Keypoints

- In the Wisconsin study [1], proliferative diabetic retinopathy (PDR) occurred in 67% of persons with type 1 diabetes mellitus (T1DM) for 35 or more years. One would therefore expect that two-thirds of people with T1DM would need laser treatment for PDR during their lifetime.
- In the same study, the 4-year incidence of panretinal photocoagulation was 2.5 times higher than the rate of macular laser.
- In patients with type 2 diabetes mellitus (T2DM), the rate of PDR is not as high but it is estimated that 1 in 3 patients with T2DM will develop sight-threatening diabetic retinopathy requiring laser during their lifetime.
- The prevalence of blindness is influenced by duration of diabetes, blood glucose and blood pressure control, and by the presence or absence of screening and preventive laser treatment.
- Achieving a high compliance as achieved in Iceland [2] can lower the risk of blindness to very low levels.

Introduction – a historical perspective

In 1877, Mackenzie and Nettleship [3], in one of the first pathologic reports on diabetic retinopathy (DR), observed capillary aneurysms. In 1900, the average life expectancy for men was 48.5 years and for women was 52.4 years and this rose over the next century to 76.0 years for men and 80.6 years for women. In 1921, Banting and Best discovered insulin in the laboratory of Dr. J. MacLeod. In 1923, Banting and MacLeod were awarded the Nobel Prize for Medicine. In 1943, Ballantyne and Loewenstein [4] examining flat unstained retinas, noted many capillary aneurysms and they first coined the phrase “diabetic retinopathy.” In 1953, Ashton [5] described changes in the arterioles in DR, studied in retinas removed postmortem. Examples of the Indian ink preparations published in his article [5] written in 1953 are shown in Figure 36.1.

The normal eye

The eye is an approximate globe with the innermost surface of the eye, the retina, containing specialized photoreceptor cells (Figure 36.2).

The central foveal region is thinner and is devoid of retinal blood supply; essential supply is provided through diffusion from the capillaries of the innermost vascular layer of underlying choroid through contact with the retinal pigment epithelium. The majority of the retina is provided with oxygen by means of the retinal vascular circulation (Figure 36.3).

The blood vessels in the retina exhibit tight junctions between adjacent cells maintaining the blood–retinal barrier. The normal structure of retinal vessels is shown in Figure 36.4.

The cells of the choroidal circulation have small gaps (fenestrations) between the cells in the walls of smaller choroidal vessels allowing transport of essential nutrients and other small molecules and hence support the nutrition and oxygenation of the foveal region through the retinal pigment epithelium.

Risk factors for diabetic retinopathy

Major international epidemiologic trials have established that the development of DR is related to the following modifiable and non-modifiable risk factors.

Modifiable risk factors

Blood glucose

Evidence for the link between poor glucose control and greater progression of DR was provided by numerous early studies.

The study that confirmed that intensive blood glucose control reduces the risk of new onset DR and slows the progression of existing DR for patients with type 1 diabetes mellitus (T1DM) was the Diabetes Control and Complications Trial (DCCT) [6]. In the DCCT [7], early worsening of DR was reported at the 6- and/or 12-month visit in 13.1% of patients assigned to intensive
Figure 36.1 Diabetic retinopathy showing an artery on the left and vein on the right. Hemorrhages and microaneurysms are present; in the center of the picture they are seen on an arteriole. The arteriolar side of the circulation is extensively atrophied. Injected Indian ink. Periodic acid–Schiff stain ×44. Reproduced from Ashton N. Arteriolar involvement in diabetic retinopathy. Br J Ophthalmol 1953; 37:282–292.

Figure 36.3 (a) This figure shows a retinal structure cross-section diagram. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. A Practical Manual of Diabetic Retinopathy Management. Published 2009 by Blackwell Publishing. (b) A histologic section showing the ganglion cell layer, the bipolar layer, the nuclei of the cones and rods, the pigment epithelium, Bruchs membrane and choroids vessels. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. A Practical Manual of Diabetic Retinopathy Management. Published 2009 by Blackwell Publishing.

Figure 36.4 An inner layer of endothelial cells is enclosed by a tube of basement membrane, which in turn is surrounded by pericytes.
treatment; however, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening.

Similarly, for type 2 diabetes (T2DM) the UK Prospective Diabetes Study (UKPDS) [8] demonstrated that intensive blood glucose control reduces the risk of new onset DR and slows the progression of existing DR for patients with T2DM.

**Blood pressure**
Control of systemic hypertension has been shown to reduce the risk of new onset DR and slow the progression of existing DR [9,10].

**Lipid levels**
There is evidence that elevated serum lipids are associated with macular exudates and moderate visual loss; partial regression of hard exudates may be possible by reducing elevated lipid levels [11,12].

