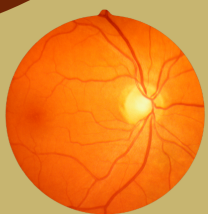
THE

RETINA DECIPHERED

"The Bridge Between Classics" – Every essential topic from Ryan and Kanski, distilled into exam-ready patterns.

EXAM READY NOTES



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RETINA EXAM READY NOTES

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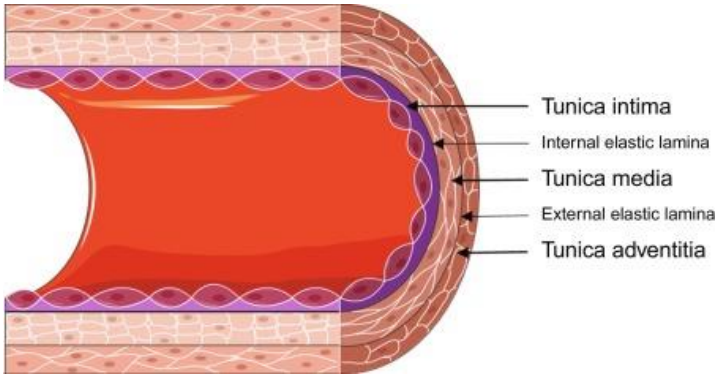
END

The 1st Lecture

RETINAL CIRCULATION

The central retinal artery:

- an end artery
- enters the optic nerve approximately 1 cm behind the globe.
- It is composed of three anatomical layers:
  - The intima: the innermost, is composed of a single layer of endothelium resting on a collagenous zone.
  - The internal elastic lamina separates the intima from the media.
  - The media consists mainly of smooth muscle.
  - The adventitia is the outermost and is composed of loose connective tissue.

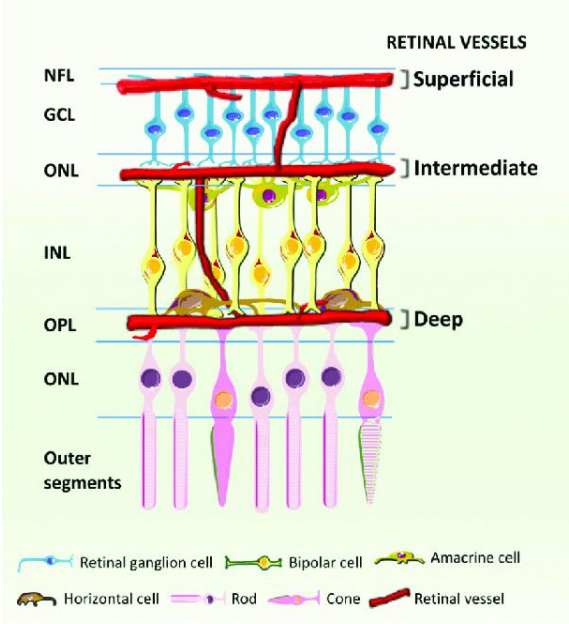


Retinal arterioles:

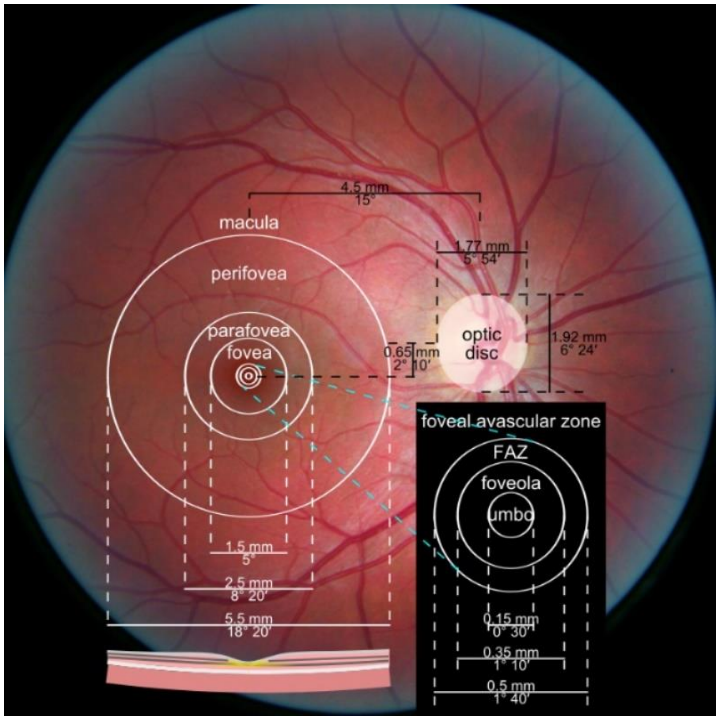
- arise from the central retinal artery
- Their walls contain smooth muscle
- in contrast to arteries the internal elastic lamina is discontinuous.

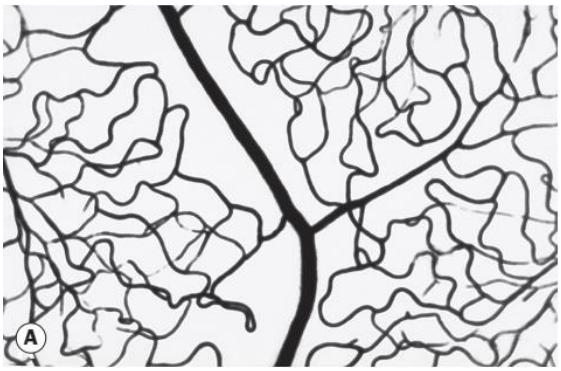
Retinal capillaries:

- supply the inner two-thirds of the retina, with the outer third being supplied by the choriocapillaris.
- The inner capillary network (plexus) is located in the ganglion cell layer
- The outer capillary network (plexus) is located in the inner nuclear layer.



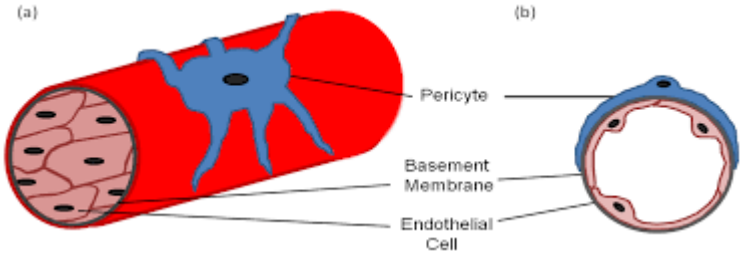
- Capillary-free zones are present:
  - ◊ at the fovea (foveal avascular zone – FAZ)
  - ◊ around arterioles and





Periarteriolar capillary-free zone

- Retinal capillaries are devoid of smooth muscle and elastic tissue.
- Their walls consist of the following:



  - ◊ Endothelial cells form a single layer on the basement membrane and are linked by tight junctions that form the inner blood–retinal barrier.
  - ◊ The basement membrane lies beneath the endothelial cells with an outer basal lamina enclosing pericytes.
  - ◊ Pericytes lie external to endothelial cells and have multiple pseudopodial processes that envelop the capillaries. Pericytes have contractile properties and are thought to participate in autoregulation of the microvascular circulation.

Retinal venules and veins:

- They drain blood from the capillaries
- Small venules are larger than capillaries but have a similar structure.
- Larger venules contain smooth muscle and merge to form veins.
- Veins contain a small amount of smooth muscle and elastic tissue in their walls and are relatively distensible. Their diameter gradually enlarges as they pass posteriorly towards the central retinal vein.

The 2nd Lecture

DIABETIC RETINOPATHY

Introduction

- Diabetes is a major concern for healthcare systems throughout the world.
- The prevalence of diabetes is relentlessly increasing, particularly in working-age adults.
- Approximately one-half of individuals with diabetes will develop retinopathy in time.
- Diabetic macular oedema (DMO) is the commonest cause of visual loss.

Common ophthalmic complications of diabetes:

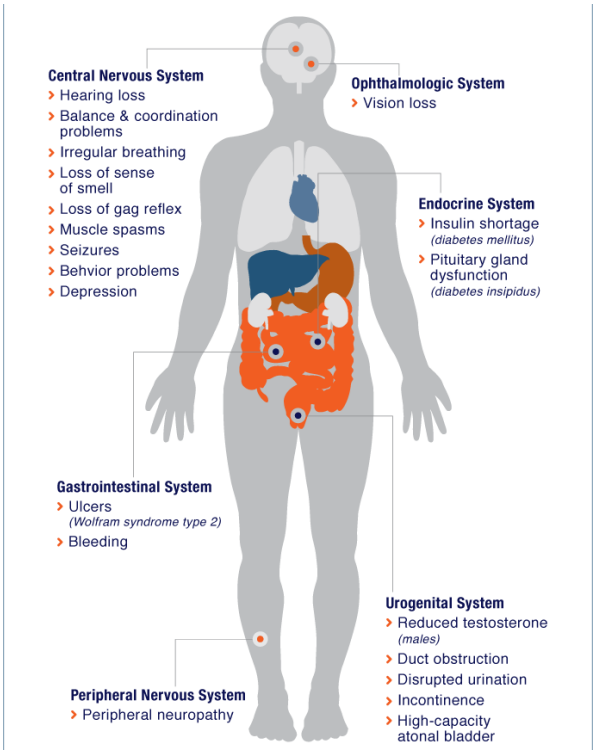
- Retinopathy: diabetic macular oedema, macular ischaemia and sequelae arising from retinal ischaemia (retinal new vessels, vitreous haemorrhage and tractional retinal detachment).
- Iridopathy: minor iris transillumination defects.
- Unstable refraction.

Uncommon ophthalmic complications of diabetes:

- Recurrent styes.
- Xanthelasma.
- Ocular motor nerve palsies.
- Reduced corneal sensitivity.
- Neovascular glaucoma (NVG).
- Accelerated age-related cataract.

Rare ophthalmic complications of diabetes:

- rhino-orbital mucor-mycosis.
- pupillary light-near dissociation
- acute-onset cataract
- Papillopathy
- Wolfram syndrome:
  progressive optic atrophy and multiple neurological and systemic abnormalities



Prevalence of diabetic retinopathy (DR):

- It is probably around 40% in individuals with diabetes.
- It is more common in type 1 diabetes than in type 2
- sight-threatening disease is present in up to 10%.
- Proliferative diabetic retinopathy (PDR) affects 5–10% of the diabetic population.
- Type 1 diabetics are at particular risk of DR, with an incidence of up to 90% after 30 years.

Risk factors for DR:

- Duration of diabetes
- Poor control of diabetes
- Pregnancy
- Hypertension
- Nephropathy
- Hyperlipidaemia
- Obesity
- Anaemia
- Smoking
- Cataract surgery

Duration of diabetes:

- It is the most important risk factor.
- In patients diagnosed with diabetes before the age of 30 years, the incidence of DR after 10 years is 50% and after 30 years 90%.
- DR rarely develops within 5 years of the onset of diabetes or before puberty, but about 5% of type 2 diabetics have DR at presentation.
- It appears that duration is a stronger predictor for proliferative disease than for maculopathy.

