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Anterior Eye Complications in Diabetes Mellitus: Part 2

COURSE CODE C-16467 O/D

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Aside from vascular changes to the retina, which are the most common effect of diabetes mellitus (DM), the anterior structures of the eye can also become dysfunctional in a state of hyperglycaemia. It is vital for eye care professionals to recognise such changes so that early and rapid treatment can prevent irreversible damage from occurring. This article continues from the previous article in this series, by outlining the complications that occur in the aqueous humour, iris, pupil, lens and refractive state of people with DM.

Aqueous humour

Aqueous humour production and flow has been reported to be reduced in the eyes of people with DM,[1-4] with the severity being dependent on the degree of retinopathy.[1,2] This finding relates to the vascular endothelial growth factor (VEGF), a chemical signal that promotes growth of new blood vessels. With increased amounts of VEGF found in the vitreous and retina of diabetic eyes, particularly those with proliferative diabetic retinopathy,[5] it follows that there is a significant increase in microvascular complications at the trabecular meshwork, as well as in the retina, and therefore a reduction in aqueous outflow can be present in patients with DM, particularly in the early stages.[3] Logically, reduced aqueous outflow should result in increased intraocular pressure (IOP) and population studies have confirmed this to be true, with IOP higher than 21mmHg common[6-8] although one study found IOP measurements to be lower, with Type 1 showing a lower IOP than Type 2 DM.[9]

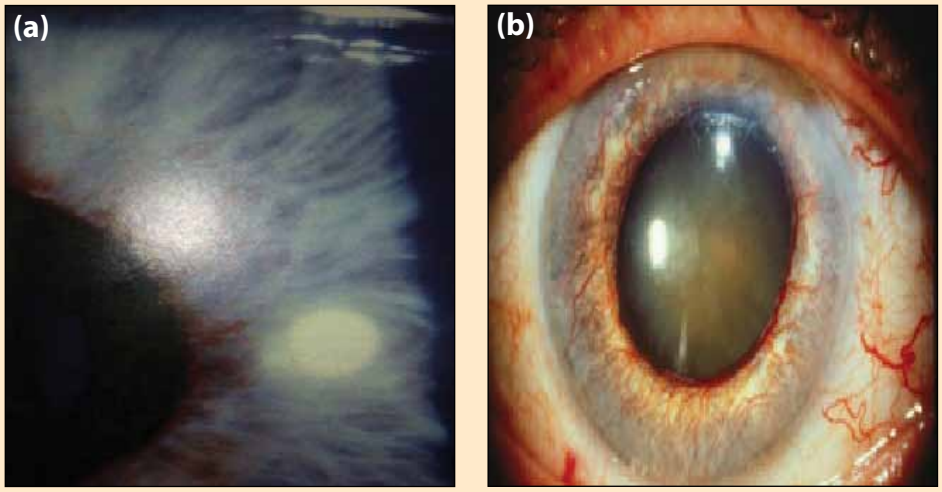

Figure 1
(a) Early rubeosis at the pupillary margin. On gross inspection, the pupillary margin appears to be pigmented, but upon closer inspection with a slit-lamp it appears to be small tufts of blood.[10] (b) Advanced rubeoss iridis. Reproduced with permission from Elsevier

Iris

Neovascularisation of the iris (NVI), also known as rubeosis iridis, occurs when new blood vessels are created from pre-existing iris capillaries found near the pupillary margin (Figure 1)[10] and iris root. Fine tufts of vessels then appear on the anterior iris and the chamber angle, which can differ in severity.[11,12] The vessels may be present for long periods of time without causing any problems. However, as shown in Figure 2, the vessels can grow with supportive fibrous tissue, resulting in occlusion of the anterior angle and ultimately causing secondary neovascular glaucoma (see later).

