DIABETIC EYE DISEASE*

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Prevalence of known diabetes within the UK is now about 2%, indicating that over one million people suffer from this condition. Of the many complications of diabetes, blindness is perhaps the most feared. Despite this, much can be done to prevent its occurrence and improve the quality of life of patients with diabetes. In this article the causative mechanisms and the clinical aspects of diabetic eye disease are discussed.

TABLE 1
Epidemiology of Diabetic Eye Disease

- Type 1 Diabetes: 72% will develop proliferative retinopathy at some time
- Type 2 Diabetes: Around 30% have eye disease at diagnosis
- Incidence of blindness: 0.8-1.8 per 100,000

1. DIABETES AND RETINOPATHY – EPIDEMIOLOGY (TABLE 1)

1.1 Epidemiology of non-sight threatening eye disease

It is impossible to separate the prevalence of diabetic retinopathy from the length of duration of the disease. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[1-3] provided the first accurate data on the prevalence of diabetic retinopathy; prior to this study most data were collected from studies of patients in secondary and tertiary care in whom severe disease is likely to be over-represented.[4]

In type 1 diabetes, diabetic retinopathy (DR) of any severity was present in 17% within five years of onset, 75% within ten years, 97% within fifteen years and 98% after twenty years or more.[1] In patients with type 2 diabetes, the figures were 29%, 60%, 70% and 82% respectively.[2] The higher initial figure in type 2 diabetes reflects the subclinical period of undetected dysglycaemia resulting in eye disease at diagnosis which does not occur with the acute onset of type 1 disease. As a simple estimate of point prevalence, unstratified by duration of disease, a study in northern Italy[5] found background DR in 24.4% of patients with diabetes; in this study type 1 and type 2 (insulin- and tablet-controlled) were combined.

The elderly are often neglected in studies of DR. In the study of patients aged over 70 years in Finland, background DR change was found in 21% of eyes (all type 2 diabetes).[6] In an Australian study of an elderly population the point prevalence of non sight-threatening DR was 30.8%,[7] whilst in Denmark non sight-threatening DR was found in 38% of 306 non insulin-treated patients.[8]

As the diagnosis of type 2 diabetes almost invariably follows a period of undiagnosed dysglycaemia during which end-organ damage may occur, signs of DR (sight-threatening or non sight-threatening) may already be present at diagnosis. Of 2,964 patients in whom intra-ocular photographs were available for both eyes at the time of their inclusion in the United Kingdom Prospective Diabetic Study (UKPDS) (type 2 diabetes only), 30.7% of patients had signs of non sight-threatening DR, but in 19% (more than half the group) this was present in only one eye.[9] This level of DR at diagnosis is much higher than in the Blue Mountains[7] (15.8%) and Beaver Dam[10] (8%) eye studies. This is explained by the diagnostic criteria used in the UKPDS in which 97% of those with DR had three, or fewer, microaneurysms only.[11]

1.2 Epidemiology of sight-threatening eye disease

On the basis of the best experimental[12-16] and epidemiologic data available, models have been developed in an attempt to describe the lifetime risk of significant retinal disease and / or visual disability in diabetes. [17-20] These models are based exclusively on US data and the screening recommendations of the American Academy of Ophthalmologists, and cautious application to other countries is advisable. According to these models, 72% of patients with type 1 diabetes will eventually develop proliferative diabetic retinopathy (PDR) and 42% will develop sight-threatening macular oedema (ST-maculopathy).[21]

In a UK series of 1,000 consecutive patients attending a diabetic clinic, 9.5% were classified as having serious DR (either ST-maculopathy (38 patients), severe non-proliferative / ischaemic retinopathy (19 patients) or PDR (38 patients))[22] requiring urgent ophthalmological assessment and, often, urgent photocoagulation. In another clinic-based study, Grey *et al*. found sight-threatening DR in 6.5% of 658 patients in a diabetic clinic.[23]

One of the earliest community-based studies,[24] based on a single general practice list, found that 11% of the 76 diabetic patients on that list had sight-threatening DR; ten years later a study in an English town found that in type 2 diabetes 2-4% of patients had PDR and 5-10% had ST-maculopathy, with 9% and 14% respectively in type 1 diabetes.[25] In a population-based retinal screening survey of over 2,000 patients, we identified 8% of patients requiring referral to an ophthalmologist.[26] In the Blue Mountain Eye Study of 253 elderly non-insulin treated type 2 diabetic patients, only 2.9% had ST-maculopathy and none had PDR.[7] In the WESDR the point prevalence of PDR in 674 insulin-treated type 2 patients was 10.7%.[2] In 696 non insulin-treated type 2 patients the prevalence of PDR was much lower at 2.2%[2] and the prevalence of ST-maculopathy 3.7%[27] In type 1 disease the prevalence of PDR was 16.8% (of 902 patients) and a further 0.3% had evidence of previous laser treatment implying regressed, treated disease.[1] In 189 patients with type 1 DM of less than 10 years' duration at baseline, during an average further follow-up of six years (range 0-12), 22% of patients developed ST-maculopathy.[28] All patients who developed ST-maculopathy had diabetes

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for more than ten years. The average incidence of ST-maculopathy in patients with disease duration greater than ten years was 7% *per annum*.

