

An overview of diabetic retinopathy for diabetes nurses

Gill Morrison, Philip Weston

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Article points

1. Diabetic retinopathy is a distressing complication of diabetes. On diagnosis, approximately 25% of people with type 2 diabetes will already have some established background retinopathy.
2. Retinopathy is a condition that affects the small blood vessels in the retina and is defined in terms of vascular endpoints; however, inflammatory and neurological processes may be involved. Retinopathy can be classified as non-proliferative retinopathy, proliferative retinopathy or maculopathy.
3. Treatment options include laser photocoagulation, vitrectomy, VEGF inhibitors and intravitreal steroids. Glycaemic control and management of blood pressure and lipids are also important.

Key words

- Diabetic retinopathy
- Eye screening

Authors

Gill Morrison is Diabetes and CSII Specialist Nurse and Philip Weston is Consultant Diabetologist & Endocrinologist, Royal Liverpool University Hospital, Liverpool.

One of the most common and distressing complications associated with diabetes is diabetic retinopathy. In the UK over recent years, there have been many significant advances in diabetes care; however, retinopathy still remains the leading cause of blindness in people of working age. Given the risk of developing retinopathy in people with diabetes, it is vital that this condition is promptly identified and treated before vision is detrimentally affected. This article aims to describe the incidence and prevalence of diabetic retinopathy in the UK, its associated pathophysiology, the classifications associated with this condition and the potential treatment options available.

One of the most common and distressing complications associated with diabetes is diabetic retinopathy (DR). The term retinopathy refers to any abnormal vascular changes in the retina, which, as a result of the associated pathology, can lead to loss of vision and even blindness (Kohner et al, 1996; Arun et al, 2003).

In the UK over recent years, there have been many significant advances in diabetes care; however, retinopathy still remains the leading cause of blindness in people of working age (Diabetes UK, 2010). This article aims to provide an overview of the extent of DR and its associated pathophysiology, highlight the classifications associated with this condition and discuss potential treatment options.

Incidence and prevalence

On diagnosis, approximately 25% of people with type 2 diabetes will already have some established background retinopathy. Following 20 years of diabetes, most people with type 1 diabetes and approximately 60% of those with type 2 diabetes will have developed some degree of DR (Klein et al 1992; Kohner et al, 1998). As found in a systematic review by Williams et al (2004), the incidence of DR

increases in older age groups who have long-standing diabetes. Population screening for DR demonstrated the baseline prevalence of sight-threatening diabetic eye disease was the highest in people with a longer disease duration in both type 1 and type 2 diabetes (Younis et al, 2002).

There is some evidence that indicates children as young as 12 years are at risk of developing DR (Kernell et al, 1997) and some case reports have demonstrated that even younger children can be at risk of background retinopathy, for example, an 8-year-old child with a 5.6-year history of diabetes (Donaghue et al, 1999). It has been shown that for each prepubertal year of diabetes, the risk of retinopathy increases by 28% and for each year post-puberty year, the risk rises by 36% (Donaghue et al, 2003). Traditionally DR has been viewed as a rare occurrence in children. However, work by Donaghue et al (2005) has highlighted that after 6 years' duration of type 1 diabetes in prepubertal children, the prevalence of DR is 12%. Currently in the UK, children age 12 and over with type 1 diabetes undergo annual screening for DR; however, authorities such as the International Society for Pediatric and Adolescent Diabetes (Donaghue et al,

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1. Given the risk of developing retinopathy in people with diabetes, it is vital that this condition is promptly identified and treated before vision is detrimentally affected.
2. Risk factors for diabetic retinopathy include long duration of diabetes, suboptimal glycaemic control, hypertension, nephropathy and minority ethnic origin. Pregnancy can be associated with a rapid progression of retinopathy.
3. Retinopathy is considered a condition that affects the small blood vessels in the retina and is defined in terms of vascular endpoints.

2009), American Academy of Ophthalmology (2003) and American Diabetes Association (ADA, 2002) suggest that retinal screening for children should start before the current UK age of 12 years. The Royal College of Ophthalmologists (2012) has also made a recommendation that children should be screened for DR from the age of 10 in the UK.

Given the risk of developing retinopathy in people with diabetes, it is vital that this condition is promptly identified and treated before vision is affected.