**Smoking**
There is some evidence that smoking may be a risk factor in the progression of DR in T1DM as described by Muhlhauser et al. [13] and Karamanos et al. [14]; however, in T2DM the evidence is controversial.

**Non-modifiable risk factors**

**Duration**
The major non-modifiable determinant of progression of DR is duration of diabetes [15,16].

**Age**
There is a rather complex link with age, with the Wisconsin Epidemiological Study [1,17,18] demonstrating that in those whose age of diagnosis was less than 30 years and who had diabetes of 10 years’ duration or less, the severity of retinopathy was related to older age at examination, whereas when the age at diagnosis was 30 years or more, the severity of retinopathy was related to younger age at diagnosis. In the UKPDS [19], in those who already had retinopathy, progression was associated with older age.

**Genetic predisposition**
Early studies of identical twins with diabetes suggest familial clustering of DR. An association between severity of DR and human leukocyte antigens has been suggested in a number of studies [20,21], although this has not been uniformly accepted [22]. The majority of candidate genes studied exhibit weak or no association with retinopathy status, and where associations have been detected these results have not been replicated in multiple populations.

**Ethnicity**
Emanuele et al. [23] reported a higher prevalence of DR scores >40 in Latin Americans (36%) and African-Americans (29%) than for whites of Northern European ancestry (22%). Simmons et al. [24] compared ethnic differences in the prevalence of DR in European, Maori and Pacific peoples with diabetes in Auckland, New Zealand. They demonstrated that moderate or more severe DR is more common in Polynesians than Europeans. In neither of these two studies could the differences be accounted for by an imbalance in traditional risk factors such as age, duration of diagnosed diabetes, HbA1c, and blood pressure.

**Pathophysiologic events in diabetic retinopathy**

**Basement membrane thickening**
An early histopathologic sign of DR is thickening of the basement membrane (Figure 36.5) [25].

**Pericyte loss**
Fallout of pericytes, which are sensitive to high glucose concentrations and undergo apoptosis [26], is an early and crucial event
Diabetic Retinopathy  Chapter 36

Retinal blood flow
Most clinical hemodynamic studies in diabetes conclude that increased blood flow and impaired autoregulation are features of DR [30]. Persistent dilatation of retinal arterioles is a well-known phenomenon in diabetes [31]. As DR progresses, increasingly large and widespread areas of retinal ischemia develop, caused by capillary occlusion and intravascular coagulation, which is considered to be enhanced by increased platelet stickiness in some studies [32], but not others [33].

The consultation
A carefully taken history and high quality clinical examination is a vital component of the care of any patient with DR.

Practical assessment
• History, which includes past ocular, diabetes, medical, family, drug and psychosocial history.
• Eye examination, which includes assessment of visual acuity and, where appropriate, color vision, inspection of external structures, visual fields to confrontation, ocular movement, pupillary reactions to light and accommodation, red reflex with an ophthalmoscope and slit-lamp biomicroscopy of the anterior eye.
• Both pupils are dilated with 1% tropicamide and in many patients 2.5% phenylephrine as well.
• Direct ophthalmoscopy has a limited two-dimensional field of view and has been shown to have a limited sensitivity and specificity for the detection of sight-threatening DR but is useful for ad hoc detection of DR.
• Slit-lamp biomicroscopy of the retina is the most common method employed by ophthalmologists to diagnose and monitor retinal disease using condensing lenses or fundus contact lenses (contact lens biomicroscopy).
• Binocular indirect ophthalmoscopy is useful for evaluating the posterior segment and retinal periphery. A larger area can be viewed than with slit-lamp biomicroscopy but this view is less magnified.

Multidisciplinary management
It is very important for an ophthalmologist to be aware of the control of risk factors in the individual patient and to have good communication with the diabetic physician or general practitioner who is looking after this aspect of the patient’s management.

Investigative techniques to assess diabetic retinopathy

Retinal photography
Digital color retinal photography is increasingly being used as a record of retinal lesions.

Fundus fluorescein angiography
This is a diagnostic procedure, when sodium fluorescein injection is given rapidly into the arm and the fluorescence of the dye in
Perimetry
Perimetry is the systematic measurement of differential light sensitivity in the visual field by the detection of the presence of test targets on a defined background in order to map and quantify the visual field, normally testing each eye independently but binocularly for driving field assessment.

Screening for diabetic retinopathy

The definition of screening that was adapted by the World Health Organization (WHO) [34] in 1968 was “the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with pos-
The costs of screening and effective treatment of sight-threatening DR balance economically in relation to total expenditure on health care [47–50], including the consequences of leaving the disease untreated.

