

Diabetes: Chronic Complications



THIRD EDITION

Edited by Kenneth M. Shaw and Michael H. Cummings

 WILEY-BLACKWELL

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THIRD EDITION

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Contents

Contributors, vii

Preface to Third Edition, ix

- 1 Diabetes and the Eye, 1
Kevin Shotliff and Nigel Davies
- 2 Diabetic Chronic Kidney Disease, 34
Richard J MacIsaac, George Jerums and Gerald F Watts
- 3 Diabetes and the Liver, 67
Lisa Jones and Anna Mae Diehl
- 4 Diabetes and the Gastrointestinal Tract, 83
Zeeshan Ramzan and Henry P Parkman
- 5 Diabetes and Foot Disease, 101
Kate Marsden, Sharon Tuck and Darryl Meeking
- 6 Diabetes and Autonomic Neuropathy, 119
Andrew F Macleod
- 7 Diabetes and Sexual Health, 141
Michael H Cummings
- 8 Diabetes and the Heart, 165
Miles Fisher and Kenneth M Shaw
- 9 Diabetes and the Brain, 190
Iain Cranston
- 10 Diabetes and Mental Health, 214
David P Osborn and Richard IG Holt
- 11 Musculoskeletal Complications of Diabetes Mellitus, 239
Stratos Christianakis, Minh Chau Nguyen and Richard S Panush
- 12 Diabetes and Oral Health, 252
Philip M Preshaw

vi Contents

13 Diabetes and the Skin, 273

Hywel L Cooper, Amita Bansal and Adam E Haworth

14 Diabetes and Cancer, 294

Steven S Coughlin and Edward L Giovannucci

Multiple Choice Questions, 306

Answers, 318

Index, 327

Colour plate section is found facing page 244

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Preface to Third Edition

For the individual person diagnosed with diabetes today, we believe that the prospects of future good health are substantially better than they were a generation ago. Greater scientific understanding of underlying molecular and metabolic mechanisms, innovative technologies and new therapies, along with expanding evidence-based clinical management, have all contributed to a major risk reduction to the individual in terms of developing long-term complications of diabetes. However, for the population as a whole with escalating numbers of people developing diabetes within the current global pandemic of ‘diabesity’, the overall prevalence of diabetic complications has not diminished. Indeed, the consequences of diabetes now so predominate present-day health-care services and costs that changing concepts in the way prevention and clinical care of such need to be addressed. It is also evident that complication risk differs from one individual to another for a variety of reasons. How much differences are due to genetic susceptibility or to metabolic variation is unclear, but recognizing that some people with diabetes are more at risk than others does lead to the principle of risk stratification and personalized individual clinical management.

A large number of substantive clinical trials in recent years have consolidated a firm evidence base for the treatment of diabetes aimed at reducing long-term complications, not forgetting the parallel need to ensure the present day-to-day quality of life as well. Treatment guidelines derived from expert bodies and consensus opinion have defined important surrogate markers of risk, particularly hypertension, dyslipidaemia and hyperglycaemia (in that order), and the defining of ‘quality’ target-based standards has been associated with significant progress in risk factor management. Research studies indicate that good blood pressure control, optimal lipid status and improved glycaemia will all contribute to a substantial reduction in long-term microangiopathic diabetic complications, and the positive expectation is that this will be replicated in the real world of the diabetes population as a whole. With the current pattern of diabetes complications changing towards a greater emphasis on macroangiopathy, particularly coronary heart disease, the importance of early metabolic control and its potential, beneficial, long-term ‘legacy’ effect

have highlighted the significance of early detection of diabetes through screening and ensuring optimal control in the early years after diagnosis.

Providing clinical support for people with diabetes has become almost as complex as the nature of diabetes itself. Most diabetes care these days is well provided within a primary care community setting, but, for those identified with higher risk or when developing complications are detected, involvement of a multidisciplinary team and liaison with specialist services will be needed. Integrated models of diabetes care are evolving to meet overall clinical needs according to local circumstances, with the configuration of clinical care pathways enabling those at highest risk to be individually managed. The epidemiology of long-term diabetes complications is changing, with greater understanding of underlying causative mechanisms and improved metabolic control arising from better therapeutic regimens and more structured models of care. The development of diabetic complications should not be seen as inevitable, but sadly the consequences of diabetes are still prevalent and it is evident that some are more at risk than others. Significant strides have been made towards mitigating the more classic complications of retinopathy and nephropathy, whereas other diabetes-related issues, such as mental health and certain cancers, are becoming increasingly clinically significant. In our preface to the previous edition of this book, we conceded that there was still much more to be done to reduce the considerable burden of diabetes both to the individual and to society, but we also recognized that many advances had been made. Much progress has indeed been made in the understanding of how complications arise and how they can be prevented, while ensuring that in today's world such knowledge is shared between professionals and people with diabetes alike.

With this new edition of *Diabetes: Chronic Complications*, we have extensively revised earlier chapters on traditional complications, providing the latest science and current therapeutic guidance. In addition, as other long-term problems related to diabetes continue to emerge, we have introduced a number of new chapters, including mental health, disorders of the mouth, cancer and problems of the liver. Illustrative case histories and a selection of multiple choice questions have also been included. We are most grateful to all of the authors who have contributed their expertise and experience. Although, for the purpose of this book, these complications of diabetes are considered separately, the reality is that development of one complication will signal increased susceptibility to other problems. Most of the complications discussed have issues specific to the particular organ or tissue concerned, but equally all have shared generic components and common management considerations.

