Practice pearls and hot topics in diabetic retinopathy

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In the first of a series of articles summarising lectures presented at the 2018 Primary Care Academy of Diabetes Specialists (PCADS) meeting, Kevin Fernando outlines the challenges that primary care faces in the safe handling of eye problems in people with diabetes.

Diabetic retinopathy is a complication of diabetes that damages the blood vessels in the retina and remains one of the leading causes of blindness in the UK. This article describes the different types of the condition and outlines how its progression can be reduced. Advice on what to consider during a consultation is provided in "practice pearls", while "hot topics" provide the latest evidence on prevention and treatment.

Diabetic retinopathy (DR) is one of the leading causes of blindness in people of working age in the United Kingdom. The main risk factors are increasing duration of diabetes and chronic hyperglycaemia. Additionally, the presence of hypertension, diabetic kidney disease, dyslipidaemia and smoking contribute to an increased risk of DR. The condition is characterised by pathological microvascular changes leading to retinal ischaemia, neovascularisation and macular oedema.

Non-proliferative (or "background") diabetic retinopathy is characterised by the development of capillary microaneurysms, "dot-and-blot" haemorrhages, soft exudates (or "cotton wool spots") and hard exudates.

DR can also be proliferative, which is characterised by the formation of new vessels (neovascularisation) within the retina or growing into the vitreous gel. Proliferative retinopathy is a sight-threatening emergency with a high risk of pre-retinal and vitreous haemorrhage as well as an increased risk of retinal detachment.

Diabetic maculopathy is the commonest cause of blindness in diabetes and is associated with retinal changes within the macular region of the retina. The macula is an oval-shaped pigmented area near the centre of the retina and is responsible for central, high-resolution colour vision.

Reducing the progression of diabetic retinopathy

Tight glycaemic control, aiming for an HbA_{1c} <53 mmol/mol (<7%), prevents the development and progression of DR. The seminal DCCT (Diabetes Control and Complications Trial) and EDIC (Epidemiology of Diabetes Interventions and Complications) studies demonstrated that an intensive insulin strategy in those with type 1 diabetes achieved a 2% reduction in HbA_{1c} compared to a conservative insulin regimen (DCCT Research Group, 1993; EDIC Research Group, 1999). This translated into a 76% relative risk reduction in the risk of new-onset retinopathy and a 56% relative risk reduction in the risk of progression of retinopathy.

However, DCCT/EDIC also observed that an intensive insulin therapy regimen can be associated with recurrent hypoglycaemia and early worsening of DR. Reassuringly, this latter effect was reversed by 18 months and no case of early worsening of DR resulted in serious visual loss.

There are many theories on the underlying

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Article points

1. The main risk factors for diabetic retinopathy are increasing duration of diabetes and chronic hyperglycaemia.
2. Tight glycaemic control prevents the development and progression of diabetic retinopathy.
3. People with diabetes should be screened regularly for diabetic retinopathy.

Key words

- Diabetic maculopathy
- Diabetic retinopathy (non-proliferative)
- Diabetic retinopathy (proliferative)

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Page points

1. Anyone with any form of diabetes who complains of the onset of blurred vision, floaters or field loss should be taken seriously, with urgent referral considered.
2. With underlying retinal or optic nerve disease, the pupil in the affected eye abnormally dilates when a pen light is swung towards it in a dimly lit room.
3. Diabetic kidney disease nearly always coexists with diabetic retinopathy.
4. Diabetic retinopathy is strongly predictive of cardiac autonomic neuropathy, a stealthy complication of diabetes.

cause of this early worsening of DR. One is the osmotic movement of water out of retinal vessels as a result of the rapid reduction in blood glucose, leading to retinal ischaemia. Whilst biologically plausible, this does not explain all the changes seen in DR and we await further research to fully elucidate the underlying mechanism of early worsening of DR.

Tight blood pressure control, aiming for <130/80 mmHg, also prevents the progression of DR (SIGN, 2010), but blood pressure targets need to be individualised to ensure that the benefits of treatment outweigh any harms, such as postural hypotension and falls.

Practice pearls

1. Acute or subacute visual loss in those with diabetes

Any individual with any type of diabetes complaining of acute or subacute onset of blurred vision, floaters or field loss should ***always*** be taken seriously, with consideration of ***urgent*** referral.