Based on these and other data[20,21,29] and the prevalence of diabetes in 1998, it has been estimated that 63,000 new cases of PDR, 56,000 cases of ST-maculopathy and 5,000 new cases of blindness (that could be registered as such by law) occur each year in the US.[30] Given that the US population is four-fold greater and the prevalence of diabetes is about two-fold greater than the UK, one would expect the equivalent figures to be very approximately eight-fold less in this country compared to the US. Epidemiological data from developing countries is less robust. The prevalence of diabetes seems to be escalating in these countries, especially in the Indian sub-continent, as the incidence of obesity increases. Within the diabetic population the prevalence of diabetic eye disease seems to be broadly similar to that seen in the WESDR, with an overall prevalence of 37% and a 10% prevalence of PDR in one study of 47,499 patients referred to an outpatient clinic.[31]

1.3 Epidemiology of visual disability and blindness

Obtaining accurate data on the true prevalence and incidence of visual disability is, however, remarkably difficult. In terms of diabetic morbidity few complications are as feared, perhaps, as blindness. DR is the commonest cause of blindness[24,32,33] and blind registration[34-36] in adults aged between 16 and 64 years, the second commonest cause of registered blindness in those aged between 45 and 74 years[37] and the third commonest cause of severe visual disability in all age groups.[36] DR is estimated to be responsible for blindness in over 2.5 million people world-wide.[38] It is estimated that a person with diabetes is ten to twenty times more likely to suffer blindness than someone without and that a patient with diabetes has had a risk of visual loss of 33% over a 40-year follow-up period.[39]

Blindness is defined by WHO, and in the UK, as vision less than 3/60 in the better eye, although better acuity may be accepted if concomitantly the field of vision is significantly impaired. Partial-sighted registration is more loosely defined, but is rarely considered if the vision is better than 6/24.

In West Germany citizens registered as blind are entitled to a substantial financial allowance (500-1000 Deutschmarks per month), and consequently registration data are more likely to be complete.[40] Based on such data over the three-year period from 1990-93 in West Germany, an incidence of blind registration of 60 per 100,000 patient-years (after direct standardisation to German population) was estimated.[40] Diabetes was unlikely to be the sole cause in 59% of registered cases and the incidence of blindness to which diabetes was the sole contributory cause was thus 34.7 per 100,000 patient-years. The relative risk of blindness in this group compared to the non-diabetic population was 3.0 (95% CI 1.54-5.81). In Britain pecuniary privileges are considerably less and the Royal National Institute for the Blind (RNIB) estimate that only 36% of those entitled to blind registration and 13% of those entitled to partial-sight registration are actually registered.[41] This renders problematic estimates of the burden of visual loss from all causes, and from diabetes in particular, derived from these data. Further problems derive from the fact that blindness due to diabetes is not always coded as such, and conversely blindness from other causes occurring in the presence of concurrent but unrelated diabetes may be assumed to be due to diabetes.[42] Non-diabetic causes of blindness in blind patients with diabetes have been found to account for between 34%[40] and 78% of registered blindness.[43,44] It is also worth noting that forms sent to the OPCS are anonymous and de-registration, for example after restoration of sight by cataract extraction, cannot take place.[36] Data from the OPCS are released only occasionally, and in consequence the prevalence and incidence of registered blindness in the UK is unknown. In Tayside the incidence of blind registration due to diabetes was 53 per 100,000 patient-years in a screened population, of which 18% was blind registration and the remainder partial-sighted registration.[43] Estimates of 81[45] and 90[44] per 100,000 patient-years have been obtained elsewhere.

Studies addressing visual disability in diabetes as a percentage of the general population have found fairly consistent rates. A Swedish study based on self-referrals to vision rehabilitation centres estimated an incidence of legal blindness in diabetes of 0.85 per 100,000 of the general population.[46] This compares with the 0.95 per 100,000 found by Evans in the UK.[42] In Avon, Grey recorded that 6% of the overall rate of blind registration of 30 per 100,000 of the general population was due to diabetes, and DR was recorded as present in a further 8.4% (where it may have had a contributory role but was not sole cause of visual disability).[35] The resulting figure of 1.8 per 100,000 of the general population is approximately twice that found by Evans and Backlund[42,46] but almost identical to the rate of 1.6 per 100,000 of the general population in West Germany.[40] Estimates based on clinical studies are also problematic. Early data was based on self-reported visual disability[47] and are open to selection bias by being based on a highly selected patient group.[48] In the WESDR the ten-year incidence of blindness was 1.8%, 4.0% and 4.8% and of visual impairment (a loss of three lines of ETDRS acuity) 9.4%, 37.2% and 23.9% in type 1, type 2 insulin treated and type 2 non-insulin treated disease respectively.[49] Again diabetes was not the sole cause of the blindness. In an earlier report of the same cohort, diabetes was thought to account for 69%, 42% and 26% of visual impairment in these three groups.[50]

Such studies based on incidence data may underestimate the lifetime risk of blindness since the major cause of loss to follow-up was death of patients and it has been shown that the incidence of blindness in those that died during the follow-up period of another study was three times that of the surviving cohort.[51] It has been estimated that in the UK, 8,000-10,000 diabetic patients are blind and over 90% of those identified are over the age of 70 years.[52]

2. PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

Basement membrane thickening, capillary closure (possibly as a result of endothelial dysfunction), and capillary hyperperfusion causing tissue oedema all act synergistically to promote retinal ischaemia. Reduction in the content of heparan sulphate and other charged membrane-bound particles are also associated with an increased membrane permeability. Increased protein and carbohydrate content of the basement membrane with protein glycation, and production of advanced glycation end-products (AGE) also occurs. These AGE, along with retinal hypoxia, stimulate release of growth factors such as VEGF,[53,54] hepatocyte growth factor,[55,56] IGF-1[57] fibroblast growth factor and other

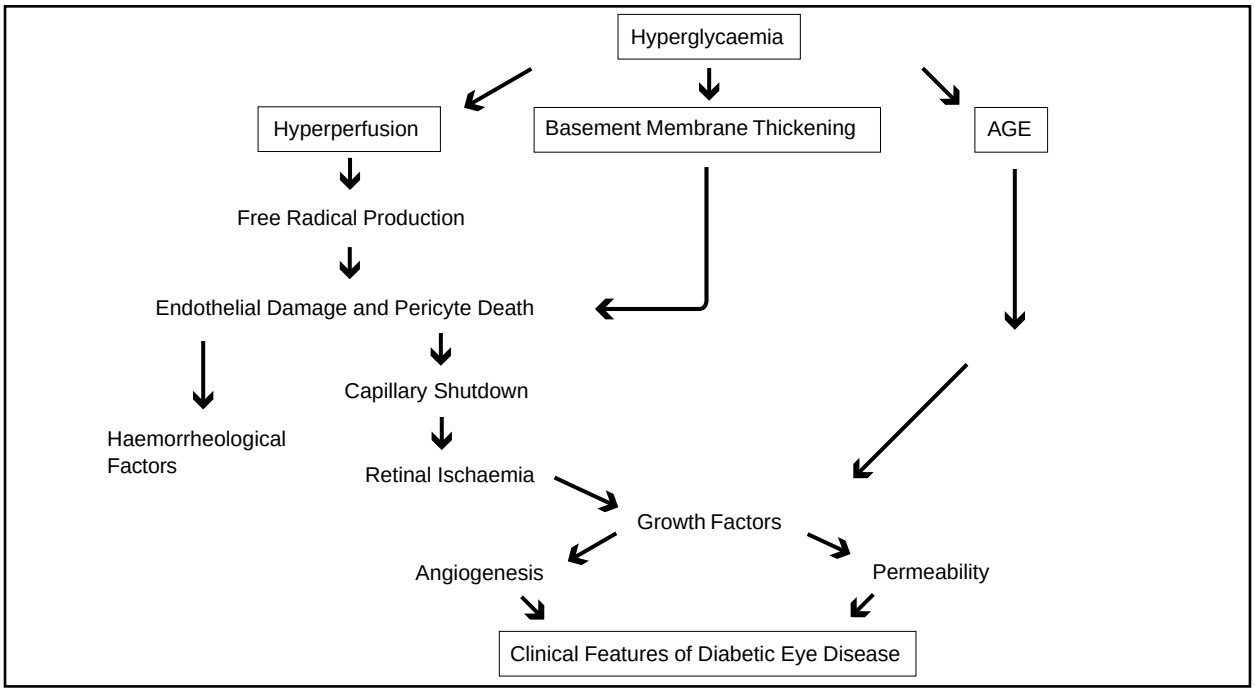

FIGURE 1
Pathophysiological pathways leading to the development of background retinopathy and proliferative retinopathy

soluble agents, which are found in increased concentrations in the vitreous,[58,59] and stimulate new vessel formation and increased permeability (Figure 1). In diabetic maculopathy increased permeability of the blood-retinal barrier[60] resulting in exudates of lipid and proteinaceous material, with or without extracellular oedema, cause physical distortion of the retinal micro-architecture. Exudates can occur anywhere in the retina, but are clinically significant if near the macula, particularly if within one disc diameter of the fovea. Increasing age and hypertension are thought to be particularly associated with maculopathy,[61] as are increased serum concentrations of total and LDL-cholesterol.[62]

The role of tissue hyperperfusion in the development of diabetic glomerulonephropathy has been well demonstrated.[63] Both experimentally[64] and in observational studies[65] hyperglycaemia has been shown to result in retinal hyperperfusion. The hyperperfusion is not seen in controls matched for disease duration who do not have any microvascular complications.[66] This indicates that hyperperfusion is probably a key step in the development of retinopathy as it appears to be for nephropathy. The acceleration of DR seen in association with the hyperdynamic changes of pregnancy, the synergistic effect of hypertension, and the relative protection conferred by unilateral internal carotid stenosis, confirm the importance of hyperperfusion injury in the process of vascular damage in DR.

The possible role of IGF-1 as an important factor in proliferative retinopathy is demonstrated by two examples. Raised serum growth hormone (GH) concentrations are found in patients with diabetes, and in particular if complications are present;[67] GH is a stimulus for IGF-1. Lowering GH by ablating the pituitary with yttrium implants is an effective treatment for proliferative retinopathy.[68] DR often deteriorates after a time of tightening diabetic control; this is usually associated with increased doses of insulin which is another stimulus for IGF-1 production. Although total serum concentrations of IGF-1 in patients with diabetes are lower than controls,[69] diabetic patients with retinopathy have higher IGF-1 concentrations in the vitreous[58] than diabetic patients without retinopathy. This indicates that high serum GH concentrations may be important in stimulating local tissue IGF-1 concentrations which act as local growth stimulators, despite serum total IGF-1 concentrations being lower. Ironically, IGF-1 administration has been used as a treatment in diabetes, lowering GH concentrations by negative feedback mechanisms and achieving improved glycaemic control.[70] The long-term impact of IGF-1 on diabetic complications such as retinopathy will require close scrutiny as theoretically it could be argued both to slow or to accelerate progression of retinopathy.[67]

Haemorrheological factors such as increased fibrinogen and increased erythrocyte adhesiveness are associated with DR as well as altered plasminogen activator inhibitor 1 (PAI-1) and possibly act to exacerbate the problems of capillary fragility and retinal hypoxia. *A priori* conditions exacerbating retinal ischaemia, such as smoking, would be expected to cause a deterioration in retinopathy although epidemiological data are conflicting as to the importance of this additional confounding factor.

