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Diabetic Retinopathy

New guidelines for referral and appropriate care

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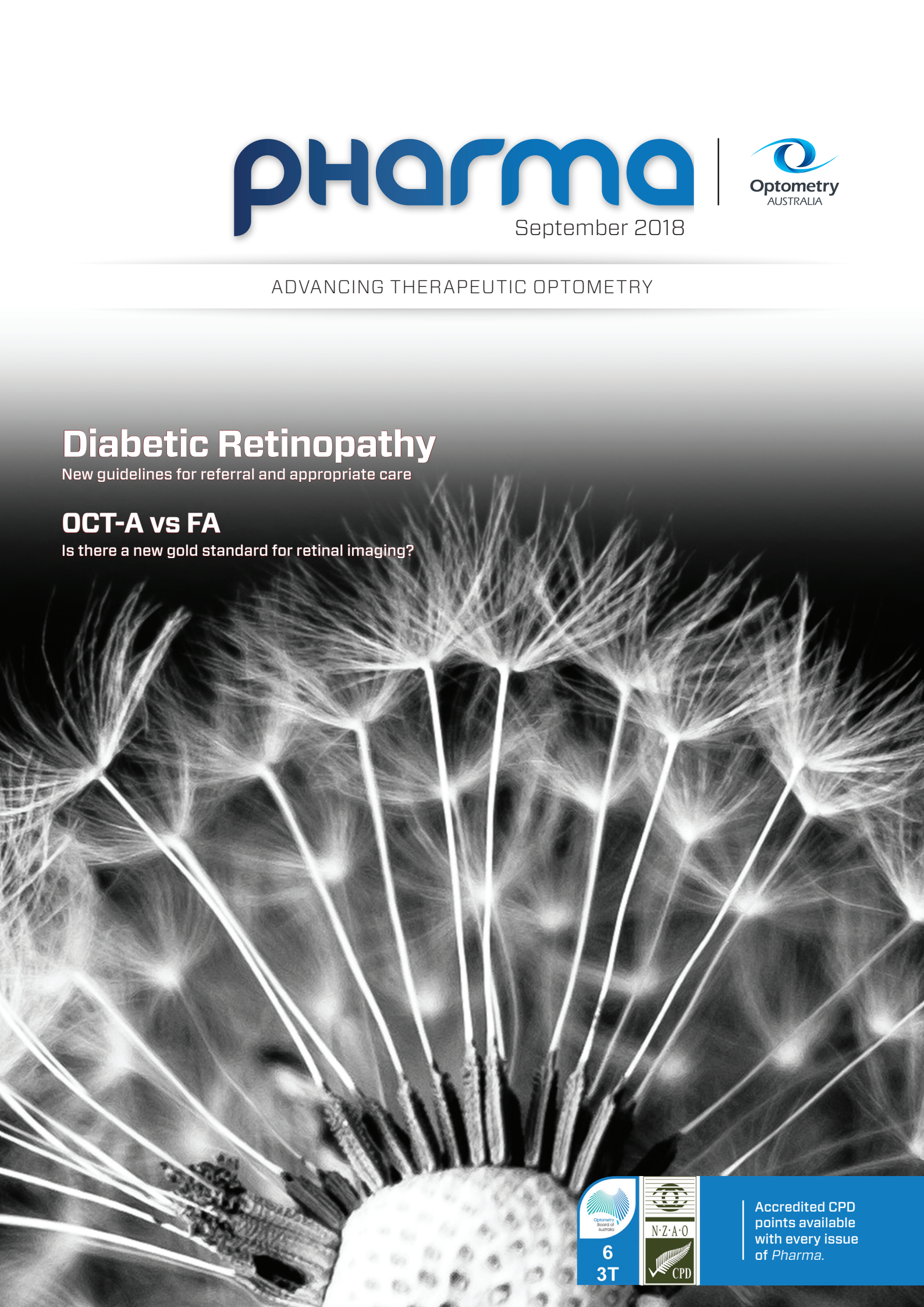

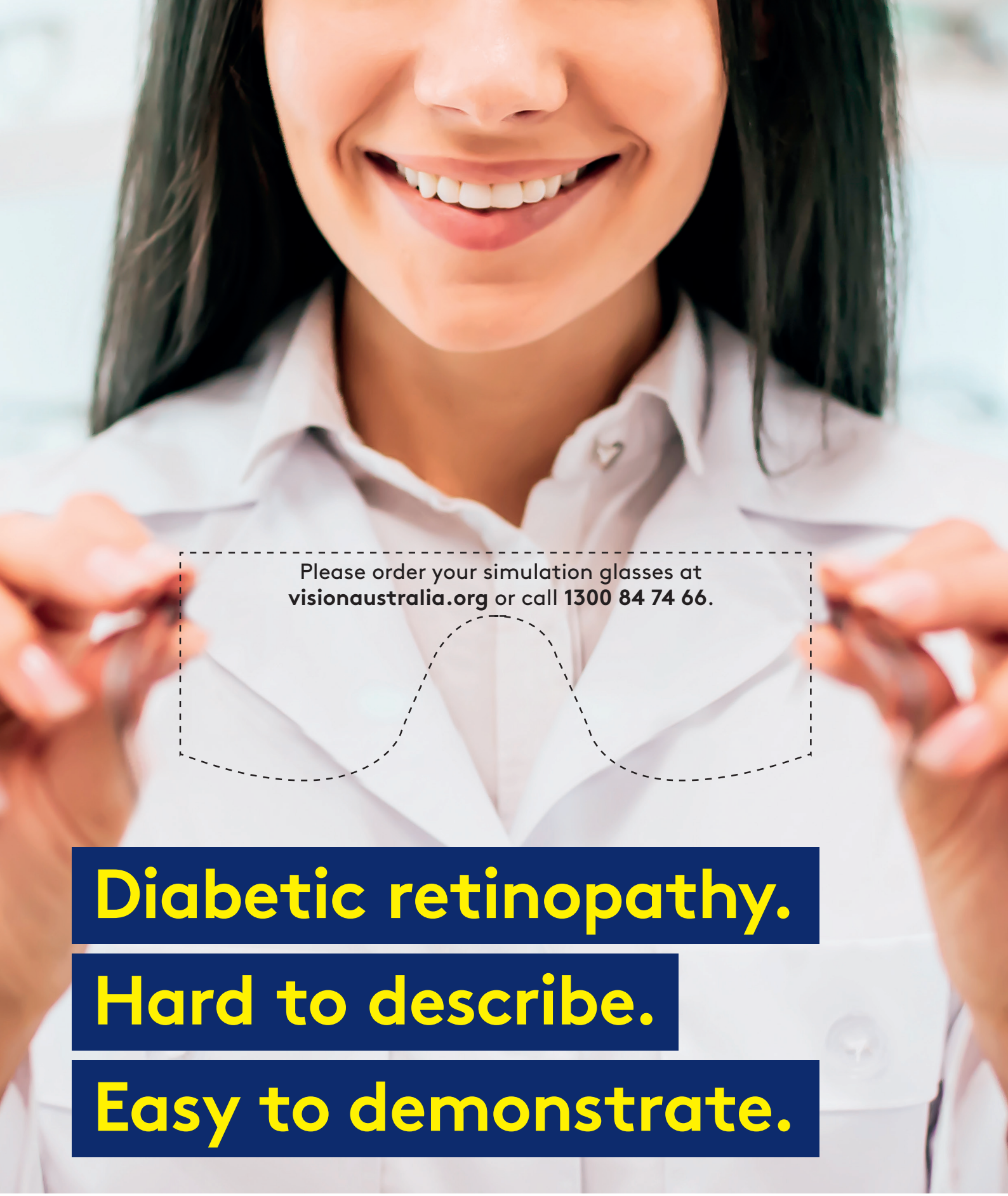

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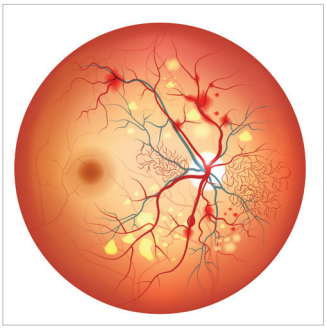

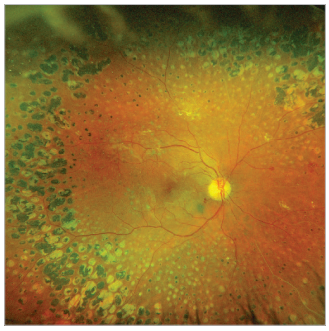

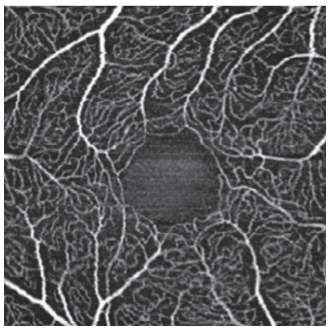

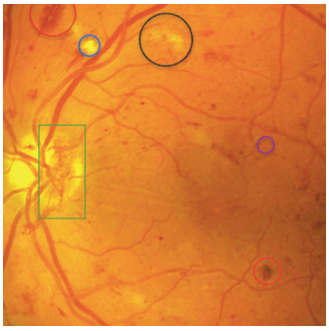

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Optometry Australia revises

Recommendations on the assessment,

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BOptom

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The Optometry Australia Diabetes Guidelines Working Group

Diabetes is the fastest growing chronic condition in Australia. As of 2017, around 1.7 million Australians have diabetes. This includes all types of diagnosed diabetes (1.2 million known and registered) as well as silent, undiagnosed type 2 diabetes (up to 500,000 estimated).[1]

Each patient is different; each presents with their own combination of factors that can increase their risk of developing diabetic retinopathy. A large percentage of people with type 1 diabetes and more than 60 per cent of those with type 2 diabetes will develop some form of diabetic eye disease within 20 years of diagnosis.[3] The 2016 National Eye Health Survey found that 90 per cent of vision impairment in Australia is preventable if detected and treated early enough.[4] This highlights the critical role of optometrists in optimising eye health outcomes for many patients. Not only can optometrists increase patient awareness, facilitate early detection and assist in the management of diabetes, optometrists may detect signs of diabetic retinopathy in those previously undiagnosed with diabetes, enabling holistic health management to commence.

Optometry Australia's *Clinical guidelines for the examination and management of patients with diabetes* provides concise guidance and a convenient point of reference for optometrists. It has been four years since the guidelines were developed, but even in that short time span, there have been advances in imaging technology and treatment regimens for diabetes and diabetic retinopathy. The Optometry Australia Diabetes Guidelines Working Group has revised and updated the guidelines to ensure they accord with contemporary best practice.

WHAT'S NEW

GP referral and fenofibrate recommendation

General practitioners are often central in the diabetic patient's health care team, and require a complete picture of patient health to optimise health care. Through the revised guidelines, Optometry Australia reiterates the importance of informing the patient's GP of the outcomes of their eye examination. Correspondence with the referring GP should include visual acuities; whether a dilated ocular fundus exam was performed; whether there is presence of retinopathy, and if so, its classification; and the next recommended eye examination. Optometrists may also like to suggest to the GP (based on the patient's medical history and risk factors), that they consider fenofibrate as one option to slow progression of diabetic retinopathy.

Frequency of examination

Optometry Australia's recommendation on the frequency of examinations aligns with recommendations from the National Health and Medical Research Council

Patient classifications	Frequency of examination
All patients with diabetes (T1DM or T2DM)	At diagnosis and two yearly thereafter. Annually for higher-risk patients: Aboriginal and Torres Strait Islander patients, longer duration of diabetes, poor glycaemic control, blood pressure or blood lipid control.[2] For children with pre-pubescent type 1 diabetes, Optometry Australia advises introducing eye examinations early in the course of diabetes, to assess patient's ocular fundus, measure baseline VA and perform other tests appropriate for child's age and stage of development. Otherwise, children with pre-pubertal diabetes should undergo annual examinations from puberty.
Patients with non-proliferative diabetic retinopathy (NPDR) Mild NPDR	Depending on level of DR present, 6–12 monthly or annually • Mild NPDR without diabetic macular oedema: 6–12 months. • Mild NPDR with diabetic macular oedema: ophthalmology referral — see Table 2.
Moderate non-proliferative diabetic retinopathy (NPDR)	• Moderate NPDR without diabetic macular oedema: 3–6 monthly or referral if at high risk of progression. • Moderate NPDR with diabetic macular oedema: ophthalmology referral — see Table 2.
Pregnant women with diabetes	Pregnancy in females with T1DM or T2DM may accelerate the development and progression of DR. Hence, women with diabetes who become pregnant should: • have a comprehensive eye exam prior to conception if planning pregnancy • have a comprehensive eye examination in the first trimester • base the frequency of examinations during the pregnancy on first trimester exam results and blood glucose control during pregnancy • have a comprehensive eye exam 6–12 weeks post-partum
Women with gestational diabetes	Women with gestational diabetes do not need ophthalmic surveillance during or after pregnancy, unless diabetes persists.

Table 1. Recommended frequency of eye examinations according to patient classifications[4]

guidelines for diabetic retinopathy

monitoring and referral of patients with diabetes

that if diabetic retinopathy is not present and the patient isn't at high risk,* then a two yearly review is recommended.

Classification of diabetic retinopathy

In the past, the modified Airlie House Classification (previously known as the 'Wisconsin system') was recommended as the basis for detailed grading of diabetic retinopathy. To simplify classification of DR and to standardise communication between heath care providers, Optometry Australia now recommends that the International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scales are used.

Table 2 offers an overview of the five clinical levels of DR and two broad levels of DMO; now recommended.

WHAT'S NEXT

Low vision referral pathways

Where an optometrist encounters a patient with advanced stages of diabetic retinopathy, a referral to blindness and low vision support providers may be appropriate.

Optometry Australia is collaborating with Vision 2020 Australia in developing a referral pathway for low vision patients to help ensure people with low vision access care to support best visual outcomes and support to maximise independence.

Holistic patient care

When a patient advises they have diabetes, the patient needs to be reviewed holistically. Optometrists should look at educating the patient around their condition, including by asking if they are working with their health care team to support effective chronic disease management and if they have connected with peak bodies like Diabetes Australia, who can offer them more information about their condition. It is useful for patients to learn how the management of their diabetes can effect their eye health and vision. Download *Clinical guidelines for examining and managing patients with diabetes* from the Optometry Australia website: www.optometry.org.au/for-optometrists/guidelines/

*For Aboriginal and Torres Strait Islander people in whom no diabetic retinopathy is present, annual eye examinations are recommended in respect of the significantly increased risk of diabetes. ▲

Continued page 4

Retinopathy stage	Findings on ophthalmoscopy	Management and review/referral time frame**
No apparent retinopathy	No abnormalities	In line with NHMRC guidelines, recommend 2 yearly reviews. High risk patients to be seen annually: hypertension, poor HbA1c, long duration of diabetes, Indigenous status, non-compliance to follow-up.
Mild non-proliferative diabetic retinopathy (NPDR)	Microaneurysms (MA) only	Review 6–12 months taking into consideration proximity of MA to fovea.
Moderate non-proliferative diabetic retinopathy (NPDR)	More than just MA but less than severe NPDR. This may include: • dot haemorrhages • blot haemorrhages • cotton wool spots • intraretinal microvascular anomalies (e.g. venous beading)	Refer or closely monitor.† Depending on level of DR present, 3-6 monthly or annually (see Table 1). Communicate level of DR to the GP and endocrinologist and mention the possible benefits of fenofibrate in slowing DR progression for high risk patients with mild or moderate DR.
Severe non-proliferative diabetic retinopathy (NPDR)	Any of the following: • more than 20 intraretinal haemorrhages in each of 4 quadrants • definite venous beading in 2+ quadrants • prominent IrMA in 1+ quadrant AND no signs of proliferative retinopathy.	Ophthalmology referral.**
Proliferative diabetic retinopathy (PDR)	One of the following (or unexplained fall in visual acuity): • neovascularisation • vitreous/pre-retinal haemorrhage	Urgent ophthalmology referral (days – weeks).**
Macula oedema		
Absent	No retinal thickening or hard exudates (HEx) in posterior pole	Follow-up or need to refer should be based on the level of NPDR or DR (Table 1).
Present	Mild – some retinal thickening or HEx in posterior pole but distant from the macula Moderate – retinal thickening or HEx approaching the centre of the macula but not involving the centre Severe – retinal thickening or hard exudates involving the fovea	Ophthalmology referral and management (within 4 weeks for HEx within 1DD of fovea)**
Unexplained vision loss		Ophthalmology referral and management. In the first instance, OCT, OCT-A may be useful to rule out diabetic macular oedema or macular ischaemia.

