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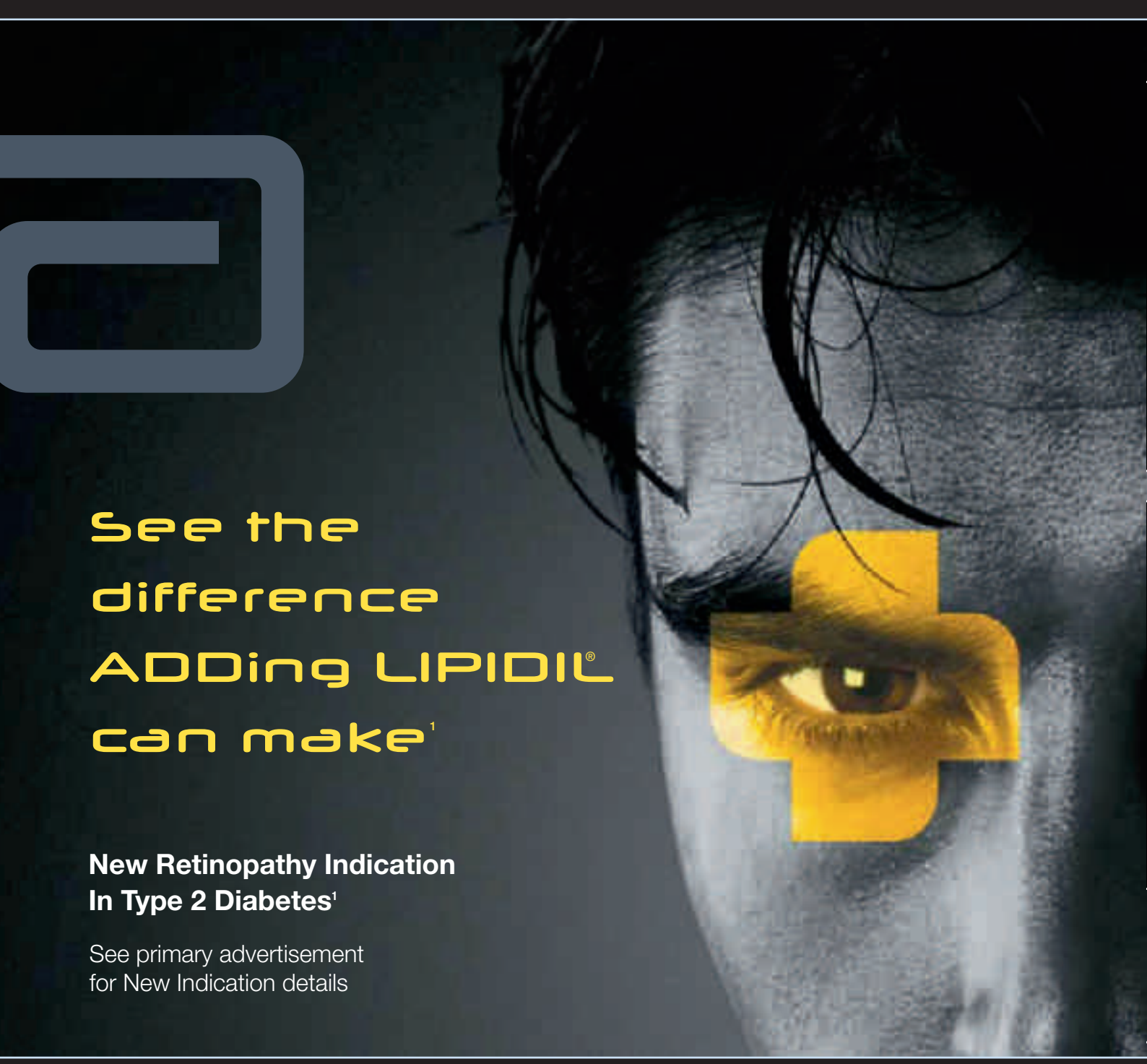
Diabetic retinopathy
Stages, signs and treatments



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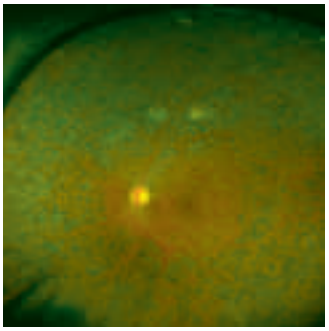
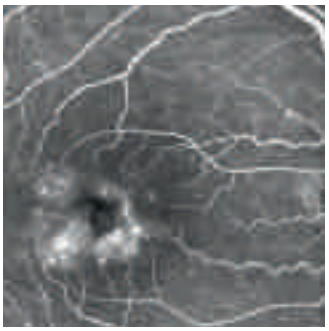
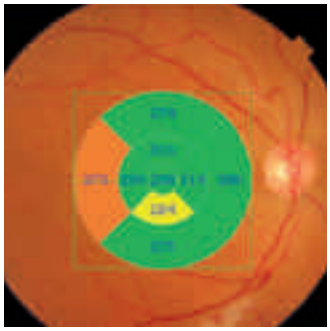
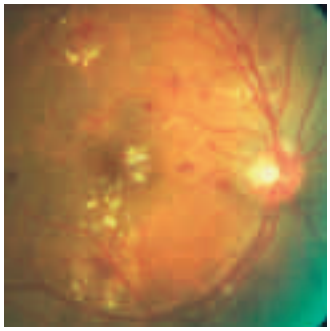








Management of diabetic retinopathy

More than just saying 'you're OK'

Mary Travis

MOptom
Vision Eye Institute
Melbourne VIC

THE AUSTRALIAN Diabetes, Obesity and Lifestyle Study (AUSDIAB 2012) presents sobering statistics regarding the prevalence of diabetes and the clinical characteristics of the Australian population with diabetes.[1] Optometrists have a crucial role in the screening and diagnosis of diabetic retinopathy, and this primary care responsibility provides a unique opportunity for optometrists to take the lead in the efforts to reduce the public health impact of diabetic retinopathy.

The AUSDIAB 2012 defines diabetes as those with fasting blood glucose > 7.0 mmol/L and two-hour glucose tolerance > 11.1 mmol/L. The current Australian population prevalence of diabetes is 7.4 per cent, and those with pre-diabetes comprise a further 16.3 per cent. Over the 12 study years 1999-2011, patients with diabetes were more than five times more likely to die than those with normal glucose tolerance.

The NHMRC diabetic retinopathy guidelines (2008) detail Level I evidence for improving glycaemic control (HbA1c < 7.0 per cent) and Level II evidence for blood pressure and serum lipids (systolic BP < 130 mmHg, LDL cholesterol < 2.5 and triglycerides < 2.0 mm/L) indicating that a multi-disciplinary approach will achieve the best results.[2] This evidence is provided by the seminal DCCT, EDIC, UKPDS and ACCORD studies among others, which also highlight parallel risk reductions in the other microvascular complications of diabetes, namely peripheral neuropathy and nephropathy.

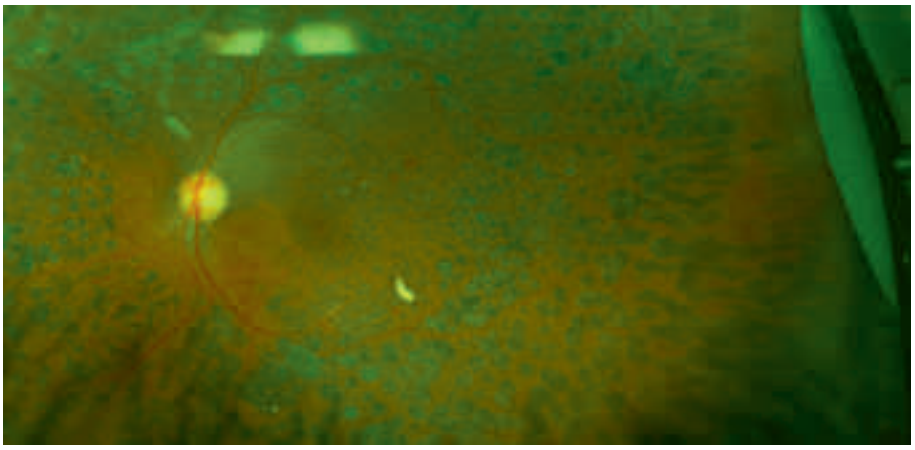
Taking a thorough history should include asking patients about their diabetic parameters. For the patient, this further reinforces the importance of adherence to targets and shows that their optometrist is a well-informed practitioner who cares about their progress.

The Diabetes MILES Australia study (2011) found that the top two causative areas behind the development of psychological distress in patients with diabetes relate to the concern for the future and worrying about future serious complications, and the feelings of guilt and anxiety when diabetic management goes off track.[3] In advising the patient at the conclusion of consulting, the ability of compliance with diabetic targets to reduce the risk of development and/or progression of their retinopathy should be emphasised, but with a considerate and empathetic approach.

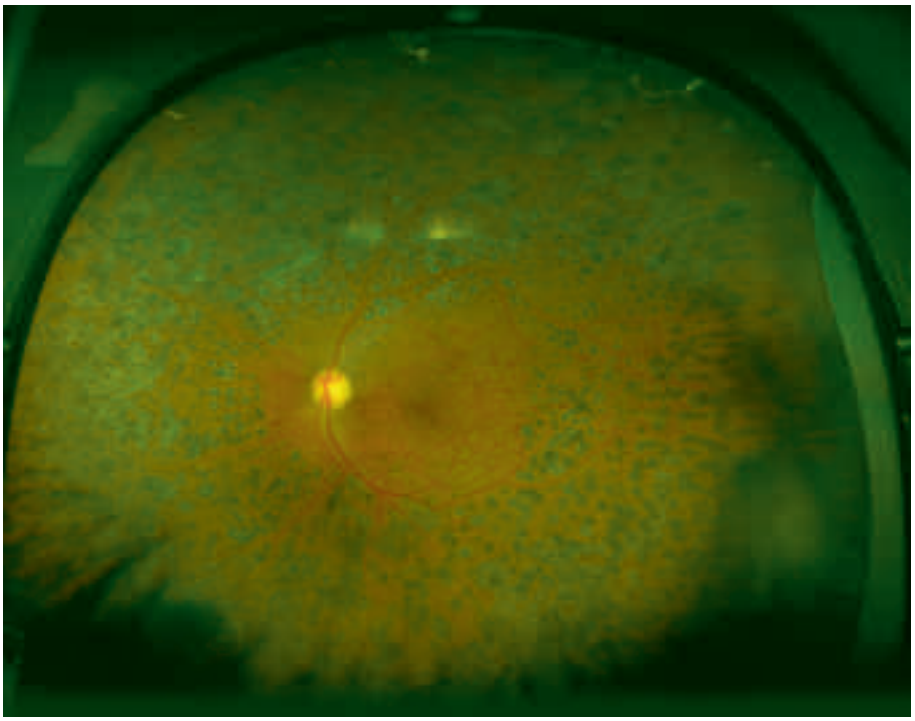
CASE REPORT

The following figures relate to a case history of a female of Somali background and born in 1959, who presented originally in August 2010 with a 10-year history of 'gestational diabetes' using only diet and oral hypoglycaemic medication. Visual acuity at first visit was OD 6/12 and OS 6/36 with bilateral visually significant cataract. At presentation, there was severe NPDR, gross CSME with hard exudates and angiographically demonstrated confluent areas of capillary non-perfusion.

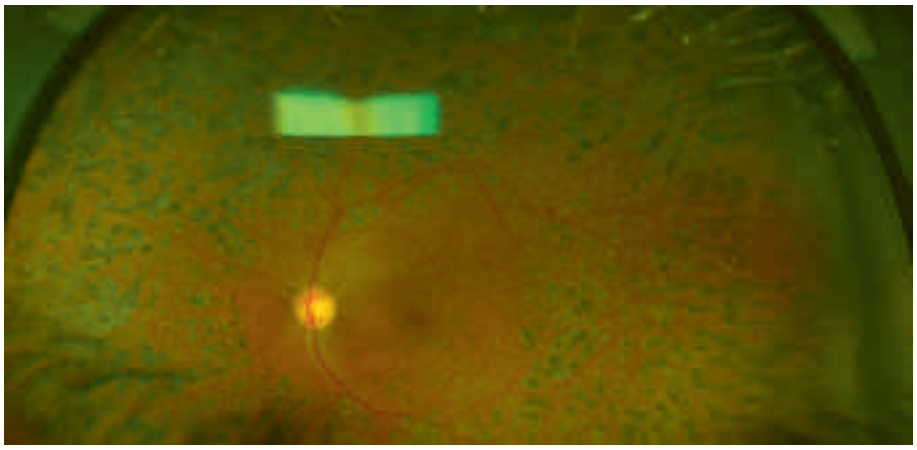
At the last visit in April 2014, the VA is R and L 6/6 and there is relatively normal kidney function. In both eyes, treatment has involved pan-retinal photocoagulation (PRP), multiple intravitreal injections of Avastin and periodically triamcinolone, cataract surgery, and focal laser to the macula.



▲ Figure 1. Retinal colour photograph of the left eye, 2012 (Optos ultra wide field retinal image)



▲ Figure 2. Level of retinal haemorrhages unchanged, 2013



▲ Figure 3. Retina mostly free of haemorrhages, 2014

Figure 1 is a retinal colour photograph of the left eye acquired using Optos digital retinal photography from August 2012, where despite good visual acuity there are significant hard exudates and retinal haemorrhages in the retina which has not undergone PRP.

The patient was advised that further pregnancies would be detrimental to her health in general and in particular her vision. About this time, the patient had finally put into practice increased diligence in monitoring her blood sugar, and insulin administration which had commenced in 2011.

Figure 2 shows the left eye in June 2013. The hard exudates have significantly resolved, although the level of retinal haemorrhages has not changed overall. The patient then began to take the lipid lowering (statin and fenofibrate) and ACE-inhibitor medications regularly. With further effort to reduce the average level of blood sugar, the result was a stable retina that is mostly free of haemorrhages (Figure 3).

This more advanced case of diabetic retinopathy shows that if this improved outcome is possible in a patient with advanced disease, the impact on retinal physiology for a patient with lesser degrees of diabetic retinopathy is less visible but no less significant. By discussing optimal diabetic parameters and helping to motivate patients to improve compliance with all aspects of their diabetes management plan—using an empathetic approach—optometrists can make a significant contribution to reducing the public health impact of diabetic retinopathy. ▲

Acknowledgement

I thank Dr Nandor Jaross for his permission to publish the retinal photography images.

1. Tanamas SK, Magliano DJ, Lynch B, Sethi P, Willenberg L, Polkinghorne KR, Chadban S, Dunstan D, Shaw JE. AusDiab 2012. The Australian Diabetes, Obesity and Lifestyle Study. Melbourne: Baker IDI Heart and Diabetes Institute 2013.
2. Guidelines for the management of Diabetic Retinopathy. National Health and Medical Research Council 2008.
3. Speight J, Browne JL, Holmes-Truscott E, Hendrieck C, Pouwer F on behalf of Diabetes MILES - Australia reference group. Diabetes MILES - Australia 2011 Survey Report. Diabetes Australia: Canberra; 2012.

