Diabetic retinopathy

Peter H Scanlon

Abstract

Diabetic retinopathy is a key cause of blindness in the working-age population. Despite the available treatments, some patients present late in the course of the disease when treatment is more difficult. If diabetic retinopathy is detected, tightening of modifiable risk factors (e.g. blood glucose, blood pressure) can slow disease progression. When sight-threatening retinopathy is detected, laser treatment and treatment with vascular endothelial growth factor inhibitors reduces the risk of visual loss. When a stage of advanced retinopathy is detected, vitrectomy operations with modern surgical techniques provide improving results for patients. Advances in optical coherence tomography technology have seen the development of high-definition three-dimensional imaging of the retina and of non-invasive, dye-free angiography, which has enhanced the understanding of and diagnostic capabilities within the field of diabetic retinopathy management.

Keywords Diabetic retinopathy; laser therapy; MRCP; optical coherence tomography; risk factors; screening; vascular endothelial growth factor

Key points

- Diabetic retinopathy is still a key cause of blindness in the working population
- Screening and early treatment, with good blood pressure and glycaemic control, are effective in preventing visual loss
- VEGF inhibitors are successful in treating many patients with centre involving diabetic macular oedema
- Laser treatment is still the standard of care for treating proliferative diabetic retinopathy with vitrectomy operations for advanced disease

Definition and pathophysiology of diabetic retinopathy (DR)

DR refers to pathology of the capillaries, arterioles and venules in the retina, and the subsequent effects of leakage from or occlusion of the small vessels. Changes that occur within the retinal capillaries include:

- thickening of the basement membrane
- pericyte loss
- epithelial cell dysfunction (loss of epithelial tight junctions)
- loss of endothelial cells
- smooth muscle cell death
- capillary weakening
- increased capillary permeability
- capillary occlusion
- microaneurysm formation.

The microaneurysm is the hallmark of retinal microvascular disease in patients with diabetes mellitus. It has been suggested that microaneurysms may be asymmetrical dilatations of the capillary wall where it has been weakened or damaged by the loss of supporting pericytes and localized increases in hydrostatic pressure.

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The Early Treatment Diabetic Retinopathy Study (ETDRS)

The ETDRS described the progression of DR in relation to the development of the following lesions (Figure 1):

- microaneurysms
- small retinal haemorrhages
- haemorrhage/microaneurysm (HMa)
- other larger retinal haemorrhages
  - flame haemorrhages
  - blot haemorrhages
- hard exudates (often just referred to as exudates)
- cotton wool spots (referred to in the ETDRS as soft exudates, although that term is now rarely used)
- intra-retinal microvascular abnormalities (IRMAs)
- venous abnormalities
- arteriolar abnormalities
- fibrous proliferation at the disc
- fibrous proliferation elsewhere
- new vessels at the disc (NVDs)
- new vessels elsewhere (NVEs)
- vitreous haemorrhage
- pre-retinal haemorrhage
- laser treatment – laser scars.

The ETDRS defined microaneurysm and haemorrhage as follows:

- A microaneurysm is defined as a red spot <125 micrometres in size (approximately the width of a vein at the disc margin) and with sharp margins.
- Haemorrhage is defined as a red spot that has irregular margins and/or uneven density, particularly when surrounding a smaller central lesion that is considered to be a microaneurysm. If a red lesion is >125 micrometres in its longest dimension, it is usually a haemorrhage unless features such as a round shape, smooth margins or central light reflex suggest it might be a microaneurysm.
- Because the ETDRS recognized that it was very difficult to differentiate between microaneurysms and small haemorrhages, the concept of 'HMa' was introduced, which is a small haemorrhage or microaneurysm.

The ETDRS defined hard exudates as small white or yellowish-white deposits with sharp margins, typically located in the outer layers of the retina.

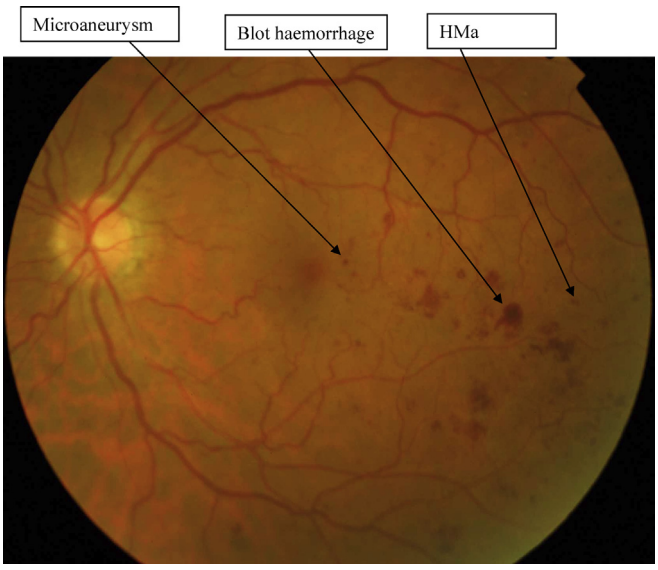

Figure 1 Microaneurysms, small HMas and blot haemorrhages.

