New management paradigms in diabetic retinopathy

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New approaches to treating diabetic retinopathy have yielded excellent outcomes and continue to be refined. Primary care providers have a key role in optimising medical treatment, co-ordinating care and providing education to improve disease awareness.

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Key points

- **The most important determinants of ocular health in patients with diabetes are early detection, optimisation of blood glucose levels and treatment of associated hypertension.**
- **Vision-threatening diabetic retinopathy most commonly refers to diabetic macular oedema (DMO) and/or proliferative diabetic retinopathy (PDR).**
- **DMO typically presents gradually, with blurred vision, central distortion and difficulty reading. In contrast, early PDR is often initially asymptomatic and a high index of suspicion is required in patients with poorly controlled diabetes of significant duration.**
- **There is now extensive evidence for the safety and superiority of intravitreal anti-vascular endothelial growth factor agents for the treatment of DMO and PDR, with the potential to improve vision in addition to stabilising disease.**

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Diabetic retinopathy is the leading cause of visual impairment in patients of working age, which represents a significant health and economic burden in developed countries. A recent large meta-analysis of population studies for diabetes mellitus determined an overall prevalence of 34.6% for diabetic retinopathy, with the key risk factors being longer duration of diabetes, poor glycaemic control and uncontrolled systemic hypertension.[1] Therefore, we can see that the most important determinants of ocular health in patients with diabetes are early detection, optimisation of blood glucose levels and treatment of associated hypertension. These are key roles of the GP in collaboration with the patient and treating specialists.

All patients with diabetes mellitus presenting with vision loss should be referred for specialist eye examination. However, most patients will first present to a GP (or, increasingly, an optometrist, who may perform retinal photography), where appropriate clinical assessment must occur to determine the cause of vision loss, accompanied by prompt referral to an ophthalmologist.

Determining the cause of vision loss

Vision-threatening diabetic retinopathy most commonly refers to diabetic macular oedema (DMO) and/or proliferative diabetic retinopathy (PDR). Briefly, DMO occurs as a result of direct microvascular injury to retinal blood vessels with subsequent leakage; in addition, microvascular occlusion may occur as a result of vessel wall injury, leading to the release of vascular endothelial growth factor (VEGF), which in turn increases vascular permeability, contributing to macular oedema. Figure 1 shows a typical example

Figure 1. Right fundus photograph showing severe nonproliferative diabetic retinopathy and diabetic macular oedema. Note the presence of perifoveal microaneurysms, macular hard exudate, retinal haemorrhages and thickening.

Figure 3. Montage fundus photograph of the right eye showing extensive neovascularisation and tractional retinal detachment adjacent to the optic disc. Note the presence of some peripheral scatter laser as partial treatment of the proliferative retinopathy.

of DMO; a corresponding optical coherence tomography scan is shown in Figure 2. With increasing ischaemia throughout the retina, VEGF drives the development of abnormal neovascularisation at the disc (new vessels at the disc [NVD]) and elsewhere (NVE), which is defined as PDR. Although NVD and NVE do not cause direct damage, they often progress to vitreous haemorrhage and tractional

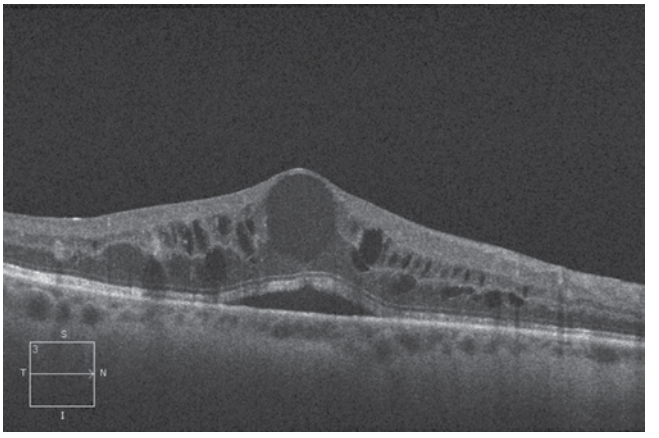

Figure 2. Optical coherence tomography scan of the right macula, showing gross intraretinal fluid, thickening and foveal subretinal fluid, consistent with diabetic macular oedema.

retinal detachment, which are associated with severe loss of vision. Figure 3 shows a montage fundus photograph of a patient with florid PDR and tractional detachment adjacent to the optic disc. It should also be noted that vision might be limited in advanced disease by macular ischaemia.

