Q&A
Diabetic retinopathy

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Q What is the difference between retinopathy and maculopathy?

"Diabetic retinopathy" describes any changes in the retina which are caused by hyperglycaemia in people with diabetes of any aetiology (and so includes people with both type 1 and type 2 diabetes). These changes include:

- Microaneurysms.
- Dot and blot haemorrhages.
- Hard exudates.
- Cotton wool spots.
- Venous abnormalities.
- New blood vessels (proliferative diabetic retinopathy).

When any of these changes occur within the macular region, it is termed "diabetic maculopathy". The macular region is an area which is arbitrarily defined (i.e. it does not have a true anatomical delineation), usually as a circle with a radius of two optic disc diameters from the fovea. The macula is responsible for central vision, and so any pathology in this area is potentially sight-threatening.

Q How common are retinopathy and maculopathy in people with type 2 diabetes?

Approximately 30% of people with type 2 diabetes have some form of diabetic retinopathy (Thomas et al, 2015). The International Diabetes Federation estimates that 3.9 million people had diabetes in the UK in 2021 (Sun et al, 2022), and 90% of these have type 2 diabetes; this means that just over a million people in the UK with type 2 diabetes would have diabetic retinopathy. The majority of this is background retinopathy.

Approximately 3% of those with type 2 diabetes (105 000 people in the UK) would have a sight-threatening form: pre-proliferative or proliferative diabetic retinopathy, or diabetic maculopathy (Thomas et al, 2015). Diabetic maculopathy is more common in people with type 2 diabetes, while proliferative retinopathy is more common in those with type 1 diabetes. The majority of those with type 2 diabetes with sight-threatening retinopathy would have diabetic maculopathy alone or in combination with pre-proliferative and proliferative retinopathy.

Q What is the significance of developing background retinopathy? What is the risk of progression of retinopathy and what are the risk factors?

After 20 years of having diabetes, approximately 80–90% of people with type 1 diabetes, and approximately 50% of people with type 2 diabetes, will have diabetic retinopathy (Yau et al, 2010). The majority of this will be background diabetic retinopathy. Once background diabetic retinopathy develops, the risk of progression to the sight-threatening levels increases.

Hyperglycaemia, hypertension and dyslipidaemia are all known risk factors for the development and progression of diabetic retinopathy. Studies have shown that an 11 mmol/mol (1.0%) reduction in HbA_{1c} levels reduces the risk of diabetic retinopathy by 40%, progression to vision-threatening retinopathy by 25% and to laser therapy by 15% (Cheung et al, 2010). A 10 mmHg reduction in systolic blood pressure decreases the risk of diabetic retinopathy by 35%, need for laser therapy by 35% and visual loss by 50%.

Note that the changes of background retinopathy are not fixed and they can regress and/or disappear between screening assessments.

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Q What action should we take to reduce the risk of retinopathy progression, especially when background retinopathy is reported?

Background diabetic retinopathy is usually the first complication of diabetes to occur. Therefore, it should be an early warning that changes are required to ensure the risk of progression of diabetic retinopathy, and of development of other complications, is reduced.

The cornerstone of diabetic retinopathy prevention and delaying progression is glycaemic and blood pressure management. Both should be optimised from the time of diagnosis of diabetes to prevent diabetic retinopathy from developing and to allow people to benefit from the legacy effect of intensive glycaemic management, as shown in the UKPDS and DCCT studies (Stratton et al, 2001; Lachin et al, 2015).

Once background retinopathy develops, the aim is to reduce the risk of progression, and so we should again look at optimising glycaemic and blood pressure control. This should include a review of diet and lifestyle, education, peer support, medication and technology that may help in the management of diabetes.

Q Who will be changed onto 2-yearly retinopathy screening?

Retinal screening has been recommended to be changed from annual to biennial since 2016 by the UK National Screening Committee. The change will affect those people considered to be at low risk of developing diabetic retinopathy. Those considered to be low-risk are those with two consecutive negative screening results (no evidence of diabetic retinopathy at two previous screening appointments 1 year apart). Therefore, anyone with diabetes would need to have had two annual screening results without evidence of diabetic retinopathy prior to being placed on the 2-year pathway.

Q Are there common reasons for non-attendance and are there groups who are less likely to attend for retinopathy screening? How can we help improve attendance?

Common reasons for not attending screening are (van Eijk et al, 2012; Lawrenson et al, 2021):

- Not understanding the importance of screening.
- Not understanding the screening process or what will happen.
- Prioritising other things over screening (e.g. work, other health appointments).
- Not being able to get to appointments.
- Not being able to take time off for appointments.
- Not being able to drive after eye drops.
- Discomfort from the eye drops.

Common groups that are less likely to attend screening include (Thomas et al, 2021):

- 18–34 year age group.
- From areas of high deprivation.
- Ethnic minority groups.

How to help improve attendance?

- Ensure your patients understand the importance of eye screening and what it achieves. They need to know why they should prioritise this appointment: what's in it for them.
- Ensure they know what the process of screening entails.
- Let them know that all appointments and locations can be changed to better suit them.
- Translation services are available for screening.

Q Have services caught up after the COVID-19 pandemic? How have retinal screening services had to change?

Screening programmes, like all routine services, stopped during the initial phase of the pandemic and, when they restarted, there were issues with social distancing and ensuring patient and staff safety, which slowed the throughput of people through screening and meant services needed to reduce the number of people who could be seen in each clinic. In addition, clinic spaces used by screening were reconfigured and used for other services, creating a lack of venues for screening. All of this impacted how screening caught up.

