Retinopathy

Ocular effects of systemic therapies for managing diabetes

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Ophthalmologists largely concern themselves with direct treatment of the eye, be it with conventional laser or with newer intravitreal agents. The more enlightened have learnt that management of risk factors can delay the onset and slow the progression of complications, including diabetic retinopathy. They now know to advise their patients of the importance of meeting targets for HbA_{1c}, blood pressure and lipid levels.

This article by Silva et al (2010; summarised alongside) provides not only a comprehensive review of the systemic medications used in the management of diabetes and related comorbid medical conditions, but also a fascinating consideration of the specific ocular effects they may have, and how this influences the complex inter-related mechanisms at play in the pathogenesis of diabetic retinopathy. The authors have reviewed the specific effects of systemic medications to control hyperglycaemia, hypertension, dyslipidaemia, cardiac disease, anaemia, inflammation and cancer. This challenges us to consider which systemic medications should actually be used primarily to prevent or treat diabetic retinopathy. Of particular interest are agents for glycaemic control, anti-inflammatory agents and antihypertensive agents.

The discovery of insulin has to be the most significant step in the history of diabetes care; prior to this, people with type 1 diabetes would die before there was any consideration of complications. The Diabetes Control and Complications Trial (DCCT; DCCT Research Group, 1993) clearly demonstrated that intensive insulin therapy reduces the progression of diabetic retinopathy and showed a legacy effect independent of subsequent glycaemic control. However, insulin is known to have pro-angiogenic effects and early worsening of retinopathy following rapid improvements in glycaemic control can occur, which is attributed to insulin's ability to increase gene expression of growth factors such as vascular endothelial growth factor (VEGF). This should always be borne in mind when managing patients with existing retinopathy.

Thiazolidinedones are commonly used in the person with type 2 diabetes, either alone or in combination with other oral antidiabetes agents or insulin. Evidence suggests that they can reduce microvascular complications, particularly proliferative retinopathy, through a mechanism that is independent of their effect on glycaemic control. However, they have rarely been shown to be responsible for the apparently idiosyncratic development of macular oedema.

Changes in retinal biochemistry and physiology occur long before retinopathy is clinically evident. Chronic inflammatory changes have been observed and have led to theories that inflammation, rather than hyperglycaemia, is causal. Anti-inflammatory agents may therefore have a direct or an indirect effect on diabetic retinopathy. Aspirin treatment has been controversial for many reasons but is widely used to prevent diabetes-related cardiovascular complications and may well have a beneficial effect in diabetic retinopathy.

Locally administered steroids, particularly intravitreal, are effective in reducing macular oedema, but unfortunately the effect is short-lived and the complications of treatment (cataract and glaucoma) are high. However, the use of systemic steroids is unlikely to be adopted because of their adverse systemic complications and the effect they have on glycaemic control.

Probably the most convincing evidence surrounds the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. The renin–angiotensin system has been implicated in the pathogenesis of diabetic retinopathy. Their effect on VEGF levels may indicate a direct effect on the eye independent of their effect on systemic blood pressure.

An understanding of the potential ocular effects of systemic therapy should inform the decision-making process for both diabetes specialists and ophthalmologists.

Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **329**: 977–86

NATURE REVIEWS ENDOCRINOLOGY

Systemic medications impact diabetic retinopathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 People with diabetes are at increased risk of chronic microvascular and macrovascular complications such as diabetic retinopathy, which is the main cause of visual loss worldwide.

2 People with diabetes are also at increased risk of multiple systemic comorbidities, which are treated with an extensive array of medications.

3 It is not clear whether systemic medications have a beneficial or deleterious effect on the onset or progression of diabetic retinopathy.

4 The authors review the ocular-specific effects of systemic medications commonly used by people with diabetes, including those that target hyperglycaemia, dyslipidaemia, hypertension, cardiac disease and cancer.

5 The renin–angiotensin system has been implicated in the pathogenesis of diabetic retinopathy.

6 The benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) on diabetic retinopathy may represent direct effects on the eye that are at least partially independent of their effects on systemic blood pressure.

7 Clinical evidence is thus strongest for the use of ACE inhibitors and ARBs in preventing the onset or slowing the progression of early diabetic retinopathy.

8 To a lesser extent, evidence exists for the beneficial use of fibrates for diabetic macular oedema.

9 The authors concluded that there is a role for systemic medications in reducing ocular complications of diabetic retinopathy.

Silva PS, Cavallerano JD, Sun JK et al (2010) Effect of systemic medications on onset and progression of diabetic retinopathy. *Nat Rev Endocrinol* **6**: 494–507

DIABETES CARE

Ranibizumab improves visual acuity in DMO

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 Vascular endothelial growth factor (VEGF) contributes to the development and progression of diabetic macular oedema (DMO), a major cause of visual impairment in people with diabetic retinopathy.

