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An update on **Diabetic maculopathy**

Despite advances in the management of diabetes, diabetic retinopathy is already the commonest cause of blindness among the working population and is set to be the most common cause of sight loss in the world given the rising prevalence of diabetes. Diabetic retinopathy affects a third of all diabetic patients.

Whereas proliferative diabetic retinopathy (PDR) is the most common sight-threatening lesion in type 1 diabetes, diabetic macular oedema (DMO) is more frequent in type 2 diabetes. Given the overall higher prevalence of type 2 diabetes, DMO is the more common cause of moderate visual loss. (Fig 1)

Encouragingly, there is evidence from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) that the prevalence and incidence of severe DR, including PDR and DMO may be decreasing in people more recently diagnosed with type 1 diabetes. However it is not clear if this trend is seen in patients with Type 2 diabetes.

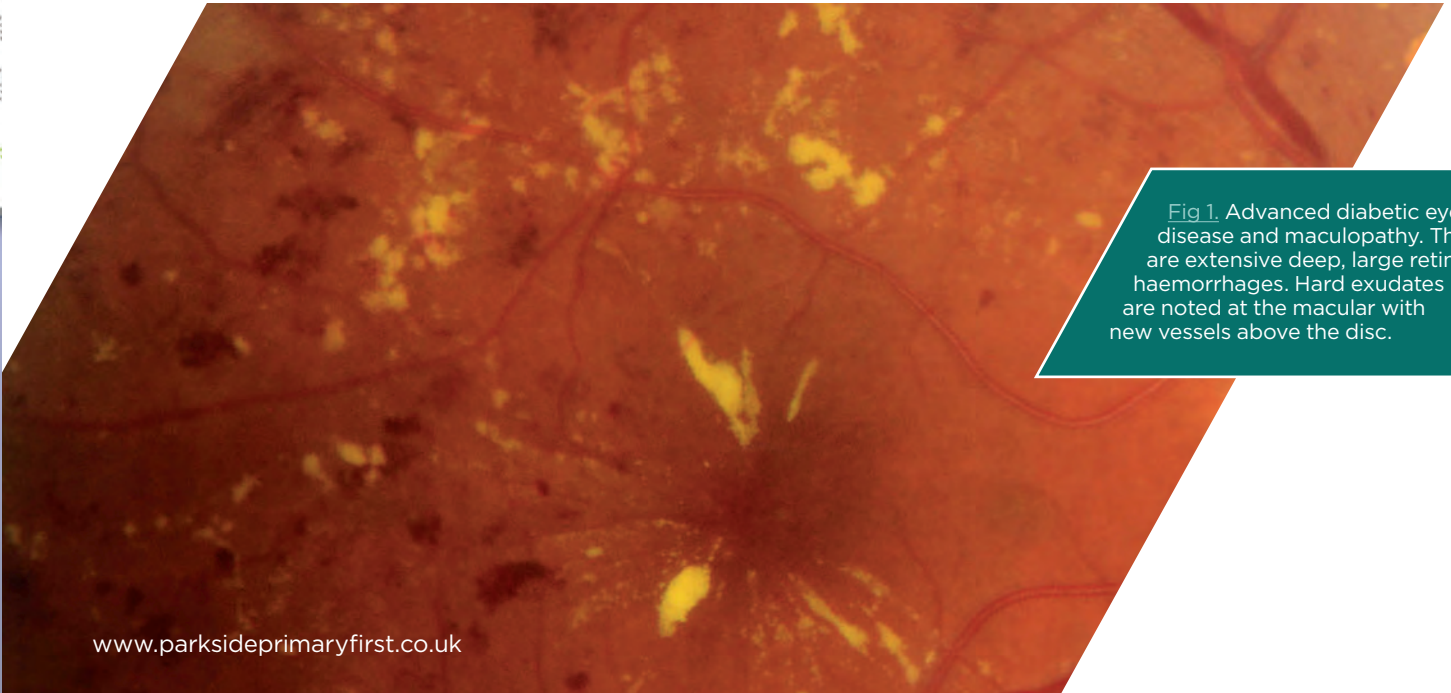


Fig 1. Advanced diabetic eye disease and maculopathy. There are extensive deep, large retinal haemorrhages. Hard exudates are noted at the macular with new vessels above the disc.