One of the most important characteristics of the new vessels is that the thin walls are prone to leakage, which means fluorescein angiography is essential in determining the stage of NVI.[11,13] Stage 1 NVI involves the appearance of thin-walled blood vessels in the iris near the root and the pupillary margin. In Stage 2 NVI, the new vessels have 'pierced' the anterior iris surface near the pupil and the root of the iris; the two sets of blood vessels will extend and merge, and more new vessels will form in the iris stroma. In Stage 3 NVI, new vessels with fibrous support tissue cover part or all of the anterior surface of the iris, the anterior surface flattens, there is development of ectropion uvea, loss of dilator muscle, and peripheral anterior synechiae, causing the peripheral iris to attach to the cornea, blocking the anterior chamber angles.

People with proliferative retinopathy are at the highest risk of developing NVI.[11,13] However, it is possible to develop NVI without any vascularisation of the retina.[14] Iris vessels are thought to be the most susceptible to VEGF, which arises due to retinal hypoxia.[15]

Neovasacular glaucoma

The most common, and indeed the most problematic, complication of rubeosis iridis is secondary neovascular glaucoma.[11,14,15] It is an extreme diabetic complication that can result in blindness and cause excruciating pain to the patient,[11,13,14] to the extent that the affected eye can end up being enucleated.[11] However, recent studies have shown modern treatments (anti-VEGF therapy) can halt this new vessel growth on the iris.[14] Characteristics of neovascular glaucoma other than NVI include high IOP and trabecular meshwork blockage[16] (Figure 2). Neovascular glaucoma may occur many years after the presence of NVI.[11]

Aside from rubeosis of the iris, other complications of the iris that relate to DM have been associated with iris colour. Blue/grey irides have been reported to carry a higher incidence of macular oedema and cataracts, whilst brown irides are reportedly more prone to high IOP.[17]

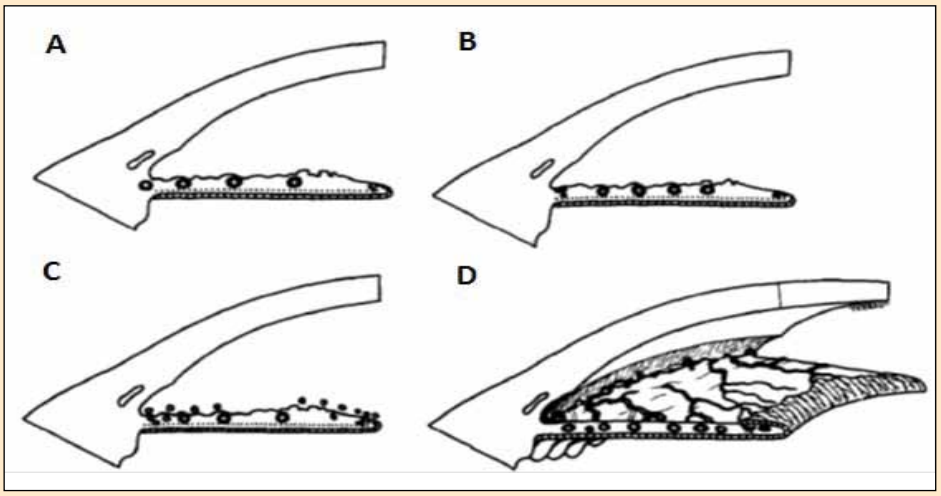

Figure 2
Stages of iris neovascularisation (a) cross-section of a normal iris and chamber angle, (b) Stage 1 iris neovascularisation, (c) Stage 2 iris neovascularisation, and (d) Stage 3 iris neovascularisation.[13] (see text for details). Reproduced with permission from Elsevier

Pupil

The diabetic eye exhibits a miotic pupil,[18-24] and it has been reported that pupil diameter becomes smaller with increasing duration of DM.[22] People with DM but without any sign of diabetic retinopathy had approximately the same pupil size as those who do not have DM, while significantly smaller pupils were found in people with proliferative diabetic retinopathy.[25] The pupils may appear to show a reduced response to light too, although the pupillary light reflex is relatively the same as in healthy patients when the small pupil size is taken into account.[18,19]

A small pupil is a diagnostic characteristic of diabetic autonomic neuropathy, and pupillary function abnormalities can be detected earlier than abnormalities of any cardiovascular autonomic functions.[23,26] Furthermore, a miosed pupil has been associated with the development of retinopathy when the duration of DM has reached 12 years.[23] Patients with autonomic neuropathy also show a reduction in hippus (a small, rhythmic and fast fluctuation of the pupil) during continuous illumination compared to healthy patients.[18]