Poor control of diabetes:

- Tight blood glucose control, particularly when instituted early, can prevent or delay the development or progression of DR.
- However, a sudden improvement in control may be associated with progression of retinopathy in the short-term.
- Type 1 diabetic patients appear to obtain greater benefit from good control than type 2.
- Raised HbA1c is associated with an increased risk of proliferative disease, so the aim should be an HbA1c value of 6–7% (8% in frail elderly patients).
- By decreasing the HbA1c by 1%, the microvascular complications can be reduced by one-third.

Pregnancy

- It is sometimes associated with rapid progression of DR.
- Predicating factors for progression of DR include:
  - ◊ greater pre-pregnancy severity of retinopathy
  - ◊ poor pre-pregnancy control of diabetes
  - ◊ control exerted too rapidly during the early stages of pregnancy
  - ◊ pre-eclampsia.
- The risk of progression is related to the severity of DR in the first trimester.
- Approximately 5% with mild DR and a third of those with moderate DR will progress to PDR during the pregnancy.
- If substantial DR is present, frequency of review should reflect individual risk and can be up to monthly.
- Diabetic macular oedema usually resolves spontaneously after pregnancy and need not be treated if it develops in late pregnancy.

Hypertension:

- It is very common in patients with type 2 diabetes
- It should be rigorously controlled (<140/80 mmHg).
- Tight control appears to be particularly beneficial in type 2 diabetics with maculopathy.
- Cardiovascular disease and previous stroke are also predictive.

Nephropathy:

- if severe, it is associated with worsening of DR.
- Conversely, treatment of renal disease (e.g. renal transplantation) may be associated with improvement of retinopathy and a better response to photocoagulation.

TIP

Patients with diabetes need to undergo regular retinal screening

Pathogenesis

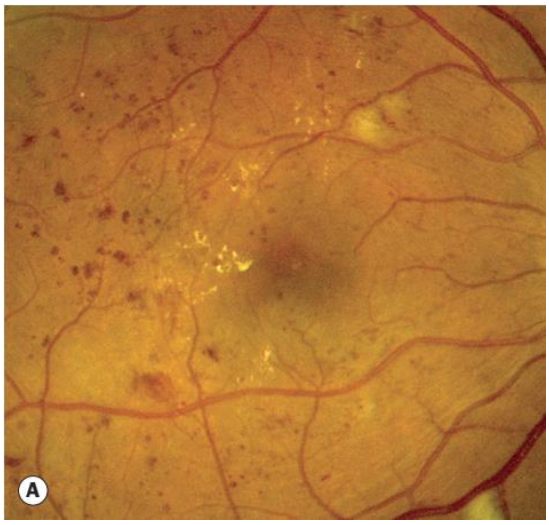
- DR is predominantly a <u>micro</u>angiopathy in which small blood vessels are particularly vulnerable to damage from high glucose levels.
- Direct hyperglycaemic effects on retinal cells are also likely to play a role.
- Vascular endothelial growth factor (VEGF) appears to be of particular importance.

Signs

- Microaneurysms
- Retinal haemorrhages (flame-shaped haemorrhages, dot and blot H.; deep dark H.)
- Exudates
- Diabetic macular oedema (DMO)
- Ischaemic maculopathy
- Clinically significant macular oedema (CSMO)
- Cotton-wool spots
- Venous changes (dilatation, tortuosity, looping, beading, and segmentation)
- Intraretinal microvascular abnormalities (IRMA)
- Arterial changes (ischaemic dysfunction → dilation, significant ischaemia → peripheral narrowing, 'silver wiring' and obliteration)
- Proliferative retinopathy (NVD, NVE, and NVI)

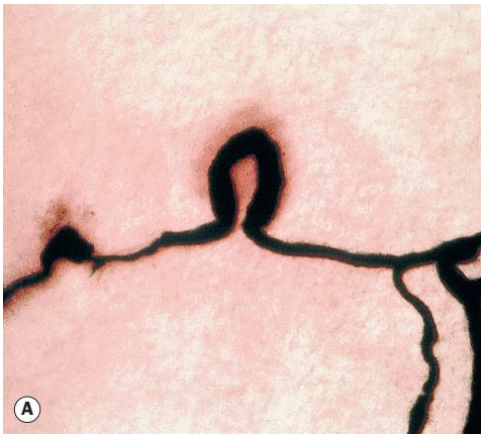
Microaneurysms:

- Tiny red dots, often initially temporal to the fovea



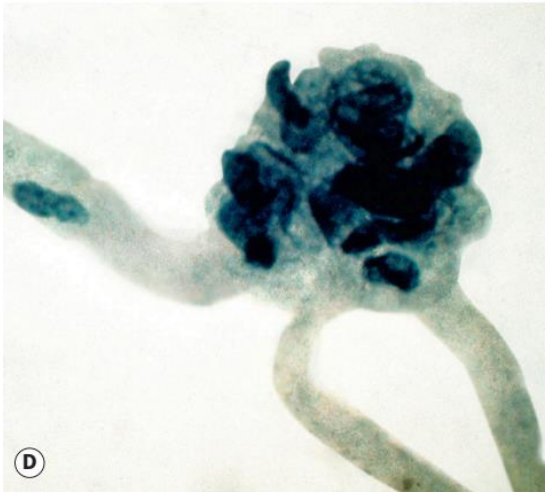
Microaneurysms and dot/blot haemorrhages
at the posterior pole

- Microaneurysms are localized outpouchings, mainly saccular, of the capillary wall.
- They may form either by focal dilatation of the capillary wall where pericytes are absent, or by fusion of two arms of a capillary loop.



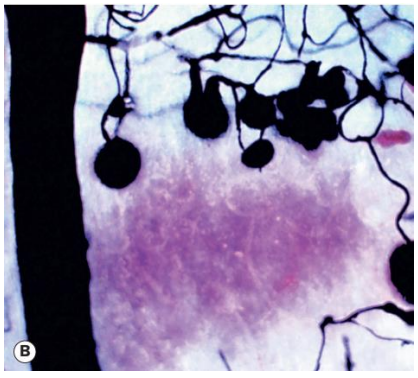
Two arms of a capillary loop that
may fuse to become a microaneurysm

- Loss of pericytes may also lead to endothelial cell proliferation with the formation of 'cellular' microaneurysms.



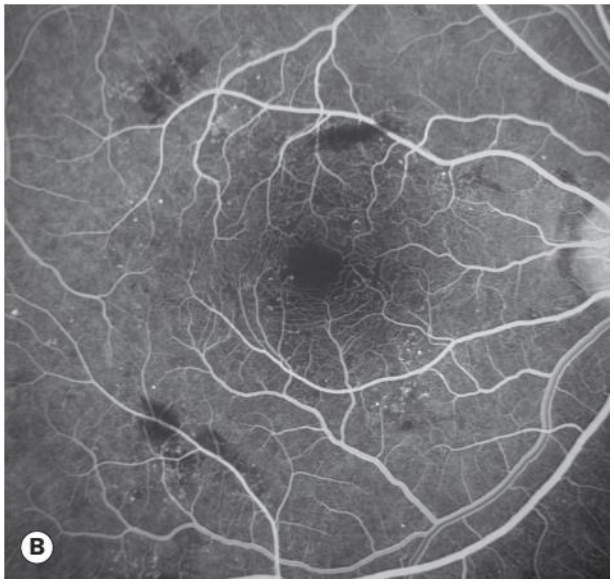
Microaneurysm with endothelial cell proliferation
(cellular microaneurysm)

- Most microaneurysms develop in the inner capillary plexus (ganglion cell layer), frequently adjacent to areas of capillary non-perfusion



An area of capillary non-perfusion
and adjacent microaneurysms

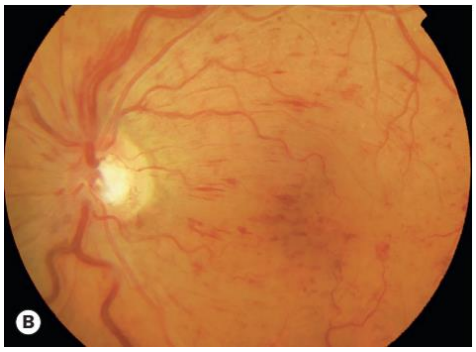
- Microaneurysms may leak plasma constituents into the retina as a result of breakdown in the blood–retinal barrier, or may thrombose.
- Microaneurysms tend to be the earliest sign of DR.
- Microaneurysms may be indistinguishable clinically from dot haemorrhages.
- Fluorescein angiography (FA) allows differentiation between dot haemorrhages and non-thrombosed microaneurysms:
  - Early frames show tiny hyperfluorescent dots, typically more numerous than visible clinically.
  - Late frames show diffuse hyperfluorescence due to leakage.



FA showing scattered hyperfluorescent spots in the posterior fundus

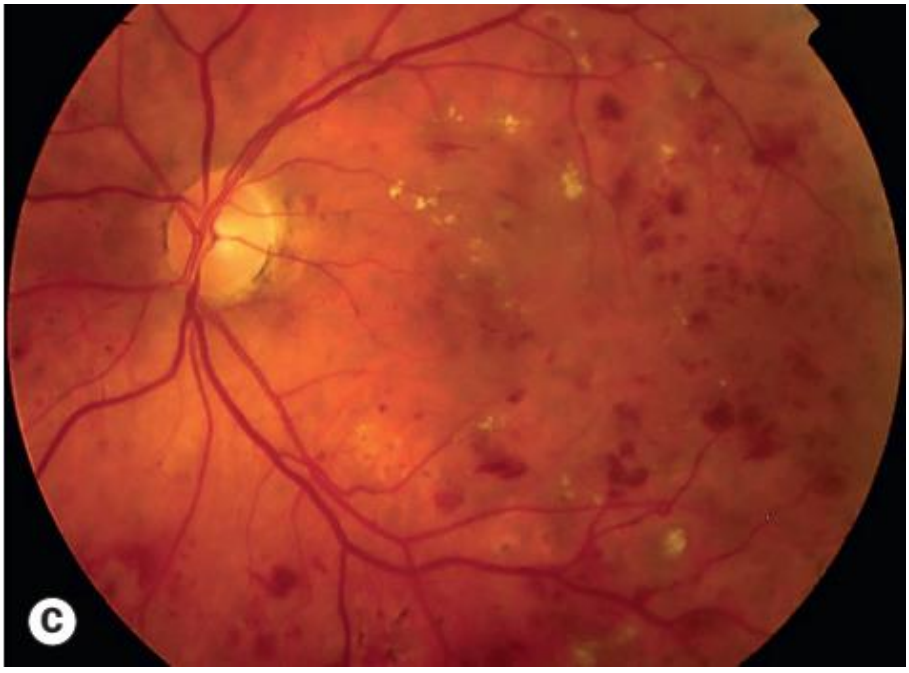
Retinal haemorrhages:

- Flame-shaped haemorrhages:
  - They are retinal nerve fibre layer haemorrhages
  - They arise from the superficial arterioles
  - They assume their characteristic shape (flame) because of the architecture of the retinal nerve fibre layer.



