Diabetic eyecare part 6: Preventing diabetic retinopathy through control of systemic factors

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Outline:
In this article the author takes an evidence-based look at factors that modify the rate of onset and progression of diabetic retinopathy or the development of visual loss owing to DR. There are a number of systemic conditions or other factors which can exacerbate or accelerate the course of diabetic microvascular and macrovascular disease which are discussed in detail.

About the author:
Chris Steele graduated from City University in 1988 and qualified in July 1989 after his pre-registration year at The Royal East Sussex Hospital, Hastings. He is Consultant Optometrist, Head of Optometry at Sunderland Eye Infirmary (SEI) in Sunderland. Over the past 22 years he has developed a wide range of extended roles within his optometry team involving medical retina, cataract, glaucoma, anterior segment and paediatric case loads. He has maintained his special interest in medical therapeutic contact lenses and still runs a specialist scleral lens tertiary referral service at SEI. He has also continued to undertake regular locum work in community optometric practice.

He has authored over seventy publications re: glaucoma, ocular therapeutics, medical retina, specialist medical contact lenses, refractive surgery, and clinical risk management and has undertaken many presentations both nationally and internationally on these topics. He has also authored a book in the Eye Essentials series: Diabetes and the eye first published in 2007. A fully updated second edition is due out soon.

Chris is a member of the AOP Hospital Optometrists Committee and was Chairman from 1999-2001. He has been a College Examiner for Pre-registration Final Exit Examinations and Post Graduate Higher Qualifications (Diabetes and Glaucoma) since 1996. He is now a questions writer/ editor for The College of Optometrists Therapeutics Central Final Assessments in Independent Prescribing as well as a co-editor for Specsavers' Profile journal.

Chris was a member of the NICE Glaucoma Guideline Development Group from 2007 that produced the NICE glaucoma guidelines (CG85) published in 2009, and is still involved in the on-going NICE periodic reviews of this Glaucoma Guideline. In the past 2-3 years he was also a member of the College of Optometrists Medical Retina Development Group that produced the new Medical Retina Higher Qualifications for optometrists.

Introduction
Earlier in this series the epidemiology, pathogenesis and treatment of diabetes and diabetic retinopathy (DR) have been discussed. The final part of this series concentrates on the risk factors that modify the rate of onset and progression of DR or the development of visual loss owing to DR. The main risk factors appear to be duration of diabetes and blood glucose control. In addition to these, there are a number of systemic conditions or other factors which can exacerbate or accelerate the course of diabetic microvascular and macrovascular disease. These include:

- smoking
- pregnancy
- genetic predisposition
- alcohol
- sleep apnoea
- obesity

All of these factors will be discussed in detail below.

Duration of diabetes
Duration of diabetes is defined for clinical purposes as the time since diagnosis of diabetes. However, it is recognised that sub-clinical diabetes may be present for a significant period prior to diagnosis.

There is a clear relationship between the duration of diabetes and the development of retinopathy in both type 1 and type 2 diabetics. This has been demonstrated for type 1 diabetes in the US Diabetes
Control and Complications Trial (DCCT) and less clearly in The United Kingdom Prospective Study UKPDS) for type 2 diabetics see below). The duration of diabetes is a very important risk factor for the progression and severity of DR in type 1 and type 2 diabetics.

Hyperglycaemia

Prolonged exposure to hyperglycaemia causes microvascular complications, such as retinopathy, nephropathy and neuropathy. Studies have demonstrated that hyperglycaemia predicts incidence and progression of DR. The DCCT and the UKPDS were two randomised clinical trials with results that conclusively demonstrated the efficacy of glycaemic control in preventing DR1,2.

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) remain the most highly cited diabetes research trials and have truly altered the course of diabetes management forever3. The DCCT study showed that intensive glycaemic control in Type 1 diabetes, with no baseline retinopathy or mild to moderate DR, demonstrated a decrease in the rate of progression of DR, the development of severe DR, or the need for laser photocoagulation. The DCCT/ EDIC showed that intensive insulin therapy effectively delays the onset and slows the progression of DR in patients with type 1 diabetes. In the primary prevention cohort (those with no DR at baseline), intensive therapy reduced the adjusted mean risk for the development of DR by 76% compared with conventional therapy. In the secondary intervention cohort (those with mild DR at baseline), intensive therapy slowed the progression of DR by 54% and reduced the development of proliferative or severe non-proliferative DR by 47%4.