Even today the discussion of diabetic complications can still be emotive and subject to misunderstanding, but with the substantial knowledge and evidence base that are now available to everyone involved in diabetes care, much wisdom is in place to secure a life with diabetes but very positive moves towards a life without complications. In this book we have endeavoured to provide a practical analysis and reflection on current issues related to the prevention and management of long-term diabetic complications, knowledge that we trust will be found useful by all involved in the clinical practice of diabetes care, and importantly knowledge that can be shared to advantage with the many individuals now living with diabetes who wish to enjoy long-term good health free of complications.

*Kenneth M. Shaw
Michael H. Cummings*

CHAPTER 1

Diabetes and the Eye

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Key points

- Of people with diabetes in the UK 2 per cent are thought to be registered blind.
- Of patients with type 1 diabetes 87–98 per cent have retinopathy seen after 30 years of the disease.
- Eighty-five per cent of those with type 2 diabetes on insulin and 60 per cent on diet or oral agents have retinopathy after 15 years of the disease.
- Optical coherence tomography (OCT) is a technique allowing visualization of retinal layers and assessment of maculopathy.
- New treatments such as intravitreal therapy and vitrectomy are emerging as treatments that maintain or improve vision but laser remains the primary treatment of choice.



Therapeutic key points

- Poor glycaemic control is associated with worsening of diabetic retinopathy and improving glycaemic control improves outcome.
- Systolic hypertension is associated with retinopathy in type 1 and type 2 diabetes; reducing this improves retinopathy.
- Reducing lipid levels with fibrates and statins has been shown to improve retinopathy.
- Intraretinal injections of vascular endothelial growth factor (VEGF) receptor blockers may improve maculopathy.
- Laser therapy remains the primary treatment of choice for sight-threatening diabetic retinopathy, both proliferative disease and maculopathy.

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1.1 Introduction

Since the invention of the direct ophthalmoscope by Helmholtz in 1851 and von Jaeger's first description of changes in the fundus of a person with diabetes 4 years later, there has been increasing interest in the retina because it contains the only part of the vasculature affected by diabetes that is easily visible. Interestingly, these first retinal changes described in 1855 were actually hypertensive, not diabetic.

Despite the target outlined in the St Vincent Declaration in 1989 to reduce blindness caused by diabetes by one-third within 5 years, and the advances made in laser therapy and vitreoretinal surgical techniques, diabetic retinopathy remains the most common cause of blindness in the working-age population of the western world. Furthermore, with predictions of a dramatic increase in the number of people diagnosed with diabetes, the detection and treatment of diabetic retinopathy continues to be a focal point for healthcare professionals. Indeed the recent National Service Framework (NSF) for Diabetes has prioritized diabetic retinopathy by setting specific targets associated with retinal screening and implementing the development of a National Screening Programme.

Visual loss from diabetic retinopathy has two main causes: maculopathy, described as disruption of the macular region of the retina, leading to impairment of central vision; and retinal ischaemia, resulting in proliferative diabetic retinopathy.

As well as the retina, other parts of the eye can also be affected in people with diabetes. Cataracts are more prevalent and are actually the most common eye abnormality seen in people with diabetes, occurring in up to 60 per cent of 30–54 year olds. The link between diabetes and primary open-angle glaucoma, however, continues to be disputed. Vitreous changes do occur in people with diabetes, such as asteroid hyalosis, seen in about 2 per cent of patients. These small spheres or star-shaped opacities in the vitreous appear to sparkle when illuminated and do not normally affect vision. Branch retinal vein occlusions and central retinal vein occlusions are associated with hypertension, hyperlipidaemia and obesity, and are often found in people with diabetes. Hypertensive retinopathy features several lesions in common with diabetic retinopathy, and care must be taken not to confuse the two conditions.

1.2 Epidemiology of diabetic retinopathy

Currently 2 per cent of the UK diabetic population is thought to be registered blind,¹ which means that a person with diabetes has a 10- to 20-fold

increased risk of blindness. The prevalence of diabetic retinopathy depends on multiple factors and, as for many microvascular complications, is more common in the ethnic minorities compared with white people.

A prevalence of 25–30 per cent for a general diabetic population is often quoted. Every year about 1 in 90 North Americans with diabetes develops proliferative retinopathy and 1 in 80 develops macular oedema.

In patients with type 1 diabetes:^{2,3}

- <2 per cent have any lesions of diabetic retinopathy at diagnosis
- 8 per cent have it by 5 years (2 per cent proliferative)
- 87–98 per cent have abnormalities 30 years later (30 per cent of these having had proliferative retinopathy).

In patients with type 2 diabetes:^{4,5}

- 20–37 per cent can be expected to have retinopathy at diagnosis
- 15 years later, 85 per cent of those on insulin and 60 per cent of those on diet or oral agents will have abnormalities.

The 4-year incidence of proliferative retinopathy in a large North American epidemiological study was 10.5 per cent in patients with type 1 diabetes, 7.4 per cent in patients with older-onset/type 2 diabetes taking insulin and 2.3 per cent in patients with type 2 diabetes not on insulin.^{2,3,5}

Currently in the UK, maculopathy is a more common and therefore more significant sight-threatening complication of diabetes. This is due to the much greater number of people with type 2 diabetes compared with type 1, and the fact that maculopathy tends to occur in older people. About 75 per cent of those with maculopathy have type 2 diabetes and there is a 4-year incidence of 10.4 per cent in this group.⁵ Although patients with type 2 diabetes are 10 times more likely to have maculopathy than those with type 1, 14 per cent of patients with type 1 diabetes who become blind do so because of maculopathy.¹

The risk factors for development/worsening of diabetic retinopathy are:

- duration of diabetes
- type of diabetes (proliferative disease in type 1 and maculopathy in type 2)
- poor diabetic/glycaemic control
- hypertension
- diabetic nephropathy
- recent cataract surgery
- pregnancy
- alcohol (variable results which may be related to the type of alcohol involved, e.g. effects are worse in Scotland than in Italy)
- smoking (variable results, but appears worse in young people with exudates and older women with proliferative disease)
- ethnic origin.