Table 2. International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scales and recommended referral patterns.[5]

† Optometry Australia advises optometrists practice within their scope and note NHMRC guidelines state only that 'Patients with any level of DME, severe NPDR or any PDR require prompt care from an ophthalmologist experienced in DR management. Referral is also needed if there is any unexplained loss of vision, or if a screening examination cannot be performed.'

**Optometry Australia recommends that optometrists communicate with ophthalmologists to determine their preferred referral time lines to prevent vision loss.

DR guidelines

From page 3

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Procedure	Comments
Visual acuity (with correction)	Distance and Near, monocularly, including pinhole acuity if indicated
Pupil reactions	Direct/Consensual and Near pupillary responses
Ocular motility and cover test	Extent, fluency and symmetry of ocular movements in all directions of gaze, ruling out eye movement anomalies. Relevant history taking regarding the onset and direction of diplopia is necessary. If diplopia is manifest, cover test and prism neutralisation is also indicated.
Visual field screening	• Confrontation • Note: visual field screening and baseline testing in the absence of actual or suspected pathology of the visual pathways or brain will not attract a Medicare rebate for item 10940 or 10941.
Refraction	• On indication • Where patient reports a change in vision or visual function (e.g. increased glare sensitivity) or where a change in habitual visual acuity is measured.
Slitlamp biomicroscopy	• Recommended at every visit • Examination for iris neovascularisation (NVI), diabetic cataract, corneal integrity
Tonometry	Pre-dilation; post-dilation as indicated
Stereoscopic fundus examination with pupil dilation	• NHMRC guidelines describe pupil dilation using 0.5 to 1.0% tropicamide as safe (noting dilated ocular fundus examination increases the sensitivity of DR screening) and so consider it mandatory in performing ophthalmoscopy or slitlamp biomicroscopy[4] unless contraindicated by the presence of potentially occludable anterior chamber angles. • Gonioscopy may be necessary to evaluate whether narrow angles are potentially occludable. Where potentially occludable angles are detected, the patient should be referred to an ophthalmologist for an opinion on management e.g. suitability for PI. • People with diabetes can show a poor response to mydriatic agents. 2.5% phenylephrine hydrochloride, unless contraindicated, may help achieve maximum pupillary dilation in patients with DM, particularly those of Aboriginal and Torres Strait Islander descent and patients with heavy iris pigmentation. • Optometry Australia pupil dilation guidelines can be viewed at http://www.optometry.org.au/media/274917/clinical_guideline_pupil_dilation_v2_02.03.16.pdf. • Symptoms of VA reduction or distortion of vision or a significant change of DM control should always prompt dilated pupil examination.

Table 3. Recommended examination procedures for examining patients with diabetes

The members of the Optometry Australia Diabetes Guidelines Working Group: Paula Katalinic, Centre for Eye Health; Roman Serebrianik, Australian College of Optometry; Dr Josephine Li, Australian College of Optometry; David Pye, UNSW Faculty of Science; Lisa Penrose, Eye Health Consultant.

Pharmacology: systemic treatment for ocular disease

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With the wide availability of eye drops, gels, ointments and injections, one would rightly wonder what role—if any—systemic medications have in the management of diseases of the eye. Additionally, due to both the blood-aqueous and blood-retinal barriers, it is difficult for systemically-administered substances to accumulate appreciably in the eye without high systemic doses, which increases the potential for side effects. However, even with these limitations, systemic oral therapy does have a role in ocular disease management and it is important for optometrists to be aware of this mode of administration as a potential treatment option.

Not all structures within the eye can be effectively reached with just topical application. The deeper ocular adnexal structures, for example, typically do not respond to externally-applied therapies. In addition, not all drugs are available commercially as ophthalmic preparations. Hence, alternative modes of drug administration must be considered if the financial and time costs of compounding are to be avoided.

Clinical workup

The clinical workup of a patient considered for oral therapy is not substantially different to that for topical therapy, but with a greater emphasis on investigations into overall systemic health. Clinicians should be mindful and probing in their patient's case history prior to prescribing oral therapies, particularly into any prior history of hypersensitivity or adverse reactions to medications, both in general and for the specific drug under consideration.

A thorough understanding of the drug's pharmacological actions and potential side effects needs to be considered and discussed with the patient and their general practitioner, particularly if the drugs have potential impact on other organs or functions within the body.

The systemic health of the patient should be carefully reviewed as not only does this impact the effectiveness of therapy but also the risk for adverse drug reactions.[1] The health of the gastrointestinal, circulatory, hepatic, pulmonary and renal systems are of particular interest, as these systems greatly impact oral drug absorption, distribution, metabolism and eventual excretion.[1] Decreases or changes in the function of these critical body systems do not necessarily preclude systemic therapy, but they do suggest the need for additional clinical vigilance in monitoring and discussion of potential adverse effects with the patient and the rest of the health care team to ensure safe medication use.

Legislative aspects of oral drug prescribing by optometrists

In some areas of the world, including Canada, the United States and New Zealand, oral prescribing of medications is available on optometric prescriptions, including provisions up to narcotic analgesic drugs in some states within the US.

While oral prescribing is not currently possible by therapeutically-endorsed optometrists in Australia, knowledge of the clinical indications for oral therapy and available treatments allows for more effective and efficient co-management.[2] In many instances, this will involve liaising with the patient's primary care provider, where the optometrist's skill and expertise in diagnosing and examining the eye is a particularly useful asset.

Over-the-counter oral medications for ocular conditions

There are several over-the-counter oral medications which can be recommended by optometrists to patients to manage ocular conditions.

These drugs generally are classified as Schedule 2 or 3 poisons in Australia, meaning that, while they have to be obtained from a pharmacy or in consultation with a pharmacist, they do not require a written prescription.

Systemic antihistamines and ocular allergy

Management of ocular allergy usually involves topical antihistamines, mast cell stabilisers or combination agents. Whether to include oral antihistamine preparations as part of management is based on the severity of the ocular presentation as well as the degree to which other organ systems such as the nose, skin, mouth, throat and lungs are also affected.

Oral antihistamines are generally classified based on their 'generation' of release. The first generation of antihistamines, including diphenhydramine hydrochloride (marketed as Benadryl and others), are known as the 'sedating' or 'drowsy' antihistamines.[3] The ability of these agents to affect consciousness is due to their ability to cross past the blood-brain barrier, affecting the action of central histamine receptors resulting in sleepiness symptoms.[3]

Later generation antihistamines such as cetirizine, loratadine and fexofenadine have been extensively modified to be less likely to cross the blood brain barrier and so have been marketed as 'non-drowsy,' less sedating formulations. It should be noted, however, that these later generation agents can still cause drowsiness if taken at doses exceeding over-the-counter recommendations.

With only minimal increases in managing allergy symptoms compared to later generations, use of first generation, sedating antihistamines are generally discouraged for routine use.[3] A typical dosing of the less-sedating antihistamines to manage allergy

Continued page 6

Ocular therapy

From page 5

symptoms is one tablet a day (10 mg cetirizine or 120 mg fexofenadine).[3] Some formulations for children are also available at lower dosages.

Due to the fact that antihistamines all have some level of antimuscarinic activity, they can potentially impair exocrine secretions and cause dry eyes and dry mouth.[3] If oral antihistamines are necessary, additional dry eye interventions may be necessary and patients should be forewarned of this possibility.

Management of ocular pain and inflammation

Some of the most commonly-used drugs for the management of mild-to-moderate pain are available over the counter. Management of pain associated with ocular conditions ranging from corneal abrasions, refractive surgery and ocular surface infection can all be effectively managed using available over-the-counter analgesics. The two main classes of analgesic agents available over the counter are paracetamol and the non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol is the most commonly-prescribed analgesic in Australia. Paracetamol exerts both analgesic and antipyretic (fever reducing) actions through an unknown, presumed centrally-acting, mechanism.[4] Despite its ubiquity, paracetamol should be used with caution due to its significant liver toxicity. Overdose of paracetamol is the most common cause of acute liver failure reported in the United States.[5] In Australia, the recommended maximum daily dose is 4000 mg, which should be lowered further in cases of pre-existing liver disease.[3]

The risk of overdose is amplified when one considers that paracetamol is a component in many available formulations, some of which are not specifically marketed for pain relief. Over-the-counter cough, cold and flu medicines often contain paracetamol and the agent is also often a component in stronger prescription analgesic formulations. Thus, patients should be counselled to carefully read the labels of all medications for inclusion of paracetamol to ensure that they do not exceed the daily maximum dose from all sources combined.

Over-the-counter NSAIDs such as ibuprofen, naproxen and diclofenac are also commonly used to manage pain and are particularly effective in the management of pain associated with inflammation. NSAIDs other than aspirin generally have a wider safety profile in comparison to paracetamol when used short term as directed and are much less likely than aspirin to cause gastrointestinal bleeding or issues with blood clotting.[6]

However, despite their ubiquity, recent population-based studies have indicated that all NSAIDs may, to some degree, increase adverse cardiovascular events such as myocardial infarction or stroke, particularly if there are pre-existing cardiovascular risk factors. Patients should be informed of these risks if NSAIDs are to be used chronically or at higher doses than recommended over the counter.[7]

Due to their anti-inflammatory effects, over-the-counter oral NSAIDs can also have a role in the management of ocular inflammation. Episcleritis, inflammation of the superficial episcleral tissue, has been found to be somewhat responsive to oral NSAIDs, particularly if topical anti-inflammatory management has failed or when there is also a systemic association.[8] Doses of 250–500 mg naproxen twice daily or 200–600 mg ibuprofen four times a day have been reported to be effective, but the response does appear to be variable between patients and NSAIDs.[8] Not all of these doses for episcleritis may be available over the counter or they may exceed the recommended over the counter daily dose, so liaising with the patient's primary care provider may be necessary.

PRESCRIPTION ORAL MEDICATIONS FOR ACUTE OCULAR CONDITIONS

Ocular bacterial infections

Bacterial infections of the lids and adnexae, including internal hordeola, preseptal cellulitis and dacryocystitis, are usually treated with oral therapy. Topical therapies are ineffective.

Empirical therapy of these infections generally assumes they are caused by Gram-positive bacterial species, leading to management with agents within the penicillin or cephalosporin antibiotic classes.[3]

Amoxicillin in combination with clavulanic acid is resistant to bacterial-produced penicillinase and is an excellent choice in managing these conditions. The dosage schedules of these drugs are between 500 to 875 mg, four times a day for five to seven days.[3] The formulation is generally considered to be safe for use in pregnancy and with children, with some modification to dose depending on the weight of the child.

Alternatively, cephalosporins such as cephalexin are also commonly used, with a recommended dosage of 250 to 500 mg four times a day for five to seven days deemed effective and also safe for children and during pregnancy.[3] If patients are prescribed these classes of drugs, they should be counselled on the potential for common adverse reactions including nausea and diarrhoea, which may be construed by some patients as a penicillin allergy which would contraindicate use.[9] The incidence of true penicillin hypersensitivity is thought to be rare, and patients who report a previous penicillin allergy should be questioned carefully to delineate whether symptoms of a true hypersensitivity reaction were experienced (including urticaria, angioedema, vasoconstriction) or whether an expected, common adverse effect was experienced.[10]

Ocular manifestations of systemic infections are also an indication for systemic therapy. Adult inclusion conjunctivitis, a recurrent or chronic bacterial conjunctivitis caused by the sexually-transmitted serotypes of chlamydia, will need oral therapy as definitive treatment; a one-time dose of 1000 mg of azithromycin is the current treatment regimen.[3]

Azithromycin is a macrolide antibiotic, and its long half-life due to tissue uptake allows for this simple, single administration to be effective in managing this condition. Other manifestations of systemic infection in the eye, such as tuberculosis and syphilis uveitis will also require systemic therapy for ultimate management.

Ocular herpetic disease

Antivirals in eye care primarily centre on the management of herpetic disease, including herpes simplex and herpes zoster. While topical formulations are available and useful in herpes

simplex associated epithelial disease, presentations of stromal or endothelial herpes simplex and herpes zoster ophthalmicus (HZO) are best managed with oral therapy.[11]

Paradoxically, since the introduction of the varicella zoster vaccine as a universal childhood vaccination in Australia in 2005, the incidence of shingles in the elderly has been increasing in the country.[12]

consciousness and delirium.[13] In situations of renal impairment, aciclovir dosage should thus be titrated based on kidney function measured by creatinine clearance rate in conjunction with the patient's primary care provider.

Emergency intraocular pressure management

In cases of markedly elevated intraocular pressure (IOP) such as due to angle closure, immediate IOP-lowering therapy must be instituted to prevent permanent retinal ganglion cell loss. For these clinical scenarios, in addition to topical IOP-lowering therapy, oral acetazolamide, a carbonic anhydrase inhibitor (CAI) is usually prescribed.

Inhibition of the CAI within the ciliary body has a profound effect on decreasing aqueous humour production, lowering IOP. Optometrists are advised as part of the first aid process of emergency acute angle closure to liaise with the patient's medical practitioner to obtain and administer a supply of oral acetazolamide (500 mg) as soon as possible.[2] In these emergency situations, the primary contraindication to acetazolamide use is a previous history of a severe anaphylactic reaction to similar non-antibiotic sulphonamide drugs such as hydrochlorothiazide, a diuretic; or glyburide, a diabetic drug.[14] Importantly, the structure of the sulphonamide antibiotics is sufficiently different as to confer little cross-reactivity to acetazolamide, and thus could be generally considered safe to use for patients with a reported sulphonamide antibiotic allergy history.[14]

Oral antivirals in eye care

Drug	Herpes Simplex (prophylaxis)	Herpes Simplex (active infection management)	Herpes zoster (within 72 hours of rash appearance)
Aciclovir	400 mg 2x a day	400 mg 5x a day	800 mg 5x a day
Valaciclovir	500 mg 1x a day	500 mg 3x a day	1,000 mg 3x a day
Famciclovir	250 mg 1x a day	250 mg 3x a day	500 mg 3x a day

Table 1. Recommended oral dosages of antivirals for manifestations of herpetic eye disease [11]

This increased incidence is thought to be tied to fewer exposures to the virus in the environment in one's lifetime due to the vaccination program, leading to decreased long-term immunity, virus reactivation and shingles presentation.[12] To help preserve immunity, the zoster vaccine is currently recommended for adults in Australia over 60 years of age who have previously not received a dose.

Aciclovir and derivatives such as famciclovir and valaciclovir are guanine analogues activated by viral thymidine kinase enzymes, resulting in selective toxicity to virus-infected cells and impairing viral DNA replication.[11] The recommended dosages for these agents when used for prophylaxis, herpes simplex or herpes zoster infection are found in Table 1.

Inflammatory manifestations of herpes simplex disease such as stromal keratitis or endotheliitis are treated with topical corticosteroids in addition to oral therapy.[11] These antivirals are primarily cleared through the kidneys, so there is a risk of overdose in patients with renal impairment which manifests as a reversible neurotoxicity.[12] Symptoms of aciclovir-associated neurotoxicity include hallucinations, changes in

Conclusion

While topical medications will likely continue to be the most common route of administration prescribed by optometrists for the management of ocular disease, there are clinical scenarios where oral therapy is indicated. Optometrists in Australia should be aware of these treatment avenues to ensure the most appropriate management of their patients. ▲

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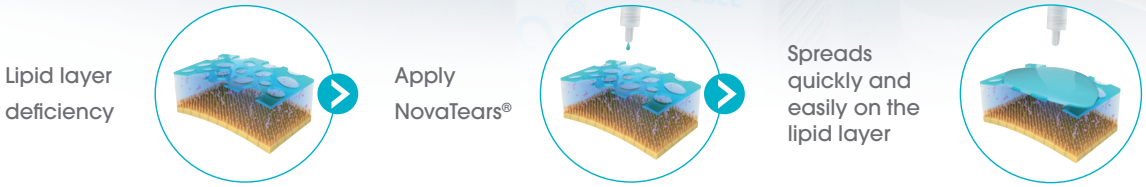

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Ultra-wide field imaging and diabetic retinopathy

Clinical use of UWF to detect, diagnose and monitor retinal changes

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Therapeutic Medicines Prescriber

Diabetes Australia Ambassador

The growing use of ultra-wide field (UWF) imaging to enhance the early diagnosis and management of diabetic retinopathy has been quite evident for several years.[1] Clear correlations between conventional Early Treatment Diabetic Retinopathy Study (ETDRS) seven-standard field colour fundus photographs and UWF images in assessing diabetic retinopathy have been established, where Optomap UWF (Optos) images enable a rapid extended view of the retina and periphery.[2]

When Price et al.[3] compared the diabetic retinopathy severity grading between UWF images and an ETDRS seven-standard field view, it was found that 19 per cent of the images were assigned a higher retinopathy level in the UWF view compared to the ETDRS seven-field view.