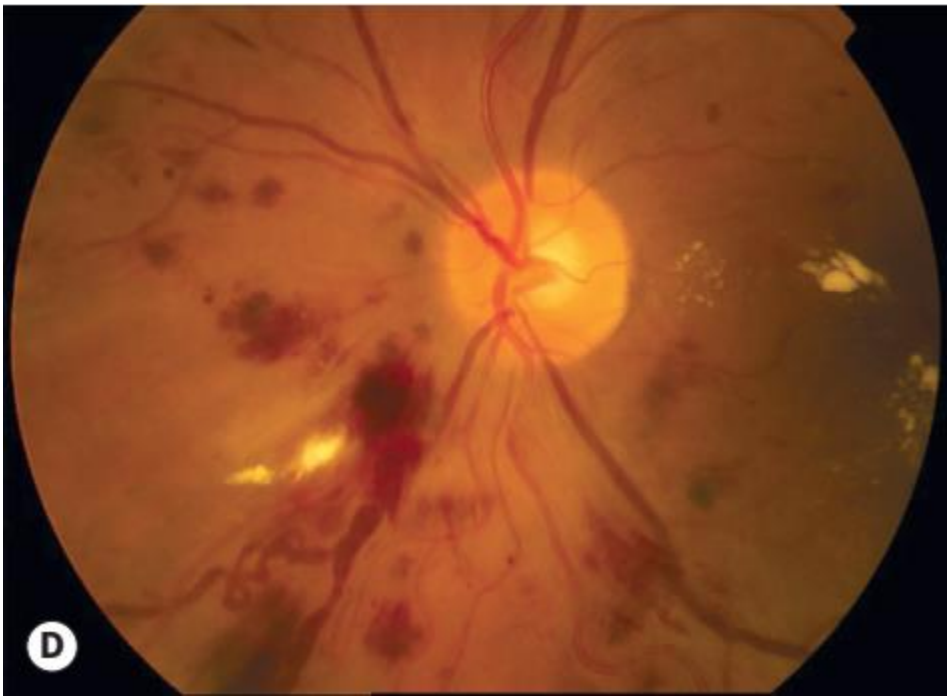
Retinal nerve fibre layer (flame) haemorrhages

- Dot and blot haemorrhages:
  - They arise from the venous end of capillaries
  - Located in the compact middle layers of the retina (intraretinal haemorrhages)



Dot and blot haemorrhages

- Deep dark haemorrhages:
  - They represent haemorrhagic infarcts located within the middle retinal layers

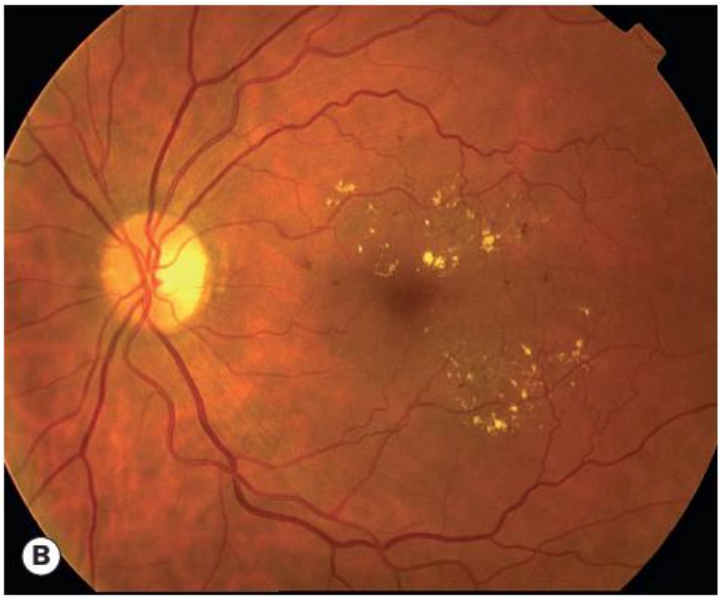


Deep dark haemorrhages

  - The involvement extent is a significant marker of the likelihood of progression to PDR.

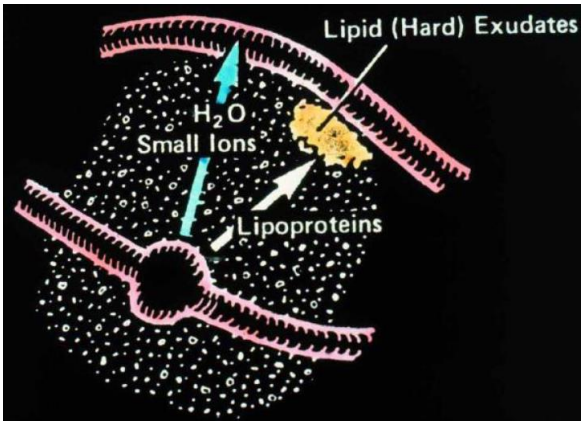
Exudates:

- Waxy yellow lesions with relatively distinct margins
- arranged in clumps and/or rings at the posterior pole
- often surrounding leaking microaneurysms.

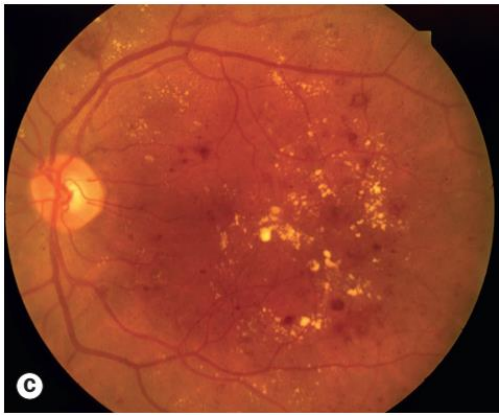


Small exudates and microaneurysms

- Exudates are caused by chronic localized retinal oedema.
- They develop at the junction of normal and oedematous retina.

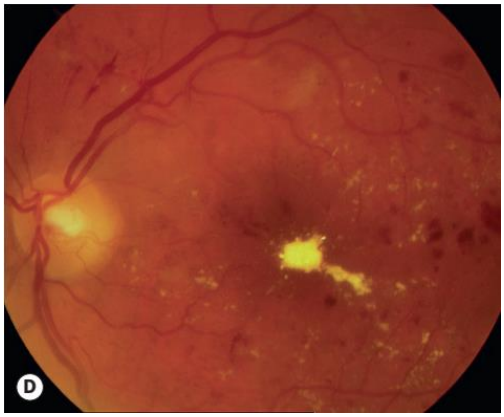


- they located mainly within the outer plexiform layer.
- They are composed of lipoprotein and lipid-filled macrophages
- Hyperlipidaemia may increase the likelihood of exudate formation.
- With time the number and size of exudates tend to increase and the fovea may be involved.



Extensive exudates forming a circinate pattern

- When leakage ceases, exudates absorb spontaneously over a period of months, either into healthy surrounding capillaries or by phagocytosis.
- Chronic leakage leads to enlargement and the deposition of crystalline cholesterol.

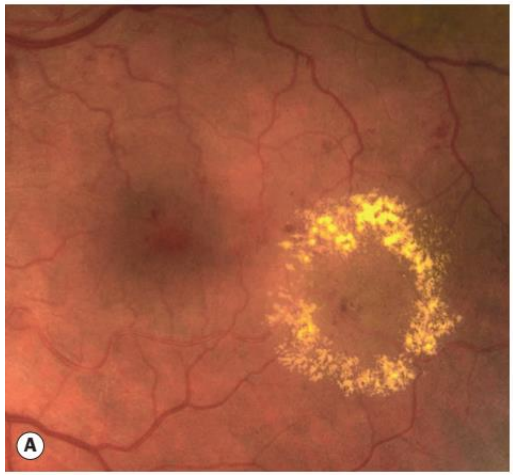


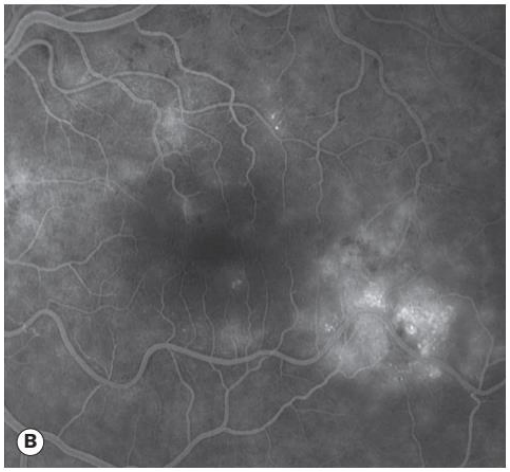
Exudates involving the fovea, including central crystalline cholesterol deposition

- FA will commonly show hypofluorescence only with large dense exudates because retinal capillary fluorescence is generally preserved overlying the exudates.

Diabetic maculopathy:

- It strictly refers to the presence of any retinopathy at the macula, but is commonly reserved for significant changes, particularly vision-threatening oedema and ischaemia.
- It is the most common cause of visual impairment in diabetic patients, particularly type 2.
- Focal diabetic maculopathy:
    - ◊ well-circumscribed retinal thickening associated with complete or incomplete rings of exudates.
    - ◊ FA shows late, focal hyperfluorescence due to leakage, usually with good macular perfusion.



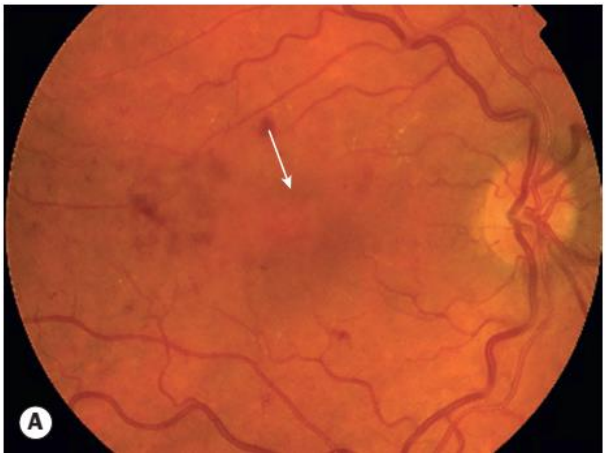


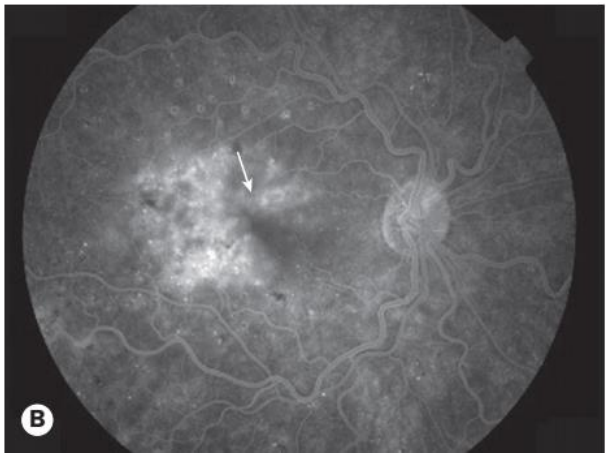
Focal diabetic maculopathy

A ring of hard exudates temporal to the macula

FA late phase showing focal area of hyperfluorescence due to leakage corresponding to the centre of the exudate ring

- Diffuse diabetic maculopathy:
  - ◊ diffuse retinal thickening, which may be associated with cystoid changes.
  - ◊ There are typically also scattered microaneurysms and small haemorrhages
  - ◊ Landmarks may be obscured by oedema, which may render localization of the fovea impossible.
  - ◊ FA shows mid- and late phase diffuse hyperfluorescence and demonstrates CMO if present.