Lesions and classifications of diabetic retinopathy

Microaneurysms and retinal hemorrhages

The lesions that the Early Treatment Diabetic Retinopathy Study (ETDRS) (Table 36.1) [51] described as critical to the stages of progression of DR were:

- **Microaneurysms** – a microaneurysm is defined as a red spot <125 μm (approximate width of vein at disc margin) and sharp margins.
- **Small retinal hemorrhages** – a hemorrhage is defined as a red spot, which has irregular margins and/or uneven density, particularly when surrounding a smaller central lesion considered to be a microaneurysm.
Figure 36.9  An example of the venous phase of a fluorescein angiogram showing small hemorrhages (dark), microaneurysms fluorescing, some of which are leaking shown by the fluffy edge.

Figure 36.11  An example of exudates in the right macular area.


- **Hemorrhage/microaneurysm (HMa)** – because the ETDRS recognized that it was very difficult to differentiate between microaneurysms and small hemorrhages, the concept of HMa was introduced, which is a small hemorrhage or microaneurysm (Figure 36.9).

- **Flame hemorrhages** – superficial hemorrhages just under the nerve fiber layer (Figure 36.10).

- **Blot hemorrhages** – deeper hemorrhages, which are a sign of retinal ischemia in the area of the retina in which they occur.

**Hard exudates**

Hard exudates (sometimes now just referred to as exudates) are defined as small white or yellowish-white deposits with sharp margins, located typically in the outer layers of the retina, but they may be more superficial, particularly when retinal edema is present (Figure 36.11).

**Cotton wool spots**

Cotton wool spots (referred to as soft exudates in the ETDRS, but this term is now rarely used) are fluffy white opaque areas caused by an accumulation of axoplasm in the nerve fiber layer of the retina, which is caused by an arteriolar occlusion in that area of retina that is apparent on a fluorescein angiogram (Figure 36.12).
Intraretinal microvascular abnormalities
IRMA are defined as tortuous intraretinal vascular segments, varying in caliber, derived from remodeling of the retinal capillaries and small collateral vessels in areas of microvascular occlusion and are therefore a sign of retinal ischemia (Figure 36.13).

Venous abnormalities
- *Venous loops* – abrupt curving deviations of a vein from its normal path (Figure 36.14).
- *Venous beading* – in the ETDRS, venous beading is described as a localized increase in caliber of the vein and the severity is dependent on the increase in caliber and the length of vein involved. It is associated with retinal ischemia (Figure 36.15).

  Other venous changes that occur in DR are as follow:
  - Venous dilatation;
  - Venous narrowing;
  - Opacification of the venous wall; and
  - Perivenous exudate.

Arteriolar abnormalities
Other arteriolar changes that occur in DR are as follow:
- Arteriolar narrowing;
- Opacification of arteriolar walls; and
- Arteriovenous nipping.

Fibrous proliferation at the disc
Fibrous proliferation at the disc (FPD) usually occurs when new vessels at the disc start to regress and fibrosis occurs.

Fibrous proliferation elsewhere
Fibrous proliferation elsewhere (FPE) usually occurs when new vessels elsewhere start to regress and fibrosis occurs.

New vessels on and/or within 1 disc diameter of the disc
For new vessels on and/or within 1 disc diameter (DD) of the disc (NVD), see Figure 36.16.

New vessels elsewhere
For new vessels elsewhere (NVE), see Figure 36.17.

Vitreous hemorrhage
Vitreous hemorrhage (VH) is a hemorrhage that is in the vitreous gel.

Preretinal hemorrhage
Preretinal hemorrhages (PRH) are boat-shaped hemorrhages and roughly round, confluent or linear patches of hemorrhage just anterior to the retina or under the internal limiting membrane (Figure 36.18).
Maculopathy

Clinical classification of diabetic maculopathy
Diabetic maculopathy may be classified into focal (subdivided into focal exudates and focal/multifocal edema), diffuse and ischemic diabetic maculopathy (Tables 36.2 and 36.4).

Pathophysiology of macular edema
In focal macular edema, focal leakage tends to occur from microaneurysms, often with extravascular lipoprotein in a circinate pattern around the focal leakage [57].

In diffuse macular edema, there is a generalized breakdown of the blood–retina barrier and profuse early leakage from the entire capillary bed of the posterior pole [58] causing extracellular fluid accumulation, often accompanied by cystoid macular edema [57], which is caused by cellular swelling. In ischemic maculopathy, enlargement of the foveal avascular zone as a result of capillary closure is found.

The fluorescein angiographic appearance
In diabetic maculopathy, most leakage occurs in the venous phase of the angiogram and hence examples of venous phase angiograms are shown in Figure 36.20.

Post laser treatment
Photocoagulation laser scars may be seen both after macular or panretinal laser treatment (Figure 36.19; Tables 36.1–36.4).