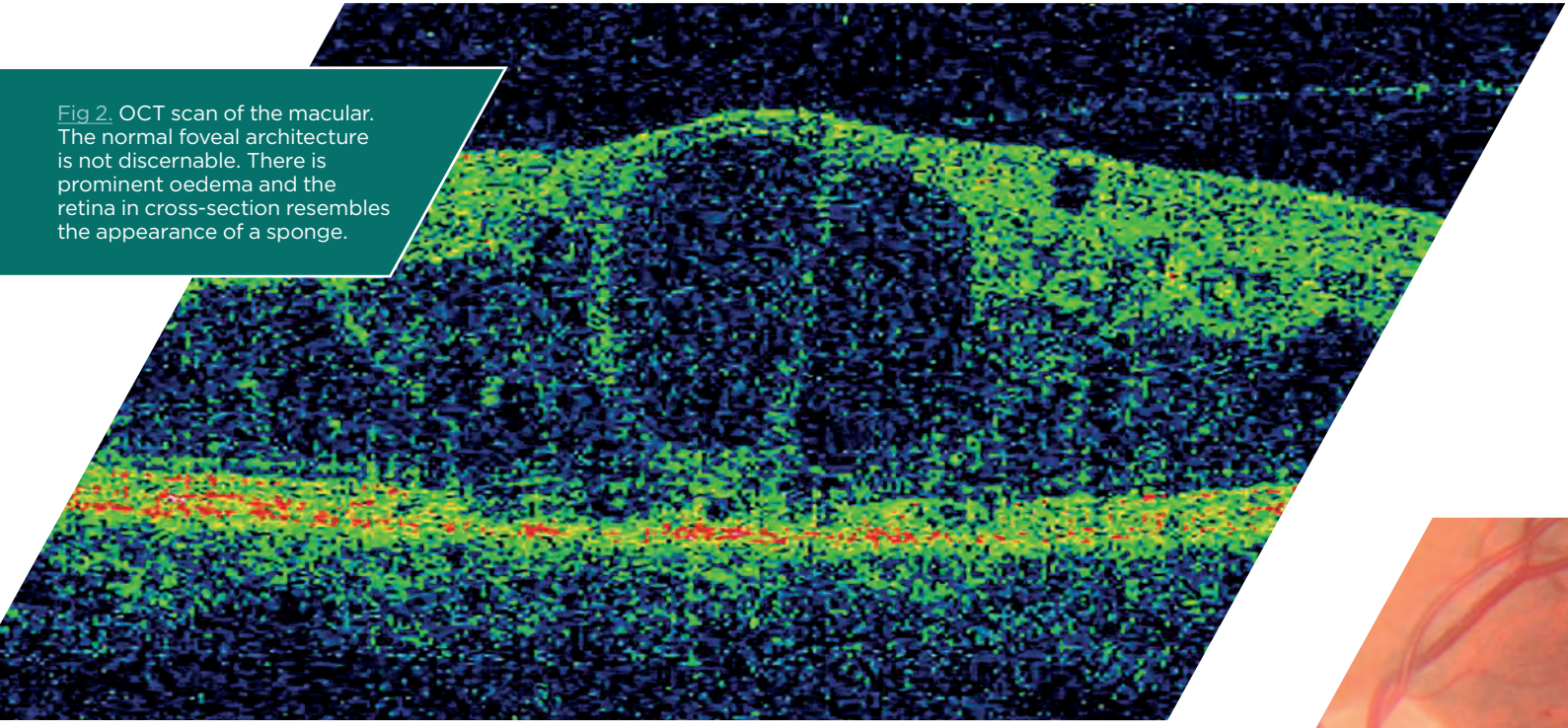
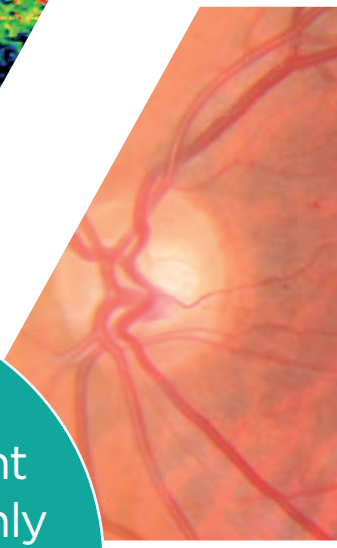


Fig 2. OCT scan of the macular. The normal foveal architecture is not discernable. There is prominent oedema and the retina in cross-section resembles the appearance of a sponge.

