What’s NEWish in diabetic retinopathy prevention, diagnosis, and treatment (innovation & tech?)

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Moorfields, 19th Century
Moorfields, 21st Century

The Next Generation
Diabetes in the UK

- In 2015, there were an estimated 3.8 million adults with diabetes\(^1\)
  - Almost 1 million people were estimated to have undiagnosed diabetes

- By 2035, diabetes prevalence is expected to increase to 4.9 million\(^1\)

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Epidemiology in the UK

**Diabetic retinopathy**

Of 3569 individuals screened within 6 months of T2DM diagnosis:
- 29.1% had background retinopathy (in one eye or both eyes)
- 2.3% had referable retinopathy

**Prevalence of treatable DMO**

United Kingdom National Ophthalmology Database Study of ~24,000 patients with diabetes

- CSMO 13.9%
- Non-centre involving CSMO 6.5%
- Centre involving DMO 7.4%

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T2DM = Type 2 diabetes mellitus; DMO = Diabetic macular oedema; CSMO = Clinically significant macular oedema

Risk factors
Risk factors

Modifiable:
• Diabetic control / HbA1c
• Glycaemia
• Blood pressure
• Lipid levels
• BMI
• Vitamin D

Non-modifiable:
• Genetic factors
• Duration of diabetes
• Gender

Additional factors:
• Carotid arterial disease
• Pregnancy
• Renal impairment
• Smoking

HbA1c = Glycated haemoglobin.
1. RCOphth, Diabetic Retinopathy Guidelines, Dec 2012.
Co-morbidities2

- Comorbidity should be considered in the treatment of patients with diabetes1
- There are significant levels of increased comorbidity in patients with DR1
- Depression has also been shown to be more prevalent in the diabetic population compared to the non-diabetic population1

DR = Diabetic retinopathy.
Managing HbA1c to reduce the risk of retinopathy

A 1% reduction in HbA1c is associated with a 37% decrease in microvascular disease.

UKPDS: Hazard ratios (95% CI) as estimate of association between mean HbA1c and microvascular end points (mostly requirement for photocoagulation)

Managing blood pressure to reduce the risk of retinopathy

Intensive blood pressure control (144/82 mm Hg) is associated with a 37% decrease in microvascular endpoints.

UKPDS: Proportion of patients who developed microvascular endpoints (mostly requirement for photocoagulation)
Practical challenges in diabetes management

**Patient**
- Decreased QoL
- Hypoglycaemic events
- Increased costs
- Monitoring of blood glucose
- Polypharmacy
- Adherence
- Weight gain

**Healthcare team**
- Lifestyle modification
- Professional skills
- Organisational constraints
- Geographical location
- Patient load
- Clinical setting
- Resources

**Adherence**

**Diabetes**

**Education**

**Weight gain**

**Multiple appointments**

**Organisational constraints**

**Professional skills**

**Geographical location**

**Patient load**

**Clinical setting**

**Resources**

Innovation in Diabetes Eye Care

Role of the diabetes nurse specialist in eye department

- Health promotion & education
- Multispecialty working local physicians
- Bespoke counselling new patients & follow up
- Training & Development staff – diabetes care

Diabetic Eye Passport innovation: summary

- App – smart phones
- Treatment response measurements
- BCVA summary
- DVLA regulations
- Injection appointment reminders
- Interpretation

BCVA: Best corrected visual acuity.
Community Based Retinal Screening
GPs identify diabetic patients (aged ≥12 years) and provide details to the screening service

Local programmes organise a screening call and recall process

Results sent to the patient and GP within 6 weeks

Depending on the results: Patient recalled for annual screening, more frequent surveillance scheduled, or referral made to hospital eye services
Diabetic retinopathy screening service

* Fundus photography system carried out by Nurse/Optometrist/Technician
* Screener subsequently examine & grade the images for evidence of DR lesions
* Images graded by Nurse/Optometrist
* Patients with sight threatening disease correctly identified by graders and follow NSC guidelines

NSC = National Screening Committee.
Enhanced Digital Surveillance Service:

• Designed as high patient throughput
  • Minimal clinician contact
  • Maximising Capacity

• Technological advances – ophthalmic imaging
Virtual R1 M1 (maculopathy) monitoring clinics

- VA, IOP, History, Dilation & OCT
- OCT Scans reviewed (2 days later)
- Clinical Decision
- False Negative - Discharge DRSS
- True Positive - MR Clinic
- Borderline - Monitor

Reviewing 40 patients per session
Digital Innovation and Diabetes Eye care

- Low Cost
- Digital Imaging
- Automated Grading
- Future AI application
- Shorter clinic Visits
- Digital apps; VA self check, symptoms self monitoring and appointment reminders
Progression and classification of DR\textsuperscript{1,2}

