Review article

Prevention of blindness in diabetic retinopathy

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Summary. Diabetic retinopathy, hitherto the most common cause of blindness in those between 30–64 years of age has become treatable. Both diabetic maculopathy and proliferative retinopathy can be treated effectively by photocoagulation. The treatment is most successful if given early, before visual loss becomes irreversible. Recently, vitrectomy with addi-

tional microsurgical techniques has been developed and shown to be effective in restoring vision to many patients blind from the complications of proliferative retinopathy.

Key words: Diabetic maculopathy, proliferative retinopathy, photocoagulation, vitrectomy.

Diabetic retinopathy, uncommon only a few decades ago, has in two generations become the single most common cause of registered blindness in England and Wales between the ages of 30 and 64 years [1]. In the United States, for the years 1969–1970, it was responsible for 19% of all new cases of legally registered blindness in the 20–64 year age group [2]. It is, therefore, a real advance in treatment when severe visual loss can be prevented by photocoagulation or when vision, already lost, can be restored by vitreous surgery.

The purpose of this review is to examine the causes of blindness in diabetic retinopathy, discuss the results of photocoagulation and vitrectomy and review some of the techniques used.

Causes of blindness in diabetic eye disease

Diabetic retinopathy can be subdivided into four categories: background retinopathy, the sight-threatening forms of maculopathy, proliferative retinopathy and advanced diabetic eye disease.

Background retinopathy is characterised by microaneurysms and haemorrhages, usually most marked at the posterior pole, starting just lateral to the macula. Other features include scattered hard exudates and venous dilation. Mild background retinopathy is not associated with visual loss and it will therefore not be considered further in this review.

Diabetic maculopathy (background retinopathy with macular oedema) is probably the commonest cause of

visual loss in diabetes. The visual loss is due to accumulation of oedema fluid or hard exudate plaques at the fovea. The cause of the oedema is abnormal permeability of the retinal microvasculature at the posterior pole. In diabetic macular oedema, peripheral vision is often maintained; therefore, although incapacitated, patients retain navigational vision. When proliferative retinopathy supervenes in maculopathy, complete blindness may develop.

Similar to background retinopathy, *proliferative diabetic retinopathy* does not cause visual loss per se. However, its complications, such as vitreous haemorrhage, retinal detachment, and retinal distortion, are major causes of profound visual loss, resulting in a severity of blindness that renders the patient totally socially dependent.

The patient with diabetic retinopathy and visual loss can often identify the precise cause of further visual deterioration. He can distinguish between gradual increase of haziness of central vision caused by macular oedema, the 'blackness' of retinal detachment extending to the macula and the 'floaters' and 'cobwebs' of vitreous haemorrhage.

Diabetic maculopathy

Clinical features

Diabetic maculopathy is characterised by features of background retinopathy associated with macular oedema, the oedema leading to visual loss. It is primarily a

Table 1. Relationship between age at diagnosis of diabetes and the known duration of diabetes at entry into the British Multicentre Study of Photocoagulation in patients with either diabetic maculopathy or proliferative retinopathy

Known duration of diabetes (years)	Age at diagnosis of diabetes (years)						Total	
	0-29		30-59		≥ 60		Patients with maculopathy (n)	Patients with proliferative retinopathy (n)
	Patients with maculopathy (n)	Patients with proliferative retinopathy (n)	Patients with maculopathy (n)	Patients with proliferative retinopathy (n)	Patients with maculopathy (n)	Patients with proliferative retinopathy (n)		
0-5	0	1	18	19	22	3	40	23
6-10	1	0	10	6	3	1	14	7
11-15	1	11	14	4	1	0	16	15
16-20	3	22	10	3	0	0	3	25
> 20	4	29	4	3	0	0	8	32
Total	9	63	56	35	26	4	91	102

Data from patients with maculopathy are from [5]; data from patients with proliferative retinopathy are from [29]