The ETDRS graded images from seven-field stereophotography (14 photographs of each eye), using these seven fields to describe the progression of retinopathy in the study. This level of detail can make this approach difficult to use in clinical practice, so there have been attempts to simplify it.

The ETDRS '4:2:1 rule', which is used in the simplified International Classification, defines severe non-proliferative DR as:

- extensive (>20) intra-retinal (blot) haemorrhages in four quadrants *or*
- definite venous beading in two or more quadrants *or*
- prominent IRMA in one or more quadrants
- *and* no signs of proliferative diabetic retinopathy.

Screening for DR

National screening programmes were announced in 2002–2003 in Scotland, Wales, England and Northern Ireland, all using digital photography.

The national screening programmes in England and Wales use two-field mydriatic digital photography, and the Scottish methodology involves one-field non-mydriatic digital photography with dilation and repeat photography for individuals with poor-quality images. In the Northern Ireland Screening Programme, patients <50 years of age do not routinely have their pupils dilated. A recent study has shown that, for the first time in at least five decades, DR/maculopathy is no longer the leading cause of certifiable blindness among working-age adults in England and Wales, having been overtaken by inherited retinal disorders.[1] This change may be related to factors including the introduction of nationwide DR screening programmes in England and Wales and improved glycaemic control.

English screening classification for DR progression

The classification used in England for progression and referral of DR is a simplified classification with a referral level that has been determined according to the need of a patient to be reviewed more than annually.

Each patient screened is given an R (retinopathy) level and an M (maculopathy) level, and the outcome depends on the grade of the worse eye (Table 1):

- R0M0 – no DR, no maculopathy
- R1M0 – background DR, no maculopathy
- R1M1 – background DR, maculopathy
- R2M0 – pre-proliferative DR, no maculopathy
- R2M1 – pre-proliferative DR, maculopathy
- R3M0 – proliferative DR, no maculopathy
- R3M1 – proliferative DR, maculopathy
- U – unassessable images.

People with diabetes who have unassessable images are referred for slit-lamp biomicroscopy investigation.

Treatment of associated risk factors

Systemic hypertension: good blood pressure control is crucial in terms of the progression of DR. Control of systemic hypertension has been shown to reduce the risk of new-onset DR and slow the progression of existing DR.

Glucose control: the importance of good blood glucose control in the progression of DR has been shown in both the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study.

Blood lipids: two studies have shown the importance of good blood lipid control in the progression of diabetic maculopathy.

Smoking: there is some evidence that smoking may be a risk factor in the progression of DR in type 1 diabetes as described by Muhlhauser and Karamanos (see Further reading). The evidence in type 2 disease is, however, controversial.

Non-modifiable risk factors for DR

The non-modifiable determinants of progression of DR include duration of diabetes, and a complex relationship with age, genetic predisposition and ethnicity.

The 'early worsening' phenomenon

In 1998, the DCCT described the effect of early worsening of DR at the 6- and/or 12-month visit in 13.1% of 711 patients assigned to intensive treatment. Early worsening led to high-risk proliferative retinopathy in two patients in the DCCT. The most important risk factors for early worsening were higher concentrations of glycated haemoglobin at screening and reduction of this concentration during the first 6 months after randomization. In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening.

Background DR

In the UK, patients who are screened and who show signs only of background DR are re-screened annually. For background DR with microaneurysms only, there is a 6.2% risk of progression to proliferative DR in 1 year. Microaneurysms in increasing numbers have been shown to be an important early measure of progression of DR.

English diabetic retinopathy screening classification

Retinopathy or R level	Maculopathy or M level
R0	**M0**
Currently screen annually	None of the features of M1 below
R1	
Screen annually	
Background:	
• Microaneurysm(s) or HMas	
• Retinal haemorrhage(s)	
• Venous loop	
• Any exudate or cotton wool spots in the presence of other non-referrable features of DR	
R2	**M1**
Refer to ophthalmologist or surveillance clinic	Refer to ophthalmologist or surveillance clinic
Pre-proliferative:	Exudate within one DD of the centre of the fovea
• Venous beading	**M1**
• Venous reduplication	Refer to ophthalmologist
• IRMAs	Circinate or group of exudates within the macula (A circinate exudate needs to be at least one half of the disc area, which needs to be within the macular area)
• Multiple deep, round or blot haemorrhages	
R3A	**M1**
Urgent referral to ophthalmologist	Refer to ophthalmologist or surveillance clinic
R3A	Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea
Proliferative:	but only if associated with a best visual acuity of $\leq$6/12 (if no stereo)
• NVDs	**M1**
• NVEs	Refer to ophthalmologist or surveillance clinic
• Pre-retinal or vitreous haemorrhage	Retinal thickening within 1 DD of the centre of the fovea (if stereo available)
• Pre-retinal fibrosis ± tractional retinal detachment	

