Diabetic retinopathy

- Diabetic retinopathy (DR) is the leading cause of vision loss in working-age adults in most developed countries.
- More than 1 in 3 people living with diabetes will develop DR.[1]
- The majority of people remain asymptomatic until the late stages of DR, when sight is threatened.
- Symptoms usually result from complications:
  - dark or empty areas in vision
  - floaters (resolution of vitreous bleed)
  - a "curtain falling" (vitreous bleed)
  - reduced vision (acuity) or blindness.

Risk factors

- Hyperglycaemia:
  - The risk of the development and progression of DR increases with HbA_{1c}.
- Type and duration of diabetes:
  - Prevalence of DR is greater in people with type 1 diabetes compared to those with type 2 diabetes, and increases with duration of diabetes.
  - **Maculopathy** is more common in people with type 2 diabetes.
  - **Proliferative DR** is more common in people with type 1 diabetes.
- Blood pressure:
  - Systolic BP >140 mmHg is associated with increased risk of DR.
- Dyslipidaemia.
- Smoking.
- Presence of other microvascular complications of diabetes (e.g. nephropathy, neuropathy).
- Pregnancy.
- Genetic predisposition.

Pathophysiology

- Chronic hyperglycaemia leads to a series of changes to retinal vasculature:
  - pericyte loss
  - basement membrane thickening
  - endothelial damage
  - increased retinal blood flow
  - microthrombosis
  - microaneurysms (a pathognomonic sign).
- This triggers a cascade of pathophysiological changes:
  - Retinal ischaemia results in retinal hypoxia, which stimulates vascular endothelial growth factors that cause retinal neovascularisation.
  - Increased vascular permeability and subsequent retinal oedema.
- Chronic hyperglycaemia also results in the accumulation of advanced glycation end-products (AGEs) and increased oxidative stress, again resulting in retinal neovascularisation.

Grading of DR–see *Table 1*.

Screening

- Screening is essential to detect those at risk before visual symptoms occur.
- Treatment can prevent blindness in 90% of those at risk, if applied early and adequately.
- The NHS Diabetic Eye Screening (DES) Programme offers regular retinopathy screening for all people with type 1 and type 2 diabetes aged ≥12 years.
- The current screening interval for all eligible people with diabetes is yearly, but that might change.
- In 2016, the UK National Screening Committee recommended that the DES programme:
  - Extend screening intervals for people with low risk of sight loss* from 1 year to 2 years. (*Two successive clear diabetic eye screenings.)
  - Retain the current screening interval for people with a higher risk of sight loss.

Outcomes in England and Wales

- Between 2009 and 2010, DR/maculopathy stopped being the leading cause of certifiable blindness in working age adults in England and Wales.[2]
- Between 2007 and 2015, there was an almost 50% reduction in new certifications of sight impairment in Wales.[3]

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Management

Prevention: management of risk factors

1. Glycaemic management

- An 11 mmol/mol (1%) decrease in HbA_{1c} reduces the incidence and progression of DR by approximately 40% and progression to vision-threatening DR by 25%.
- Target HbA_{1c}:
  - 53 mmol/mol (7.0%) for type 2 diabetes[4]
  - 48 mmol/mol (6.5%) for type 1 diabetes (not at the expense of severe hypoglycaemia).[5]
- In those with elevated blood glucose and existing DR, rapid reduction may result in acceleration of DR.

2. Blood pressure management

- Target BP:
  - 135/85 mmHg for type 1 diabetes[5]
  - 140/90 mmHg for type 2 diabetes aged <80 years; 150/90 mmHg for type 2 diabetes aged >80 years[6]
  - 130/80 mmHg if microalbuminuria present or at risk of cardiovascular disease
  - Not recommended for systolic BP to be below 120 mmHg.

3. Lipid modification

- Combination treatment (simvastatin and fenofibrate) reduces DR progression.[7]
- Fenofibrate reduces the need for laser therapy for DR.[8]
  - If fenofibrate is discontinued, there is no further benefit (no legacy effect).

4. Pregnancy

- Pre-conception care:
  - Offer retinal assessment at the first pre-conception clinic visit (unless an annual retinal assessment has been done in the last 6 months).[9]
- Pregnancy with pre-existing diabetes:
  - For all women with diabetes who become pregnant, the relevant DR screening programme should be notified and the relevant national pathway adopted.
  - Offer retinal assessment at or soon after first antenatal clinic visit (unless a retinal assessment has been done in the last 3 months) and again at 28 weeks.
  - Perform an additional retinal assessment at 16–20 weeks if any DR present at first antenatal clinic visit (or in the prior 3 months).
  - Any women who have DR during pregnancy must receive retinal assessment within 3 months of delivery.
  - Any women who have pre-proliferative DR or any form of referable DR should be under the care of ophthalmology.

Treatment

The aims of treatment are to: prevent blindness; restore impaired vision loss (where possible); prevent further vision loss; and improve visual function.

1. Laser therapy

- Aims to protect vision and prevent further vision loss, rather than to improve vision.
- Adverse effects: pain during treatment; transient rise in intraocular pressure; corneal abrasions; retinal fibrosis; choroidal scarring; macular oedema; visual acuity loss; visual field loss; and loss of dark adaptation.

