Macular oedema

Aetiology, differential diagnosis, and management

In the first of two articles looking at retinal eye disease, Nathan Walker and Bishwanath Pal look at macular oedema. Module C16600, one general CET point for optometrists and dispensing opticians

Macular oedema refers to the accumulation of fluid in retinal layers around the fovea, usually as a result of blood-retina barrier dysfunction. Macular oedema is not a specific entity, but rather a non-specific response to an abnormal retinal environment.

Vision is impaired due to disruption of the normal cellular relationships in the retina, mechanical stress, and a mild inflammatory response. The process begins with diffuse swelling of the outer retinal layers, and may advance to form the typical cyst-like spaces (termed ‘cystoid macular oedema’ – CMO) most often in the outer plexiform (Henle’s) and inner nuclear layers (Figure 1). With increasing severity and duration, the cysts may enlarge, coalesce, and extend to involve all retinal layers from the retinal pigment epithelium to the internal limiting membrane (Figure 2). Uncommonly, the cysts may rupture, resulting in a type of macular hole.1,2

Causes
Macular oedema can occur in a wide variety of ocular conditions including diabetes, retinal vascular disease, age-related macular degeneration (AMD), uveitis, vitreoretinal traction, retinal dystrophies, and following intraocular surgery and trauma. It can be broadly classified by aetiology into inflammatory macular oedema and retinal vascular decompensation macular oedema, which influences the choice of treatment.2

Although the exact mechanism remains uncertain, it is thought that macular oedema most commonly results from dysfunctions of the inner blood-retina barrier which is comprised of tight junctions between endothelial cells lining the retinal vessels. This barrier serves to restrict entry of plasma proteins and transude from the vasculature to the neurosensory retina and maintain homeostasis. Meanwhile, tight junctions between retinal pigment epithelial cells form the outer blood-retina barrier which limits passage of fluid from the choroidal vessels to the neuroretina. Electrolytes and larger molecules undergo active transport. Inner or outer blood-retina barrier compromise leads to accumulation of fluid in the retina, with a predilection for cystic pooling at the fovea. Drainage of excess fluid from this region may be limited due to the absence of vasculature at the central macula, known as the ‘foveal avascular zone’.2,3

Diabetes
Diabetes is the most common cause of blindness in the working age population in developed countries. It is estimated that around 8 per cent of the adult population has diabetes, with approximately half of these being undiagnosed. Landmark studies in the 1980-90s, the ‘Diabetes Control and Complications Trial’ (which looked at type 1 diabetics) and the ‘United Kingdom Prospective Diabetes Study’ (which examined type 2 diabetics), showed us that even with intensive blood sugar control, approximately three-quarters of these patients will develop some degree of diabetic retinopathy within 10 years of diagnosis. The risk of diabetic maculopathy increases with the duration of diabetes, affecting approximately 30 per cent of patients after 30 years of disease; 10 per cent develop vision threatening macular oedema. Interestingly, macular oedema can develop at any level of diabetic retinopathy.

Diabetes adversely affects blood vessels in several ways. The retinal capillaries undergo degenerative changes in the vessel wall (namely, loss of endothelial cells and pericytes) resulting in luminal narrowing, impaired perfusion, ischaemia, microaneurysm formation, and transudation (leakage of fluid). These effects can be focal or diffuse. Generalised capillary incompetence leads to retinal swelling with a predilection for the macula.2,5

The ‘Early Treatment Diabetic Retinopathy Study’ defined clinically significant macular oedema (‘CSMO’) as: (a) retinal oedema within 500 microns of the fovea, (b) hard exudates within 500 microns of the fovea if associated with an area of retinal thickening, or (c)
As diabetes is a chronic, slowly progressive disease, long-term control of the oedema can prove challenging. Radiation retinopathy can mimic diabetic retinopathy including the macular oedema. A history of radiotherapy to the eye or head will be present and the signs are usually unilateral.

**Retinal vascular occlusion**

Retinal vascular occlusive disease is the second most common cause of macular oedema after diabetic retinopathy. Obstruction of the retinal venous system causes vascular engorgement upstream from the sites of occlusion. This increases hydrostatic pressure on the inner blood-retina barrier which may also be impaired as a result of ischaemia, allowing fluid to leak from the retinal capillaries. The location and severity of venous occlusion determines the extent and severity of the resulting macular oedema such that central retinal vein occlusions carry a poorer prognosis than branch retinal vein occlusions.²

Branch retinal vein occlusion occurs in approximately one in 500 adults aged over 40, per year (Figures 3a, 3b). It is a major cause of visual loss as a result of macular oedema, retinal haemorrhages, and the consequences of retinal ischaemia (neovascularisation, vitreous haemorrhage, and tractional retinal detachment). The primary cause of the occlusion is typically compression of the vein at an arteriovenous crossing as a result of arteriosclerosis. Hence the risk factors are those of cardiovascular disease – advancing age, hypertension, diabetes, hypercholesterolaemia, obesity, and smoking. Blood clotting disorders and vasculitis are occasionally implicated, particularly in younger patients. The landmark Branch Vein Occlusion Study showed that macular laser treatment roughly doubled the likelihood of significant visual improvement from 37 per cent to 65 per cent when applied to patients with chronic macular oedema and reduced vision (6/12 or worse) in the absence of macular ischaemia. It has recently been shown that vision may continue to improve for at least 2-3 years in those treated with macular laser. Localised (sectoral) panretinal photocoagulation was suggested for neovascularisation.⁹