The 200-degree field of view of UWF colour imaging enables detection of more anomalies than standard fields of view, allowing for earlier and more accurate assessment of DR severity that could be otherwise missed.[4,5] This was also confirmed by Aiello et al. who stated as much as a third of lesions are found outside the field of view of ETDRS.[6] These lesions included peripheral microaneurysms, neovascularisation, vascular nonperfusion and vascular leakages.

CASE REPORT

A 39-year-old male with type 1 diabetes for 33 years presented to the clinic after noticing a brown-like lesion obscuring his left eye's vision for over 48 hours. On history taking, it was noted his last HbA1c was 8.2 per cent and has been in this range for the last two years. Prior, his HbA1c had been between 11 and 12 per cent.

Current medications included the insulin pump (Humalog) and self-ceased atorvastatin for cholesterol. The patient also disclosed that he had minimal peripheral retinal photocoagulation some years ago.

On examination, best corrected visual acuity was recorded as OD 6/9, OS 6/9, OU 6/9. On ultra-wide field imaging, the following was noted:

OD (Figure 1)

- Proliferative diabetic retinopathy
- Neovascularisation at the disc (NVD)
- Neovascularisation elsewhere (NVE)
- Intraretinal microvascular abnormality (IrMA)
- Spot and blot haemorrhages
- Extensive long-standing pan retinal photocoagulation (PRP) scars
- Scattered exudates

OS (Figures 2 and 3)

- Proliferative diabetic retinopathy
- Inferior vitreal haemorrhage
- Inferior and superior scar tissue
- Extensive NVD
- Extensive NVE
- IrMA
- Spot and blot haemorrhages
- Long standing PRP scars
- Scattered exudates

Continued page 10

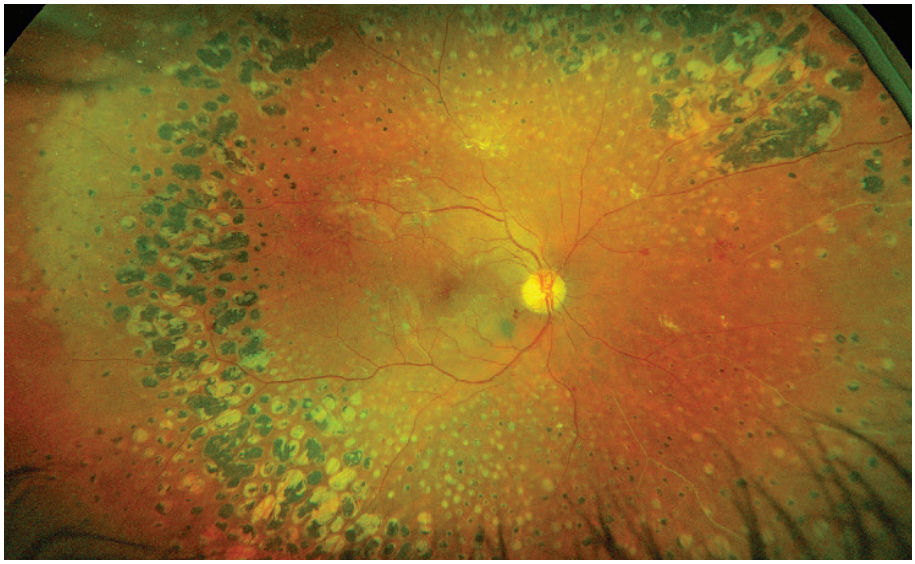

Figure 1. Right eye: extensive pan retinal photocoagulation. Proliferative diabetic retinopathy, VA 6/9.

UWF

From page 9

The patient was referred immediately to a retinal ophthalmologist whereby he underwent PRP. The patient was advised that a follow-up would be required in three weeks and, pending healing, compliance and progression potential vitrectomy may be considered if necessary.

At two weeks post-treatment, UWF imaging was repeated revealing the dissolving of the vitreal haemorrhage and best corrected vision of 6/7.5-2 both right and left eyes respectively (Figures 4 and 5). The patient is still under continual retinal care and treatment.

Discussion

This case demonstrates not only the photo-documentation of diabetic retinopathy, but the extent of retinal treatment history by enabling an extended view into the periphery that otherwise may have been overlooked due to the patient's recollection and version of history and events. It also enabled—and will continue to enable—long term monitoring of progression which will be crucial in deciding the next steps of his treatment plan.

Diabetes mellitus is a subgroup of metabolic diseases characterised by hyperglycaemia resulting from deficiency in insulin secretion and/or action. Pathogenic processes include autoimmune destruction of the beta cells of the pancreas precipitating an absolute deficiency of insulin secretion in type 1 diabetes, and a combination of resistance to insulin action and an inadequate compensatory insulin secretory response in type 2 diabetes.[7]

Symptoms of hyperglycaemia typically include polyuria, polydipsia, weight loss, polyphagia and blurred or fluctuating vision. It is well established that several complications may develop due to the chronic and progressive nature of diabetes where the risk increases with the duration of the condition: poor blood glucose control and poor blood pressure. Complications include peripheral vascular disease, nephropathy, cardiovascular disease and neuropathy including peripheral neuropathy that can, in some cases, lead to limb amputations. One of the most common complications encountered with diabetes is diabetic retinopathy.[8]

Almost all those living with type 1 diabetes and more than 60 per cent with type 2 diabetes will develop some form of diabetic retinopathy within 20 years of diabetes diagnosis.[9]

The Australian Diabetes, Obesity and Lifestyle study (AusDiab) indicated 19.3 per cent of those with diabetes had non-proliferative diabetic retinopathy, 2.1 per cent had proliferative retinopathy and 3.3 per cent had diabetic macular oedema.[10]

Locally in Australia, The Melbourne Vision Impairment Project found 29.1 per cent of those living with diabetes over the age of 40 years developed diabetic eye disease, with 4.2 per cent being proliferative and 5.6 per cent clinically significant macular oedema (CSME). This was also confirmed by The Blue Mountains Eye Study which showed 32.4 per cent of those 49 years and older living with diabetes had diabetic eye disease and 4.3 per cent had CSME.[11]

In contrast, due to limitations in health care and eye care access, Indigenous Australians are four times more likely than non-Indigenous Australians to develop diabetes and hence more likely

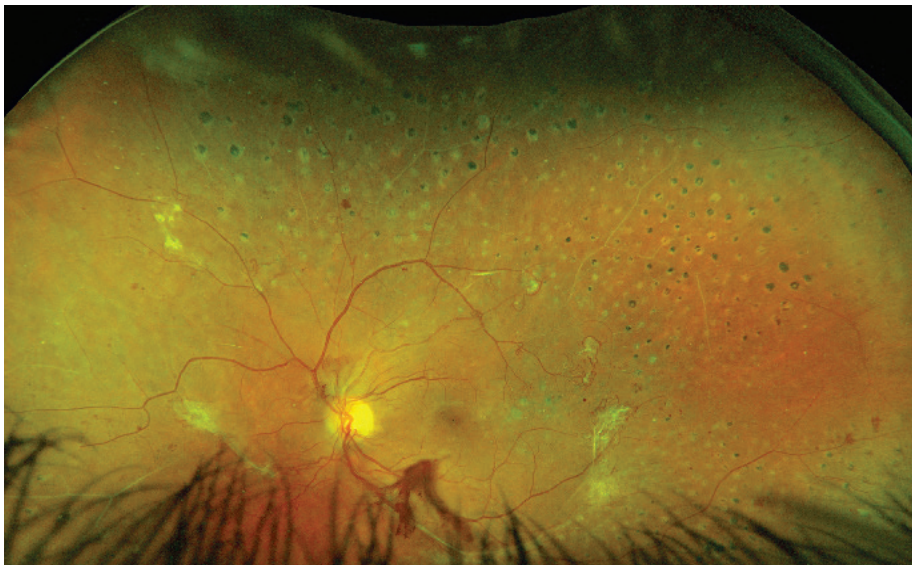

Figure 2. Left eye inferior vitreal haemorrhage, proliferative diabetic retinopathy VA 6/9

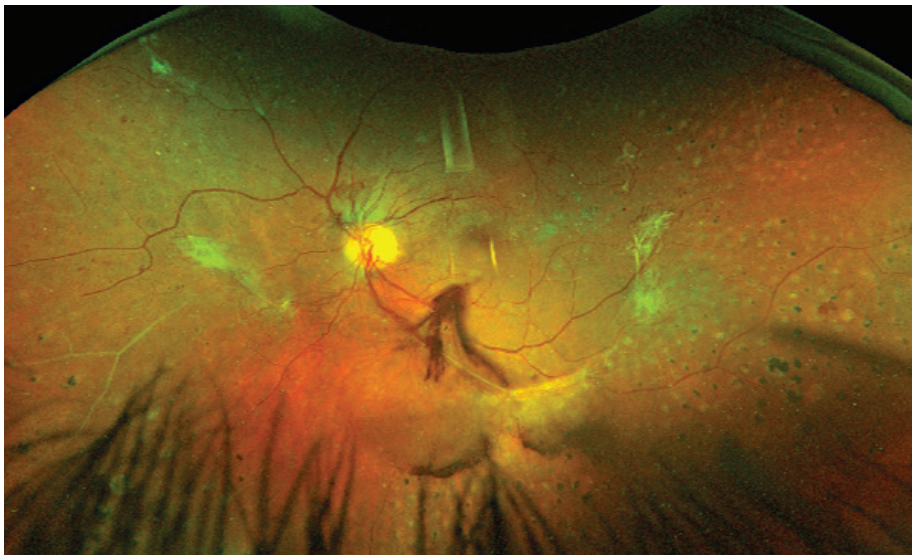

Figure 3. Left eye utilising inferior eye steering feature: vitreal haemorrhage, proliferative diabetic retinopathy. VA 6/9

to develop diabetic eye disease.[12]

Projections

According to the International Diabetes Federation forecast, there will be 552 million people living with diabetes by 2030. Consequently, unless large scale screening initiatives are implemented, half these cases are predicted to remain undiagnosed.[9]

The cost impact of diabetes to the Australian economy by 2033, according to The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) is forecast to be AUD $20 billion.[9]

Silva et al. showed that eyes with predominantly peripheral diabetic retinopathy lesions have over three times increased risk of diabetic retinopathy progression.[6] These eyes also had almost a five times increased risk of progression to proliferative diabetic retinopathy.[6]

Retinal imaging, and in particular UWF imaging, allows practitioners to gain a 'blueprint' of a patient's ocular status at any given moment that can not only be viewed and assessed by several practitioners and specialists, but can also detect change over time while minimising subjective bias.

In a bid to reduce the statistics around the rate of blindness due to diabetic retinopathy and other retinal related conditions, it is essential that extensive, objective analysis, photo-documentation and continual monitoring of the retina and periphery are conducted.

The integration of UWF imaging techniques into the ocular health examination process has enabled—and continues to enable—eye care practitioners to better detect, diagnose and monitor retinal changes which can ultimately mean earlier and better treatment options and outcomes for patients. UWF imaging is a rapidly growing choice of practising optometrists and can potentially redefine the gold standard of eye examinations in the very near future. ▲

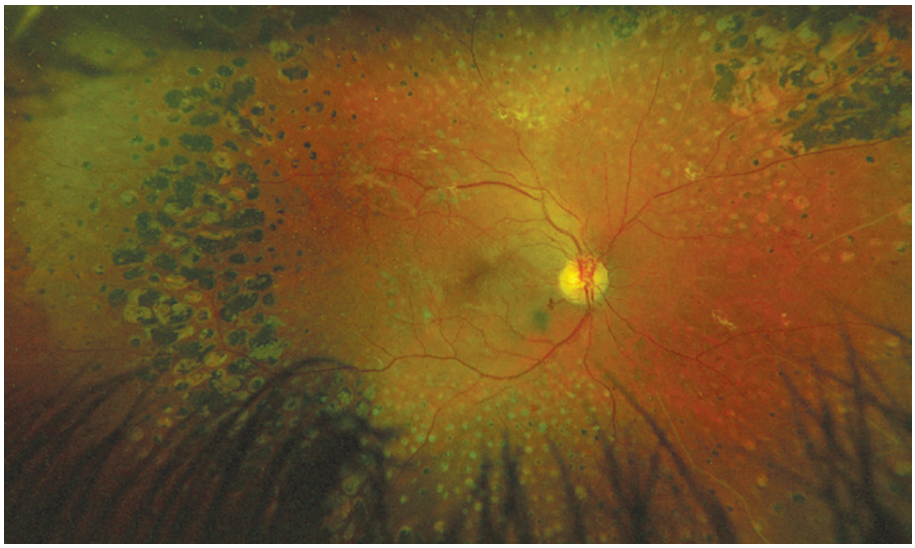

Figure 4. Right eye two weeks post initial UWF, condition unchanged

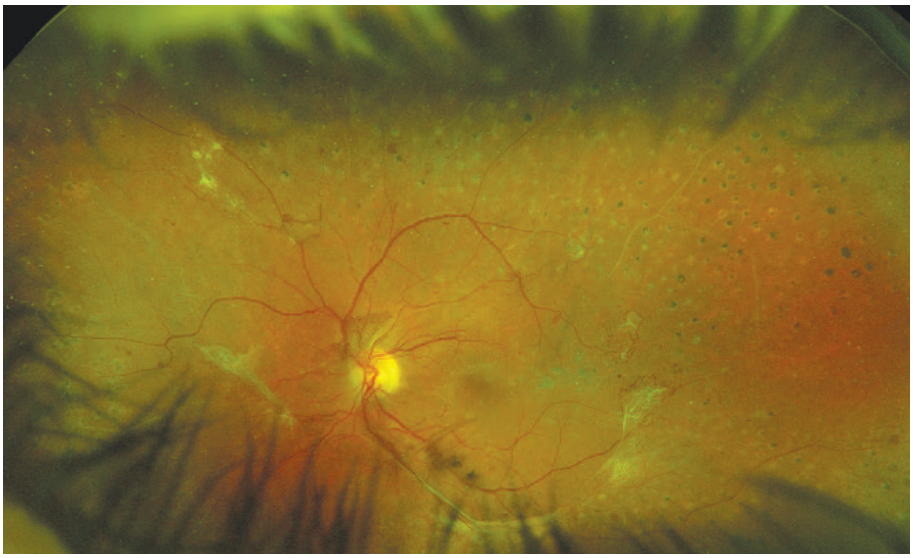

Figure 5. Left eye two weeks post initial UWF, vitreal haemorrhage almost completely self-resolved VA 6/7.5-2

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Treating CSCR with oral eplerenone

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Central serous chorioretinopathy (CSCR) is a common cause of central vision loss, particularly among middle-aged Caucasian males. It is characterised by focal serous detachment of the sensory retina, at the macula. This causes blurred vision, metamorphopsia, micropsia and mild dyschromatopsia in the affected eye.[1]

CSCR has an estimated annual incidence of 1:10,000 and most cases are unilateral.[2] Risk factors for CSCR include hypertension, Type-A personality, psychological stress, Cushing syndrome and use of corticosteroids in any form.[1] CSCR often resolves spontaneously within 3–6 months, although recurrences occur in 50 per cent of cases.[1] Chronic, non-resolving CSCR is associated with retinal atrophy and permanently reduced vision. These changes are also seen with multiple recurrent attacks.

First-line treatment of newly diagnosed CSCR is observation and discontinuation of corticosteroids. All interventions are reserved for chronic, non-resolving or recurrent cases. To date, no treatments for CSCR have been studied in large-scale prospective clinical trials. The most common treatments are focal laser photocoagulation and photodynamic therapy. Other proposed treatments include intravitreal anti-VEGF agents and a number of oral medications.[1] This case study describes a case of non-resolving CSCR where treatment with oral eplerenone was successful and explores some of the literature on this new treatment option.

CASE REPORT

A 53-year-old Caucasian male presented for a routine optometry examination. He had a history of two previous episodes of CSCR in the left eye—both had resolved spontaneously, with a return to normal vision. He reported well-controlled hypertension and denied high levels of stress at home or work. He reported a history of a steroid injection for foot pain, but several years prior. His best-corrected visual acuities (BCVA) were R 6/7.5- and L 6/6. An Amsler grid test showed distortion at fixation in the right eye. A fundus examination showed a round, well-demarcated retinal elevation at the right macula. Optical coherence tomography (OCT) showed an optically-empty sensory retinal detachment (Figures 1A and B). Right CSCR was diagnosed, and the patient was reviewed on a monthly basis.

The patient's CSCR was stable, until progression was noted at six months after initial presentation (Figures 2A and B). The patient was referred to an ophthalmologist, who agreed with the diagnosis based on OCT and fluorescein angiogram (FA) findings. As the areas of leakage shown on FA were too close to the right macula for laser treatment, the patient was prescribed oral eplerenone 50 mg daily for three months.