Risk factors associated with retinopathy

According to Emanuele et al (2005), Shotliff and Duncan (2005) and The Royal College of Ophthalmologists (2012), some of the risk factors associated with retinopathy are:

- Long duration of diabetes.
- Suboptimal glycaemic control.
- Hypertension.
- Nephropathy.
- Minority ethnic origin.
- Pregnancy can be associated with a rapid progression of retinopathy.

Although there appears to be no clear relationship between smoking and DR, in some people with type 1 diabetes, smoking has been shown to be associated with microangiopathy, particularly when complications occur early in the course of their diabetes (Moss et al, 1991). It is, of course, good practice to ensure that all individuals are discouraged from smoking (Li et al, 2010).

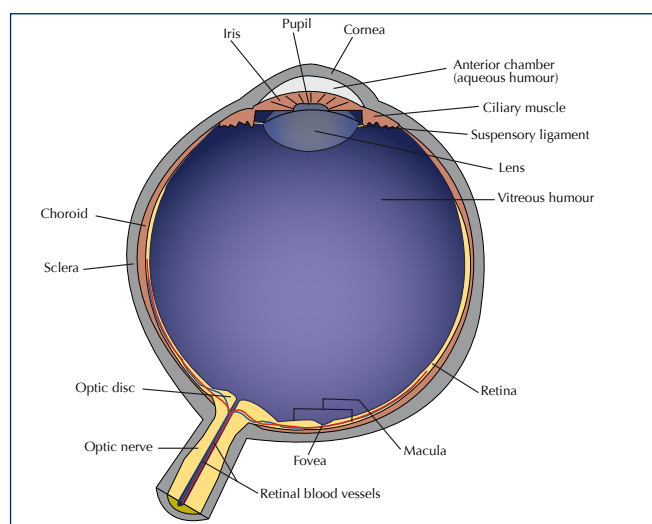


Figure 1. Diagram of the human eye.

Pathophysiology of retinopathy

A schematic diagram of the eye can be seen in *Figure 1*. *Figure 2* shows ophthalmoscopy of an eye showing diabetic retinopathy. Conventionally, retinopathy is considered a condition that affects the small blood vessels in the retina and is defined in terms of vascular endpoints (The Royal College of Ophthalmologists, 2012). However, there is evidence available suggesting that physiological changes to the retina are present before vascular changes occur. These changes comprise of an inflammatory (ADA, 2006), and a neurological, process (Van Dijk et al, 2010).

In the body, the glycation process slowly creates by-products known as advanced glycation end-products (AGEs). Low concentrations of blood glucose will slow down AGE formation and high blood glucose levels will damage protein structures and functions within the body (Peppas et al, 2003). In people with diabetes, the retinal cells and blood vessels all contain AGEs and any linear rise of these by-products directly correlates to the severity of any retinopathy that is present. The increased levels of AGE receptors provide evidence that supports the concept of an inflammatory response in retinopathy.

Research undertaken by Van Dijk et al (2010) demonstrated that prior to the development of any vascular changes on the retina, there is thinning of the retinal nerve fibre layer first. This work is highly suggestive that there is a neurodegenerative effect on the retina. The concept that retinopathy, in the early stages of its development, is actually a form of a neuropathy is controversial, given that vascular damage is unlikely to occur in isolation from the rest of the retinal cells. More studies are required to determine the exact interaction of the different cells within the retinal tissue and ascertain if there is any association between abnormal physiology and long-standing diabetes.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is required for blood vessel development and conservation. If abnormally high levels of VEGF are present, as found in diabetes, it causes abnormal growth of retinal blood vessels (The Royal College of Ophthalmologists, 2012). VEGF levels have been found to be elevated in the vitreous and retina in people diagnosed with DR (Adamis et al, 1994). Indeed, it has been found that VEGF is a

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1. A potential cause of diabetic retinopathy is the sorbitol–aldose reductase pathway, otherwise known as the polyol pathway. Elevated blood glucose levels are responsible for triggering excessive action of the polyol pathway.
2. Background retinopathy, otherwise known as non-proliferative retinopathy, is the earliest visible change on the retina associated with diabetes. At this stage there is no immediate threat to sight; however, it is a warning that the retina is at an increased risk of further microvascular damage.
3. Severe non-proliferative retinopathy is also called pre-proliferative retinopathy. In this condition there are various venous abnormalities in the retina, such as an irregularity in the calibre and looping of the capillaries.

key component responsible for the development of macular oedema (The Royal College of Ophthalmologists, 2012).

