Management of diabetic retinopathy

The number of diabetics in the UK is growing exponentially and is expected to rise to 2.67 million people by the year 2030.[1] However, the mortality rate associated with the macrovascular complications of diabetes is decreasing along with a general increase in life expectancy for this population.[2,3] This could lead to an increase in the time that people live with the morbidity associated with microvascular complications. Microvascular damage in the retina results in diabetic retinopathy and this article reviews the management of this condition in older people.

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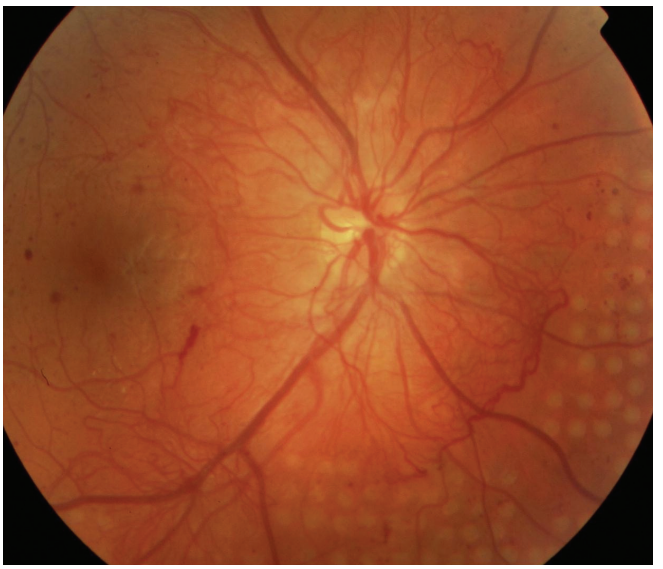
Diabetic retinopathy is a leading cause of blindness in England and Wales.[4] For voluntary blind registrations between April 1999 and March 2000, the majority (18% or 290 registrations) of those aged between 16–64 years were due to diabetes. The condition is also a dominant cause of blindness in people aged 65–74 (15% or 255 registrations), but is overtaken by age-related macular degeneration in older age groups. It is the cause of blindness in 4·2% (206 registrations) of those aged 75-84 and just 0·8% (38 registrations) of those over 85. New onset blindness in middle age or the later years often has devastating effects on quality of life and self-sufficiency with very substantial socioeconomic implications.



Clinical definitions of diabetic retinopathy

Most diabetic retinopathy is asymptomatic. Disease is progressive and various systems of classification are used. The most commonly used system amongst physicians divides the stages of diabetic retinopathy into: background retinopathy, pre-proliferative retinopathy, proliferative retinopathy, advanced diabetic eye disease, and maculopathy.[5] The gold standard for research and clinical trials is the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, which requires detailed assessment of 7 photographic fields.[6]

A fourth system was recently devised by the National Screening Committee.[7] The changes seen are divided into diabetic retinopathy (involving the disc and area outside the vascular arcades) and diabetic maculopathy (involving the central macular region). Proliferative diabetic retinopathy is diagnosed when new vessels are present (Figure 1), and patients may be classified as having a high or low risk of severe visual loss (according to the criteria of the Diabetic Retinopathy Study).[8]

Screening

Systematic screening is being set up as a component of the National Service Framework for Diabetes, and it aims to uncover treatable asymptomatic disease so that sight-threatening complications can be avoided. The socioeconomic benefits of early and effective treatment are enormous, particularly in elderly patients with multiple comorbidities. Since 2003, the National Screening Committee has published standards specifically designed to improve quality and parity of provision of care for diabetic retinopathy.[7] All diabetics above the age of 12 years are invited to screening. This includes 2 digital colour photos of each eye taken by a trained and accredited screener after

pupil dilation. Images are graded by accredited graders, according to the English Retinopathy Minimum Grading Classification. This differs from the clinical classification for diabetic retinopathy. Patients with ungradeable images are identified and examined with biomicroscopy before being referred to the Hospital Eye Service as required. Those with no retinopathy receive annual screening and all those with referable levels of retinopathy are referred to the hospital eye service within a specified time frame. Arbitration and quality assurance are an intrinsic part of the process.