More recently, the BRAVO Study (2010) demonstrated the efficacy of monthly Lucentis injections for this condition. By month six, approximately 60 per cent of patients gained at least three lines of vision, compared to less than 30 per cent in the sham treatment group. This study is ongoing and long-term results are keenly awaited. In contrast, intravitreal steroid injections have been shown to be inferior to laser treatment for this condition (SCORE Study).¹⁰

Central retinal vein occlusions are approximately one-fifth as common as branch vein occlusions. Macular oedema, retinal haemorrhages, and ischaemia occur over a larger area and neovascular complications are much more common – hence the poorer visual prognosis. The Central Vein Occlusion Study showed macular laser treatment to be ineffective at improving vision in this condition. However, the recent CRUISE Study (2010) showed monthly intravitreal Lucentis is effective with nearly 50 per cent of patients gaining at least three lines of vision after six months of treatment, compared to only 17 per cent in the sham treatment group. These early reports are very encouraging, and ongoing research will elucidate optimal dosing schedules, cost-effectiveness, and the long-term effects of these new treatments.¹¹,¹²

**Age-related macular degeneration**

Thirty per cent of the population aged over 75 has some degree of AMD. Ten to
15 per cent of those have the ‘wet’ form (exudative AMD) which is characterised by choroidal neovascularisation (CNV), retinal pigment epithelial detachments, and their sequelae; while 85-90 per cent have the ‘dry’ form (atrophic AMD), characterised by intermediate or large drusen, retinal pigment epithelial changes, and slowly progressive chorioretinal atrophy. Macular oedema is a very important sign of CNV activity (Figure 4), as the new vessels have a tendency to leak (and bleed), causing visual loss as a result of subretinal and intraretinal oedema, haemorrhage, and scarring. While fundus fluorescein angiography (FFA) is typically required for definitive diagnosis of CNV, the presence of macular oedema on OCT is used to guide treatment with anti-vascular endothelial growth factor (anti-VEGF) medication (Avastin and Lucentis). Risk factors for AMD are advancing age (the strongest determinant of risk), family history, smoking (the most important modifiable risk factor), and other cardiovascular risk factors (hypertension, obesity etc). Ocular risk factors for exudative AMD are the presence of soft drusen, macular pigment changes, and the presence of CNV in the fellow eye. A poor diet (low in antioxidants and omega 3 fatty acids) and exposure to sunlight are suspected risk factors. Some genetic markers have been linked to AMD risk (eg complement factor H polymorphisms), but these are not yet clinically applicable.

Treatment has been revolutionised in recent years with the arrival of Lucentis. The MARINA and ANCHOR Studies showed that vision can be stabilised in around 95 per cent of patients and improved in around 35 per cent (Table 2). Monthly dosing is most efficacious but expensive and onerous for patients. Avastin has recently been shown to offer equivalent efficacy at a significantly lower cost, which will help improve access to treatment and reduce the financial burden placed on patients, governments, and insurers.13

Uveitis

Nearly half of all patients with uveitis have some degree of visual impairment from macular oedema, which is often the presenting complaint. Anti-inflammatory medication (corticosteroids) administered topically, systemically (orally), as a periocular depot injection, or intravitreally are usually required.2

Postoperative

Between 1 and 5 per cent of patients who undergo cataract surgery develop CMO with peak incidence 6-10 weeks postoperatively. Most cases are subclinical and resolve spontaneously but may be observed on OCT or FFA. It is thought to result from sterile inflammation caused by release of inflammatory mediators from the iris, ciliary body, and retinal pigment epithelium. Risk factors include complicated or prolonged surgery with manipulation of the iris and/or vitreous, diabetic retinopathy, and history of CMO in the other eye. The release of inflammatory mediators causes inner blood-retinal barrier compromise leading to macular oedema. Other forms of ocular ‘trauma’ may cause macular oedema through similar mechanisms.2

As prostaglandins are thought to play a key role in the development of postoperative CMO, treatment involves non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to inhibit prostaglandin synthesis. Topical NSAID eyedrops have better ocular penetration than oral NSAIDs, and Acular is the drug of choice.

For those patients who fail to improve on topical treatment, periocular or intravitreal steroid injections can be efficacious. Non-responders to this treatment may benefit from vitrectomy, although this is rarely needed.