- Classified into different stages of severity of its progression

- **Mild NPDR**
  - Characterised by microvascular intraretinal changes, including microaneurysms, haemorrhages, exudates, cotton wool spots and venous beading

- **Moderate – severe NPDR**
  - Next stage of DR

- **Proliferative DR**
  - Characterised by growth of new blood vessels on the retina and posterior surface of vitreous

**Macular oedema**
- Can occur at any stage of DR

NDPR = Non-proliferative diabetic retinopathy.
Diabetic retinopathy

BDR

Pre-proliferative DR

PDR

BDR = Background diabetic retinopathy. Images courtesy of Nigel Kenawy.
Proliferative diabetic retinopathy

Fibrosis & traction
NVD
NVE
NVE
Fibrosis & traction
NVE

NVD = neovascularisation of the disc; NVE = neovascularisation elsewhere.
Why is DMO so important?

- The macula is responsible for central vision.
- Diabetic macular oedema may be asymptomatic at first. As the oedema moves in to the fovea (the center of the macula) the patient will notice blurry central vision. The ability to read and recognise faces will be compromised.
The differences

Normal

Macular oedema
Confirming diagnosis

- History taking
- Visual acuity
- Non invasive investigations
- Invasive investigations

“80% of the diagnosis made is based on the history alone”

Sir William Osler (1849-1919)
Why does retinopathy/maculopathy (DMO) occur?

- Ischaemia/ Angiogenesis
  - NVE/NVD/rubeosis (R3a)

- Leakage
- Exudates (M1)
What causes sight loss in diabetes?

- Diabetic retinopathy and maculopathy
- Diabetic retinopathy/maculopathy is the second leading cause of certifiable blindness among working-age adults in England and Wales – superseded by inherited retinal disorders
  - Attributed to the introduction of UK screening programmes and improved glycaemic control
- The condition can be well advanced before symptoms develop
- Vision loss occurs through:

  2. Clarke M. Diabetic Retinopathy. Dodson PM (ed.). Oxford University Press; 2008;

  Image courtesy of Samantha Mann.
Causes of visual loss

- Advanced Proliferative with Vitreous haemorrhage/ Extensive pre-retinal haemorrhage
Causes of visual loss

- Extensive maculopathy/ DMO
Investigation of retinopathy/ maculopathy
Investigation techniques

- **Slit-lamp Biomicroscopy**
  - 3-D view
  - No permanent record
  - Can identify CSME
  - Poor correlation between OCT and CSME

- **Fluorescein Angiography**
  - Involves injection of fluorescein dye
  - Can be wide field/macular
  - Identifies
    - Focal oedema
    - Diffuse oedema
    - Ischaemic
    - Mixed

- **OCT**
  - Has become routinely used to assess retinal thickness
  - Treatment algorithms consider whether oedema is:
    - Centre involving
    - Non-centre involving

- **OCT-A**
  - Visualises the vasculature of the retina and choroid
  - No need for dye
  - Assesses foveal ischaemia
  - Limited by artefacts and file size

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CSMO

Fundus photograph

Fundus fluorescein angiography
Ischaemic maculopathy
New Vessels (NVD/ NVE)
Spectral domain OCT scanning

- Non-invasive test that uses light waves to take cross-sectional pictures of your retina.
DMO >400 microns

- Consider Anti-VEGF therapy
Diabetic eye disease  Treatment of Proliferative Diabetic Retinopathy and Diabetic Macula Oedema
Role of PRP in proliferative diabetic retinopathy


- PRP destroys pigment epithelium and oxygen-consuming photoreceptors\(^1\)
- Overall oxygen demand of the retina is reduced, leading to reduced VEGF production
- Role of PRP in ischaemia is controversial – steroids and anti-VEGF agents can reduce oedema without destroying photoreceptors\(^2\)
Focal/macular grid photocoagulation in DMO

Mainstay of treatment for DMO since ETDRS\(^1\)

Effective in preventing further vision loss

Conventional laser (as used in the ETDRS) associated with various ocular side effects, including:\(^2\)

- Laser burn scarring
- Vision loss

Laser techniques have since evolved to avoid collateral damage to healthy retina, and to improve accuracy and treatment time\(^3,4\)

- Subthreshold diode micropulse laser
- PASCAL laser

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What are the current treatment options for DMO?
What are the current treatment options for DMO?

