

DIABETIC RETINOPATHY

Diabetes mellitus

Diabetes mellitus is an abnormality of the blood glucose metabolism due to altered insulin production or activity. There are two types diabetes mellitus- Insulin dependent diabetes mellitus [IDDM, early onset or Type-1] and non-insulin dependent diabetes mellitus [NIDDM, late onset or Type-2]. Diabetes affects around 2% of the population in the United Kingdom. The prevalence of diabetes is rising all over the world. The systemic complications of diabetes include retinopathy [eyes], nephropathy [kidneys], neuropathy [nervous system] and involvement cardiovascular system [heart and blood vessels]. Diabetes has an enormous socio-economic impact as it mainly affects individuals in the working age group.

Retinopathy

Diabetic retinopathy is a serious complication of diabetes mellitus. This is the commonest cause of blindness in the western world in people between 20 and 74. In the younger onset diabetics [<30 years] retinopathy of any severity is found in 17% of them after 5 years and in 98% after 15 years or more after onset of diabetes. In the late onset diabetes [>30 years] any retinopathy is present in 29% after 5 years and 80% after 15 years or more. Around 10% of patients with diabetes develop sight threatening retinopathy. Diabetic retinopathy is the commonest cause of registered blindness in U.K. in those between 30 and 65 years of age. The St. Vincent declaration [1989] aims to reduce new blindness caused by diabetic retinopathy by one-third or more. Screening for diabetic retinopathy was identified as a priority. The government recognising the importance of this condition has published the National

Service Framework [NSF] for diabetes mellitus that includes recommendations for management of diabetic retinopathy.

Pathophysiology of Diabetic Retinopathy

Even when there is no clinically detectable retinopathy, changes at haemodynamic and cellular levels take place. The endothelial [inner lining of the blood vessels] cell supporting cells called pericytes are affected early resulting in endothelial damage. The retinal blood flow is decreased. The retinal autoregulation that maintains the level of blood supply to retina is impaired. Clinically evident retinopathy appears as the disease progresses. The various signs that appear are microaneurysms, dot and blot retinal haemorrhages, cotton wool spots, venous calibre changes and retinal capillary non-perfusion. Increasing retinal ischaemia [reduced blood flow] triggers the production of vasoproliferative factors that causes development of new vessels seen in proliferative diabetic retinopathy. Diabetes also causes retinal blood vessels to be more permeable resulting in transudation of serum components. This results in retinal thickening and causes macular oedema.

Clinical features

Diabetic retinopathy can be divided into two stages - background [non-proliferative] diabetic retinopathy including pre-proliferative diabetic retinopathy and proliferative diabetic retinopathy.

Background Diabetic Retinopathy [BDR]

Microaneurysms are the early signs of diabetic retinopathy that are ophthalmoscopically visible. These appear as red dots and are difficult to distinguish

from small dot haemorrhages. The rupture of these aneurysms result in haemorrhages. The haemorrhages in the deeper layers of retina appear as blot haemorrhages. Superficial haemorrhages may appear as flame shaped haemorrhages as those seen in hypertensive [high blood pressure] retinopathy.

Pre-proliferative Diabetic Retinopathy

Increasing retinal ischaemia results in multiple retinal haemorrhages, cotton wool spots, venous beading, venous loops and intra-retinal microvascular abnormalities [IRMA]. The term pre-proliferative diabetic retinopathy is used to describe retinopathy with these features. Cotton wool spots are retinal infarcts. Venous calibre changes indicate retinal ischaemia. IRMA are dilated capillaries. These changes are found in areas of retinal capillary non-perfusion. These changes indicate the severity of the non-proliferative changes. Background diabetic retinopathy can be graded mild, moderate and severe retinopathy. The early treatment diabetic retinopathy study [ETDRS] identified multiple retinal haemorrhages, venous calibre changes and IRMA as signs indicative of risk of progression to proliferative diabetic retinopathy. ETDRS also used standard photographs with various retinal signs to help with grading of diabetic retinopathy. Severe non-proliferative diabetic retinopathy is identified by using the 4-2-1 rule. Four quadrants of retinal haemorrhages or microaneurysms, at least two quadrants of venous beading or at least one quadrant of IRMA indicates severe non-proliferative diabetic retinopathy. Presence of two or more of these indicates very severe non-proliferative diabetic retinopathy. These patients need to be very closely monitored for development of retinal new vessels. By one year about half of these patients would have progressed to high-risk diabetic retinopathy.

