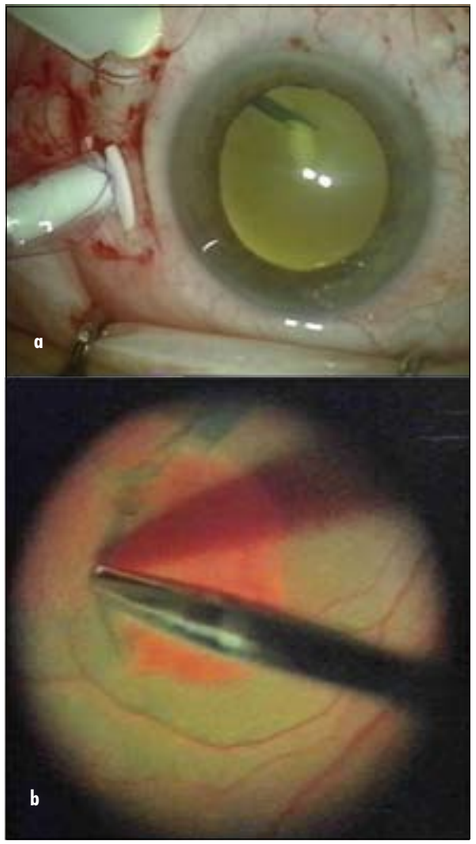



***Figure 9. Pars plana vitrectomy with (a) delivery of depot steroid and (b) retinal membrane peeling.***

diabetes mellitus, but only after 6 months in type 2, where an initial period of observation to allow haemorrhage to clear does not adversely affect visual outcome. Surgery should also be considered where tractional retinal detachment has involved the macula.

Fine-cut cross-sectional optical coherence tomography of non-resolving macular oedema occasionally shows 'tenting' of the macula caused by tangential traction from the posterior vitreous face (*Figure 11*). In this instance, relieving the traction by removing the vitreous and peeling associated membranes from the surface of the retina may help restore visual function (Thomas et al, 2005).

Vitreo-retinal surgery can also be used to deliver retinal laser directly. Vitrectomy can be combined with cataract surgery when indicated, and it provides an opportunity to deliver drugs to the posterior segment, such as triamcinolone (below).

## New treatments

Intravitreal injections may be carried out in clinic under topical or local anaesthetic, using sterile techniques. There is some evidence that intravitreal injection of triamcinolone acetate, a glucocorticoid, may reduce macular oedema and improve vision in the short term although results of a formal randomized controlled trial are still awaited (Jonas et al, 2005) (*Figure 12*).

There is also a risk of steroid-induced glaucoma and endophthalmitis. Other steroid preparations (e.g. Posurdex, Allergan, Irvine CA) are currently under investigation. Other intravitreal preparations under investigation by randomized controlled trial include pegaptanib (Macugen, Eyetech Pharmaceuticals, New York NY), a short nucleotide aptamer which binds VEGF and may reduce vascular permeability and oedema.

***Figure 10. Treatment of advanced diabetic eye disease by vitrectomy and endolaser. Note (a) the fibrovascular bands at the arcades and (b, c) the extensive areas of capillary non-perfusion visible on fluorescein angiography. d. Tractional bands have been excised and ischaemic areas lasered (bottom right).***

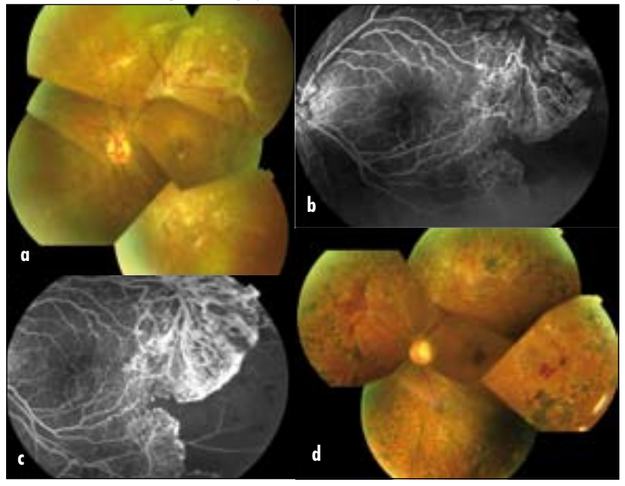
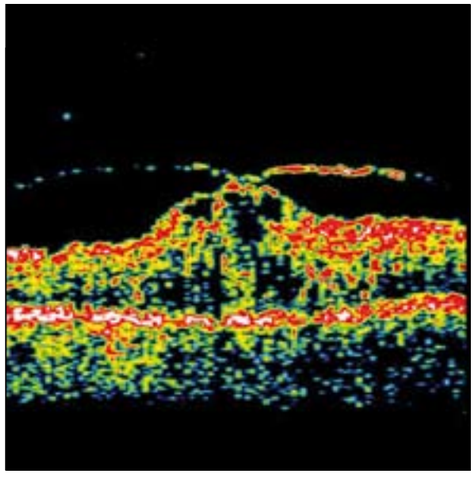



***Figure 11. Ocular coherence tomography scan showing tangential vitreous traction on fovea and loss of the normal foveal depression centrally.***







