

Diabetic Eye Disease

Introduction

Microangiopathy is a disorder of the small blood vessels specific to diabetes and is clinically apparent in the eye as retinopathy as well as in other organs such as the kidneys (nephropathy) and nerves (neuropathy). Diabetic retinopathy is still one of the most common causes of blindness in the working population of the Western World and also a significant cause of blindness in the elderly population. The risk of diabetic complications is related to disease duration. The Wisconsin epidemiological studies have shown that the prevalence of diabetic retinopathy (DR) is greater than 95% after 15 years of disease in patients diagnosed with diabetes before the age of 30 (principally type 1 diabetes). For those diagnosed after that age, 30% have signs of retinopathy at diagnosis, rising to 60% after 15 years of diabetes (type 2 diabetes). In the diabetic population in the UK approximately 30% of patients will have diabetic retinopathy, 2% will be registered partially sighted or blind, and approximately 400 new cases of blindness will be registered per year.

Visual impairment in diabetic subjects is not necessarily due to diabetic retinopathy per se. In a recent survey of patients in a general diabetic clinic, 50% of severe visual impairment was due to causes other than diabetic retinopathy. (3) The most common ocular complication of diabetes is cataract which occurs prematurely in diabetic compared with non-diabetic subjects, and even with modern cataract surgical techniques a few patients have poor visual outcome. Because of the increase in cardiovascular risk factors associated with diabetes, retinovascular disease (retinal vein occlusion, retinal

artery occlusion and ischaemic optic atrophy) are more common in diabetic subjects and may lead to unilateral or bilateral visual impairment. In addition, glaucoma occurs in at least 1% of the diabetic population, with visual morbidity. Age-related macular degeneration and amblyopia are also a major cause of severe visual impairment in this population. Cranial nerve palsies may also result in visual problems owing to diplopia.

The major susceptibility factors for diabetic retinopathy are listed in Table 1. Whilst the pathogenetic role of hyperglycaemia is proven, the pivotal role played of increasing systolic blood pressure and hypertension has also been emphasised by recent studies.

Table 1 :Established Risk Factor for the Development of Diabetic Retinopathy

1. Increasing duration of diabetes
2. Type of diabetes (more common in type 1 than type 2 diabetes)
3. Systemic hypertension
4. Glycaemic control
5. Presence of macro- or microalbuminuria
6. Dyslipidaemia, particularly increasing LDL cholesterol levels
7. Pregnancy
8. Cigarette smoking

(NB. insulin therapy is a major predictor of the presence of sight-threatening diabetic retinopathy, due principally to the fact that this therapy identifies patients with type 1 diabetes and those with type 2 diabetes of longer disease duration).

There is no single explanation for how glucose toxicity provokes the development of retinopathy. The consequences of hyperglycaemia include:

- capillary cell death
- alteration of retinal pericyte/endothelial cell ratio
- vascular occlusion

Increased blood flow in the capillaries occurs due to loss of pericytes in the normal retina, which leads to disruption of retinal blood flow auto-regulation. The resulting increased blood flow affects the capillary wall by stimulating production of vaso-active substances and increasing endothelial cell proliferation, eventually resulting in the closure of the capillary circulation. This leads to a state of chronic hypoxia in the retina, and increase in the levels of a number of growth factors, including vascular endothelial growth factor (VEGF), insulin growth factor 1 (IGF-1) and fibroblast growth factor (FGF).

A number of mechanisms have been studied in an attempt to elucidate and prevent microvascular complications of diabetes (Figure 1), with the identification of hypertension and its consequent increased retinal blood flow and disrupted retinal autoregulation, being particularly important.

Aggressive antihypertensive treatment is of proven benefit and there may be a specific role for ACE inhibitors, by reducing angiotensin levels (the latter has been implicated as

an angiogenic growth factor). In addition, there is some evidence of reduction of leakage and exudation in the macula by statin and fibrate lipid lowering therapies. Fibrate therapy has specifically been shown to reduce laser treatment in diabetic subjects in the FIELD study.

Research trials of new medical therapies for diabetic retinopathy are ongoing. A large trial programme is evaluating the potential clinical benefit of an oral agent which inhibits the Protein Kinase C (PKC) enzyme system and reduction of VEGF levels. VEGF promotes both angiogenesis and also capillary leakage in the retina and blockade of this system could result in a reduction of retinopathy progression, particularly diabetic maculopathy and macula oedema.. Current studies of the use of intra vitreal therapies include steroids, and VEGF antibodies and aptamers which all show promise as adjuncts to laser therapy.