Polyol pathway

Another potential cause is the sorbitol–aldose reductase pathway, otherwise known as the polyol pathway (Forbes et al, 2008). Elevated blood glucose levels are responsible for triggering excessive action of the polyol pathway (Abhary et al, 2010). The associated pathophysiology that causes retinal cell damage is that an increase in sorbitol triggers oxidative damage, activates protein kinase C and decreases both nitric oxide and glutathione concentrations (Brownlee, 2001; Das Evcimen and King, 2007; Anil Kumar and Bhanuprakash Reddy, 2007).

Classification

Background retinopathy

Background retinopathy, otherwise known as non-proliferative retinopathy, is the earliest visible change on the retina associated with diabetes (Department of Health [DH], 2003). At this stage there is no immediate threat to sight; however, it is a warning that the retina is at an increased risk of further microvascular damage (The Royal College of Ophthalmologists, 2012). Key lesions include:

- Microaneurysms are caused by distension of the capillary wall, which forms small saccular pouches. The Royal College of Ophthalmologists (2012) suggests several theories that may account for their appearance, such as an unsuccessful attempt to form a new vessel, or a weakness of a capillary vessel

wall. These abnormalities appear as small red dots on the retina.

- Blot haemorrhages are caused by small blood vessels rupturing within the middle layer of the retina. Such haemorrhages may occur throughout the full thickness of the retina and they represent a deep retinal infarct (The Royal College of Ophthalmologists, 2012). Despite the fact that these features appear as large red lesions on screening, they do not cause any visual disturbances (Taylor, 2006).
- Exudates are recognised as yellow/white lesions with well-defined margins. These anomalies develop as a result of plasma leaking from damaged capillary walls (Taylor, 2006). Exudates usually occur at the edge of a microvascular leakage forming a circinate pattern around a leaking microaneurysm. Any exudates located well away from the macula region of the retina are not of any clinical concern. If, however, the lesion is within one disc diameter of the fovea, the classification changes to exudative maculopathy, which is a serious sight-threatening condition and warrants immediate ophthalmology referral (Shotliff and Duncan, 2005; Taylor, 2006; The Royal College of Ophthalmologists, 2012).
- Cotton wool spots occur due to poor oxygenation of the nerve fibres by the retinal capillaries. The affected fibres swell causing a pale and hazy area on the retina. Cotton wool spots are more prevalent in areas where the nerve fibre is dense such as the nasal side of the optic nerve (The Royal College of Ophthalmologists, 2012).

Severe non-proliferative retinopathy

Severe non-proliferative retinopathy is also called pre-proliferative retinopathy. In this condition there are various venous abnormalities in the retina, such as an irregularity in the calibre and looping of the capillaries (Taylor, 2006).

Blood vessels supplying the retina can become obstructed, thus depriving areas of the retina of an adequate blood supply. To compensate, new blood vessels will start to develop in the affected areas of the retina; however, these are fragile and tend to bleed (The Royal College of Ophthalmologists, 2012).

If severe non-proliferative retinopathy is found, round haemorrhages and other widespread retinal abnormalities will be seen including:

- Deep, round haemorrhages can develop, which will



Figure 2. Ophthalmoscopy of an eye showing diabetic retinopathy.

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1. If any exudates, haemorrhages or microaneurysms are identified in the macular region, retinopathy is termed "maculopathy".
2. Proliferative retinopathy is an advanced stage of retinopathy where new blood vessels grow in an attempt to provide sufficient oxygen and nutrients for the retina to function adequately. Unfortunately these new blood vessels are at very high risk of bleeding as they are abnormal and very fragile.
3. The incidence of sight-threatening retinopathy has declined since the induction of a comprehensive, annual population-wide screening programme for retinopathy.

be larger and darker than blot haemorrhages. This is a sign of capillary fragility in the deep areas of the retina (Taylor, 2006).

- Intraretinal microvascular abnormalities (IRMA) are small, dilated vessels on the retina, which do not appear to be connected to veins or arteries. These vascular channels appear as twisting, winding microvascular abnormalities in the areas of capillary occlusion within the retina (The Royal College of Ophthalmologists, 2012).
- Venous abnormalities are loops with clear irregularities developed from calibre of a vein. These structures are indicative of proliferative change (Taylor, 2006).