It seems that both parasympathetic and sympathetic pupillary damage occurs in people with DM, with the latter occurring at a later stage than the former.[21] There is a chronic progressive loss of parasympathetic innervation rather than an acute loss, and this results in increased denervation hypersensitivity. Additionally, this could explain why pupil size is smaller in those that have had DM for a longer duration, since there is long-lasting hypersensitivity to acetylcholine.[22]

A small pupil in a patient with a family history of DM can be checked using 0.1% pilocarpine drops, as a greater constriction of the pupil demonstrates post-ganglionic parasympathetic damage.[27] To achieve adequate dilation to examine the retina in patients with DM, one study suggests using a combination of the topical drugs tropicamide and phenylephrine.[28]

The pupil can be affected by aneurysm compression of the oculomotor (IIIrd) nerve, for example at the junction of the internal carotid artery and the posterior communicating artery, resulting in a small degree of anisocoria (1mm or less).[29] However, a IIIrd nerve palsy in a patient with DM normally results in the pupil being spared.[30] The reason for this is that the pupillomotor fibres lie along the outer layer of the third nerve, but an ischaemic lesion affects the centre of the fascicle, sparing the pupillomotor fibres and leaving the pupil unaffected.

Lens

It is estimated that the lens in an adult person with DM ages by approximately 15 years, when compared to age-matched controls.[31] People who have had DM for longer and those with poor glucose control are at higher risk of developing diabetic cataracts.[32] There are two major types of diabetic cataracts that can be formed: true diabetic cataract, or 'snowflake' cataracts, and the more frequent adult-onset diabetic cataracts.

Snowflake cataracts are characterised

by flake opacities and fine white punctate spots in the anterior and posterior subcapsular areas of the lens (Figure 3),[33] and they appear mainly in younger Type 1 DM, although it is known to appear in Type 2 DM as well.[31,34] It is recommended that all new cases of Type 1 DM, especially those presenting with blurred vision or glare, have their lenses thoroughly examined to diagnose cataracts early and to prevent irreversible changes.[35] Adult-onset diabetic cataracts are similar in appearance to nuclear sclerosis cataracts (Figure 4)[36] and, as the name suggests, appear mainly in older middle-aged patients with Type 1 and Type 2 DM.[37] This is a type of cataract that occurs with age, but develops quicker in patients with DM.[32]

Early symptoms of adult-onset diabetic cataract are persistent refractive changes, glare, and monocular diplopia or polyopia.[32] Snowflake cataracts can be reversed once the hyperglycaemic condition has been addressed. However, adult-onset cataracts are slightly more permanent and may end up requiring cataract surgery.[31,32,37]

In one case study,[38] a newly diagnosed patient with DM was prescribed Metformin 750mg twice daily to reduce the serum glucose level. Upon initiation of the treatment, the patient presented with sudden onset blurry vision. Upon examination 'sugar cracks' going largely through the central lens nucleus were noted,[38] and early signs of posterior subcapsular opacification were present too. After five months of therapy, vision returned to baseline and the lens appeared healthy with no cracks or opacification.

Patients with DM can possibly experience an increase in colour vision defects[39] too, usually along the blue-yellow axis, which one study[40] attributed to the yellowing of the lens.

Cataract Surgery

If the cataract has progressed to the point where a clear retinal picture cannot be seen, for the purposes of digital photographic retinopathy screening, cataract surgery would be considered to allow accurate diagnosis and treatment.[41] There are many conflicting studies regarding the effects of cataract surgery on a patient with DM. Some studies suggest that cataract surgery will accelerate the development or progression of diabetic retinopathy,[42,43] while others found no such evidence,[44-46] with one study suggesting that phacoemulsification should not be considered as a contraindication in patients with DM.[47]

The incidence of post-surgery posterior capsular opacification (PCO) is reduced in patients with DM,[48] however, a conflicting study showed that a higher rate of PCO is found in patients with advance diabetic retinopathy.[49] Reasons for this conflicting evidence are not yet clear.