Detection and treatment of diabetic

The vital role of OCT

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BScOptom(Hons) GradCertOcTher
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CASE REPORT

THE PRESENT Optometry Clinic at UNSW Australia, Kensington opened in 2000 with the purpose of teaching Year 4 and 5 students the clinical skills necessary to become competent practitioners. The clinic is open to members of the public, university staff and students. About 4,000 patients present annually, many of whom have vision-threatening pathology.

According to the International Diabetes Federation, diabetes mellitus (DM) affects 366 million people worldwide. That number is predicted to rise to 552 million by 2030.[1] Prevalence and incidence of type 1 and 2 DM varies greatly among different populations and affects male and females equally.[2]

Diabetic eye disease is rare on initial diagnosis of type 1 DM and about 20 per cent of type 2 DM, rising to 90 per cent and 60 per cent, respectively, after 20 years disease duration.[3] It is common for undiagnosed type 2 DM, retinopathy discovered during a routine eye examination to be the first sign of systemic disease.

A 59-year-old Bangladeshi male presented to the UNSW optometry clinic in June 2013. He had been experiencing reduced vision in his right eye for three months and wanted a second opinion. He reported himself to have been a well-controlled type 2 diabetic sufferer for eight years, with average blood sugar levels (BSL) of 6-7 mmol, blood pressure (BP) levels of 110/70 and three-to-four monthly checks with his general practitioner. Ocular history was unremarkable apart from bilateral cataract extraction.

Presenting vision was R 6/12 and L 6/7.5. Best-corrected vision with a low hyperopic script were R 6/7.5 (niph) and L 6/6. Intraocular pressures were 17 mmHg both eyes with Perkins applanation tonometry.

Dilated fundus examination revealed scattered dot-blot haemorrhages at both posterior poles. Scattered exudates and micro-aneurysms were found within the right macula region whilst the left eye had an unusual inner-limiting membrane (ILM) reflex at the macula with dot haemorrhages and microaneurysms. (Figures 1A, 1B, 2A and 2B)

After an urgent assessment at the eye hospital two weeks later, the registrar recommended better BSL control, in conjunction with the general practitioner, as first line treatment. On review in October 2013, the registrar decided to continue to monitor the retinopathy, while maintaining strict glycaemic and blood pressure control.

The patient returned to UNSW optometry clinic February 2014 with a review booked at the eye hospital in April 2014. He reported no visual complaints with well controlled BSL and BP levels. Best-corrected vision was R 6/6-2 and L 6/6-2. Slitlamp examination was unremarkable. Fundus examination (Figures 3A and 3B) revealed an increase in retinal haemorrhages and exudates within the right macula region. In the left eye, there was a cotton wool spot near the disc and a circinate ring of exudates within one disc diameter of the macula. OCT also reflected these new findings (Figures 4A and 4B).

In light of these findings, the eye hospital was contacted to organise a more urgent assessment. Despite the patient reporting compliance with systemic control, it was evident that this alone was not enough to prevent retinopathy progression.

Discussion

Hyperglycaemia induces a number of biochemical reactions such as vascular endothelial growth factor (VEGF), aldose reductase and angiotensin enzyme expression.[4,5] These culminate into vessel leakage, haemorrhaging and ischaemia. Inflammatory pathways and leukostasis are also being investigated as pathomechanisms of diabetic eye disease.[5]

Diabetic retinopathy (DR) is the leading cause of preventable blindness of the working age population in developed countries[4] and is graded based on the clinical features present. The Early Treatment of Diabetic Retinopathy Study (ETDRS) scale is the gold standard from which a number of other grading scales have been adapted.[6]

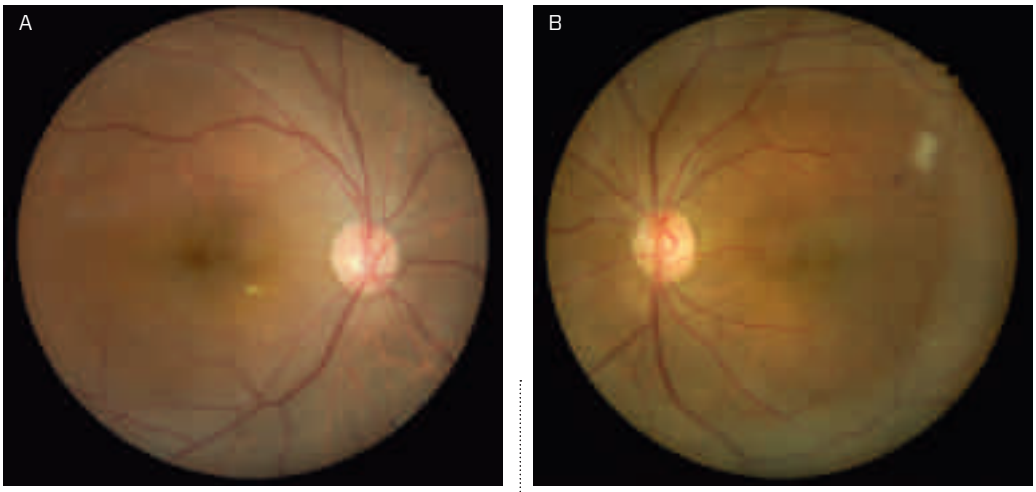
In the case of this patient, on first presentation, he had mild NPDR both eyes and diffuse macula oedema in the right eye. On second presentation, he had moderate NPDR both eyes and CSME in the left eye. This is also classified as vision threatening (VTDR).

Global estimates worldwide found DR present in 34.6 per cent, PDR in 7.0 per cent, DME in 6.8 per cent and VTDR in 10.2 per cent of diabetic patients.[7,8]

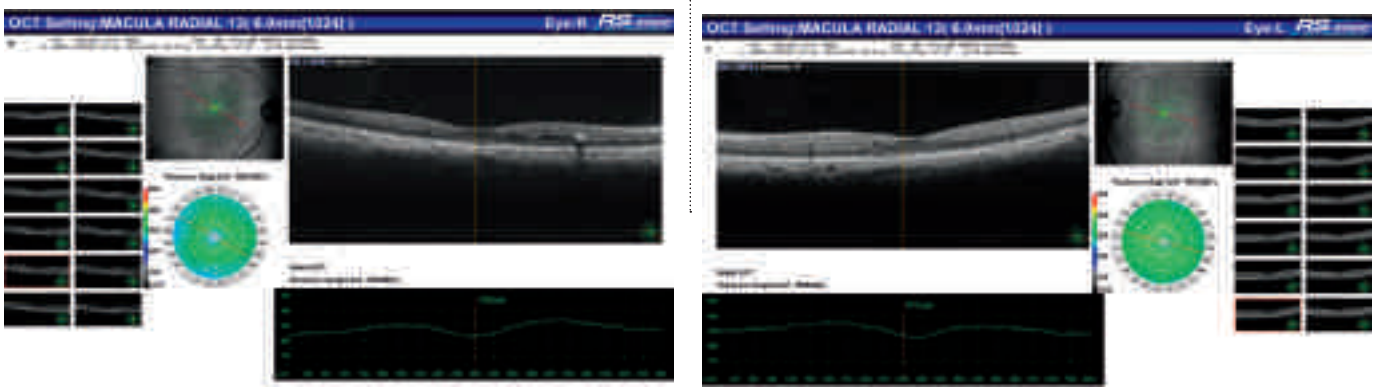
Microaneurysms are small round 'protrusions' that occur locally at capillary walls which have weakened due to capillary closure. These can present de novo or within circinate exudate rings.[9]

macular oedema

in diagnosis and effective comanagement



▲ Figure 1A and Figure 1B. Fundus images of patient (artefact at 2 o'clock)



▲ Figure 2A and Figure 2B. OCT of OD revealed exudates and cystic spaces confirming the presence of macular oedema. This also supported the reduced vision findings in OD.

Intra-retinal haemorrhages occur as a result of blood vessel rupture and are classified based on their location within the retina. Flame haemorrhages lie within the tightly packed nerve fibre layer (NFL). Dot haemorrhages are round, well-defined and found within the outer plexiform layer (OPL). Blot haemorrhages are larger and less defined compared to dots and occur within the less compact inner nuclear layer (INL).[9]

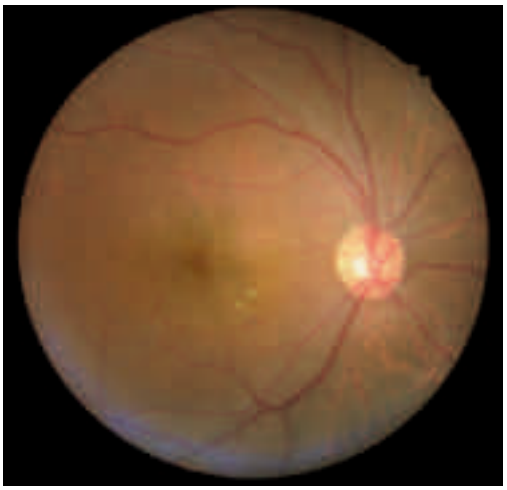
Hard exudates occur at the OPL and represent leakage from increasingly permeable capillary walls. These can form singularly or as a circinate ring following rupture of a microaneurysm.[9]

In the presence of increasing non-perfusion, venous beading presents as focal dilation and thinning of a venous wall and is highly associated with risk of PDR developing. Cotton wool spots represent localised NFL swelling secondary to obstructed axoplasmic flow.[9]

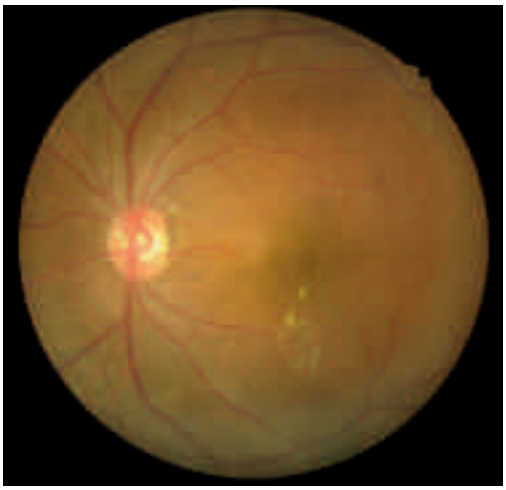
Intraretinal microvascular abnormalities (IRMA) represent abnormal communication between arterioles and venules and look similar to neovascularisation (NV). Unlike NV, IRMA lie within the retina, do not leak and do not form abnormal attachments to the vitreous.[9]

Proliferative changes occur when significant retinal ischemia stimulates angiogenic factors such as VEGF, resulting in new blood vessel formation on the retinal surface.[10]

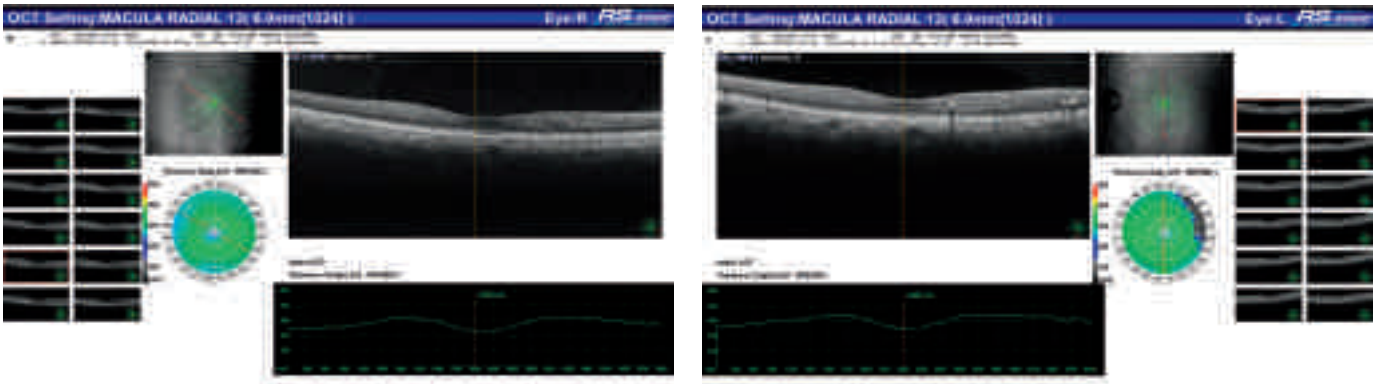
Continued page 6



▲ Figure 3A. Increase in retinal haemorrhages and exudates within the right macula region



▲ Figure 3B. Single cotton wool spot adjacent to optic disc and a circinate ring of exudates within 1 disc diameter of the macula in the left eye



▲ Figure 4A and Figure 4B. OCT confirms findings of bilateral macula oedema

Vital role of OCT

From page 5

Diabetic macula oedema (DME) is defined as retinal thickening (build-up of fluid and proteins in the Henle Layer and INL) secondary to a breakdown of the blood retinal barrier.[11] DME is the leading cause of vision loss in type 2 diabetese.[3] As this case illustrates, urgent ophthalmological assessment is essential.

Treatment

The three major risk factors for DR are duration of diabetes, hyperglycaemic levels and hypertension.[2] The Diabetes Control and Complication Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) both found that intensive systemic treatment—maintaining blood glucose levels as close to the normal range (HBA1c 7.0 per cent) and strict blood pressure control (< 140/80)—delays the onset and progression of micro-vascular complications of type 1 and 2 diabetes including retinopathy.[12,13]

It is essential that a multi-disciplinary team of GPs, endocrinologists, dietitians and nurse educators is involved in achieving this alongside eye-care providers.