Types of retinopathies

Clinically, retinopathy is best divided into categories which enable the clinician to plan management and assess risk to visual loss. The four major sub-divisions are:

- Background diabetic retinopathy
- Maculopathy
- Preproliferative retinopathy
- Proliferative retinopathy

Knowledge of retinal anatomy and function will aid in understanding the relationship between diabetic retinopathic changes and visual loss. Of crucial importance is the identification of the macular region (Figure 2), which is defined as a circular area centred on the fovea (this is 2.5 disc diameters (DD) temporally from the optic disc) with a radius of 2 DD . The macula is largely responsible for colour and central vision, therefore lesions within this area are described as sight-threatening. However it should be noted that a retinopathic lesion on the periphery of the macula may not affect vision and therefore be asymptomatic. This leads to the important concept that **screening** is required to identify sight threatening macula disease by regular retinal examination or retinal imaging techniques.

Maculopathy is not the only mechanism of visual loss resulting from diabetic retinopathy, as angiogenesis (new vessel formation) may result in retinal and vitreous haemorrhage, retinal gliosis and traction, which may have a major adverse effect on vision. Like maculopathy, prior to the complications arising from new vessels, these too will be asymptomatic, reinforcing the screening concept.

Background retinopathy

The early changes of microaneurysm formation, dot retinal haemorrhages and the formation of exudates are classified as background retinopathy (Figure 3) . Providing these changes do not affect the macula region, the patient will remain asymptomatic.

Background changes are common, particularly with long duration of type 1 diabetes, as 90% of patients will have diabetic retinopathy changes after 20 years duration. Diabetic retinopathy is also common in type 2 diabetes, occurring with a four year incidence of

31 % in non – insulin and 41 % of insulin users, and may be present in newly diagnosed diabetic patients .

Maculopathy

Retinopathic changes due to diabetes in the macular region are highly significant, as diabetic maculopathy is the commonest cause of blindness in diabetic subjects. Three forms of macular disease may occur, namely: 1) exudative, 2) ischaemic, and 3) a mixed pattern of exudation and ischaemia.

The first and most common is **exudative maculopathy** , characterised by yellow waxy deposits which form a ring shape (circinate pattern), which may surround or encroach into the fovea (Figure 4)..

The second form is due to ischaemia in the macular region and is termed **ischaemic maculopathy** which occurs due to capillary closure directly within the macular area. It is often difficult to identify clinically as the macula has a rather featureless and grey appearance (see Figure 5). It is often heralded by a reduction in visual acuity with subtle retinal signs. Fluorescein angiography is required to make an exact diagnosis as this technique delineates the macula circulation and integrity of the foveal avascular zone (figure 6) .

The third pattern of maculopathy is the **mixed form** , in which both ischaemic and exudative maculopathy features occur together.

Macula Oedema

As diabetic maculopathy progresses, retinal oedema may occur due to leakage of water and albumin into the macula region. The development of macula oedema with its consequent damage to the delicate structure of the retina within the macula and especially the fovea, is the major cause of visual loss, affecting central and colour vision. Macula oedema can be seen stereoscopically by slit lamp biomicroscopy examination as thickening of the retina. The oedema can also accumulate into a cystic pattern, termed Cystoid macula oedema.

Macula oedema is difficult to assess by other methods of retinal examination (e.g. retinal photography or direct ophthalmoscopy) as these methods are not stereoscopic. Screening by photographic methods, therefore, rely on prediction of macula oedema from surrogate retinal or other changes (for example, exudation, ischaemic haemorrhages, or loss of visual acuity).

From a laser treatment perspective, maculopathy presents in two types. Focal maculopathy is the presence of an area of macular oedema which is well defined, sometimes clearly focussed around a leaking microaneurysm, and responds well to focal laser treatment. In contrast when the oedema is extensive and involving the fovea, it is termed diffuse macula oedema. Grid laser therapy is the usual therapy for diffuse macula oedema, but there is less benefit than with focal laser therapy..