Fig. 1. Left macular region in a Type 1 diabetic patient, aged 42 years, with 22 years of duration of diabetes and advanced diabetic nephropathy. Note extensive confluent hard exudates occupying most of the macular field

disease of Type 2 (non-insulin-dependent) diabetes, diagnosed after the age of 30 years and presents frequently within a few years of the diagnosis of diabetes [3-5]. Out of 91 patients with maculopathy in the British Multicentre Study [5], only nine were under the age of 30 years at the time of diagnosis and 40 had their disease for less than 6 years (Table 1). Macular oedema is also common in Type 1 (insulin-dependent) diabetes (Early Treatment of Diabetic Retinopathy Study Groups, personal communication). However, in the majority of these patients, it only leads to minor degrees of visual loss of about 6/12 to 6/18. In these patients, it is the complications of new vessels which lead to severe visual loss. Diabetic maculopathy also leads to severe impairment of vision in Type 1 diabetes when there is advanced diabetic nephropathy. This retinopathy can usually be recognised by the widespread, confluent hard exudates (Fig. 1).

Clinically, the main groups of diabetic maculopathy are the exudative, oedematous and the ischaemic types. The exudative form is characterised by hard exudates and the prognosis is best when there are hard exudate rings around central microvascular abnormalities. When hard exudates form more scattered plaques and are associated with blot haemorrhages, the prognosis is less good. The oedematous type can also be subdivided into the more common form, with cystoid macular oedema, and the rare form, when all vessels in the macular area leak and the entire area between the superior and the inferior temporal vessels is oedematous [8, 9]. The ischaemic type is characterised by perifoveal ischaemia, often associated with peripheral non-perfused areas [6, 7].

At present there is no evidence for any medical treatment to be effective in reducing macular oedema. In particular, good or even excellent diabetic control and drugs, such as diuretics (Doxium, Calcium Dobesilate, Delalande, Cologne, FRG or Diamicron, Gliclazide, Laboratoire Servier, Neuilly-sur-Seine, France), have not resulted in any sustained improvement. The only effective treatment to date has been photocoagulation.

Photocoagulation for diabetic maculopathy

Results of treatment: The first study of photocoagulation for maculopathy which only treated one randomly selected eye out of two similarly affected ones, came from Irvine and Norton [10]. In this small series followed for only a short period of time, there was no difference between treated and control eyes. Spalter [11] also using only xenon arc, treated exudative maculopathy and, in his series of 29 patients, demonstrated treatment to be advantageous. Patz et al. used the argon laser in a randomised controlled clinical study [12]. In their 63 patients, the treated eyes fared better than the untreated ones and none of the patients with initial vision of 6/60 or worse responded to treatment.

The longest, and largest study, reported to date, is the British Multicentre Study [5]. Here, 99 patients with two similarly affected eyes, had one eye (chosen by a random procedure) treated, while the other one remained untreated as a control. While the treated and untreated eyes had similar vision initially, by one year, the deterioration was significantly greater in the control than in the treated eyes. The mean visual acuity stayed unchanged throughout the seven years of study in the treated eyes, while the control eyes deteriorated gradually by two lines [5].

The best results were obtained in those who had good vision initially (6/6 to 6/9). Twenty such patients entered the study, 10 untreated eyes were blind with 6/60 or worse vision by the end of a 5-year follow up period, while only one treated eye had this degree of visual loss. Out of the 99 randomised patients, 13 were blind in both eyes, six in the treated eye only, but 26 in the untreated control eye only, when the treated eye could still see.

Methods of treatment: Since the availability of lasers, xenon arc treatment is no longer advised for the treatment of diabetic maculopathy, because of the large size of individual xenon burns and the frequency of complications. Treatment with the argon laser is now the only method used. The newer lasers, which filter out the blue light are best, because green light is taken up to a lesser degree by the macular pigment, allowing treatment nearer the fovea.

Patz et al. used enlarged fluorescein angiograms as a guide to treatment, picking out individual leaking areas with the laser [12]. This is now not thought to be necessary, although occasionally, when the macular oedema persists after treatment, fluorescein angiograms can indicate lesions left untouched.