The ETDRS found that following focal laser photocoagulation, there was 50 per cent reduction in moderate vision-loss in CSME patients[14] and for a number of years focal laser has been mainstay treatment for such patients. Focal laser seals leaking microaneurysms, while grid laser is used in diffuse cases. It is hypothesised that the reduced retinal blood flow, due to increased local oxygenation via photocoagulation, results in reduction of macula fluid.[15]

Anti-VEGF therapy, such as bevacizumab is fast replacing laser as first-line treatment for centre involved macular oedema, due to its greater efficacy and increased safety involving the central macula.[5,15] It is an antibody of VEGF-A and inhibits angiogenesis.[5,10] For proliferative retinopathy, pan-

retinal photocoagulation is still first-line treatment for fibrous regression of neovascularisation, reduction in vitreous haemorrhage and reduction in tractional retinal detachment.[5]

Conclusion

Effective screening programs are essential for early diagnosis of diabetic retinopathy. This case report shows that OCT is a valuable tool that can make a rapid diagnosis of macular oedema as well as monitor for progression. It would be worthwhile for all optometrists to have access to an OCT to use alongside dilated fundus examination and stereo-photos in ensuring timely diagnosis, effective comanagement and appropriate treatment. ▲

1. Scanlon PH, Aldington SJ, Stratton IM. Epidemiological issues in diabetic retinopathy. Middle East African Journal of Ophthalmology 2013; 20: 293-300.
2. NHMRC. Guidelines for the Management of Diabetic Retinopathy. Edited by Ageing DoHa2008.
3. Chistiakov DA. Diabetic retinopathy: pathogenic mechanisms and current treatments. *Diabetes & Metabolic Syndrome* 2011; 5: 165-172.
4. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003; 26: 2653-2664.
5. Heng LZ et al. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments. *Diabetic Medicine* 2013; 30: 640-650.
6. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991; 98: 786-806.
7. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Current Diabetes Reports* 2012; 12: 346-354.
8. Yau JW et al. Meta-Analysis for Eye Disease Study G. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; 35: 556-564.
9. Hudson C. The clinical features and classification of diabetic retinopathy. *Ophthalmic Physiol Optics* 1996; 16 Suppl 2: S43-48.
10. Gupta N, Mansoor S, Sharma A, Sapkal A, Sheth J, Falatoonzadeh P, Kuppermann B, Kenney M. Diabetic retinopathy and VEGF. *The Open Ophthalmology Journal* 2013; 7: 4-10.
11. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Seminars In Ophthalmology* 1999; 14: 223-232.
12. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *New England J Med* 1993; 329: 977-986.
13. Krentz AJ. UKPDS and beyond: into the next millennium. United Kingdom Prospective Diabetes Study. *Diabetes, Obesity & Metabolism* 1999; 1: 13-22.
14. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Archives Ophthalmol* 1985; 103: 1796-1806.
15. Shamsi HN, Masaud JS, Ghazi NG. Diabetic macular edema: New promising therapies. *World J Diabetes* 2013; 4: 324-338.

Micropulse laser therapy for DME

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PERHAPS THE MOST feared complication of macular laser treatment for experienced medical retina specialists is macular scarring and scar expansion over time. The latter may result in an increasing paracentral scotoma over many years and may potentially expand to involve the fovea. A tissue-sparing alternative to the standard modified Early Treatment of Diabetic Retinopathy Study (mETDRS) laser is 'micropulse' macular laser therapy.[1]

Micropulse laser therapy differs from standard laser as the continuous wave laser emission is 'chopped' into smaller 'pulses' over the same duration (Figures 1A–1D). For example, in a five per cent duty cycle, the laser emission is switched 'on' for 0.1 milliseconds and then switched 'off' for 1.9 milliseconds. This is repeated 100 times during a 200-millisecond treatment.

The cooling in the 'off' period prevents the temperature from reaching the threshold required to create a thermo-destructive burn. A concept similar to 'pulse mode' in phacoemulsification, in which the phaco-energy is divided into pulses, allowing cooling of the phaco-tip and preventing wound burn.

Retinal tissue is spared while maintaining the benefits of the photothermal stress response on the retinal pigment epithelium (RPE) and retina. The latter results in the induction of intracellular biological factors (PEDF,[2] TSP1,[3] SDF1 and B-Actin[4]), which play a role in anti-angiogenesis and the resolution of the macular oedema.

Does micropulse laser therapy work for diabetic macular oedema?

In short, yes. It has been shown to work as effectively as modified ETDRS laser in at least three randomised clinical trials. Vujosevic et al compared 810 nm micropulse laser with mETDRS in a randomised prospective trial on 62 eyes in 50 patients with diabetic macular oedema (DME).[1] They demonstrated an equivalent stabilisation of vision and reduction in macular oedema in both treatment arms. However, in the 'micropulse' arm there was no evidence of RPE destruction on autofluorescence imaging and the retinal sensitivity improved rather than declined on microperimetry ($p < 0.0001$) (Figure 2A).

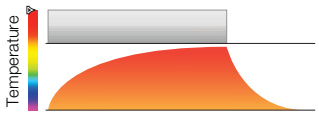
In a prospective double blind controlled trial on 123 eyes, Lavinsky et al showed that contiguous or high-density micropulse therapy (no spacing between burns) was superior to low density and mETDRS guided laser at one year.[5] The high-density group gained 12 letters on average compared to the four letters in the mETDRS group. Forty-eight per cent of patients in the high-density micropulse group gained ≥15 letters compared to 23 per cent in the mETDRS group. The average central macular thickness reduction at one year in the high density micropulse group was 154 µm compared to 126 µm in the mETDRS group.

Figueira et al (Oxford Group) also demonstrated comparable efficacy between micropulse diode laser and modified ETDRS at one year in a prospective randomised controlled trial involving 84 eyes in 53 patients.[6]

Is it safe?

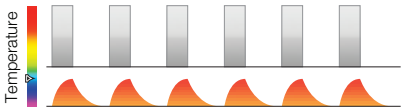
Perhaps the greatest advantage of micropulse macular laser treatment is the minimal risk of macular scarring. In a long-term retrospective review of patients with DME or macular oedema related to branch retinal vein occlusion, Luttrull et al found no laser-induced retinal damage in patients treated with a five per cent duty cycle over a 10-year period.[7] Fundus photos, infrared, autofluorescence, fluorescein and ICG angiography images were completely unremarkable and free of scarring.

Only eight per cent of the 10-15 per cent duty cycle micropulse patients experienced macular scarring similar to that of mETDRS macular laser. The study authors not only noted an absence of retinal scarring, but also an improvement in retinal sensitivity post micropulse laser treatment, which correlated with the resolution of the macular oedema[1] (Figure 2B).

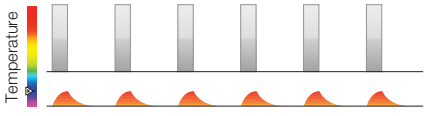


1A. Continuous wave laser exposure: 100 per cent duty cycle (DC)

1B. Micropulse high duty cycle (15 per cent)

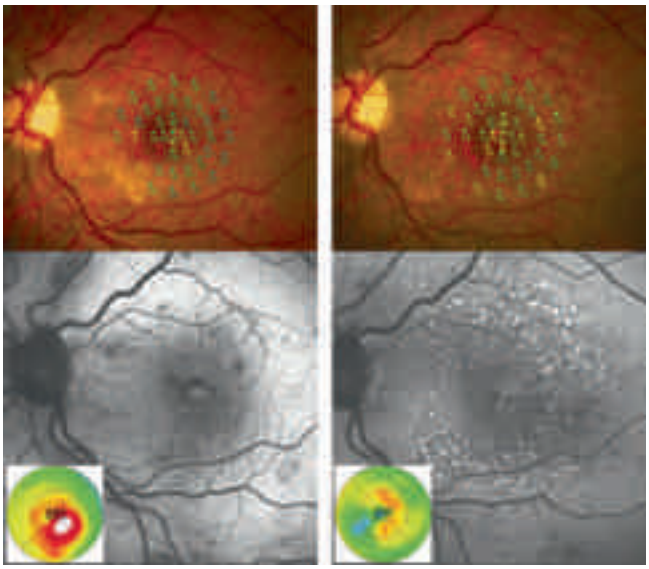


1C. Micropulse medium duty cycle (10 per cent)

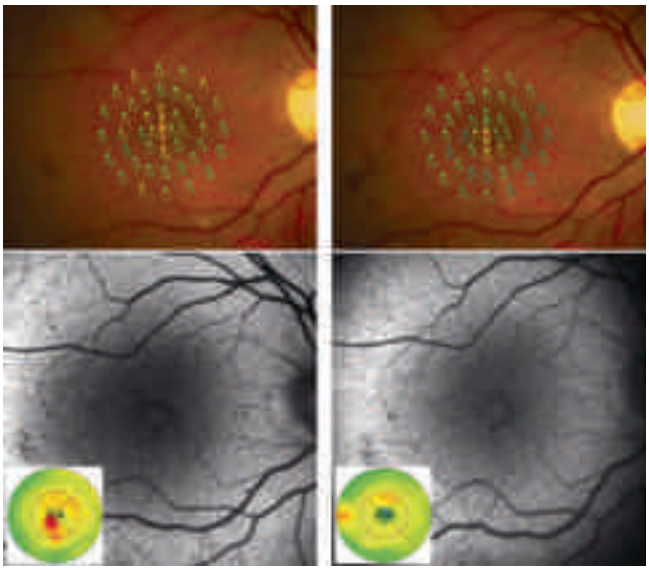


1D. Micropulse low duty cycle (5 per cent)

▲ Figure 1. Correlation between tissue



▲ Figure 2A. Modified ETDRS laser for diffuse diabetic macular oedema resulting in resolution of macular oedema at one year, but also in macular scarring which is seen on autofluorescence (seen on the right). The retinal sensitivity also declines post mETDRS laser at one year (top images).[1]



▲ Figure 2B. High density micropulse macular laser treatment also results in resolution of the diabetic macular oedema (see OCT); however, there is no evidence of retinal scarring on autofluorescence. The retinal sensitivity also improves after micropulse macular laser therapy (top images).[1]

By comparison, the modified ETDRS group experienced a decline in retinal sensitivity, with the macular scars being visible on autofluorescence (Figure 2B). In Figure 3, macular scarring from ETDRS grid laser has expanded to involve the fovea and has resulted in long-term irreversible central visual loss—a risk that is significantly reduced by micropulse macular laser therapy. With micropulse laser, treatment may be applied much closer to the fovea without the fear of creating a scar and correlating central scotoma which expands over time.

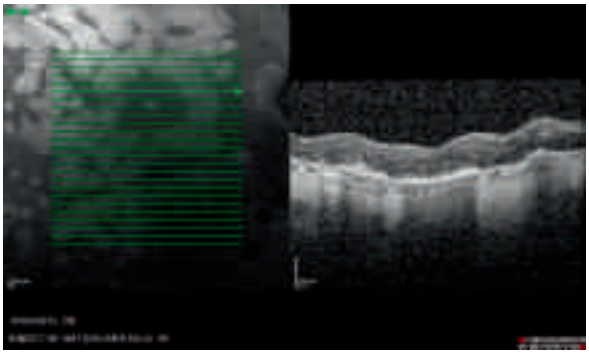
CASE REPORT

A 37-year-old accountant with long-standing type 1 diabetes presents with slightly blurred vision in his right eye over the previous two months. He had a myocardial infarction six months prior to the appointment. He also has hypertension and hyperlipidaemia. He is a non-smoker, has no renal impairment, and his most recent glycaemic control has improved (HBA1c 7.0 per cent).

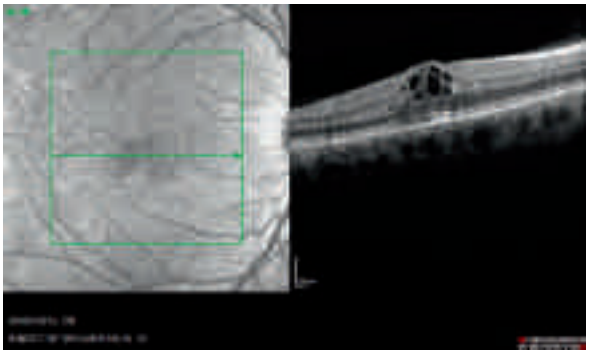
On examination, his visual acuity is reduced to BCVA 6/9 OD and 6/6 OS. Fundoscopy reveals multiple microaneurysms in close proximity to both foveae in association with clinically significant diabetic macular oedema. In the right eye the macular oedema is foveal-involving (Figure 4).

There is background moderate non-proliferative diabetic retinopathy bilaterally. Early and late frames on fluorescein angiography confirm the presence of multiple leaking microaneurysms and the fovea-

Continued page 10



▲ Figure 3. Traditional ETDRS grid laser resulting in late-stage macular scar expansion and loss of central vision



▲ Figure 4. Right foveal-involving clinically significant macular oedema

Micropulse macular laser

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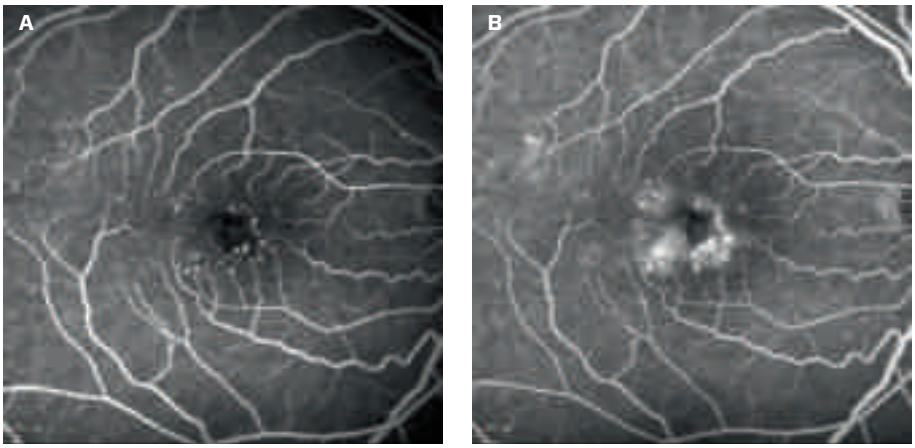
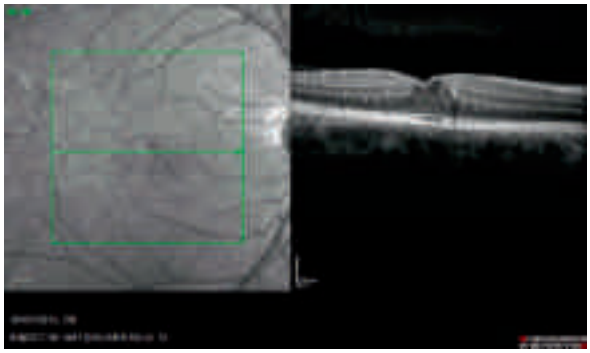
involving macular oedema (Figures 5A and 5B). There is minimal macular ischaemia on fluorescein angiography. After a discussion of the treatment options, he declines intravitreal anti-VEGF therapy. He is concerned about the theoretical risk to his cardiac health posed by repeated anti-VEGF injections, particularly in light of his recent myocardial infarction.

After consent is obtained, confluent 577 µm yellow micropulse laser with a five per cent Duty Cycle[8] is applied to the oedematous macular area. The macular oedema slowly resolves and four months later his visual acuity improves to 6/6 in the right eye. OCT examination at four months demonstrates mild residual macular oedema confined to the inner retina (Figure 6). This residual macular oedema continues to resolve and is managed conservatively.

This case demonstrates that micropulse laser therapy may be applied close to the fovea without the fear of central scarring and scotoma. It is particularly useful in patients in whom there is a contraindication to anti-VEGF therapy and who have either centre-involving diabetic macular oedema or clinically-significant macular oedema threatening the fovea.