Preproliferative diabetic retinopathy

Certain retinal changes predict the high risk of new vessel formation (angiogenesis). The changes observed in the retina reflect retinal ischaemia (figure 7). The common lesion is the cotton wool spot, which are retinal infarcts, and may be associated with widespread retinal capillary closure, and ischaemia. The main changes associated with preproliferative diabetic retinopathy are:

1. Cotton wool spots (> 5 suggests more widespread peripheral retinal ischaemia)
2. Large blot (strawberry pattern) haemorrhages (> 3)
3. Venous abnormalities – tortuosity, beading, looping, or venous reduplication (figures 8,9)
4. Arteriolar abnormalities
5. Intra-retinal microvascular abnormalities (IRMA), which consist of dilated retinal capillaries (figure 10)

The risk of developing proliferative retinopathy if the above physical signs are present is approximately 50% over 2 years. The strongest predictors are the presence of venous changes of irregularity and beading, and the presence of intra retinal microvascular abnormalities.. It should be noted though that the presence of one or two cotton wool spots alone does not indicate preproliferative retinopathy since this may not be associated with peripheral retinal capillary closure. Most studies have suggested that presence of three to five cotton wool spots are more predictive of widespread retinal ischaemia. One

or two cotton wool spots (not in the macula area) would still therefore be classed as background diabetic retinopathy.

Proliferative retinopathy

In this stage of diabetic retinopathy, severe retinal ischaemia leads to new vessel formation (angiogenesis) on the optic disc, the retina or the iris (see Figures 11 & 12). Short and long term consequences of new vessel formation are serious. 16% of diabetic patients with proliferative disease will develop severe visual loss within 2 years, if left untreated.

It is thought that new vessels develop in response to the production of angiogenic factors, (eg VEGF), which are released by the ischaemic retina. The new vessels form fine, fan-like networks that grow into the vitreo-retinal interface. They are usually asymptomatic until they rupture, leading to pre-retinal, subhyaloid or vitreous haemorrhage (Figure 13). Initially, haemorrhage into the vitreous results in symptoms of seeing floaters in the vision, described as tadpoles, spiders or cobwebs. Major haemorrhage into the vitreous gel may result in sudden and profound visual loss, which may take many months to resolve. The new vessels will in time become avascular and fibrose (gliose), and this is the aim of pan- retinal photocoagulation (PRP) treatment. Gliosis of the new vessels may be associated with recurrent haemorrhage and vitreo-retinal traction , which may result in retinal detachment, which is of particular concern if the macula region is threatened. (Figure 14).

An advanced change of proliferative diabetic retinopathy includes angiogenesis of the iris, termed iris neovascularisation (rubeosis iridis) (figure 15) which may lead to rubeotic glaucoma and often carries a poor visual prognosis .

Laser therapy

Laser treatment is carried out through a dilated pupil using a contact lens applied to the cornea anaesthetised by topical anaesthetic drops (Figure 16). There are a number of different lasers used, but the most common is the Argon laser with wavelengths chosen between 488 to 577 nm. Laser treatment causes thermal damage by absorption of light energy into pigmented retinal tissues and is a destructive treatment.

Maculopathy

The rationale of laser treatment of maculopathy is to resolve the areas of macula oedema before encroachment on the fovea and hence prevent reduction of vision. Laser treatment is applied either as focal or grid treatment (figures 17 & 18), guided by the site and degree of macula oedema. (7)The exact mechanism of the benefit of macula laser is still unclear. Some authors believe it may result from regeneration of healthy retinal pigment epithelium (RPE) resulting in restoration of normal fluid control processes , hence reducing the oedema.. Other authors suggest that it is crucial to apply laser directly to leaking microaneurysms, leading to their resolution.

Resolution of the signs of maculopathy may take some months to occur. Where sight-threatening macula oedema exists, laser treatment will reduce the risk of visual

deterioration in at least 50-60% of patients. The response to macula laser for focal diabetic maculopathy is better than grid macula laser treatment performed for diffuse macula oedema. If ischaemic maculopathy is clinically suspected, fluorescein angiography should be performed to assess the foveal and macula capillary circulation. If significant macula ischaemia is identified, laser treatment is likely to be of limited benefit and, indeed, may be deleterious to visual outcome. The latter emphasises the importance of fluorescein angiography in maculopathy assessment.

. Complications of macula laser treatment include scotoma, and rarely, loss of acuity due to accidental direct foveal laser treatment. Visual loss may also result from extension of a laser reaction / scar close to the para-foveal region, extending over time into the central fovea.

Treatment of proliferative diabetic retinopathy

The initial diagnosis of proliferative retinopathy with new vessel formation on the optic disc or in the peripheral retina should be treated with urgency. Treatment of this condition with pan retinal photocoagulation (PRP) (figure 19) is comfortable for most patients with modern laser settings. Discomfort can mostly be alleviated by carrying out treatment with prior simple oral analgesics, but on rare occasions can require local or general anaesthesia. Recent refinements in the settings of power and duration of laser burns have reduced the discomfort of this treatment.

PRP consists of multiple laser burns applied to the peripheral retina, including the peripheral macular area and nasal to the optic disc, and usually requires 3,000 laser

burns. These would typically be given in three treatment sessions of 1,000 burns each, but some patients may be laser resistant and require up to 9,000 laser burns .