Optical coherence tomography
An example of diabetic maculopathy is shown in Figure 36.21. Macular traction can occur from contracture of fibrotic proliferations, particularly as new vessels regress after panretinal photocoagulation, and also from a taut posterior hyaloid. If macular traction is severe, surgical intervention is required (Figure 36.22).

Laser treatment for diabetic maculopathy
In 1985, the ETDRS [59] demonstrated that focal (direct/grid) laser photocoagulation reduces moderate vision loss caused by
Table 36.1 Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group diabetic retinopathy classification of progression to proliferative diabetic retinopathy based on 7 × 30° field stereo photographs of each eye.

<table>
<thead>
<tr>
<th>ETDRS final Retinopathy Severity Scale</th>
<th>ETDRS (final) grade</th>
<th>Lesions</th>
<th>Risk of progression to PDR in 1 year (ETDRS Interim)</th>
<th>Practical clinic follow-up intervals (not ETDRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>10</td>
<td>DR absent</td>
<td>Level 30 = 6.2%</td>
<td>1 year</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>14, 15</td>
<td>DR questionable</td>
<td>Level 30 = 6.2%</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Microaneurysms only</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>One or more of the following:</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>Venous loops ≥ definite in 1 field</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>SE, IRMA, or VB questionable</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>Retinal hemorrhages present</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>HE ≥ definite in 1 field</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td></td>
<td>e</td>
<td>SE ≥ definite in 1 field</td>
<td>Level 41 = 11.3%</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>43a</td>
<td>H/Ma moderate in 4–5 fields or severe in 1 field or IRMA definite in 1–3 fields</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>IRMA definite in 1–3 fields</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td>Moderately severe NPDR</td>
<td>47</td>
<td>Both level 43 characteristics – H/Ma moderate in 4–5 fields or severe in 1 field and IRMA definite in 1–3 fields</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>IRMA in 4–5 fields</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>H/Ma severe in 2–3 fields</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>VB definite in 1 field</td>
<td>Level 41 = 11.3%</td>
<td>6 months</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>53</td>
<td>One or more of the following:</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>≥2 of the 3 level 47 characteristics</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>H/Ma severe in 4–5 fields</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>IRMA ≥ moderate in 1 field</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>VB ≥ definite in 2–3 fields</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td>Mild PDR</td>
<td>61a</td>
<td>FPD or FPE present with NVD absent or NVE = definite</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>NVE = definite</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td>Moderate PDR</td>
<td>65a</td>
<td>1 NVE ≥ moderate in 1 field or definite NVD with VH and PRH absent or questionable or</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>2 VH or PRH definite and NVE &lt; moderate in 1 field and NVD absent</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td>High risk PDR</td>
<td>71</td>
<td>Any of the following:</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>1 VH or PRH ≥ moderate in 1 field</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>2 NVE ≥ moderate in 1 field and VH or PRH definite in 1 field</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>3 NVD = 2 and VH or PRH definite in 1 field</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>4 NVD ≥ moderate</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td>High risk PDR</td>
<td>75</td>
<td>NVD ≥ moderate and definite VH or PRH</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
<tr>
<td>Advanced PDR</td>
<td>81</td>
<td>Retina obscured due to VH or PRH</td>
<td>Level 51 = 44.2%</td>
<td>3 months</td>
</tr>
</tbody>
</table>

DD, disc diameter; DR, diabetic retinopathy; HE, hard exudate; HMa, small hemorrhage or microaneurysm; IRMA, intraretinal microvascular abnormality; NPDR, non-proliferative DR; NVD, new vessels on disc; NVE, new vessels elsewhere; PDR, proliferative diabetic retinopathy; PRH, preretinal hemorrhage; SE, soft exudate, a term that has now been replaced by cotton wool spot; VB, venous beading; VH, vitreous hemorrhage.

Table 36.2 Early Treatment Diabetic Retinopathy Study (ETDRS) maculopathy classification.

<table>
<thead>
<tr>
<th>ETDRS</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant macular edema [54] as defined by:</td>
<td>Consider laser</td>
</tr>
<tr>
<td>• A zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula</td>
<td>Consider laser</td>
</tr>
<tr>
<td>• Retinal thickening at or within 500μm of the center of the macula</td>
<td>Consider laser</td>
</tr>
<tr>
<td>• Hard exudates at or within 500μm of the center of the macula, if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening)</td>
<td>Consider laser</td>
</tr>
</tbody>
</table>

Because of the difficulty in correlating 7 field stereo-photography to the clinical setting, two further simplified classifications have been developed (International Classification and the English Screening Classification).
Table 36.3 International and English retinopathy classifications.