It has long been observed that in some patients DR advances rapidly despite appropriate treatment, whilst in others many years of disease are associated with only mild retinal signs. A genetic predisposition towards developing severe complications has been observed[72] and markers for increased risk of developing severe retinopathy have been identified in type 1 (HLA DQB 1*0201/0302) diabetics.[73] Risk factors classically associated with PDR are shown in Table 4.

3. CLINICAL FEATURES

3.1 Background retinopathy

Background retinopathy may include microaneurysms, dot haemorrhages, a few scattered hard exudates, some venous dilatation.[74] 'Cotton wool' spots are now believed to be

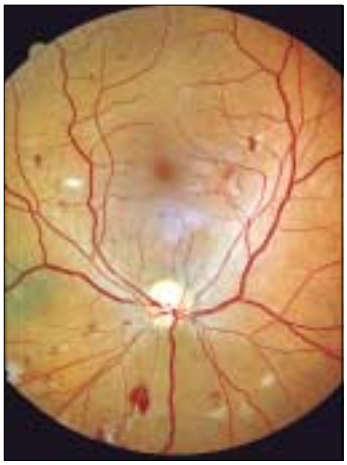

FIGURE 2
Pre-proliferative changes with multiple haemorrhages, deep red haemorrhages, around 6 cotton wool spots and venous distension.

FIGURE 3
New vessels at the disc (NVD).

FIGURE 4
Vitreous haemorrhage resulting in visual loss.

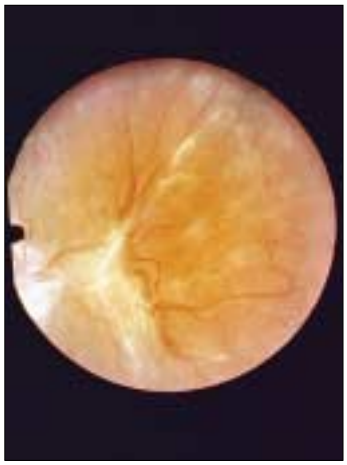

FIGURE 5
Fibrous scarring.

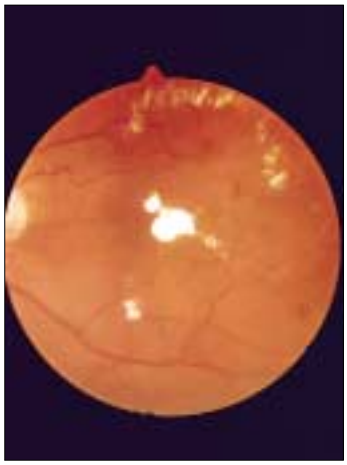

FIGURE 6
Focal macular exudate.

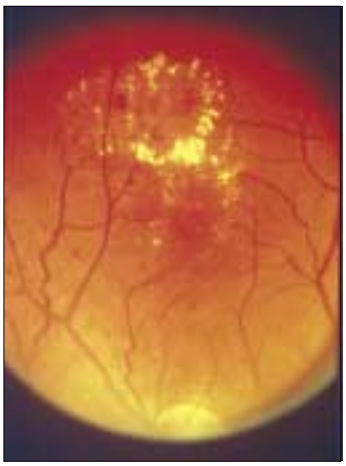

FIGURE 7
Macular circinate (ring) within one disc diameter of the fovea.

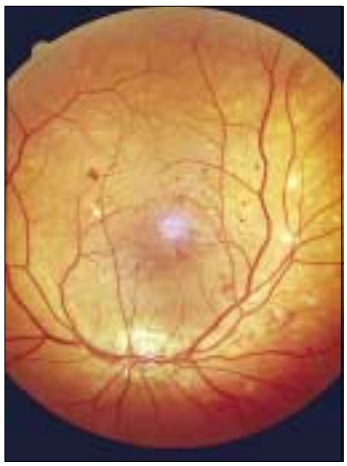

FIGURE 8
Macular oedema resulting in impaired vision.

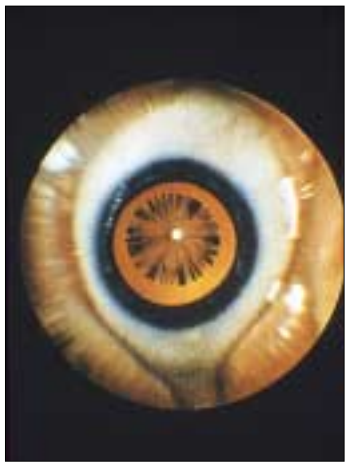

FIGURE 9
Stellate cataract, classical of diabetes.