The macula is defined as that part of the retina which lies within a circle centred on the centre of the fovea whose radius is the distance between the centre of the fovea and the temporal margin of the disc.
DD, disc diameter.

Table 1

Cotton wool spots are fluffy white opaque areas caused by an arteriolar occlusion in an area of retina that results in an accumulation of axoplasm in the nerve fibre layer. These are not good signs in terms of the progression of DR as they are often associated with hypertension.

A venous loop is an abrupt curving deviation of a vein from its normal path. It is not considered to be associated with an increase in risk of progression over other features of background DR.

For the purposes of the English national screening programme, background DR is defined by the following lesions:

- one or more microaneurysm(s)
- one or more retinal haemorrhage(s)
- any exudate caused by DR.

Pre-proliferative DR

The main features that classify DR level in pre-proliferative DR are increasing signs of retinal ischaemia including venous beading, IRMAs and multiple blot haemorrhages:

- **Venous beading** is defined as a localized increase in calibre of the vein. The severity depends on the increase in calibre and the length of vein involved.

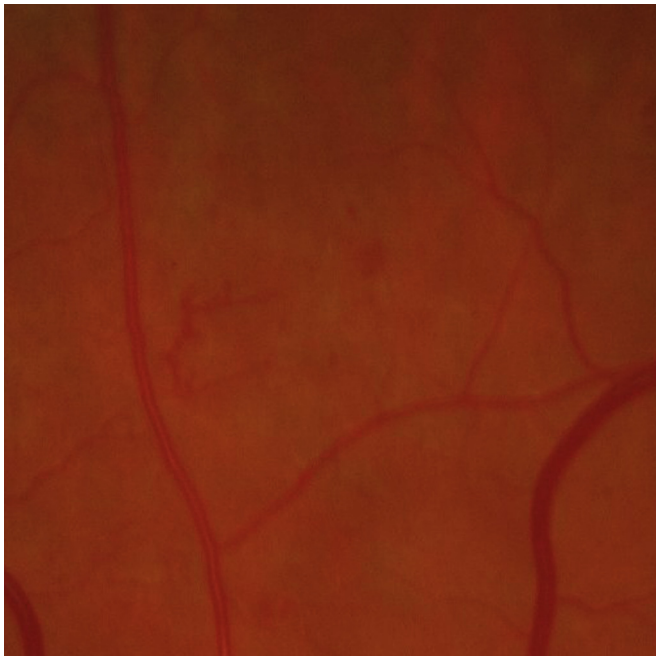

Figure 2 An example of an intra-retinal microvascular abnormality.

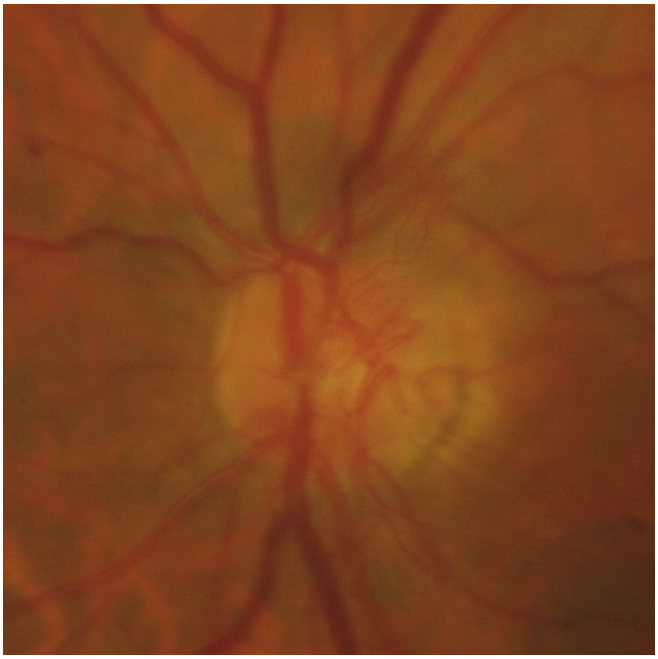

Figure 3 NVD formation.