2 As ranibizumab binds to and inhibits multiple VEGF variants, the study objective was to determine its safety and efficacy in people with DMO.

3 In this randomised, controlled, 1-year study, people with DMO were assigned to ranibizumab 0.3 mg (n=51), 0.5 mg (n=51) or control (n=49).

4 At study end, visual acuity improved from baseline in people treated with ranibizumab by a mean gain of 10.3±9.1 letters and declined in those in the control group by 1.4±14.2 letters (P<0.0001).

5 Mean central retinal thickness reduced by 194.2±135.1 µm in people treated with ranibizumab and by 48.4±153.4 µm in those in the control group (P<0.0001).

6 Ranibizumab was well tolerated and significantly improved best-corrected visual acuity and central retinal thickness in people with DMO in this cohort.

Massin P, Bandello F, Garweg JG et al (2010) Safety and efficacy of ranibizumab in diabetic macular oedema (RESOLVE study). *Diabetes Care* **33**: 2399–405

HEALTH AND QUALITY OF LIFE OUTCOMES

Strong SOC associated with good glycaemic control

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 Self-care behaviour can be evaluated using the concept of sense of coherence (SOC), and can be applied to the self-management of T1D to achieve good glycaemic control.

2 The authors used a questionnaire to evaluate SOC in 1264 people with T1D; HbA_{1c} was also determined.

3 People with higher SOC scores, reflecting a stronger SOC, more frequently achieved an HbA_{1c} level <7.5% (<58 mmol/mol; P=0.016).

4 The authors found that SOC is associated with good glycaemic control and suggest that interventions to improve a person's SOC could improve glycaemic control and reduce diabetic complications.

Ahola AJ, Saraheimo M, Forsblom C et al (2010) The cross-sectional associations between sense of coherence and diabetic microvascular complications, glycaemic control and patients' conceptions of type 1 diabetes. *Health Qual Life Outcomes* **8**: 142

DIABETES CARE

Diabetic retinopathy found within narrow glycaemic ranges

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 To examine the relationship between HbA_{1c} and diabetic retinopathy, the authors analysed pooled international data (n=44 623 people) on gradable retinal photographs.

2 "Any" and "diabetes-specific" (DSR; defined as moderate or more severe) retinopathy was observed in 6.7% and 1.5% of the study population, respectively. In known cases of diabetes the prevalence of DSR was 9.4%; in impaired glucose tolerance, impaired fasting glucose and normal glucose tolerance, prevalences of DSR were all 0.1%.

3 Diabetic retinopathy plotted against measures of glycaemia revealed a curvilinear relationship between fasting plasma glucose (FPG) and HbA_{1c}.

4 The authors suggest that the current diabetes diagnostic level for FPG could be lowered to 6.5 mmol/L and an HbA_{1c} of 6.5% (48 mmol/mol) could be a suitable alternative diagnostic criterion.

Colagiuri S, Lee CMY, Wong TY et al (2010) Glycaemic thresholds for diabetes-specific retinopathy. *Diabetes Care* [Epub ahead of print]

BRITISH JOURNAL OF OPTHALMOLOGY

Automated grading efficiently identifies diabetic retinopathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 It has been suggested that automated grading for diabetic retinopathy could reduce the manual grading workload without compromising sensitivity and specificity.

2 This audit was commissioned to determine whether implementing an automated grading software into the Scottish National Diabetic Retinal Screening Programme would be safe, robust and effective.

3 Automated grading software was used to examine 78 601 retinal images from 33 535 people, which had previously been manually graded by clinical experts.

4 The automated grading software identified all people (n=180) with proliferative retinopathy, all people (n=324) with referable background retinopathy, all people (n=193) with observable background retinopathy, 97.3% (1099/1130) of people with referable maculopathy, 99.2% (384/387) of people with observable maculopathy and 99.8% (1824/1827) of people with ungradable images.

5 Of the 33 535 participants screened, 12 185 would not require manual grading as the automated grading software had assessed them as having adequate quality and no microaneurysms; this would reduce the manual grading workload by 36.3%.

6 The authors concluded that automated grading software may be a useful tool in mass diabetic retinopathic screening programmes.

Fleming AD, Goatman KA, Philip S et al (2010) Automated grading for diabetic retinopathy: a large-scale audit using arbitration by clinical experts. *Br J Ophthalmol* **94**: 1606–10

"Ranibizumab significantly improved best-corrected visual acuity and central retinal thickness in people with diabetic macular oedema and was well tolerated."