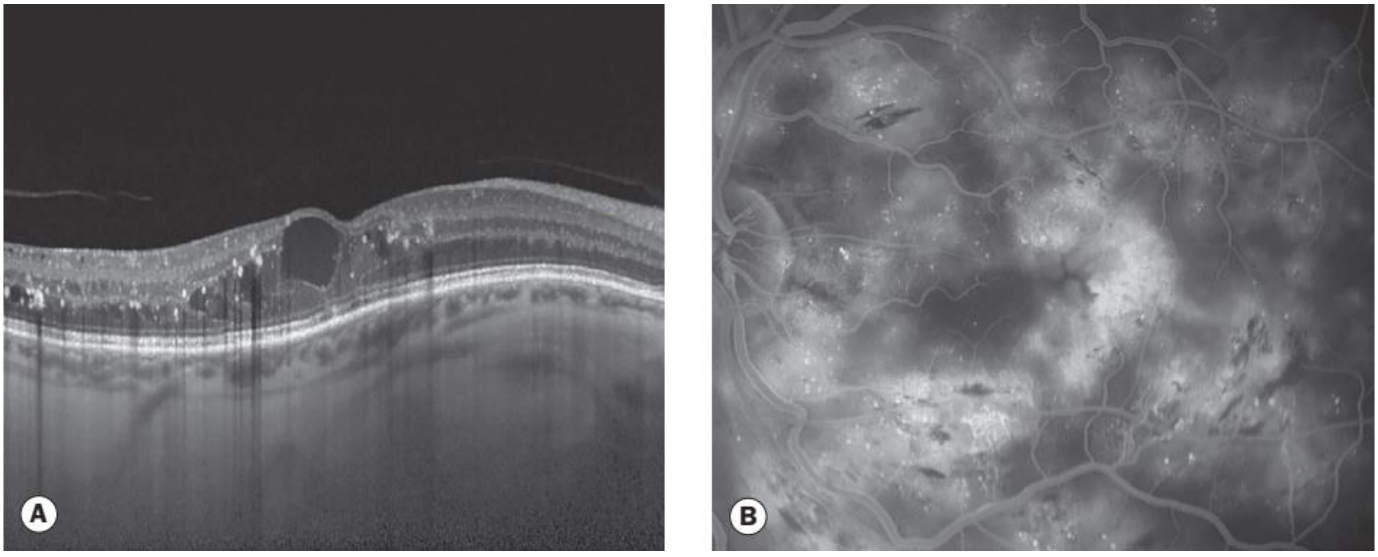
Diffuse diabetic maculopathy

Dot and blot haemorrhages – diffuse retinal thickening is present (arrow), which can be difficult to see clinically

late phase FA showing extensive hyperfluorescence (arrow) at the posterior pole due to leakage in the same patient

Diabetic macular oedema (DMO)

- Diffuse retinal oedema is caused by extensive capillary leakage
- Localized retinal oedema is caused by focal leakage from microaneurysms and dilated capillary segments.
- The fluid is initially located between the outer plexiform and inner nuclear layers. Later it may also involve the inner plexiform and nerve fibre layers, until eventually the entire thickness of the retina becomes oedematous.
- With central accumulation of fluid, the fovea assumes a cystoid appearance – cystoid macular oedema (CMO) that is readily detectable on optical coherence tomography (OCT) and assumes a central flower petal pattern on FA.



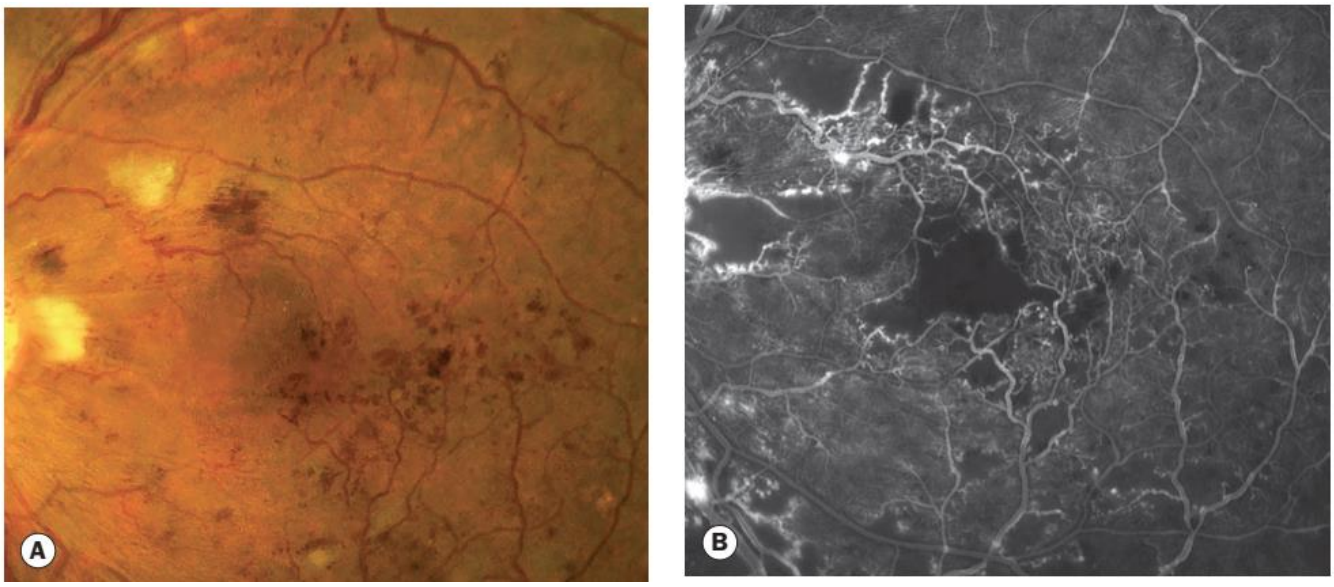
Cystoid macular oedema

OCT showing retinal thickening and cystoid spaces

FA showing leaking microaneurysms and central diffuse hyperfluorescence with a flower petal configuration

Ischaemic maculopathy:

- It has variable signs:
  the macula may look relatively normal despite reduced visual acuity. In other cases, preproliferative diabetic retinopathy (PPDR) may be present.
- FA shows capillary non-perfusion at the fovea (an enlarged FAZ) and frequently other areas of capillary non-perfusion at the posterior pole and periphery.



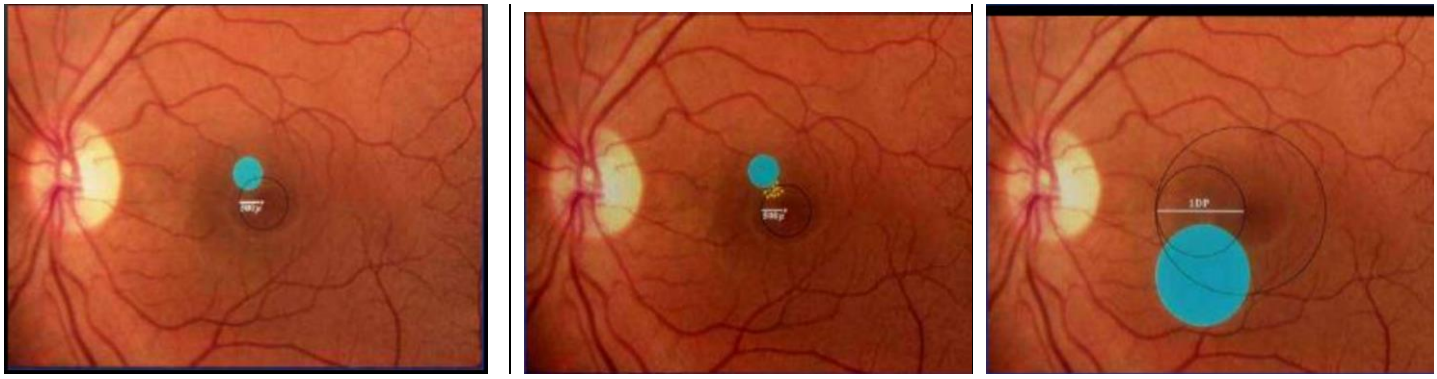
Ischaemic diabetic maculopathy.

Dot and blot haemorrhages and cotton-wool spots

FA venous phase showing hypofluorescence due to capillary non-perfusion at the macula and elsewhere

Clinically significant macular oedema

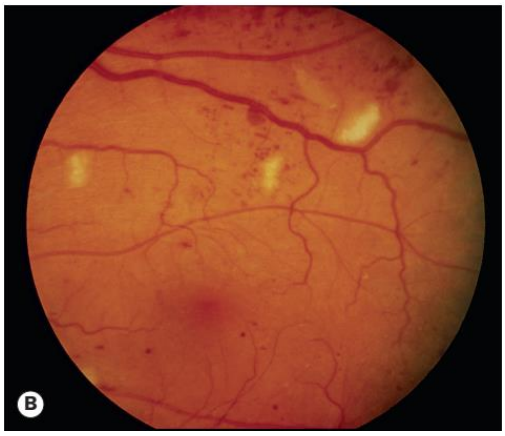
Clinically significant macular oedema (CSMO) is detected on clinical examination (i.e., visible with your slit lamp) as defined in the ETDRS:



- Retinal thickening within 500 µm of the centre of the macula.
- Hard exudates within 500 µm of the centre of the macula, if associated with retinal thickening. The thickening itself may be outside the 500 µm.
- Retinal thickening one-disc area (1500 µm) or larger, any part of which is within one disc diameter of the centre of the macula.