1.3 Retinal anatomy

To understand how diabetic retinopathy is classified and treated, a basic grasp of retinal anatomy is essential. The retina is the innermost of three successive layers of the globe of the eye, the others being:

- the sclera – the rigid outer covering of the eye, which includes the cornea
- the choroid – the highly vascularized middle layer of the eye, which has the largest blood flow in the entire body.

The retina comprises two parts: the neurosensory retina, the photoreceptive part composed of nine layers and the retinal pigment epithelium (Figure 1.1).

The normal retina is completely transparent to visible wavelengths of light, its bright red/orange reflex the result of the underlying vasculature of the choroid. The retina has a number of distinct features. The optic nerve (often described as the optic disc) is a circular structure varying in

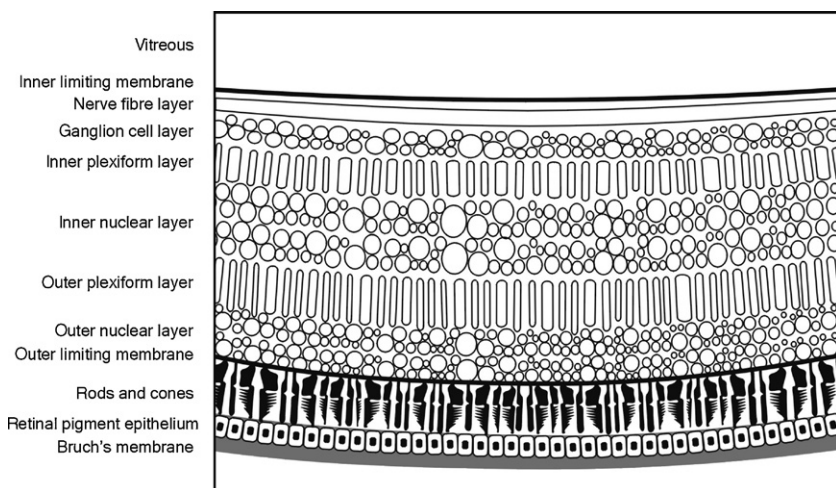


Figure 1.1 Cross-section of the retina illustrating the 10 layers of the retina: inner limiting membrane (glial cell fibres forming the barrier between the retina and the vitreous body), optic nerve fibres (axons of the third neuron), ganglion cells (cell nuclei of multipolar ganglion cells of the third neuron), inner plexiform layer (synapses between axons of the second neuron and dendrites of the third neuron), inner nuclear layer (cell nuclei of the amacrine cells, bipolar cells and horizontal cells), outer plexiform layer (synapses between axons of the first neuron and dendrites of the second neuron), outer nuclear layer (cell nuclei of rods and cones, the first neuron), outer limiting membrane (porous plate of processes of glial cells, which rods and cones project through), rods and cones (true photoreceptors), retinal pigment epithelium (single layer of pigmented epithelial cells) and Bruch's membrane.

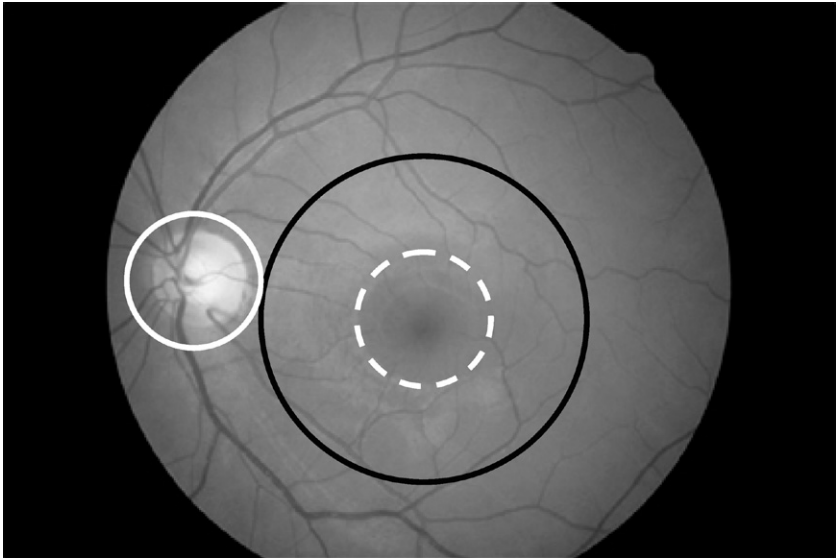


Figure 1.2 Fundus photograph illustrating the normal retina with optic nerve head (optic disc) circled in white, macula circled in black and fovea circled with a broken white line.

colour from pale pink in the young to yellow/orange in older people. It is located approximately 15° nasally from the visual axis and slightly superior (Figure 1.2). The optic nerve is essentially a 'cable' connecting the eye to the brain, which carries information from the retina to the visual cortex via the optic chiasma. The optic nerve may exhibit a central depression known as the optic or physiological cup. Both the central retinal vein and artery leave and enter the eye through the optic nerve. The 'blind spot' on visual field testing occurs because the optic disc contains no photoreceptor rod and cone cells.

The macula is the round area at the posterior pole within the temporal vessel arcades 3–4 mm temporal to and slightly lower than the optic disc (Figure 1.2). It is approximately 5 mm in diameter. At the centre of the macula and roughly the same size as the optic disc is the fovea, a depression in the retinal surface. The fovea is the point at which vision is sharpest; the foveola, the thinnest part of the retina and forming the base of the fovea, contains only cone cells, giving this area anatomical specialization for high-resolution vision in relatively bright levels of light. The fovea is 0.3 mm in diameter. At the very centre of the foveola lies the umbo, a tiny depression corresponding to the foveolar reflex.