The epidemiology of diabetes interventions and complications (EDIC) research group followed patients for 4 years after the conclusion of the DCCT trial and found that the benefits of intensive diabetes control persisted even with increasing hyperglycaemia (HbA1c increased from 7.2% to 79%). The intensive glycaemic control group continued to demonstrate a decrease in DR endpoints, including worsening DR, proliferative DR, diabetic macular oedema and the need for laser treatment5.

The UKPDS revealed that improved control in patients with type 2 diabetes not only led to a reduction in DR but also reduced overall microvascular complications by 25%. A one-point decrease in HbA1c was associated with a 35% reduction in risk of microvascular complications. The American Diabetes Association advocates an HbA1c goal of less than 7%6.

Diet and exercise are also important factors in the care of a patient with diabetes. Exercise alone reduces the concentration of HbA1c by about 0.65% and should be strongly encouraged. Risks of progressive nephropathy and neuropathy are also reduced with tight glucose control4.

Intensive insulin therapy is associated with certain risks including more frequent hypoglycaemic episodes, increased wound infections and weight gain. Despite these risks, patients should be advised to keep glycaemic control as good as possible.

In patients with impaired glucose tolerance (IGT), the Hoorn study found that the prevalence of developing DR was 13.6% in individuals with impaired glucose metabolism and 17.5% in individuals with newly diagnosed diabetes. The Hoorn study also showed that the prevalence of DR increased as HbA1c increased7.

Any reduction in HbA1c is beneficial in reducing the development of new and progression of existing DR. Patients should be aware of their HbA1c, what it means and how it can be lowered. Patients should be encouraged to maintain their HbA1c below 5-6% (31.1 - 42.1 mmol/mol) and ideally 4.5% (20.2 - 31.1 mmol/mol). Caution should be exercised where HbA1c is reduced too quickly as this can result in temporary worsening of DR, however long term benefits should be emphasised8.

Hypertension

The regulation of blood flow within the retinal microvasculature is impaired in diabetes, leading to increased microvascular hypertension and to increased susceptibility to injury from even modest levels of systemic hypertension. Even relatively small increases in either systolic or diastolic blood pressure (BP) that may be within the normal range for non diabetic people, significantly increases the risk for the development and progression of DR compared with diabetic patients with lower blood pressures.

Multiple trials addressing aggressive BP treatment have demonstrated improved outcomes in DR and nephropathy (kidney damage). The NHS regards a BP of below 120/80 as the ideal. The NICE target BP for both type 1 and type 2 diabetes, should be aggressively treated to levels less than 130mmHg systolic and less than 80mmHg diastolic and to less than 75mmHg where there is any evidence of proteinuria (protein in the urine). The BP in diabetics is often unstable with an increased prevalence of neurogenic orthostatic hypertension (low blood pressure upon standing) as well as nocturnal supine hypertension (low blood pressure during the night). Care should be taken to avoid attributing elevated BP to white coat hypertension, as this may delay appropriate intervention. Twenty four hour BP monitoring is recommended for treatment decisions, aiming to control all BP measurements (i.e. diastolic and systolic) to target levels. Interestingly, nocturnal supine hypertension may account for some of the worsening vision in the morning often experienced by some diabetics9.

In both the Wisconsin Epidemiologic Study of Diabetic Retinopathy10,11,12 and the UKPDS, DR progressed significantly more slowly with more tightly controlled BP. The hypertensive and normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) studies were trials with 5 years of follow-up that examined the role of intensive versus standard BP control in a total of 950 patients with type 2 diabetes mellitus. In the hypertensive ABCD study, a significant decrease in mortality was detected in the intensive BP control group when compared with the standard BP control group. In the tight control groups there was a significant reduction in myocardial infarction rate and significant slowing of the progression of nephropathy (as assessed by urinary albumin excretion) and DR, as well as fewer strokes13.