- Laser
- Steroid
- Anti-VEGF
- Vitrectomy
- Systemic control
DMO treatment evolution

- ETDRS\(^1\) 1985
- Avastin\(^\circledast\) (bevacizumab) use begins (unlicensed) ~2006\(^2\)
- EYLEA\(^\circledast\) (aflibercept) EU approval 2014\(^6\)
- Laser 'gold standard'
- Anti-VEGF 'new gold standard'

1980

- Triamcinolone use begins (unlicensed) ~2001\(^2\)
- Lucentis\(^\circledast\) (ranibizumab) EU approval 2011\(^4\)
- OZURDEX\(^\circledast\) (dexamethasone) implant EU approval 2014\(^7\)
- ILUVIEN\(^\circledast\) (fluocinolone acetonide) implant UK approval 2013\(^5\)

Nurse delivered intravitreal therapy
Rationale for anti-VEGF treatment in DMO

Macular laser photocoagulation was historical standard of care for DMO¹,²

Mainstay in stabilising vision

Has demonstrated some success in improving vision

Steroid treatment has demonstrated efficacy in improving vision²⁻⁴

Cataracts and increased IOP are important adverse events to consider

Iluvien® is recommended for patients with recalcitrant DMO and in pseudophakic eyes

Identification of VEGF-A as an important pathophysiological mediator of DMO suggested that anti-VEGF-A therapy might improve vision³


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Anti-VEGF treatment for DMO

Treatments for DMO
Summary: Anti-VEGF for the treatment of DMO

- Greater improvements in VA compared with laser or sham

- Considered the new ‘gold standard’ for eyes with centre-involving macular oedema and reduced vision

CHALLENGES

- Intravitreal injection is an invasive procedure that is associated with a risk of serious complications such as endophthalmitis

- Oedema may persist despite monthly treatment

- High costs are associated with licensed anti-VEGF treatment
Treatment of centre-involving maculopatphy: Anti-VEGF/ Steroid injections\textsuperscript{1-6}

**Anti-VEGF injections**
- Aflibercept (Eylea)
- Ranibizumab (Lucentis)

**Steroid implants**
- Dexamethasone (Ozurdex)
- Fluocinolone (Iluvien)

<table>
<thead>
<tr>
<th>NICE</th>
<th>SMC</th>
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<tbody>
<tr>
<td>If CMT ≥400 µm</td>
<td>BCVA ≤75 ETDRS letters at baseline</td>
</tr>
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NICE = National institute for health and care excellence; SMC = Scottish medicines consortium; CMT = Central macular thickness; BCVA = Best corrected visual acuity; ETDRS = Early treatment diabetic retinopathy study.

Steroid treatment for DMO

Treatments for DMO
Role of steroids in DMO: overview and approvals

- Reduce the levels of multiple elevated inflammatory factors, including VEGF\(^1\)
- Demonstrated efficacy (alone and in combination with laser) for treating DMO\(^2\)

- Steroid therapy is most often considered for patients with:\(^3\)
  - Recalcitrant DMO
  - Pseudophakic eyes
  - Those with recent MI/CVA

- Reduced treatment frequency/lower cost can make steroids appealing\(^3,4\)
  - Frequency of secondary cataracts and increased IOP are important considerations

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Products</th>
<th>Administration</th>
<th>Dose frequency</th>
<th>Approval status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone acetonide(^5)</td>
<td>Kenalog(^\circledast)</td>
<td>Intravitreal steroid injection</td>
<td>Up to 3 months</td>
<td>Unapproved for intraocular use</td>
</tr>
<tr>
<td>Dexamethasone(^6,7) (DEX)</td>
<td>Ozurdex(^\circledast)</td>
<td>Intravitreal steroid injection</td>
<td>6 months</td>
<td>EU approved</td>
</tr>
<tr>
<td>Fluocinolone acetonide(^8) (FA)</td>
<td>Illuvien(^\circledast)</td>
<td>Extended-release steroid implant</td>
<td>2–3 years</td>
<td>EU approved, Recommended in UK(^9)</td>
</tr>
</tbody>
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When to consider a steroid implant?

- Poor/no response to anti-VEGF
- In pseudophakic patients
- In patients with recent MI/CVA
- Patient travelling and unable to attend monthly
- In patients WITHOUT glaucoma
- In patients with previous vitrectomy
- ??pregnancy

MI = myocardial infarction; CVA = cerebrovascular accident
DMO Management Plan and response

BCVA 6/12

BCVA 6/18

BCVA 6/9

BCVA 6/9
On Predicting the Future

*Prediction is very difficult, especially about the future.*
Niels Bohr (1885-1962)

*The best way to predict the future is to invent it.*
Alan Kay

Thank you for listening and your attention
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