The fovea features an avascular zone of variable diameter extending beyond the foveola, which is usually about 0.5 mm in diameter (Figure 1.3).

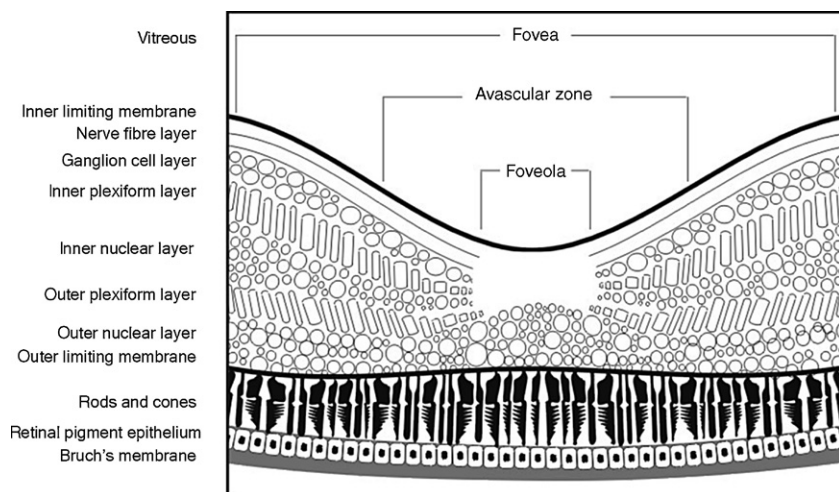


Figure 1.3 Cross-section of the retina at the fovea illustrating the fovea, foveola and foveal avascular zone.

The five innermost layers of the retina, from the inner limiting membrane to the inner nuclear layer, receive their blood supply from the central artery of the retina.

This enters the retina at the optic disc and forms four branches. There are three retinal capillary plexus which supply the inner and middle retina: the radial peripapillary plexus around the optic disc, which is at the level of the nerve fibre layer, a superficial capillary plexus at the junction of the ganglion cells and inner plexiform layers, and a deep capillary plexus, at the junction of the inner nuclear layer with the outer plexiform layer. The five outer layers of the retina, from the outer plexiform layer to the pigment epithelium, receive their blood supply from the capillaries of the choroid by means of diffusion.

The retinal veins exit the retina at the optic disc and with the arteries form the four vessel arcades of the retina – superior and inferior temporal arcades and superior and inferior nasal arcades (Figure 1.4). Retinal arteries appear bright red, with a sharp reflex strip that becomes lighter with age, and retinal veins are a darker red with little or no reflex strip.

The retinal pigment epithelium (RPE) is the base layer of the retina. The level of adhesion between the RPE and the sensory retina is weaker than that between the RPE and Bruch's membrane, resulting in a potential space. A retinal detachment is the separation of the sensory retina from the RPE as a result of subretinal fluid infiltrating this potential space.

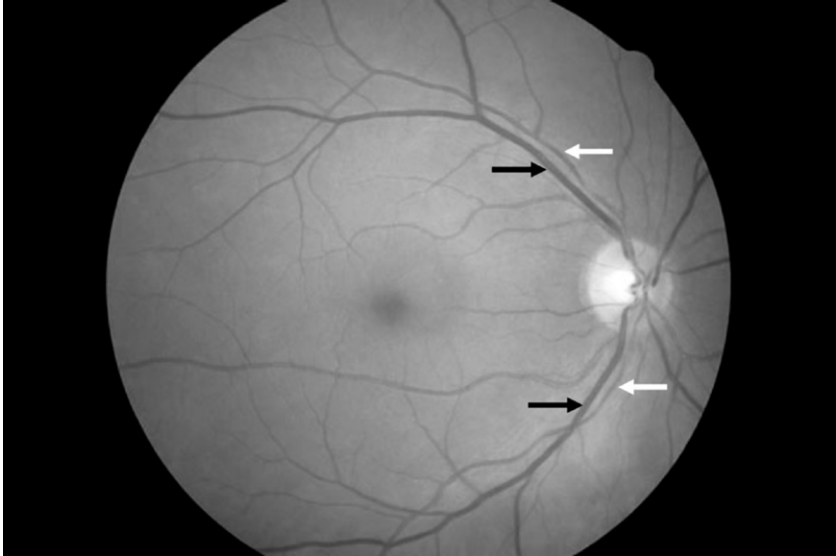


Figure 1.4 Retinal veins (black arrows) and retinal arteries (white arrows) of the superior and inferior temporal arcades.

1.4 Pathophysiology and anatomical changes of diabetic retinopathy

The pathophysiology of diabetic retinopathy is still being unravelled. Hyperglycaemia and the other metabolic effects of diabetes all play a part in triggering a series of biochemical and anatomical changes that manifest as the systemic complications of the disease.

Biochemical changes

The pathways that are affected by high blood glucose and lack of insulin and contribute to the damage include accumulation of advanced glycosylated end-products, oxidative stress, inflammation, the accumulation of sorbitol via the aldose reductase pathway, activation of protein kinase C, the release of VEGFs, fibroblastic growth factors and platelet-derived growth factors. There is also involvement of the renin–angiotensin system and recently there has been the finding that erythropoietin is a promoter of neovascularization in ischaemic tissues.

Anatomical changes

The initial microscopic anatomical change is thickening of basement membranes around the body. Basement membranes can act as passive

regulators of growth factors, by binding them to their components and thus providing an altered biochemical environment.

Glycated haemoglobin has a greater affinity for oxygen than haemoglobin, which may reduce oxygen delivery to tissues, and red blood cell membranes become more rigid, which can impede their flow along the small retinal capillaries. Increased platelet adhesiveness can accelerate plaque formation in vessels.