Primary interventions

High blood glucose

The Diabetes Control and Complications Trial (DCCT)[9] showed a clear benefit of intensive control of hyperglycaemia (aiming for a HbA_1c of less than 6·05%) compared with conventional therapy. All of the patients recruited had type-1 diabetes and were aged between 13 and 39 at baseline. The average period of follow up was 6·5 years (range 3–9). Blood glucose was reduced by 20% in the intensive control compared with the control group (7·1% versus 9%, respectively). Retinopathy was the primary outcome measure, and intensive control reduced the risk of developing retinopathy by 76% and slowed the progression of retinopathy by 54%. Patients needed to be on tight control for at least 3 years before the beneficial effects on retinopathy became evident. More patients in the intensive group experienced worsening of established retinopathy than in the control group in the first year (22% versus 13%, respectively), but this effect disappeared after 18 months. Furthermore, patients with early worsening in the intensive control group still maintained a 74% reduction in their risk of subsequent progression compared with the conventional therapy group. Recent re-analysis of the study has confirmed that HbA_1c explains virtually all of the differences in risk between the intensive and the conventionally treated groups, and that a given HbA_1c level has similar effects within the two treatment groups.[10] A 3-fold increase in hypoglycaemia in the intensive group was the main adverse event reported.

The UK Prospective Diabetes Study (UKPDS) confirmed the value of intensive control of hyperglycaemia in type-2 diabetics.[11] UKPDS was designed to establish whether intensive blood glucose control in patients with type-2 diabetes reduced the risk of macrovascular or microvascular complications and whether any particular therapy was advantageous. It started in 1977 and ended in 1997, with a median follow up of 10 years. Participants were newly diagnosed and were aged 65 or younger (median 54 years). Intensive blood glucose control involved oral hypoglycaemics or insulin aiming to maintain a fasting plasma glucose below 6 mmol/l. Patients in the conventional group were treated with diet alone unless they had symptoms of hyperglycaemia or had a fasting plasma glucose greater than 15 mmol/l. Intensive control reduced HbA_1c by 11% compared with the conventional group (HbA_1c 7% versus HbA_1c 7·9%). At 10 years, patients assigned intensive treatment had a 25% reduction in microvascular endpoints compared with conventional treatments (p=0·0099). Most of this reduction in microvascular endpoints was due to a reduced need for photocoagulation (p=0·0031). Again intensive control was associated with a significant increase in hypoglycaemic episodes, and these were most common for patients on insulin therapy—36·5% of whom had a hypoglycaemic episode. Intensive control in UKPDS was also associated with increased body weight.

UKPDS did not find any differences in terms of the microvascular endpoints between the treatments used in the intensive group. Nor were there any differences between the treatments in the reduction of the need for retinal photocoagulation. However, other studies have reported that the use of glitazones is linked to clinically significant macular oedema associated with peripheral oedema.[12] Fluid retention and peripheral oedema that does not respond to treatment with diuretics occurs in up to 15% of patients whose management regimen includes the use of glitazones.

A case note review of 30 patients found that macular oedema was difficult to control in patients who had clinically significant macular oedema associated with peripheral oedema and glitazone use. A number of patients had severe visual loss despite laser treatment. Stopping glitazone therapy was associated with a reduction in macular oedema over a period of months for the majority of patients in whom cessation was attempted. Another retrospective review of 102 diabetic patients treated with rosiglitazone did not confirm this connection with refractory macular oedema,[13] but none of the patients in the review had clinically significant macular oedema. Liazos and colleagues reported a case study in which macular oedema was resolved without the need for ocular therapy 3 months after treatment with rosiglitazone was stopped.[14]

Thus, caution with the use of glitazones in patients with clinically significant macular oedema may be advisable, pending further studies.