<table>
<thead>
<tr>
<th>International clinical classification of diabetic retinopathy severity or diabetic macular edema [55]</th>
<th>Recommended International outcome</th>
<th>English Screening program levels [56] and recommended outcome</th>
</tr>
</thead>
</table>
| Microaneurysms only | Optimize medical therapy, screen at least annually | R0: no DR
Outcome: currently screen annually |
| More than just microaneurysms but less severe than severe NPDR | Refer to ophthalmologist | R1: background DR
Microaneurysm(s)
Retinal hemorrhage(s) ± any exudate
Outcome: currently screen annually |
| Severe NPDR | Consider scatter photocoagulation for T2DM | R2: preproliferative DR
venous beading
venous loop or reduplication
IRMA, multiple deep, round or blot hemorrhages
Outcome: refer to ophthalmologist |
| Any of the following: (a) Extensive intraretinal hemorrhage (>20) in 4 quadrants (b) Definite venous beading in 2+ quadrants (c) Prominent IRMA in 1+ quadrant and no signs of PDR | | |
| Neovascularization Vitreous/preretinal hemorrhage | Scatter Photocoagulation without delay for patients with vitreous hemorrhage or neovascularization within 1 DD of the optic nerve head | R3: proliferative
NVD
NVE
Preretinal or vitreous hemorrhage
Preretinal fibrosis ± tractional retinal detachment
Outcome: urgent referral to ophthalmologist |

DD, disc diameter; DR, diabetic retinopathy; IRMA, intraretinal microvascular abnormality; NPDR, non-proliferative DR; NVD, new vessels on disc; NVE, new vessels elsewhere; PDR, proliferative diabetic retinopathy.

Figure 36.19 (a,b) Right macular and nasal views following panretinal photocoagulation to show laser treatment scars in the superior, inferior, temporal and nasal retina.
**Table 36.4** International and English maculopathy classification.

<table>
<thead>
<tr>
<th>International classification [55]</th>
<th>Outcome</th>
<th>English classification [56]</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Diabetic macular edema present as defined by some retinal thickening or hard exudates in the posterior pole and subclassified into:  
Mild diabetic macular edema: Some retinal thickening or hard exudates in the posterior pole but distant from the macula | Referral | Circinate or group of exudates within the macula (The macula is defined as that part of the retina that lies within a circle centered on the fovea whose radius is the distance between the center of the fovea and the temporal margin of the disc) Any microaneurysm or hemorrhage within 1 DD of the center of the fovea only if associated with a best VA of ≤6/12 (if no stereo) | Referral |
| Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center | Referral | Exudate within 1 DD of the center of the fovea | Referral |
| Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula | Referral | Retinal thickening within 1 DD of the center of the fovea (if stereo available) | Referral |

DD, disc diameter; VA, visual acuity.

Figure 36.21 (a) Venous phase fluorescein angiogram showing leakage superotemporal to the macula. (b) Cross-sectional optical coherence tomography (OCT) image showing clinically significant macular edema. (c) Topographic map superimposed on red free photograph. (d) Topographic map of clinically significant macular edema.

changes and the application of Starling’s law and improved oxygenation.

Adverse effects of macular laser treatment
Potential side effects specific to macular laser are:
- Laser close to the central fovea, resulting in a drop in visual acuity. Laser burns may be associated with paracentral scotomas and may become larger than the original spot size and encroach on fixation.
- Choroidal neovascular membrane developing in an area that has received laser treatment – this complication is extremely rare.

Intravitreal triamcinolone
Promising results in the short term for improving the vision in eyes with chronic diabetic macular edema unresponsive to conventional laser treatment, reducing macular thickness and induc-

Figure 36.23 (a) Focal maculopathy pretreatment. (b) Focal maculopathy immediately after treatment showing blanching from laser treatment. (c) Focal maculopathy 6 months after treatment showing clearing of the exudate.

diabetic maculopathy edema by 50% or more. It also described “clinically significant macular edema,” which defined the parameters for treatment as:
- Thickening of the retina at or within 500μm of the center of the macula;
- Hard exudates at or within 500μm of the center of the fovea, if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening);
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 DD of the center of the macula (Figure 36.23).

Mechanisms of action of laser for macular edema
The effectiveness of focal laser treatment may be caused, in part, by the closure of leaky microaneurysms. Other methods suggested have been histopathologic changes and the application of Starling’s law and improved oxygenation.

Adverse effects of macular laser treatment
Potential side effects specific to macular laser are:
- Laser close to the central fovea, resulting in a drop in visual acuity. Laser burns may be associated with paracentral scotomas and may become larger than the original spot size and encroach on fixation.
- Choroidal neovascular membrane developing in an area that has received laser treatment – this complication is extremely rare.