Vision loss in diabetic maculopathy results from a combination of ischaemic changes of the retinal microvasculature, neuronal damage and the development of retinal oedema.

The pathogenesis of DMO is multifactorial. Breakdown of the blood-retina barrier increases retinal capillary permeability leading to retinal oedema. Inflammation is an eminent factor in this process. (Fig. 2)

Although the risk of vision loss due to diabetic retinopathy can be reduced by effective control of serum glucose and blood pressure, until now, laser treatment has been the only effective means of preventing visual loss once sight threatening eye disease is diagnosed.



FACT

Laser treatment has been the only effective means of preventing visual loss

MACULAR LASER

Laser treatment for clinically significant macular oedema (CSMO) has been the mainstay form of treatment after the findings by the Early Treatment Diabetic Retinopathy Study (ETDRS) that demonstrated a 50% reduction in moderate visual loss (from 24% to 12%) at 3 years. Laser treatment still remains the first choice for patients within the NHS for most types of oedema. Recurrent laser does result in permanent structural changes to the retina and is less effective in managing diffuse oedema or centre (fovea) involving oedema. Inadvertent laser to the fovea, as may occur with patient eye movement, carries the risk of immediate loss of vision. (Fig 3)

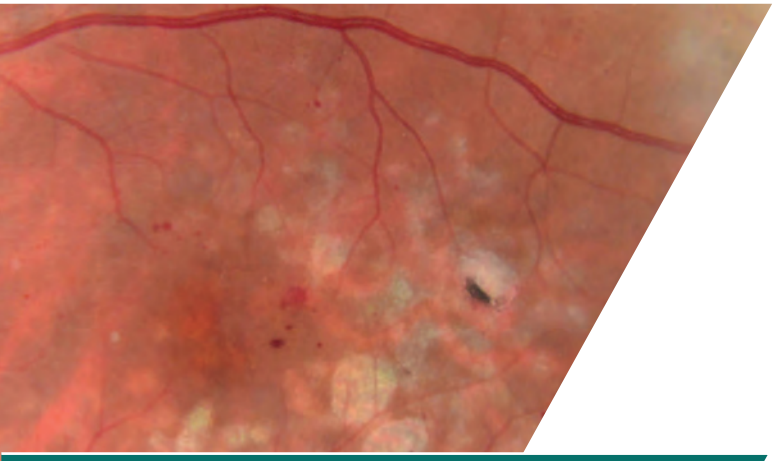


Fig 3. The laser scars here are more prominent than would be expected and used to be a feature of the early forms of macular laser. The modern macular lasers that use the 577nm wavelength and give a much more predictable and acceptable outcome. Macular scarring as shown can also result from the use of excessive energy and results in irreversible structural changes and visual loss.

Recent advances in pharmacotherapy have rapidly seen laser treatment being replaced with intravitreal agents to manage macular oedema.

This exciting development means that ophthalmologists now have a toolbox consisting of a choice of treatments and are now able to improve vision rather than simply aim to prevent further visual loss. Factors influencing treatment choice include location of oedema (centre involving versus non centre involving) extent of oedema and duration of oedema.

There are two main classes of drugs used in the management of diabetic maculopathy. These include the anti-vascular endothelial factor (anti-VEGF) drugs such as ranibizumab (Lucentis), aflibercept (Eylea) or bevacizumab (Avastin) and secondly, corticosteroids. All these agents are injected directly into the vitreous.

ANTI-VEGF INJECTIONS

When oedema involves the fovea, it carries a higher risk of visual loss and anti-VEGF agents would constitute the first choice of treatment. Recent NICE guidelines have made Lucentis and Eylea available in the NHS for patients who have centre-involving oedema greater than 400µm in thickness on ocular coherence tomography (OCT) scans. Injections of either agent are effective for about 4-6 weeks. Patients often require a course of treatment, typically ranging from 6-8 injections in the first year and 3-5 in the second year.