Complete resolution of subretinal fluid (SRF) was observed, and has been maintained since withdrawing treatment (Figures 3A and B). BCVA in the right eye modestly improved to 6/7.5++.

The mineralocorticoid pathway

The exact pathogenesis of CSCR is not fully understood, though research indicates that the corticosteroid pathway in the choroid has a key role in development. In CSCR patients, enhanced depth imaging OCT has shown thickened choroid in both the affected eye and contralateral eye.[3,4] Indocyanine green angiography has highlighted choroidal vessel dilation and hyperpermeability in CSCR.[1] SRF is thought to accumulate secondary to leakage from underlying choroidal vessels, through disruptions of the retinal pigment epithelium, leading to CSCR.

Glucocorticoids (a class of corticosteroids) act by binding to both glucocorticoid receptors and mineralocorticoid receptors (MR). Zhao et al. identified that MR activation in rat eyes produced dilation and leakage of choroidal vessels.[5] They demonstrated that this process could be prevented using an MR antagonist. Given the risk factors associated with corticosteroids, they hypothesised that a similar MR-signalling pathway in humans may

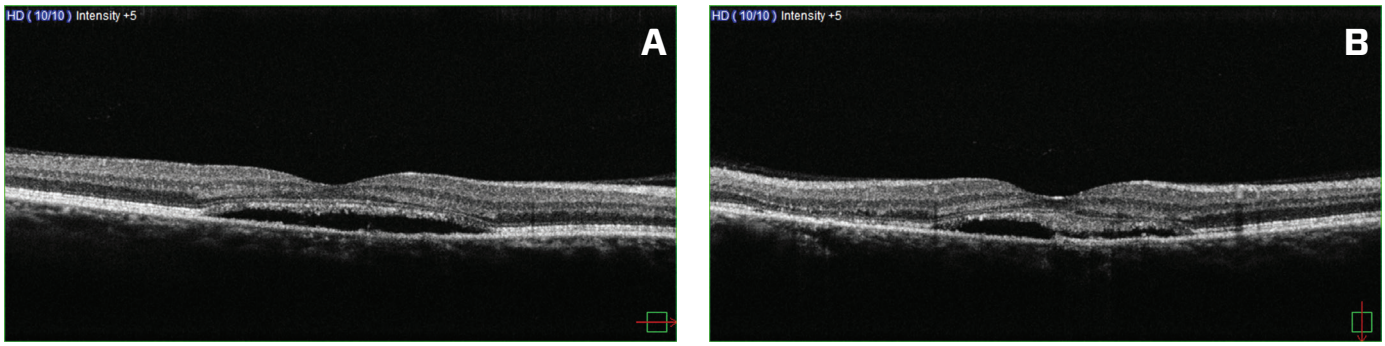

Figure 1. A: horizontal and B: vertical. At initial presentation, when CSCR was diagnosed.

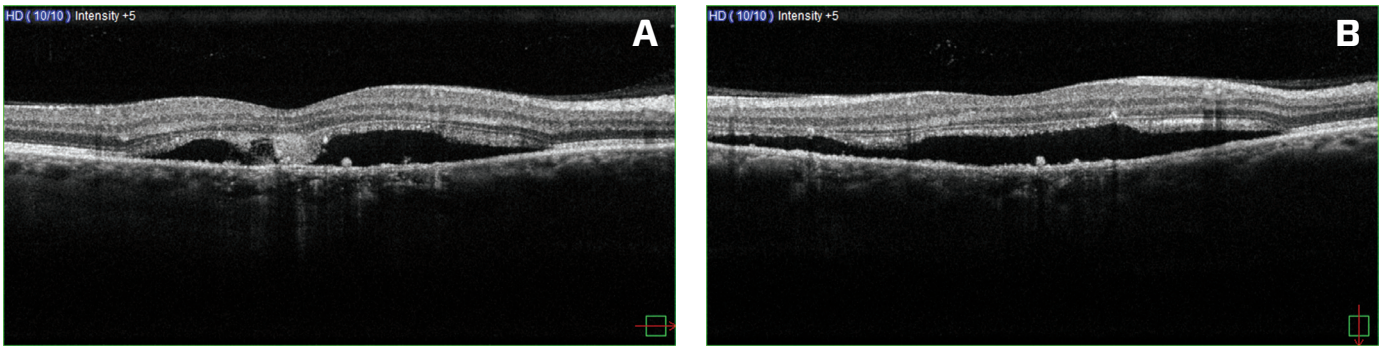

Figure 2. A: horizontal and B: vertical. Six months after initial presentation, showing worsening of CSCR.

cause the choroidal changes seen in CSCR. The researchers treated two patients with chronic CSCR with oral eplerenone (an MR antagonist), and observed resolution of SRF, choroidal vasodilation and improved visual acuity.[5]

Current evidence

Oral eplerenone is a diuretic that is prescribed primarily for cardiovascular disease. The evidence base for eplerenone in the treatment of chronic CSCR is currently comprised of small-scale studies. The reported treatment efficacy in different studies (as percentage of subjects achieving complete resolution of SRF on OCT) ranges from 23 to 75 per cent.[6-9] Some subjects experienced transient decrease of SRF followed by recurrent oedema, while others failed to respond to treatment.[6-9] Several studies reported significant improvement in BCVA, with mean improvement ranging from one to two lines.[6-8] However, the results of a recent placebo-controlled study found that eplerenone treatment was not superior compared to placebo.[9] This variability in reported treatment effect is partly due to the small sample sizes, variation in inclusion and exclusion criteria, differences in prescribed treatment and lack of a placebo group in many studies. This highlights the necessity for larger randomised controlled trials to address these limitations.

The need for future research

Further advancements in imaging technology may continue to improve our understanding of CSCR pathogenesis. More extensive research is required to determine the clinical value of eplerenone treatment. This includes identifying predictors of treatment response (that is, patient subgroups who may benefit most from treatment), the influence of prior treatment with other therapies, optimal dosage and duration of treatment, incidence of side effects and any potential rebound effects.

Oral eplerenone has many potential advantages over other treatment options for chronic CSCR. It is less invasive than other interventions, targets the entire retina and is not limited by proximity to the macula. However, evidence from randomised controlled trials is needed to guide health practitioners in prescribing eplerenone treatment for CSCR, and to maximise patient outcomes. ▲

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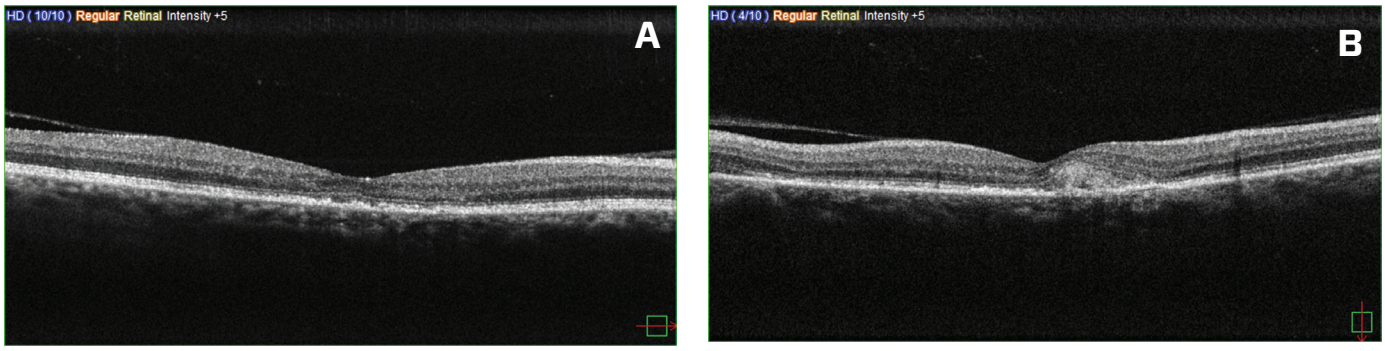

Figure 3. A: horizontal and B: vertical. After treatment with oral eplerenone, showing complete resolution of SRF.

WHAT WILL YOUR PATIENTS MISS MOST IF YOU MISS THEIR RETINOPATHY?

Patients with type 2 diabetes should undergo regular screening to diagnose and manage diabetic retinopathy early[1,2]

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Lipidil® (fenofibrate) 145mg tablets, 30's and 48mg 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: One 145 mg tablet once daily with or without food. Start with one 48 mg tablet once daily in patients with moderate renal impairment (CrCl >30ml/min, ≤ 60ml/min), refer to full PI*. **CONTRAINDICATIONS:** Children; liver dysfunction; severe renal impairment; existing gallbladder disease; co-administration 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; haematologic changes; paradoxical decreases in HDL-C; pregnancy and lactation; drugs exacerbating hypertriglyceridaemia (oestrogen, β-blocker, thiazides); fructose and/or galactose intolerance; lecithin or related product allergy. **INTERACTIONS:** Oral anti-coagulants; HMG-CoA reductase inhibitors (risk of muscle toxicity is increased if used concurrently); other fibrates; cyclosporin (monitor renal function); phenylbutazone; drugs metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2A6, and CYP2C9. **ADVERSE EFFECTS:** GI disorders; skin reactions (including rash, photosensitivity, severe cutaneous reactions); raised LFT; increase in serum creatinine; pancreatitis; gallstones; thromboembolism; muscle toxicity; increase in serum homocysteine and rarely rhabdomyolysis. **Min PI Updated:** 10 Jan 2018.

*Please note changes in PI

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GUIDE

RETINAL VASCULAR DISEASE CHAIR-SIDE REFERENCE GUIDE PAGES 16-18

Should optometrists recommend fenofibrate?

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Diabetes mellitus (DM) affects 7.5 per cent of Australians over the age of 18,[1] and constitutes a major health concern due to the large number of associated and potentially life-threatening complications. These are commonly categorised into macrovascular complications, encompassing cardiovascular diseases such as heart attack and stroke, and microvascular complications including diabetic retinopathy (DR), diabetic nephropathy (DNP) and diabetic neuropathy. Once complications develop, the financial burden of diabetes management increases dramatically, with estimated annual health costs of $5,935 compared to $2,357 for patients without complications.[2]

DR is the most common cause of preventable vision loss in the working age population. The prevalence of DR is higher in Indigenous Australian populations (39.4 per cent) compared to non-Indigenous Australians (28.5 per cent).[3] To prevent or minimise diabetes-related vision impairment and blindness, a collaborative approach to the early detection of DR and appropriate management is key, which may include optimisation of blood glucose levels, blood pressure and cholesterol management, intravitreal injections, laser treatment or vitrectomy. More recently, oral fenofibrate has been discussed as a treatment option for DR; it may provide practitioners with an additional strategy to reduce the risk of progression in patients with non-proliferative DR.

Fenofibrate is a peroxisome proliferatoractivated receptor-alpha (PPAR-alpha) agonist that is primarily used to treat hypertriglyceridaemia, as well as a second line treatment for dyslipidaemia associated with type 2 DM (T2DM) and hypercholesterolaemia.[4]

In 2014, the Therapeutic Goods Administration expanded the indications of fenofibrate to include 'the reduction in the progression of DR in patients with T2DM and existing DR.'[5] This article will provide a short overview of the pharmacological properties of fenofibrate, contemporary evidence of its utility to treat DR and current recommendations to the practicing optometrist.

Pharmacokinetics

Fenofibrate is absorbed in the gastrointestinal (GI) tract, which is optimised when taken with food.[6] Upon absorption, the drug is hydrolysed by tissue and plasma esterases to its active metabolite fenofibric acid.[7] The transport of fenofibric acid is facilitated by serum proteins, especially albumin, as 99 per cent of plasma fenofibric acid is protein bound.[6] Maximum plasma concentrations can be typically detected four to six hours after ingestion with an established half-life for the drug of approximately 20 hours.[6] In healthy subjects, 60 per cent of fenofibrate is subsequently excreted as fenofibric acid glucuronide through urine, another 25 per cent in the faeces.[6]

Pharmacodynamics

Mechanisms underlying the lipid-modifying effects of fenofibrate have been well described, leading to modifications in the cholesterol profile through decreased triglyceride and low-density lipoprotein and increased high density lipoprotein concentrations. As a PPAR-alpha agonist, fenofibrate binds directly to the receptor, which, in its active form, prevents the formation of triglycerides and very low density lipoproteins by promoting the expression of proteins responsible for fatty acid transport and beta-oxidation.[7] Triglyceride levels are further decreased through impact on enzymatic activity such as the activation of lipoprotein lipase and apolipoprotein (Apo)V synthesis, and the inhibition of ApoCIII synthesis.[7] As a result, the composition of low-density lipoproteins (LDL) are altered from small, dense molecules to comparatively large, buoyant units, which can be cleared more easily by LDL receptors. At the same time, the concentration of high density lipoproteins are raised due to increased ApoAI and ApoAII production.[7]

Recently, it has been postulated that fenofibrate also reduces the progression of DR, likely associated with PPAR-alpha activated anti-inflammatory processes, while it may also have antiapoptotic and antioxidant effects.[7] Through the upregulation of sirtuin 1, fenofibrate indirectly inhibits nuclear factor kappa B, which in turn controls genes involved in inflammation.[8] *In vitro* studies suggested that fenofibrate down-regulates inflammatory cascades by suppressing the expression or production of interleukin (IL)-6, prostacyclin, cyclooxygenase-2, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and matrix metalloproteinase-9.[9-12] In patients with T2DM and either nonproliferative DR (NPDR) or proliferative DR, oral fenofibrate resulted in significantly decreased serum levels for IL 1 beta, tumour

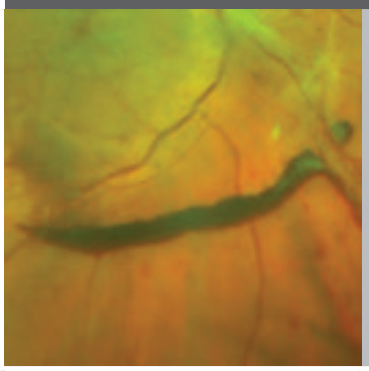
Continued page 19

Centre for Eye Health

Chair-side Reference

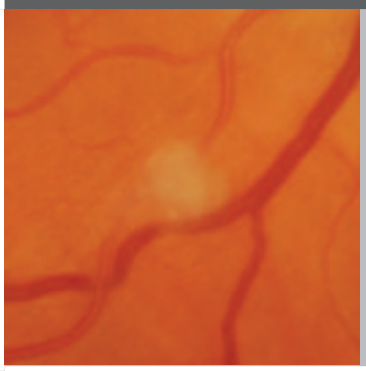
Retinal vascular diseases are a leading cause of vision loss in the western world. Diagnosis can be challenging as clinical signs can overlap between different retinal vascular conditions. Understanding the pathophysiology and clinical characteristics of the common retinal vascular pathologies can

Pre-retinal haemorrhage

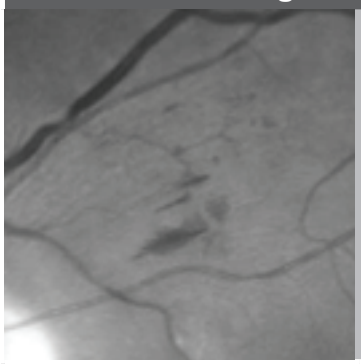


- Between the internal limiting membrane and the posterior hyaloid of the vitreous
- Can be boat-shaped secondary to gravity, linear or arcuate
- Mechanisms can include new vessels prone to bleeding, normal vessels that rupture under stress (e.g. trauma or posterior vitreous detachment), or extension from an adjacent source
- Can cause a scotoma corresponding to the affected area

Cotton wool spot (CWS)

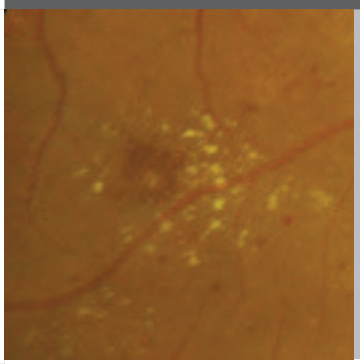


Flame haemorrhage

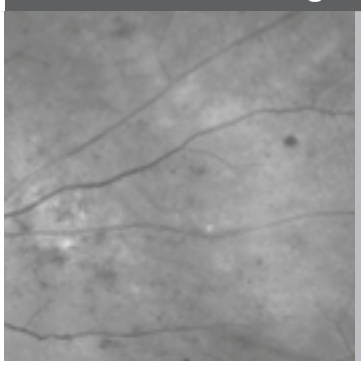


- From the superficial or radial capillary system
- Have a feathered, splinter or flame-shaped appearance as the blood spreads within the nerve fibre layer
- May form in areas of ischaemia or secondary to high capillary pressure
- Can be associated with any condition affecting the superficial retinal vessels (e.g. hypertensive retinopathy, glaucoma, vein occlusion, anterior ischaemic optic neuropathy)
- Reabsorption usually occurs over 2–3 months