The type of treatment advised today depends on the type of maculopathy. Thus, there is general agreement that hard exudates disappear when the microvascular lesion in the centre of the rings is treated [7]. For oedematous maculopathy, Whitelocke et al. advise a close grid surrounding the fovea [7]. Unfortunately with this treatment, success is not always assured [9]. However, treatment often maintains prevailing vision. Although ischaemic maculopathy is unlikely to have any visual improvement, treatment of the ischaemic area at the posterior pole and the retinal periphery can prevent complete loss of vision by preventing the development of new vessels.

Proliferative diabetic retinopathy

Clinical features

Proliferative diabetic retinopathy is characterised by intraretinal, surface and pre-retinal new vessels arising from either the retinal periphery or the optic disc. In contrast with maculopathy, it is most commonly seen in

Type 1 diabetic subjects after a long duration of diabetes (> 10 years) [13] (Table 1). It may also be the final cause of complete loss of vision in some patients with maculopathy [5].

As abnormal permeability of the retinal microvasculature is the fundamental cause of diabetic macular oedema, so retinal ischaemia is the keynote to the evolution of the proliferative form of the disease. Retinal ischaemia may be demonstrated by areas of capillary non-perfusion clearly visible on fluorescein angiograms. Such areas are recognised by the clinician by the presence of large deep, round haemorrhages, cotton wool spots, and changes in the larger vessels, such as venous beading, venous reduplication and obliteration of small arteriolar branches. The latter lead to an 'empty' featureless appearance of the peripheral retina. When these features are present, new vessels are likely to develop within one year and they are therefore termed 'pre-proliferative'.

The earliest proliferative lesions are intraretinal microvascular abnormalities. Later, fine new vessels arise from these or from larger vessels, usually veins. These new vessels rapidly develop a fibrous tissue cover. Initial out-growths of these fibrovascular buds break through the internal limiting membrane of the retina and form dense adhesions to the overlying cortical vitreous. These adhesions are crucial to the understanding of the subsequent tractional complications [14]. Subsequently, a fibrovascular epiretinal membrane comes to lie on the retinal surface and overlying cortical vitreous. Subsequent contraction of the membrane results in vitreous haemorrhage, retinal detachment or retinal distortion. Partial posterior vitreous detachment results in antero-posterior vitreoretinal traction and the vector of this force tends to pull the retina at attached foci into the centre of the globe. Thus, tractional retinal detachment occurs [15]. This tractional detachment may remain localised, or it may extend and detach the macula. Progression of the tractional force may cause a retinal tear and progression to rhegmatogenous retinal detachment. In any event, detachment of the centre of the macula is associated with profound loss of central vision. Progressive epiretinal membrane formation may render the macular detachment technically inoperable.

In the past, pituitary ablation was found to be effective in reducing or even reversing proliferative retinopathy [16, 17]. This treatment carries considerable mortality and morbidity and is now no longer performed even in florid retinopathy [18]. Recently, improved diabetic control using continuous subcutaneous insulin infusion has been advocated in order to improve diabetic retinopathy [19]. This treatment, while it may reduce formation of new areas of capillary non-perfusion (for which, at present, there is no evidence), will not affect proliferative lesions already present [20, 21]. Indeed, the clinical impression is that, if anything, proliferative lesions may advance more rapidly with, than without continuous subcutaneous insulin infusion [20].

Photocoagulation for proliferative retinopathy

Photocoagulation is primarily directed towards *prevention* of the tractional complications. Photocoagulation destroys ischaemic retina and thus reduces the formation of a presumed vasoproliferative substance, liberated by the ischaemic retina [22].

Results of treatment: That photocoagulation can be effective in proliferative retinopathy has been shown by many [23, 25]. Most of the studies were uncontrolled or chose the 'worse' eye for treatment. Therefore, clear indications for, and exact benefit from, treatment were not established until the publication of two large scale multi-centre studies [26–28].

The larger of the two, the 'American Diabetic Retinopathy Study Research Group' involved over 1700 patients. In this study, the greatest benefits were obtained in those with 'high risk characteristics', which included new vessels arising from the optic disc, with or without new vessels in the retinal periphery, and with or without vitreous haemorrhage. Peripheral new vessels alone only constituted 'high risk' for visual loss if they had associated vitreous haemorrhage. The highly significant reduction in severe visual loss (visual acuity of 6/60 or less) in treated eyes after 2 years follow-up in these groups is summarised in Table 2. The difference between treated and control eyes was less marked when these high risk characteristics were absent. In patients with pre-proliferative retinopathy, treatment conferred no advantage over this period of time.