Without laser intervention, the risk of severe visual loss in these patients is 50-70% at 2 and 5 years follow-up. The beneficial effects of pan retinal photocoagulation have been demonstrated in large randomised trials, showing at least 50% reduction in severe visual loss in eyes that have been laser treated eyes . Indeed, the combination of improved glycaemic control, effective treatment of cardiovascular risk factors, timely laser treatment, and vitrectomy surgery, has resulted in blindness now being relatively rare in type 1 diabetes.

Pan retinal photocoagulation is not without complications. As the new retinal vessels involute and gliose, they may bleed and give rise to vitreous haemorrhage. Loss of peripheral vision may occur which after full pan retinal photocoagulation treatment may result in visual field reduction by 40-50%. If treatment involves both retinae (bilateral) , this can reduce the peripheral visual fields sufficient to affect legal driving status. Other adverse effects include reduction in night vision and contrast sensitivity. Of importance to PRP treatment is the presence of coexisting macula oedema with proliferative disease. PRP may exacerbate co-existing macula oedema, and therefore focal or grid macula laser treatment should be applied prior to pan retinal photocoagulation, particularly in type 2 diabetics.

Vitrectomy

Pars plana vitrectomy is a microsurgical operation which involves the insertion of surgical instruments into the vitreous cavity, under general or local anaesthesia.

This technique allows removal of the vitreous, dissection of new vessels and traction present, as well as laser endo-photocoagulation.

The aim of vitrectomy is to remove the scaffold along which further fibrovascular proliferation occurs, removal of existing vitreous haemorrhage, as well as repair of retinal detachment and excision of tractional membranes.

Whilst the results from appropriate and timely vitrectomy surgery are excellent, with > 70% patients having visual improvement and stabilisation of diabetic retinopathy, serious complications may occur. These include progressive iris rubeosis, glaucoma, retinal detachment, recurrent vitreous haemorrhage, and cataract.

Medical management of diabetic retinopathy

The UKPDS, DCCT, and the many hypertension trials have provided proof that tight control of hyperglycaemia and hypertension are of major benefit to patients with diabetic complications, including retinopathy.⁽⁴⁾ Targets for medical management include:

- Glycated haemoglobin <7%
- Blood pressure – systolic <130 and diastolic <80 mmHg
- Serum cholesterol <4.8 mmol/l
- Discontinuation of cigarette smoking.

- All patients with diabetic retinopathy should be aspirin (75mg daily) (unless medical contraindication).

Whilst there is firm evidence that ACE inhibition benefits the progression of diabetic nephropathy, the data for diabetic retinopathy is less robust. Studies looking at potential benefit of angiotensin II receptor antagonists in diabetic retinopathy are currently being performed.

The benefit with tight control of all risk factors in terms of visual outcome for patients has been clearly demonstrated in the large UKPDS study in type 2 diabetes. This showed a 25% reduction in mainly focal laser treatment requirement through tight glycaemic and blood pressure control, which should have a significant impact on medical and ophthalmological practise. Despite the improved knowledge regarding medical management there will remain for the future the necessity to screen for, and treat diabetic retinopathy. In addition, the numbers of patients with type 2 diabetes continue to increase in an exponential fashion.

Diabetic Retinopathy Screening

It is widely accepted that screening for the early changes of sight threatening diabetic retinopathy is worthwhile and cost effective. This centres around the low cost of

detection of retinopathy, set against the large monetary and social costs of blindness, and most

importantly, **that laser treatment is most effective before there are visual symptoms, as it generally prevents visual loss (visual protection) rather than improving visual acuity .**

Whilst in Europe and the USA there are sufficient ophthalmologists for screening, in the UK and other countries this is not the case. This has led to the National Diabetic Retinopathy Screening Programme currently being implemented. The core components of this are shown in Figure 20. This programme is to provide systematic retinal screening through dilated pupils on an annual basis to all diabetics, with a requirement for accurate diabetic patient registers, and a target to screen 100 % of diabetic patients by the end of 2007.

Digital photography has been chosen as the screening method of choice, largely as it provides excellent retinal images , with a high sensitivity (93%) and specificity (97 %), as well providing a hard copy of the screen which can be quality assured. The schemes will have standard digital retinal photographs of a macula centred , and /or an optic disc centred view. A detailed description of the National DR Screening programme is available on the National Screening Website - www.nscretinopathy.org.uk.

Grading and Referrals

Grading of retinal images will be performed according to three levels of expertise.

