Delaying and preventing diabetic retinopathy in primary care

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  - If you choose to use the **clickers** there will be some questions you **will not** be able to answer.

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Delaying and preventing diabetic retinopathy in primary care

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Diabetes Research Unit
Cymru
Swansea University
Medical School

A chronic progressive, potentially sight-threatening disease of the retinal neurovasculature associated with diabetes mellitus
**Diabetic Eye Health: Global Perspective:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetes (Millions)</th>
<th>Any DR Million (%)</th>
<th>STDR Millions (%)</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>425</td>
<td>149 (35%)</td>
<td>47 (11%)</td>
<td></td>
</tr>
<tr>
<td>2045</td>
<td>629</td>
<td>220 (35%)</td>
<td>69 (11%)</td>
<td>+48%</td>
</tr>
</tbody>
</table>

DR = Diabetic Retinopathy; STDR = Sight-threatening DR

**Diabetes Pandemic:**
- 2017: 7% of world population
- 2045: 10% of world population

Population expansion, increased ageing, urbanisation, reduced physical activity, dietary changes

---

**SUMMARY**

- 2017: 149 million adults with diabetes have any DR, 47 million have vision threatening DR
- 2045: 220 million adults with diabetes have any DR, 69 million have vision threatening DR

---

629 m
Adults with diabetes

425 m
Adults with diabetes

149 m
Have any DR

47 m
Have Vision Threatening DR

220 m
Have any DR

69 m
Have Vision Threatening DR
Diabetic Eye Disease: GLOBAL Prevalence & Risk Factors

Pooled analysis of 35 studies (n=22,896) based on retinal images (1980-2008)

Overall Prevalence (%):
- Any DR ~35%
- Proliferative DR ~7%
- Diabetic Macular Edema ~7%
- Vision-Threatening DR ~11%

Global estimates (millions):
- Any DR ~93
- Proliferative DR ~17
- Diabetic Macular Edema ~21
- Vision-Threatening DR ~28

<table>
<thead>
<tr>
<th>DM Type</th>
<th>Duration of diabetes (years)</th>
<th>Age-standardised Prevalence per 100 aged 20-79 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>1</td>
<td>&lt;10</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>10-22</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>86.2</td>
</tr>
<tr>
<td>2</td>
<td>&lt;10</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>52.2</td>
</tr>
</tbody>
</table>

Prevalence of DR greater with increasing HbA1c, BP and duration of diabetes
Prevalence higher in Type 1 than Type 2DM

Yau et al Diabetes Care 2012;35:556-564
## Causes of Blindness: England and Wales


<table>
<thead>
<tr>
<th></th>
<th>1990-1991* (% of Total)</th>
<th>1999-2000** (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blind</td>
<td>Blind</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>16-64</td>
<td>16-64</td>
</tr>
<tr>
<td>AMD</td>
<td>48.5</td>
<td>57.2</td>
</tr>
<tr>
<td></td>
<td>11.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>11.7</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>5.3</td>
<td>5.4</td>
</tr>
<tr>
<td>D Retinopathy</td>
<td>3.4</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>11.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>9.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>3.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Major causes of **AVOIDABLE Blindness:**
1. Diabetic Retinopathy
2. Glaucoma & 3. Cataract

= 85% of potentially avoidable cases of visual impairment……..

Major Causes of **ALL** Blindness Certifications Remaining as:
1. Age related **Macular Degeneration (AMD)**
2. Glaucoma
3. Diabetic Retinopathy
4. Optic atrophy

**Working age group (16-64 years)**…
**DR leading cause with the most marked increase** from 11.9 to 17.7%
Conclusions: For the first time in at least five decades, diabetic retinopathy/maculopathy is NO longer the leading cause of certifiable blindness among working age adults in England & Wales.

“This change may be related to factors which include introducing a Nationwide Diabetic Retinopathy Screening in England & Wales…”

Liew et al bmjopn.bmj.com 4th August, 2014
Blindness & Visual impairment due to DR in Wales 2007-2015 (across all age groups)

A 49.4% reduction in serious sight loss (blindness) after 8 years of screening.

Prediction: “A National program delivered to a high quality can reduce new blindness due to diabetic retinopathy by 40% within 5 years”

National Screening Committee, 2001

Can you identify the optic disc?
Can you identify the fovea/macula?
Which eye (Right or Left) is this?

