Diabetic Maculopathy – Through an Artist's Eyes

WRITER Dr. Christolyn Raj

Managing diabetic macular edema (DME) clinically, necessitates gauging response to treatment, detecting change and prognosticating for future disease behaviour.

Every hour in Australia, approximately 11 Australians are diagnosed with diabetes. Around the world, diabetes is predicted to increase by 55 per cent by the year 2040. The aetiology of this increase involves changes in diet with higher fat intake, sedentary lifestyle, and decreased physical activity[2] (Figure 1). Among the ocular complications of diabetes, diabetic maculopathy is the most common and potentially blinding. Typically, it affects individuals in their most productive years and has devastating complications on the patient as well as society as a whole. A recent epidemiology study estimated the prevalence of diabetic maculopathy to be 7 per cent of the Australian population but, within this group, almost half (39 per cent) had associated visual impairment (Figure 2).[3]

"Gauging how well a patient is responding to therapy in DME can be a challenge"

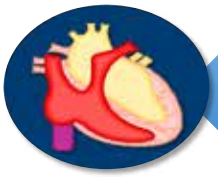
As eye care professionals, optometrists and ophthalmologists are the gatekeepers for this disease. If we educate our patients to manage their diabetes well, present early to their optometrists, and then refer them for treatment in a timely manner, this disease may be entirely reversible.

To illustrate the nature of diabetic maculopathy I wanted to use the example of famous American impressionist Mary Cassatt, who was diagnosed with diabetes and developed severe complications of retinopathy. This, in addition to other ocular complications of cataracts, caused a premature end to her artistic career. Her fellow Impressionist artists gleaned rather inaccurately, from her poor progress, that cataracts alone – not diabetic retinopathy – was the grim reaper of an artist's life.

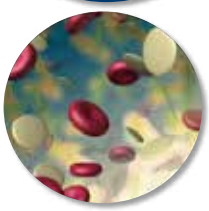
DME – WHEN SHOULD YOU REFER?

DME is a relatively slow progressing disease, especially compared with other maculopathies such as neovascular age related macular degeneration (nAMD). This means a period of observation may

Figure 1. Diabetic maculopathy risk factors



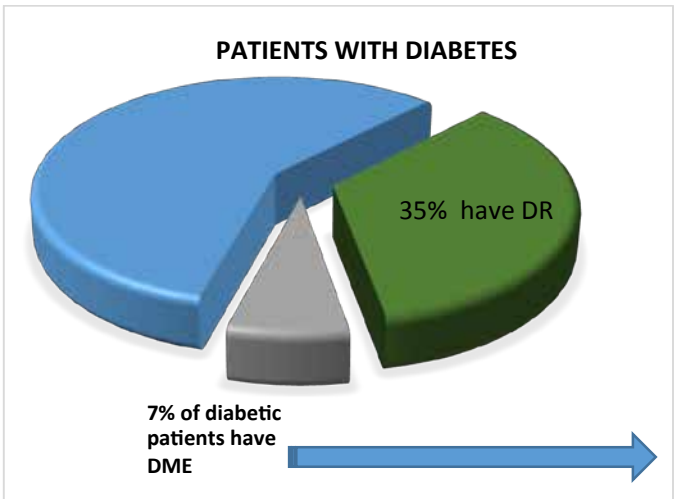
High systolic blood pressure is a risk factor for DME[1]
(HR per 10 mmHg = 1.15; 95% CI, 1.04-1.26)



Increased total serum cholesterol associated with increased risk of hard exudates[2]
(OR = 2.0; 95% CI, 1.35-2.95)[a]

High HbA_{1c} levels are a risk factor for DME[1]
(HR per 1% = 1.17; 95% CI, 1.10-1.26)

Figure 2. Impact of visual impairment from diabetic maculopathy.



39% of patients with DME have visual impairment

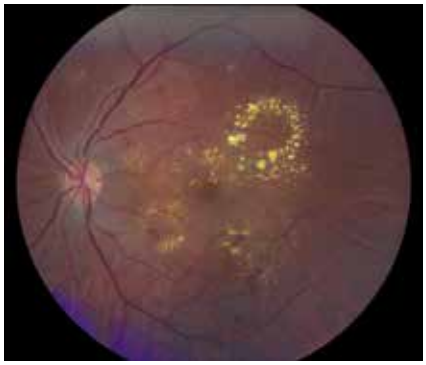


Figure 3. Centre involving macular edema

be warranted. But, as in the case of Mary Cassatt, it is likely that subtle changes will still occur in every patient with existing DME.