Intravitreal triamcinolone
Promising results in the short term for improving the vision in eyes with chronic diabetic macular edema unresponsive to conventional laser treatment, reducing macular thickness and induc-
Part 7  Microvascular Complications in Diabetes

...ing reabsorption of hard exudates, have been described in numerous studies [64–67]. The effects are reported to last for 3–8 months, which may be partially dependent on the dose given, varying between 1 and 25 mg.

Serious side effects, however, have been reported such as early rapid increases in intraocular pressure requiring surgical intervention [68] and infectious endophthalmitis [69]. Randomized controlled trials utilizing varying doses of steroid are now required to assess the long-term efficacy, safety and to define optimum treatment regimens.

Vascular endothelial growth factor treatments
For anti-vascular endothelial growth factor (anti-VEGF) treatments, see the section on the use of intravitreal vascular endothelial growth factor inhibitors later in this chapter.

Mild non-proliferative diabetic retinopathy (ETDRS & International) and background diabetic retinopathy (English Screening)

The earliest sign of mild non-proliferative DR (mild NPDR) or background DR is microaneurysms.

Microaneurysms
Patients with no DR and microaneurysms only were not included in the ETDRS study. In the Wisconsin Epidemiological Study of Diabetic Retinopathy, the rate of progression to proliferative retinopathy 4 years after the initial evaluation showed “no DR” was 0.4% for young patients <30 years with T1DM, 0% for older patients ≥30 years with diabetes taking insulin and 0.6% for those not using insulin. For those with microaneurysms or one hemorrhage in one eye only, the rate of progression to proliferative retinopathy 4 years after the initial evaluation was 3.0% for young patients <30 years with T1DM, 0% for older patients ≥30 years with T1DM and 1.5% for those not using insulin.

The other signs of mild NPDR are one or more of the following:

• Retinal hemorrhages. In mild NPDR, retinal hemorrhages are usually small dot hemorrhages or flame-shaped hemorrhages (Figures 36.9 and 36.10). Because small retinal hemorrhages can be difficult to differentiate from microaneurysms they are commonly referred to as HMa.
• Exudates (or hard exudates) are a feature of mild NPDR (Figure 36.11).
• Cotton wool spots may be present in mild NPDR or background DR but are caused by an arteriolar occlusion in that area of retina, but despite this being the underlying cause, they are not a good sign of increasing retinal ischemia. They are often associated with hypertension (Figure 36.12).
• A single venous loop. The ETDRS included a single venous loop in their classification of mild NPDR; however, this rarely occurs in isolation without other significant signs of retinal ischemia and a venous loop is therefore not a feature of the English Screening definition of background DR (Figure 36.14).

For mild NPDR, there is a 6.2% risk of progression to proliferative retinopathy within 1 year.

The International classification of DR recommends that anyone who has a more severe disorder than microaneurysms is referred to an ophthalmologist [55]. In the UK, patients who are screened and who show signs of background DR are only rescreened annually. For the purposes of the English National Screening Programme, background DR is defined by the following lesions [56]:

• Microaneurysm(s); and
• Retinal hemorrhage(s) with or without any exudate (Figure 36.24).

Moderate and severe non-proliferative diabetic retinopathy (ETDRS & International) and pre-proliferative diabetic retinopathy (English Screening)

The main features that warrant classifying a DR level in the higher levels of moderate and severe NPDR [55] (or pre-proliferative DR [56]) are increasing signs of retinal ischemia.

Lesions associated with increasing retinal ischemia:

• Retinal hemorrhages especially blot hemorrhages (Figure 36.25).
• Intraretinal microvascular abnormality (Figure 36.25). Intraretinal microvascular abnormalities are derived from remodeling of the retinal capillaries and small collateral vessels in
areas of microvascular occlusion. They are usually found on the borders of areas of non-perfused retina.

- Venous beading (VB; Figure 36.25) is found to be associated with retinal ischemia and is used for assessment of severity of DR.

  With increasing ischemia, there is an increasing risk of progression to proliferative in 1 year. The risk increases from approximately 11.3% in the lower levels of moderate NPDR to 54.8% progression to proliferative in 1 year in the most severe NPDR level.

  ETDRS definitions have been simplified to make them easier for everyday clinical use both in the International classification and in the English classification for screening.

  The ETDRS “4:2:1 rule” indicates that the presence of severe hemorrhages in four quadrants (≥20), VB in two quadrants or IRMA in a single quadrant represents this severity of retinopathy, severe NPDR.

  In the International classification, severe NPDR is defined by any of the following:

  - Extensive intraretinal hemorrhages (>20) in four quadrants;
  - Definite VB in two or more quadrants;
  - Prominent IRMA in one or more quadrants, and no signs of PDR.

  Moderate NPDR is classified in the International classification as more than “microaneurysms only” and less severe than the 4:2:1 rule.