▲ Figures 5A and 5B. Early and late phases of the fluorescein angiogram confirming leakage from multiple peri-foveal microaneurysms and DME



▲ Figure 6. Resolution of DME four months post right micropulse macular laser therapy

Summary

Micropulse macular laser is an evidence-based, repeatable and safe treatment for diabetic macular oedema. Relative to standard modified ETDRS laser, there is less risk of macular scarring, scotoma, and scar expansion over time. The retinal sensitivity is also preserved in micropulse laser, whereas it is reduced after standard modified ETDRS laser treatment for DME.

It is a useful adjunct to intravitreal anti-VEGF therapy and is particularly useful in foveal-sparing clinically significant macular oedema or in patients in whom there is a contraindication to anti-VEGF therapy. The reduced risk of macular scarring allows treatment closer to the fovea than with standard mETDRS laser. Micropulse laser is also useful in other retinal disorders such as branch retinal vein occlusion and central serous chorioretinopathy.

Micropulse laser is another major step in the natural evolution to more refined and less destructive treatments for diabetic macular oedema. ▲

1. Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. *Retina* 2010; 30: 6: 908-916.
2. Ogata N, Tombran-Tink J, Jo N, Mrazek D, Matsumura M: Upregulation of pigment epithelium-derived factor after laser photocoagulation. *Am J Ophthalmol* 2001; 132: 3: 427-429.
3. Binz N, Graham CE, Simpson K, Lai YK, Shen WY, Lai CM, Speed TP, Rakoczy PE. Long-term effect of therapeutic laser photocoagulation on gene expression in the eye. *FASEB J* 2006; 20: 2: 383-385.
4. Yu AK, Merrill KD, Truong SN, Forward KM, Morse LS, Telander DG. The comparative histologic effects of subthreshold 532- and 810-nm diode micropulse laser on the retina. *Invest Ophthalmol Vis Sci* 2013; 54: 3: 2216-2224.
5. Lavinsky D, Cardillo JA, Melo LA Jr, Dare A, Farah ME, Belfort R Jr. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2011 Jun 17; 52: 7: 4314-4323.
6. Figueira J, Khan J, Nunes S et al. Prospective randomised controlled trial comparing sub- threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. *Br J Ophthalmol* 2009; 93: 10: 1341-1344.
7. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. *Retina* 2012; 32: 2: 375-386
8. Iridex IQ 577 Laser System

• Dr Jabbour uses an Iridex Micropulse laser supplied by OptiMed

Blepharoplasty and blood thinners

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DERMATOCHALASIS refers to loose or redundant skin of the eyelid. This is a common condition, thought to be a part of the normal ageing process. The exact cause is unknown but contributing factors include reduced elasticity of the skin around the eyelid, gravity, weakened connective tissue and systemic conditions.[1]

As the eyes and the periocular area are the focal point of human conversation and communication, droopy eyelids may seem to others to be inappropriate tiredness or sadness. In moderate to severe cases, there may be concerns related to dissatisfaction of eyelid appearance or superior visual field loss.[2] Other patients may have difficulty reading or endure frontal headaches due to constant brow elevation.[1]

Upper lid blepharoplasty is a common surgery to relieve asthenopic symptoms and to help improve facial appearance. This is considered a very safe and relatively simple surgery; however, any surgical procedure can be affected by blood thinning medications or natural supplements taken by the patient.

The blepharoplasty procedure

Preoperative examination should start with a detailed history, enquiring about periorbital trauma, thyroid conditions, dry eye syndrome and skin conditions.[1] Automated visual fields should be performed prior to surgery to demonstrate any superior visual field loss. This testing is repeated with the lids taped to decrease the field loss and simulate post-operative results.

A photograph of the eyes should be taken and included to document the natural position of the lids. Visual acuities, ocular motilities and a Schirmer dry eye test must be completed preoperatively to look for any amblyopia, diplopia or dry eyes that can cause postoperative patient dissatisfaction.[3]

After an appropriate consent for surgery is signed, the patient is brought into the operating room and placed in a supine position. Topical anaesthetic, commonly proparacaine 0.5% or tetracaine 0.5% is instilled into the lower cul-de-sacs of both eyes.

Using a marking pen and forceps, the redundant upper lid tissue is measured and marked from the lateral to the medial canthus, paying attention to the natural crease demarcations (Figure 1).

The marked areas in both eyes are measured in width and height to ensure that the eyelids will look symmetrical postoperatively. Five to six millilitres (cc) of lidocaine 2% with 1:100,000 epinephrine is injected into the right and left upper eyelid. The patient's lids are then prepared in a sterile manner with povidine-iodine swabs and isolated with surrounding facial drapes.

Using a #15 Bard-Parker blade, an incision is made through the skin and subcuticular tissue along the previously made markings of the right upper eyelid. Then, using blunt-tipped

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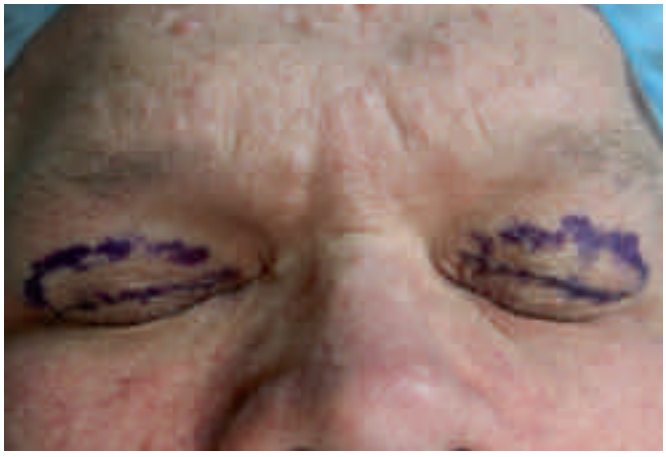
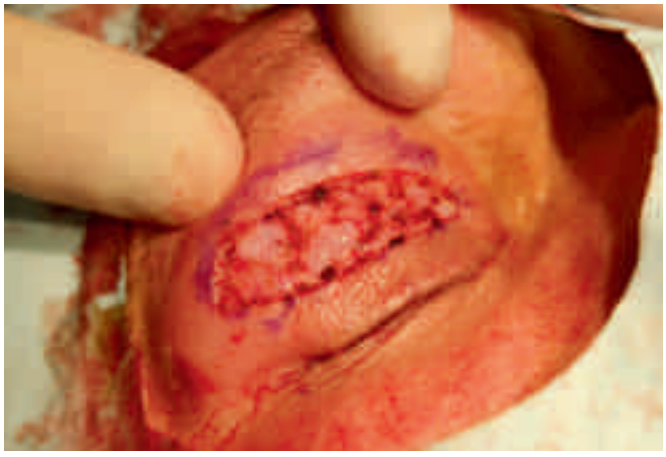


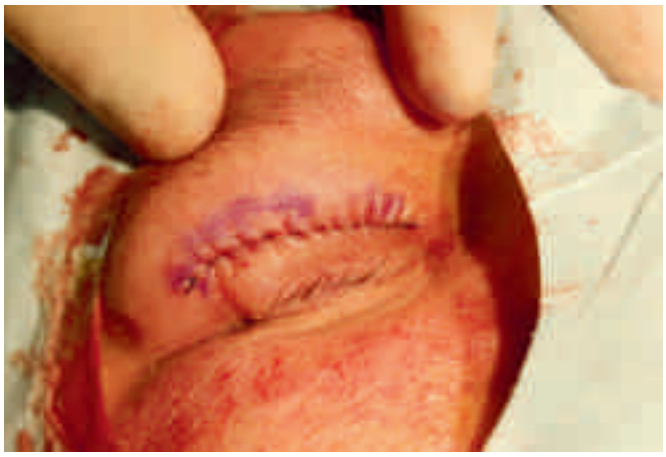
▲ Figure 1. With attention to natural crease demarcations, upper eyelids are marked indicating area of skin to be excised



▲ Figure 2. Haemostasis achieved with cautery after removing excess skin and subcuticular tissue of the upper lid

Blepharoplasty

From page 11



▲ Figure 3. A running suture closes incision in the upper lid at the completion of the blepharoplasty surgery

Westcott scissors and toothed forceps, the redundant skin is lifted up and excised.

Bleeding is controlled at this time with gauze pads and cautery (Figure 2). Once haemostasis is achieved, a 6-0 silk suture is used to create a running stitch from the lateral to the medial side, reapproximating the remaining skin (Figure 3).

In the USA, an ophthalmic antibiotic ointment such as erythromycin or bacitracin is applied over the suture and incision site. Exactly the same procedure is then repeated on the left upper eyelid. The ophthalmic antibiotic ointment is to be continued postoperatively twice a day for the next week to 10 days.[1] The sutures are removed in one week.

Bleeding and pharmaceutical prevention

Surgeons should routinely inform patients of complications that can occur during and after blepharoplasty surgery. Bleeding complications, in particular, include retrobulbar haemorrhage and superficial haematoma or bruising. Although rare, retrobulbar haemorrhage is a very serious complication that may quickly lead to partial or total vision loss.

Estimated incidence of retrobulbar haemorrhage is between one in 2,000 to one in 25,000 patients.[4] With an acute retrobulbar haemorrhage, blood starts to fill the orbit behind the eye. It accumulates in a compartment fashion within four bony walls and the orbital septum. As the orbit becomes filled with blood, pressure is put on the optic nerve. Secondarily, intraocular pressure of the globe rapidly rises, causing the patient to lose vision.

Recognition during the surgery is key, as is a rapid response. Treatment beyond one to six hours of total or near-total vision loss is unlikely to be effective. A superficial haematoma or bruising is not a complication but rather an expected side-effect. Some bleeding is likely during surgery. It can be minimised with meticulous intraoperative surgical cautery and preoperative cessation of any anticoagulant medication by the patient.

Commonly prescribed blood-thinning medication includes warfarin, heparin and aspirin. Other prescription medications that have blood-thinning properties are found in Table 1.

Warfarin	Heparin
Aspirin	Ibuprofen
Naproxen	Allopurinol
Amiodarone	Cimetidine
Clopidogrel	Diclofenac
Fluconazole	Indomethacin

▲ Table 1. Medications with blood-thinning properties[7,8]

Some natural substances, in the herbal form or supplementation, can have blood-thinning properties as well. There are thousands of herbal and related substances used presently and available for consumption with a growing population seeking holistic or over-the-counter health care.[5]

A study of 755 surveys showed that 32 per cent of patients admitted to the hospital are self-administering one or more herb-related compounds. Nearly 70 per cent of these patients did not report this information when asked about it during routine anaesthetic assessment before the scheduled surgery.[5] Specific natural supplements that contribute to blood thinning are vitamin E, Ginkgo biloba, omega-3 or fish oil and garlic.[6]

Other popular blood-thinning, over-the-counter substances can be found in Table 2. Warfarin is stopped two days before surgery. All the other prescription medications and holistic substances are stopped one week before surgery.

Vitamin E
Gingko biloba
Omega-3 (fish oil)
Garlic (allium sativum)
Ginseng (panax)
Ginger (zingiber officinale)

▲ Table 2. Popular holistic substances with blood-thinning properties[5,6,7,8,9]

One of our patients did not report taking any blood-thinning medication or substances prior to surgery. The morning of his scheduled blepharoplasty, he mentioned he was currently taking omega-3. When we became aware, we took precautions for any excessive intraoperative bleeding. Even with the precautions in place, it was apparent that haemostasis with cautery took longer to achieve than in a patient taking no blood thinners.

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Reticular pseudodrusen

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PHOTOCLINIC

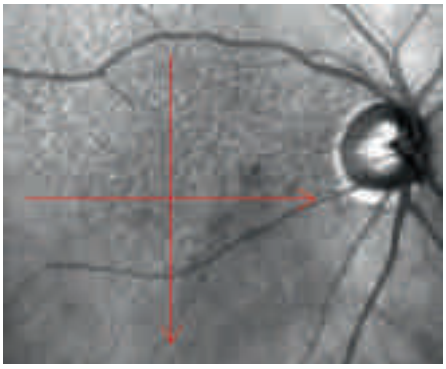
RETICULAR PSEUDODRUSEN (RPD) are yellow-white deposits in the outer retina, distributed in a reticular pattern typically in the superior retina (Figure 1). They are associated with an increased risk of progression to advanced age-related macular degeneration (AMD).

Regular drusen are deposits of lipid and lipoprotein waste products situated between the Bruch's membrane and the retinal pigment epithelium (RPE). Reticular pseudodrusen are similar in composition to drusen but the deposits are situated between the RPE and the photoreceptors, rather than beneath the RPE.

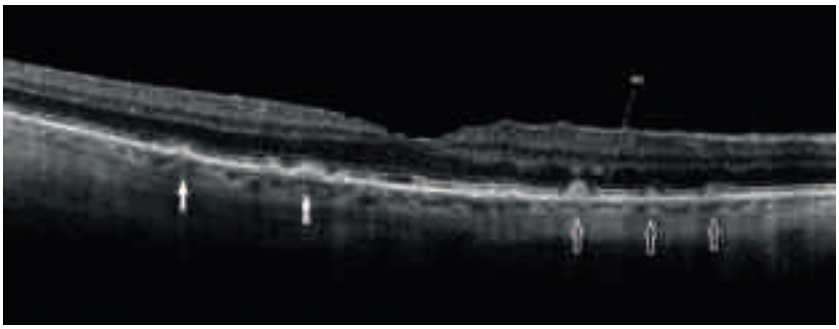
Classification

A classification has been proposed where Stage 1 deposits are those that do not disturb the photoreceptor array, Stage 2 deposits cause an undulation in the photoreceptor outer segments and Stage 3 deposits break through the photoreceptor integrity line, also known as the inner segment/outer segment line.

Figure 2 demonstrates a patient with both regular drusen and reticular pseudodrusen in the one cross-sectional retinal OCT scan. On the left side are regular drusen causing undulation in the overlying RPE (solid arrows) while on the right side of the scan are three instances of RPD (hollow arrows), two of which are Stage 3 as they have broken through the photoreceptor integrity line. ▲



▲ Figure 1. Confocal scanning laser ophthalmoscope en face image of reticular pseudodrusen predominantly in the superior macula (Nidek RS 3000)



▲ Figure 2. Spectral domain OCT retinal cross-section showing both regular drusen (solid arrows) and reticular pseudodrusen (hollow arrows) in the one scan (Nidek RS 3000). Two of the pseudodrusen have broken through the photoreceptor integrity line.

