Diabetic retinopathy: medical management and assessment

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Diabetic retinopathy is a common and potentially devastating complication. This review discusses the practical assessment and management of retinopathy, focusing on the treatment of concomitant systemic disorders that influence the development and progression of this complication.

Diabetes mellitus can lead to macrovascular and microvascular long-term complications. Of microvascular complications diabetic retinopathy is the most common cause of blindness in developed countries, affecting both patients with type 1 or type 2 diabetes. After 20 years of type 1 diabetes, almost all patients have retinopathy, while 60% progress to sight-threatening proliferative retinopathy. In type 2 diabetes, 20% of newly diagnosed patients already have diabetic retinopathy, and most will subsequently develop diabetic retinopathy (American Diabetes Association, 2002).

Diabetic retinopathy, however, is an end-organ response to a systemic disease, representing only one of many microvascular and macrovascular diabetic complications. Other concomitant systemic disorders can have marked effects upon the progression of diabetic retinopathy and the risk of visual loss. In recent years the management of diabetic retinopathy has extended to the management of factors predisposing to this complication and it is these risk factors and their management which will be the focus of the rest of this article.

MANAGEMENT OF DIABETIC RETINOPATHY

Risk factors related to the onset and progression of diabetic retinopathy are multifactorial and include genetic factors, disease duration, blood glucose levels, hypertension, diabetic nephropathy, lipid levels, insulin resistance and pregnancy (Van Leiden et al, 2002).

Primary prevention, that is preventing the disease before it develops, remains the most effective way to treat diabetic retinopathy, and involves limiting modifiable risk associated with glucose control, blood pressure and lipid levels.

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Glucose control

The introduction of glycosylated haemoglobin (HbA_{1c}) as an index of blood glucose control enabled Klein (1995) to study the relationship between HbA_{1c} and diabetic retinopathy in type 2 diabetes patients from diagnosis. Remarkably he found that levels of HbA_{1c} at baseline were correlated with risk of progression to retinopathy, as well as proteinuria.

In the Diabetes Control and Complications Trial (DCCT) a definitive relationship was established between hyperglycaemia in type 1 diabetes and diabetic microvascular complications (DCCT Research Group, 1993) and this relationship was confirmed in the UK Prospective Diabetes Study (UKPDS) in patients with type 2 diabetes (UKPDS Group, 1998a).

In DCCT intensive therapy was compared with conventional insulin treatment in 1441 patients with type 1 diabetes followed for a mean of 6.5 years. The goals of intensive treatment included a lower HbA_{1c} in the intensive therapy group and this was achieved with a mean difference of 2%. In the primary prevention cohort progression to retinopathy was slowed by 54%, the development of proliferative retinopathy reduced by 47%, while laser treatment was also reduced by 56%. The best results were obtained in those who started intensive treatment when they did not have retinopathy (*Figure 1*). Reductions were also observed for the development of microalbuminuria, proteinuria and neuropathy.

UKPDS confirmed these conclusions but in patients with type 2 diabetes. UKPDS was a 12-year follow-up study of 3867 newly diagnosed patients randomly assigned to intensive treatment with either a sulphonylurea (glibenclamide, chlorpropamide or glipizide) or insulin, or diet alone. Metformin was included

for overweight patients (n=1704). In UKPDS the mean HbA_{1c} was reduced by a mean of 0.9% in the intensively treated group compared with the conventionally treated group. The intensive therapy group showed a 21% decreased risk of progression of diabetic retinopathy and a 29% decreased need for laser coagulation compared with the conventional group (*Figure 2*). There was no difference in the HbA_{1c} among agents in the intensive group nor any advantage in terms of outcome between sulphonylureas or insulin.

Both DCCT and UKPDS demonstrated the importance of maintaining good metabolic control (HbA_{1c} values below 7%) to prevent worsening or development of diabetic retinopathy. In broad terms, for every 1% fall in HbA_{1c}, there is a reduction in microvascular risk by about 25% irrespective of whether the patient has type 1 or type 2 diabetes. From the DCCT it was apparent that the impact on primary prevention, i.e. development of retinopathy, was greater than that on secondary prevention, i.e. progression of established retinopathy. However, in these and other studies few achieved the target level of HbA_{1c} (Klein et al, 1998).