The Early Treatment Diabetic Retinopathy Study (ETDRS) comments on centre involving and non-centre involving DME.[5] A prompt referral for centre-involving DME is warranted as this is most sight-threatening. These patients are more likely to be treated with intravitreal injections (Figure 3).

Non-centre involving DME may still require referral. These patients may require focal grid laser to stop leaking micro-aneurysms which, if left unattended, can result in spread to the foveal centre, as well as contribute to lipid exudate deposition in the retinal layers. Once this process occurs, DME is less amenable to laser and/or intravitreal injections (Figure 4).

Regardless of their DME status, all patients with any diabetic retinopathy should be counselled regarding the importance of optimal control of blood glucose, serum lipids, and blood pressure. According to the UKPDS (Type 2 DM), a reduction in HbA1c of 2 per cent decreased the progression of diabetic retinopathy by 25 per cent.[6] The ACCORD-Eye study also showed a decrease in progression of retinopathy in patients with pre-existing retinopathy when treated with a fenofibrate and statin combination.[7]

"Once ischemia has occurred, there is a guarded prognosis for vision recovery"

Mary Cassatt: An Artist Avant Garde

Mary Stevenson Cassatt (1844 –1926) was an American born artist and printmaker who lived much of her adult life in France, where she became a close colleague of the Impressionists. Cassatt's paintings often featured images of the social and private lives of women and told the story of the unique bonds of motherhood. Among her most renowned paintings are Portrait of the Artist (self-portrait), Little Girl in a Blue Armchair, and Reading Le Figaro (portrait of her mother). In her early works we see the contrast in colours and attention to technical detail which were unique to the Impressionist movement (Images 1–3a,3b).

A decade later, Cassatt displayed a total of eleven works with Degas and the other Impressionists including her famous work La Loge. Critics often claimed that Cassatt's colours were too bright, that the colours chosen did not accurately depict her subjects, and in some cases were unflattering to them. Although she was at the prime of her career at the time, perhaps the critics were correct in that her contrast was being slowly affected by diabetic maculopathy – a surreptitious disease (compare Images 3a with 3b; and Images 4a with 4b).

Cassatt used delicate pastel colours in her paintings and avoided black, which was considered a 'forbidden' colour among the Impressionists. She had been acclaimed as adding a new chapter to the history of graphic arts with technicality in colour prints considered so unique that they have never been surpassed. However, over the years her colour prints changed. The colours she chose for her paintings became duller and without contrast, and they lacked the technique, brush strokes and rendition of her previous work. This was very likely due to a combination of intractable maculopathy which, left untreated, would have led to the development of macular ischemia (Images 5,6)

Cassatt was officially diagnosed with cataract in 1911. "I fought against it but it conquered" was her distraught response to her affliction with eye disease. Not wanting to slow down, she reluctantly underwent cataract surgery soon after. Unrecognised and unexpected at the time by her and her surgeons, diabetes and cataract complications likely ensued and her post-operative vision was worse than it had been. In 1914 she was forced to stop painting as she lost her sight completely.[4]

Image 1. Portrait of a little girl.

Image 2. Self-portrait.

AN UPDATE ON TREATMENTS FOR DME

Over the past decade there has been much in the literature about optimal management of diabetic maculopathy. Intravitreal pharmacotherapy has replaced focal/grid photocoagulation as the most commonly used first-line treatment for centre-involved DME. It is up to the clinician to tailor an appropriate regimen for each patient. This may involve solitary or combination treatment and is likely to vary throughout the management of the disease.

Intravitreal Anti-Vegf

Currently available anti-VEGF agents include aflibercept (Eylea), ranibizumab (Lucentis), and off-label bevacizumab (Avastin). The preference for anti-VEGF agents as first-line therapy is based largely on the results of Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I, in which treatment with intravitreal ranibizumab was associated with generally more favourable outcomes than laser photocoagulation or intravitreal corticosteroids.