Blepharoplasty From page 12

Conclusion

Blepharoplasty is a safe and effective eyelid corrective surgery. Like any ophthalmic surgery, there are possible complications with bleeding that can occur from the expected superficial haematoma to the very serious and vision-threatening retrobulbar haemorrhage. All blood-thinning medications, conventional and holistic, should be addressed and stopped before surgery to minimise these bleeding complications, and maximise the postoperative benefits and patient satisfaction. ▲

1. Sudtelgte A, Skorin Jr L. Functional blepharoplasty: Diagnosis and surgical management. *Optometry Today* 2002: 38-40.
2. Castro E, Foster JA. Upper lid blepharoplasty. *Facial Plastic Surgery* 1999; 15: 3: 173-181.
3. Iliff C. Dermatochalasis and blepharochalasis of the upper lids. *Ophthalmology* 1978; 85 (7 Pt 1); 709-711.
4. Oestreicher J, Mehta S. Complications of blepharoplasty: Prevention and management. *Plastic Surgery International* 2012; article ID 252368; http://dx.doi.org/10.1155/2012/252368; accessed April 15, 2014.
5. Kaye AD, Clarke RC, Sabar R et al. Herbal medicines: Current trends in anesthesiology practice—a hospital survey. *Journal of Clinical Anesthesia* 2000; 12: 468-471.
6. Hannon J, Skorin Jr L. Supplementation and surgery: Can optometry play a role? *Optometry Pharma* 2011: 12-13.
7. Shore J, Menke A. Hemorrhage associated with ophthalmic procedures: Focus on blepharoplasty. Ophthalmic Mutual Insurance Company: A Risk Retention Group; http://www.omic.com/wp.../04/Hemorrhage-and-Ophthalmic-Procedures.pdf; accessed April 4, 2014.
8. Stuart A. Bleed or clot concerns in the anticoagulant patient. American Academy of Ophthalmology; http://www.aao.org/publications/eyenet/200802/feature.cfm (accessed March 30, 2014).
9. Tsen LC, Segal S, Pothier M et al. Alternative medicine use in presurgical patients. *Anesthesiology* 2000; 93: 148-151.

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BOptom PhD(Melb) PGCertOcTher FACO FAAO DipMus(Prac) AMusA

ABSTRACTS

Link between low-dose oral anti-inflammatory therapy and improvement in inner retinal function
A 'proof of concept' randomised, double-masked clinical trial involved 30 patients with one or more eyes having severe NPDR or PDR less than Early Treatment Diabetic Retinopathy Study (ETDRS)-defined high-risk PDR. Subjects were randomised to receive daily doxycycline monohydrate (50 mg) or placebo for two years.

From baseline to 24 months, the mean frequency doubling perimetry (FDP) sensitivity decreased in the placebo group (-1.9 dB) and increased in the doxycycline group (+1.2dB, $p = 0.02$). Compared with controls, a higher mean FDP foveal sensitivity in the doxycycline group was detected at six months ($p < 0.05$); this effect persisted at 12 and 24 months. There were no differences between groups detected for other functional parameters.

The authors claim this study is the first observation suggesting a link between low-dose anti-inflammatory therapy and sub-clinical improvement in inner retinal function.

The study results also suggest that FDP, which primarily measures inner retinal function, is responsive to intervention and may be useful as clinical trial endpoint for proof-of-concept studies in patients with DR.

JAMA Ophthalmol 2014; Mar 6. Epub ahead of print.

Choroidal thinning in Alzheimer's disease
Patients with Alzheimer's disease have been found to have a thinner choroid than healthy age-matched controls. A prospective, cross-sectional study involved 21 patients (mean age 73.1 ± 6.9 years) with mild to moderate Alzheimer's disease and 21 age-matched controls (mean age 70.3 ± 7.3 years). All subjects underwent neuropsychological and ophthalmological examination.

Choroidal thickness was measured using spectral domain optical coherence tomography (SD-OCT) with manual segmentation of the choroid. Choroidal thickness was found to be significantly thinner in patients with Alzheimer's disease than in control eyes ($p < 0.05$). No significant difference in central retinal thickness or peripapillary retinal nerve fibre layer thickness was found between groups ($p > 0.05$).

It was suggested that choroidal thinning may represent an adjunctive biomarker for the diagnosis and follow-up of patients with Alzheimer's disease.

J Alzheimer's Dis 2014; Feb 20. Epub ahead of print.

Dermal injection of cosmetic fillers can lead to irreversible blindness
Cosmetic facial fillers are not approved for use in the forehead; however, off-label use for enhancement in this region is common. A recent paper describes the first reports of blindness in patients caused by the procedure.

The case series describes irreversible vision loss from central retinal artery occlusion in three patients and partial vision recovery in one patient, following cosmetic facial enhancement. It is hypothesised that the filler enters the central retinal artery via the rich external-internal carotid anastomoses and becomes embedded in the retinal tissues, potentially leading to irreversible and severe vision loss.

The authors emphasise the need for physicians performing cosmetic enhancement procedures involving facial fillers to be aware of this potential complication and to inform patients of such risks.

JAMA Ophthalmol 2014; Mar 6. Epub ahead of print.

Needle contamination with intra-vitreal injections: speak or stay silent?
Speaking versus remaining silent makes no significant difference with regard to needle contamination with oral flora during intra-vitreal injection.

A prospective study evaluated the risk of intra-vitreal needle contamination through speaking versus breathing in an ophthalmologic office setting.

Participant physicians (n = 10) held a sterile 30-gauge half-inch needle 25 centimetres from their mouth for 30 seconds under two conditions: while speaking and while breathing silently. Each physician was sampled 15 times. Needles were then cultured and assayed after six days of incubation. Absolute colony-forming units (CFUs) were compared between the two conditions and against control sterile needles and oral swab cultures.

Participants were found to grow an average of 0.21 colonies (median = 1 CFU) from their talking samples and 0.07 colonies (median = 1 CFU) from their silent breathing samples. Oral swab plates grew an average of 373.4 colonies. None of the control needle plates grew CFUs. A nominal regression analysis showed no significant difference in contamination between samples that were collected with a physician talking compared with remaining silent ($p=0.48$).

Retina 2014; Feb 6. Epub ahead of print.

Donor health may disturb corneal biochemistry
A small pilot study conducted in Poland has found that some chronic systemic diseases, which do not obviously impact ocular function, may significantly and permanently disturb corneal metabolism.

The content of selected low molecular weight metabolites were compared in corneas harvested from donors who died suddenly from accidental causes or non-poisoning suicide (n = 4), or from chronic cardiovascular or liver disease (n = 4). Metabolite contents were assessed using high-resolution magic angle spinning proton spectroscopy.

Significant differences in corneal biochemical profiles were evident between the study groups. Some of the alterations were described to be most likely related to permanent aberrations in corneal metabolism. The authors concluded that these findings justify the need for a study in larger donor

groups to assess the potential impact of liver cirrhosis and cardiovascular disease on corneal metabolism.

Ann Transplant 2014; Mar 12; 19: 129-37.

Possible association between pseudoexfoliation syndrome and coronary artery ectasia

A cross-sectional study was undertaken at Bulent Ecevit University's Ophthalmology and Cardiology Departments, Turkey. Eighty consecutive patients who underwent coronary angiography were classified into one of two groups: normal coronary arteries (n = 40) and coronary artery ectasia (n = 40).

PXF was diagnosed ophthalmologically through the observation of typical exfoliative material on the anterior surface of the lens, iris or pupillary border. Age, sex, presence of pseudoexfoliative material, hypertension, diabetes mellitus, hyperlipidaemia rates, cigarette smoking history and family history of coronary artery disease were compared between groups.

There were no significant differences in demographic data between groups. PXF was found to be significantly more common in patients with coronary ectasia compared with controls (n = 21 (52.5 per cent) vs n = 8 (20 per cent), p = 0.005).

This is the first study to show a potential relationship between coronary artery ectasia and PXF. Future studies in larger populations are needed to clarify this relationship and other potentially unknown systemic associations of PXF.

Eye (Lond) 2014; Mar 7. Epub ahead of print.

Travoprost therapy for glaucoma can compromise the ocular surface

A study investigated corneal epithelial and Langerhans cell (LC) densities, along with dry eye parameters, in patients with primary-open angle glaucoma (POAG) using one of two commercially-available Travoprost 0.004 per cent topical medications with differing preservatives: benzalkonium chloride 0.015 per cent (TravBAK), or polyquaternium-1 0.001 per cent (TravPQ).

The consecutive case series consisted of 19 POAG patients using TravBAK (age: 64.8 ± 13.6 years), 19 POAG patients using TravPQ (age: 66.8 ± 11.3 years) and 19 age-matched healthy controls (age: 63.8 ± 8.2 years). Ocular surface disease index, lid parallel conjunctival folds, Schirmer test and tear break up time (TBUT) were assessed. Corneal epithelial and Langerhans cell densities were investigated using confocal microscopy.

Tear production was significantly reduced and Langerhans cell densities were greater in both POAG groups compared with controls ($p < 0.05$). TBUT was significantly reduced and epithelial cell densities were significantly greater in TravBAK eyes compared with healthy individuals ($p < 0.05$).

TravPQ eyes demonstrated relatively less disturbance to the ocular surface and more controlled corneal homeostatis than TravBAK eyes.

Pathol Oncol Res 2014; Mar 13. Epub ahead of print.

Use of statistical analyses in the ophthalmic literature

A recent cross-sectional study of the peer-reviewed ophthalmic literature has found that readers of clinical journals in ophthalmology need to possess substantial knowledge of statistical methodology to understand the results of published studies.

All articles published in 2012 in the journals *Ophthalmology*, *American Journal of Ophthalmology* and *Archives of Ophthalmology* were reviewed. A total of 780 peer-reviewed publications were included. Two reviewers examined each article and assigned categories to each one depending on the type of statistical analyses that were used. Discrepancies between reviewers were resolved by consensus.

It was found that readers with little or no statistical knowledge would be expected to be able to interpret the statistical methods in only 20.8 per cent of studies. To understand more than half of the published articles, readers would be expected to be familiar with at least 15 different statistical methods. Articles related to retina and glaucoma sub-specialities showed a tendency for using more complex analyses when compared with articles from the cornea subspeciality.

The results of the study can also be used to provide guidance to direct the training of optometrists, ophthalmologists, researchers and clinical educators in the area of statistics.

Ophthalmology 2014; Mar 5. Epub ahead of print.

Alterations to choroidal thickness during migraine

Choroidal thickness has been found to be significantly increased in migraine patients during the attack period when compared with basal levels.

An observational, cross-sectional study involved 58 eyes of 29 subjects with a diagnosis of migraine with or without visual aura. Using the enhanced depth imaging mode, two optical coherence tomography scans were performed for each patient: one during the peak period of the migraine attack and other during a headache-free interval.

In patients with unilateral headaches, choroidal thickness measurements during the attack period were significantly increased only in eyes on the headache side ($p < 0.001$) compared with baseline. Foveal choroidal thickness in the pain-free interval was 373.45 ± 76.47 (mean ± SD) µm and increased to 408.80 ± 77.70 µm during the attack period ($p < 0.001$). When the choroidal thickness of patients with bilateral headaches were compared to basal levels, a statistically significant increase was observed at five out of seven measured points in right eyes and at all seven measured points in left eyes ($p < 0.05$).

The authors acknowledge that this study is a preliminary report with some limitations. Larger studies investigating the neurovascular structures of the eye during migraine may provide further insights into both the pathogenesis of migraine and the association between migraine and glaucoma.

Br J Ophthalmol 2014; Feb 26. Epub ahead of print. ▲

21st century solutions for a 21st century epidemic

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DIABETIC EYE DISEASE is the leading cause of blindness among the working population (20-60 years old) in Australia.[1] According to Diabetes Australia, 280 Australians develop diabetes every day. It is the fastest growing chronic health condition in Australia. An estimated 3.2 million Australians are diabetic or pre-diabetic.[1] These statistics are hard to grasp and difficult to ignore.

There is no nationwide screening program to ensure that all diabetic patients have regular eye examinations to detect and appropriately manage their ocular complications, let alone a system robust enough to withstand clinical audit to ensure the most cost-effective delivery of appropriate care and optimal outcomes.

Without a formal comprehensive structure for diabetic eye care, only about 50 per cent of people with diabetes in Australia receive regular eye care.[2] Structures designed to detect and appropriately treat cases of diabetic eye disease have been shown to reduce the human and financial costs involved.[3,4]

Virtually every type 1 diabetic patient and more than 60 per cent of type 2 diabetic patients will have some form of diabetic eye disease within 20 years of diagnosis of their diabetes.[2]

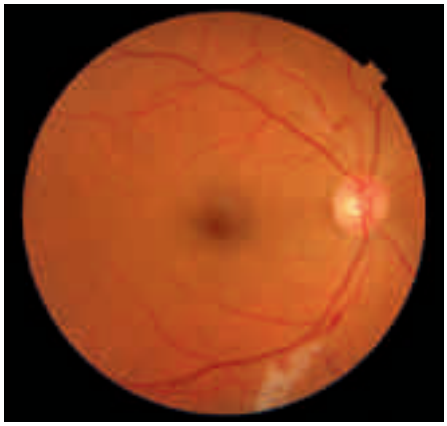
Classification and management

In major studies, diabetic retinopathy has been classified using the modified Airlie House protocol (Wisconsin system).[5] In short, retinopathy is classified as non-proliferative (NPDR) or proliferative (PDR) and within that, maculopathy is classified as 'monitor' or 'treat'. In the most simple of terms, minimal or mild NPDR can be diagnosed and monitored by optometrists, but patients with severe NPDR or PDR should be comanaged with an ophthalmologist, preferably a specialist in medical retina. The Blue Mountains Eye Study found diabetic retinopathy in 32 per cent of known or newly-diagnosed diabetic patients.[8] Of those, 1.6 per cent had PDR and 5.5 per cent had macular oedema. Interestingly, 16 per cent of people found to have undiagnosed diabetes had retinopathy as well, so optometrists will often be the first health-care professionals to detect signs of diabetes in these patients as they may present for a routine comprehensive eye examination for other reasons.

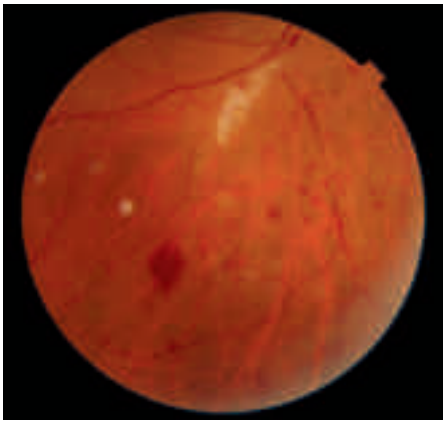
If referral to an ophthalmologist is required, it should be graded for urgency, made appropriately, and copied to the other health professionals involved in the care of the patient—for example, general medical practitioner, endocrinologist—to achieve a holistic approach to diabetes, which has numerous potential systemic complications.

All diabetic patients should have visual acuity checked and retinae assessed, at least annually if there is mild NPDR. Retinal photographs should be taken to document any pathology. Optometrists are the obvious choice to provide this service, as practitioners have the skills and expertise to perform a dilated posterior eye examination. Additionally, most optometric practices have retinal cameras to perform baseline photography.