- **IRMAs** are defined as tortuous intra-retinal vascular segments that vary in calibre (Figure 2). They derive from remodelling of the retinal capillaries and small collateral vessels in areas of microvascular occlusion.
- **Blot haemorrhages** are usually in a deeper retinal layer than more superficial dot haemorrhages and flame haemorrhages.

With increasing ischaemia, there is an increasing risk of progression to proliferative DR in 1 year. The risk increases from approximately 11.3% for the lower levels of pre-proliferative DR to 54.8% for the most severe DR level.

Proliferative DR

New vessels developing in DR are characterized according to whether they develop at or near the optic disc (NVDs) or elsewhere in the retina (NVEs):

- **NVDs** are defined as any new vessel developing at the optic disc (Figure 3) or within one disc diameter of the edge of the optic disc.
- **NVEs** are defined as any new vessel developing more than one disc diameter away from the edge of the optic disc (Figure 4).

They usually develop from the venous circulation and grow forwards in the vitreous gel, but they can also arise from the arterial circulation. New vessels growing into the vitreous are fragile and likely to bleed, causing significant floaters and blurring of the vision. In the more advanced stages, they can contract and cause retinal detachment.

The Diabetic Retinopathy Study (DRS) recommended prompt treatment in the presence of DRS high-risk characteristics, which reduced the 2-year risk of severe visual loss by 50% or more. These high-risk characteristics were defined as:

- the presence of pre-retinal or vitreous haemorrhage
- eyes with NVDs that equalled or exceeded one-quarter to one-third of the disc area in extent, with no haemorrhage

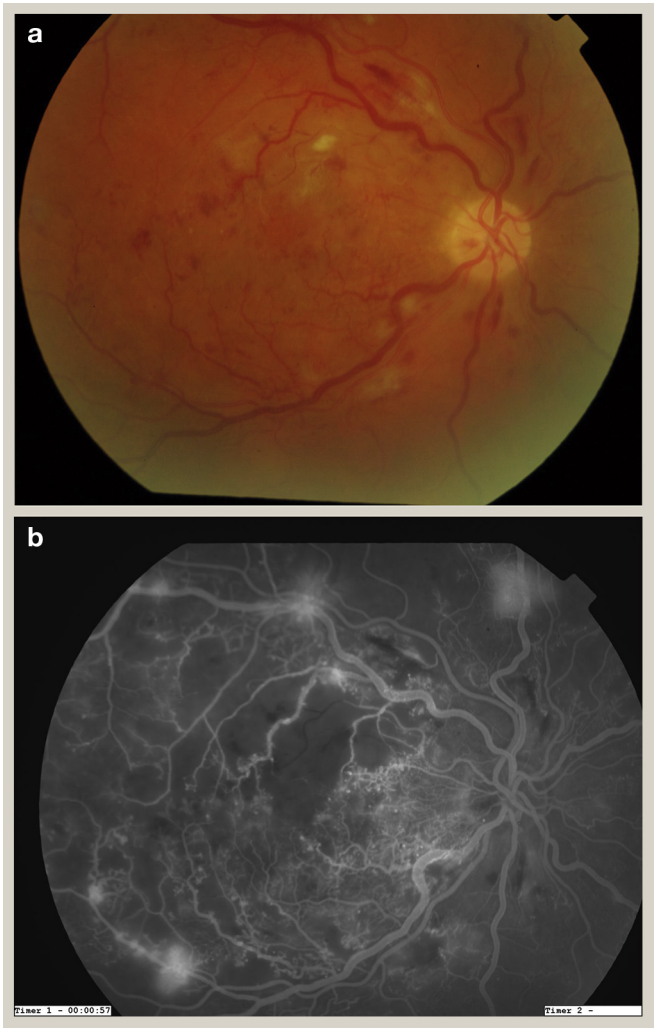

Figure 4 (**a**) Flame haemorrhages, cotton wool spots, IRMA and blot haemorrhages. (**b**) A mid-phase fluorescein angiogram showing IRMA ischaemic areas and early leakage from NVEs.

- NVE equalling more than half a disc area, with haemorrhage (from the NVEs).

Untreated, eyes with high-risk characteristics had a 25.6 −36.9% chance of severe visual loss within 2 years.

Eyes with proliferative DR without high-risk characteristics showed the following risks of severe visual loss:

- untreated − 7.0% at 2 years, and 20.9% at 4 years
- treated − 3.2% at 2 years, and 7.4% at 4 years.

If a vitreous haemorrhage obscures the retinal view, it is usual to perform an ultrasound B-scan to check that the retina is flat. The vitreous haemorrhage often clears within 1 month, making laser treatment possible.

The adverse effects of laser treatment, particularly cystoid macular oedema and peripheral field loss related to laser treatment (as opposed to the disease process), have reduced since the early studies. Hence there has been an increasing tendency to treat eyes with proliferative DR and low-risk characteristics.