As the basement membrane thickens, it loses its negative charge and becomes 'leakier'. In normal retinal capillaries there is a one-to-one relationship between endothelial cells and pericytes, which is the highest ratio for any capillary network in the body. Pericytes may control endothelial cell proliferation, maintain the structural integrity of capillaries and regulate blood flow. In diabetes there is a significant loss of pericytes in the retinal capillaries, which, along with increased blood viscosity, abnormal fibrinolytic activity and reduced red cell deformity may lead to capillary occlusion, tissue hypoxia and the stimulus for new vessel formation.

Classification of diabetic retinopathy

The classification of diabetic retinopathy, as shown in Figure 1.5, is based on visible/ophthalmoscopic features, but the unseen changes described above occurring before these help explain the clinical findings.



Figure 1.5 Background diabetic retinopathy with microaneurysm (white arrow), haemorrhages (black arrows) and hard exudates (white circles).

The natural progression is from background to pre-proliferative/pre-maculopathy then to proliferative retinopathy/maculopathy and ultimately sight-threatening disease.

Non-proliferative diabetic retinopathy (Figure 1.5)

Capillary microaneurysms are the earliest feature seen clinically, as red 'dots'.

- Small intraretinal haemorrhages or 'blots' also occur, as can haemorrhage into the nerve fibre layer, often flame shaped.
- With increased capillary leakage intraretinal oedema occurs. The RPE acts as a pump to remove water from the retina, but serum proteins that leak into the deeper retinal layers can not pass through the outer limiting membrane. Retinal oedema therefore persists as the protein accumulation holds water molecules osmotically. At the border of the areas of capillary leakage, serum lipids deposit in the retina, forming exudates.

Pre-proliferative retinopathy (Figure 1.6)

- Cotton-wool spots or soft exudates are infarcts in the nerve fibre layer occurring at areas of non-perfusion. Axoplasmic transport is disrupted

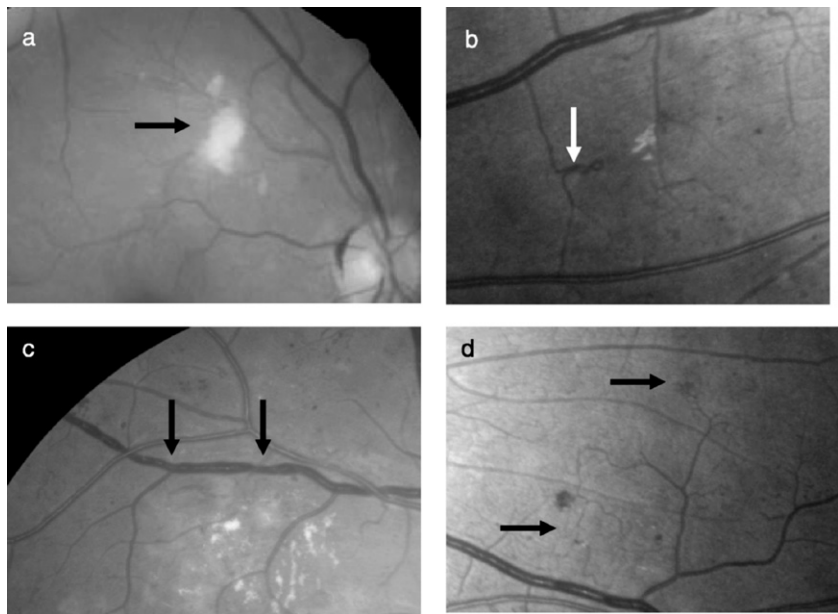


Figure 1.6 Pre-proliferative diabetic retinopathy with (a) cotton-wool spots, (b) venous loop, (c) venous beading and (d) IRMAs (intraretinal microvascular abnormalities).

in the nerve fibres of ganglion cells, giving oedematous infarcts that are seen as pale/grey fuzzy-edged lesions.

- Intraretinal microvascular abnormalities (IRMAs) are tortuous dilated hypercellular capillaries in the retina, which enlarge enough to be visible and occur in response to retinal ischaemia.
- Further changes include alternating dilatation and constriction of veins (venous beading), and other venous alterations such as duplication and loop formation.
- There are also large areas of capillary non-perfusion occurring in the absence of new vessels. These ischaemic areas may not be visible with an ophthalmoscope but can be seen on fluorescein angiography.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) suggested that certain of these features matter and suggested a '4-2-1' rule:⁶

- four quadrants of severe haemorrhages or microaneurysms
- two quadrants of IRMAs
- one quadrant with venous beading.

If a patient has one of these features, there is a 15 per cent risk of developing sight-threatening retinopathy within the next year. If two are present this rises to a 45 per cent risk.

Proliferative retinopathy (Figure 1.7)

New vessels form and grow either into the vitreous or along the vitreoretinal interface (this tends to occur in younger patients in whom the posterior vitreous face is well formed). The vitreous forms a reservoir for the angiogenic agents released by the ischaemic retina and acts as scaffolding for neovascularization and fibrosis. There are two forms of new vessels:

- those on the disc or within one disc diameter of the disc (NVDs)
- new vessels elsewhere (NVEs).

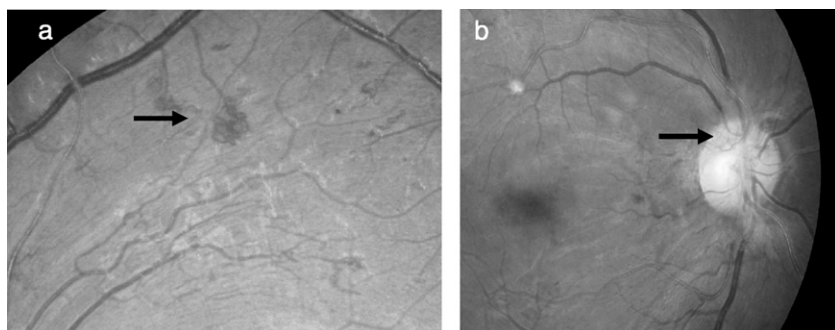


Figure 1.7 Proliferative diabetic retinopathy with (a) neovascularization on the surface of the retina (NVE) and (b) neovascularization at the optic disc (NVD).