Hard exudate

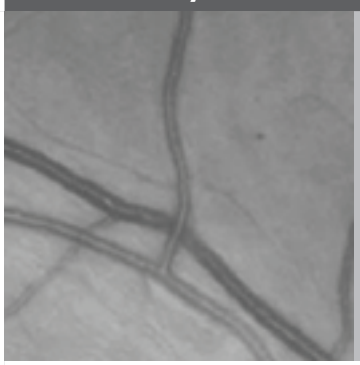


Dot/blot haemorrhage

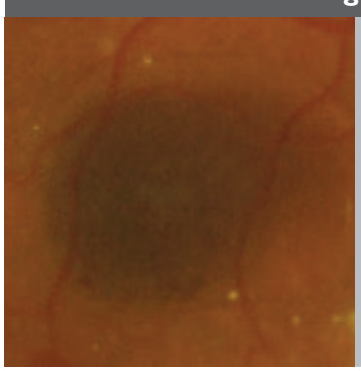


- Located within the inner nuclear layer or outer plexiform layer, which determines the shape of the haemorrhage
- Caused by compression of vessels in the prevenular deep capillary bed, or a ruptured microaneurysm or capillary
- Associated with retinal oedema and venous stasis (e.g. diabetic retinopathy, vein occlusion, retinal telangiectasia, ocular ischaemic syndrome)

Microaneurysm

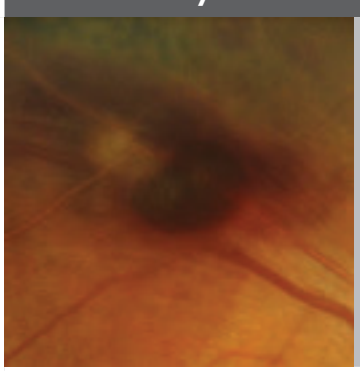


Sub-retinal haemorrhage



- Beneath the retinal pigment epithelium (RPE) or sensory retina
- Arise from the retinal or choroidal circulation
- Appear red or grey-green (sub-RPE)
- Photoreceptor damage is caused by the release of toxins or fibrosis creating a barrier to retinal perfusion
- Commonly occur secondary to choroidal neovascularisation but can also arise from choroidal rupture, breaks in Bruch's membrane or a vascular abnormality causing breakdown of the outer blood-retinal barrier

Macroaneurysm



Retinal Vascular Disease

Optometry
NEW SOUTH WALES
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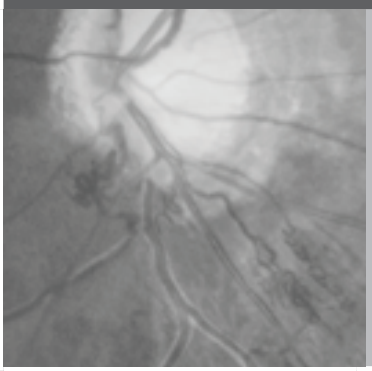
assist clinicians in making a diagnosis and developing an appropriate patient management plan, which may involve ongoing monitoring or on-referral to GPs, ophthalmologists or hospital emergency.

- Appear clinically as a yellow-white or grey-white, slightly elevated cloud-like lesion
- Usually found at the posterior pole and less than 1/3 disc diameter in size
- Caused by ischaemia of the nerve fibre layer due to arteriolar obstruction or other causes of focal disruption of axoplasmic flow
- May be ischaemic, immune, inflammatory, infective, embolic, neoplastic, traumatic, idiopathic or related to medication
- Resolves in 6–12 weeks but can persist longer in diabetic retinopathy

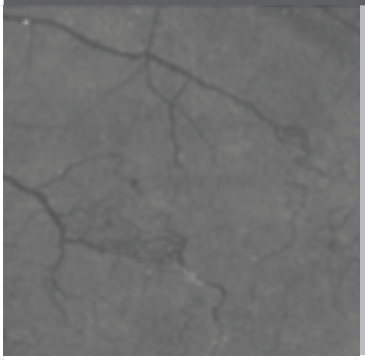
Collateral



- Develop within existing vessel networks close to areas of non-perfusion to redistribute vascular flow
- Typically cross the horizontal raphe and do not leak on fluorescein angiography
- Occur between occluded and unoccluded retinal veins (e.g. vein occlusions) between retinal and choroidal veins or on the surface of the optic nerve
- Can also occur with optic nerve sheath meningiomas, compressive lesions, disc drusen, high myopia and diabetic retinopathy

- Discrete yellow-white lipid deposits in the outer retinal layers
- May be isolated, circinate, diffuse or star-shaped
- Associated with increased vascular permeability or breakdown of the blood retinal barrier and resulting oedema
- Can be seen in conditions such as diabetic retinopathy, hypertensive retinopathy, retinal arterial macroaneurysm, and choroidal neovascularisation

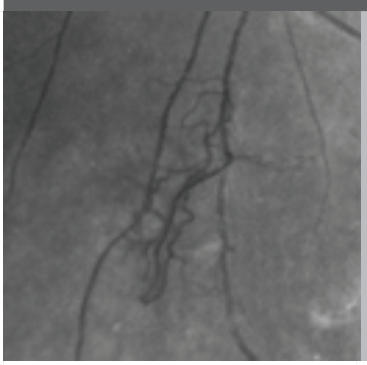
Intraretinal microvascular abnormality (IRMA)



- Intraretinal shunt vessels that act to supply areas of retinal non-perfusion in diabetic retinopathy
- Appear either as abnormal branching or dilation of existing capillaries within the retina
- Have a similar appearance to neovascularisation, however, with a slightly larger vessel calibre
- Neovascularisation may form in close proximity to IRMA

- Originate from the deep capillary bed
- Due to hypoxia, hyperglycaemia or venous stasis weakening the capillary wall causing a subsequent small (50–100 µm) out-pouching, pericyte loss and proliferation of endothelial cells
- Typically cluster at the margins of zones of capillary non-perfusion
- Have a tendency to leak causing intraretinal oedema

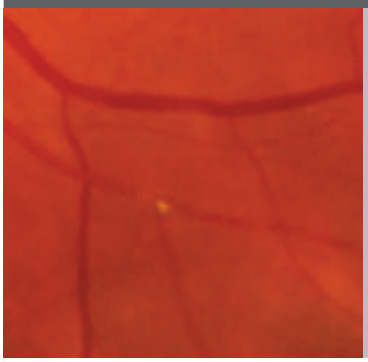
Retinal neovascularisation



- Occurs secondary to hypoxia and subsequent vascular endothelial growth factor (VEGF) release
- Develops from the pre-existing vascular bed, typically at the border of an area of hypoxia
- Prone to leakage, causing pre-retinal haemorrhages, vitreous haemorrhages and/or fibrosis

- Focal dilated area of the large arterioles of the retina
- Caused by localised damage to the vessel wall
- Typically unilateral, large (~280 µm) and have no associated microvascular changes
- Can traverse the full thickness of the retina and cause oedema, haemorrhage and exudation
- Often associated with systemic hypertension and can follow a central retinal vein occlusion

Embolism



- Material from endogenous or exogenous sources causing arterial occlusion, most commonly at a bifurcation
- Commonly cholesterol (Hollenhorst plaques), calcific (cardiac valve disease) and platelet-fibrin emboli
- Rarely, they can be talc emboli (injected drug use), fat emboli (bone fractures), septic emboli (infective endocarditis) or secondary to trauma, sickle cell disease, pregnancy, infection, inflammation, connective tissue disorders or oral contraceptives

Centre for Eye Health

Retinal Vascular Signs

Optometry
NEW SOUTH WALES
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Vascular disease	Haemorrhages																								
	Pre-retinal haemorrhage	Flame haemorrhage	Dot/blot haemorrhage	Sub-retinal haemorrhage	Vitreous haemorrhage	Roth spot	Cotton wool spot	Intraretinal oedema	Hard exudate	Microaneurysm	Macroaneurysm	Telangiectasia	Collateral	Shunt	Intraretinal microvascular abnormality	Neovascularisation	Arteriovenous nipping	Arterial attenuation	Calibre changes	Vessel tortuosity	Sheathing/vasculitis	Lipaemia retinalis	Embolism	Cherry red spot	Retinal whitening (ischaemia)
Anaemias	●	●	●	●	●	●	●	●	●	●						●			●	●					
Behçet's disease		●	●		●			●	●							●		●	●		●				
Branch retinal artery occlusion								●					●										●		●
Branch retinal vein occlusion		●	●				●	●	●	●			●	●		●	●			●	●				
Central retinal artery occlusion								●															●	●	●
Central retinal vein occlusion		●	●				●	●	●	●	●		●	●		●				●	●				
Coats' disease/Leber's miliary aneurysm			●	●					●		●		●	●					●	●	●				
Cytomegalovirus		●	●				●	●										●	●						●
Diabetic retinopathy	●	●	●		●	●	●	●	●	●			●		●	●				●					
Dysproteinemias		●	●				●	●	●	●										●					
Eales disease			●		●					●		●				●			●	●	●				
Endocarditis	●	●	●			●	●																		
Familial exudative vitreoretinopathy	●		●		●				●	●						●					●				
Fetal alcohol syndrome			●																	●					
Glaucoma		●																	●						
Human immunodeficiency virus		●	●			●	●			●		●				●		●	●		●				
Hyperlipidaemia/hyperproteinaemia		●																	●			●			
Hypertension	●	●	●		●	●	●	●	●	●	●						●	●	●	●	●		●		
Ischaemic optic neuropathy		●	●				●									●	●	●	●						
Leukaemias	●	●	●	●		●	●			●						●			●		●				
Macular telangiectasia type 2			●	●				●	●			●		●		●			●						
Multiple myeloma			●			●	●			●															
Multiple sclerosis		●	●		●											●					●				
Neovascular macular degeneration	●		●	●	●			●								●									
Neuroretinitis		●	●				●	●	●																
Ocular ischaemic syndrome		●	●			●	●	●		●		●				●		●	●					●	
Oral contraceptives		●	●																●				●		
Papillitis		●	●				●		●								●	●	●		●				
Papilloedema		●	●				●		●					●			●	●	●						
Papillophlebitis		●	●				●											●	●		●				
Periphlebitis		●	●		●													●	●		●				
Posterior vitreous detachment	●	●	●		●																				
Racemose haemangioma		●	●		●														●	●	●				
Retinopathy of prematurity	●		●		●											●			●	●	●				
Sarcoidosis			●				●				●					●	●	●	●		●				
Systemic lupus erythematosus	●	●	●	●	●		●		●	●				●		●		●		●	●				
Toxoplasmosis			●					●											●		●				●
Trauma	●	●	●	●	●	●																			●
Valsalva manoeuvre	●		●	●	●			●																	
Von Hippel-Lindau angiomatosis			●		●			●	●										●	●	●				

Please note that this table is designed as a general reference tool and needs to be utilised in conjunction with clinical results, observations and other resources. Not all vascular signs for a particular condition listed may be present at the time of examination and in some circumstances, a condition may exhibit other vascular signs and non-vascular associations may co-exist. Vascular signs from more than one disease process may be present at the same time.

Fenofibrate

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necrosis factor-alpha, vascular endothelial growth factor and lipoprotein-associated phospholipase A2 after 12 weeks of therapy.[13]

In summary, these studies suggest a potential benefit for the use of fenofibrate in the treatment of DR.

Fenofibrate and its effects in DR

To date, two landmark studies, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) have investigated the effects of fenofibrate in patients with T2DM. (It should be noted that the primary outcome for both of these multinational, double-blind, randomised controlled trials was focused on the assessment of the effect of fenofibrate on cardiovascular disease events).[14,15]

The FIELD study analysed 9,795 subjects aged 50–75 years with T2DM.[16] Eligible subjects were randomly allocated either fenofibrate or placebo therapy and had a median follow-up period of five years. Although none of the participants were taking statins at study entry, statin therapy was initiated throughout this period if clinically indicated. In regard to DR, history of DR was self-reported and occurrence of laser treatment for DR was a tertiary endpoint of the FIELD study. Within these parameters, patients in the fenofibrate group had significantly less initiation of laser treatment for DR than those in the placebo group (164 patients [3.4 per cent] vs 238 patients [4.9 per cent], p = 0.0002), corresponding to an absolute risk reduction of 1.5 per cent.[16]

A subset of 1,012 participants from the FIELD study were assessed on retinal photography and graded according to an expanded Early Treatment Diabetic Retinopathy Study (ETDRS) scale.[16] Approximately 80 per cent of patients did not exhibit DR and, for these, no difference in progression, defined as a two-step change of DR grade, was identified between the fenofibrate and placebo group.

Interestingly, in patients with pre-existing mild-to-moderate NPDR, significantly fewer patients progressed in the fenofibrate versus the placebo group, albeit overall numbers were very small (three patients [3.1 per cent] vs 14 patients [14.6 per cent], p = 0.004). Other clinical parameters, such as one-step progression of DR, two-line worsening of VA, and occurrence of diabetic macular oedema (DMO), did not change with fenofibrate therapy.[16] (It is important to also note that this study pre-dates the ubiquity of optical coherence tomography in diagnosing DMO.)

Apart from the discussed impact on DR progression, the FIELD study highlighted that fenofibrate therapy significantly reduced non-fatal myocardial infarction, cardiovascular events, coronary revascularisation (percutaneous transluminal coronary angioplasty and coronary artery bypass grafting), hospitalisations for acute coronary syndromes, amputations and progression to albuminuria, a well-established marker for DNP.[14,17] However, mortality rates of patients with T2DM were not affected by fenofibrate.

The ACCORD study enrolled 5,518 participants aged 62.3 ± 6.8 years with T2DM enrolled in a lipid study, where subjects received statin monotherapy or a combined therapy with statin and fenofibrate.[15] Unlike the FIELD study, ACCORD did not find a benefit in fenofibrate in reducing non-fatal myocardial infarction and cardiovascular events, but did confirm the demonstrated significantly lower incidence of albuminuria in the fenofibrate group.[15]

The ACCORD Eye study, encompassing 1,593 participants, also graded DR according to a modified ETDRS scale, but defined DR progression as three-step worsening, requiring photocoagulation or vitrectomy.[18] At four years follow-up, progression of DR was significantly less in the fenofibrate than placebo group among all patients (52 patients [6.5 per cent] vs 80 patients [10.2 per cent], p = 0.006) and those graded two-four (defined as microaneurysms [Ma] or mild NPDR one eye, no DR or Ma only other eye) on study entry (eight patients [3 per cent] vs 26 patients [10.1 per cent], p = 0.0009).[19] Again, the incidence of moderate vision loss, defined as the loss of three or more lines, was not impacted.[18] The ACCORDION eight-year follow-up study confirmed that this effect was retained if fenofibrate therapy was maintained.[20]

Side effects of fenofibrate

Current studies suggest that fenofibrate is generally well tolerated. Similar to the ACCORD study,[15] patients allocated to fenofibrate in the FIELD study exhibited greater risk for pancreatitis (23 patients [0.5 per cent] vs 40 patients [0.8 per cent], p = 0.031) and pulmonary embolism (31 patients [0.7 per cent] vs 53 patients [one per cent], p = 0.022) than those on placebo.[14] Incidences of deep vein thrombosis, myositis, rhabdomyolysis, and increases in serum levels for alanine aminotransferase, creatine phosphokinase or creatinine were less than two per cent in either group.[14] While raised serum creatinine can indicate decreased kidney function, levels reverted to within normal range after discontinuation of fenofibrate.[21]

Based on the pharmacokinetics and pharmacodynamics of fenofibrate, other side effects including increased aminotransferase concentrations, GI disturbances, urticaria, rash, gallstones, photosensitivity, hepatitis, cholestatic jaundice, anaemia, leukopenia, myopathy and hypersensitivity reactions may occur on occasion as indicated by the *Australian Medicines Handbook*.[4]

When should an optometrist recommend fenofibrate?

Current evidence suggests that patients with T2DM and mild to moderate NPDR are ideal candidates for fenofibrate therapy. As this effect appears to be independent of lipid levels, fenofibrate may be recommended irrespective of lipid levels, including patients with normal lipid profiles. While there are currently no high quality data on the effect of fenofibrate in those who progress to or have severe NPDR, PDR or macular oedema, or in patients less than 40 years of age, it may be reasonable, with precaution, to continue or commence fenofibrate in collaboration with their general practitioner (GP) or endocrinologist.

Fenofibrates may also be beneficial in the treatment of T1DM, as suggested in mouse models.[22] Although the currently ongoing Fenofibrate and Microvascular Events (FAME) 1 Eye

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Fenofibrate

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Study is actively investigating the effects of fenofibrate in patients with T1DM and NPDR, to date no data are available to guide recommendations.[23] Therefore, fenofibrate therapy in T1DM for DR is not supported.