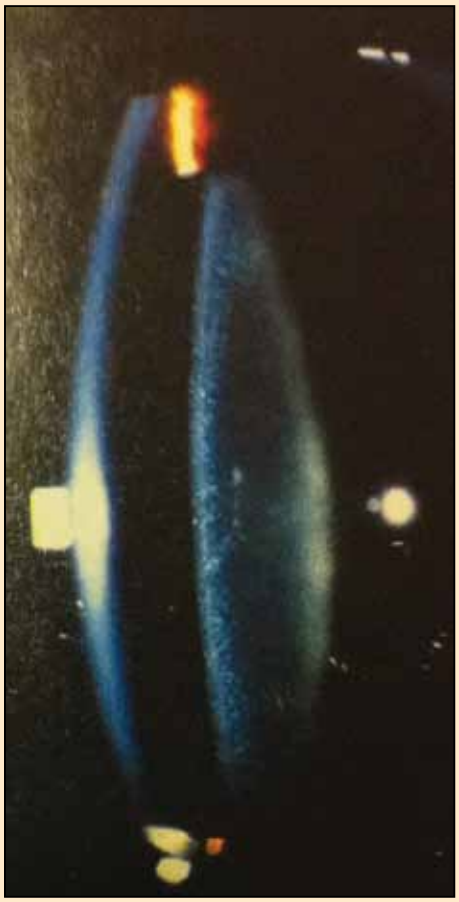

Figure 3
Snowflake cataract.[33] Reproduced with permission from Elsevier

Refraction and accommodation

People with uncontrolled blood sugar levels are known to experience a general fluctuation in their vision. The nature of refractive error change is believed to depend on the status of the underlying DM. If the patient is undiagnosed ie, in a state of hyperglycaemia, he/she can become more myopic[50] or more hyperopic.[51-53] Under intensive glycaemic control, the refractive error generally shifts in a hypermetropic direction,[54-56] with a larger degree of initial myopia showing larger shifts in refractive error.[57] Recovery of the refractive error back to baseline without any more fluctuating takes about 6-10 weeks when treated with insulin, while oral hypoglycaemic medication takes approximately twice as long.[51] There is no link between the sex, age, duration of DM, type of therapy, or the amount of hyperopic change seen, in a patient with DM.[57] General physical inactivity is also thought to contribute to fluctuating vision.[58]

The total refractive power of the eye is made up of several different parts including corneal curvature (posterior and anterior), central corneal thickness (CCT), the depth of the anterior chamber, thickness and axial length of the lens. There are no significant changes in corneal curvature or axial length during the period of instable refractive error, however, a thicker lens and decreased depth of the anterior chamber has been found.[54] It has been suggested that the thicker lens found in people with DM results in a lowering of the refractive index and this results in a shift towards increased hyperopia.[54]

Accommodation has been found to be significantly reduced in people with

Figure 4
Nuclear sclerotic cataract.[36]

DM compared with those who do not have DM, and this is one reason why such patients can reportedly experience more headaches, blurred vision and vertigo upon attempting to read.[59] The association has found to be due to an increase in the blood sugar level, which leads to a decrease in the amplitude of accommodation (AoA).[59] Interestingly, it has been found that females with DM present with a greater decrease in the AoA compared with males,[60] a finding that is not true of those without DM;[61,62] the reason for this is not yet clear.

Tear Film	Dry eye Reduced stability Decreased reflex tearing and total tear secretions Reduced mucin layer
Conjunctiva	Conjunctival aneurysm Increased blood vessel tortuosity Acute infectious conjunctivitis Thickened basement membrane Conjunctival metaplasia
Cornea	Epithelial keratopathy (recurrent corneal erosion, superficial punctate keratitis, corneal epithelial defects) Impaired epithelium barrier function Delayed epithelial re-epithelisation (healing) Endothelium polymegathism and pleomorphism Increased central corneal thickness Folds in Descemets membrane Increased corneal hysteresis Reduced corneal sensitivity Neurotrophic keratopathy
Aqueous Humour	Increased VEGF concentrations Reduced aqueous formation
Iris and Pupil	Neovascularisation of the iris (leading to secondary neovascular glaucoma) Miosed pupil and reduced hippus
Lens	Snowflake and adult-onset cataracts