The choice of anti-VEGF agent is controversial. DRCR.net Protocol T reported that in patients with presenting Best Corrected Visual Acuity (BCVA) between 6/9.5 and 6/12 BCVA, improvement at one year was similar among patients randomised to receive aflibercept, bevacizumab or ranibizumab. Aflibercept was however, associated with the greatest mean reduction in central macular thickness measured on ocular coherence tomography (OCT).

In patients with presenting BCVA of 6/15 or worse, aflibercept was associated with significantly greater BCVA improvement at one year than ranibizumab or

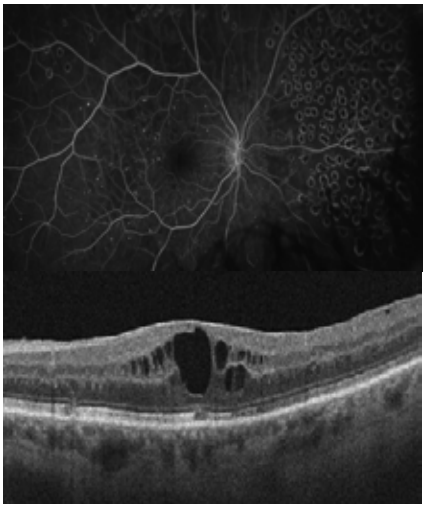


Figure 4. FFA showing evidence of non-centre involving DME. Corresponding OCT below (figure 5) shows evidence of macular edema reducing vision to 6/24, illustrating that follow up of all patients with DME is imperative.

Image 3a (left) and 3b(right). Reading Le Figaro.

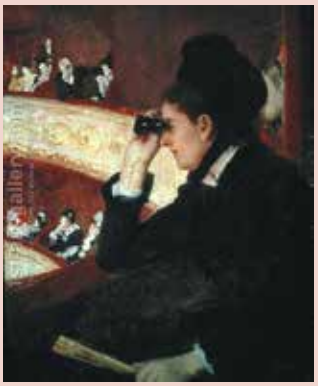


Image 4a (left) and 4b (right). In La Loge, painted using alternative tones, perhaps due to the way Cassatt perceived colours and contrast owing to her diabetic maculopathy.

Images 5 and 6. When comparing Cassatt's early work (above, The mandolin player) with her later work, (left, Girl's head on a green background), it is possible to appreciate the differences in technique, colour and contrast.

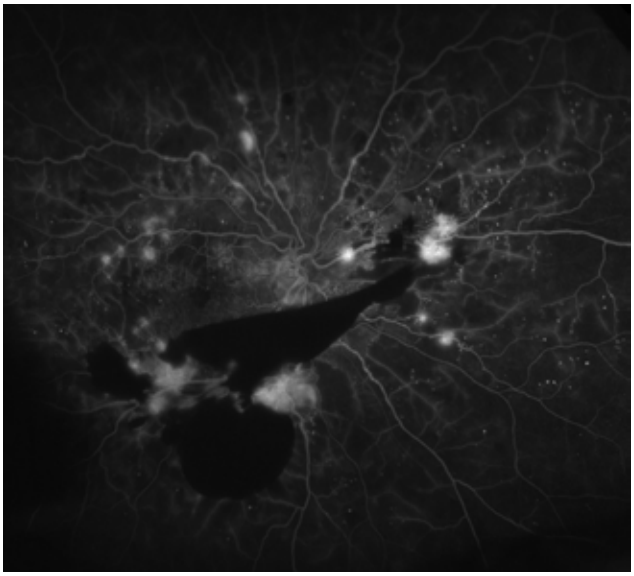


Figure 5. FFA showing an irregular and enlarged foveal avascular zone (FAZ) typical of macular ischemia.