Conclusion

In accordance with current evidence, optometrists are well placed to suggest fenofibrate therapy for patients with T2DM within their capacity as primary ocular health care providers. Respective suggestions to the patient's GP provide an opportunity to reduce the risk of T2DM-associated complications, including but not limited to DR, thereby significantly improving quality of life and decreasing the burden of disease. Recommendations supported through reference to the relevant clinical findings will allow GPs to assess the appropriateness of therapy and drive optometrist directed intervention for patients with complex diseases such as T2DM. ▲

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CLINICAL AND EXPERIMENTAL
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In this issue, CXO *Deputy Editor Maria Markoulli offers an overview of a study published in the September issue that suggests retinal neural changes may be present in diabetic eyes prior to clinically-detectable retinal vasculopathy, and that macular and retinal nerve fibre layer thickness measurements may be useful indicators for early detection of diabetic retinopathy in the future.*

As clinicians, one systemic condition that we frequently encounter in our practices is diabetes. Worldwide, diabetes is thought to affect 422 million people and continues to be on the rise.[1] Systemically, diabetes is associated with premature mortality, macrovascular complications such as cardiovascular disease and microvascular complications including retinopathy, nephropathy

Pharma and Optometry Australia's official journal *Clinical and Experimental Optometry (CXO)* are collaborating to bring our readers up to date with some of the most interesting articles, reviews and original research available in the latest issue of *CXO*.

Quantitative evaluation of early retinal changes in children with type 1 diabetes mellitus without retinopathy

Summary and comment provided by Maria Markoulli
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and neuropathy.

In optometric practice, patients can present with signs that span the clinical spectrum of diabetic retinopathy, from scattered microaneurysms through to neovascularisation and vision-threatening macular oedema.

Also known as insulin-dependent or juvenile diabetes, type 1 diabetes makes up about five to 10 per cent of the diabetic population, with an age of onset usually before 30 years. When type 1 diabetes affects our youngest patients, eye-care providers are even more conscious of the need to monitor their progression, particularly given the lifelong impact of the disease.

We now have the equipment available to measure retinal changes at much greater detail than ever before. With this background, Tekin et al. at the ophthalmology department of Kars State Hospital in Turkey set out to investigate the impact of type 1 diabetes on the retina in children using spectral domain optical coherence tomography (SD-OCT).

The researchers recruited 73 children with type 1 diabetes and 62 age-matched healthy controls and measured their macular and peripapillary RNFL thickness using Spectralis SD-OCT following dilation. Three scans were taken and averaged for the analysis. Segmentation errors were examined by a clinician who was masked to the participant's disease status. The investigators also recorded details of the participants' systemic disease, such as how long they'd had the disease. Blood samples were taken on the same day as the ocular measurements from the participants with type 1 diabetes only so as to determine the level of control as judged by their glycosylated haemoglobin, or HbA1c.

Participants were seen for one visit only. Importantly, participants with type 1 diabetes did not have any clinical signs of retinopathy at recruitment and were required to have their condition under good control. All participants were under the age of 18. All participants with diabetes were receiving insulin treatment and were free of neuropathy or nephropathy. Participants with any known ocular diseases were excluded.

The investigators found that there were significant differences between the two

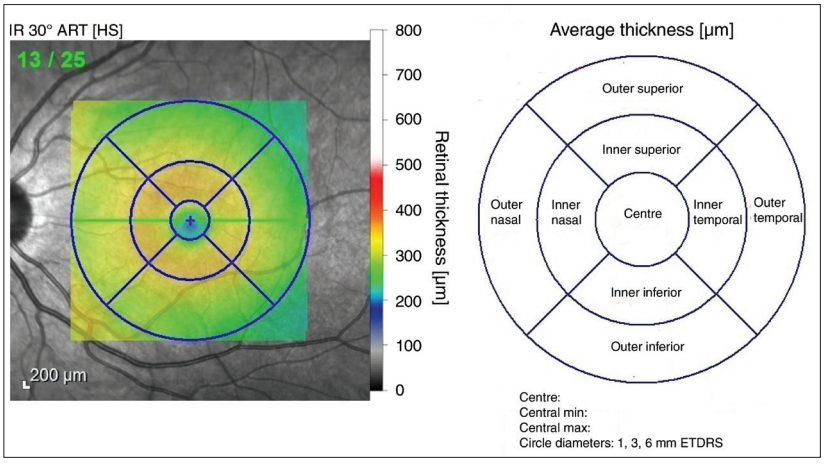

Figure 1. Macular thickness measurement analysis of a child with type 1 diabetes mellitus is shown. The measurement was performed in the central macular region (1 mm) and in the inner (3 mm) and outer (6 mm) rings around the central macular region. The inner and outer rings were divided into four quadrants, defining the temporal, nasal, superior and inferior areas.

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CXO

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groups of children: children with type 1 diabetes had significantly thinner macular thicknesses, specifically in the temporal inner and outer areas and the inferior outer area. They also had thinner RNFL thicknesses.

When the investigators examined the relationship between the duration of the disease and both retinal and macular thicknesses, an inverse relationship was found, suggesting that the longer the disease had been present, the thinner the RNFL and macular. A similar relationship was found between these SD-OCT measures and HbA1c.

Based on their findings, the authors conclude that even in the absence of clinically-apparent retinopathy, children with type 1 diabetes may have changes to their RNFL.

They further suggest that such changes could be predictive of future diabetic retinopathy. Therefore type 1 diabetes can result in both vascular and neural changes in the retina, with the latter potentially preceding the signs of retinopathy.

The authors do highlight that the differences between groups are in the order of 5–10 µm which may not be clinically significant. A letter to the editor by Sahin et al.[2] suggested that differences in axial length could also impact the outcomes measured in this study, highlighting the need to take this into account.

Based on their findings, the authors recommend that children with type 1 diabetes have yearly eye exams that include advanced imaging with devices such as the SD-OCT in order to monitor progression. They also recommend further studies on longitudinal changes in type 1 diabetes. ▲

	¥Duration of DM (years)	HbA1c values (%)
Central macular thickness	r = -0.090, p = 0.945	r = -0.213, p = 0.089
Temporal inner macula	**r = -0.287, p = 0.021**	r = 0.164, p = 0.146
Superior inner macula	r = -0.222, p = 0.114	r = -0.130, p = 0.184
Nasal inner macula	r = 0.096, p = 0.259	r = -0.147, p = 0.399
Inferior inner macula	r = -0.114, p = 0.365	r = -0.013, p = 0.471
Temporal outer macula	**r = -0.337, p = 0.033**	**r = -0.414, p = 0.026**
Superior outer macula	r = -0.021, p = 0.311	r = -0.220, p = 0.105
Nasal outer macula	r = 0.306, p = 0.434	r = 0.117, p = 0.098
Inferior outer macula	r = -0.412, p = 0.105	r = -0.317, p = 0.083
RNFL-G	**r = -0.313, p = 0.011**	**r = -0.317, p = 0.023**
RNFL-N	r = 0.451, p = 0.111	r = -0.309, p = 0.451
RNFL-NS	r = -0.131, p = 0.712	r = -0.021, p = 0.603
RNFL-TS	r = -0.407, p = 0.090	**r = -0.317, p = 0.043**
RNFL-T	r = -0.507, p = 0.512	r = 0.220, p = 0.805
RNFL-TI	r = -0.501, p = 0.534	r = -0.317, p = 0.341
RNFL-NI	r = -0.273, p = 0.064	r = -0.317, p = 0.071

DM: Diabetes mellitus; RNFL: retinal nerve fibre layer; G: global; N: nasal; NI: nasal inferior; NS: nasal superior; TS: temporal superior; T: temporal; TI: temporal inferior;
r: Pearson correlation co-efficient
¥The duration of DM refers the duration since the diagnosis of type 1 DM.
Bold values indicate statistically significant correlations.

Table 1. Correlations between the duration of DM and HbA1c levels with the macular and RNFL thickness measurements in children with type 1 DM.

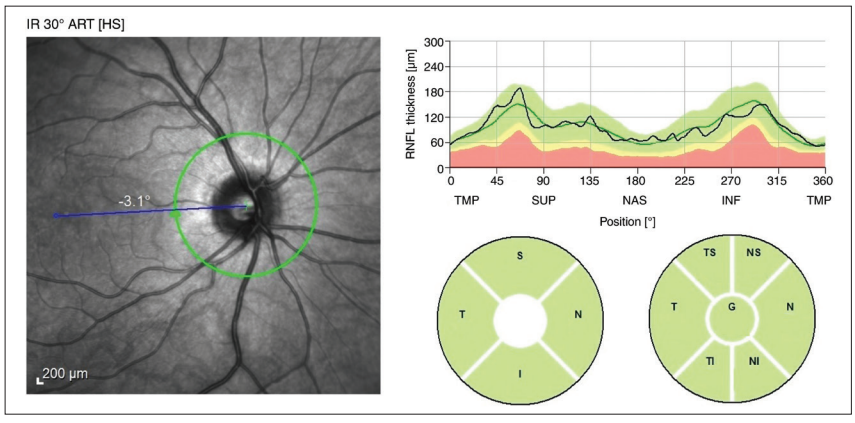

Figure 2. Peripapillary retinal nerve fibre layer thickness analysis of a child with type 1 diabetes mellitus is shown. The analysis was obtained around the optic disc with a diameter of 3.46 mm and the measurement was performed in the global and each six sectors centred on the optic disc (T: temporal, TS: temporal superior, TI: temporal inferior, N: nasal, NI: nasal inferior, NS: nasal superior).

Tekin K, Inanc M, Kurnaz E, et al, *Clinical and Experimental Optometry* Issue 101, Volume 5.

Clinical and Experimental Optometry is the official journal of Optometry Australia, the New Zealand Association of Optometrists, the Hong Kong Society of Professional Optometrists and the Singapore Optometric Association. It is published online six times a year.

1. WHO. Global Report on Diabetes [Internet]. Geneva: World Health Organization; 2016 [cited 2018 Jul 27]. Available from: http: //apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng. pdf; jsessionid = 73B1D848D4152A1DE9FE443687928A2E? sequence=1
2. Sahin M, Sahin A, Turkcu FM. The factors influencing retinal thickness in diabetic patients. *Clin Exp Optom* 2018; 101: 680-685.

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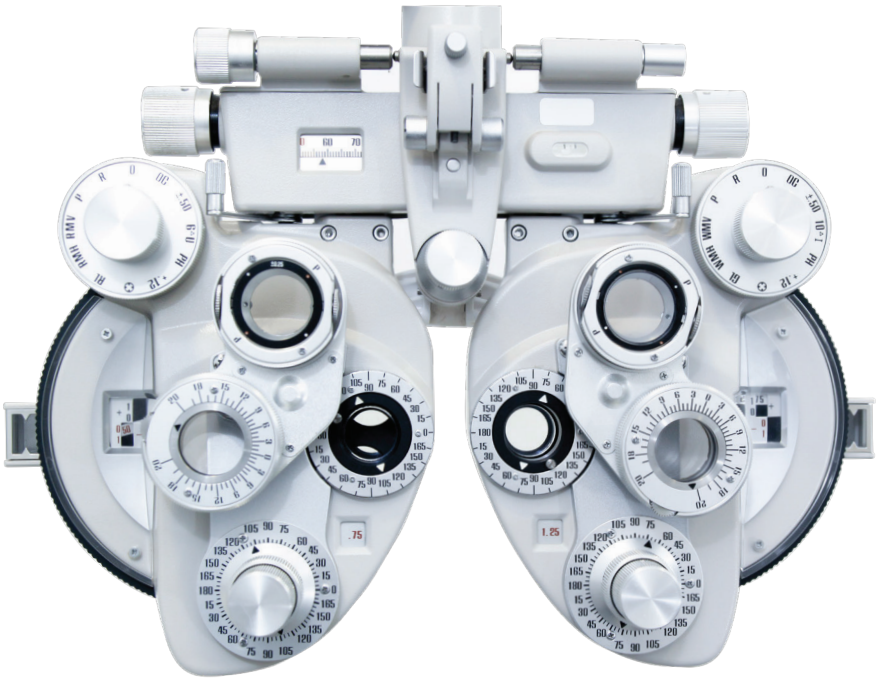

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OCT-A vs FA

Comparing fluorescein angiography and OCT-angiography in diabetic retinopathy

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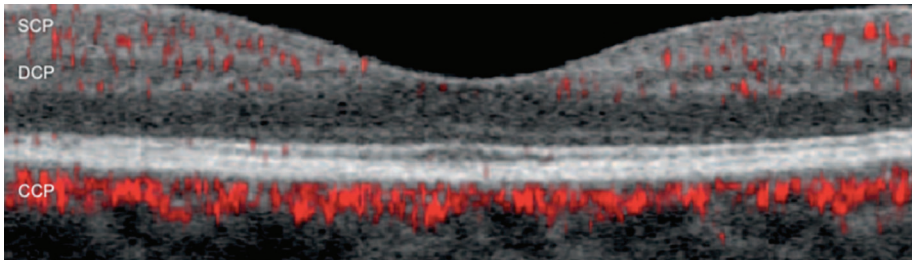

Figure 2. Structural OCT cross-sectional image overlaid with OCT-A data. The CCP has significantly greater signal strength compared to the SCP and DCP. Note the absence of vascular supply in the outer retina and RPE which receive oxygen and nutrients via diffusion from the CCP.

Since its development in the early 1960s, fluorescein angiography (FA) has been the only procedure for *in vivo* imaging of the blood flow in the eye, providing vital information in a number of ocular conditions such as diabetic retinopathy, retinal vascular occlusions and age-related macular degeneration. However FA is not without its downsides, including the requirement for intravenous injection, nausea and potentially life-threatening anaphylaxis. Although 13 states in the USA allow optometrists to perform FA, the procedure is not currently within the scope of practice for Australian optometrists.

The recent introduction of OCT-angiography (OCT-A) provides an alternate method to image retinal vessels and capillaries without the injection of fluorescein dye. The new technology relies on the ability of OCT instruments to sequentially image the exact same retinal location multiple times in rapid succession. Since the retinal structures are fixed and unchanged in the sequential scans, any variation in the image is due to the motion of red blood cells within the vessel walls.

So, does OCT-A give the equivalent information to FA and potentially replace it as our vascular imaging method of choice, particularly in diabetic retinopathy?

Understanding vascular anatomy

In order to correctly interpret OCT-A and FA images, the practitioner needs to understand the anatomy of the ocular vasculature and how it is affected in disease.

The ophthalmic artery branches from the internal carotid artery and enters the orbit where it further divides into the short and long posterior ciliary arteries and the central retinal artery (Figure 1).

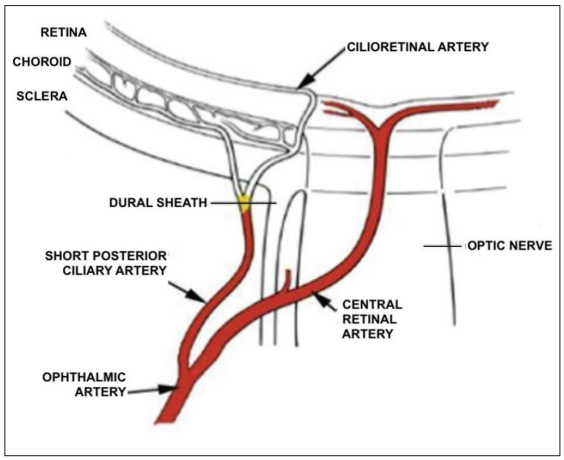

Figure 1. Arterial vascular supply to the eye. The central retinal artery feeds the inner retinal layers while the posterior ciliary arteries supply the optic nerve, choroid, RPE and photoreceptors.

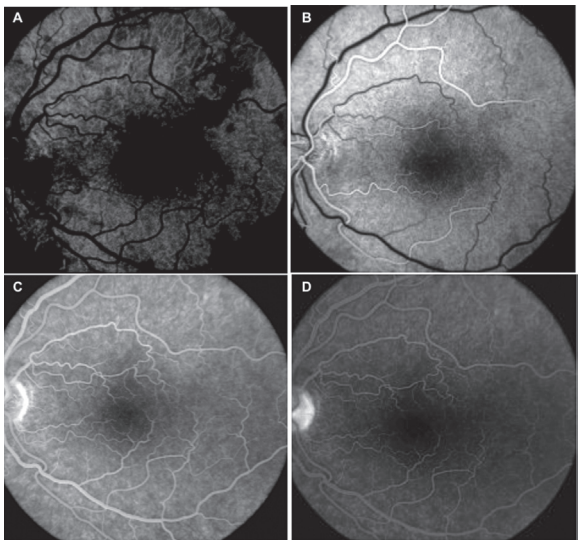

Figure 3. Stages of fundus FA

Time	Stages of fluorescein angiography
0 sec	Injection
10 sec	Choroidal flush (A)
12 sec	Retinal arterial stage (B)
13 sec	Capillary stage
15 sec	Venous stage (C)
30 sec	Dye recirculation
300+ sec	Late staining stage (D)

Table 1. FA times

Approximately 15-20 short posterior ciliary arteries enter the globe in an annulus around the optic nerve, providing the predominant blood supply to the optic nerve head (circle of Zinn) and to the choroid via three layers of progressively smaller choroidal vessels: Haller's layer, Sattler's layer and the choriocapillaris (CCP). Approximately 20 per cent of the population has a cilioretinal artery that provides blood to the fovea from what is typically choroidal blood flow. The short posterior ciliary vessels supply the choroid up to the equator of the globe, while the long posterior ciliary arteries supply the peripheral choroid and the ciliary body.