Cotton-wool spots:

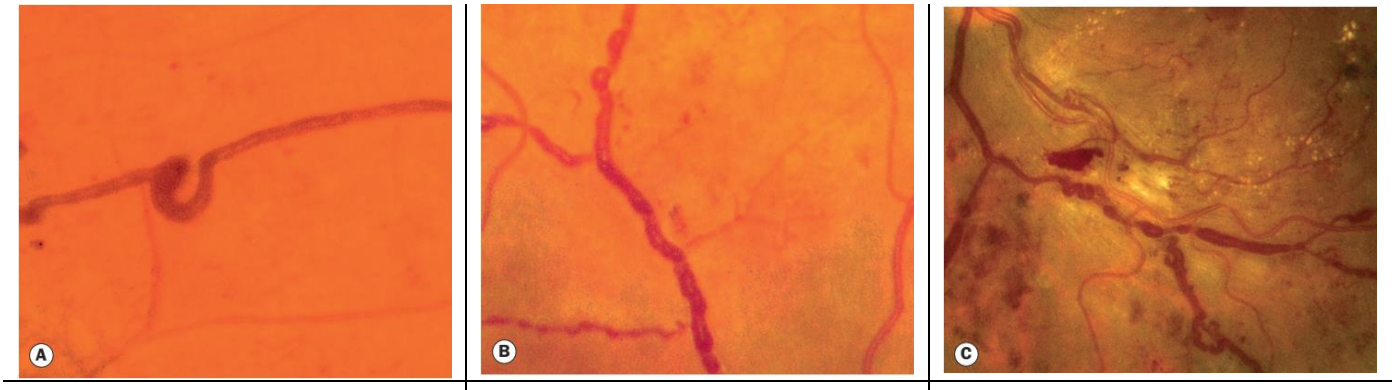
- Small fluffy whitish superficial lesions that obscure underlying blood vessels



- They are composed of accumulations of neuronal debris (seen as cystoid bodies on light microscopy) within the nerve fibre layer.
- They result from ischaemic disruption of nerve axons.
- They are clinically evident only in the post-equatorial retina, where the nerve fibre layer is of sufficient thickness to render them visible.
- As cotton-wool spots heal, debris is removed by autolysis and phagocytosis.
- FA shows focal hypofluorescence due to local ischaemia and blockage of background choroidal fluorescence.

Venous changes

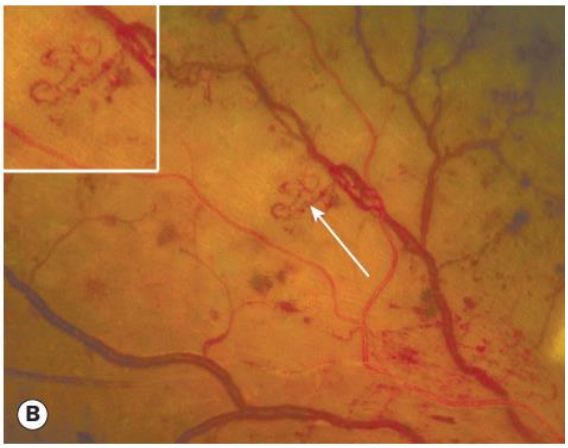
- Venous anomalies seen in ischaemia consist of:
    - generalized dilatation and tortuosity
    - looping
    - beading (focal narrowing and dilatation)
    - sausage-like segmentation
- The extent of the retinal area exhibiting venous changes correlates well with the likelihood of developing proliferative disease.

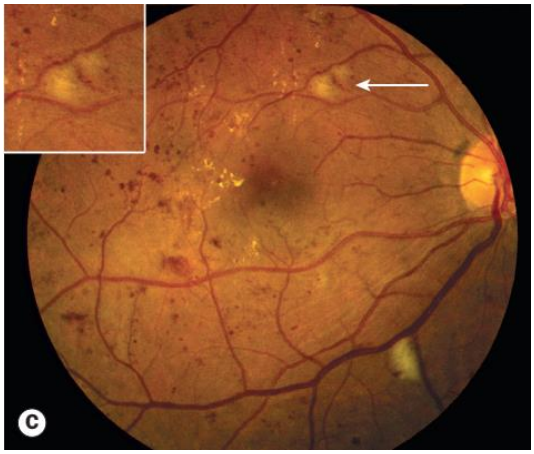


Looping	Beading	Severe segmentation

Intraretinal microvascular abnormalities (IRMA):

- Fine, irregular, red intraretinal lines that run from arterioles to venules, without crossing major blood vessels
- They are arteriolar–venular shunts that run from retinal arterioles to venules, thus bypassing the capillary bed and are therefore often seen adjacent to areas of marked capillary hypoperfusion.
- FA shows focal hyperfluorescence associated with adjacent areas of capillary closure (‘dropout’) but without leakage.





Arterial changes:

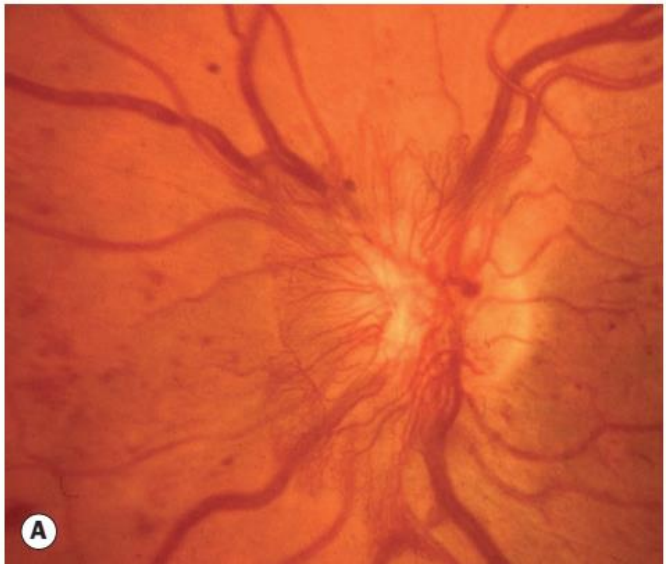
- Subtle retinal arteriolar dilatation may be an early marker of ischaemic dysfunction.
- When significant ischaemia is present signs include peripheral narrowing, ‘silver wiring’ and obliteration, similar to the late appearance following a branch retinal artery occlusion.

"copper wiring": Retinal arterioles appear orange or yellow instead of red

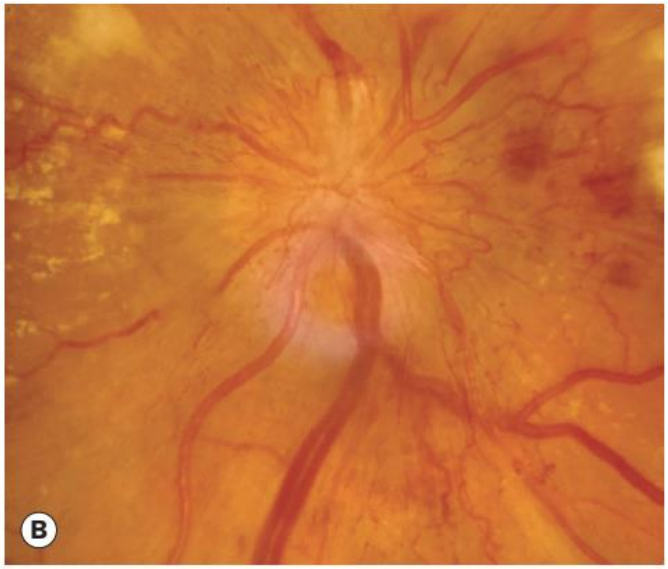
"silver wiring": Retinal arterioles look white if they have become occluded

Proliferative retinopathy:

- It has been estimated that over one-quarter of the retina must be non-perfused before PDR develops.
- Although preretinal new vessels may arise anywhere in the retina, they are most commonly seen at the posterior pole.
- Fibrous tissue, initially fine, gradually develops as vessels increase in size.
- NVD (New vessels at the disc) describes neovascularization on or within one disc diameter of the optic nerve head.

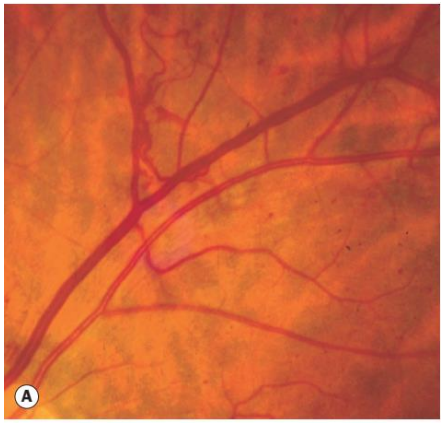


Moderate NVD

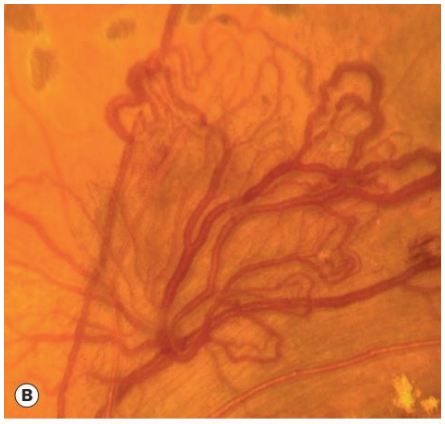


Severe NVD with cotton-wool spots

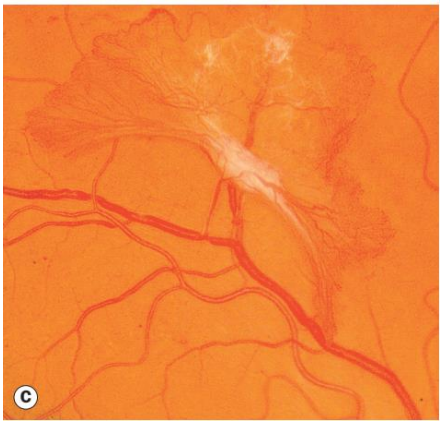
- NVE (New vessels elsewhere) describes neovascularization further away from the disc. It may be associated with fibrosis if long-standing.



Mild NVE

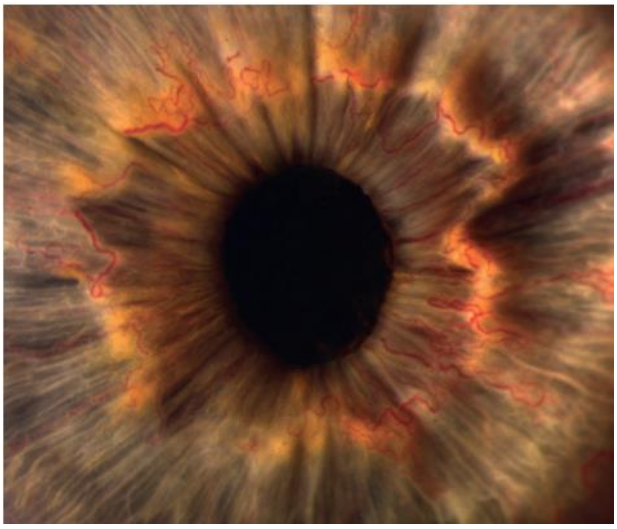


Severe NVE

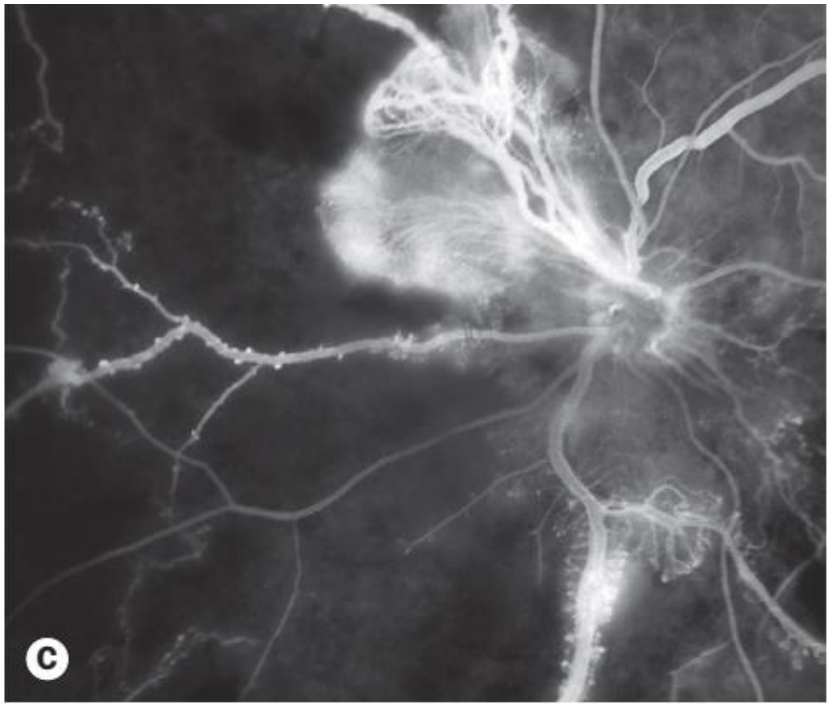


NVE associated with fibrosis

- NVI (New vessels on the iris), also known as rubeosis iridis, carry a high likelihood of progression to neovascular glaucoma.