The UKPDS evaluated the effects of BP and glycaemic control in the prevention and progression of DR in Type 2 diabetes. The UKPDS was a landmark randomised, multicentre trial of glycaemic therapies including 5102 patients with newly diagnosed type 2 diabetes. It ran for twenty years (1977 to 1997) in 23 UK clinical sites and showed conclusively that the complications of type 2 diabetes, previously often regarded as inevitable, could be reduced by improving blood glucose and/or BP control. Subjects were randomly assigned to two groups. The first group were assigned to intensive BP control (of <144/82). The second group were assigned to a less tightly controlled BP (<145/87). There was a 34% reduction in the risk of DR progression and a 3% reduction in diabetic microvascular endpoints in the first group (intensive control)9.

In the UKPDS study nearly a third (29%) of patients needed three or more antihypertensive drugs to reach the target BP levels. At least 60% of patients needed two antihypertensive drugs after 9 years. In practice many patients need combinations of treatments from different drug classes to manage their hypertension and this should be aggressively pursued. According to NICE guidelines, having been initially given lifestyle advice, particularly regarding diet and exercise, if the BP is still >140/80 (or >130/80 if there is kidney, eye or cerebrovascular damage) BP lowering therapy should be commenced9.
renal disease evolves through a stage of normo-albuminuria, the urinary albumin excretion rates. In both types 1 and 2 diabetes, The most common way of evaluating renal function is by measuring diabetes, especially in certain ethnic groups.

Diabetic nephropathy

Diabetic nephropathy is microvascular kidney disease that develops in diabetes mellitus. There is a definite association between DR and all levels of abnormal renal function, independent of duration of diabetes and level of glycaemic control, in both types 1 and 2 diabetes, especially in certain ethnic groups.

The most common way of evaluating renal function is by measuring the urinary albumin excretion rates. In both types 1 and 2 diabetes, renal disease evolves through a stage of normo-albuminuria, progressing to abnormal levels with micro-albuminuria and finally to persistent albuminuria (established nephropathy). Traditional measurements of renal function e.g. urea and creatinine, may well remain normal until well into the established stage of nephropathy (persistent proteinuria). All stages of abnormal renal function with abnormal urinary albumin excretion are associated with increased incidence of DR.

Certainly all patients with DR and macular oedema should have their renal status regularly assessed. Proteinuria is a known predictor of the development of proliferative diabetic retinopathy in type 1 diabetics. In severe proteinuria there is a 95% increased risk of developing diabetic macular oedema among type 1 diabetics. Whether this is due to hyperglycaemia or nephropathy is an independent risk factor for development of DR, remains uncertain.

Anaemia

Anaemia is a condition which occurs when there is an abnormally low amount of red blood cells which can result from a number of different causes including, low levels of iron or vitamin B12 in the diet, gastrointestinal bleeding (e.g. duodenal ulcers, tumours) and heavy periods in women. In anaemia, haemoglobin levels are typically below 10-11 g/dl. Anaemia often accompanies diabetic kidney disease and is thought to exacerbate the ischaemic aspect of DR. Anaemia in diabetic patients commonly develops during the stage of overt proteinuria but before the onset of even modest renal impairment. The connection between anaemia and DR is still undergoing further investigation, but the link with progression of nephropathy is now beyond doubt. It is therefore important to aggressively treat anaemia in diabetic patients particularly where there is evidence of nephropathy and/or DR.

Hyperlipidaemia

Evidence suggests that hyperlipidaemia contributes to the progression and morbidity of DR and maculopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the presence of retinal hard exudates was significantly associated with increased serum cholesterol levels in patients taking insulin. In the Early Treatment Diabetic Retinopathy Study, subjects who had an elevated total cholesterol or low-density lipoprotein cholesterol level were significantly more likely than those with normal levels to have retinal hard exudates. Accumulation of retinal hard exudates can lead to vision loss either from a foveal lipid plaque or from the development of fibrosis. Risks of progressive nephropathy and neuropathy also are reduced with lipid control.