Table 1
A summary of complications of the anterior segment of the eye that can be present in patients with diabetes mellitus

Refractive surgery

Considering the numerous corneal complications that can present in a patient with DM (see part 1 of this series, *Optometry Today*, July 15 2011), one would think that refractive surgery is not a valid option for the correction of refractive error. In Photorefractive Keratectomy (PRK), the cells of the corneal epithelium are removed, allowing new cells to re-grow post-surgery. As patients with DM can exhibit delayed epithelial healing and abnormal epithelial adhesion, it is not generally considered a good idea to carry out PRK.[63] Indeed, the same can be said of Laser Epithelial Keratomileusis (LASEK) surgery, which has predominantly replaced PRK, as it still relies on re-epithelisation of the cornea.

In contrast, Laser-Assisted In Situ Keratomileusis (LASIK), in patients with a stable refractive error and no active diabetic retinopathy, can be considered as an option.[63] Post-LASIK, there is an increased incidence of epithelial in-growth in patients with DM,[64,65] which would be an unwanted complication, as it may require removal of the epithelial cells.[66] There is also a risk of further epithelial in-growth if enhancement surgery is required after the initial surgery, although it is unclear why this occurs.[64] In one study, all patients with DM that underwent LASIK had post-operative visual acuity of 6/6,[64] which displays the positive visual outcomes that can be achieved.

Optometric considerations

There are several signs that are highly indicative of diabetic eye disease, which optometric practitioners should familiarise themselves with. Fluctuations of vision, neovascularisation of the iris and snowflake cataracts should set the proverbial alarm bells ringing. Early signs that could warrant further investigation include an increase in CCT, a miosed pupil and reduced

aqueous outflow (linked to IOP measurements). One study goes far enough to suggest that corneal sensation can be used as a screening method for diabetic neuropathy.[67]

When assessing a patient with DM, or a patient at high risk of developing DM, the clinician should know what to specifically look for when assessing the anterior eye structures (Table 1), so that initial complications can be detected and the patient can be given advice on metabolic control, or can be referred to their General Practitioner for a more thorough diabetic assessment.

Conclusion

A wide range of complications can occur in the anterior segment of the eye of a person that has DM. They mostly seem to occur as a result of poor metabolic control. The early detection of signs and symptoms is key to prevent any long-lasting and irreversible damage, and with new drugs and treatment options available, these can help to halt and possibly even reverse visually-damaging problems.

About the author

Alan Hawrami obtained his optometry degree at City University and has completed a post-graduate degree at Aston University.

References

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Module questions

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1. Stage 3 neovascularisation of the iris involves:
a) Neovascular glaucoma
b) Peripheral anterior synechiae
c) Flattening of the iris surface
d) All of the above

2. Which of the following statements about the lens in diabetes mellitus is FALSE?
a) The lens ages at an accelerated rate
b) Poor-glucose control can lead to lens opacifications
c) There is no need for cataract surgery in a patient with advanced cataracts
d) Lens thickening occurs in a patient with hyperglycaemia

3. LASEK may not suitable for a person with uncontrolled diabetes mellitus because of:
a) Abnormal re-epithelisation
b) Delayed healing
c) Unstable refractive error
d) All of the above

4. A person with diabetic autonomic neuropathy:
a) Exhibits a large pupil
b) Shows an increase in hippus
c) Will always have associated ptosis
d) May have a reduced pupillary light reflex

5. A hypermetropic shift in refractive error, in a person with diabetes mellitus, is MOST likely to be due to:
a) Intensive glycaemic control
b) Long-standing diabetes
c) The gender of the patient
d) The age of the patient

6. Which of the following statements about diabetes mellitus is FALSE?
a) Aqueous humour outflow is reduced
b) IOP measurements are always reduced
c) VEGF can be found in the aqueous humour
d) Aqueous humour production is related to the degree of retinopathy

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