Primary grading is grading of retinal images identifying whether the images are **normal** or **abnormal** . **Secondary** grading categorises the **precise** diabetic retinopathy disease

level . **Tertiary** grading is confirming or refining the exact diagnosis, leading to an appropriate **clinical action** and **outcome**.

A national grading system has been formulated to ensure appropriate referral at the right time to diabetic eye services. The grading categories and clinical outcomes (figure 21) will be familiar, but have been allocated a number coding eg R 1 = background DR. Maculopathy requiring referral to the diabetic eye service has been defined according to the best surrogate predictors of macula oedema (figure 22). Whilst this grading system and categorisation is the one chosen for England, there are variations between the four nation schemes of the UK. For example, it is recommended that the common combination of microaneurysms within the macula region and normal vision, has annual follow-up in the English scheme, but in other schemes of the four nations, the recommendation is for a 6 monthly retinal re-screen. Recent data has however suggested that only annual follow-up is required.

Quality Assurance (QA) and Staff Training

Quality assurance, regular reports and audits will underpin the whole national diabetic retinopathy screening programme, with checks required at each stage of the screening process. A summary of the key quality assurance (QA) areas for the National Diabetic Retinopathy Screening programme are shown in figure 23.

It is note worthy that a number of the QA targets not only relate to the screening process, but of the timings and outcomes of the diabetic eye services. In addition, there are requirements for appropriate timing of laser therapy as well as recording visual outcomes. A requirement that the schemes show a 50 % reduction of blindness rate in

diabetic subjects over 5 years has been stipulated , but this may already partly have been achieved in areas that have well established screening programmes .

For grading of retinal images, the QA standard is regrading of 10 % of all normal images, and of all abnormal images at primary and secondary grading levels.. To achieve this will require additional staffing. A typical screening programme of 10,000 diabetic patients will require additional screening personnel of 0.5 whole time equivalent (for example, trained photographer or optometrist). It is expected that approximately 10% of patients' images will be ungradeable owing to the presence of cataract reducing the image clarity. Provision needs to be made for such patients to be screened in diabetic eye services or dedicated screening clinics.

New and existing staff will need to be appropriately trained for the national diabetic retinopathy scheme. An accreditation programme has been devised of 8 learning units (and competencies, to secondary level grading), which after assessment, will lead to a new nationally recognised diploma award.

Implications for Health Care Providers

Health care providers (HCP) for diabetic populations will be responsible for meeting the targets defined by the national screening programme, and costings have been calculated for typical schemes (see NSC website). HCP 's with a diabetic population significantly less than 12,000 in number , should join with other neighbouring scheme/s to provide this minimum number of patients . Common adopted models for screening programmes is shown in table . Staff should be identified early to take part in the scheme and appropriate training provided. At present, the costs of this are not available from

workforce confederations but it is anticipated that funding for new retinal screening staff should subsequently become available from PCT's.

Does screening prevent blindness in diabetic patients

The main requirement of the national screening programme is that this should be the case i.e. screening, and correct and timely referral to diabetic eye services with appropriate laser therapy should prevent visual loss. Laser does not have a 100% success rate, and indeed digital imaging has inaccuracies, largely due to the fact that the images are not stereoscopic (i.e. they do not identify macula oedema) and not all the peripheral retina is photographed (i.e. the screening can miss peripheral new vessels).

Despite these limitations, the available evidence is that screening can have a major impact on visual outcome. The most comprehensive study has been performed in Stockholm County which undertook a detailed screening programme with mobile fundus photography in addition to enhanced hospital eye services.(16) This study showed a mean reduction of patients registered blind by 47%, reflecting a change of five year average annual incidence rate from 1.2 to 0.33 per 100,000 population. Data from two studies in the United Kingdom support this favourable impact.

Summary

Diabetic retinopathy is still one of the common causes of blindness in the world, despite available proven medical and ophthalmological treatments. The achievement of cardiovascular risk factor and glycated haemoglobin targets are emphasised, but

identification of diabetic retinopathy early in the disease process is critical for optimal treatment outcomes , leading to the important concept of screening.

All healthcare professionals involved in diabetes care will become involved to some measure in the new National Diabetic Retinopathy Screening Programme. Correct implementation will undoubtedly save vision and should have a major effect on reduction of blindness within our diabetic population, and should be cost effective. It will be the duty of all healthcare professionals involved in diabetes care, for example, diabetologists, ophthalmologists, general practitioners, optometrists, diabetes specialist nurses, practice nurses, (and the empowered diabetic subject) to be involved in making sure of the goal that all diabetics have an annual diabetic retinopathy digital retinal photographic screen.

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