Anecdotally, it has been reported by a number of clinicians that early diabetic maculopathy which presents with just parafoveal streak exudates does improve with the initiation of lipid lowering statin therapy and there is now evidence to support this. One prospective randomised study of 30 diabetic patients with macular oedema and dyslipidaemia found a statistically significant reduction in hard exudates versus controls after initiation of Atorvastatin, although visual acuity was not affected.

Thrombosis predisposition and the use of aspirin

It has now been shown that diabetic patients have platelets which are more prone to thrombosis (clotting). This is thought to result from increased levels of plasma plasminogen activator inhibitor in diabetes compared with non-diabetics. A meta-analysis of studies...
investigating aspirin therapy for other medical indications in patient with DR, found that its use neither increased nor decreased the risk of development or progression of DR\(^\text{24}\). Also daily use of aspirin is not associated with increased risk of retinal haemorrhages, vitreous haemorrhage or progression of diabetic macular oedema\(^\text{25}\).

Cigarette smoking

The association between smoking and DR is complex and the effects of smoking on DR seem rather inconsistent\(^\text{22,23}\). There is however no doubt that smoking is a definite risk factor for other complications of diabetes, in particular cardiovascular disease. Smoking can affect DR in a number of ways by increasing the number of circulating activated leucocytes, causing severe retinal vasocostriction, increasing lipid levels and carboxyhaemoglobin-induced hypoxia. Consequently all diabetic patients should be encouraged not to smoke and referred for cessation counselling and advice.

Pregnancy

Pregnancy is a major risk factor for the progression of DR in the short term, but this is typically a transient progression\(^\text{4}\). The long term risk of progression of DR does not appear to be increased by pregnancy. Altered systemic and retinal haemodynamics seen in pregnancy affect the course of DR with increased retinal blood flow in pregnant women and 6 months thereafter.

The Diabetes in Early Pregnancy Study (DEPS), prospective cohort study found that the risk of progression of retinopathy in pregnancy prior to week 14, was increased by elevated HbA1c levels. The increased risk may be caused by a number of factors namely poor metabolic control or metabolic control which is achieved too rapidly\(^\text{26}\). The recommendation now is that diabetic women should carefully plan their pregnancies as much as possible in order to allow optimum metabolic and BP control to be achieved prior to conception. There are a number of risk factors which affect progression of DR during pregnancy including:

- diabetes duration
- level of DR at conception
- blood glucose control
- co-existing vascular disease and hypertension

Provided that the diabetic woman in pregnancy is carefully monitored and all systemic disease optimally controlled, the long-term effects on vision can be minimised.

Genetics

As discussed above, hyperglycaemia and duration of diabetes are important risk factors for the progression of DR. However despite this, it is well recognised that some individuals with diabetes who maintain poor control of their diabetes do not develop significant DR even over many years. Conversely other individuals progressively have worsening DR despite maintaining good control of their diabetes. This strongly suggests that there is a genetic factor involved which, in some people, has a protective effect. There is now emerging evidence that indicates the essential role of genetic factors in the development of diabetic retinopathy (DR). In this regard it should be highlighted that genetic factors account for 25-50% of the risk of developing DR\(^\text{27}\). Although there is clear demonstration of a genetic contribution in the development and progression of DR, the identification of a particular gene is still some way off. The greatest obstacles remain a lack of statistical power because of small sample size of available studies and a lack of phenotype standardisation.

Alcohol

Alcohol consumption is associated with increased risk of deterioration of visual acuity, but not with retinopathy in individuals with type 2 diabetes\(^\text{28}\).

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a disorder that is relatively common, occurring in approximately 2 % of women and 4 % of men over the age of 35. It takes its name from the Greek word aponea, which means “without breath." People with sleep apnoea literally stop breathing repeatedly during their sleep, often for a minute or longer and as many as hundreds of times during a single night. Sleep apnoea can be caused by either complete obstruction of the airway (obstructive apnoea) or partial obstruction (obstructive hypopnoea involving slow, shallow breathing). There are three types of sleep apnoea; obstructive, central, and mixed. Of these, obstructive sleep apnoea (OSA) is the most common.