  In the English Screening classification, pre-proliferative DR is defined by any of the following:

  - VB;
  - Venous loop or reduplication;
  - IRMA; or
  - Multiple deep, round or blot hemorrhages.

**Proliferative diabetic retinopathy and advanced diabetic retinopathy**

**Pathogenesis of retinal angiogenesis (new vessel formation)**

New vessels arise from the post capillary venule in areas of ischemic retina. New vessel growth originates either within 1 DD of the optic disc (new vessels at the disc [NVD]) or developing from retinal vessels more than 1 DD away from the edge of the optic disc (new vessels elsewhere [NVE]).

The central role of growth factors in retinal neovascularization was suggested as early as 1948 by Michaelson [70], who proposed that a diffusible factor released from the ischemic retina was responsible for angiogenesis. The growth factors that have been extensively studied are fibroblast-derived growth factor (FGDF) [71], insulin-like growth factor 1 (IGF-I) [72], platelet-derived growth factor (PDGF) [73], hepatocyte growth factor (HGF) [74] and VEGF [75]. Another consequence of generalized retinal ischemia can be neovascularization in the anterior chamber on the iris (rubeosis iridis).

**Fluorescein angiographic appearance**

The characteristic appearance of new vessels on the fluorescein angiogram, once they have penetrated the internal limiting membrane, is leakage appearing in the arteriovenous phase of the angiogram (Figure 36.26).

**Presentation**

Some patients present asymptomatically from screening, others with visual loss arising from hemorrhage from new vessels.

**Laser treatment for proliferative diabetic retinopathy**

For laser treatment for proliferative diabetic retinopathy (PDR), see Figure 36.27.
Other possible adverse effects of panretinal laser treatment are as follow:
- Unintended laser absorption (e.g. to the lens) or uptake of laser from a flame-shaped hemorrhage, which may result in a burn and destruction of the nerve fiber layer that lies on its surface.
- Inadvertent coagulation (e.g. to the fovea).
- Choroidal detachment is usually as a result of a large dose of laser treatment being applied in a single session, which usually resolves spontaneously within 10 days.

**Risks to the ophthalmologist**
There has been some concern in the past that the ophthalmologist is exposed to excessive amounts of reflected light, particularly blue light; however, modern technology with appropriate filters has significantly reduced this risk.

**Risks to an observer**
The risk to an observer is extremely small but, as a precaution, it is advised that any observer wears the appropriate spectacle protection.

**Factors other than high risk characteristics influencing the decision to laser**

**Anterior segment neovascularization**
Extensive neovascularization in the anterior chamber angle is an urgent indication for scatter laser photocoagulation, if it is feasible (Figure 36.28).

**Signs of ischemia**
Large IRMA, VB in more than one quadrant, extensive retinal hemorrhages and opaque small arteriolar branches are signs suggesting severe retinal ischemia.
Macular edema
See the section on laser for PDR and concurrent diabetic maculopathy.

Pregnancy
See the section on pregnancy and DR (below).

Renal failure
Treatment needs to coincide with renal dialysis or transplantation. It is also important to control hypertension.

Past history
The past history of retinopathy, both in the eye for which scatter laser photocoagulation and in the fellow eye, needs to be considered.

Duration of the laser burn
There has been an increasing tendency in the last year for operators to reduce the duration of the burn and increase the power to produce an apparently similar mild bleaching because of the clinical impression that this is more comfortable for the patient.

Pattern scan laser
With conventional methods of retinal laser photocoagulation, the ophthalmologist uses a mechanical joystick and foot pedal to deliver single 100-ms laser pulses to the peripheral retina. With the pattern scan laser, the laser pulse time is reduced from 100 ms to just 10–20 ms, and automated multiple spots are produced with each depression of the foot pedal. Higher power is required for shorter burns. Predetermined pattern types can administer up to 25 spots at a time for scatter laser treatment.

Stage R3 with M1: proliferative diabetic retinopathy with maculopathy
The ETDRS [77] compared giving immediate panretinal photocoagulation with either simultaneous or delayed focal treatment. The conclusion was that, where possible, clinically significant macular edema should be treated by applying focal/grid photocoagulation for macular edema before beginning scatter laser treatment. When the risk of vitreous hemorrhage or neovascular glaucoma seems high, combine treatment of clinically significant macular edema by applying focal/grid photocoagulation for macular edema with panretinal photocoagulation to the inferior half of the peripheral retina, followed 2 weeks later by panretinal photocoagulation to the superior half.

Hamilton et al. [78] recommended an exception to this approach for young patients with T1DM who have rapidly accelerating peripheral ischemia associated with macular edema that may resolve following panretinal photocoagulation (Figure 36.29).