Furthermore, those in DCCT treated with an intensive insulin regimen resulted in a transient worsening of diabetic retinopathy. Therefore, it is important to check the fundi before starting an intensive regimen and maintain frequent follow up if diabetic retinopathy is present.

Finally, not all patients with optimal glycaemic therapy will be protected from complications, for example, in the DCCT by 8 years 25% of patients in the intensive care group progressed to microalbuminuria, as did about 18% in UKPDS. This observation raises the possibility that factors other than blood glucose are important in the pathogenesis of diabetic complications.

The targets for blood glucose control are much clearer following DCCT and UKPDS. There are no thresholds within the diabetic range of blood glucose for risk of microvascular complications. To reduce risk normal blood glucose levels should be aimed for. This target may be unrealistic for some, but targets for HbA_{1c} should be set and they should be as close to the normal values as is practical. Early diagnosis and, therefore, population screening may be important. Primary prevention is more effective than secondary prevention. Finally, a reduction in HbA_{1c}, irrespective of the initial value and the degree of reduction, is of value, so persistence is important, even in patients who fail to achieve their targets.

Blood pressure

The critical questions in terms of blood pressure management are who should be treated, what should they be treated with, and what target blood pressure one should aim to achieve. The assumption that treatment of hypertension is worthwhile is based on the value of such treatment in non-diabetic subjects studied in large randomized controlled studies. Since hypertension in association with diabetes carries a high risk, patients with type 1 or type 2 diabetes are immediately identified as at risk and are candidates for antihypertensive therapy when the blood pressure is more than 130 mmHg systolic or 85 mmHg diastolic. Others currently aim for a systolic pressure less than 140 mmHg.

UKPDS (1998b) clearly showed that controlled blood pressure substantially reduces the risk of both diabetic retinopathy progression and visual loss in diabetic patients. Of 1148 type 2

Figure 1. Cumulative incidence of a sustained change in retinopathy in patients with type 1 diabetes without diabetic retinopathy (primary prevention cohort) or with mild diabetic retinopathy (secondary intervention cohort) receiving intensive or conventional therapy. From Diabetes Control and Complications Trial Research Group (1993).

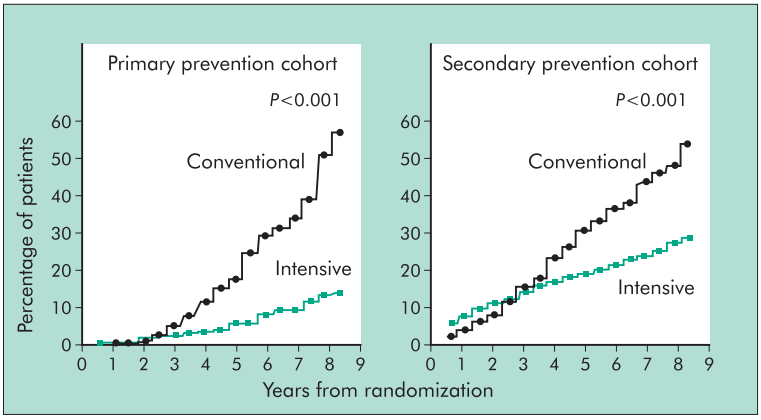
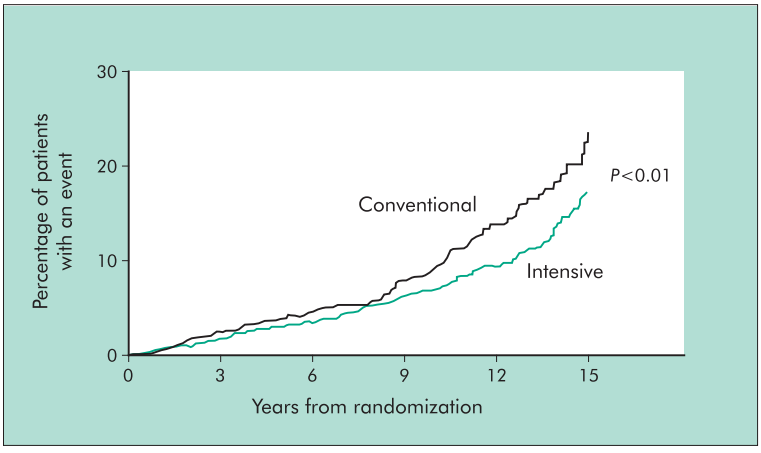


Figure 2. Risk reduction in microvascular endpoints in patients on intensive blood glucose control compared with conventional treatment. From UK Prospective Diabetes Study (1998a).