TABLE 2
Clinical Features of Diabetic Retinopathy

Pre-proliferative changes	Proliferative changes
Venous irregularities (beading, loops)	New Vessels at Disc (NVD)
Multiple and increasing haemorrhages	New Vessels Elsewhere (NVE)
Several deep red haemorrhages	Fibrous proliferation
Multiple cotton wool spots (6 or more)	Vitreous/pre-retinal haemorrhage
IRMA	

less significant, and as long as there are five or less, these can be considered as non-aggressive and categorised as background changes.[74] Features classified as rendering patients 'at risk' of proliferative changes are termed 'pre-proliferative', and these include venous irregularities (beading, loops), multiple and increasing haemorrhages, several deep red haemorrhages, multiple cotton wool spots (six or more) and intra-retinal microvascular abnormalities (Figure 2). In some circumstances, pre-proliferative changes may warrant laser photocoagulation, but otherwise, certainly four-monthly review (Table 2).

The number of microaneurysms identified is a useful predictor of progression towards proliferative diabetic eye disease,[75] and probably reflects the extent of microvascular disease. The rate of change of microaneurysm count is most predictive. If the number of microaneurysms increases by sixteen or three-fold, then the rate of sight-threatening diabetic eye disease increases to three to nine times.[76]

3.2 Proliferative retinopathy and maculopathy

The presence of new vessels (Figure 3), either at the disc (NVD) or elsewhere (NVE) are usually asymptomatic until vitreous haemorrhage occurs (Figure 4), which in turn results in fibrous scarring (Figure 5). Vessels usually have a fan-like appearance, and can be flat or spread forward into the vitreous. These vessels are 'leaky', and this can be demonstrated clearly by fluorescein angiography. At this stage pan-retinal photocoagulation is required (see below).

Since the onset of effective laser treatment, diabetic maculopathy (Table 3) is now a more common cause of visual loss in diabetic patients than is proliferative retinopathy. Maculopathy becomes clinically significant when foveal oedema occurs. It may be focal (Figure 6) with rings, or circinates, of exudates which occur around a focal site of increased permeability (Figure 7), and may result in macular oedema (Figure 8). If the increased permeability is more generalised, then diffuse exudates may be seen and are associated with cystoid macular oedema. Finally, ischaemic maculopathy is associated with a few deep haemorrhages, some fine vessels and a pale featureless appearance. Ischaemic maculopathy may be difficult to identify clinically but can be confirmed by fluorescein angiography. Focal or grid laser is the treatment of choice for maculopathy. Clinically significant macular oedema is an indication for laser

TABLE 3
Clinical Features of Maculopathy

- Focal – circinates
- Diffuse
- Cystoid
- Ischaemic

photocoagulation and can develop from any of the above forms of maculopathy. It is defined as:

A. thickening of the retina at or within 500 mm of the centre of the macula;
B. hard exudate within 500 mm of the macula if associated with retinal thickening; or
C. a zone of retinal thickening one disc area or larger within one disc diameter of the macula.

3.3 Other eye disease

Cataract occurs more frequently and develops earlier in diabetes than in age-matched controls (Figure 9). Cataract may also progress more rapidly in diabetes and, in addition to operating to restore sight, surgery may be required to aid screening for sight-threatening retinopathy. DR may develop *de novo* or progress following cataract extraction, particularly if the procedure is complicated, possibly due to disruption of the blood-retinal barrier. Diabetic patients who have undergone surgery should probably remain under the care of the ophthalmologist until it is clear that there has been no progression of disease. An association between diabetes and angle closure glaucoma has been reported[77] and it has been postulated that the autonomic diabetes-induced neuropathy of the iris sphincter may be responsible for this. Several well-conducted population-based studies have confirmed an association between open angle glaucoma (POAG) and diabetes[78-80] with a relative risk of between 1.6 and 3.11 for the development of POAG. The largest study to date, however, failed to confirm any association apart from that explained by referral bias,[81] and it has been estimated that the number needed to screen to detect one case of POAG is between 760 and 1,120 previously unscreened patients *per annum* (unpublished data).

TABLE 4
Risk factors for the onset and progressionof diabetic retinopathy

- Duration of Diabetes
- Glycaemic control
- Smoking
- Hypertension
- Pregnancy

4. PREVENTION

4.1 Duration

The main aetiological factors for DR are shown in Table 4, and most are modifiable; even duration of diabetes could be influenced. For a patient who has a high genetic risk of developing diabetes, concerted weight reduction and a healthy diet will probably delay the onset of diabetes and may reduce their life-time duration of diabetes, thus reducing their risk of late complications such as sight-threatening

TABLE 5
Component parts of a screening programme for diabetic retinopathy

1. Identification of diabetic patients in region
2. Enabling patients to attend screening process
3. Effective screening tool
4. Creating efficient referral links
5. Effective treatment
6. Follow-up
7. Quality assurance of system (audit / reappraisal)

retinopathy. Such health promotion could be targeted at those with a strong family history of diabetes and those who have had gestational diabetes.