Advances in laser treatment have seen the introduction of multispot lasers, which allow multiple burns to be applied with

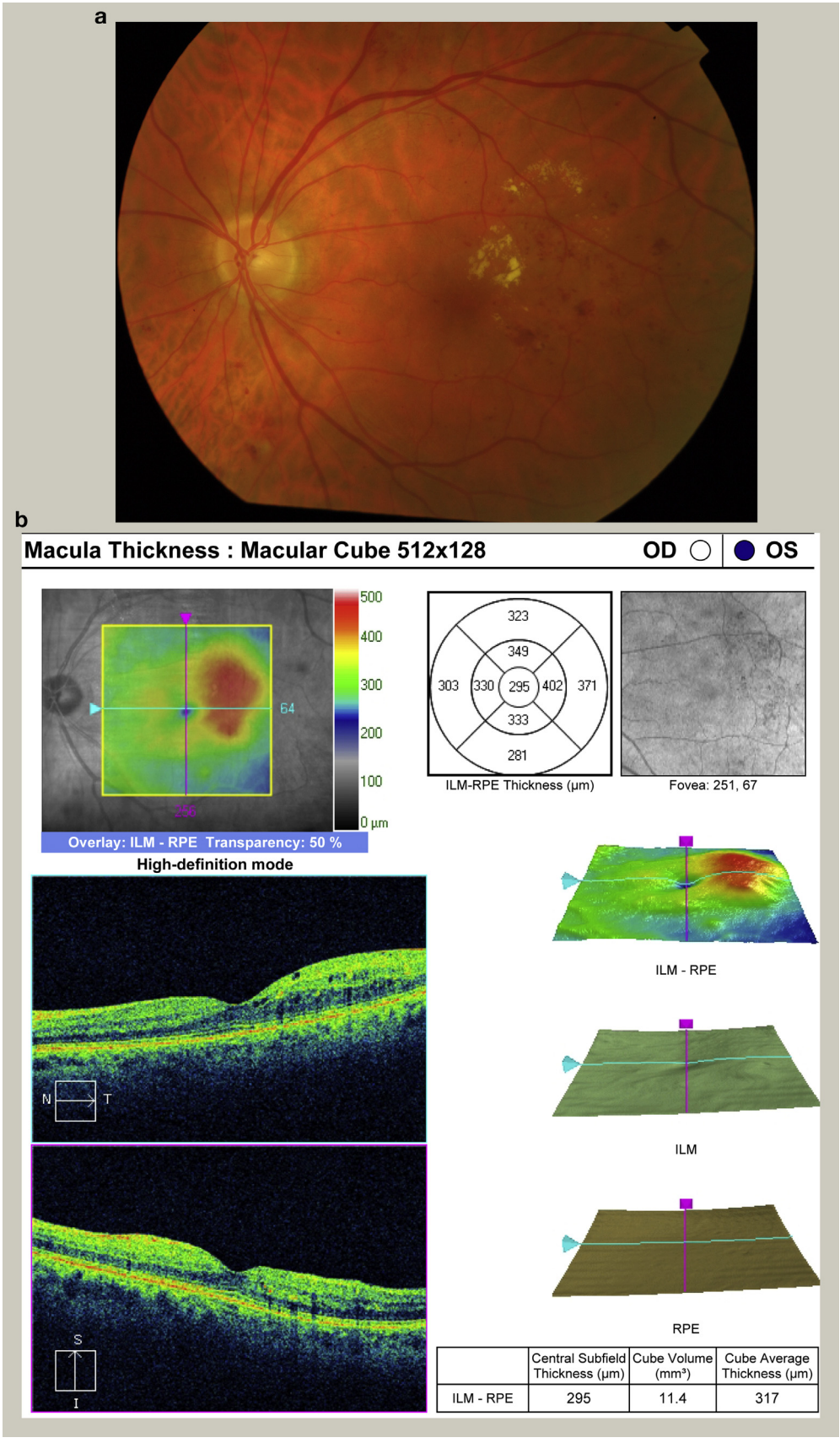

Figure 5 (**a**) Exudates in focal maculopathy. (**b**) OCT of the left macular area from (**a**).

one depression of the foot pedal. Multispot lasers have the advantages of increased uniformity and precision of spot placement, reduced discomfort felt by the patient (probably related to the reduced burn duration) and reduced overall treatment time.