The exact cause of OSA remains unclear. The site of obstruction in most patients is the soft palate, extending to the region at the base of the tongue. There are no rigid structures, such as cartilage or bone, in this area to hold the airway open. During the day, muscles in the region keep the passage wide open, But as a person with OSA falls asleep, these muscles relax and allow the tongue to come into contact with the back of the throat. There is now strong evidence that this condition may cause exacerbation of DR with development of more diffuse macular oedema associated with progressive ischaemia . OSA is thought to aggravate DR because of the associated nocturnal recurrent hypoxaemia (inadequate oxygen in the blood) with hypercapnia (where there is excess carbon dioxide in the blood >45mmHg). The same abnormalities of retinal auto-regulation that are induced by hyperglycaemia, make the retina susceptible to ischaemic injury from hypoxia and hypertension and are made worse by hypercapnia.

In most cases OSA is treated with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (bi-PAP) delivered during sleep by a special nasal/mouth mask.
**Obesity**

Finally, obesity is the single most important factor for the current increase in diabetes and therefore risk of developing DR. There are different types of obesity: abdominal obesity is linked with diabetes and heart disease and certain genetic factors also play a part (see above). The UK is officially the ‘fattest’ country in Europe, with approximately 1 in 5 adults now overweight (BMI >25) and one in every 15 obese (BMI >30).

Over the next 20 years, the number of obese adults in the UK is predicted to increase by a staggering 73% to 26 million people. Theories regarding how obesity could be leading to these increased levels of type 2 diabetes include:

1. **Obesity disrupts fat metabolism**

   It is now thought that being overweight triggers changes to the body's metabolism. This causes fat tissue (known as adipose tissue) to release fat molecules into the blood. The fat molecules are then transported into cells that react to insulin (known as insulin responsive cells), such as muscle and liver cells. These fat molecules can then disrupt how these cells work, damaging the cells' ability to respond to insulin.

2. **Obesity triggers an inflammatory response**

   It is now widely accepted that carrying excess weight around the girth puts people at greater risk of type 2 diabetes. It is thought that increased abdominal fat causes fat cells to release 'pro-inflammatory' substances within the body which also affect insulin responsive cells, ultimately leading to insulin resistance. Weight control is therefore very important in avoiding the development of diabetes.

3. **Obesity causes a fault inside cells**

   Obesity may cause ‘pre-diabetes’. This is where blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. In pre-diabetes, there is an increase in the level of fatty acids (the building blocks of fat) circulating in the blood. These fatty acids can then enter cells and inhibit the normal function of the mitochondria (the cell “powerhouse” where high-energy compounds (e.g. ATP) are produced). This results in cells that can no longer function normally.

   In summary, all three theories above suggest that the more fatty tissue there is, the more resistant the cells become to insulin.

**Conclusions**

It is now becoming increasingly evident that control of systemic factors, particularly obesity and the use of different systemic therapeutic agents are also important in controlling DR progression.

The management of the diabetic patient with DR requires multidisciplinary teamwork between optometrists, general practitioners, ophthalmologists, specialist diabetes nurses, hospital based physicians, paramedical staff including podiatrists, dietician and retinal screeners. Only by working together, communicating effectively and also keeping the patient fully informed, will all these systemic factors discussed above be tackled coherently and effectively. The value of good control of diabetes by eating a healthy diet, exercising, smoking cessation, and maintaining weight control will all help to reduce the complications caused by diabetes generally.

**References**


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GOC’s Enhanced CET Scheme

CET and CPD regulators require practitioners to reflect on their learning. Additional activities are required to gain CET for distance learning.

When you have completed your reading, close this window and return to iLearn/Spectrum to choose your practitioner group and either interactive or non-interactive CET quiz.

If you choose ‘non-interactive’ you have to pass (>60%) a 6-question multiple choice quiz. If you choose ‘interactive’ you must pass a MCQ quiz and complete a further 30-minute discussion with a colleague, and upload a short summary of your discussion and reflections within 30 days. Note you must complete both tasks before your CET can be awarded. If you want the CET counted within a calendar year make sure you submit the online record of discussion and remind your colleague to verify it online at least 2 weeks before the end of the year.