4.2 Hyperglycaemia

Chronic hyperglycaemia is an established risk factor for both the onset and the progression of DR and macular oedema.[82,83] Each 1% increase in glycosylated haemoglobin (HbA1c) approximately doubles the risk of retinopathy.[82] In the DCCT trial, intensive glycaemic control in type 1 diabetes reduced the rate of onset of DR from 4.7 to 1.2 per 100 patient-years, whilst the progression from background to proliferative retinopathy was reduced from 2.4 to 1.1 per 100 patient-years, with a more than two-fold reduction in the need for laser treatment.[83] More recently a similar benefit has been demonstrated in type 2 diabetes. Intensive compared to conventional diabetic control resulted in a reduction in need for laser from 1.1 to 0.79 per 100 patient years ($p=0.003$).[84] Although the risk reduction seems less in the type 2 patients, when comparing intensive and conventional treatment, the glycosylated haemoglobin differential was only 0.9% in the trial involving type 2 patients, compared to 2% in the type 1 patients of the DCCT. If the difference in the glycosylated haemoglobin between the two groups in the UKPDS study was larger, it is reasonable to speculate that the risk reduction in DR may have been greater.

4.3 Smoking

Although smoking seems to be closely correlated with the risk of DR in most, but not all, studies,[85,86] no good studies have evaluated the effects of stopping smoking on the subsequent development and progression of retinopathy.

4.4 Blood pressure

The association with hypertension is variable and is based mainly on observational data. Although most workers have found an association between DR and hypertension,[61,87-90] in a study of older diabetic patients hypertension was not found to be an independent association with retinopathy;[7] this has been supported by other studies[91] and it is unclear whether the association is causal. The difficulties encountered are two-fold. Hypertension is associated with age, duration of diabetes and early diabetic kidney disease which is associated with glycaemic control. These variables are also all associated with retinopathy, making it difficult to be sure whether hypertension is a causative factor or an associated factor. The second issue is that hypertension and increasing age in non-diabetic patients is associated with the development of non-diabetic retinopathy which makes it difficult to distinguish between true diabetic and background retinopathy.[92,93] Thus the reported association between hypertensive and diabetic retinopathy may partially reflect the misclassification of hypertensive retinopathy. In type 2 diabetes at least, aggressive blood pressure control does delay and slow the progression of clinically significant DR,[94] indicating that control of blood pressure is very important in the management of DR and that many of these theoretical concerns are misplaced.

TABLE 6
Screening options for diabetic eye disease

Screening Tools	Personnel
Ophthalmoscope	Diabetologist
Retinal Camera	Optometrist (Community/Hospital)
Slit Lamp Biomicroscope	General Practitioner
	Technical Photographer

4.5 Pregnancy

Pregnancy is known to accelerate pre-existing DR but has less impact if there is an absence or only minimal retinopathy at conception.[95]

5. SCREENING FOR DIABETIC EYE DISEASE

Diabetic eye disease is an asymptomatic and common condition, with a potentially severe outcome. It has been estimated that eye examination had not previously been performed in 50% of diabetic patients who became blind even though they were known to be diabetic.[96] Techniques are available to detect diabetic eye disease at a modifiable stage, and the outcome of optimal early treatment is excellent, which makes DR disease an ideal condition to screen for. Screening can prevent blindness,[97,98] but in England and Wales nearly 10% of regions have no diabetic eye screening service, and of the remainder 27% may be screening less than half their diabetic population.[99]

There are several steps involved in an effective screening programme (Table 5), of which achieving a high-rate of coverage is probably the most difficult and at least as important as any of the other aspects. A comprehensive population-based district diabetes register is an essential pre-requisite to enable a co-ordinated, effective and efficient programme. It is clear that community health issues are important, but beyond this what is the best way to screen for diabetic eye disease?

Although flourescein angiography and seven-field stereoscopic photography are the gold standard tests for DR, they are not practical options for screening programmes. The main tools available are direct, and possibly indirect, ophthalmoscopy, retinal photography and possibly slit lamp biomicroscopy. Screening can be performed by diabetologists, community optometrists, hospital optometrists, general practitioners (GPs) or photography technical assistants, whilst ophthalmologists should be used to treat patients needing laser therapy and to arbitrate in difficult cases. In theory, any one of these tools can be

used by virtually any of these operators (Table 6).

In practice, the majority of patients are screened by a diabetologist or GP using an ophthalmoscope. Many GPs lack confidence and practice with an ophthalmoscope, and studies have reported sensitivities of such primary care screening as low as 40%[100] or less. Consequently most GPs prefer not to be responsible for retinal screening. However, direct ophthalmoscopy as performed by an expert ophthalmologist has been identified as only 65% sensitive at achieving the correct diagnosis when compared to slit lamp biomicroscopy.[101] For a screening programme, the accuracy of diagnosis is less important than the accuracy of referring, i.e. referring the correct patients even if it is for the wrong reasons. As a result the current debate is whether ophthalmoscopy is an adequate screening tool or not. In practice, the main alternatives to this are retinal photography and community optometry screening.

5.1 Retinal photography

Retinal cameras, whether static or housed in mobile vans, have been shown to be successful in screening for previously unrecognised DR in a number of clinical settings;[26,101-107] and in particular in rural settings.[108] The sensitivity of retinal photography was initially variable at 35-74% when compared to ophthalmoscopy[100,103] but the most recent cameras have demonstrated sensitivities of nearly 90% against the more exacting standards of slit lamp biomicroscopy.[101]

Various modifications can be used to try and improve the sensitivity of screening by retinal photography. Most UK units use mydriasis to avoid the problems caused by small pupils,[107] and some use multiple field photography to identify peripheral lesions:[101] screening sensitivity increased from 61% to 81% using a combination of mydriasis and three-field photography.[102] Although peripheral lesions can be missed,[104] their importance in determining need for referral is debated,[109] and most units photograph just one-field per eye. The quality of Polaroid film can be variable, and artifact can be difficult to distinguish from microaneurysms. The difference between normal photographs and mild background retinopathy makes no difference in terms of referral criteria to ophthalmology, but unfortunately it can have a profound effect on the patient. Some centres use 35 mm film; many others are moving towards digital imaging which give better quality images.[110] Digital imaging also makes administration and image storage easier. Future developments may enable automated analysis of digital imaging which could save considerable personnel time and hence reduce the costs of screening.