However, for the first time since 1976 an alternative treatment is being suggested — regular injections of vascular endothelial growth factor (VEGF) inhibitors. A study by the Diabetic Retinopathy Clinical Research Network assessed the non-inferiority of intravitreal ranibizumab compared with PRP for visual acuity outcomes in patients with proliferative DR.[2] Among eyes with proliferative DR, treatment with ranibizumab resulted in visual acuity that was no worse than with panretinal photocoagulation (PRP) treatment at 2 years. A study from the UK found that patients with proliferative DR who were treated with intravitreal aflibercept had an improved outcome at 1 year compared with those treated with PRP standard care.[3] However, the long-term requirements of a large number of injections to maintain this benefit and the economic costs are currently unknown, so PRP continues to be standard care for proliferative DR.

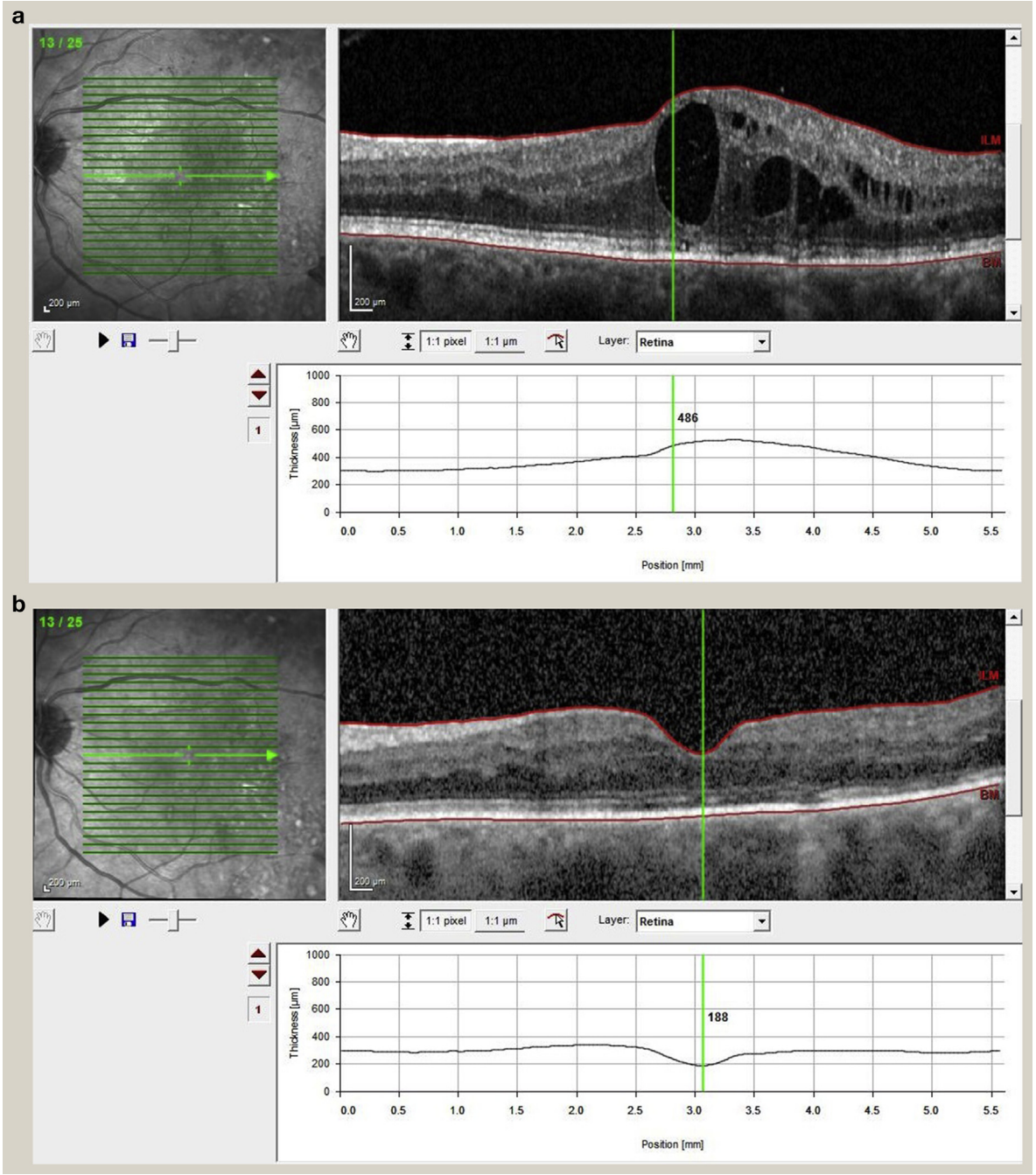

Figure 6 (**a**) Before treatment with a VEGF inhibitor, showing central oedema and a visual acuity of 6/24. (**b**) After treatment with a VEGF inhibitor, showing a normal appearance after clearing of central oedema; the visual acuity improved to 6/9.