A. Right eye

☑️ B. Left eye

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Early Diabetic Retinopathy: Retinal Vasculature

**HYPERGLYCAEMIA**

- loss of pericytes
  - Polyol pathway overactivity

**endothelial cell proliferation**

- Growth factors
- white cell migration, ‘plugging’
- increased adhesion molecules
- pro-coagulant status

- increased intra-luminal pressure

1. **Micro-aneurysms**
Early Diabetic Retinopathy: Retinal Vasculature
Early Diabetic Retinopathy: Retinal Vasculature

Disruption of endothelial cells -
  Oxidative ‘stress’ - free radical damage
  Advanced glycation end products (AGEs)
  Vascular permeability factor (VPF)
  Release of kinins, PGs, adhesion molecules

Disruption of endothelial ‘tight’ junctions

‘fenestrations’

2 Excessive capillary permeability
Early Diabetic Retinopathy: Exudates (maculopathy)
Diabetic Retinopathy (DR) : Pathogenesis

Intra-vascular coagulation -

- Increased platelet ‘stickiness’
- Adherance of white blood cells to endothelium
- Exposed basement membrane
- Pro-coagulant status

3 Capillary closure
Diabetic Retinopathy (DR) : Pre-Proliferative DR
Diabetic Retinopathy (DR) : Pre-Proliferative DR
Diabetic Retinopathy (DR) : Pathogenesis

Endothelial cell proliferation -

‘growth - promotion’- loss of inhibitors of endothelial cell proliferation

Angiogenic factors

Local: VEGF / VPF
Fibroblastic growth factor (FGF)
Transforming growth factor β (TGF β)

General : circulating, IGF1, PDGF.

4 Proliferation of new vessels
Diabetic Retinopathy (DR) : Proliferative DR
Diabetic Retinopathy (DR) : Proliferative DR
What lesions of Diabetic retinopathy can you see in this image?

A. None
B. Microaneurysm(s)
C. Haemorrhage(s)
D. Microaneurysm(s) and Haemorrhage(s)
E. Microaneurysm(s), Haemorrhage(s), and exudate(s)

The correct answer is D. Microaneurysm(s) and Haemorrhage(s).
Can you find the microaneurysm?
What lesions of Diabetic retinopathy can you see in this image?

A. Haemorrhages
B. Cotton Wool Spots
C. Exudates
D. Microaneurysms
E. All of the above

✓ E. All of the above
What lesions of Diabetic retinopathy can you see in this image?

A. Haemorrhages, Microaneurysms, exudates
B. Haemorrhages, Microaneurysms, exudates, New Vessels
C. Haemorrhages, Microaneurysms, exudates, New Vessels, Pre-retinal Haemorrhages
D. Haemorrhages, Microaneurysms, exudates, New Vessels, Pre-retinal Haemorrhages, Vitreous Haemorrhages
What do you think is happening in this eye?

- Jogging
- Bungee jumping
- Ice fishing
- Kayaking
- Video games
- Hiking
- Running
- Rock climbing
- Swimming
- Weight lifting

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Diabetic Retinopathy (DR) : Classification

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NO apparent Diabetic Retinopathy</td>
<td>NO abnormalities</td>
<td></td>
</tr>
<tr>
<td>Mild non-proliferative DR</td>
<td>1</td>
<td>Microaneurysms only</td>
</tr>
<tr>
<td>Moderate non-proliferative DR</td>
<td>2</td>
<td>More than just microaneurysms, less than severe non-proliferative DR</td>
</tr>
<tr>
<td>Severe non-proliferative DR or</td>
<td>3</td>
<td>Any of the following:</td>
</tr>
<tr>
<td>Pre-proliferative DR (PPDR)</td>
<td></td>
<td>• Intra-retinal haemorrhages (≥20 in each quadrant), or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Venous beading (≥2 quadrants), or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intra-retinal microvascular abnormalities (≥1 quadrant), with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No signs of proliferative DR</td>
</tr>
<tr>
<td>Proliferative DR (Active)</td>
<td>4</td>
<td>One or more of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neo-vascularisation and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vitreous or pre-retinal haemorrhage</td>
</tr>
</tbody>
</table>

ICDR: International Clinical Diabetic Retinopathy Severity Level
ICO: International Council of Ophthalmology Guidelines for Diabetic Eye Care
Diabetic Retinopathy (DR) : Classification: Maculopathy

<table>
<thead>
<tr>
<th>DME absent (M0)</th>
<th>No retinal thickness* or hard exudates in posterior pole</th>
</tr>
</thead>
<tbody>
<tr>
<td>DME present (M1)</td>
<td>Retinal thickness* or hard exudates in posterior pole</td>
</tr>
<tr>
<td>Mild DME</td>
<td>Retinal thickness* or hard exudates in posterior pole, but outside central subfield of macula (diameter 1000 μm)</td>
</tr>
<tr>
<td>Moderate DME</td>
<td>Retinal thickness* or hard exudates within central subfield of macula, but not involving centre point (‘centre-threatening’ DME)</td>
</tr>
<tr>
<td>Severe DME</td>
<td>Retinal thickness* or hard exudates involving centre of macula (‘centre-involved’ DME)</td>
</tr>
</tbody>
</table>