Proliferative Diabetic Retinopathy [PDR]

Proliferative Diabetic Retinopathy is characterised by new vessels arising from retinal vasculature. When they are located at or within 1 disc diameter of the optic disc they are called neovascularization of the disc [NVD]. When they are further than one disc diameter from the optic disc they are called neovascularization elsewhere [NVE]. The stimulus for the development of these new vessels is thought to come from the ischaemic retina. These vessels grow well on connective tissue framework like the partially detached posterior vitreous face. Traction on these new vessels result in vitreous [gel inside the eye] haemorrhage. Fibro-vascular proliferation can also result in tractional retinal detachment. Traction on the retina can also cause retinal breaks resulting in rhegmatogenous retinal detachment.

Maculopathy

Diabetic maculopathy can be part of both background and proliferative diabetic retinopathy. Diabetic maculopathy is a leading cause of legal blindness in diabetics.

Macular oedema can be detected by slit lamp biomicroscopic examination.

Maculopathy is classified into focal, diffuse, ischaemic and mixed types. Focal maculopathy is associated with a leaking microaneurysm and a ring of exudates.

Diffuse maculopathy is caused by diffuse leakage from the retinal capillaries resulting in diffuse oedema. This may result in cystoid macular oedema. Ischaemic

maculopathy is diagnosed when there is disruption of foveal capillaries resulting in enlarged foveal avascular zone. The term clinically significant macular oedema

[CSMO] is maculopathy that involves or threatens the centre of the macula and is a form of sight threatening retinopathy. This is defined by

1. Retinal thickening at or within 500 μ of the fovea

2. Hard exudates at or within 500 μ of fovea with associated thickening
3. An area of thickening one optic disc area or more any part of which is within one disc diameter of the fovea.

Presence of CSMO is an indication for laser treatment.

Treatment of Diabetic Retinopathy

Control of the diabetes is important. The Diabetes Control and Complications Trial [DCCT] showed that improved glucose control delays the onset of retinopathy and slows the progression of retinopathy when present. The advent of laser treatment has made a significant impact in reducing the risk of severe loss of vision. Two well-conducted multicentre studies evaluated the effects of laser treatment on diabetic retinopathy. Diabetic Retinopathy Study [DRS] recruited 1758 patients whose eyes were randomised to treatment and no-treatment groups. Panretinal photocoagulation [PRP] was found to reduce the progression to severe visual loss [$<5/200$] by more than 50%. The trial was terminated due to the well-observed benefits of laser treatment. DRS identified the high-risk characteristics when PRP was indicated.

High-risk characteristics identified by DRS:

1. NVD $>1/4 - 1/3$ disc diameter
2. NVD $<$ than above with vitreous haemorrhage
3. NVE $>1/2$ disc diameter with vitreous haemorrhage

The next study called Early Treatment Diabetic Retinopathy Study [ETDRS] was conducted to identify the optimal stage of intervention. This trial evaluated 3928 patients with various stages of diabetic retinopathy before high-risk characteristics developed. The patients were randomised to either immediate treatment in the form pan retinal photocoagulation or deferred treatment until high-risk characteristics

develop. The study results showed that PRP was indicated when high-risk characteristics develop. Treatment benefit was also found in stages before the high risk characteristics developed. When PRP was done as the patients approached high-risk characteristic disease severe visual loss was reduced by more than 90% to 5% over 5 years. Treatment may be beneficial at earlier stages although beneficial effects are less marked and side effects and complications have to be considered.