2. Medical therapy

- Anti-vascular endothelial growth factor (anti-VEGF) for treatment of diabetic macular oedema (DMO) and proliferative DR.
- Anti-VEGF agents: ranibizumab, bevacizumab, aflibercept.
- For resistant DMO, intravitreal corticosteroid therapy is an option.
- Corticosteroid/vitreous inserts (sustained delivery) include: triamcinolone acetonide, dexamethasone, fluocinolone acetonide.
- Polytherapy with laser plus anti-VEGF plus intravitreal steroid may be required.

Practical tips

- Assess the severity of DR before initiating stringent glycaemic control.
- Avoid a huge reduction in HbA_{1c} >22 mmol/mol (>2%) in those with pre-existing severe DR.
- Exercise caution with the introduction of GLP-1 receptor agonist therapies in the following situations because of a risk of worsening DR:[10]
  - Proliferative DR or maculopathy requiring active follow-up
  - HbA_{1c} >91 mmol/mol (10.5%)
  - Current insulin treatment.
- Pioglitazone should be used with caution in people with maculopathy as it can increase the rate of fluid retention and thus DMO.

Communication and education

- Ensure the person with diabetes understands the benefits of good diabetes management so they are suitably empowered.
- Regular screening will help to ensure that vision is protected.

Table 1. Staging of diabetic retinopathy.[11]

Grading level	Retinopathy level	Features
R0	No DR	
R1	Background DR (*Figure 1*)	• Microaneurysms • Blot haemorrhages • Cotton-wool spots • Hard exudates (outside 1 disc-diameter of fovea) • Venous loop
R2	Pre-proliferative DR (*Figure 2*)	• Multiple blot haemorrhages • Intraretinal microvascular anomalies (IRMA) • Venous beading • Venous duplication
R3A	Active proliferative DR (*Figure 3*)	• New vessels on disc • New vessels elsewhere • New vitreous or pre-retinal haemorrhage • New retinal detachment • New retinal fibrosis
R3S	Stable treated proliferative DR	One of the following features, with evidence of peripheral retinal laser treatment: • Stable pre-retinal fibrosis • Stable fibrous proliferation • Stable R2 features • R1 features
P1	Evidence of laser photocoagulation	
U	Unassessable	
M0	No maculopathy	
M1	Maculopathy (*Figure 4*)	Clinically significant macular oedema: • Retinal thickening within 500 microns of the fovea • Hard exudates within 500 microns of the fovea if associated with adjacent retinal thickening, or • One or more areas of retinal thickening at least 1500 microns in diameter that is within one disc-diameter (1500 microns) of the fovea

R=retinopathy; P=photocoagulation; M=maculopathy.

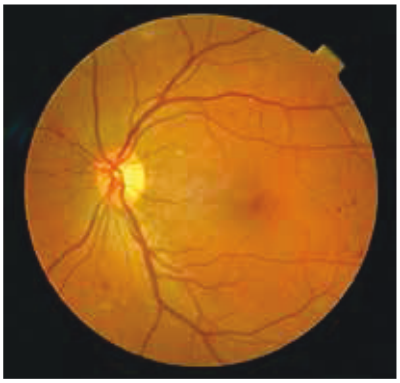

Figure 1: Background DR.

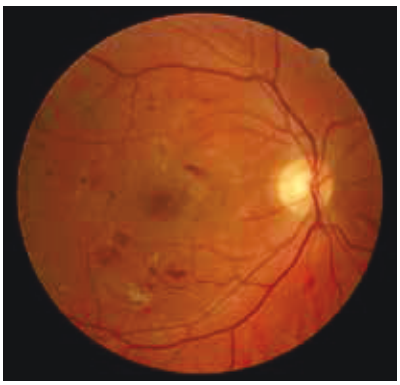

Figure 2: Pre-proliferative DR.

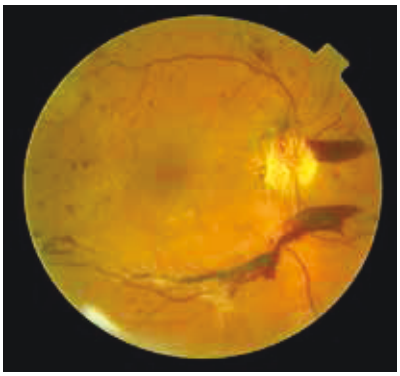

Figure 3: Proliferative DR.

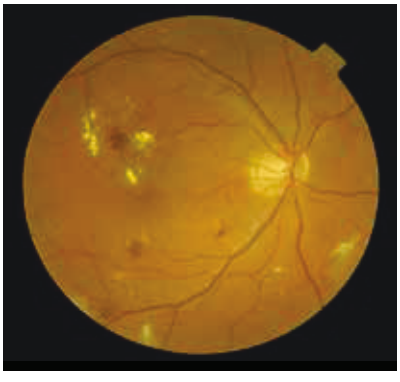

Figure 4: Maculopathy.

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