However, only a small proportion of patients meet this criteria. Consequently, many who would benefit from Lucentis injections are not able to access it on the NHS and are forced to seek treatment in the private sector. Such patients can also be successfully treated with Avastin when the cost of Lucentis is prohibitive. Although Avastin is unlicensed for use in the eye, there is extensive randomised controlled trial evidence to support its use and it has a similar efficacy profile to Lucentis for the management of DMO.

The really exciting evidence about the use of Anti-VEGF agents is that they may actually modify the long-term prognosis of diabetic macular oedema for the better.

Systemic Safety Concerns of Anti-VEGF agents

Anti-VEGF agents injected into the eye are known to enter the systemic circulation in small doses. Serum VEGF levels have been shown to be supressed after intravitreal injections but the significance of this is unknown. None of the randomised controlled trials have been powered to assess safety. There are no reported increased risks of arterial thrombotic events with any of the Anti-VEGF drugs. However, Royal College of Ophthalmologist guidelines still recommend a three month treatment break following a cardiovascular or cerebrovascular event. Such patients may be safely treated with intravitreal corticosteroids.

Corticosteroids for Macular Oedema

Evidence from the RIDE and RISE trials identified that when oedema had been present for 2 years or more, it was less responsive to treatment with Anti-VEGF agents and the visual outcomes were worse in these patients. It is hypothesized that microenvironmental changes occurring in chronic DMO may need a treatment strategy that targets multiple inflammatory mediators. This is possible with corticosteroids.

The three steroid agents that are available for intravitreal injections include triamcinolone (unlicensed), fluocinolone acetonide (licensed) and dexamethasone (licensed). Although unlicensed, intravitreal triamcinolone (IVTA) has been widely used in the management of refractory DMO or as an alternative to macular laser when laser is not a suitable option.

Fluocinolone acetonide (Iluvien) is a steroid implant that has a duration of action of up to 3 years. Dexamethasone (Ozurdex) is available as a medium duration implant. It is effective in managing oedema for a period of about 3-4 months after which retreatment will be required.

All steroid agents result in a high incidence of cataracts (near 100% with repeat treatment) and raised eye pressure occurs in about 40% of patients. This can usually be managed well with eye drops.

NICE guidelines have recommended the use of Iluvien or Ozurdex as second or third line agents for treating refractory DMO in patients who have had cataract surgery. My personal preference is to use Ozurdex first as it has a shorter duration of action and is biodegradable in the eye. However, if patients require multiple repeat injections, I would be more inclined to switch to Iluvien.

Although the side effect profile of corticosteroids may appear alarming, the potential risk from treatment is certainly outweighed by the benefits of preventing central visual loss from untreated chronic macular oedema and the consequent high socioeconomic burden and loss of independence.

There are no reported increased risks of arterial thrombotic events with any of the Anti-VEGF drugs

Table 1. Summary of Treatment Options & Outcomes

Treatment agent	Lucentis	Avastin (unlicensed)	Iluvien	Laser
Indication	All types of diabetic oedema < 18 months duration	All types of diabetic oedema < 18 months duration	Chronic oedema	*Localised, non centre involving oedema *Oedema less than 400µm in thickness
Average vision gain	+10 letters	+8 letters	+5 letters	0 to +3 letters
Adverse effects	1:1000 risk of loss of vision with each injection	1:1000 risk of loss of vision with each injection	Cataracts progression near 100%, raised pressure in the eye (40%), 1:000 risk of blindness with each injection	Macular scarring, loss of vision if laser involves fovea, poor efficacy in chronic and diffuse oedema

Special Circumstances in Managing Macular Oedema

CATARACT SURGERY

Diabetic patients are particularly susceptible to developing macular oedema post cataract surgery. This requires careful evaluation and early management to prevent visual loss. Prophylactic treatment with topical Nevanac has been found to reduce the risk of developing macular oedema from 16.7% to 3.2%.

PREGNANT WOMEN

Diabetic patients need to be screened for progression of their retinopathy and maculopathy at least once in each trimester. Anti-VEGF agents are not recommended in pregnancy. If maculopathy develops, laser or intravitreal steroid injections would be suitable management options.

SUMMARY

The management of DMO has now entered an exciting era. With intravitreal injections, we can now improve vision rather than simply aiming to prevent visual loss. These agents also permit the treatment of oedema that cannot be safely treated by conventional macular laser.