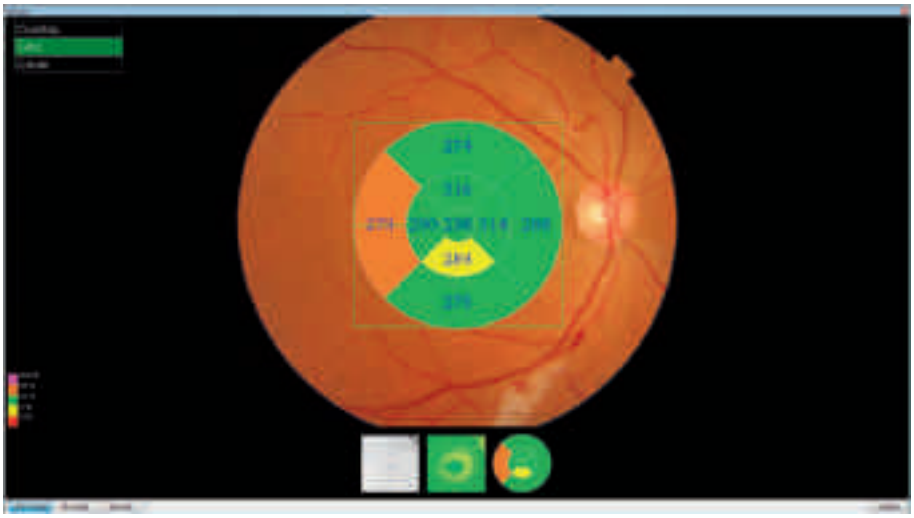
It could be argued that retinal photography should be part of the minimum standard of record-keeping, especially for these at-risk patients.[6] At the same visit, patients can be checked for macular oedema, the most common cause of vision loss in diabetic patients.[7] Indirect ophthalmoscopy with a 66 D or equivalently high magnification lens can be used. Ideally, macular oedema should also be assessed by imaging with optical coherence tomography (OCT) as this can detect subclinical central macular thickening. Retinal photography and OCT scans are not part of the Medicare-funded comprehensive eye examination, so currently the cost of these services must be covered by the patient.



▲ Figure 1. Central retinal image showing inferior branch vein occlusion



▲ Figure 2. The same eye as in Figure 1, showing the extent of haemorrhaging inferiorly



▲ Figure 3. OCT EDTRS grid showing near-normal macular thickness

Given the current circumstances discussed above, we present two case studies to illustrate the present pattern of referral and treatment of diabetic eye disease in Australia. In the first case, the patient, who presented to her optometrist (SL) was yet to be diagnosed as having diabetes mellitus. In the second, the patient was referred by his optometrist to an ophthalmologist sub-specialising in medical and surgical retina (AK).

Undiagnosed diabetic patients may have symptomatic co-existing ocular pathology (Case 1) and established diabetic patients may have asymptomatic eye disease (Case 2). These situations illustrate the need for regular, easily-accessible comprehensive eye care and screening, preferably without the burden and disincentive of prohibitive costs to the individual.

CASE 1: PRIMARY CARE

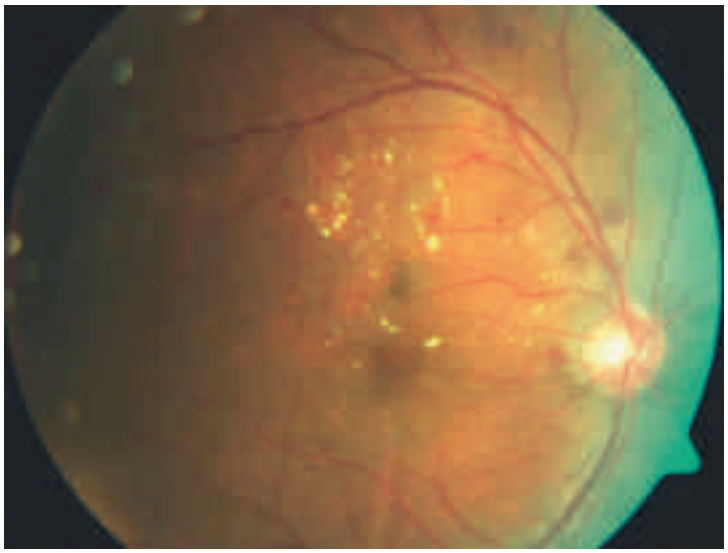
KR, a 44-year-old bank teller who lists her spare time activities as netball, swimming, and 'running around after the kids', presented to her optometrist (SL) with a three-week history of seeing a small distorted patch in her superior field on down-gaze. When she looked down at the money she was counting, she could see a distorted patch on her customer's face.

KR, a previous patient of the practice, had always reported good general health, no prescribed medications, and no family history of eye problems. In particular, she believed there were no diabetic sufferers in her family. Her best corrected Snellen visual acuities were 6/6+ in R&L with her -2.00 DS R&L and N4.5 R&L up to 30 cm with a +0.75 Add.

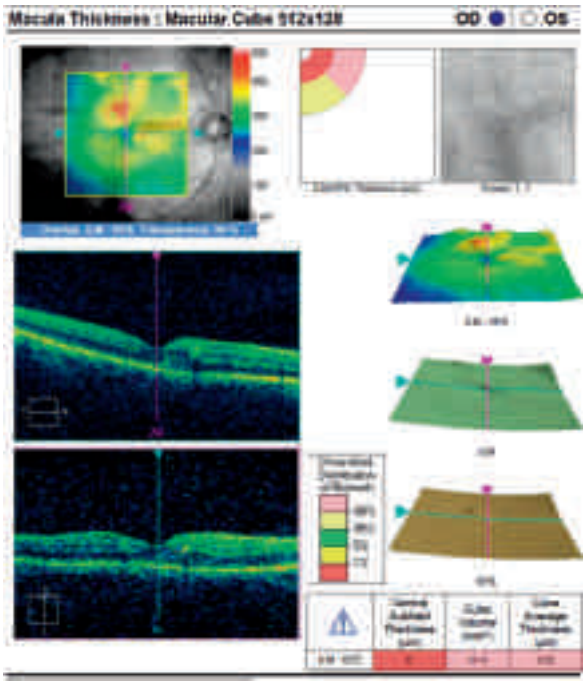
Fundus biomicroscopy revealed an inferior branch vein occlusion (BRVO) in the right eye, with localised exudation and significant haemorrhaging (Figures 1 and 2). The position of this lesion corresponded to her symptoms. The OCT scan revealed no significant macular oedema associated with the BRVO (Figure 3).

The patient was referred to a local specialist in medical retina, and a report was sent to her GP. Type 2 diabetes, which can be associated with RVO, was discovered by the GP. An ophthalmologist followed the case for two months while the symptoms were settling spontaneously. KR was discharged back to the care of her optometrist once the haemorrhage had largely cleared.

Continued page 18



▲ Figure 4. Right eye 2009 pre-treatment



▲ Figure 5. Right eye OCT 2009 pre-treatment

Multi-disciplinary approach

From page 17

KR still reported minimal distorted vision in the same location in the subsequent visits, with no other signs of complications from the BRVO or any diabetic retinopathy after three months.

As this case illustrates, primary care optometry plays an important role in the management of retinal disease in the context of diabetes. KR was diagnosed and subsequently monitored locally, and did not need expensive specialist care in a private clinic or public hospital. Her GP has instigated a primary care plan to include education on management of type 2 diabetes, and involvement of a dietitian, endocrinologist, podiatrist and optometrist, with the GP serving as gatekeeper and co-ordinator.

CASE 2: SECONDARY CARE

TC, a 56-year-old property developer, was referred to a specialist in medical and surgical retina (AK) for management of diabetic retinopathy in 2009 when his optometrist noted diabetic retinopathy in both eyes. He was first diagnosed with late onset diabetes mellitus in 2008 but his diabetic symptoms pre-dated that. His blood sugar control was poor and he was asymptomatic. Visual acuities were 6/6 in each eye.

Fundal examination showed moderate NPDR and diabetic macular oedema without foveal involvement (Figure 4). Macular OCT scans showed some extra-foveal macular thickening (Figure 5). TC underwent focal laser treatment in his right eye to stabilise his vision. He subsequently required bilateral panretinal laser photocoagulation due to the progression to PDR.

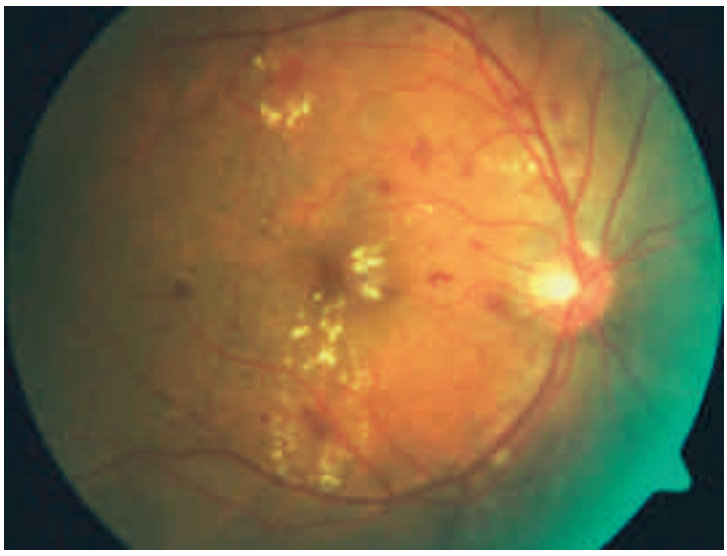
In 2013, after a few years of poorly-controlled diabetes, TC noted progressive blurring vision in his right eye with a reduction of best corrected visual acuities to 6/15 in that eye (Figures 6 and 7). He developed a recurrence of macular oedema with central macular involvement. Anti-VEGF therapy was recommended and monthly off-label intravitreal Avastin injections were administered. The macular oedema was stabilised in his right eye and visual acuity was maintained at 6/12 (Figures 8 and 9).

This case highlights the importance of screening for diabetic retinopathy and the importance of good diabetic control to halt the progression of diabetic retinopathy. With better glycaemic control, TC's diabetic eye disease may not have progressed to the extent that it did.[2] This case also demonstrates that focal laser treatment is useful in the management of diabetic maculopathy when the vision is good and the central macula is not involved.[9] Regular anti-VEGF injections are the treatment of choice once the central macula is involved and vision is affected.[10]

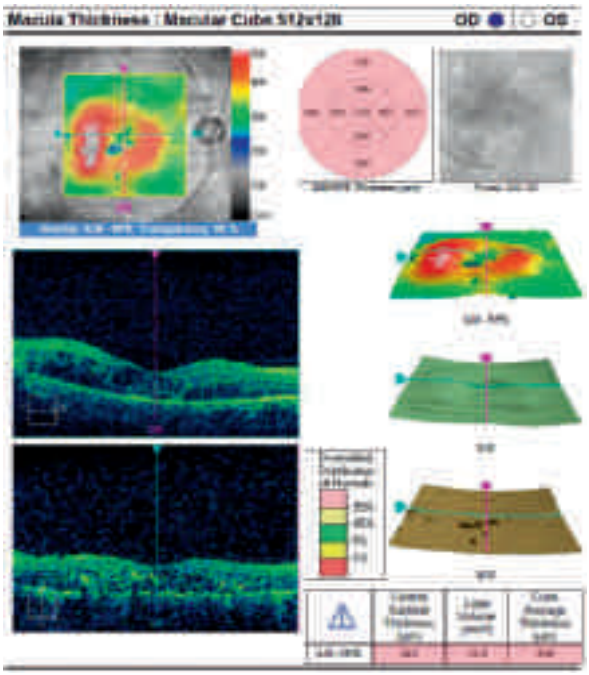
Summary

More must be done to educate the Australian public and general medical practitioners about the risks, signs and symptoms of diabetes and the necessity for regular comprehensive eye care, and a diabetic retinopathy screening program for all Australians, whether symptomatic or not. Public perception still appears to be that eye care is needed only if symptoms are present or when spectacles are needed. Even then, many people buy ready-made reading glasses and do not have their eyes examined.

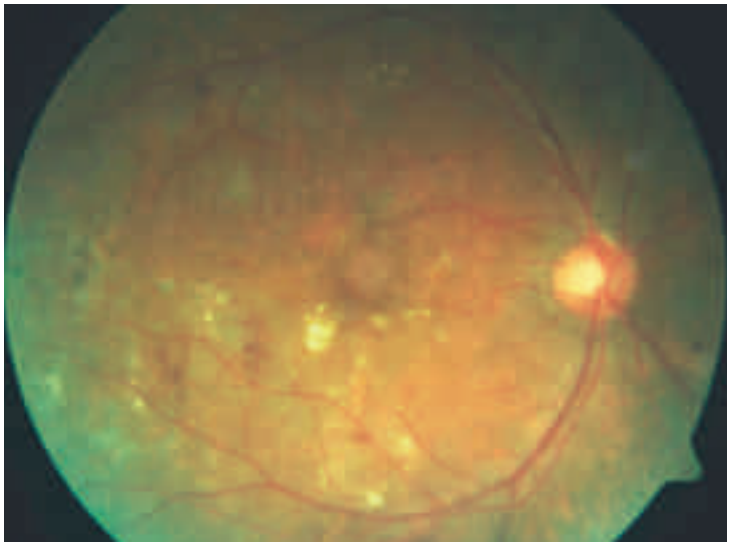
Primary care optometry has great case-finding potential. The role of the optometrists in the detection and monitoring of diabetic eye disease should be recognised and funded as an important aspect of diabetic health care.



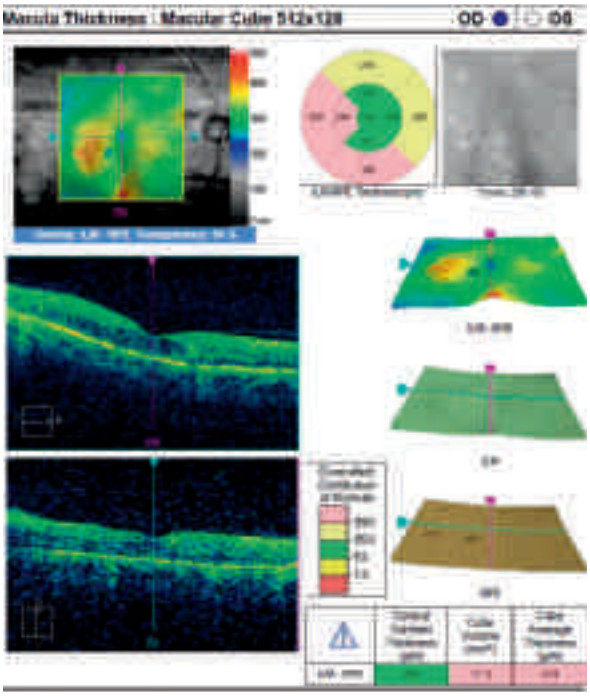
▲ Figure 6. Right eye 2013 pre-Avastin



▲ Figure 7. Right eye OCT 2013 pre-Avastin



▲ Figure 8. Right eye 2013 post PRP and Avastin



▲ Figure 9. Right eye OCT 2013 post PRP and Avastin

At present, scheduled Medicare benefits for eye examinations by optometrists cover only about 25 per cent of the costs of providing the service and therefore there is significant cross-subsidy from other services optometry provides.