Individuals with diabetes are at high risk of serious eye disease, particularly diabetic maculopathy and vitreous haemorrhage secondary to proliferative retinopathy. Importantly, diabetic maculopathy can occur at ***any*** stage of DR and remains the most common cause of blindness in diabetes.

2. The "swinging light" test

Consider the "swinging light" test to check for a relative afferent pupillary defect (RAPD) in ***all*** individuals complaining of blurred vision, flashes, floaters or visual field loss. The presence of a RAPD signifies serious underlying retinal or optic nerve disease.

The swinging light test should be undertaken in a dimly lit room. The patient is asked to gaze into the distance while the examiner swings the beam of a pen light back and forth from one pupil to the other, observing the size of pupils and reaction in the eye that is lit. Normally, each lit pupil quickly constricts and the opposite pupil also constricts consensually. If there is underlying retinal or optic nerve disease, the sensory (afferent) stimulus to the brain is impaired and the pupil in the affected eye abnormally dilates when the light is swung towards it.

3. The relationship between DR and diabetic kidney disease

Diabetic kidney disease (DKD) nearly always coexists with DR. Consider alternative underlying causes of kidney disease if:

- ***No*** diabetic retinopathy is present.
- A short duration of diabetes is evident.
- Heavy proteinuria is present (consider nephrotic syndrome and IgA nephropathy).
- Haematuria is present (consider glomerulonephritis, especially if red cell casts are also present).

4. Cardiac autonomic neuropathy and DR

Cardiac autonomic neuropathy (CAN) is a stealthy complication of diabetes and is associated with a resting tachycardia, postural hypotension and, more worryingly, an increased risk of myocardial ischaemia and infarction. Moreover, CAN has a poor prognosis and is associated with a significantly increased risk of total and cardiovascular mortality (Bissinger, 2017).

A recent small Taiwanese study (Huang et al, 2016) found that DR is strongly predictive of CAN in those with type 2 diabetes. Whilst not immediately generalisable to those with type 2 diabetes in the UK, it does provide a useful message for all of us working in primary care:

In those with significant DR, consider further investigation for signs and symptoms of CAN:

- Resting tachycardia (>100 bpm).
- Postural hypotension (>20-mmHg fall in systolic blood pressure).
- Evidence of previous myocardial infarction (e.g. pathological Q waves on an electrocardiogram).
- Exercise intolerance.

Hot topics

1. Screening intervals for DR

The NICE guideline on the management of type 2 diabetes in adults (NG28; NICE, 2015) suggests annual structured eye screening after diagnosis, whilst SIGN 116 (2010) suggests retinal screening at diagnosis and

then individuals should be screened 2-yearly thereafter. However, if individuals have established DR, SIGN recommends annual screening.

A recent report by the Clinical Director of the NHS Diabetic Eye Screening Programme (Scanlon, 2017) suggested that if individuals with diabetes have no evidence of DR in either eye, they have a low risk of progression to sight-threatening DR over a 2-year period, with a rate of <5 DR events per 1000 person-years.

The report concluded that people in low-risk groups (low risk was defined as two consecutive screening episodes with no retinopathy) should have their screening interval lengthened to 2 years.

2. Fenofibrate for those with DR

The FIELD study (Keech et al, 2005; 2007) found that use of fenofibrate reduced non-fatal myocardial infarction in those with type 2 diabetes, but there was no overall mortality benefit. However, there were significant reductions observed in the need for laser treatment in those with maculopathy or proliferative retinopathy. The number needed to treat (NNT) was 90 for those without pre-existing DR; for those with a history of DR, it was just 17. Interestingly, the benefits appeared very quickly – within 8 months of treatment allocation – suggesting an underlying mechanism unrelated to improvements in blood lipids and related to fenofibrate itself.

It should be noted that DR was not a primary endpoint of the FIELD study and, whilst there were significant reductions in the need for laser treatment, there was no overall improvement in visual acuity.

The effects of fenofibrate seen in the FIELD study were echoed in the ACCORD Eye study (ACCORD Study Group and ACCORD Eye Study Group, 2010). However, these effects were only seen in "mild" retinopathy and there was no impact observed on macular oedema. Interestingly, there was no impact of intensive blood pressure control on retinopathy endpoints seen in the ACCORD Eye study, highlighting the importance of individualising blood pressure targets for those with diabetes.