The central retinal artery enters the eye through the optic nerve and branches internally into four major arterioles supplying each retinal quadrant while progressively bifurcating into smaller vessels to form the superficial capillary plexus (SCP) that supplies the ganglion cells/retinal nerve fibre layer, and the deep capillary plexus (DCP) which supplies the bipolar/amacrine cell layer. The photoreceptors and retinal pigment epithelium (RPE) do not have a capillary plexus and derive their nutrition via diffusion partly from the DCP and more predominantly from the CCP (Figure 2).

How FA works

A baseline image with angiography filters in place is taken to assess fundus autofluorescence. Sodium fluorescein dye is then injected into the patient's arm and sequential retinal images are taken to assess different stages of retinal vessel filling. Due to the more direct vascular pathway to the choroid, the choroidal vessels fill a few seconds prior to the retinal vessels, and because the CCP has fenestrated capillaries, the fluorescein dye leaks readily giving an early choroidal 'flush' (Figure 3/ Table 1). The retinal capillaries have tight junctions that form the blood-retinal barrier which is impervious to fluorescein dye and will only leak if there is retinal vascular pathology.

Advantages of FA

FA allows us to assess blood transit time, which is not possible with OCT-A. For example, carotid stenosis may cause a long delay in fluorescein reaching the retinal arterial stage. FA also shows areas of extravascular blood leakage and pooling while OCT-A can only image motion of the erythrocytes but not their leakage or areas of stagnation. Using wide-field angiography cameras, up to 200 degrees of central and peripheral retina can be imaged, looking for peripheral capillary drop-out or neovascularisation elsewhere (NVE) that forms at the border of the perfused and non-perfused retina.

Disadvantages of FA

FA is unable to differentiate the distinct layers of the retinal and choroidal vasculature. Fluorescence of the superficial capillary plexus obscures the image of the deep capillary plexus which is unable to be directly viewed. Choroidal vessels are also difficult to image and require the injection of indocyanine green dye to visualise the different layers of choroidal vasculature. Significant areas of retinal or pre-retinal haemorrhage will obstruct view of the angiographic images, particularly areas of capillary non-perfusion. FA is a unilateral procedure and is unable to take early images of both eyes, only late stage images of the fellow eye. If the second eye needs to be assessed fully, another fluorescein injection is required after a washout period.

Continued page 26

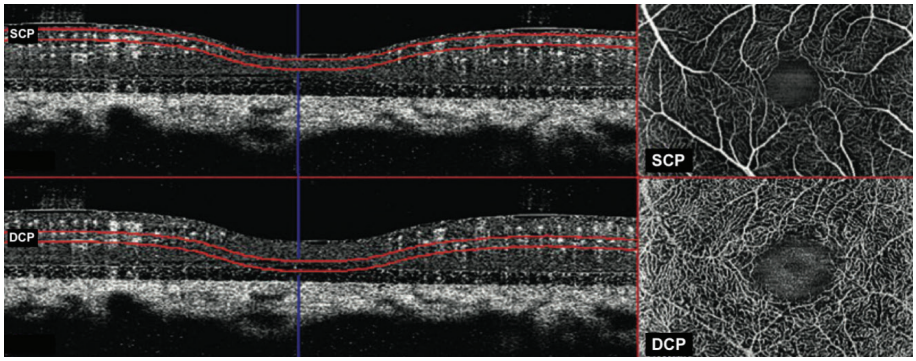

Figure 4. Structural OCT segmentation 'slabs' at the SCP and DCP in a normal eye, with corresponding *en face* OCT-A images centred on the fovea. Note the DCP has an absence of the large retinal vessels which are only seen in the SCP.

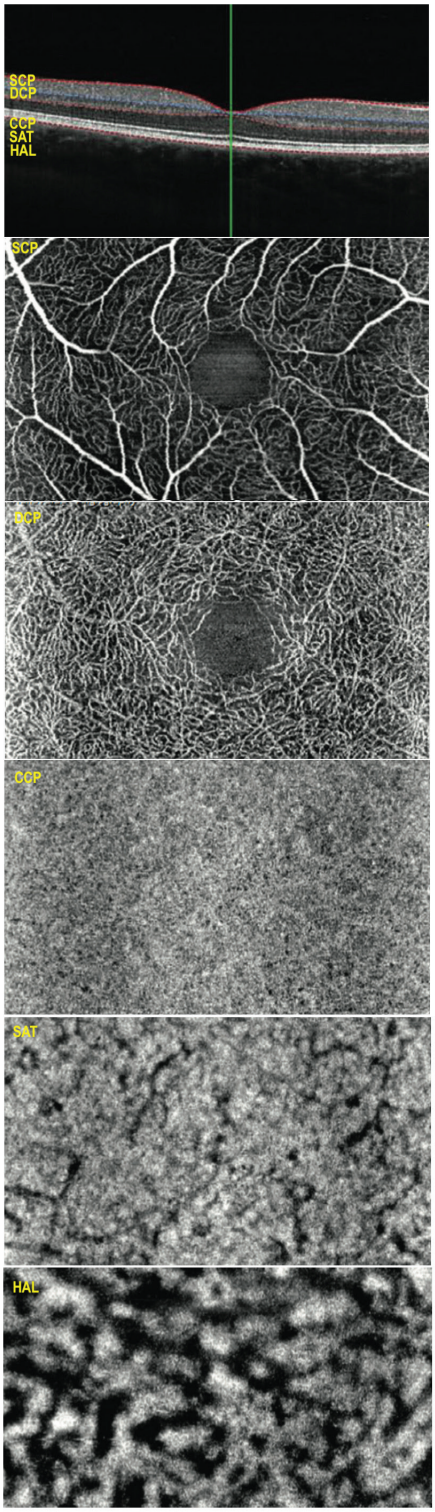

Figure 5. OCT-A images of all the segmented vascular layers of the retina and choroid. The outer retina and RPE contain no blood vessels and are not shown here.

OCT-A vs FA

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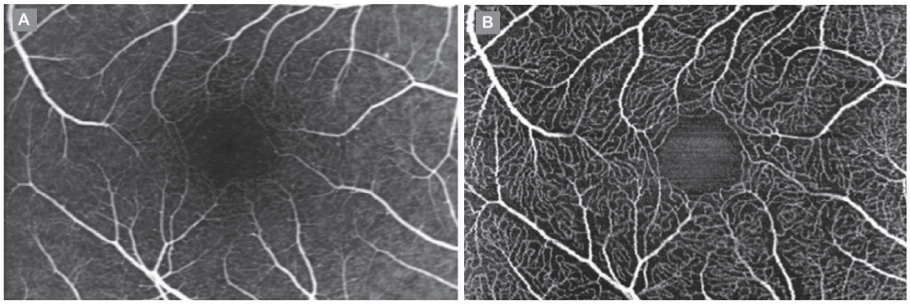

Figure 6. A: Fluorescein angiogram and B: OCT-A image of the macular in the same patient, showing higher capillary detail and resolution in OCT-A

How OCT-A works

Multiple sequential OCT B-scans are taken of the same area of retina, subtracting any stationary structures that are present in all the images, leaving only images of the moving blood. After software correction for head and eye motion, the variances between the sequential images can only be due to movement of the red blood cells within the retinal vessels. A number of strategies are used by different OCT manufacturers to detect erythrocyte motion: phase decorrelation, amplitude decorrelation or a combination of both algorithms. There is no consensus as to which algorithm, if any, is more 'accurate.' An *en face* image is then produced showing the vasculature in different retinal layers alongside the structural OCT cross-section for localisation (Figures 4 and 5).

Advantages of OCT-A

Unlike traditional FA, OCT-A is able to image different layers of the retina and choroid, and provides much greater resolution of the capillary beds. No dye injection is required obviating the risks of blood borne infection or anaphylaxis. OCT-A image acquisition time is significantly shorter compared to FA, and OCT-A has the ability to image both eyes in the same session. OCT-A has the capability to differentiate between all the vascular layers of the retina and choroid, and dynamically shift through the different regions via software tools after the images have been captured. OCT-A analysis software allows colour-coding of different capillary layers, while analytic software measures information such as capillary density and areas of capillary non-perfusion, looking for change over time as an indication of worsening disease. Repeating OCT-A scans multiple times in the same location improves resolution by eliminating speckle noise from the images, resulting in a remarkable improvement in capillary detail and greater resolution compared to FA (Figure 6.) OCT-A is better able to image through extravascular blood and haemorrhage, particularly using longer wavelength swept source OCT-A systems.

Fluorescein Angiography	OCT-Angiography
Invasive dye injection	**Non-invasive**
Risk of anaphylaxis or death	**No risk to patient**
20 minute imaging time	**Five minute imaging time**
Essentially unilateral	**Bilateral**
200 degree field of view	40 degree field of view
Time-based dynamic measure of blood flow	Static snap-shot of blood flow
Detects retinal leakage	Unable to detect retinal leakage
Lower resolution	**High resolution**
Two-dimensional image	**Three-dimensional image**
Layer segmentation not possible	**Layer segmentation**
Images superficial retina only	**Images superficial retina, deep retina and outer retina**
Requires indocyanine green dye to image choroid	**Images all layers of choroid**
No software analytics	**Software analytics and progression analysis**
Fluorescence blocked by haemorrhage	**Able to image through haemorrhage**

Table 2. OCT-A vs FA. Advantages shown in **bold.**

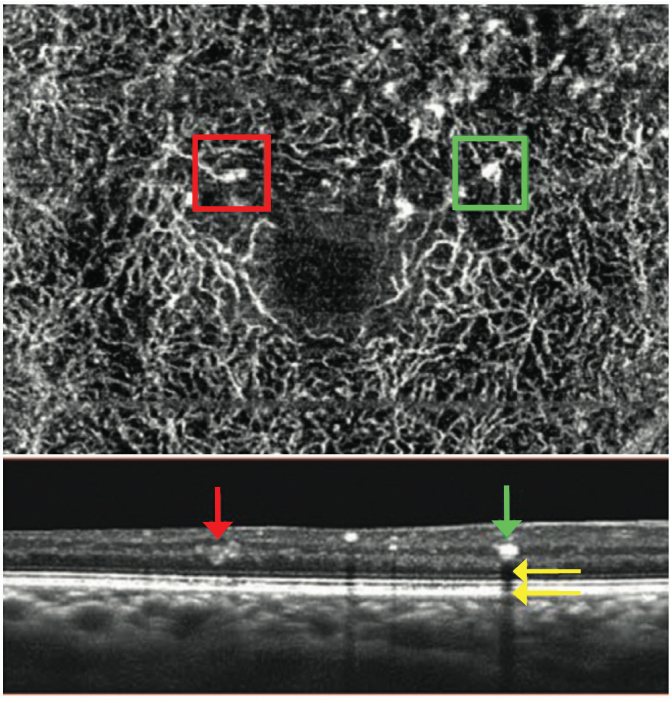

Figure 7. Upper image of the DCP showing the similar appearance of a microaneurysm (red box) and hard exudate (green box). On structural OCT (lower image) the denser hard exudate causes shadowing of the retina below (yellow arrows) while the less dense microaneurysm allows signal to pass through.

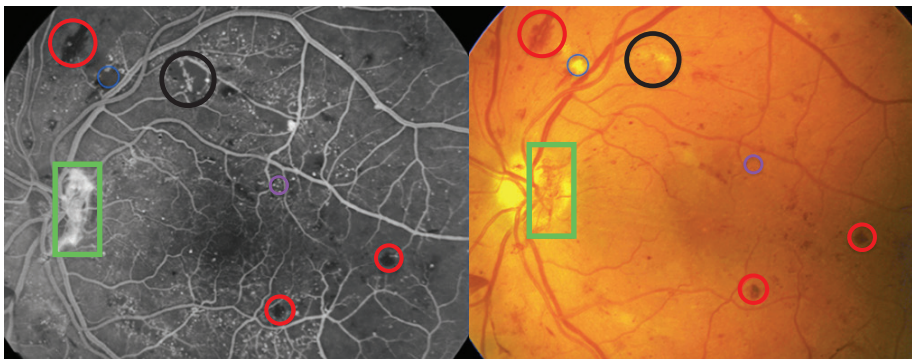

Figure 8. Fluorescein angiogram (left) and colour fundus photograph (right) of a patient with proliferative diabetic retinopathy. Microaneurysms (purple), retinal haemorrhages (red), cotton wool spots (blue), hard exudates (black) and neovascularisation of the disc (green) are compared and contrasted in each of the images.

Disadvantages of OCT-A

Because OCT-A doesn't use an injection of intravenous dye, it's unable to provide information on blood flow rates or areas of vascular leakage. OCT-A is only able to detect erythrocyte motion in a finite range of velocities, and if the blood flow is slow or stagnant, it will not be detectable to OCT-A. The area of imaging is typically 3 x 3 mm (10 degrees) which is much smaller than in FA (up to 200 degrees in one image). Scan areas can be increased to 12 x 12 mm (40 degrees) but with a reduction in image quality and capillary detail. Montage of smaller images is possible, but requires numerous scans in multiple areas which greatly increases test times and patient fatigue. Projection artefacts occur when larger superficial retinal blood vessels reflect their images onto deeper retinal layer which do not have any vasculature such as the outer retina and RPE, and require software correction to remove the artefacts.

Diabetic retinopathy imaging in OCT-A

Diabetic retinopathy occurs secondary to hyperglycaemic damage to the vascular wall of the capillaries, leading to loss of vascular pericytes, leakage of serous fluid, lipid exudate and red blood cells, and eventual destruction of the capillary itself, resulting in areas of capillary non-perfusion. These areas of non-perfusion have diminished blood supply, become hypoxic and upregulate the production of vascular endothelial growth factor (VEGF) in an attempt to produce new vessels and improve tissue oxygenation. Unfortunately the excessive VEGF leads to worsening of the retinal oedema and also subsequent neovascularisation.

Microaneurysms

Microaneurysms are outpouchings of weakened capillary walls, which may leak, causing diabetic macular oedema. They have moderately high reflectivity on structural OCT and OCT-A. They are an important early sign of diabetic retinopathy and can be seen in the SCP and DCP on OCT-A, but can only be visualised in the SCP of FA. FA reveals a greater number of microaneurysms than OCT-A, presumably because some microaneurysms contain stagnant pockets of blood where the erythrocytes are not moving sufficiently to be detected on OCT-A.

Microaneurysms have a focal bright appearance in both OCT-A and FA images (Figures 7 and 8).

Hard exudates

Lipid exudates leaking from damaged retinal vessels typically occur in the middle retinal layers. They can be difficult to differentiate from microaneurysms in OCT scans but have a higher brightness/reflectivity and cause greater shadowing of underlying retinal structures than microaneurysms.

Exudates appear bright on OCT-A images but darker in FA images as their density blocks capillary dye fluorescence (Figures 7 and 8).

Retinal haemorrhages

Dot, blot and flame-shaped retinal haemorrhages are not directly imaged by OCT-A or FA, but appear dark on structural OCT and OCT-A, and also dark on FA where they block dye fluorescence (Figure 8).

Cotton wool spots

Infarcts in the retinal nerve fibre layer (RNFL) due to arterial occlusions in the SCP cause localised oedema and swelling of the ganglion cell axons. On OCT they are thickened and hyper-fluorescent, however on OCT-A, they are hypofluorescent and cause distortion to the inner retinal architecture by pushing larger vessels in the SCP down into the DCP layers where normally only capillaries exist. Cotton wool spots are also dark in FA imaging due to blockage of dye fluorescence (Figures 8 and 9).