If optometry is to continue as a health-care profession, this funding gap must be addressed. This might be done by increasing benefit levels for consultations where the patient has a specific eye pathology or other conditions requiring ongoing management other than refraction. Introduction of a Medicare item for examination by optometrists of patients with a range of systemic diseases referred by their GP may be useful.

Removing the cap on optometrists' fees where Medicare benefits apply is a common-sense approach and we welcome it, but it will not assist our most vulnerable patients and groups such as diabetic patients who need more comprehensive services more regularly and can least afford them.

Ophthalmologist specialist care is essential in the moderate to advanced stage of diabetic retinopathy as a delay in appropriate treatment may result in permanent visual loss. The advent of intra-vitreal anti-VEGF injections, adjunct fenofibrate therapy, improved laser equipment and treatment protocols means that the risks of permanent vision loss from diabetic retinopathy are greatly reduced. Of course, this relies on case finding and timely referral for secondary care.[9,10]

The cases presented here illustrate the benefits of inter-disciplinary co-operation and communication by all health-care professionals concerned, promoting a patient-centred approach to diabetic care in general and diabetic eye care in particular.

We should no longer accept that it is inevitable that blindness is a common consequence of diabetes. With an appropriately-funded national structure in place to find such cases, there would be potential for savings in both financial and human costs. ▲

1. Diabetesaustralia.com.au/understanding-diabetes/diabetes-in-australia. Accessed 11/4/14.
2. Out of Sight: A Report into Diabetic Eye Disease in Australia. Baker IDI publication 2013.
3. Arun CS, Al-Bermani A, Stannard K, Taylor R. Long-term impact of retinal screening on significant diabetes-related visual impairment in the working age population. *Diabet Med* 2009; 26: 489-492.
4. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. *Annals Internal Medicine* 1996; 124 (1 Pt 2): 164-169.
5. Lecaire T, Palta M, Zhang H, Allen C, Klein R, D'Alessio D. Lower than expected prevalence and severity of retinopathy in an incident cohort followed during the first 4-14 years of type 1 diabetes: the Wisconsin Diabetes Registry Study. *Am J Epidemiol* 2006; 164: 143-150.
6. Williams GA, Scott IU, Haller JA, Maguire AM, Marcus D, McDonald HR. Single-field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology. *Ophthalmology* 2004; 111: 5: 1055-1062.
7. Mitchell P, Wong TY. Management paradigms for macular edema. *Am J Ophthalmol* 2014; 157: 3: 505-513.
8. Mitchell P, Smith W, Wang JJ, Attebo K. Prevalence of diabetic retinopathy in an older community. The Blue Mountains Eye Study. *Ophthalmology* 1998; 105: 406-411.
9. Kwan AS. Laser photocoagulation for diabetic macular oedema in the era of anti-vascular endothelial growth factor therapy: is there a role? *Clin Exp Ophthalmol* 2012; 40: 6: 535-536.
10. Bandello F, Cunha-Vaz J, Chong NV, Lang GE, Massin P, Mitchell P, Porta M, Prünte C, Schlingemann R, Schmidt-Erfurth U. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye (Lond)* 2012; 26; 4: 485-493.

DR: an endocrinologist's view

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DIABETIC RETINOPATHY (DR) is the quintessential diabetes-related complication. The observed relationship between blood glucose levels and the presence of DR is used to identify the threshold glucose levels that define the presence of diabetes.[1] DR, along with its associated complications, is the single most common and preventable cause of blindness in people with diabetes over 75 years of age. This emphasises the importance of the early detection of DR and the instigation of measures to prevent its development and progression.

Grading of DR

The National Health and Medical Research Council of Australia (NHMRC) guideline for the management of DR suggests using a five-stage grading system: no DR, minimal non-proliferative DR, mild to moderate DR, severe DR, and proliferative DR. Macular oedema is graded according to its absence or presence.[2]

Epidemiology

For patients with type 1 diabetes (T1DM), less than two per cent will have a DR lesion at diagnosis whereas 87-98 per cent will have an abnormality after 30 years of diabetes. For patients with type 2 diabetes (T2DM), 20-37 per cent will have a lesion at diagnosis but after 15 years of diabetes, 85 per cent on insulin and 60 per cent on oral agents will have a DR related abnormality. A global study involving 12,620 participants with diabetes has suggested that the prevalence of any form of DR is 35per cent with a prevalence of vision-threatening DR being 10 per cent.[3]

Risk factors for DR: 'GLOBES'

The above study showed that diabetes duration, glycaemic control (glycated haemoglobin levels), blood pressure (BP) control and diabetes type (with the prevalence of diabetes being 77 per cent in T1DM versus 25 per cent in T2DM) were the major risk factors for DR. A simple acronym to help identify the risk factors for DR is 'GLOBES': glucoses, lipids, obesity, blood pressure, education status, smoking.

Screening for DR

Screening for DR and diabetes-related eye problems involves measurement of visual acuity, intraocular pressure, dilated fundoscopy, and/or retinal photography by an optometrist or an ophthalmologist. Screening for DR should be performed at the time of diagnosis with T2DM and within five years of the diagnosis of T1DM. The frequency of follow-up depends on the severity of DR. If no DR is detected or there are no significant risk factors, then the frequency of follow-up can be extended to three years. However, in high risk patients (using insulin, diabetes duration > 20 years or both), yearly screening is recommended. Even more frequent follow should occur in instances of rapid improvement in glycaemic control, puberty and pregnancy where acceleration of DR may occur.[2]

Management of DR: risk factor reduction

Randomised controlled trials have demonstrated that it is possible to improve diabetes-related eye outcomes with good glycaemic control. Primary prevention of DR with good glycaemic control is paramount in reducing risk of visual loss, whereas secondary prevention has a smaller effect but still remains effective. An emerging concept is that the beneficial effects of good glycaemic control continue to accrue over many years despite possible later deteriorations in glycaemic control. This concept is commonly referred to as 'metabolic memory'.[4,5]

Other important contributing variables include aggressive management of BP and dyslipidaemia, and smoking cessation. Blocking the renin-angiotensin (R-A) system with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) has also been shown to slow the progression of DR. It is possible that this effect is due to a direct effect of blockade of the retinal R-A system independent of any BP lowering effects of ACE inhibitors or ARBs.[6,7]

Retinal photocoagulation

One of the main reasons for DR screening is the established effectiveness of retinal photo-coagulation in preventing visual loss. The Diabetic Retinopathy Study (DRS) demonstrated that pan-retinal photocoagulation was beneficial for reducing the risk of further visual loss in patients with proliferative DR.8 The Early Treatment Diabetic Retinopathy Study (ETDRS) also established the benefits of focal laser photocoagulation for patients with macular oedema.[9]

New treatment for DR

Fenofibrate, a medication that is usually used to lower triglyceride levels, has been approved by the Therapeutics Goods Authority (TGA) for the indication to slow the progression of existing DR in type 2 diabetes. This approval was based on the results of two large placebo, controlled trials that showed that the use of fenofibrate was associated with a reduction in the rate of progression of DR and the need for retinal photocoagulation.[10,11] The effects of fenofibrate on the eye are independent of changes in lipid levels and likely involve an inhibition of

growth factors or cytokines.[12]

The intra-vitreal injection of a recombinant monoclonal neutralising antibody to vascular endothelial growth factor (VEGF) improves vision and reduces the need for photocoagulation in patients with macular oedema. It is now a treatment that is being offered to patients in everyday clinical practice. Anti-VEGF treatment may also slow the progression of proliferative DR but this effect is yet to be established. Intra-vitreal delivery of fluocinolone is also another emerging therapy for the treatment of DR.[1,2,13]

Conclusion

Although the prevalence of diabetes continues to increase, which is mostly driven by an increase in type 2 diabetes, there is some good news regarding the eye health of patients with diabetes. In particular, better screening is yielding earlier detection and there are better treatments to control the risk factors for DR development and progression. Optometrists continue to play a vital role in the screening and management of diabetic eye disease.

1. Standards of medical care in diabetes 2014. *Diabetes Care* 2014; 37 Suppl 1: S14-80.
2. National Health and Medical Research Council, Guidelines for the Management of Diabetic Retinopathy. 2008.
3. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; 35: 3: 556-564.
4. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008; 359: 15: 1565-1576.
5. Aiello LP, Group DER. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 2014; 37: 1: 17-23.
6. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH et al. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 2008; 372: 9647: 1394-1402.
7. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; 361: 1: 40-51.
8. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. *Amer J Ophthalmol* 1976; 81: 4: 383-396.
9. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985; 103: 12: 1796-1806.
10. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; 370: 9600: 1687-1697.
11. ACCORD Study Group et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *New Eng J Medicine* 2010; 363: 3: 233-244.
12. Noonan JE, Jenkins AJ, Ma JX, Keech AC, Wang JJ, Lamoureux EL. An update on the molecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. *Diabetes* 2013; 62: 12: 3968-3975.
13. Cheung N, Wong IY, Wong TY. Ocular anti-VEGF therapy for diabetic retinopathy: overview of clinical efficacy and evolving applications. *Diabetes Care* 2014; 37: 4: 900-905.

Adjunct fenofibrate therapy: what

Clinical trials show it can be

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DIABETIC RETINOPATHY (DR) remains the leading cause of severe vision loss in working-age people in the industrialised world. Tight blood glucose and blood pressure control are the mainstays of delaying the onset and preventing the progression of diabetic retinopathy to a stage that requires laser or anti-VEGF intervention. Nonetheless, it is estimated that 10 per cent of people living with diabetes have sight-threatening diabetic retinopathy (STR), proliferative diabetic retinopathy (PDR) and/or diabetic macular oedema (DME).[1]

Validated risk analysis shows that among newly-diagnosed diabetes patients with excellent metabolic control (glycosylated hemoglobin of 6.5 per cent and blood pressure of 120/80), four per cent will develop STR within 10 years.[2] With the appearance of even mild non-proliferative diabetic retinopathy (NPDR), the 10-year risk jumps to eight per cent. The risk for most patients is substantially higher, given the fact that more than 50 per cent have an HbA1c greater than seven per cent.[3] Though photocoagulation and intra-vitreal injections reduce the risk of significant vision loss from STR substantially, they don't eliminate that risk, may cause loss of visual function and require considerable expenditure.

Is there anything more we can do to prevent our patients from progressing to sight-threatening diabetic retinopathy?

Two large clinical trials examining more than 11,000 type 2 diabetes patients have recently demonstrated that use of the oral lipid agent, fenofibrate significantly reduced the risk of DR progression and need for first laser treatment. The FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes) conducted in Australia showed that patients with mild to moderate NPDR and non-clinically significant DME treated with 200 mg fenofibrate over five years were 78 per cent less likely to have significant (two-step Early Treatment Diabetic Retinopathy Study) progression of retinopathy, had a 31 per cent lower risk of laser for Clinically Significant Macular Edema (CSME), and a 30 per cent lower risk of laser for PDR over five years (37 per cent overall reduced risk of laser for both conditions).[4] The effect was much smaller and non-significant for patients without pre-existing retinopathy. Though only one in five patients had retinal photography to document DR severity, the benefits appear robust.

In addition, a sub-study of the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) conducted in North America, ACCORD-Eye also showed that type 2 patients with high cardiovascular risk and mild-to-moderate retinopathy placed on 160 mg fenofibrate (+/- statin therapy) were 40 per cent less likely to have either a three-step ETDRS progression of retinopathy (documented by serial retinal imaging) and/or laser treatment for PDR over four years.[5]

Subjects in ACCORD-Eye had longer diabetes duration and higher prevalence of any DR than subjects in FIELD at baseline and, again, these positive effects were present but much weaker in patients without pre-existing retinopathy. Of significance, only 17 patients need to be treated with fenofibrate to prevent one case of initial laser therapy (per FIELD) and 9/14 patients to prevent significant progression of NPDR (FIELD and ACCORD-Eye, respectively), NNTs that are much lower than those for commonly used therapies such as statins and antihypertensives.

The benefits of fenofibrate for DR in these studies appear to be largely independent of both the drug's

Children	Severe renal dysfunction
Liver dysfunction	Pancreatitis not caused by high triglycerides
Primary biliary cirrhosis	Gallbladder disease
Pregnant or nursing women	Co-administration with oral anti-coagulants
	Co-administration with other fibrate derivatives

▲ Table 1. Contraindications to fenofibrate therapy[12]

the optometrist needs to know

effective in early intervention

lipid-lowering effects[6] and patients' glycosylated hemoglobin levels. Proposed mechanisms include inhibition of retinal capillary apoptosis (via AMPK-dependent pathways),[7] retinal oxidative stress (via suppression of nfK),[8] and leukocyte adhesion to capillary endothelium (via suppression of intracellular adhesion molecule-1); neuro-protection afforded by peroxisome proliferator-activated receptor-alpha (PPAR-);[9] strengthening of capillary tight junctions;10 PPAR-mediated suppression of VEGF and hypoxia inducible factor-1.[11]

Unfortunately, there are no reported data from either FIELD or ACCORD-Eye for treatment efficacy among patients with varying degrees of NPDR or specific retinopathic findings. Subjects with severe NPDR, PDR, and CSME were excluded from both trials. Further investigations of benefit in DME and patients with type 1 diabetes are underway in Australia and the US (FAME-1 Eye).

Which patients with diabetes and DR merit consideration for adjunctive treatment with fenofibrate?

Australia's Therapeutic Goods Administration recently approved fenofibrate (Lipidil, Abbott Pharmaceuticals) to slow the progression of existing DR in patients with type 2 diabetes, and some ophthalmologists and optometrists are beginning to recommend patients discuss the risks and benefits of fenofibrate with their primary care physicians, internists and endocrinologists. Pharmacology experts with whom I have consulted tell me fenofibrate is generally safe and well-tolerated (Table 1).

The recommended dosage is one tablet (144 mg) daily, or one to two (48 mg) tablets in patients with renal insufficiency, depending on creatinine clearance values. Common side-effects include gastrointestinal upset. Several drug interactions are reported, including increased risk of muscle pain/weakness (low risk almost exclusively in patients also on statin therapy),[13] bleeding in patients taking anticoagulants (close monitoring of serum coagulation laboratory markers—primarily prothrombin time (PT) in patients on warfarin—recommended), and use with other drugs potentially impairing liver/renal function. Hypoglycemia is rare (less than one per cent of patients) but all patients on insulin or sulfonylureas should be cautioned to closely monitor their glucoses when initiating therapy.

Though recent analysis of glucagon-like Peptide-1 (GLP-1) diabetes drugs like exenatide (Byetta, Lilly) and liraglutide (Victoza, NovoNordisk) has shown no increased risk of pancreatitis,[14] patients simultaneously using these agents with fenofibrate should be specifically informed about symptoms of acute pancreatitis like acute abdominal pain, nausea and fever.