ETDRS had an arm of the study looking at the effect of focal laser photocoagulation for clinically significant macular oedema. The results showed that those who did not receive the treatment were twice as likely to progress to moderate visual loss [doubling of visual angle] than those receiving treatment.

Panretinal Photocoagulation [PRP]

This involves applying laser burns of 500 μ diameter separated by $_$ burn width scattered on the retina up to the mid and far periphery leaving an area of untreated retina around the optic disc and macula. The minimum numbers are specified by DRS and ETDRS. The Royal College of Ophthalmologists' document on Diabetic Retinopathy also gives recommendation on the appropriate numbers for the various stages of severity of the disease.

Focal / Grid Laser

This form of laser is used for treatment of maculopathy independent of whether the diabetic retinopathy is proliferative or non-proliferative. If PRP is also to be performed then the maculopathy is treated before or at times at the same sitting as PRP. This is especially important in type-2 diabetics. Focal treatment is used for focal

maculopathy and involves placing smaller size burns that are separated by one burn width and covering the area of retinal thickening leaving the central 500 μ m around the fovea. Grid laser application is used for diffuse maculopathy and involves placing the burns in a grid pattern around the fovea in multiple rows to cover the area of retinal thickening. Ischaemic maculopathy is untreatable.

Laser treatment should take into consideration various other factors such as laser wavelength, spot sizes, energy used and the magnification factor associated with the contact lenses used for the procedure.

Screening for Diabetic Retinopathy

St Vincent declaration identified as one of its targets, reduction in new blindness due to diabetes by one-third or more. Screening is useful in a disease where there is effective treatment and where the patients remain symptom-free when the treatment is very effective.

Diabetic retinopathy is a condition for which treatment is available. The treatment is effective in reducing sight loss. Hence there has been a major emphasis on screening for diabetic retinopathy. Identification of sight threatening retinopathy is an important aim of the screening programme. Referral for evaluation and treatment at an appropriate time is important to reduce severe visual loss due to diabetic retinopathy. National Service Framework [NSF] for diabetes has identified money for capital investment mainly on the cameras for establishing systemic screening through out the country. Ophthalmic photographers from various backgrounds would be involved in capturing the fundus images. These persons may also be involved in the grading of

the retinopathy and organise referrals to the ophthalmologist. Standards have been set for screening programmes. The specificity should be > 95% and > 80% sensitivity.

The technical failure rate allowed is < 5%.

There are two screening methods that are in current use. One is by retinal photography and the other is the optometrist screening. The national screening committee [NSC] has chosen digital fundus photography with dilated pupils to be the preferred method of screening. The NSF on diabetes has identified money for capital expenditure to cover costs of purchase of digital cameras.

Each of these techniques has its advantages and disadvantages. The various factors that have to be considered are the specificity and sensitivity of the system, technical failure rate and quality control. Success or failure of a screening system depends upon ease of access, availability of trained personnel and mechanisms in place for auditing the process.

The following gives the details of the proposed grading scheme and the advice for referral to the appropriate medical personnel following screening.

GRADING AND REFERRAL AFTER SCREENING: National Screening

Committee proposal

RETINOPATHY [R]

Level -0 None

Level -1 Background

Microaneurysms

Haemorrhages +/- Exudate

Level-2	Pre-proliferative	<p>Venous beading</p> <p>Venous loop or reduplication</p> <p>IRMA</p> <p>Multiple deep, round or blot haemorrhages</p> <p>[Cotton wool spot – careful search for above features]</p>
Level-3	Proliferative	<p>NVD / NVE</p> <p>Pre-retinal or vitreous haemorrhage</p> <p>Pre-retinal fibrosis +/- Tractional retinal detachment</p>