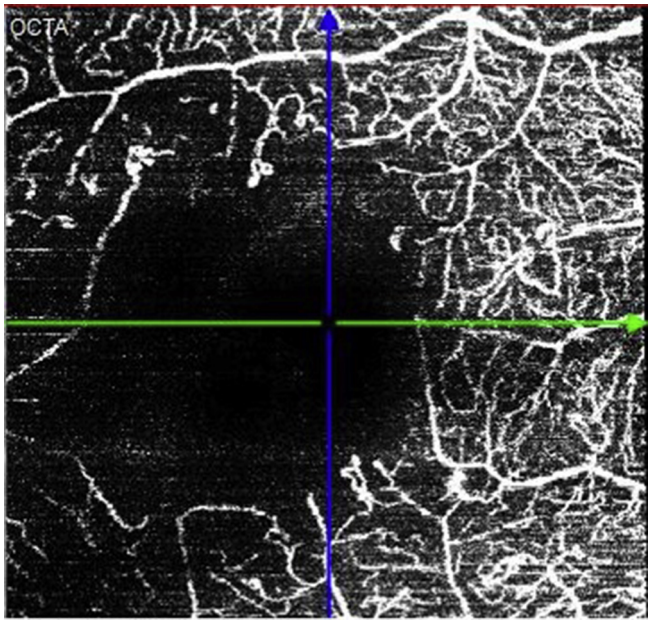

Figure 7 This patient's vision has dropped to 6/18 and she is complaining of blurred central vision. OCTA shows a poor blood supply in the macular area consistent with diabetic macular ischaemia.

Maculopathy

Diabetic maculopathy can be classified into the following types:

- focal (subdivided into focal exudates and focal/multifocal oedema)
- diffuse
- ischaemic.

In focal maculopathy, focal leakage tends to occur from microaneurysms, often with a circinate pattern of exudates around the focal leakage.

In the diffuse variety, there is a generalized breakdown of the blood–retina barrier and profuse early leakage from the entire capillary bed of the posterior pole, sometimes accompanied by cystoid macular changes.

In ischaemic maculopathy, enlargement of the foveal avascular zone caused by capillary closure is found, with variable degrees of visual loss.

Optical coherence tomography (OCT) is widely used in the assessment and monitoring of patients with diabetic macular oedema. It is an imaging technique that interprets the 'time of flight' and intensity of reflected optical waves using interferometry (Figure 5). As a result of the high level of resolution, OCT is particularly suitable for retinal thickness measurements, offering penetration to approximately 2–3 mm with micrometre-scale axial and lateral resolution.

The ETDRS reported that focal photocoagulation of 'clinically significant' diabetic macular oedema substantially reduced the risk of visual loss. Clinically significant' macular oedema was defined as:

- thickening of the retina at or within 500 micrometres of the centre of the macula
- hard exudates at or within 500 micrometres of the centre of the fovea, if associated with thickening of the adjacent retina (not residual hard exudates remaining after the disappearance of retinal thickening)
- a zone or zones of retinal thickening one disc in area or larger, any part of which is within one disc diameter of the centre of the macula.