Maculopathy

The macular is the area in the eye that is one disc diameter from the fovea (Taylor, 2006). This is the area of the retina that contains cone nerve cells, which are responsible for detailed colour vision (Baggaley, 2001). The rest of the retina provides low definition vision, which is "filled in" by the brain to give the impression of detailed colour all-round vision (Baggaley, 2001). Loss of vision at the fovea is defined as legal blindness (Taylor, 2006). If any exudates, haemorrhages or microaneurysms are identified in the macular region, retinopathy is termed "maculopathy". This classification identifies any individual at risk of losing fovea function (Taylor 2006). Macular oedema occurs when damaged blood vessels leak fluid and lipids onto the retina. These fluids make the macula swell, which causes blurred vision. This situation can cause loss of sight (The Royal College of Ophthalmologists, 2012).

Proliferative retinopathy

Proliferative retinopathy is an advanced stage of retinopathy where new blood vessels grow in an attempt to provide sufficient oxygen and nutrients for the retina to function adequately. These blood vessels are at very high risk of bleeding as they are abnormal and fragile (The Royal College of Ophthalmologists 2012). Proliferative retinopathy includes:

- Pre-retinal haemorrhages, which occur when blood enters the space in front of the retina.
- Vitreous haemorrhages, which develop when the vitreous humour moves away from the retina, leaving a large area, which then fills with blood (Taylor, 2006).

Proliferative retinopathy can be present in the absence of major background changes and it is asymptomatic until it is very advanced (Taylor, 2006).

Reasons for ophthalmologist referral

Immediate referral

- Proliferate retinopathy.
- Rubeosis iridis/neovascular glaucoma.
- Vitreous haemorrhage.
- Advanced retinopathy with fibrous tissue or retinal detachment.
- Sudden loss of vision.

Early referral

- Pre-proliferative changes.
- Maculopathy, including hard exudates within 1 disc diameter of the fovea, and macular oedema.
- A fall of more than two lines on a Snellen chart.
- Unexplained retinal findings.

Routine referral

- Cataracts.
- Non-proliferative retinopathy with large circinate exudates not threatening the macular/fovea (Hutchinson et al, 2001; Shotliff and Duncan, 2005)

Eye screening

The incidence of sight-threatening retinopathy has declined since the induction of a comprehensive, annual population-wide screening programme for retinopathy as defined by the *National Service Framework for diabetes: Delivery strategy* (DH, 2003). As already highlighted, some stages of retinopathy do not require any clinical treatment; however regular screening for all individuals with diabetes is essential so that any disease progression can be identified, mapped and appropriately treated (DH, 2003; The Royal College of Ophthalmologists, 2012).

Laser photocoagulation

The first-line treatment for proliferative diabetic retinopathy and maculopathies is laser photocoagulation. Evidence suggests that laser treatment reduces the incidence of partial sight in an eye affected by macular oedema by 50% at two years (ETDRS [Early Treatment Diabetic Retinopathy Study], 1991) and in proliferative eye disease, blindness by 50% at two years (The Diabetic

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1. During laser treatment, minute laser beams are used to destroy damaged parts of the retina and the growth of abnormal blood vessels, which would eventually bleed and damage vision. The key aim of laser treatment is to prevent further vision loss.
2. Vitrectomy is performed in individuals who have persistent vitreous haemorrhages and retinal traction. Removing scar tissue, haemorrhage or any opacity may help restore vision and will aid both intra-operative and post-operative laser treatment.
3. VEGF inhibitors are now available and are known as “anti-VEGFs”. These pharmaceutical agents are administered via an intravitreal injection.
4. Studies have demonstrated that improving overall glycaemic control delays the progression of retinopathy in both type 1 and type 2 diabetes.

Retinopathy Study Research Group, 1994).

During laser treatment, minute laser beams are used to destroy damaged parts of the retina and the growth of abnormal blood vessels, which would eventually bleed and damage vision (Shotliff and Duncan, 2005). The key aim of laser treatment is to prevent further vision loss, rather than restore vision; this is an important distinction that must be highlighted to the individual undergoing the procedure (Shotliff and Duncan 2005). Laser treatment is not without risk; should the eye move during the procedure, the fovea could be accidentally burnt, which would cause blindness. Other negative outcomes associated with laser treatment include a reduction in night vision and an adverse effect on visual field, which can be severe enough to affect ability to drive (The Royal College of Ophthalmologists, 2012).

Vitrectomy

Vitrectomy is performed in individuals who have persistent vitreous haemorrhages and retinal traction. Removing scar tissue, haemorrhage or any opacity may help restore vision and will aid both intra-operative and post-operative laser treatment (The Royal College of Ophthalmologists, 2012). Surgical vitrectomy helps to reduce retinal traction and facilitates retinal reattachment. Although a 70% success rate for restoring vision is seen, there is a risk of causing deterioration in vision due to detaching the retina or worsening any lens opacities (Shotliff and Duncan, 2005).