Use of intravitreal vascular endothelial growth factor inhibitors
Ocular neovascularization (angiogenesis) and increased vascular permeability have been associated with VEGF, which does also have a neuroprotective effect. There are three potential VEGF inhibitors:
1 Pegaptanib (Macugen);
2 Ranibizumab (Lucentis);
3 Bevacizumab (Avastin).
Ranibizumab (Lucentis) is an antibody fragment derived from bevacizumab (Avastin), which is a full-length humanized monoclonal antibody against human VEGF.

There are reports of reduction in macular thickness using intravitreal injections of these agents [79]; however, the effect does not last and repeated injections would be required to sustain any beneficial effects.

Favorable results have been reported with some regression of neovascularization and reduction in fluorescein leakage in some studies using bevacizumab [80,81] and using pegaptanib [82] but the effect is only transient (2–11 weeks [81]).
Vitreous hemorrhage in 80 patients (86.1%); tractional retinal detachment in three patients (3.2%); and vitreous hemorrhage associated with tractional retinal detachment in 10 patients (10.7%).

Lewis [86] suggested that for clinically significant macular edema, OCT should be performed to test for posterior hyaloid thickening and vitrectomy should be considered when a shallow macular detachment is found. Studies by Okamoto et al. [87] and Emi et al. [88] have shown that vitrectomy is effective in increasing the quality of life of patients with DR (Figure 36.30).

Intravitreal injection is an effective means of delivering anti-VEGF drugs to the retina but has the potential complications of endophthalmitis and retinal detachment. Randomized controlled trials utilizing varying doses of the VEGF inhibitors are required to assess the long-term efficacy, safety and to define optimum treatment regimens.

**Vitrectomy**

Smiddy and Flynn [83] wrote an excellent review where they noted that, according to the ETDRS, at least 5% of eyes receiving optimal medical treatment will still have progressive retinopathy that requires laser treatment and pars plana vitrectomy.

Two recent reports of vitrectomy case series have demonstrated that the most common reason for vitrectomy for DR is vitreous hemorrhage [84,85]. In the latter study, the indications for vitrectomy were:

- Vitreous hemorrhage in 80 patients (86.1%);
- TrACTIONAL retinal detachment in three patients (3.2%); and
- Vitreous hemorrhage associated with tractional retinal detachment in 10 patients (10.7%).

Lewis [86] suggested that for clinically significant macular edema, OCT should be performed to test for posterior hyaloid thickening and vitrectomy should be considered when a shallow macular detachment is found. Studies by Okamoto et al. [87] and Emi et al. [88] have shown that vitrectomy is effective in increasing the quality of life of patients with DR (Figure 36.30).

**Pregnancy and the diabetic eye**

**Risk factors for progression of diabetic retinopathy in pregnancy**

The known risk factors for progression of DR in pregnancy are:
• Pregnancy itself is independently associated with progression of DR [89,90];
• Baseline severity of DR [91–93];
• Poor metabolic control at conception [91];
• Rapid improvement of glycemic control [90–93];
• Poor metabolic control during pregnancy or the early postpartum period [89,90,93,94];
• Duration of diabetes [93,95,96]; and
• Chronic hypertension and pregnancy-induced hypertension [93].

Recommendations for patients

• Plan pregnancies early in life – women with T1DM should be encouraged to plan pregnancies early in life [94].
• Improving metabolic control before conception is recommended both for the mother and infant [91].
• Improving metabolic control during pregnancy is recommended both for the mother and infant [89,90,93,94].
• Control of hypertension both before conception and during pregnancy is recommended both for the mother and infant [93].
• Photocoagulation before conception and during pregnancy [95]. It is recommended that, if a patient is found to have significant retinopathy before conception, pregnancy is delayed where possible until appropriate laser treatment has been applied and good metabolic control has been achieved for a 9-month period to overcome any effects of the early worsening phenomenon [7]. Photocoagulation before pregnancy may protect against rapidly progressive PDR. Aggressive treatment of PDR developing in pregnancy may prevent further progression of the disease.

Low vision and blindness from diabetic retinopathy

In 2001, Cunningham [97] reported that 45 million people worldwide fulfil the WHO criteria for blindness. Twenty-four percent of all blindness, affecting people in both developed and developing nations, is caused by a combination of DR and macular degeneration with a small contribution from other eye diseases. In 2002, Kouc and Resnikoff [36] reported that in people of working age in Europe, DR is the most frequently reported cause of serious visual loss, confirmed in the UK by two studies [98,99].

In 2004, Fong et al. [100] reported that DR is a leading cause of adult blindness in the USA, resulting in blindness for more than 10,000 people per year.

The most progress in reduction of blindness has been made in Iceland [2] where the prevalence of legal blindness from DR dropped from 4.0% to 0.5% over 15 years, beginning in 1980.

References

18 Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year inci-