Some areas of the UK have eliminated their backlog, while others are still screening below pre-COVID levels. Screening programmes have adapted and changed to try and resolve their issues; some have utilised non-clinical venues, such as hotels and community centres, while others have outsourced screening to optometrists for people considered to be at high risk.

Q Are there risks associated with physical activity for people with retinopathy?

Physical activity has been linked to delaying the onset and progression of diabetic retinopathy, having both a protective and anti-inflammatory effect. The risks of exercising with diabetic retinopathy mainly apply in the sight-threatening forms when people are undergoing treatment. The risks are associated with more strenuous exercises such as heavy lifting, breath holding and high-impact activities. This type of strenuous activity could cause the fragile new vessels in proliferative retinopathy to bleed, thus affecting vision. There is, however, little evidence for a link between high levels of physical activity and worsening of diabetic retinopathy.

Q What important eye signs and symptoms should we be aware of which would indicate the need for immediate eye assessment by an optometrist?

The signs of an eye issue that requires urgent assessment would be:

- Sudden vision loss.
- Floaters.
- Blurred or patchy vision.
- Eye pain/redness.
- Flashing lights.
- Cobweb-type appearance in vision.
- Curtain-like shadow over vision.
- Reduced peripheral vision.

These symptoms should be checked immediately by an optometrist or in the emergency eye department.

Q What treatments are available for diabetic retinopathy, and what practical information should we know about these in non-specialist care?

There are a few different treatments available for diabetic retinopathy/maculopathy:

- Laser photocoagulation.
- Anti-vascular endothelial growth factor (anti-VEGF) injections.
- Steroid injections.

Treatment is given when proliferative diabetic retinopathy or diabetic macular oedema develops. Prior to this, people with pre-proliferative diabetic retinopathy or diabetic maculopathy will be closely monitored. Laser photocoagulation is the most commonly used treatment for proliferative diabetic retinopathy. The aim of laser is to stabilise the changes in the eye caused by diabetes; it is unlikely that this treatment will improve vision. How much laser and how often will be decided by the ophthalmologist on an individual basis, and will be determined by how the retinopathy responds. Anti-VEGF injections can also be used for proliferative diabetic retinopathy.

Diabetic maculopathy is monitored until there is evidence of fluid build-up within the retina (oedema), and is treated with anti-VEGF injections once central retinal thickness reaches ≥400 µm. There are several anti-VEGF treatments, including bevacizumab, ranibizumab and aflibercept, with faricimab being the newest therapy recommended by NICE in 2022; this targets both the VEGF and angiopoietin-2 pathways. These injections are given every 4–16 weeks. The number of injections and the time between them will be decided on an individual basis and will depend on the individual's response to treatment. Some improvement in vision may occur with these injections. Laser photocoagulation can also be used in addition to anti-VEGF injections.

If anti-VEGF therapy cannot be used or has not worked, then steroid injections/implants can be used. The implant is injected into the eye and slowly releases dexamethasone over the period of a few months.

It is important for clinicians to understand that the treatment period for diabetic retinopathy and maculopathy can be prolonged (over a number of years) and is a frustrating and scary time for people with diabetes, increasing anxiety and stress. This is because there is no definitive timeframe for treatment or how often it will be needed, and you also cannot predict how much vision will be maintained.

Q What is the link between GLP-1 receptor agonists and retinopathy progression? What action should we take? What groups are at risk?

In the cardiovascular outcome trials of GLP-1 receptor agonists (GLP-1 RAs), there were higher

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levels of retinopathy detected in the groups taking the active drug compared with placebo. There was a significant difference in the group taking semaglutide (Marso et al, 2016; Vilsbøll et al, 2018), and there was a higher level of retinopathy in those taking liraglutide and dulaglutide compared with placebo, although this did not reach significance (Zinman et al, 2018; Gerstein et al, 2019). In systematic reviews, the progression of retinopathy has been shown to be an overall class effect of GLP-1 RAs (Bethel et al, 2018).

This is not thought to be a direct effect of the GLP-1 RA, but rather the effect the agent has on the lowering of blood glucose levels and how quickly this is achieved (Bain et al, 2019). The phenomenon is known as early worsening of diabetic retinopathy and is not unique to GLP-1 RAs. It was also seen in the DCCT trial with intensification of insulin therapy (DCCT Research Group, 1998), as well with initiation of insulin in type 2 diabetes (UKPDS Group, 1998), during pregnancy (Morrison et al, 2016), and following bariatric surgery (Thomas et al, 2014). This only occurs in situations where retinopathy (background retinopathy, maculopathy, pre-proliferative retinopathy or proliferative retinopathy) has already developed. It also occurs when the starting HbA_{1c} is high, normally above 86 mmol/mol (10.0%).

For more information, see *At a glance factsheet: GLP-1 receptor agonists and diabetic retinopathy*.

What should we do?

Before the initiation of a GLP-1 RA, we should ensure there has been a recent retinal screening. If there has, and the result means the patient is on a 12-month (or longer) screening interval, then it should be safe to initiate a GLP-1 RA.

If there is no recent retinal screening, then ask the screening programme to expedite the screening and await the result before initiating a GLP-1 RA.

If there is a recent retinal screening result which means the individual is being recalled within 12 months or the patient is under the care of an ophthalmologist, caution should be applied before initiating a GLP-1 RA. Consider other glucose-lowering therapies first or discuss the initiation of the GLP-1 RA with the ophthalmologist. Patients should also be made aware of the risks involved, so that they can be diligent in attending ophthalmology follow-up and/or chase up a cancelled outpatient appointment.

If a woman with diabetes becomes pregnant, inform the screening programme as the patient will need to be placed on the pregnancy pathway for more frequent screening invitations due to this risk of early worsening. ■

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