Further instructions for interactive learning are as follows:

The following steps must be completed within 30 days of completing the MCQ quiz:

1. Discuss the interactive questions below with a registered colleague. Note if you are an optometrist, the colleague must also be an optometrist. If you are a dispensing optician, the colleague may be a dispensing optician, a contact lens optician or an optometrist. The discussion should be in a quiet environment where you are not interrupted for at least 30 minutes. Discuss the set questions and record a summary of the output of your discussion. Please ensure to create a paper copy of your record, sign and date the document and keep it safely stored in case your CET is audited in future by the GOC.

2. In the event of an audit we need to be able to show the GOC that the interaction has taken place in accordance with the instructions. Therefore, before you can be given points for this activity you must, within 30 days, record your answers to the set questions in the online Discussion Record and Reflection form (link provided on iLearn/Spectrum).

3. You will be asked for the GOC number, name and email address of the colleague who has completed the interaction with you, so please have those ready. Your colleague will be contacted by email (so please make sure you enter their correct email address) and will be sent a link to verify the interaction took place.

4. You can only be awarded interactive CET points if these steps are completed within 30 days.

The learning objectives for the interactive article are:

8.1.4 Dispensing opticians will have an evidence-based understanding of factors which influence the development or progression of diabetic retinopathy and their modification enabling them to contribute to a multidisciplinary team providing optimum care for patients with diabetes.

6.1.10 Optometrists will have an evidence-based understanding of factors which influence the development or progression of diabetic retinopathy enabling them to give appropriate advice to patients about interventions which may modify their risks

2.1.6 Therapeutic optometrists will have an evidence-based understanding of factors which influence the development or progression of diabetic retinopathy and their modification enabling them to give appropriate advice to patients about interventions which may modify their risks.

2.10.1 Optometrists will have an evidence-based understanding of factors which influence the development or progression of diabetic retinopathy and their modification enabling them to contribute to a multidisciplinary team providing optimum care for patients with diabetes.

Consider how you will use the learning from this article to enhance your patient care and what changes reading this article will make to the way your practice.

The discussion tasks for the interactive learning option are as follows.

1. Discuss with your colleague the effect of hyperglycaemia on diabetic retinopathy. What have the various trials shown about its effects and how the patient may modify it? What advice would you offer a patient with hyperglycaemia?

2. Discuss with your colleague the effect of hypertension on diabetic retinopathy. What have the various trials shown about its effects and how the patient may modify it? What advice would you offer a patient with hyperglycaemia?

3. Reflecting on the reading and discussion...
   a. what are the main things you learned from the reading?
   b. how will you apply this learning in your future practice?
   c. has this module identified for you any areas in which you wish to pursue further learning?

Instructions on how to gain an interactive CET point from this article:

First, you must choose the interactive option from your CET dashboard. You cannot complete both options. First you will be presented with a 6-question multiple choice quiz (60% pass mark). When you have passed the quiz you have to complete an interaction and register the results online to gain your points. The following steps must be completed within 30 days of completing the quiz:

1. Discuss the interactive questions relating to this learning with a registered colleague. Note if you are an optometrist, the colleague must also be an optometrist. If you are a dispensing optician, the colleague may be a dispensing optician, a contact lens optician or an optometrist. The discussion should be in a quiet environment where you are not interrupted for at least 30 minutes. Discuss the set questions and record a summary of the output of your discussion. Please keep it safely stored in case your CET is audited in future by the GOC.

2. In the event of an audit we need to be able to show the GOC that the interaction has taken place in accordance with the instructions. Therefore, before you can be given points for this activity you must log back into this CET via your iLearn account within 30 days and record your answers to the set questions in the online form provided.

3. You will be asked for the GOC number, name and email address of the colleague who has completed the interaction with you, so please have those ready. Your colleague will be contacted by email (so please make sure you enter their correct email address) and will be sent a link to verify the interaction took place.

4. You can only be awarded interactive CET points if these steps are completed within 30 days.