*Retinal thickness requires three-dimensional assessment (Optical Coherance Tomography)

ICO: International Council of Ophthalmology Guidelines for Diabetic Eye Care
# Diabetic Eye Screening grading UK

<table>
<thead>
<tr>
<th>R</th>
<th>Lesions</th>
<th>M</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 No DR</td>
<td>No lesions</td>
<td>M0 No Maculopathy</td>
<td>No lesions within 1dd of fovea</td>
</tr>
<tr>
<td>R1 Background</td>
<td>Microaneurysms  &lt;8 haemorrhages Venous loop Exudate in the presence of DR Cotton Wool Spots in the presence of DR</td>
<td>M0 No Maculopathy</td>
<td>Microaneurysms or haemorrhages within 1dd of fovea with best corrected VA 6/12 or worse where the cause is known</td>
</tr>
<tr>
<td>R2 Preproliferative</td>
<td>Venous beading Venous reduplication &gt;8 blot haemorrhages IRMA</td>
<td>M1 Maculopathy</td>
<td>Exudate within 1dd of fovea Microaneurysms or haemorrhages within 1dd of fovea with best corrected VA 6/12 or worse where the cause is unknown</td>
</tr>
<tr>
<td>R3s Proliferative</td>
<td>Stable pre-retinal fibrosis + laser Stable fibrous proliferation + laser Stable R2 + laser R1 features + laser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R3a Proliferative</td>
<td>New vessels on disc New vessels elsewhere Pre-retinal or vitreous haemorrhage Fibrosis Retinal detachment Reactivation of previous R3s</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What would you expect the grade of diabetes related retinopathy to be?

A. R0 M0
B. R1 M1
C. R2 M0
D. R2 M1
What would you expect the grade of diabetes related retinopathy to be?

A. R3 M0
B. R2 M0
C. R1 M0
D. R1 M1
What would you expect the grade of diabetes related retinopathy to be?

A. R0 M0
B. R1 M0
C. R2 M0
D. R1 M1

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What would you expect the outcome of screening to be?

A. Rescreen 12 months
B. Rescreen 6 months
C. Refer to Ophthalmology
D. Other

✅ C. Refer to Ophthalmology
What would you expect the outcome of screening to be?

A. Rescreen 12 months
B. Rescreen 6 months
C. Refer to ophthalmology
D. Other
What would you expect the outcome of screening to be?

A. Rescreen 12 months
B. Rescreen 6 months
C. Refer to ophthalmology
D. Other

Correct answer: C.
Risk of progression of Diabetic retinopathy

No DR (R0M0) the risk of developing DR and progressing to referable eye disease within 3 years is less than **1 in 50**

Background DR in 1 eye (R1M0, R0M0) the risk of developing DR and progressing to referable eye disease within 3 years is less than **1 in 20**

background DR in 2 eyes (R1M0, R1M0) the risk of developing DR and progressing to referable eye disease within 3 years is less than **1 in 4**
Diabetic Retinopathy: Risk Factors

What can primary care do to prevent or delay progression of diabetic retinopathy?

Modifiable Risk factors:

- Hyperglycaemia
- Hypertension
- Dyslipidaemia

Therapy eg insulin*

* Cohort studies highly heterogeneous
Zhao et al Diagnostic Pathology, 2014

Unmodifiable Risk Factors:

- Diabetes duration,
- Ethnicity,
- Pregnancy,
- Puberty,
- Age
- Genetic makeup

DR also associated with nephropathy, anaemia, hypothyroid

Less consistent: Obesity, smoking, alcohol, physical inactivity

Risk increases with multiple ‘risk factors’
### DIABETIC RETINOPATHY: ‘Risk-factors’

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Age-standardised Prevalence per 100 diabetic subjects aged 20-79 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any DR</td>
</tr>
<tr>
<td><strong>Haemoglobin A1C (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 7.0</td>
<td>17.9</td>
</tr>
<tr>
<td>7.1-8.0</td>
<td>33.1</td>
</tr>
<tr>
<td>8.1-9.0</td>
<td>43.1</td>
</tr>
<tr>
<td>&gt; 9.0</td>
<td>51.2</td>
</tr>
<tr>
<td><strong>Blood pressure (mmHg)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 140/90</td>
<td>30.8</td>
</tr>
<tr>
<td>&gt;140/90</td>
<td>39.6</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mmol/L)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>31.6</td>
</tr>
<tr>
<td>≥ 4</td>
<td>31.1</td>
</tr>
</tbody>
</table>
United Kingdom Prospective Diabetes Study (UKPDS):

Intensive glucose and BP management slowed progression of DR in people newly diagnosed with T2DM. Continued benefit demonstrated that benefits of lifestyle intervention and BP management as well as the use of fibrates on the progression of diabetic retinopathy have been shown. Legacy effect for at least 10 years after clinical trial ended.