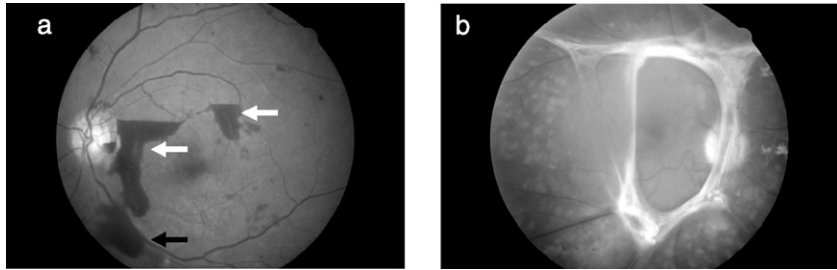


Figure 1.8 Advanced diabetic retinopathy with (a) pre-retinal haemorrhages (white arrows) and vitreous haemorrhage (black arrow), and (b) fibrous proliferation.

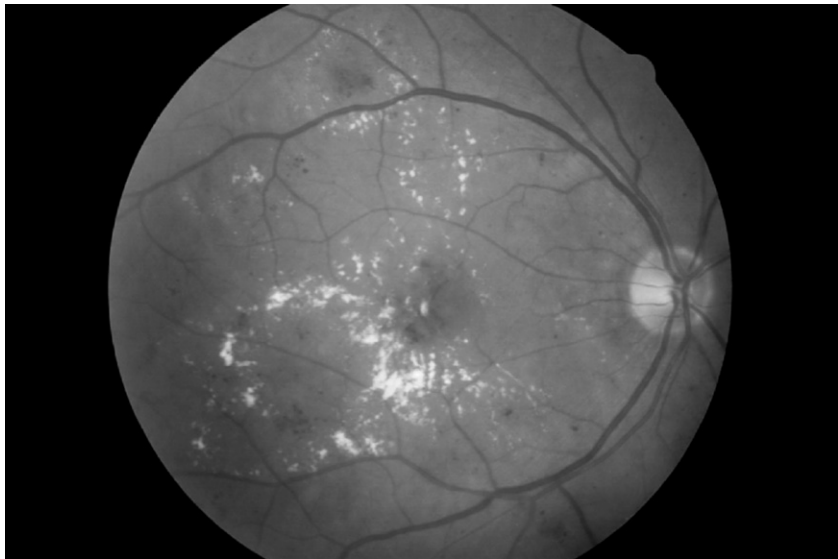


Figure 1.9 Diabetic maculopathy with retinal haemorrhages and hard exudates.

Both give no symptoms but cause the problems of advanced retinopathy (Figure 1.8) such as haemorrhage, scar tissue formation, traction on the retina and retinal detachment, which actually result in loss of vision.

Diabetic maculopathy

Oedema in the macula area can distort central vision and reduce visual acuity. Any of the above changes can coexist with maculopathy. The changes seen can be:

- oedematous (clinically it may just be difficult to focus on the macula with a hand-held ophthalmoscope, or visual acuity may have altered or may worsen when a pinhole is used)
- exudative (with haemorrhages, hard exudates and circinate exudates – Figure 1.9)

Box 1.1 Classification, features and grading scheme for diabetic retinopathy

Mild-to-moderate non-proliferative retinopathy (grade R1)

Microaneurysms

Haemorrhages

Hard exudates

Severe non-proliferative retinopathy (grade R2)

Soft exudates/cotton-wool spots

Intraretinal microvascular abnormalities (IRMAs)

Venous abnormalities (e.g. venous beading, looping and reduplication)

Proliferative retinopathy (grade R3)

New vessels on the disc or within one disc diameter of it (NVD)

New vessels elsewhere (NVE)

Rubeosis iridis (\pm neovascular glaucoma)

Maculopathy (grade Mo – absent M1 – present)

Haemorrhages and hard exudates in the macula area

Reduced visual acuity with no abnormality seen

Other grades

R0: normal fundus appearance

A: advanced eye disease including vitreous haemorrhage, fibrosis and retinal detachments

P: evidence of previous laser therapy

U: un-gradable image

OL: other non-diabetic changes/lesion seen

- ischaemic (capillary loss occurs but clinically the macula may look normal on direct ophthalmoscopy, although poorly perfused areas will show up on fluorescein angiography)
- any combination of these (Box 1.1).

1.5 Diagnosis and clinical investigation

Slit-lamp biomicroscopy

Indirect ophthalmoscopy with a slit-lamp biomicroscope performed by an Ophthalmologist is considered to be the gold standard for diagnosing diabetic retinopathy. The use of high magnification biomicroscope lenses such as a 78-, 66- or 60-D lens allows the detection of retinal oedema and neovascularization because of the level of stereoscopic vision achieved.

Fundus photographs

Colour fundus photographs are used extensively in screening (see below) and are also an important part of documenting the changes when the

patient is under the care of an Ophthalmologist. The current generation of retinal cameras now produce very-high-resolution digital images.

Optical coherence tomography

Optical coherence tomography (OCT) is a relatively new method of tissue imaging that has rapidly become an important part of assessment of patients with maculopathies of any cause.

OCT is based on the optics of a Michelson interferometer and produces a set of images that show changes in refractive index through tissues. This allows visualization of layers that correspond to the anatomical layers in the retina. The most recent devices use a Fourier transform method to produce high-resolution images with a short acquisition time.