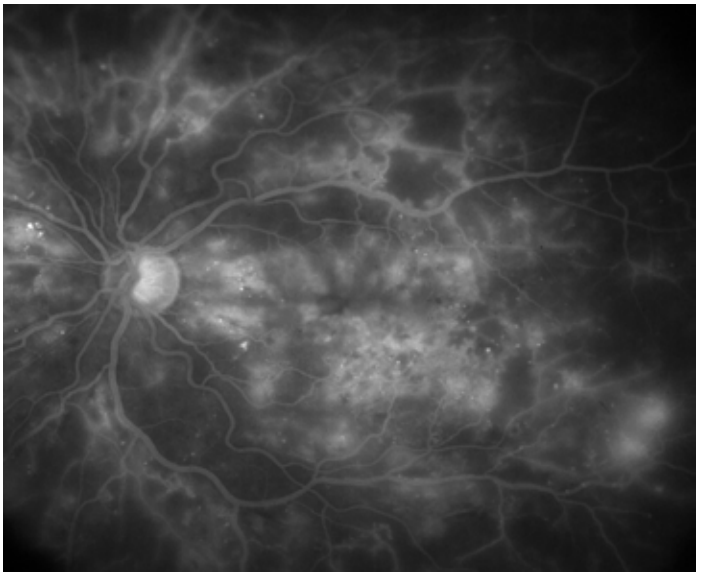


Figure 6. FFA showing severe maculopathy characterised by multiple points of macular leak predisposing to macular ischemia. Areas of capillary non-perfusion is seen in the superior retina. Both carry a poor visual prognosis.

bevacizumab.[8] At two years, among patients with presenting BCVA of 6/15 or worse, aflibercept was still associated with significantly greater BCVA improvement, compared with bevacizumab but not when compared with ranibizumab.

In summary, all three commercially available anti-VEGF agents are effective for patients with centre-involved DME. For eyes with a presenting BCVA of 6/15 or worse, aflibercept is associated with better BCVA outcomes than bevacizumab at one and two years.[9]

Intravitreal Corticosteroid

Not all patients will respond effectively to anti-VEGF. For example, in Protocol I, approximately 40 per cent of participants randomised to receive ranibizumab had persistent macular thickening at 24 weeks.[10] Similarly, in Protocol T, central macular thickness at one year was >250 µm in 34 per cent to 64 per cent of patients.[11]

For a cohort of patients who are not responsive to anti-VEGF therapy, alternative treatment with intravitreal corticosteroids may be an option.[11,12] Currently available corticosteroids include the dexamethasone delivery system (Ozurdex) and off-label triamcinolone acetonide.

There is relatively little head-to-head comparative information of corticosteroids verses anti-VEGF therapy for the management of DME in the peer-reviewed literature. DRCR.net Protocol I randomised patients with DME to receive: (1) sham injection with prompt laser; (2) ranibizumab with prompt laser; (3) ranibizumab with deferred laser; or (4) triamcinolone with prompt laser. At both one and two years, the two ranibizumab groups (but not the triamcinolone group) experienced significantly greater improvements in BCVA. In pseudophakic patients, BCVA improvements were similar in both the triamcinolone group and the ranibizumab group.[13]

However, there is apprehension in using corticosteroids to treat DME due to the adverse effects of intraocular pressure (IOP) elevation and cataract. A recent phase 2 randomised controlled trial, comparing the dexamethasone delivery system to bevacizumab in patients with DME, reported similar rates of BCVA improvement but BCVA of patients in the steroid group was associated with a greater rate of worsening, primarily due to cataract.[14]

Still, corticosteroids may be considered as a temporising measure in certain groups such as pregnant women with worsening DME or in anti-VEGF naive patients prior to cataract surgery.

CO-MANAGING DME – TREATMENT EVALUATION

Regardless of the anti-VEGF agent selected, patients are initially treated monthly. Prompt extension of treatment intervals may be considered in patients who have a good treatment response, but treatment failure generally cannot be determined until approximately six monthly injections have been performed.

Gauging how well a patient is responding to therapy in DME can be a challenge.

Although we measure BCVA and perform an OCT at every visit, these two parameters don't have a direct correlation.

Some patients will achieve excellent anatomic results with treatment but do not achieve corresponding visual acuity improvement.

When a patient appears to not be improving on treatment, several options should be entertained. It is plausible that some patients may need longer than six months to mount a response to treatment. A retrospective review of patients from DRCR.net protocol I and the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) study concluded that patients who were not responding to treatment at six months, but were still continued on their initial anti-VEGF agent, experienced continued improvement in BCVA and macular thickness.[15] This means it is critical to allow time for response.

Another option would be to consider a switch in their treatment. This may mean switching to another anti-VEGF agent, although there is little peer-reviewed evidence to support this practice.

Should there be no response to anti-VEGF therapy, corticosteroid therapy could be used, although the only eligible candidates here are patients who are pseudophakic and who do not experience significant steroid-related IOP rise.