- FA highlights neovascularization during the early phases of the angiogram and shows irregular expanding hyperfluorescence during the later stages due to intense leakage of dye from neovascular tissue.
- FA can be used to confirm the presence of new vessels (NV) if the clinical diagnosis is in doubt and also delineates areas of ischaemic retina that might be selectively targeted for laser treatment.



FA showing:
- leaking NVD
- a small focus of leaking NVE
- extensive peripheral capillary dropout

Classification

The following descriptive categories are in widespread use in clinical practice:

- Background diabetic retinopathy (BDR):
  - It is characterized by microaneurysms, dot and blot haemorrhages and exudates.
  - These are generally the earliest signs of DR and persist as more advanced lesions appear.
- Diabetic maculopathy:
  - It strictly refers to the presence of any retinopathy at the macula
  - But it is commonly reserved for significant changes, particularly vision-threatening oedema and ischaemia.
- Preproliferative diabetic retinopathy (PPDR):
  - It manifests with cotton-wool spots, venous changes, intraretinal microvascular anomalies (IRMA) and deep retinal haemorrhages.
  - PPDR indicates progressive retinal ischaemia, with a heightened risk of progression to retinal neovascularization.
- PDR:
  It is characterized by NVD (neovascularization on or within one disc diameter of the disc) and/or NVE (new vessels elsewhere in the fundus).
- Advanced diabetic eye disease:
  It is characterized by tractional retinal detachment (TRD), significant persistent vitreous haemorrhage (VH) and neovascular glaucoma.

Early Treatment Diabetic Retinopathy Study (ETDRS) classification of diabetic retinopathy:

- it is widely used internationally.
- An abbreviated version is set out in the following table, in conjunction with management guidelines.

Category/description	Management
No DR	Review in 12 months
Very mild NPDR: • Microaneurysms only	Review in 12 months
Mild NPDR: • Microaneurysms • retinal haemorrhages • exudates • cotton-wool spots.	Review range 6–12 months (depending on severity of signs, stability, systemic factors and patient's personal circumstances)
Moderate NPDR: • severe retinal haemorrhages (20 per quadrant) < 4 quadrants • Significant venous beading < 2 quadrants. • mild IRMA	Review in approximately 6 months. (PDR in up to 26% within a year) (high-risk PDR in up to 8% within a year)
Severe NPDR: The 4–2–1 rule: • Severe haemorrhages in all 4 quadrants • Significant venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants	Review in 4 months. (PDR in up to 50% within a year) (high-risk PDR in up to 15% within a year)
Very severe NPDR: Two or more of the criteria of severe NPDR	Review in 2-3 months. (high-risk PDR in up to 45% within a year)
Mild–moderate PDR: NVD or NVE, but extent insufficient to meet the criteria of High-risk PDR	Treatment considered according to severity of signs, stability, systemic factors and patient's personal circumstances such as reliability of attendance for review. If not treated, review in up to 2 months
High-risk PDR: • NVD (about 1/3 disc area) • Any NVD with vitreous haemorrhage • NVE greater than 1/2 disc area with vitreous haemorrhage	Treatment should be performed immediately when possible and certainly same day if symptomatic presentation with good retinal view
Advanced diabetic eye disease: • Haemorrhages (preretinal, intragel or both) • Tractional retinal detachment (TRD) • NVI	

General Treatment

- Patient education:
  - It is critical
  - including the need to comply with review and treatment schedules in order to optimize visual outcomes.
  - In type 2 diabetes this also involves counselling on weight reduction programs and emphasizing the need to increase exercise.
- Diabetic control should be optimized.
- systemic hypertension (especially type 2 diabetes) and hyperlipidaemia should be controlled in conjunction with the patient's diabetologist.

- Fenofibrate:
  - Fenofibrate 200 mg daily has been shown to reduce the progression of DR in type 2 diabetics and prescription should be considered.
  - The decision is independent of whether the patient already takes a statin.
- Smoking should be discontinued, though this has not been definitively shown to affect retinopathy.
- anaemia and renal failure should be addressed as necessary.

TIP

The key to the prevention of diabetic retinopathy is patient education and long-term control of blood sugar.

Treatment of diabetic macular oedema

- there are various interventions:
  1) Intravitreal anti-VEGF agents:
     aflibercept (Eylea®), bevacizumab (Avastin®) ranibizumab (Lucentis®)
  2) Focal/grid laser photocoagulation
  3) Subthreshold (micropulse) diode laser.
  4) Intravitreal triamcinolone.
  5) Pars plana vitrectomy (PPV)

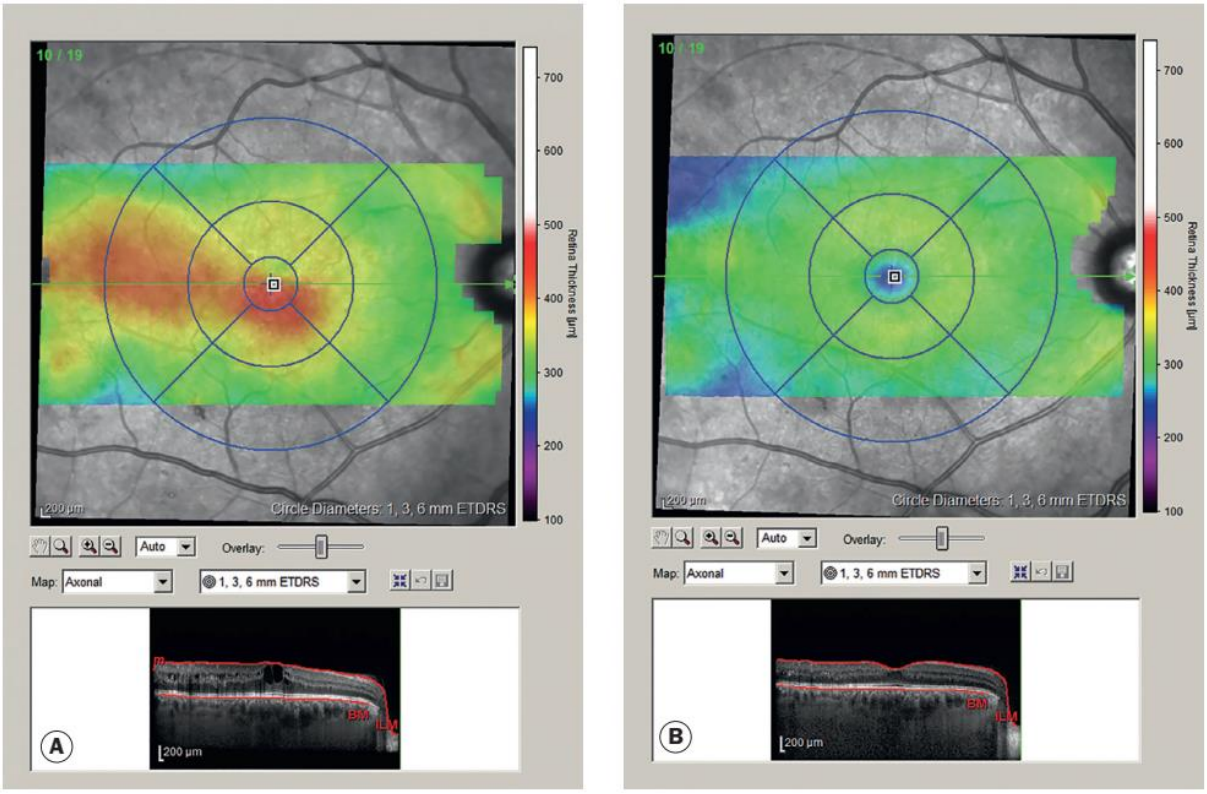
- Patients with good vision (0.8 or better) who otherwise meet criteria for treatment might prefer to be monitored once the risks of various interventions are considered

TIP

Anti-VEGF therapy has become the main therapeutic option in the treatment of diabetic macular oedema (DMO)

1) Intravitreal anti-VEGF agents

- DRCR.net Protocol I concludes that:
  - intravitreal ranibizumab more effectively improves visual acuity than focal/grid laser treatment for centre-involved DMO.
  - Laser treatment for centre-involved DMO should be deferred for 6 months after commencement of anti-VEGF therapy.
  - Good outcomes can be expected for at least 5 years, despite a sequential reduction in the number of anti-VEGF injections.
- DRCR.net Protocol T concludes that:
  - there are no differences in visual acuity at 5 years irrespective of whether aflibercept, bevacizumab or ranibizumab is used in patients with diabetic maculopathy and a visual acuity of better than 0.4
  - However, aflibercept is more likely to improve visual acuity than bevacizumab in those with vision of 0.4 or worse.



Anti-VEGF treatment for CSME

Macula thickness map and OCT appearance prior to treatment showing diffuse thickening of the macular region

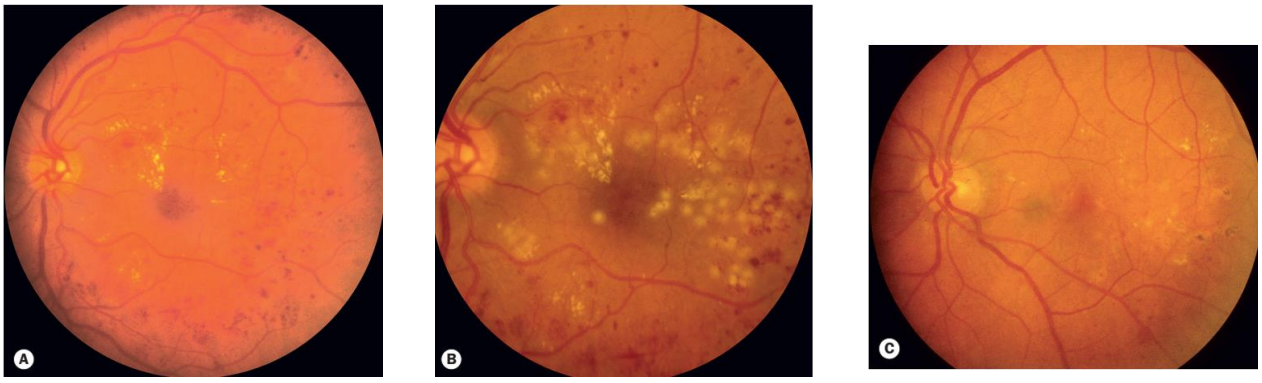
6 months after treatment showing resolution

TIP

Improvement in best corrected visual acuity after three injections of anti-VEGF medication is a strong predictor of long-term response in a patient with diabetic macular oedema.