The field of view is small, but covers the macula and fovea, which are arguably the most important areas of retina required for our day-to-day vision. OCT can also be used to image the optic nerve head.

Figure 1.10 shows a Fourier domain OCT of the normal macula, with the different retinal layers labelled.

There are several advantages of OCT, which include delineation of sites of anatomical change, storage of images and comparison of images taken at a later time. Many OCT devices contain image registration software that allows a direct assessment of change occurring during the process of disease evolution or as a result of intervention.

Some examples of OCT scan in patients with diabetes are shown in Figures 1.11 and 1.12.

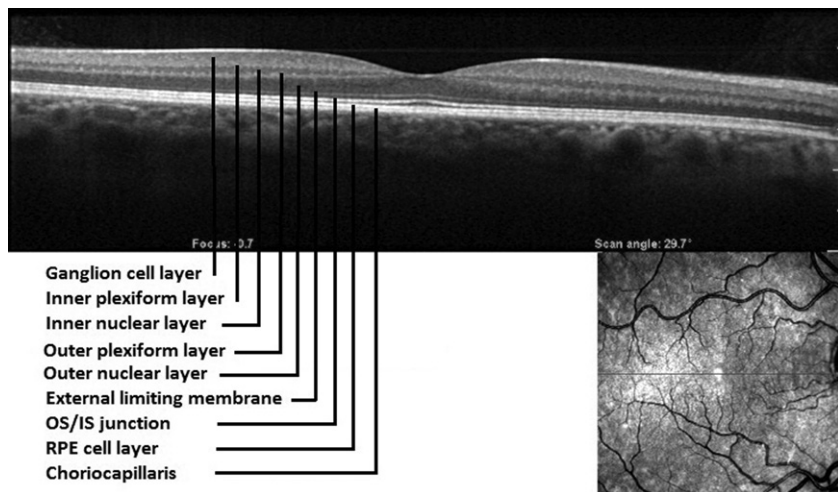


Figure 1.10 A Fourier domain optical coherence tomography (OCT) of the normal macula.

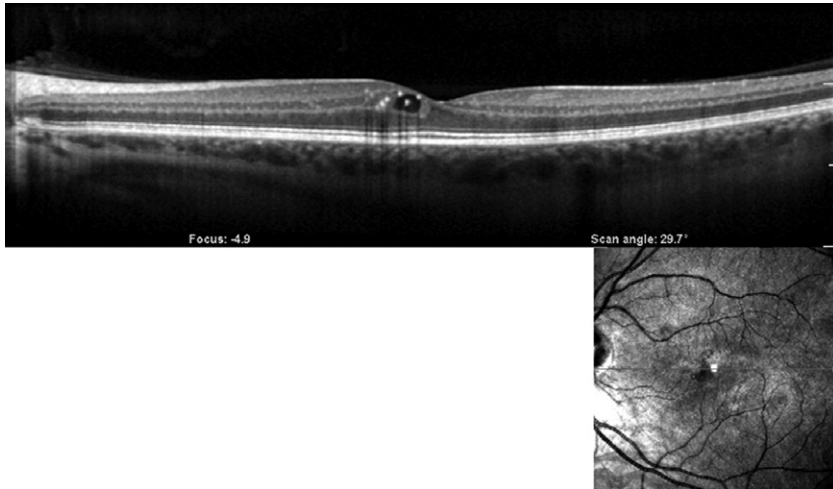


Figure 1.11 Optical coherence tomography (OCT) scan of patient with diabetic macular oedema.

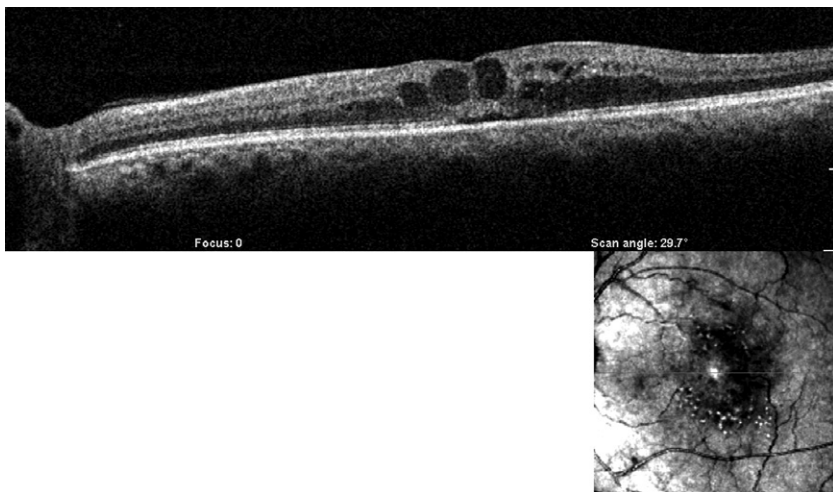


Figure 1.12 Optical coherence tomography (OCT) scan of patient with cystic diabetic macular oedema.

Free fluorescein angiography

Retinal angiography was introduced in the 1960s and remains a mainstay investigation of retinal disease. Free fluorescein angiography (FFA) systems are now digital and a series of images is acquired that tracks the passage of fluorescein through the posterior segment vasculature.