Like in any discipline in medicine, when treatment failure is considered, the etiology of the underlying disease process needs to be re-considered. Persistent macular thickening and poor BCVA may be the hallmark of underlying macular ischemia. Similarly, co-existing disease, namely a cataract, may explain an improvement in OCT appearance without corresponding visual acuity improvement.

MACULAR ISCHEMIA: THE ESCAPE ARTIST!

I have eluded to the likelihood of macular ischemia being the culprit for Mary Cassatt's deterioration in vision. Untreated maculopathy resulting in longstanding edema causes photoreceptor damage. Other risk factors for development of macular ischemia include: poor control of diabetes,

a higher prevalence in Type 2 diabetes and co-morbid disease including hypertension.

It is recognised that the foveal avascular zone (FAZ) can enlarge and become irregular as diabetic retinopathy advances. The major blood supply to the fovea is the choroid, however in diabetic patients, the blood supply to the choroid is believed to be altered. As macular edema advances, there is damage to the peri-foveal capillary network, resulting in capillary drop out, which in turn results in irreversible ischemia.[16]

Visual deterioration is often gradual and, as in the case of Mary Cassatt, the individual cannot appreciate that their vision is changing for the worse (Figure 5).

The EDTRS defined diabetic macular ischemia standards using Fluorescein Angiography (FFA). Recently, studies comparing OCT angiography (OCTA) with FFA show that it too is a useful tool to detect macular ischemia in its early stages.

Once ischemia has occurred, there is a guarded prognosis for vision recovery. It is important to counsel patients about this aspect. A late diagnosis can often result in patients becoming disillusioned with their treatment, often feeling that "the injections do not help" or that "laser made their eye disease worse", resulting in compliance issues.

DIABETES AND CATARACT

It was perhaps the combination of worsening diabetic maculopathy and the emergence of a progressive cataract in Mary Cassatt that caused the unexpected termination of her talented career.

In hindsight, cataract surgery was never going to restore her vision given the extent and severity of the maculopathy which pre-existed. Cassatt's case highlights two very important aspects about managing cataracts in patients with diabetes:

1. The main indication for cataract surgery in diabetic patients is to improve visual function, but equally, to provide the clinician adequate visualisation of the retina.

2. Any pre-existing maculopathy will compromise the visual outcome of cataract surgery – adequate management prior to surgery therefore, becomes mandatory.

We need to be aware of the prognostic indicators for severity of the disease in order to decide on optimal time for cataract surgery. Prognostic factors that are favourable include: a mild cataract, maculopathy that includes minimal hard exudates, no edema, no evidence of macular ischemia, and good peri-foveal perfusion (on FFA or OCTA). Prognostic factors that are unfavourable include lipid exudation at the fovea, diffuse edema/ multiple leaks +/- evidence of ischemia, refractory DME on OCT and pre-operative vision of less than 6/60 (see Figure 6).

Much work needs to be done in the peri and postoperative period when managing a patient with diabetic maculopathy and cataract. Patients need to be at their optimal control of their blood sugar levels and HbA1c, those on an insulin pump may need adjustments prior to surgery, this is best achieved by liaising with their medical team. Additionally, most surgeons prefer to consider intravitreal treatment at the time of cataract surgery (anti-VEGF or corticosteroids) to prevent refractory DME. And as always, a close follow-up co-management regimen needs to be instituted to detect any subtle changes early.

> "By getting patients involved in their diabetic care… they can gain control of this disease"

CONCLUSION

Many of our young diabetic patients exhibit a similar outlook to their disease as Cassatt did. They are eager to continue their lives and work unperturbed by their diagnosis. However, had the opportunity existed at Cassatt's time to allow her to embrace the management of this disease, her intelligence and diligence would surely have prevailed.

How then can we enlist our patients to help in prevention of the devastating complications of diabetic maculopathy? Education is key. By getting patients involved in their diabetic care – knowing their BSL readings, understanding the importance of a HbA1c, adhering to a tailored diet and exercise regimen that works into their lifestyle, they can gain control of this disease.

As eye specialists, we are often the first to see progression of diabetes as it frequently manifests as worsening maculopathy and/or retinopathy. It is therefore in our patients' best interests that we co-ordinate the care from physicians promptly and provide feedback when we see signs of worsening eye disease. mi

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All images depicted of Mary Cassatt's work taken with thanks from www.marycassat.org/the-complete-works.

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