2) Focal/grid laser photocoagulation

- Although anti-VEGF therapy has replaced laser treatment for most cases, this remains a well-proven therapeutic option.
- It should be considered in cases with off-centre swelling when exudates threaten the fovea.
- Focal:
  Diode or argon burns are applied to leaking microaneurysms 500–3000 µm from the foveola using a spot size 50–100 µm, duration 0.05–0.1 s with sufficient power to obtain a greyish reaction beneath the microaneurysm.
- Grid:
  - ◊ Burns are applied to macular areas of diffuse retinal thickening, treating no closer than 500 µm from the foveola and 500 µm from the optic disc using a spot size of 50–100 µm and duration 0.05–0.1 s, with power adjusted to give a mild reaction.
  - ◊ A 'modified' grid includes focal treatment to foci of leakage, usually microaneurysms.



Modified macular grid laser for CSME treatment

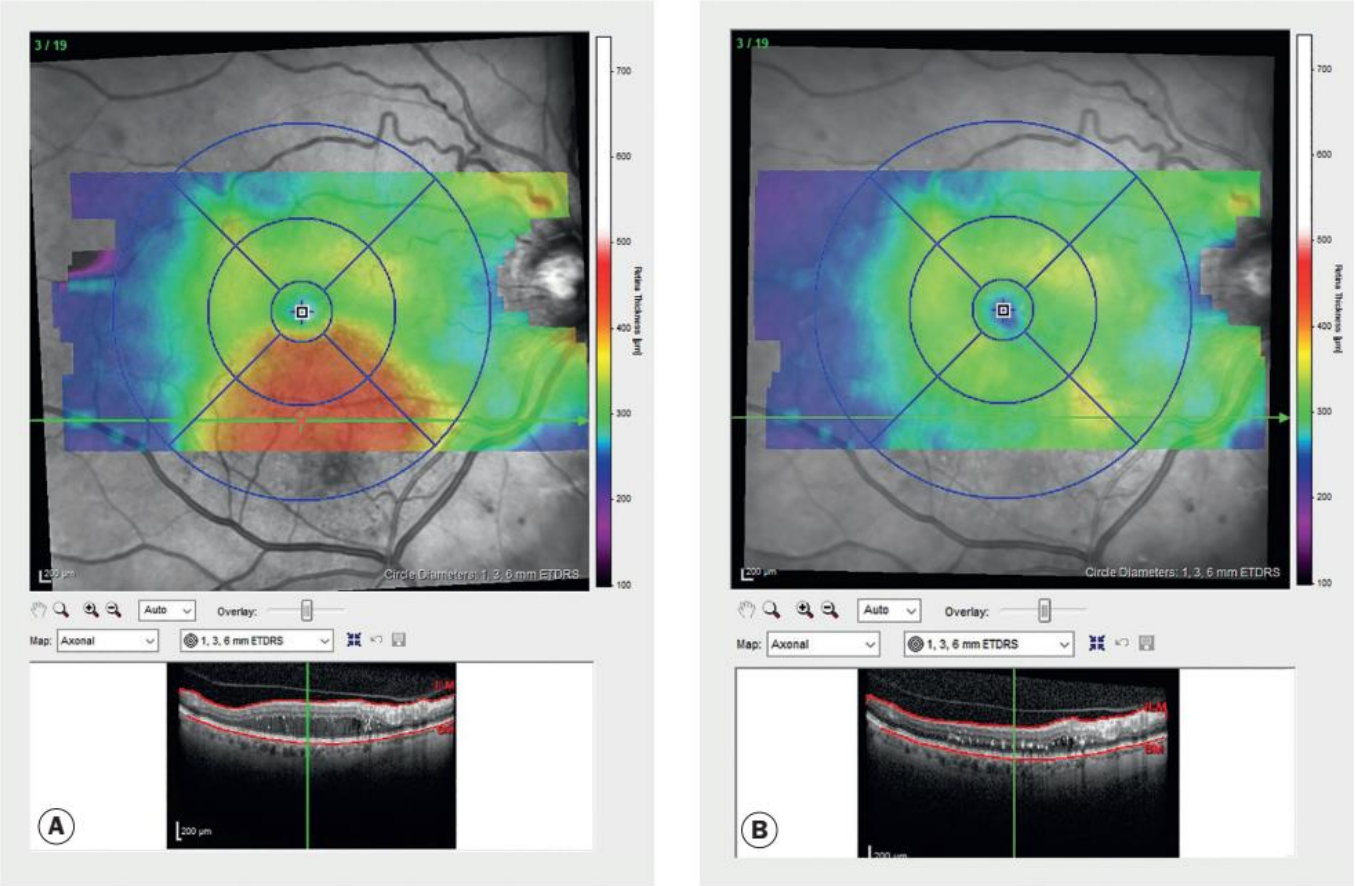
Prior to modified macular grid laser treatment

immediately post-grid laser

2 months following a limited grid laser

3) Subthreshold (micropulse) diode laser

- This modality uses very short (microsecond order) laser pulse duration combined with a relatively longer interval (e.g. 5% duty cycle), allowing energy dissipation.
- This minimises collateral damage to the retina and choroid whilst stimulating the retinal pigment epithelium (RPE).
- Subfoveal therapy is possible.
- The results from clinical experience with subthreshold laser therapy are favourable, but there are no clinical trials showing superiority to anti-VEGF treatment or conventional laser.



Subthreshold (micropulse) diode laser for CSME

Macula thickness map and OCT appearance prior to treatment showing thickening of the macular region below the fovea

3 months after treatment showing no oedema

4) Intravitreal triamcinolone

- In pseudophakic eyes intravitreal triamcinolone steroid injection followed by prompt laser is comparable to ranibizumab with regard to visual improvement and reduced retinal thickening.
- This is a good therapeutic option in pregnancy or where there is a contraindication to anti-VEGF treatment (for example recent myocardial infarct).
- However, there is a significant risk of inducing an elevation of intraocular pressure (IOP) and this must be monitored regularly.
- In a phakic eye there is an increased risk of cataract.
- Sustained-release intravitreal steroid implants have demonstrated promising results.

5) Pars plana vitrectomy (PPV)

- It may be indicated when macular oedema is associated with tangential traction from a taut thickened posterior hyaloid.
- A taut thickened posterior hyaloid is characterized:
  - ◊ Clinically: by an increased glistening of the premacular vitreous face
  - ◊ FA: typically shows diffuse leakage and prominent CMO
  - ◊ OCT: is usually the definitive assessment.
- It has also been suggested that some eyes without a taut posterior hyaloid may also benefit from vitrectomy.
- There are several other indications for PPV in the management of diabetic eye disease (see later)

Let's review

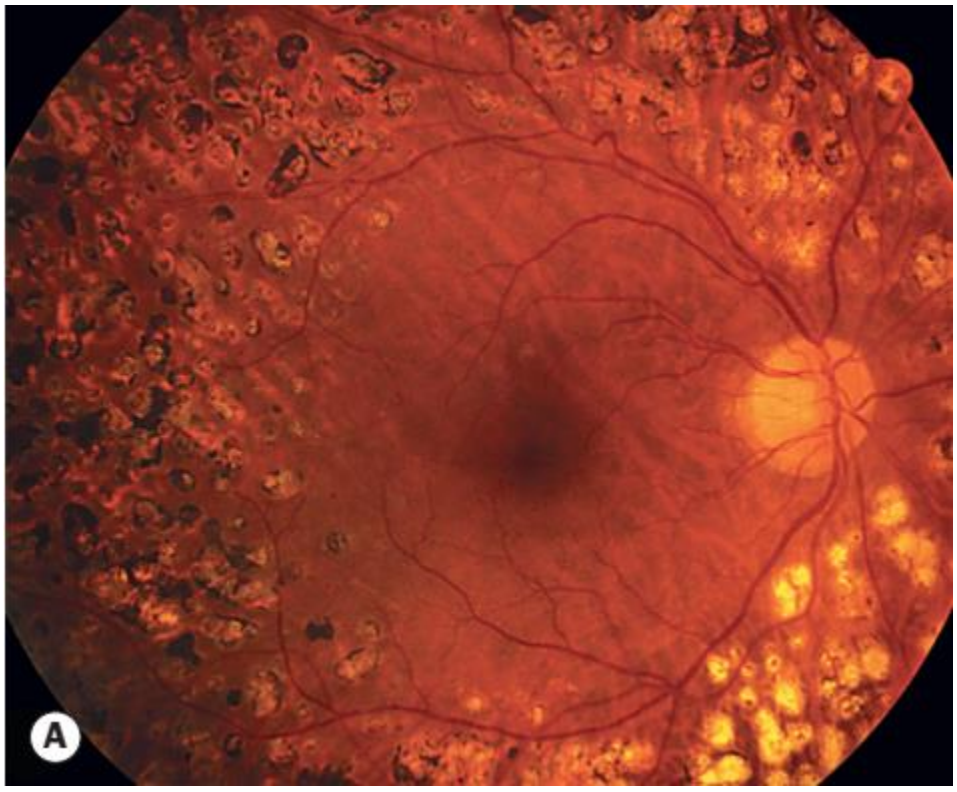
- CSMO not involving the centre of the macula (particularly where exudates threaten the fovea) may be treated with laser treatment in the form of continuous-wave focal or modified grid laser photocoagulation. If available, subthreshold macular laser treatment, intravitreal anti-VEGF therapy or an intravitreal steroid implant may be reasonable alternatives for this indication.
- CSMO involving the centre of the macula, but with a visual acuity of better than 0.4 can be treated with aflibercept, bevacizumab or ranibizumab. However, bevacizumab reduces OCT swelling less effectively and is more likely to result in persistent DMO than other agents. Alternatively, subthreshold laser can be considered. If laser is to be used, it is prudent to treat no closer than 500 µm from the perceived centre of the macula.
- CSMO involving the centre of the macula, but with a visual acuity of 0.4 or worse and significant foveolar thickening should be considered for aflibercept treatment with initial induction using monthly injections for 3–6 months. An 'as-needed' approach can subsequently be adopted. Focal/grid laser should be deferred for 6 months. An intravitreal dexamethasone implant is an alternative treatment that may be considered in patients with absolute or relative contraindications to anti-VEGF injections. In patients who have a transient but significant reduction in macular oedema switching to a fluocinolone acetonide implant is a reasonable alternative, as it is longer acting and therefore will reduce the need for repeated dexamethasone injections.
- In eyes with PDR and co-existing DMO, ranibizumab or aflibercept treatment alone should be considered (rather than PRP and ranibizumab or PRP and aflibercept).
- In eyes with persistent DMO after 6 months of anti-VEGF monotherapy, consider adding laser or switching to an intravitreal dexamethasone implant if there are no contraindications.
- Eyes with markedly reduced vision due to DMO often have associated macular ischaemia and therefore a poor prognosis. Optimal management for this group of patients has not been determined. Depending on circumstances, including the severity of macular oedema and the level of ischaemia, any of the interventions discussed above may be considered.
- In resistant cases of DMO, pars plana vitrectomy may be considered, particularly if vitreomacular traction or a marked epiretinal membrane is present.