MACULOPATHY [M]

- Exudate within 1 disc diameter of centre of fovea
- Exudate or group of exudates within macula
- Any microaneurysm or haemorrhage within 1 disc diameter of centre of fovea only if best corrected visual acuity \leq 6/12
- Retinal thickening \leq 1 disc diameter of centre of fovea [if stereo photos available]

PHOTOCOAGULATION [P], UNCLASSIFIABLE [U] AND

OTHER LESIONS [OL]

Photocoagulation [P]	<p>Focal / Grid macular</p> <p>Peripheral Scatter</p>
Unclassifiable [U]	Ungradable / Unobtainable / Unscreenable

Other Lesion [OL]	Central / Branch retinal vein occlusion
	Age related macular degeneration / Drusen
	Glaucomatous disc cupping
	Cholesterol emboli
	Pigmented lesion
	Myelinated nerve fibres

REFERRAL

R0	Annual screening
R1	Annual screening / Inform diabetes care team
R2 / M1	Refer to Hospital Eye Service [HES]
R3	Fast track referral to HES
P1	New Sreenee ----- Refer to HES
	Quiescent treated ----- Annual screening
OL	Refer to HES or inform primary physician
U	Media opacity ----- HES
	Unscreenable ----- Discharge inform GP

Relevant Articles

1. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991;98:741-56.
2. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Group. Ophthalmology 1991;98:766-85

3. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Report no. 3. The Early Treatment Diabetic Retinopathy Study Group. *Int Ophthalmol Clin* 1987;27:254-64.
4. Bailey CC, Sparrow JM, Grey RH, Cheng H. The National Diabetic Retinopathy Laser Treatment Audit. II. Proliferative retinopathy. *Eye* 1998;12:77-84.
5. Bailey CC, Sparrow JM, Grey RH, Cheng H. The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical Outcomes. *Eye* 1999;13:151-9.
6. Bailey CC, Sparrow JM, Grey RH, Cheng H. The National Diabetic Retinopathy Laser Treatment Audit. I. Maculopathy. *Eye* 1998;12:69-76.
7. Diabetes care and research in Europe: the Saint Vincent Declaration. *Diabet Med* 1990;7:360
8. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of diabetic retinopathy study [DRS] findings. *Ophthalmology* 1981;88:538-600.
9. DCCT Research Group: Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complication Trial. *Ophthalmology* 1995;102:647-61.
10. Grading diabetic retinopathy from stereoscopic colour fundus photographs – an extension of the modified Airlie House classification. ETDRS report no. 10. *Ophthalmology* 1991;98:786-806.

Links to related websites

1. www.diabetic-retinopathy.screening.nhs.uk
2. www.doh.gov.uk
3. www.diabetes.org.uk
4. www.nscoretinopathy.org.uk
5. <http://eyephoto.opth.wisc.edu/index.htm>
6. www.rcophth.ac.uk

APPENDIX-1

Fundus photographs and fluorescein angiograms demonstrating the various retinal signs

SELF-ASSESSMENT QUESTIONS

1. What are the types of diabetes mellitus?
2. What is the essential difference between background [non-proliferative] and proliferative diabetic retinopathy?
3. What are the retinal features that indicate high risk of progression to proliferative diabetic retinopathy?
4. What constitutes clinically significant macular oedema?
5. Is there any effective treatment for proliferative diabetic retinopathy and what is the evidence?

6. What is the rationale for screening for diabetic retinopathy?
7. When do you refer patient to an ophthalmologist?
8. When does the referral become urgent?
9. What are the methods of screening for diabetic retinopathy?
10. Is there any relationship between diabetic control and retinopathy progression?

Answers to the above questions can be found briefly in the above review article.

Further details on each aspect of the review can be obtained from the articles in the suggested reading section and the web sites for which links are provided.

Credit

Review of the above article and the related articles and websites should be able to provide credit for 4 hours.