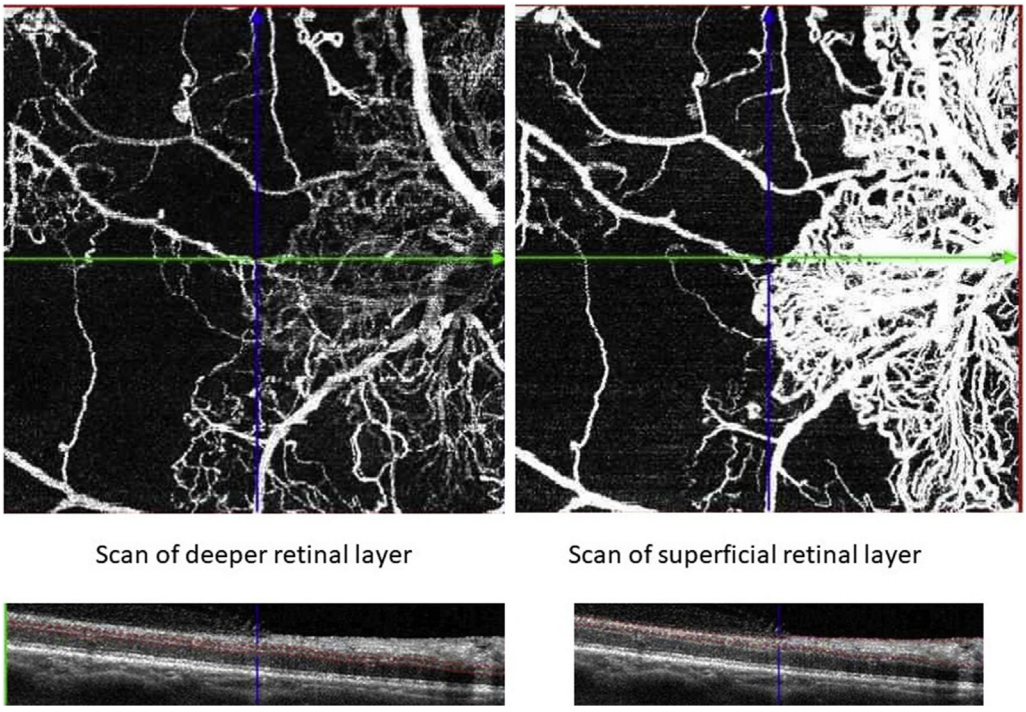

Figure 8 NVE in the supero-temporal area of the retina in a 26-year-old man. Superficial and deep OCTA demonstrates ischaemic areas with a poor vascular supply peripheral to the neovascular complex.

Treatment of diabetic maculopathy with VEGF inhibitors

Ocular neovascularization (angiogenesis) and increased vascular permeability have been associated with VEGF, which has provided a therapeutic rationale for targeting of VEGF DR.

Drugs have been developed that are given intravitreally, with an effect that lasts for approximately 1 month; therefore injections should be given as a course. There were concerns that, as VEGF has neuroprotective effects, there might be neurological or cardiovascular adverse effects with significant systemic absorption of anti-VEGF agents; however, these concerns do not appear to have been borne out in any trials or subsequent product evaluations. The main concern of any intravitreal treatment is the risk of endophthalmitis (infection being introduced into the eye at the time of the intravitreal injection; 0.04–0.06 per injection). There may also be a sustained elevation of intraocular pressure, which occurred in 9.5% of patients compared with 3.4% in a control group.

In England, National Institute for Health and Care Excellence guidelines restrict this treatment to patients with a disc centre thickness of 400 micrometres or more. A number of studies have shown that this treatment is beneficial in diabetic maculopathy when ranubizumab,[4] aflibercept[5] or the off-label bevucizumab is used. In diabetic maculopathy, there tends to be a reduction in treatment frequency required over time, with an average of 7–9 anti-VEGF injections being required in the first year, 2–4 in the second year, 1–3 in the third year and approximately one injection per year in years 4 and 5.

It has been shown that inflammation plays a significant role in the development of macular oedema in some patients with diabetes. Dexamethasone implants, which last for approximately 3 months, are often given to patients who do not respond to VEGF inhibitors and are pseudophakic. If these are successful without significant elevation of the intraocular pressure, a longer lasting fluocinolone acetonide implant is available. The response to treatment varies, with some patients responding well, some responding slowly and some not at all. An example of a patient who responded after only one treatment is shown in Figure 6.

Advances in OCT have seen the development of non-invasive, dye-free angiography – OCT angiography (OCTA). Fluorescein angiography previously involved the intravenous injection of fluorescein, which is associated with a very small risk of anaphylaxis. Fluorescein angiography delineated the vasculature as the fluorescein appeared in the choroidal, arterial, arteriovenous and venous phases, and fluorescein leakage from blood vessels was apparent. OCTA, however, detects movement of blood cells within retinal vasculature and does not detect leakage. Therefore apparent absence of a blood vessel on OCTA can just represent slow blood flow, and reading OCTA is very different from reading fluorescein angiograms. Examples of OCTA are shown in Figures 7 and 8. ◆

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FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 24-year-old woman presented with a 2-hour history of a shower of floaters in her right eye and blurring of her right vision that came on after coughing. She was able to see movement, but nothing was clear. She had type 1 diabetes but had been a regular non-attender at clinic appointments and had been running her blood sugars high because in this way she managed to retain a slim figure.

What is the most likely diagnosis?

A. Muscae volitantes
B. Diabetic macular oedema
C. Branch retinal vein occlusion
D. Retinal detachment
E. Vitreous haemorrhage

Question 2

A 45-year-old woman was being reviewed for possible eye complications. She had a 30-year history of type 1 diabetes.

Which one of the following retinal changes is most predictive of proliferative diabetic retinopathy?

A Multiple flame haemorrhages
B Exudates
C Cotton wool spots
D Venous beading
E Microaneurysms

Question 3

A 56-year-old man presented with a 3-week history of decreased vision in the right eye. There was no pain. He had had type 2 diabetes for 20 years.

On clinical examination, the retina appeared normal. Optical coherence tomography angiography examination was performed.

What is this technique most likely to demonstrate?

A. Whether blood vessels are present
B. Whether there is a reasonable flow of blood within a vessel
C. Whether there is leakage from a vessel
D. Whether haemorrhages are present
E. Whether diabetic macular oedema is present