In 2013, Australia became the first country to add DR as an indication for fenofibrate; it is approved for reducing the progression of DR in those with type 2 diabetes and existing DR (in combination with a statin). It does not, of course, replace appropriate management of blood glucose, blood pressure and lipids.

In the UK, there is no such approved indication for fenofibrate. The MHRA recommends using fenofibrate with caution and only when the expected benefits outweigh the risks. The LENS (Lowering Events in Non-proliferative retinopathy in Scotland) study is currently recruiting participants and will investigate whether fenofibrate, over 3 years, will slow the progression of DR.

3. Semaglutide and the risk of DR

Semaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist that will shortly be available in the UK. The SUSTAIN-6 cardiovascular outcome trial (Marso et al, 2016) demonstrated a 26% reduction in the primary major adverse cardiovascular events (MACE) composite endpoint with semaglutide, which was driven by a reduction in non-fatal stroke.

There were also improvements seen in new or worsening kidney disease, but, notably, a significant increase in retinopathy complications. *Post-hoc* analyses of SUSTAIN-6 data revealed a 1.2% absolute risk increase (3% versus 1.8%) with semaglutide compared to placebo (Vilsbøll et al, 2017). There was no imbalance in DR adverse events seen in the rest of the SUSTAIN trial programme. The authors argue that the majority of the effect in SUSTAIN-6 was due to the extent and rapidity of HbA_{1c} reduction seen with semaglutide during the first 16 weeks of treatment in those who had ***pre-existing DR*** and suboptimal glycaemic control at baseline, and who were treated with insulin.

4. Metformin and DR

A retrospective chart review study (Li et al, 2018) explored the effects of long-term metformin use on DR in individuals with long-standing type 2 diabetes. The study observed less non-proliferative and proliferative DR

Page points

1. National guidelines agree that regular retinal screening is required after a diagnosis of diabetes.
2. Fenofibrate is not indicated in the UK as a treatment for slowing the progression of diabetic retinopathy, although the LENS trial in Scotland is exploring potential benefits.
3. A significant increase in retinopathy complications in those with pre-existing retinopathy and sub-optimal glycaemic control at baseline has been observed with semaglutide, which may be due to the extent and rapidity of HbA_{1c} reduction in the particular study population.

Page points

1. For those with significant diabetic retinopathy who are not on metformin, evidence suggests that it may be worth considering introducing it.
2. Diabetic retinopathy is associated with vitamin D deficiency, so those with significant changes of diabetic retinopathy should be offered vitamin D supplementation.
3. For proliferative retinopathy, there are three VEGF inhibitors available in the UK, although they are only funded by the NHS if there is macular oedema present.

in metformin users, independent of gender, ethnicity, HbA_{1c} and the use of sulfonylureas and insulin. The authors concluded that long-term metformin use is independently associated with lower rates of DR.

From a primary care perspective, the majority of individuals with long-standing type 2 diabetes are likely to be on metformin. However, in those with significant DR who are not on metformin, it may be worth revisiting treatment regimens and considering introducing (or reintroducing) metformin.

5. Vitamin D deficiency and DR

A recent large meta-analysis of observational studies (Luo et al, 2017) explored the association between vitamin D deficiency (defined as vitamin D levels <20 ng/mL) and DR. The authors found a statistically significant association between DR and vitamin D deficiency, with a pooled odds ratio of 1.39. The authors concluded that all those with diabetes and low vitamin D levels should be screened for DR. However, the unanswered question is whether vitamin D supplementation improves DR outcomes; we await further research to clarify this issue. In the UK, all individuals with diabetes are screened regularly for DR so, pragmatically, from a primary care perspective it is worth ensuring that those with significant changes of DR are offered vitamin D supplementation consistent with Public Health England 2016 advice.

6. New therapies for DR

Mild and moderate non-proliferative DR are generally not treated unless there is significant associated macular oedema.

The most promising agents for the treatment of proliferative retinopathy and macular oedema are the vascular endothelial growth factor (VEGF) inhibitors. There are currently three VEGF inhibitors available in the UK: bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (Eylea). VEGF inhibitors are only funded within the NHS if there is macular oedema present. However, the recent PANORAMA trial (presented at the 2018 American Society of Retina Specialists Annual Meeting), which explored the use of aflibercept, demonstrated reversal of the progression of DR in moderate-to-severe and severe non-proliferative DR ***without*** macular oedema. It remains to be seen whether this will drive a change in the funding and use of aflibercept within the NHS. ■

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