In a study examining the causes of blindness in a population who had undergone single field, undilated retinal photography as part of a screening programme, the main causes of blindness were:

A. non-diabetes related;
B. expected failure rate of laser photocoagulation; and
C. patient compliance factors and not the failure of screening.[43]

5.2 Optometry screening

In areas without specific diabetic screening programmes, as much as 39% of an ophthalmologist's workload can come from optometrists,[111] indicating that they are already identifying much previously unrecognised serious eye pathology and with sufficient accuracy.[112] Thus in some areas, organised screening programmes for diabetic eye disease have been developed involving community optometrists using dilated ophthalmoscopy or slit lamps.[113-116] Training of a selection of interested community optometrists within an area, and continued attention to quality assurance by providing annual updating sessions, can be the basis of a very useful screening programme.[114-115] Maintaining optometry interest and encouraging patients to attend can be a problem.[116] In England and Wales 64% of areas are now using optometrists for at least part of their screening programme[99] and some optometrists are using retinal cameras.

Hospital optometrists using slit lamps have been used as an alternative to community-based optometrists,[117] and have achieved sensitivities as high as 91%; it is indeed easier to train and maintain standards with just a few dedicated hospital optometrists. Use of slit lamps can be slow, but a more practical issue is finding trained individuals willing to be employed as hospital-based optometrists.

5.3 Combination of retinal photography and ophthalmoscopy

Since neither retinal photography or ophthalmoscopy is ideal, it has been suggested that screening should be performed by combining the two modalities[118] and this has been shown to identify previously unrecognised sight-threatening retinopathy.[119-120] It has also been demonstrated that screening sensitivity of ophthalmoscopy performed by a trained expert increases from between 62-82% to 84-100% when retinal photography is done in addition,[120-122] without any significant deterioration in specificity.[120] However, it is not clear whether these results suggest that dual modality screening is better than either modality on its own or simply whether that retinal photography is superior to ophthalmoscopy. In direct comparisons it has certainly been demonstrated that retinal photography was better than ophthalmoscopy with reported sensitivities of detecting sight-threatening DR being 87% and 66% respectively,[123,124] and it remains to be shown that ophthalmoscopy can increase the sensitivity of screening when added to the use of retinal photography alone. The addition of ophthalmoscopy to retinal photography may improve upon the specificity of the screening,[119] but it is unclear whether this would be cost-effective. The relative benefits of retinal photography over ophthalmoscopy may be less apparent in patients aged over 70 years.[125,126] The benefits of dual modality screening remain yet to be clearly demonstrated, especially considering the additional organisational problems and cost.

5.4 Cost benefit analysis

The cost of screening varies considerably with the number of patients 'processed' per unit time. Estimates of the costs of screening by direct ophthalmoscopy have varied from £13 in the community to £29 in hospital.[127,128] If performed by optometrists then this very much depends on what charge the community optometrist levies. Screening by hospital optometrists was costed at £16 per patient,[117] and mobile fundus photography was costed at £10 to £25 per patient depending on the number of fields photographed per eye.[101,108,127,128] These figures reflect direct costs, whilst the overall cost-effectiveness is of more relevance. The cost per sight-saving laser treatment has been estimated to be approximately £500-1200,[107,108,128] depending on which

TABLE 7
Treatment of Advanced Diabetic Eye Disease

Laser Photocoagulation
- Proliferative retinopathy: Pan-retinal photocoagulation
  - 1500-5000 laser burns
  - < 95% success
- Maculopathy: Focal or Grid laser
  - < 75% success

Vitreoretinal Surgery
- For vitreous haemorrhage and retinal detachment

Medical Management
- Glycaemic and blood pressure control
  - Useful for secondary as well as primary prevention

system is used and where. All studies have demonstrated that screening for diabetic eye disease is cost-saving when considering the costs of supporting visually impaired people in the community.

6. MANAGEMENT OF DIABETIC EYE DISEASE (TABLE 7)

6.1 Laser photocoagulation

Laser photocoagulation is the treatment of choice for proliferative retinopathy and maculopathy.[12,129] Early pan-retinal photocoagulation for proliferative retinopathy, and early focal and / or grid laser for maculopathy can have success rates of up to 95% and 75% respectively, at preventing clinically significant deterioration in vision.[130-132] During pan-retinal photocoagulation, a minimum of 1,500-2,000 burns should be applied outside the vascular arcades.[74] In severe or unresponsive disease, such in those diabetics with renal disease,[133] up to 5,000 burns or more may be required over several visits. In patients with fibrous scarring the laser may need to be applied more gradually and has to avoid the fibrous tissue to prevent acute haemorrhage. Co-existing maculopathy may occur in up to 30% of patients[134] and, since in older patients macular oedema may be exacerbated by panretinal photocoagulation, grid laser may need to be applied first.