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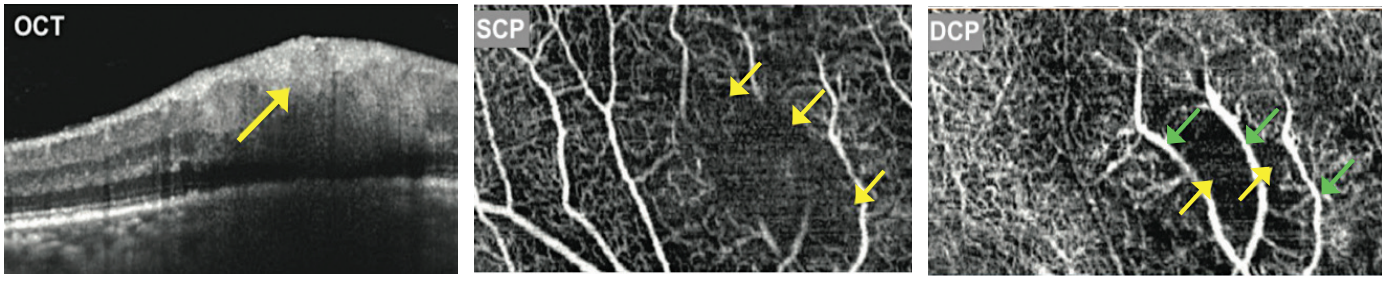

Figure 9. Cotton wool spot seen as a hyper-reflective swelling of the nerve fibre layer in structural OCT, and as a hyporeflective area devoid of capillaries in the SCP. Note the large retinal vessels normally seen in the SCP have been pushed down into the DCP.

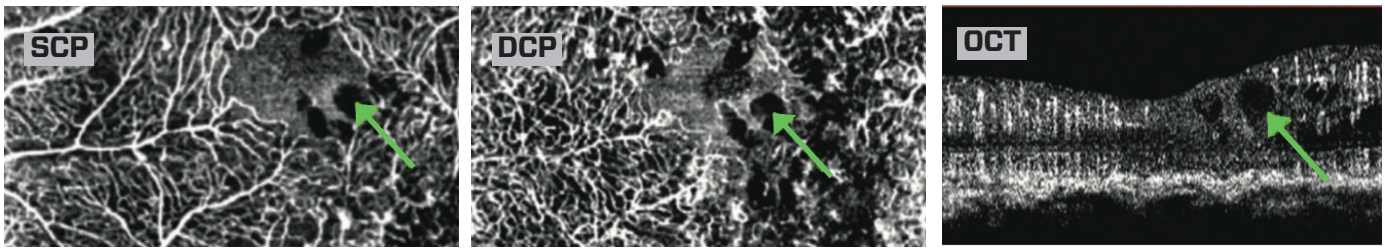

Figure 10. Cystoid macular oedema (green arrow) located at the foveal avascular zone as seen in structural OCT and OCT-A of the SCP and DCP.

OCT-A vs FA

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Diabetic macular oedema

Extravascular fluid leakage can appear as generalised thickening and/or dark cystoid spaces on structural OCT cross-sections. On *en face* OCT-A images, the areas of fluid are only visible when cystoid in nature as dark round cyst-like areas (Figure 10).

Diabetic retinal ischaemia

Chronic hyperglycaemic damage to the retinal capillaries results initially in leakage, then non-perfusion and capillary drop-out. These areas of macular and retinal hypoxia have an absence of capillaries which appear as totally dark areas on both OCT-A and FA. The larger retinal vessels are not affected and will remain visible.

Neovascularisation

Capillary non-perfusion and tissue hypoxia is a driver for upregulation of vascular endothelial growth factor (VEGF) which leads to the formation of new retinal blood vessels at the optic disc (NVD) and elsewhere (NVE) throughout the retina. FA is particularly sensitive for detecting these new vessels as their walls are highly permeable and allow ready leakage of fluorescein dye into the retina. OCT-A is unable to see leakage which makes it difficult to locate NVE which usually form at the border between perfused and non-perfused retina, but once detected, can readily image these new vessels which have quite a different morphology to existing retinal vessels (Figures 8 and 11).

Conclusion

No clinical instrument is ideal in every situation, and each test will have both areas of strength and of weakness. Ideally, multimodal imaging using a variety of instruments such as fundus photography, fundus autofluorescence, structural OCT and OCT-A can provide better sensitivity and specificity for disease detection. OCT-A is already able to replicate the majority of information that FA gives us with the advantages of ease-of-use, greater safety profile, higher resolution and intricate software analysis, at the expense of a smaller capture area that is not ideal for peripheral imaging, and the inability to detect blood flow rates and vascular leakage.

OCT-A provides the optometrist with angiography tools that were not previously available to us, allowing the practitioner to detect early diabetic retinopathy and areas of capillary non-perfusion that are not always visible on fundus examination alone. Being quick, easy and risk-free to perform, OCT-A can be used at every diabetic eye exam which will aid in early detection of disease; prompt referral can then be made should any significant areas of macular oedema, capillary drop-out and/or neovascularisation be detected.

As OCT and OCT-A instruments continue to improve in resolution, capture area and software analytics, FA will gradually become a secondary test that is not generally required in the management of diabetic retinopathy, as has become the case in neovascular age-related macular degeneration where FA is no longer required for definitive diagnosis to allow patients access to Pharmaceutical Benefits Scheme (PBS) subsidised anti-VEGF injections.

OCT-A already does a lot of things better than FA, and over time will continue to improve and may soon become the gold standard for retinal and choroidal vascular imaging. ▲

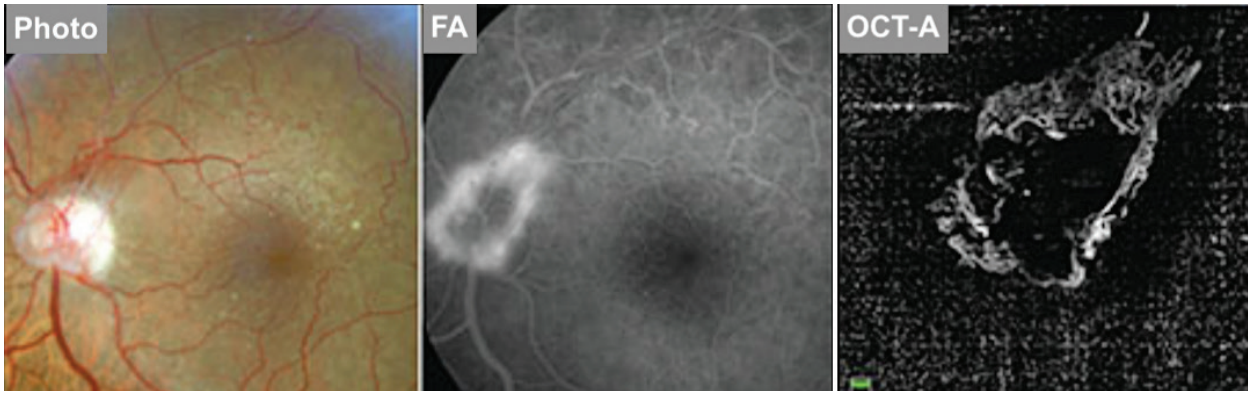

Figure 11. Multimodal imaging of neovascularisation of the disc (NVD) seen in fundus photography, diffuse leakage in late stage FA, and as a lacy network of new vessels in OCT-A

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Automatic for the people?

The pros and cons of AI-based 'diagnosis' of diabetic retinopathy

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Artificial intelligence (AI) refers to the use of computer software algorithms to approximate and surpass human cognition for analysis of complex data sets. In the health care setting, the goal is to analyse relationships among various diagnostic criteria, treatment regimens and patient outcomes.

Recently, AI has been tested and applied to eye care for the detection and staging of several important eye diseases, including age-related macular degeneration,[1] glaucoma,[2] and diabetic retinopathy.[3] Of note, such applications may be of use to eye care specialists (optometrists and ophthalmologists) for both detection and refinement of treatment decisions [4] as well as by primary care physicians (PCPs) or other clinicians outside of eye care for detection and intelligent referral of specific patients to ophthalmic providers.

The US Food and Drug Administration (FDA) just gave first approval to an AI algorithm for the detection of diabetic retinopathy in the offices of non-ophthalmic health care practitioners.[5] Dubbed the IDx-DR (IDx, LLC, Coralville, Iowa), and paired with a Topcon NW400 non-mydriatic retinal camera, captured images are sent to a cloud-based server that utilises the IDx-DR software and a 'deep learning' algorithm to detect retinal findings consistent with diabetic retinopathy based on autonomous comparison with a large dataset of representative fundus images.

The FDA statement says that if captured images 'are of sufficient quality, the software provides the doctor with one of two results: (1) "more than mild diabetic retinopathy detected: refer to an eye care professional" or (2) "negative for more than mild diabetic retinopathy; re-screen in 12 months".' Further guidance from the FDA states that 'If a positive result is detected, patients should see an eye care provider for further diagnostic evaluation and possible treatment as soon as possible.'

FDA-approval was based on submission of a 900-subject study using IDx-DR in a primary care setting (10 sites) with automated image analysis of two, 45-degree digital images per eye (one centred on the macula, and one on the optic nerve). This was compared against stereo, wide-field fundus imaging interpreted by the Wisconsin Fundus Photograph Reading Center (FPRC) based on the Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRS) and wide-field stereo photographs combined with macular optical coherence tomography (OCT) for detection of diabetic macular oedema (DME).[6]

More than minimal diabetic retinopathy was defined as the presence of ETDRS level 35 or higher (microaneurysms plus hard exudates, cotton wool spots, and/or mild retinal haemorrhages) and/or DME in at least one eye.[7] Ninety-six per cent of images acquired in primary care were deemed of sufficient quality for algorithmic assessment after human operators received four hours of training with the Topcon-IDx-DR system.

The technology was 87 per cent sensitive and 90 per cent specific for detecting more than mild diabetic retinopathy. Of note, the algorithm correctly identified 100 per cent of subjects with ETDRS level 43 or higher diabetic retinopathy (moderate non-proliferative disease or worse, defined as microaneurysms plus mild IrMA in up to three quadrants or either moderate retinal haemorrhage in four quadrants or severe haemorrhage in one quadrant).[7]

Although AI detection of diabetic retinopathy by non-ophthalmic providers has not yet received Therapeutic Goods Administration (TGA) approval in Australia, it seems highly probable that this will occur at some point in the future. So will artificial intelligence be the next 'big thing' in diabetes eye care, revolutionising the way we practice, reducing costs, facilitating accurate diagnoses and reducing diabetes-related blindness?

Upsides

The public health argument for widespread, autonomous detection of diabetes-related eye disease centres on the fact that many patients do not receive dilated retinal examinations by eye-care practitioners at recommended intervals.[8] In Australia, it has been reported that more than 75 per cent of non-Indigenous people with diabetes receive dilated eye examinations at the recommended interval of every two years, whereas among Indigenous Australians with diabetes, roughly 53 per cent receive such examinations every year per National Health and Medical Research Council (NHMRC) recommendations.[9]

Of critical importance, lack of adherence to dilated eye examinations worldwide is linked to distance from urban centres and eye-care facilities, lack of patient knowledge regarding the often asymptomatic nature of diabetes-related eye disease and male gender.[10] Greater accessibility of diagnostic AI in rural or remote settings, as well as areas with poor health literacy might remove or mitigate these barriers.

Moreover, detecting referable or treatable disease in patients who would not otherwise receive eye examinations for whatever reason (lack of knowledge, inaccessibility of eye care providers, cost, etc.) is anticipated to save both vision and money by focusing treatment resources on those who need it most, particularly in low-resource settings. Additionally, AI might allow PCPs to boost their quality measures, protect their income and may represent a new revenue stream depending on how third party payers decide to handle reimbursement for AI services.

Additionally, the marginal costs of operating AI are almost nil once the devices and supporting technologies have been acquired by PCPs.[11] Another argument in favour of AI is a failure of optometrists and ophthalmologists to send a diabetes exam report to the PCP (though, interestingly, correspondence from the PCP to the eye care provider has been shown to be more important for compliance with dilated eye examinations).[12]

'It makes far more economic sense for non-ophthalmic providers to work collaboratively with eye-care providers in their communities to ensure that patients receive the appropriate diagnosis and care, rather than spend tens of thousands of dollars to utilise a system that identifies a fraction of at-risk patients.'

Downsides

However, there are some downsides that are very important for PCPs and endocrinologists to understand about the current iteration of AI-for-diabetes-eye-care. These downsides must be thoroughly communicated to eye care providers and their patients.

1. Diabetes patients frequently have ocular disease other than diabetic retinopathy (glaucoma, AMD, cataract and dry eye, to name the most prevalent) and these require a comprehensive (dilated) eye examination for proper diagnosis and management. A 'negative' AI-based finding may give PCPs and patients a false sense of security about the totality of their ocular status. Every optometrist knows this, but many health providers outside of eye care do not.

2. The relatively high false positive rate reported in the aforementioned clinical trial means that some patients already have or will soon progress to sight-threatening eye disease. As we all know, individual patient risk of disease severity and vision loss is predicated on disease duration, degree and consistency of metabolic control and accurate staging of diabetic retinopathy – factors that determine appropriate follow-up intervals and patient-specific education.

Emerging evidence from the Joslin Diabetes Center at Harvard University shows that diabetic retinopathy lesions in the peripheral retina are highly predictive of which patients will develop proliferative diabetic retinopathy (DRCR.net Protocol AA is underway to substantiate this), the truly blinding form of the disease.

The system employed by IDx-DR does not capture the peripheral retina and, as such, may not correctly stage the disease, again giving both patients and PCPs a false sense of security. It should be noted that a 2018 *Association for Research in Vision and Ophthalmology* (ARVO) presentation showed excellent reliability and accuracy for detecting, staging and predicting progression of diabetic retinopathy, including peripheral lesions, using AI coupled with an ultrawide-field retinal imaging system;[13] however, this would almost certainly increase the cost of acquisition and decrease the return on investment.

3. The leading cause of vision loss in diabetes is diabetic macular oedema (DME), the gold-standard for detection of which is stereoscopic macular examination coupled with spectral domain optical coherence tomography (SD-OCT). Though all subjects with ETDRS level 43 or higher DR were detected via IDx-DR, we have to wonder how many cases of subtle DME were missed as this specific data was not reported by study investigators. I also have concern that AI algorithms designed to pass or fail individual patients above any specific level of disease severity may hinder appropriate education and targeted intervention for patients with milder DR. If an optometrist or his/her loved one had even mild NPDR, I suspect most of us would want to know and do everything possible to minimise its progression. Moreover, mounting evidence demonstrates that diabetes induces structural and functional retinal/visual abnormalities long before the appearance of the classic retinal vascular findings associated with DR,[14,15] and patients exhibiting early changes deserve correct diagnosis and early intervention, something for which optometry as a profession is ideally trained and suited.

4. In the US and Australia, there are roughly 58,000 optometrists and 6,000 ophthalmologists, who are specifically trained to diagnose and manage the spectrum of diabetes-related eye disease and who have committed substantial resources in education and instrumentation to help us identify patients earlier and educate appropriately based on individualised risk factors and stage of disease. The United States has about 30 million people with both diagnosed and undiagnosed diabetes (diabetes patient: eye doctor ratio = 517), whereas Australia has 1.7 million (diabetes patient: eye doctor ratio = 283). As such, it makes far more economic sense for non-ophthalmic providers to work collaboratively with eye care providers in their communities to ensure that patients receive the appropriate diagnosis and care, rather than spend tens of thousands of dollars to utilise a system that identifies a fraction of at-risk patients, especially in Australia, where doctor/patient ratios are even more favourable. As I recently told a PCP sitting in my exam chair, 'if your patient care quality scores are down due to inadequate patient adherence to

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AI for DR

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dilated eye examinations, the solution is to encourage a diabetes-savvy optometrist to open a practice adjacent to or within yours! Work collaboratively and proactively with optometrists and ophthalmologists – we are ready, willing and able to assist you.'

I have had interesting conversations with a few endocrinologists and internal medicine physicians about the IDx-DR. All of them expressed concern about false positives, false negatives and the fear of malpractice litigation ('will the device be sued for malpractice? I don't think so!' said one doctor). False positives and negatives will assuredly drop as the technology gets better, and advanced imaging AI will undoubtedly be able to detect more subtle pathology than can even the best examiner's eyes. Informed consent will help with litigious patients.

There is a strong argument for utilising AI in the detection/management/treatment/follow-up of diabetic retinopathy; to help eye care providers do a better job detecting and staging patients and efficiently treating those patients when necessary; to reach at-risk patients in remote and/or underserved areas; to reduce the global burden of blindness.

AI will almost certainly play an increasingly important role in diabetes care, especially as the number of patients in poorer nations burgeons and where resources are scarce. Autonomous detection of diabetes complications certainly has merit in underserved populations and where providers are not plentiful. This is not the case, however, in most areas of the United States and Australia. Patients with diabetes in our countries deserve a real eye examination, not merely a partially-adequate decision tool that tells them if they, in fact need an eye examination by a knowledgeable and experienced eye care provider. ▲

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