Other treatments

VEGF inhibitors are now available and are known as “anti-VEGFs”. These pharmaceutical agents are administered via an intravitreal injection (The Royal College of Ophthalmologists, 2012). There is increasing evidence that the use of VEGF inhibitors (with or without laser treatment) provides better visual outcomes for individuals with macular oedema and reduced vision (The Royal College of Ophthalmologists, 2012).

Following revision of the NICE technology appraisal in 2013, the VEGF inhibitor ranibizumab is available for use in individuals with diabetes who have macular oedema and a central retinal thickness of at least 400 micrometres (NICE, 2013). Ranibizumab has a pharmacokinetic action that inhibits the action of VEGF-A, so that

oedema is reduced and visual loss is limited or improves.

Intravitreal steroids

Many processes have been implicated in the pathogenesis of diabetic macular oedema, such as increased levels of VEGF, loss of endothelial tight junction proteins, and the production of inflammatory mediators (Cunningham et al, 2008). Corticosteroids can inhibit all of the above processes and, therefore, can be used as a potential therapeutic option for diabetic macular oedema (Royal College of Ophthalmologists, 2012). For selective individuals diagnosed with diabetic macular oedema, steroids can also be successfully used in combination with laser treatment to reduce macular oedema and improve visual acuity (Gillies et al, 2009).

Glycaemic control

Both the DCCT (Diabetes Control and Complications Trial, 1993) and the UKPDS (UK Prospective Diabetes Study, 1998) demonstrated that improving overall glycaemic control delays the progression of retinopathy in both type 1 and type 2 diabetes. Evidence indicates that a reduction in HbA_{1c} of just 11 mmol/mol (1%) reduces the need for laser therapy in the long term by 30% in both type 1 and type 2 diabetes (DCCT 1993; UKPDS 1998). Ironically though, a rapid improvement in HbA_{1c} for those individuals with pre-existing retinopathy has been associated with short-term deterioration in retinopathy (DCCT, 1993). Given this risk, glycaemic control should be slowly improved in any individual with established retinopathy (DCCT, 1993).

Blood pressure

There is good evidence to suggest that there is an association between hypertension and retinopathy, given that plasma exudation from the capillaries within the retina is increased if the pressure inside it is too high (UKPDS, 1998). For individuals with diabetes, research suggests aiming for a systolic blood pressure of 130 mmHg or less (The Royal College of Ophthalmologists, 2012).

Angiotensin-converting enzyme (ACE) inhibitors are the first treatment of choice for individuals with diabetes who have hypertension (Shotliff and Duncan, 2005). It is worthy of note that the Royal College of Ophthalmologists (2012) highlight

“In the UK, proactive screening programmes are now available for all individuals diagnosed with diabetes, which are successfully identifying retinopathy at an early stage.”

that ACE inhibitors have an anti-angiogenic effect by altering local growth factor levels. Thus, it is suggested that ACE inhibitors can help to reduce the progression of retinopathy, as well as lowering blood pressure.

Lipids

Elevated levels of oxidised low-density lipoprotein (LDL) are associated with retinopathy, particularly maculopathy with exudates. The significance of LDL cholesterol is that it has a cytotoxic effect on endothelial cells. In addition, if hyperlipidaemia is present, laser therapy is not as effective, especially in individuals undergoing treatment for maculopathy. Aggressive lipid lowering is recommended, especially in individuals with maculopathy (The Royal College of Ophthalmologists, 2012).

Education and support

Due to the potential negative impact on eyesight, it could be argued that retinopathy is one of the most feared complications of diabetes. All healthcare professionals working in diabetes have a responsibility to provide structured education regarding the associated complications of diabetes, including retinopathy, and provide adequate support for any individual with diabetic eye disease (DH, 2001; 2003). A well-versed patient is one who can make informed choices and is more likely to participate as an active partner in any management plans regarding all aspects of their care relating to diabetes, including retinopathy. Research continues to improve professional understanding of retinopathy and support evidence-based treatment algorithms. In the UK, proactive screening programmes are now available for all individuals diagnosed with diabetes, which are successfully identifying retinopathy at an early stage. A prompt diagnosis allows for swift intervention, which will help to prevent visual impairment. ■

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