Retinal dystrophies

Retinitis pigmentosa and other retinal dystrophies are associated with CMO which is thought to be secondary to increased permeability of the retinal pigment epithelium and perifoveal capillaries. Carbonic anhydrase inhibitors (eg oral acetazolamide, or topical dorzolamide or brinzolamide) can improve the oedema in some patients.3

Epiretinal membranes

Epiretinal membranes are thought to result from proliferation of metaplastic retinal glial cells. Contraction of these membranes can distort the retinal architecture, and macular oedema may develop due to mechanical traction on retinal capillaries. Vitrectomy surgery with epiretinal membrane peeling is offered when patients suffer reduced and/or distorted vision, and any associated macular oedema usually settles quickly once this traction is relieved.

Differential diagnosis

Thickening of the macula may also occur due to subretinal fluid accumulation which can be serous or rhegmatogenous in nature. The most common causes of serous macular detachment are choroidal neovascularisation (as discussed above) and central serous retinopathy (CSR) (Figure 5a, 5b). Other causes of exudative retinal detachment that may affect the macula include Coats’ disease (peripheral retinal telangiectasia), malignant hypertension, Vogt-Koyanagi-Harada syndrome, posterior scleritis, benign or malignant choroidal tumours, and optic disc pit maculopathy. Residual subretinal fluid following retinal detachment repair is common in the first few weeks or even months after successful surgery; however, untreated peripheral retinal breaks should also be considered. X-linked juvenile retinoschisis may be confused clinically with macular oedema, but the young male patient (unusual for most of the other causes listed above), bilaterality of signs (although often asymmetric), characteristic picture on OCT, and accompanying peripheral retinoschisis are clues to this condition.

Full-thickness macular holes are often surrounded by a cuff of retinal oedema and subretinal fluid. If the hole is small it may be difficult to appreciate clinically, leading to confusion over the aetiology of the oedema. Older
OCT machines would occasionally fail to illustrate the hole, as images were taken as a series of lines. This is much less of a problem with the modern, high-resolution instruments.

**Clinical approach**
Macular oedema typically presents with painless loss of vision in one eye, although it can be bilateral depending on the cause. Although the visual loss usually occurs gradually, patients may notice it suddenly when covering the fellow eye. As with any patient presentation, clinical evaluation begins with a thorough history. The age of the patient is important as it relates to the epidemiology of causative disorders, and the time-course of visual symptoms and severity of visual impairment are highly relevant as chronic severe cases are less likely to respond to treatment. A history of intraocular surgery (particularly recent cataract or vitreoretinal surgery), diabetic retinopathy, retinal vascular disease (eg retinal vein occlusion), inflammation (eg uveitis), injury, AMD, or retinal dystrophies should be sought; and general medical history of diabetes, cardiovascular disease, and radiotherapy considered. Drugs such as prostaglandins and nicotinic acid have also been implicated.

Depending on the amount of fluid present, dilated fundus examination may reveal loss of the normal foveal reflex and cystic changes at the macula.

**Investigations**
If the underlying cause is not obvious on history and ophthalmoscopy, ancillary testing with OCT and FFA may be necessary. OCT accurately determines retinal thickness and extent of oedema, affording highly valuable quantitative comparisons over time and is therefore especially useful in monitoring the response to treatment.\(^1\,\text{14}\)

**Conclusion**
Macular oedema can be caused by a wide variety of conditions. Careful history and examination, with the aid of targeted investigations, is usually diagnostic. Treatment depends on the underlying aetiology and may vary considerably from macular laser, anti-inflammatory medication, anti-VEGF injections, or a combination, and surgery is occasionally indicated. Chronic macular oedema causes retinal atrophy and gradual loss of vision, so timely referral to a retinal specialist is advisable.

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**Multiple-Choice Questions**

1. Which of the following is the commonest cause of macular oedema?
   - A Retinal vascular occlusion
   - B Diabetic eye disease
   - C Uveitis
   - D Trauma

2. What proportion of diabetics present with diabetic maculopathy?
   - A 10 per cent after 30 years
   - B 30 per cent after 10 years
   - C 30 per cent after 30 years
   - D 8 per cent

3. Macular oedema is associated with which of the following diabetic retinopathy levels?
   - A Background
   - B Pre-proliferative
   - C Proliferative
   - D All the above

4. Which of the following statements about treatment of retinal vein occlusion is false?
   - A Macular laser treatment of patients with chronic macular oedema reduces acuity in the absence of macular ischaemia
   - B Monthly Lucentis injections may improve vision in patients with branch retinal vein occlusion
   - C Intravitreal steroid injections are superior to laser treatment for branch retinal vein occlusion patients
   - D Macular laser treatment is ineffective at improving vision in patients with central retinal vein occlusion

5. What percentage of patients with uveitis have some sight loss due to macular oedema?
   - A 1 per cent
   - B 5 per cent
   - C 10 per cent
   - D 50 per cent

6. Which of the following is diagnostic of clinically significant macular oedema (CSMO)?
   - A Hard exudates anywhere on the fundus
   - B Retinal oedema of 500 microns diameter within 1 disc diameter of the disc
   - C Retinal oedema 1 disc diameter in size within one disc diameter of the fovea
   - D Hard exudates within the FAZ without retinal thickening