Systemic hypertension

The Hypertension in Diabetes study, which was part of the UKPDS,[11] provides valuable information on the effects of blood pressure on diabetic retinopathy. Two thirds of the hypertensive diabetics were randomised to tight control (defined as a blood pressure less than 150/85 mmHg) and one third were randomised to less tight control, which was initially defined as 200/105 mmHg but later reduced to 185/105 mmHg after emerging evidence showed the benefits of blood pressure control for elderly non-diabetics. Randomisation was stratified according to the presence or absence of previous therapy for hypertension. The mean HbA_1c was 7·2% in both groups in years 1–4 of the study, and 8·2% in the tight blood pressure group and 8·3% in the less tight group in years 5–8. Highly significant differences in retinopathy were reported by 4·5 years of follow up, with the tight blood pressure control group having fewer microaneurysms, hard exudates, and cotton wool spots than the less tight control group. Significantly fewer patients in the tight blood pressure group saw a progression in their retinopathy than patients in the less tight group, and this was more marked at 7·5 years (RR 0·75, p=0·02 at 4·5 years; RR 0·66, p<0·001 at 7·5 years). Patients with tight blood pressure control were less likely to require photocoagulation and in particular, were less likely to require photocoagulation for macular oedema (RR 0·58, p=0·02). Finally the tight blood pressure group had a 47% lower risk of dropping 3 or more lines of visual acuity on a Snellen chart (p=0·004%) than the less tight group. This finding may reflect the fact that tight blood pressure control appeared to delay the onset of retinopathy. One theory is that increased blood pressure leads to increased sheer stress and further damage to vessel walls. Therefore, control of blood pressure and diuresis may result in decreased retinal capillary perfusion pressure with diminished retinal leakage and macular oedema.

Secondary interventions

Laser photocoagulation

A number of prospective randomised controlled studies support the use of laser for the treatment of diabetic retinopathy and diabetic macula oedema. The Diabetic Retinopathy Study (DRS) demonstrated the efficacy of pan retinal photocoagulation (PRP) and identified high-risk characteristics that put eyes with proliferative diabetic retinopathy at an increased risk of severe visual loss.[8] PRP reduced the risk of severe visual loss by at least 50% at 2-year follow up. For patients with high-risk characteristics, this risk was 11% in treated eyes compared with 26% in control eyes. Exacerbation of macular oedema was a cause of visual loss and visual field defects were not uncommon. Patients with rubeosis iridis and neovascular glaucoma also require prompt PRP, with success being more probable if laser treatment is initiated before uncontrolled intraocular pressure develops.[15]

The ETDRS trial provided further information on the timing of treatment. It demonstrated that PRP can be safely delayed until retinopathy becomes severe, providing careful follow up can be maintained.[16] Photocoagulation for clinically significant macular oedema reduces the risk of significant visual loss (loss of 3 lines) by 50% at 3 years.

Argon laser photocoagulation is used to treat areas of focal retinal thickening that meet the criteria for clinically significant macular oedema, areas of diffuse retinal thickening that cause clinically significant macular oedema, and areas of avascular retina 500-300 microns from the macular centre if associated with clinically significant macular oedema. Treatment stabilises vision but does not significantly improve it in most patients—ETDRS found that photocoagulation improved visual acuity by 3 or more lines in less than 3% of eyes treated. Therefore, it should be done before vision is compromised if possible. Ideally, treatment of clinically significant macular oedema with focal or grid laser should be performed before PRP. Overall, macular photocoagulation treatment is not recommended for eyes with macular oedema that is not clinically significant.

Vitrectomy

The Diabetic Retinopathy Vitrectomy Study showed that early vitrectomy in patients with severe vitreous haemorrhage resulted in better visual acuity outcomes than deferral of surgery.[17] The study reported this effect in patients with type-1 diabetes but not in patients with type-2 diabetes, and patients with more severe retinopathy were more likely to benefit.

Advances in vitrectomy techniques, including delamination techniques and endolaser, have improved outcomes since

the study was undertaken and type-2 diabetics with severe vitreous haemorrhage and advanced diabetic retinopathy should also be considered for surgery. Other indications for vitrectomy in advanced diabetic retinopathy are macular threatening tractional retinal detachments and combined rhegmatogenous and tractional detachments.

Aspirin

NICE recommends antiplatelet therapy in the management of patients at high risk of cardiovascular events, such as those with type-2 diabetes.[18] ETDRS looked specifically at the value of aspirin in the management of diabetic retinopathy and found no effect of aspirin on the severity of retinopathy or duration of vitreous or preretinal haemorrhage.[19] NICE guidelines on aspirin can therefore be followed irrespective of retinopathy status.

Conclusion

The risks of diabetic retinopathy and maculopathy increase with duration of diabetes. Long-term glycaemic control and blood pressure control are the most important interventions for the management of diabetic retinopathy. Although patients are asymptomatic until the disease is advanced, screening is worthwhile because of the effectiveness of secondary interventions and the large numbers of patients involved. Appropriate management of diabetic retinopathy is essential to limit morbidity in the later years.

Dr Egan has participated in advisory work for Novartis

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