So dramatic were the treatment effects, that after the 2 year results became available, a change in protocol was instituted allowing treatment of hitherto control eyes if they had these sight-threatening lesions. The overall cumulative severe visual loss (similar to legal blindness of 6/60 or worse vision in the United Kingdom) after 5 years was 15% in the treated and 35% in the control eyes (which included those treated after the second year), a highly significant difference in favour of treatment.

The findings of the British Multicentre Study with only 107 patients were similar [28, 29]. When all patients were considered at 5 years, the mean visual acuity deteriorated by only one line on the Snellen chart in the treated eyes, but by nearly three lines in the control eyes. The difference in deterioration was significant at each yearly interval. As in the American study, those with disc new vessels at entry benefited most from treatment. In this group, 50% of control, but only 15% of treated eyes became legally blind. Even when the entire group was considered, only 10% of treated, but 31% of control eyes lost this degree of vision, indicating that photocoagulation is effective in maintaining vision in proliferative retinopathy.

Photocoagulation is effective in all groups of patients (though not in each individual). It has been used effectively in patients with diabetic renal disease [30],

Table 2. Cumulative 2-year rates of severe visual loss in eyes with high risk characteristics (20/200 or less) from [50]

Lesions	Treated eyes	Control eyes	Z value
Moderate or severe disc new vessels $\pm$ peripheral new vessels with haemorrhage	36.9	20.1	3.2
Moderate or severe disc new vessels $\pm$ peripheral new vessels without haemorrhage	26.2	8.5	4.7
Mild disc new vessels $\pm$ peripheral new vessels with haemorrhage	25.6	4.3	2.9
Moderate or severe peripheral new vessels. No disc new vessels with haemorrhage	29.7	7.2	3.0

Z value = observed difference between proportions of events observed in the untreated and treated groups, divided by the standard error. A positive Z value denotes an event rate in the treatment group that is lower than the event rate in the control group. Z value of 1.96 is approximately $p = 0.05$

where it can result in visual improvement, and in pregnant patients [31]. Indeed, in the latter group, adequate photocoagulation during one pregnancy may prevent visual loss and even recurrent retinopathy during subsequent pregnancies (unpublished observation).

Methods of treatment: Photocoagulation in proliferative retinopathy is so effective that there is much less argument regarding the method of treatment than in maculopathy. Patz et al. [32] advocated direct treatment of feeder vessels for the treatment of new vessels on the disc with the argon laser and this method of treatment was included in the American Diabetic Retinopathy Study Research Group's protocol, but has since been found to be needed only rarely. Direct, 'focal' treatment of disc new vessels when they came off the disc on the nasal side, was advocated for a long time [33] and focal treatment of peripheral new vessels, with both the xenon arc and argon laser will destroy these vessels. However, the most effective treatment, especially for new vessels on the disc, is peripheral scatter treatment (peripheral ablation, pattern bombing). This treatment was first advocated by Aiello et al. [34] and has since been amply proven in both the American and British Multicentre Studies. The aim of this method of treatment is to destroy peripheral non-perfused ischaemic retina, thus destroying the stimulus for further new vessel growth. Since large areas of retina are destroyed, the need for blood supply is reduced and, in most instances, new vessels on the disc regress (Fig. 2a and b).

The amount of treatment required for optimum results is not clearly established, but the British Multicentre Study has demonstrated that those with less extensive treatment were more likely to lose vision if they had new disc vessels and were more likely to develop disc

Fig. 2. **a** Proliferative diabetic retinopathy with new vessels arising from the optic disc before treatment. **b** Same as **a** but 5 years after peripheral photocoagulation with xenon arc. Only normal fibrous tissue remains. Visual acuity maintained at 6/6

new vessels if they had only peripheral ones at entry into the study [29]. It appears, therefore, that adequate treatment is essential. We would consider not less than 2000 argon laser burns of 500 micra spot size and an intensity which achieves superficial greying and swelling of the retina as a minimum for those with disc new vessels, but as many as 6000 burns may be required. Treatment at regular intervals should continue until the new vessels regress or become inactive.