In the primary care setting, adequate clinical assessment of the retina is difficult because it requires specialised ophthalmic equipment and pupil dilation is not routinely performed. For this reason, we have seen increased uptake of the Welch Allyn Panoptic ophthalmoscope, which allows retinal examination of the posterior pole (optic disc and macula) through an undilated pupil. In any case, on initial presentation to the GP, a careful assessment of symptoms is the key to determining the cause of visual impairment. DMO typically presents gradually, with blurred vision, central distortion and difficulty reading. In contrast, early PDR is often initially asymptomatic and a high index of suspicion is required in patients with poorly controlled diabetes of significant duration. Later, if the PDR is complicated by vitreous haemorrhage or tractional retinal detachment, the patient can present with painless sudden onset of floaters, loss of vision or worsening scotoma. Unfortunately, DMO and PDR often exist together and can prove challenging to treat.

Medical therapy

It is well established that optimisation of glycaemic control and systemic hypertension reduces the incidence and progression of diabetic retinopathy; furthermore, it is critical to achieving good outcomes in the context of specific ophthalmic treatment.[2] GPs play an important role in educating, monitoring and encouraging patients in this aspect of their clinical care. However, it should be noted that rapid, tight control of hyperglycaemia may initially worsen existing diabetic retinopathy before achieving stabilisation. The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study reported on the benefits of fenofibrate in reducing the rate of

progression of mild to moderate retinopathy in patients with type 2 diabetes (38% relative risk reduction, 3.7% absolute risk reduction).[3] However, as outlined in an editorial by Fagan and Chong, this benefit is only valid for patients with specific dyslipidaemia (elevated triglycerides and reduced high-density lipoproteins), has a number needed to treat of 27 and may be associated with side effects such as renal impairment.[4] Therefore, we would advocate for the limited use of fenofibrate in patients with dyslipidaemia and hard exudates on retinal examination, representing more significant retinopathy.

Specific treatment of diabetic macular oedema

There is now extensive evidence for the safety and superiority of intravitreal anti-VEGF agents (ranibizumab, aflibercept and bevacizumab [off-label use for bevacizumab]) for the treatment of DMO, with the potential to improve vision in addition to stabilising disease.[5] Treatment typically involves monthly injections until the DMO resolves and vision improves, followed by a maintenance phase (often up to three years) where the patient is treated at longer intervals or as needed. In some cases, DMO is recalcitrant to anti-VEGF therapy and intravitreal steroid injection may be considered, although this may be associated with the development of cataract and raised intraocular pressure, which can lead to glaucoma. There is still a role for focal macular laser treatment to areas of extrafoveal leakage, which may be done in conjunction with intravitreal therapy. Finally, vitrectomy may be beneficial in DMO when there is concurrent epiretinal membrane and/or vitreomacular traction.[6]

Management of proliferative diabetic retinopathy

As noted previously, PDR is primarily driven by intraocular VEGF release from ischaemic retinal tissue, which is therefore the key therapeutic target. In patients who are at high risk of vision loss, characterised by extensive neovascularisation and preretinal or vitreous haemorrhage, intravitreal anti-VEGF injections may be used to immediately neutralise intraocular VEGF, bring about regression of NVD and NVE and prevent progression (off-label use). Concurrently, panretinal photocoagulation (PRP) laser treatment is performed to ablate the peripheral ischaemic tissue and is completed over several sessions. One of the difficulties among patients with PDR is that vitreous haemorrhage may obscure the full view of the retina and render PRP incomplete; in this not uncommon circumstance, it may be appropriate to proceed to vitrectomy and intraoperative completion of PRP using endolaser treatment.

Role of surgery

Vitreoretinal surgery in diabetic retinopathy plays a significant role in the management of advanced disease. With modern techniques and instrumentation it has a favourable safety profile. In most patients, surgery is performed under local anaesthesia and does not require an overnight stay in hospital. Specific indications for surgery include in the following:

- longstanding vitreous haemorrhage limiting treatment or associated with anterior segment neovascularisation (which can progress to neovascular glaucoma)
- tractional retinal detachment affecting the macula
- vitreous haemorrhage in treatment-naïve eyes in high-risk patients.

In addition, there may be a lower threshold for surgery in patients whose other eye has very poor or no vision, or if there is an urgent need for visual recovery. However, it is important to appreciate that patients with diabetes mellitus often have a number of comorbidities that must be taken into consideration to ensure safety during surgery, especially if general anaesthesia is necessary.

Cataract surgery is sometimes necessary in patients with vision-threatening retinopathy. Where possible, adequate stabilisation of DMO and PDR is ideal before proceeding, with close monitoring for progression postoperatively.[7] However, significant cataract (especially posterior subcapsular cataract) may impair the view of the retina, and in this circumstance, it is often appropriate to give an intravitreal anti-VEGF injection in the week before cataract surgery.

Conclusion

Advances in treatment, particularly the use of anti-VEGF agents, have significantly improved the visual outcomes of patients with diabetic retinopathy. However, consistent control of blood glucose and coexisting vascular risk factors remains a key determinant of eye health. GPs have a critical role in managing this aspect of treatment as well as co-ordinating the overall care of the patient. **ET**

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