In diabetes, FFA is crucial to the assessment of the presence of ischaemia (hypofluorescence), vascular leakage (late hyperfluorescence) and neo-

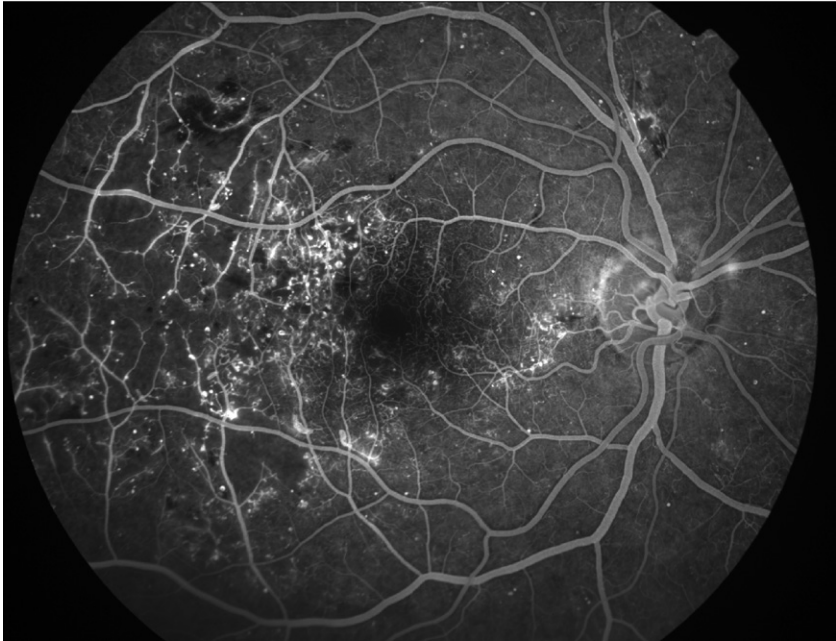


Figure 1.13 Early phase image showing loss of perifoveal capillaries and temporal capillaries in a patient with type 1 diabetes.

vascularization at the optic disc and elsewhere. The presence of leakage from vessels around the macular area guides the application of laser treatment. Examples of angiographic images are shown in Figures 1.13–1.16.

OCT scanning and fluorescein angiography are used together to investigate and monitor anatomical and vascular changes in retinal disease.

1.6 Screening for diabetic retinopathy

Diabetic retinopathy meets the World Health Organization’s four cardinal principles that determine whether a health problem is suitable for screening:

1. The condition should be an important health problem with a recognizable pre-symptomatic state – as the most common cause of blindness in the working population of the western world with a well-recognized pattern of changes visible in the eye, diabetic retinopathy fulfils this.
2. An appropriate screening procedure, which is acceptable both to the public and healthcare professionals, should be available – retinal photography is accepted by patients and the medical profession.

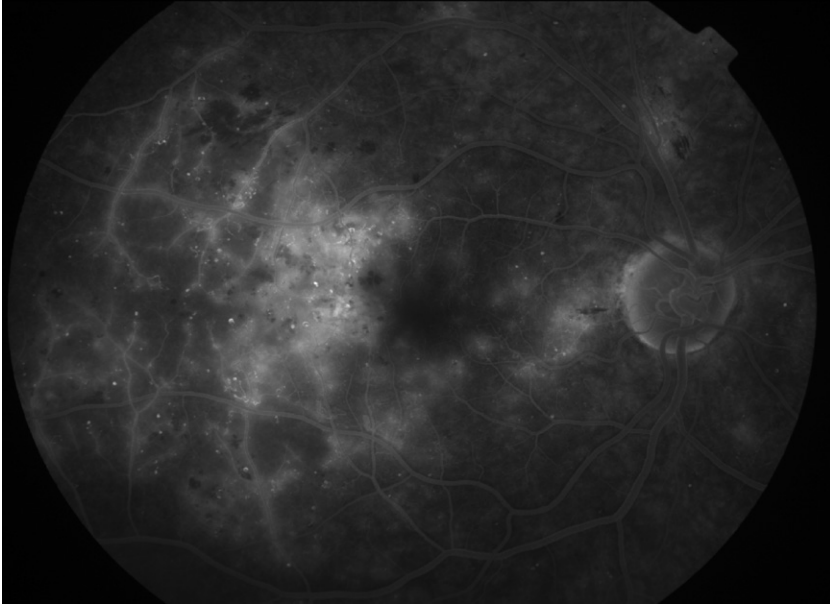


Figure 1.14 Late phase angiogram showing leakage of fluorescein in the temporal area of the macula.

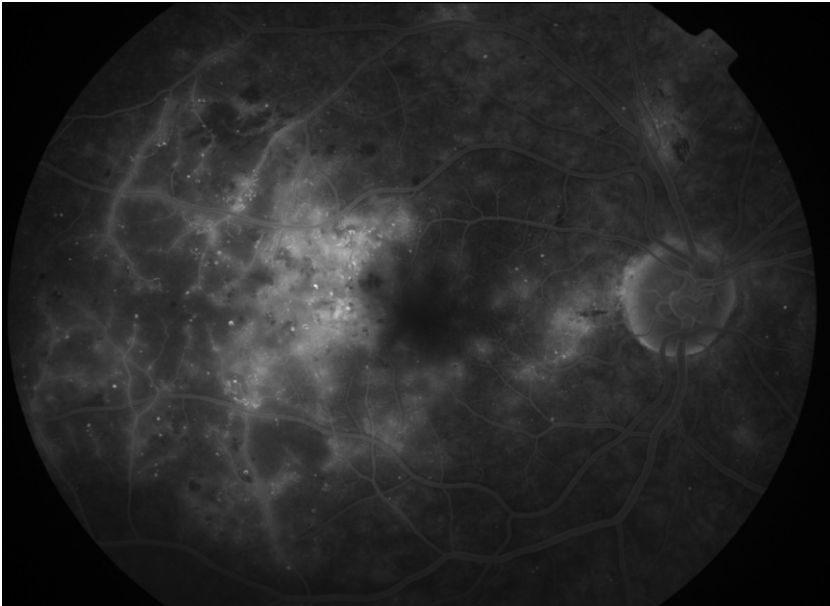


Figure 1.15 Early phase angiogram showing severe capillary shutdown, microaneurysms, and vessel dilatation and tortuosity in a patient with type 2 diabetes.