Diabetes Control and Complications Trial (DCCT):

Intensive glucose management over ~6.5 yrs in T1DM reduced risk of DR progression which was persistent for at least 18 years after trial. A ‘legacy effect’ has been demonstrated for glycaemic management long after trials have ended and HbA1c has increased.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD):

Fenofibrate reduced DR progression in people with T1DM and increased regression in people with Type 2 DM.

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study:

Intensive glucose management and addition of fenofibrate to statin reduced retinopathy progression in people with T2DM, but lowering of SBP <120 mmHg did not affect progression.

ACCORD Follow-on Study (ACCORDION):

Benefit of prior intensive glucose management in established T2DM, but the benefit of fenofibrate did not. Intensive BP control had no effect.

Evidence to date 2019
Points to remember

• Diabetic retinopathy can still occur even in people with low HbA$_{1c}$. Therefore, not all development and progression of DR is related to glycaemic management.

• If Diabetic retinopathy is present please keep in mind this can progress if glycaemic management is improved too quickly.
Diabetic Retinopathy: **T1DM & Blood glucose Control**

**Diabetes Control and Complications Trial (DCCT)**

Primary Prevention (726) Secondary Prevention (715) over 6.5 years

<table>
<thead>
<tr>
<th>Conventional Rx</th>
<th>HbA1c 9.1%</th>
<th>vs</th>
<th>Intensive Rx</th>
<th>HbA1c 7.2%</th>
</tr>
</thead>
</table>

### Progression of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Cohort</th>
<th>Secondary Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPDR/PDR</td>
<td>(95% CI 14-67%)</td>
<td>(95% CI 26-74%)</td>
</tr>
<tr>
<td>Progression of Diabetic Retinopathy</td>
<td>3-step change 54%</td>
<td>Laser Rx 56% (95% CI 39-66%)</td>
</tr>
</tbody>
</table>

Out of the 153 DCCT people in the lowest quintile of glycaemia (HbA$_{1c}$ ≤ 6.9), 10% still developed retinopathy.

Out of the 166 in the worst quintile (HbA$_{1c}$ ≥ 9.5%), 43% did not develop retinopathy.

Zhang et al. Diabetes Care 24,1275,2001

**Note:** A sub population did not benefit despite good glycaemic management !!!
Points to remember

• Diabetic retinopathy can still occur even in people with low HbA$_{1c}$. Therefore, not all development and progression of DR is related to glycaemic management.

• If Diabetic retinopathy is present please keep in mind this can progress if glycaemic management is improved too quickly.
Caution – Some studies have shown that in those with pre-existing DR and high HbA$_{1c}$ that reducing HbA$_{1c}$ quickly within 6 months, may lead to worsening of DR and possibly sight-loss.

However, the long-term benefits of intensive insulin treatment greatly outweighed the risk of early worsening.

Does bariatric surgery adversely impact on diabetic retinopathy in persons with morbid obesity and type 2 diabetes? A pilot study


However, the long-term benefits of intensive insulin treatment greatly outweighed the risk of early worsening.

Most recently seen in the Sustain-6 Cardiovascular outcome trial of Semaglutide.
If someone with a high HbA1c level develops diabetes related retinopathy should you:

A. Focus on decreasing HbA1c as quickly as possible

B. Aim to lower HbA1c steadily over time

C. Maintain HbA1c at the same level

D. Refer to ophthalmology

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Is Diabetic Retinopathy and its Progress Preventable?

Early diagnosis based on screening

Prevention and Treatment:
- Glucose management*
- BP management*
- Lipid Lowering therapy
- Timely laser therapy ± VEGF
  
* individualise

Advanced diabetic eye disease:
- Intra-vitrel steroids, VEGF inhibitors, vitrectomy

In most at least

Thank you for your attention
Prof David Owens
Prof Stephen Bain
Prof Stephen Luzio
Prof Jeffrey Stephens
Dr Sharon Parsons
Dr Gareth Dunseath
Dr Charlotte Jones
Dr Sarah Prior
Dr Rachel Churm
Dr James Rafferty
Dr Wai-Yee Cheung
Dominic Bright
Sarah Dowrick
Moria Morgan
Teena Seby