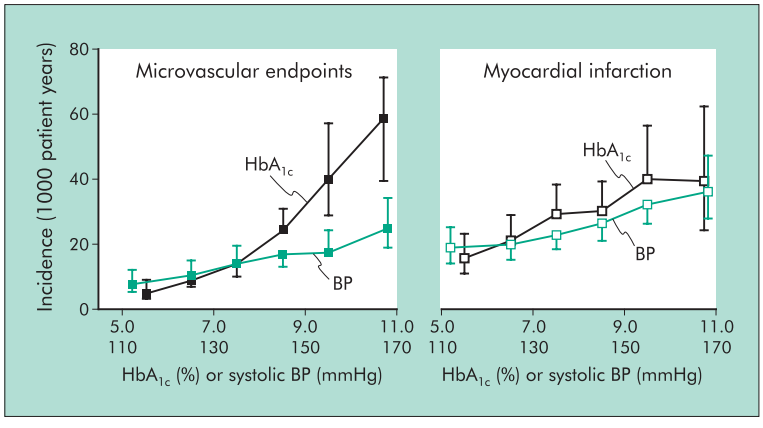


diabetes patients with hypertension, blood pressure control (aim <150/85 mmHg and achieved mean blood pressure fall in intensive *vs* conventional treatment groups was 10/5 mmHg) could reduce morbidity and mortality irrespective of therapy, that is whether on an angiotensin-converting enzyme (ACE) inhibitor (captopril) or a β-blocker (atenolol), compared with less tight control (aim <180/105 mmHg). Over 9 years follow up patients randomized to an intensive control maintained a lower blood pressure (mean 144/82 mmHg) than the less tight group (mean 154/87 mmHg). Tight blood pressure control resulted in a 35% reduction in retinal photocoagulation and a 34% reduction in progression of diabetic retinopathy.

Interestingly, the advantages of blood pressure control were seen even earlier than those of intensive blood glucose control and the degree of benefit was comparable in the two treatment regimens. Perhaps surprisingly there was no added benefit in lowering blood pressure with an ACE inhibitor as compared with a β-blocker, it was blood pressure treatment that mattered and not how it was achieved. In this, type 2 diabetic patients may differ from type 1 diabetic patients. Combinations of drugs were often required to achieve the target blood pressure. The controversy about the value of calcium-channel blocking drugs in patients with type 2 diabetes was not considered. The goal for blood pressure can probably be set at less than 140/85 mmHg and maybe lower since there was no threshold effect, as was also the case with glucose (*Figure 3*).

ACE inhibitors are effective in secondary prevention of diabetic retinopathy. This may be through the control of blood pressure, but they could also have an independent protective effect. In the EURODIAB Controlled trial of Lisinopril in Insulin Dependent diabetes mellitus (EUCLID) study, type 1 diabetes patients were tested using the ACE inhibitor lisinopril in normotensive and normo- or microalbuminuric patients (Chaturvedi et al, 1998). After 2 years follow up patients treated with lisinopril showed a 13% progression of diabetic retinopathy by at least one level, compared to 23% of those receiving placebo. Lisinopril did decrease blood pressure but only by 3 mmHg, so the impact of lisinopril may be the result of the reduction in blood pressure although it seems unlikely. A protective action of ACE inhibitors was not confirmed in other major trials, such as the Heart Outcomes Prevention Evaluation (HOPE) study (Yusuf et al, 2000) and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (Estacio et al, 2000).