Treatment options for PDR

1- Panretinal photocoagulation (PRP)
2- Intravitreal anti-VEGF
3- Targeted retinal photocoagulation (TRP)
4- pars plana vitrectomy for advanced diabetic eye disease

1- Panretinal photocoagulation (PRP)

- Panretinal photocoagulation with scatter laser continues to be the mainstay of PDR treatment in most healthcare systems.



Retinal appearance several weeks after laser

- The Diabetic Retinopathy Study (DRS) establishes the characteristics of high-risk proliferative disease and demonstrates the benefit of PRP.
- For instance, severe NVD without haemorrhage carries a 26% risk of visual loss at 2 years that is reduced to 9% with PRP.
- However, recent research (Protocol S from DRCR.net) shows that a course of injections of intravitreal ranibizumab is as effective as photocoagulation in PDR patients who are at high risk of PDR at 5 years.
- In addition, the CLARITY study provides 1-year data which show that intravitreal aflibercept injections are as effective as PRP in the treatment of PDR.

- Informed consent:
  - ◊ Patients should be advised that PRP may cause visual field defects of sufficient severity to legally preclude driving a motor vehicle. However, most patients who start with good vision are able to maintain their binocular visual field to the standard legally required in most countries.
  - ◊ They should be made aware that there is a risk to central vision (because of developing or exacerbating macular oedema; a risk that can be reduced by fractionating the treatment over 2–3 sessions) and that night and colour vision may be affected.
  - ◊ The 5-year results of the DRCR.net Protocol S and CLARITY studies should be discussed, as the patient may choose to be treated with ranibizumab or aflibercept instead of PRP. However, they should also be made aware of the risks associated with repeated injections and the short-term nature of these studies.

- Co-existent DMO:
  - ◊ If actual or imminent central-involving DMO is also present, an anti-VEGF agent should be considered. This may be used as monotherapy or as an adjunct to PRP.
  - ◊ Alternatively, in the case of CSMO not involving the centre of the macula and active PDR, laser treatment to the macula could be considered in addition to PRP. In such cases the macular laser treatment should be carried out prior to the PRP or at the same laser treatment session.

Conclusion

☺ PDR → PRP
☺ Central-involving DMO → anti-VEGF agent
☺ Non central-involving DMO → laser treatment to the macula (Focal/grid)

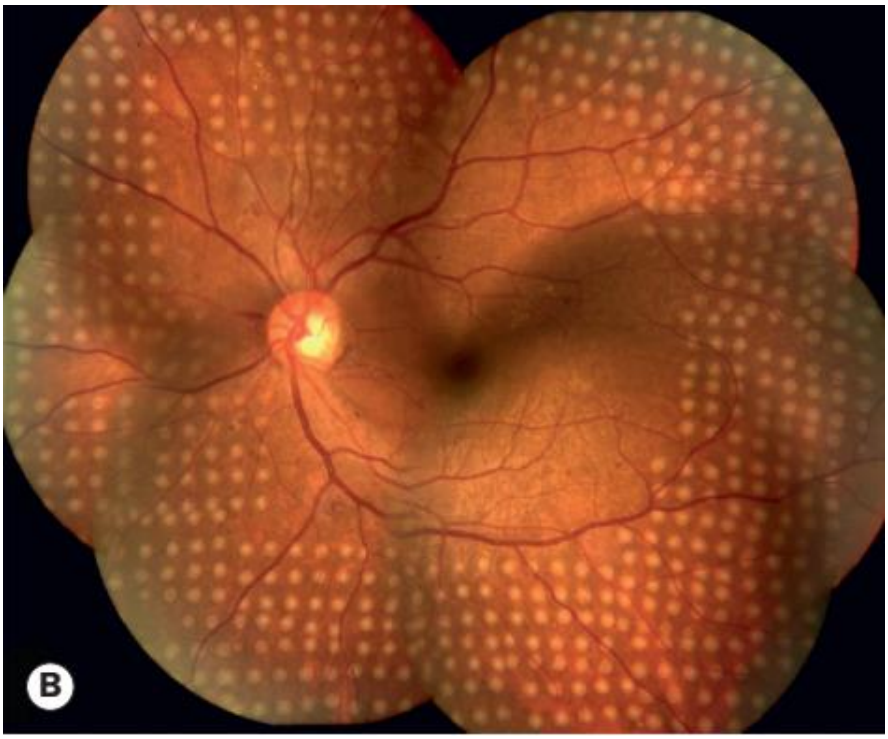
- ◊ **TIP:** In a patient with proliferative diabetic retinopathy and macular oedema, first treat the oedema then undertake panretinal photocoagulation.

- Lens:
  - ◊ A contact lens is used to provide a stable magnified fundus view.
  - ◊ A panfundoscopic lens is generally preferred to a three-mirror lens.
  - ◊ Some practitioners prefer to use a high-magnification/smaller area contact lens (e.g. Mainster®, Area Centralis®) for the more posterior component of treatment.
  - ◊ It is essential to constantly bear in mind that an inverted and laterally reversed image is seen.

- Anaesthesia:
  - ◊ The amount of treatment it is possible to apply during one session may be limited by patient discomfort.
  - ◊ Patient discomfort tends to be least at the posterior pole and greatest in the periphery and over the horizontal neurovascular bundles and may worsen with successive sessions.

◊ Topical anaesthesia is adequate in most patients, although sub-Tenon or peribulbar anaesthesia can be administered if necessary.

- Laser parameters:
  ◊ Spot size:
  A retinal burn diameter of 400 µm is usually desired for PRP. The diameter selected at the user interface to achieve this depends on the contact lens used and the operator must be aware of the correction factor for the particular lens chosen. As an approximation, with panfundoscopic-type lenses the actual retinal spot diameter is twice that selected on the laser user interface; 200 µm is typically selected for PRP, equating to a 400 µm actual retinal diameter once relative magnification is factored in. With the Mainster and Area Centralis, the retinal diameter equates closely to the interface selection, so 400 µm may be selected.
  ◊ Duration:
  It depends on the type of laser: 0.05–0.1 s was conventionally used with the argon laser, but newer lasers allow much shorter pulses to be used and 0.01–0.05 s (10–50 ms) is the currently recommended range. Multispot strategies available on some machines utilize a combination of short pulse duration (e.g. 20 ms), very short intervals and preprogrammed delivery arrays to facilitate the application of a large number of pulses in a short period.



Composite image of ‘pattern scan’ multispot array treatment

True subthreshold PRP is also under investigation and shows promising results. Shorter pulse duration seems to require a greater total number of burns for an adequate response and may be slower to achieve regression.

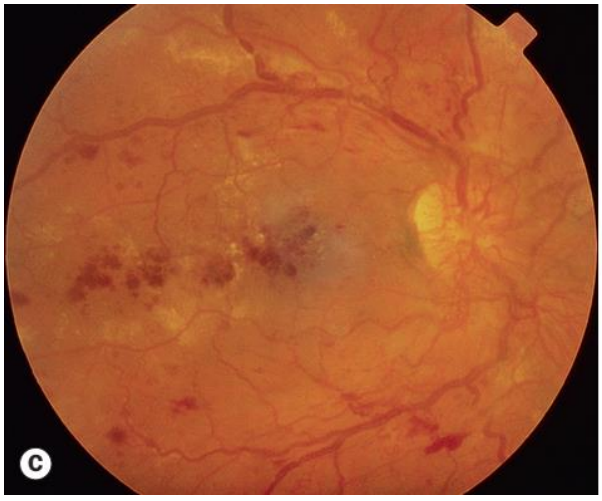
◊ Power:
it should be sufficient to produce only a light intensity burn.

◊ Spacing:
Burns should be separated by 1–1.5 burn widths.

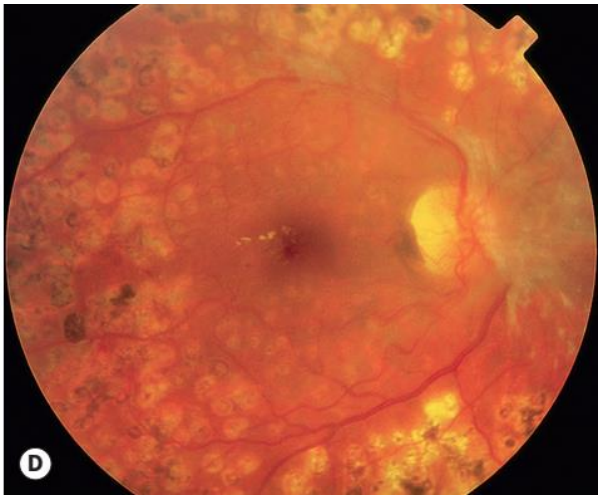
◊ Extent of treated area:
The initial treatment session should consist of 1500 burns in most cases, though more may be applied if there is a risk of imminent sight loss from vitreous haemorrhage. The more extensive the treatment at a single session, the greater the likelihood of complications. Reported figures vary, but 2500–3500 burns are likely to be required for regression of mild PDR, 4000 for moderate PDR and 7000 for severe PDR. The number of burns offers only approximate guidance, as the effective extent of treatment is dependent on numerous variables.

◊ Pattern of treatment:
Treatment is generally restricted to the area outside the temporal macular vascular arcades. It is good practice to delineate a 'barrier' of laser burns temporal to the macula early in the procedure to help to reduce the risk of accidental macular damage. Many practitioners leave two disc diameters untreated at the nasal side of the disc, to preserve paracentral field. In very severe PDR it is advisable to treat the inferior fundus first, since any vitreous haemorrhage will gravitate inferiorly and obscure this area, precluding further treatment. Areas of vitreoretinal traction should be avoided.

- Review:
  ◊ It is dependent on PDR severity and the requirement for successive treatment applications.
  ◊ Initial treatment should be fractionated over 2–3 sessions.
  ◊ Once an adequate number of burns have been applied review can be set for 4–6 weeks to check for active/regressed PDR.



before treatment of severe proliferative diabetic retinopathy



3 months later the new vessels have regressed – there is residual fibrosis at the disc