No treatment is without complications. Permanent reduction in the visual field occurs commonly in those treated with the xenon arc [26]; it is usually transient in laser treated eyes. Several eyes lose one or more lines in visual acuity as a result of treatment, again the loss is more common and more profound in xenon treated eyes, especially if treatment is required near the fovea. Because of the complications, and because of the need for retrobulbar anaesthesia in xenon-arc treatment, this equipment is only rarely used now for photocoagulation. Almost all patients are now treated with the argon laser.

Vitrectomy in the treatment of complications of proliferative diabetic retinopathy

Once tractional complications, vitreous haemorrhage and traction detachment have occurred, photocoagulation cannot restore vision, although, in many instances, closed intraocular microsurgery can. The surgical techniques in this rapidly advancing field are beyond the scope of this review. In essence, the vitreous with its contained intragel haemorrhage may be cut and aspirated and simultaneously replaced with physiological fluids [35–37]. Clarity of the optical media may thus be restored. More recent techniques allow, in addition, segmentation and stripping of epiretinal membranes, thus

releasing the tractional forces on the detached retina, permitting it to re-attach. Conventional detachment procedures, such as scleral buckling, cryopexy and internal retinal tamponade with air, gas, or silicone oil are adjunctive treatments. The crystalline lens is preserved where possible as protection against anterior segment ischaemia, albeit at the cost of delaying absorption of recurrent post-operative vitreous haemorrhage [38].

The efficacy of such surgical intervention for long-standing vitreous haemorrhage has been shown by many investigators [36–41]. In the large series of Michaels et al. [40], out of 248 eyes, 115 achieved 20/100 or better vision. The result of Machemer and Blankenship's studies were similar [39]. The results in four large studies [42–45] demonstrate that visual acuity improves in between 59%–76% of eyes and less than 20% deteriorate. Analysis of long-term studies indicates that even better results can be anticipated in the future. In particular, iris neovascularisation, resulting in severe post-operative complications, will be seen less frequently when at least some photocoagulation will have been given before the massive vitreous haemorrhage necessitating vitrectomy. The best timing of surgery for vitreous haemorrhage awaits clarification [46, 47].

Traction retinal detachment involving the macula is a frequent cause of severe visual loss in proliferative diabetic retinopathy and an indication for vitrectomy [42–45, 48]. Vitrectomy is not indicated if only the peripheral retina is detached as macular involvement is in the region of 15% per year, or less [48]. The visual outcome is less good than following vitrectomy for vitreous haemorrhage. Rice et al. [45] obtained a visual acuity of 6/60 or better in 40 out of 197 eyes without a retinal break and in 27 out of 107 with retinal breaks.

Improvement in visual acuity is variable. In Blankenship's series, it was only 26% out of 168 eyes [42],

while it reached 72% among 125 eyes treated by Aaberg [43]. However, this latter surgeon only treated patients without retinal breaks and with detachment of less than 3 months duration.

The anatomical aim of the operation is to achieve a flat macula by removing or fragmenting elevated and epiretinal fibrovascular tissue. In the Moorfields Hospital, London series, 74% of eyes achieved surgical reattachment of the macula [49]. The pre-operative extent of fibrovascular epiretinal membrane was the most important adverse risk factor.

Successful anatomical reattachment of the macula does not guarantee visual improvement. This is affected by such factors as the duration of detachment and pre-existing macular ischaemia. The role of earlier vitrectomy performed in threatened macular detachment is currently being studied [46, 47].

Although vitrectomy can restore vision in some patients with profound visual loss, the results are not predictable and it should be remembered that every vitrectomy indicates inadequate management of diabetic retinopathy in its earlier phases. Indeed, the often uncertain results of vitrectomy underline the importance of institution of screening programmes for the detection of early diabetic retinopathy, when less traumatic treatment can assure better results and preservation of vision in most.

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