Although not as successful as pan-retinal photo-coagulation for proliferative retinopathy, focal and grid laser for maculopathy is still an effective treatment. However, risks include inadvertent laser burns to the fovea and very rarely, with excessive laser energy used in focal treatment, damage to Bruch's membrane with subsequent neovascular membrane formation. Focal laser is more commonly used than grid laser, since exudative maculopathy is more frequently observed than diffuse oedematous maculopathy.[134]

Proliferative retinopathy and maculopathy can both deteriorate after cataract surgery.[135,136] Therefore, if possible, retinal disease should be stabilised prior to cataract surgery. Recently peroperative application of laser has been reported,[137] but this practice is not widespread.

Although early effective treatment of pre-symptomatic disease is optimal for diabetic patients, unfortunately this does not always occur in the UK. The referral chain can break down and up to a fifth may be referred late, jeopardizing their chances of effective laser treatment.[138] In a recent audit of patients with proliferative diabetic retinopathy, 29% presented to the ophthalmologist with symptoms and only 47% of patients needing laser were detected by organised screening, indicating that screening programmes in the UK are inadequate.[139] Up to 30% of symptomatic patients had to wait three months for an appointment and 32-40% received inadequate treatment. In 3.4% of patients less than 500 laser burns were administered, and in 18.8% of patients less than 800 burns were given,[139] despite the recommendations that a minimum of 2,000 laser burns should be applied.[15] The situation for treating diabetic maculopathy was marginally better with 62.5% of such patients being detected by screening and 35% waiting more than three months for laser treatment after detection.[134]

6.2 Vitrectomy

Vitrectomy should be considered for persistent vitreous haemorrhage to allow laser treatment and prevention of further haemorrhage.[140] Retinal detachment occurs in association, can be detected by ultrasound, and should be treated at the same time. Indications for vitrectomy are changing with improvements in instrumentation and referral for vitreo-retinal opinion should be sought sooner rather than later.

6.3 Glycaemic control

Once DR is established, achieving good glycaemic control will help prevent its progression,[83] and is worth striving for. There has been concern that rapid improvement in glycaemic control can cause a deterioration in retinopathy, and this may be one explanation for the deterioration of retinopathy observed during pregnancy, which is a time that women are often well motivated to improve their glycaemic control. This was re-emphasised in the DCCT trial where 13% of the intensive group and 7.6% of the control group had a deterioration in DR at six to twelve months after the start of the study;[141] after eighteen months the rate of DR in the intensive group was less than in controls. Even in the group who showed an initial deterioration of DR in the intensive glycaemic control, group outcomes were similar or better than those in the conventionally treated group.[141] Thus it seems that in terms of DR it is always worthwhile attempting to improve glycaemic control, except rarely when a patient has active pre-proliferative or proliferative disease when it may be advisable to wait until after successful laser treatment.

6.4 Medical treatment

Most diabetologists will treat hypertension aggressively in patients with DR in an attempt to prevent progression, as has been discussed above. In addition, recently it was shown that normotensive diabetic patients treated with the ACE inhibitor lisinopril were less likely to develop progressive retinopathy than controls,[142] indicating a protective effect of ACE inhibition; progression of retinopathy was not the primary end-point of this study, and those patients randomised to the lisinopril treatment group had a marginally, but statistically significant, lower HbA1c, indicating that this finding may be confounded or be a chance result, and needs verifying before recommending the widespread use of ACE inhibitors for patients with early retinopathy. Furthermore, the UKPDS[93] has shown that it is the absolute reduction in blood pressure rather than the drug used which is important, at least in diabetes.

Other medical treatments have been tried with variable success. In an attempt to replace the depleted content of heparan-sulphate in the retinal and glomerular basement membranes, six weeks of danaparoid has been used in patients with nephropathy and have been shown to reduce the number of hard exudates present, presumably by decreasing membrane permeability.[143] Whether these findings are of practical significance will have to be demonstrated in a larger and longer trial.

Aldose reductase inhibitors can be used to reduce sorbitol accumulation. They have been tried in DR, but they have been disappointing in practice.[144]

Aminoguanidine inhibits the formation of AGE and, in animal models, inhibits the progression of DR.[145] Trials of aminoguanidine in human patients are underway, but potential hepatotoxicity remains a major concern with this drug. A number of other medical treatments to prevent progression of DR are under development.[146] These include compounds to bind AGEs and prevent them binding to cellular receptors, agents to block the adverse effects of growth factors by inhibiting protein kinase C activity, and agents to block the increased activity of GLUT 1 receptors in the retina observed in DR patient.

7. CONCLUSIONS

The vast majority of visual impairment due to diabetes is preventable. The prevalence of diabetes is increasing, and diabetes is already the commonest cause of visual impairment in the working age group in Western countries. The tools used to screen for diabetic eye disease are ever improving, but the community health issues of screening for diabetic eye disease unfortunately are not so widely addressed. Once identified, laser photocoagulation treatment is effective for the vast majority of cases of proliferative retinopathy and maculopathy, although not 100% perfect. A number of adjunctive medical therapies are under development.

Much has been done to improve the outcome of eye disease in patients with diabetes over the last 25 years. However, attempts to continue to preserve the visual function in patients with diabetes must not be neglected in the drive to reduce the morbidity and mortality of cardiovascular disease in diabetes.

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