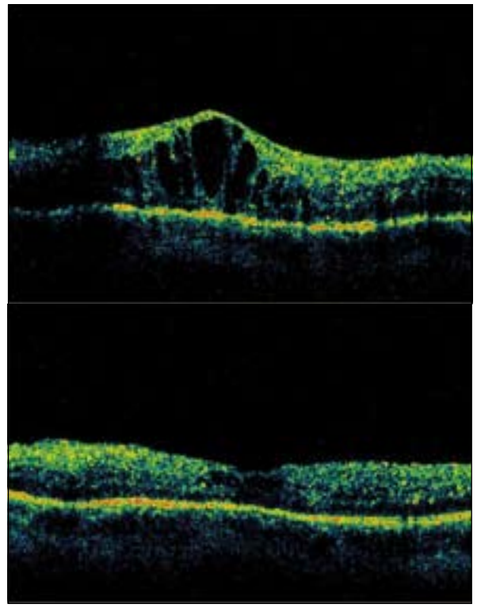


***Figure 12. Optical coherence tomography image showing resolution of clinically significant macular oedema after intravitreal triamcinolone acetate injection. The black spaces within the retina are pockets of intraretinal fluid.***

Other anti-permeability treatments, including an oral protein kinase C inhibitor (Ruboxistaurin, Eli Lilly, Indianapolis IN), are being investigated (Donnelly et al, 2004).

Pancreatic islet cell transplantation has had some remarkable success in the treatment of diabetes, with many patients achieving insulin independence (Matsumoto et al, 2005). This appears to stabilize retinopathy as part of the systemic improvement in glycaemic control. **BJHM**

*Conflict of interest: none.*

Aiello LM (2003) Perspectives on diabetic retinopathy. *Am J Ophthalmol* **136:** 122–35

Amos AF, McCarty DJ, Zimmet P (1997) The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabet Med* **14:** S7–S85

Bergerhoff K, Clar C, Richter B (2002) Aspirin in diabetic retinopathy. A systematic review. *Endocrinol Metab Clin North Am* **31:** 779–93

Bresnick GH, Mukamel DB, Dickinson JC, Cole DR (2000) A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy. *Ophthalmology* **107**: 19–24

Chaturvedi N, Sjolie AK, Stephenson JM et al (1998) Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID study group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. *Lancet* **351**: 28–31

Chaturvedi N, Sjoelie AK, Svensson A; Direct Programme Study Group (2002) The DIabetic Retinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. *J Renin Angiotensin Aldosterone Syst* **3:** 255–61

Chew EY, Klein ML, Ferris FL 3rd, et al (1996) Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. ETDRS Report Number 22. *Arch Ophthalmol* **114:** 1079–84

Department of Health (2003) *National Service Framework for Diabetes: Delivery Strategy.* Department of Health, London

Diabetic Retinopathy Study Research Group (1981) Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study findings. DRS report number 8. *Ophthalmology* **88:** 583–600

Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **29:** 977–86

Donnelly R, Idris I, Forrester JV (2004) Protein kinase C inhibition and diabetic retinopathy: a shot in the dark at translational research. *Br J Ophthalmol* **88:** 145–51

Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for Diabetic Macular Edema. ETDRS Report Number 1. *Arch Ophthalmol* **103***:* 1796–806

Jonas JB, Akkoyun I, Kreissig I, Degenring RF (2005) Diffuse diabetic macular oedema treated by intravitreal triamcinolone acetonide: a comparative, non-randomised study. *Br J Ophthalmol* **89:** 321–26

Klein R, Klein BE, Moss SE (1984) Visual impairment in diabetes. *Ophthalmology* **91**: 1–9

Klein R, Klein BE, Moss SE, Cruikshanks KJ (1998) The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* **105:** 1801–15

Lee CM, Olk RJ (1991) Modified grid laser photocoagulation for diffuse diabetic macular oedema. Long-term visual results. *Ophthalmology* **98:** 1594–602

Matsumoto S, Okitsu T, Iwanaga Y et al (2005) Insulin independence after living-donor distal pancreatectomy and islet allotransplantation. *Lancet* **365:** 1642–4

National Institute for Health and Clinical Excellence (2005) *Management of Type 2 Diabetes Retinopathy – early management and screening.* National Institute for Clinical Excellence, London

Prisant LM (2004) Clinical trials and lipid guidelines for type II diabetes. *J Clin Pharmacol* **44:** 423–30

Thomas D, Bunce C, Moorman C, Laidlaw DA (2005) A randomized controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema. *Br J Ophthalmol* **89:** 81–6

UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317:** 703–13

Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A (2004) Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye* **18:** 963–83

## KEY POINTS

- The increasing prevalence of diabetes may result in an increased incidence of blindness as a result of maculopathy and proliferative disease.
- Visual loss from diabetic eye disease is often preventable.
- A National Screening Programme will identify at-risk patients for early treatment.
- A combination of improved systemic control and laser treatment is the favoured approach to management at present.
- Laser treatment for diabetic maculopathy is moderately successful.
- New treatments under investigation include intravitreal injections of steroids and anti-vascular endothelial growth factor agents and oral agents. Pancreatic islet cell transplants show promise in carefully selected patients.