I have encountered differing opinions about add-on fenofibrate among

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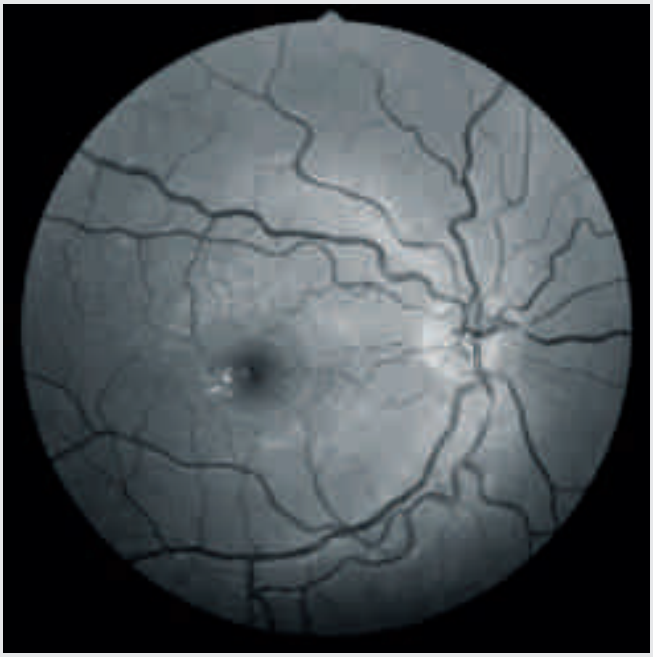
Should this patient be considered for fenofibrate therapy?



▲ Forty-one-year-old African-American man with type 2 diabetes (T2DM) x 12 years, HbA1c = 7.2 per cent, BP = 135/86, BMI = 38.4 kg/m^2 presenting with new hard exudate 600 microns from the fovea but no CSME

Fenofibrate therapy

From page 23

retinal specialists in the USA and Australia, with several indicating they do or would use fenofibrate mainly in the context of DME requiring laser intervention (interestingly, an application for which there is no randomised controlled trial evidence), whereas others see merit in earlier intervention, especially for patients with reduced vision in one eye. My thoughts about which patients deserve consideration are informed by my review of the available evidence and a commitment to earlier intervention and prevention in patients with significant risk of vision loss, and are summarised in Table 2.

Other strategies

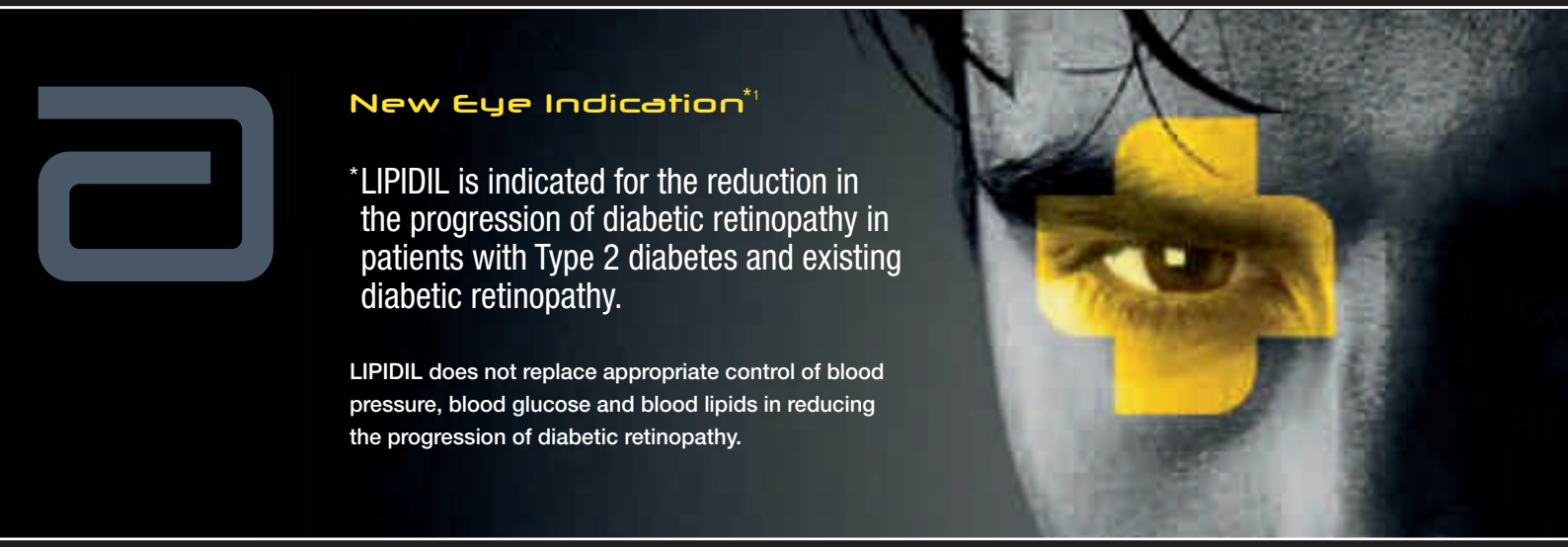
Independently of the strong evidence favouring fenofibrate against DR progression, there is emerging evidence that other novel strategies may prove useful, including blockade of the rennin-angiotensin system with ACE inhibitors and angiotensin receptor blocking (ARB) drugs[15] and micronutrient intervention with molecules like benfotiamine, Pycnogenol and zeaxanthin that block intermediate biochemical pathways linking hyperglycemia to DR.

I am currently conducting a small clinical trial—the Diabetes Visual Function Supplement Study (DiVFuSS - ClinicalTrials.gov Identifier: NCT01646047)—evaluating visual function in diabetes patients with a combination of these molecules. This combination has been shown to normalise retinal structure, metabolism and function in an animal model of the disease.[16] ▲

- ▲ T2DM with moderate NPDR (any retinopathic findings > few microaneurysms)
- ▲ T2DM with mild to moderate NPDR and history of chronic, poor glycaemic control and/or poorly controlled hypertension
- ▲ T2DM with mild to moderate NPDR and poor adherence to treatment/follow-up
- ▲ T2DM with rapid progression of DR based on serial examination
- ▲ T2DM with any DR and amblyopia or reduced visual acuity in one eye
- ▲ T2DM with any DR and first degree relative with severe vision loss from DR
- ▲ T2DM with any DR and obese (6x risk for PDR)
- ▲ T2DM with any DME/hard exudate, especially with increased risk factors for CSME (uncontrolled hypertension or dyslipidaemia, HbA1c > 7 per cent, obstructive sleep apnoea, history of diabetic neuropathy and/or nephropathy, cigarette smoking, African/Latino/Aboriginal ancestry, long disease duration)
- ▲ Type 1 diabetes (T1DM) with any of the above if/when Fenofibrate shown to be effective by RCT in this population

▲ Table 2. Diabetes patients who should be considered for adjunct preventive therapy against DR with fenofibrate

1. Yau JW, Rogers SL, Kawasaki R et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; 35; 3: 556-564. doi: 10.2337/dc11-1909.
2. Aspelund T, Thornórisdóttir O, Olafsdottir E, Gudmundsdottir A, Einarsdóttir AB, Mehlsen J, Einarsson S, Pálsson O, Einarsson G, Bek T, Stefánsson E. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. *Diabetologia* 2011; 54: 10: 2525-2532.
3. Gitt AK, Schmieder RE, Duetting E, Bramlage P, Schneider S, Tschöpe D; DIALOGUE Study Group. Achievement of recommended glucose and blood pressure targets in patients with type 2 diabetes and hypertension in clinical practice - study rationale and protocol of DIALOGUE. *Cardiovasc Diabetol* 2012; 11: 148.
4. Keech AC, Mitchell P, Summanen PA et al. FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; 370: 9600: 1687-1697.
5. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010; 363: 3: 233-244.
6. ACCORD Study Group; ACCORD Eye Study Group. Chew EY, Ambrosius WT, Davis MD, Danis RP et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010; 363: 233-244.
7. Kim J, Ahn JH, Kim JH, Yu YS, Kim HS, Ha J et al. Fenofibrate regulates retinal endothelial cell survival through the AMPK signal transduction pathway. *Exp Eye Res* 2007; 84: 886-893.
8. Okayasu T, Tomizawa A, Suzuki K, Manaka K, Hattori Y. PPARalpha activators upregulate eNOS activity and inhibit cytokine-induced NF-kappaB activation through AMP-activated protein kinase activation. *Life Sci* 2008; 82: 884-891.
9. Bordet R, Ouk T, Petrault O, Gelé P, Gautier S, Laprais M et al. PPAR: A new pharmacological target for neuroprotection in stroke and neurodegenerative diseases. *Biochem Soc Trans* 2006; 34: 1341-1346.
10. Trudeau K, Roy S, Guo W, Hernández C, Villarroel M, Simó R et al. Fenofibric acid reduces fibronectin and collagen type IV overexpression in human retinal pigment epithelial cells grown in conditions mimicking the diabetic milieu: Functional implications in retinal permeability. *Invest Ophthalmol Vis Sci* 2011; 52: 6348-6354.
11. Meissner M, Stein M, Urbich C et al. PPARalpha activators inhibit vascular endothelial growth factor receptor-2 expression by repressing Sp1-dependent DNA binding and transactivation. *Circ Res* 2004; 94: 324-332.
12. Accessed at http://www.drugs.com/pro/Fenofibrate.html, March 29, 2014.
13. Kota SK, Meher LK, Rao ES, Jammula S, Modi KD. Efficacy and safety of statin and fibrate combination therapy in lipid management. *Diabetes Metab Syndr* 2012; 6: 3: 173-174. doi: 10.1016/j.dsx.2012.09.009. Epub 2012 Oct 18.
14. Egan AG, Blind E, Dunder K et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med* 2014; 370: 794-797.
15. Sjølie AK, Dodson P, Hobbs FR. Does renin-angiotensin system blockade have a role in preventing diabetic retinopathy? A clinical review. *Int J Clin Pract* 2011; 65: 2: 148-153.
16. Kowluru RA, Zhong Q, Santos JM, Thandampallayam M, Putt D, Gierhart DL. Beneficial effects of the nutritional supplements on the development of diabetic retinopathy. *Nutr Metab* (Lond) 2014; 11: 1: 8.



New Eye Indication*[1]

*LIPIDIL is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy.

LIPIDIL does not replace appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.

In addition

LIPIDIL is indicated as an adjunct to diet in the treatment of:[1]

- Dyslipidaemia associated with Type 2 diabetes
- Types II, III, IV and V dyslipidaemia
- Hypercholesterolaemia

LIPIDIL® fenofibrate 145mg

PBS Information: Restricted Benefit. For use in patients that meet the criteria set out in the General Statement for Lipid-Lowering Drugs. Not listed for the treatment of diabetic retinopathy.

Please review the full Product Information (PI) before prescribing. Full PI available on request from Abbott Australasia by calling 1800 225 311 or at: www.medicines.org.au/files/abplipid.pdf

Lipidil® (fenofibrate): 145 mg tablets, 30's; 48 mg tablets, 60's. **Indications:** Adjunct to diet in the treatment of hypercholesterolaemia, types II, III, IV and V dyslipidaemia, dyslipidaemia associated with Type 2 diabetes. Reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes.* Does not replace appropriate control of blood pressure, blood glucose and blood lipids. **Dosage:** Dyslipidaemia and Diabetic Retinopathy: 145 mg tablet to be taken with or without food. Consider dose of 48 mg in patients with renal impairment (CrCl<60ml/min). **Contraindications:** Children; liver dysfunction; severe renal dysfunction; existing gallbladder disease; coadministration with another fibrate; hypersensitivity to fibrates or ketoprofen; chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia. **Precautions:** Attempt diet and lifestyle modifications before initiating therapy for dyslipidaemia; effect on CHD mortality/morbidity not established*; renal impairment; may increase LFT; hepatic impairment, cholelithiasis; pregnancy and lactation; drugs exacerbating hypertriglyceridaemia (oestrogen, b-blocker, thiazides); fructose and/or galactose intolerance (including, Lapp lactase deficiency or galactose malabsorption); lecithin or related product allergy. **Interactions:** Oral anti-coagulants; HMG-CoA reductase inhibitors (risk of muscle toxicity is increased if used concurrently); other fibrates; cyclosporine (monitor renal function); phenylbutazone; drugs metabolized by cytochrome P450 isoenzymes CYP2C19, CYP2A6, and CYP2C9. **Adverse Effects:** GI disorders; skin reactions (including rash and photosensitivity); raised LFT; increase in serum creatinine; pancreatitis; gallstones; thromboembolism; muscle toxicity and rarely rhabdomyolysis.

*Please note changes in Product Information.

References: 1. Lipidil Approved Product Information. Lipidil® is a registered trademark of Abbott Australasia, 32–34 Lord St, Botany NSW 2019. Free call: 1800 225 311. Date prepared: November 2013. AU-LIP-2013-91c

Abbott
A Promise for Life

FOR wAMD†

20/200

20/100

20/70

20/50

20/40

20/30

20/25

20/20

ONE INJECTION EVERY TWO MONTHS*

***EYLEA® wAMD† TREATMENT IS INITIATED WITH ONE INJECTION PER MONTH FOR THREE CONSECUTIVE MONTHS, FOLLOWED BY ONE INJECTION EVERY TWO MONTHS[1]**

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Required information for wet AMD. EYLEA is not PBS listed for CRVO.

BEFORE PRESCRIBING, PLEASE REVIEW FULL PRODUCT INFORMATION AVAILABLE ON REQUEST FROM BAYER AUSTRALIA LTD, ABN 22 000 138 714, 875 PACIFIC HIGHWAY, PYMBLE, NSW 2073 or go to www.ebs.tga.gov.au

MINIMUM PRODUCT INFORMATION EYLEA® [aflibercept (rch)] INDICATIONS: EYLEA (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wet AMD); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*. **DOSAGE AND ADMINISTRATION:** Injection volume of 50µL EYLEA (equivalent to 2mg aflibercept). For wet AMD: Treatment is initiated with one intravitreal injection per month for three consecutive months, followed by one injection every two months. For CRVO*: Treatment is initiated with one intravitreal injection per month. After the first three monthly injections, the treatment interval may be extended based on visual and anatomic outcomes. The treatment between doses should not be shorter than one month. Monitoring should be done at the injection visits. During treatment interval extension, the monitoring should be determined by the treating physician based on the individual patient's response. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; arterial thromboembolic events*; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: conjunctival haemorrhage, eye pain. Common: retinal pigment epithelium tear, detachment of retinal pigment epithelium, cataract, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, corneal oedema, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, conjunctival hyperaemia, ocular hyperaemia. Others: see full Product Information. Date of most recent amendment: November 2013

*Please note changes in Product Information.

Reference: 1. EYLEA Product Information. †wAMD = Wet age-related macular degeneration

EYL034 L.AU.SM.12.2013.0263

EYLEA®
aflibercept (rch)
solution for intravitreal injection