Figure 3. Incidence rates and 95% confidence intervals for microvascular complications and myocardial infarction by category of mean mean glycosylated haemoglobin (HbA_{1c}) concentration and mean systolic blood pressure (BP), adjusted for age, sex and ethnic group expressed for Caucasian subjects aged 50–54 years at diagnosis and mean duration of diabetes of 10 years. From Stratton et al (2000).



Diabetic nephropathy

Diabetic nephropathy is a strong predictor of diabetic retinopathy, and frequently the presence of one suggests the presence of the other (Klein et al, 1998). The interrelationship between diabetic retinopathy and proteinuria is complex and the frequent coexistence of retinal and renal microangiopathies may reflect common predisposing factors. Indeed, chronic hyperglycaemia, high HbA_{1c} levels, duration of diabetes and hypertension are risk factors for both retinopathy and albuminuria. There is also evidence that aggressive treatment of diabetic nephropathy may have a beneficial effect on the progression of both diabetic retinopathy and neovascular glaucoma. Patients with overt diabetic nephropathy and type 1 diabetes are almost certain to have diabetic retinopathy and are very likely to develop sight-threatening diabetic retinopathy; hence their fundi should be frequently examined.

Patients with early nephropathy, as evidenced by microalbuminuria, should be encouraged to aggressively follow therapeutic strategies including diet modification, blood pressure and blood glucose control and possibly the introduction of an ACE inhibitor. Patients with progressive renal dysfunction need close ophthalmological monitoring.

Lipids

Despite the possible role of lipids in diabetic retinopathy, clinical trials have not clearly showed the efficacy of lipid-lowering drugs in the prevention of this complication. In the 1960s

clofibrate was used to treat diabetic patients resulting in a reduced incidence of hard exudates, but it failed to restore vision in eyes with established macular oedema and was associated with liver toxicity.

Lipid-lowering regimens are recommended to all patients with diabetes with elevated cholesterol levels, irrespective of retinopathy status, in view of the beneficial effects on cardiovascular morbidity. There is no consensus regarding therapy with lipid-lowering agents in patients with retinopathy and the results of various trials to elucidate the role of such drugs are awaited.

Physical exercise

There is concern that an increase in systolic blood pressure associated with marked physical exercise could precipitate intraretinal, preretinal and/or vitreous haemorrhage. These considerations should be used to encourage the patient to undertake low-risk exercise, include stationary cycling, swimming and walking.

Pregnancy

Modern management has transformed the outcome of pregnancy in women with diabetes. In the past, the prognosis for pregnancy in the diabetic patient with microvacular complications was so poor that diabetic women were advised to avoid or terminate pregnancies. Forty years ago one pregnancy in three ended with the death of the fetus or neonate. Today, the results in specialized centres approach those of non-diabetic pregnancy.

Worsening of diabetic retinopathy is not unusual during pregnancy, about 25% develop diabetic retinopathy during pregnancy while 4% progress to proliferative diabetic retinopathy. Poor metabolic control, rapid improvement in control during the first trimester, diabetes duration and hypertension contribute to diabetic retinopathy risk. Nevertheless, worsening of diabetic retinopathy is usually transient without adverse consequences for vision (DCCT Research Group, 2000).

The aim is to maintain blood glucose and fructosamine levels, an index of blood glucose control, or HbA_{1c} levels as close to the normal range as is feasible.

CONCLUSIONS

Primary prevention of diabetic retinopathy is the best way to treat this complication and this is currently done by intensive therapy of blood pressure and blood glucose. However, it is difficult to obtain and maintain good metabolic and blood pressure control. Therefore, alternative medical approaches have been sought. Studies of these novel agents are underway. Once severe diabetic retinopathy is established photocoagulation remains an important and successful therapy, a therapy which over 20 years ago transformed the management of this complication of diabetes which used to carry such an appreciable risk of blindness. There is every reason to believe that the future will bring advances just as exciting as those witnessed in recent years. **HM**

Conflict of interest: none.

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KEY POINTS

- Diabetic retinopathy is common.
- Blindness is preventable.
- Lowering glycosylated haemoglobin (HbA_{1c}) levels and blood pressure reduces retinopathy risk.
- Lowering HbA_{1c} levels and blood pressure reduces retinopathy progression.