Diabetic Retinopathy: Current Approach to Diagnosis and Treatment

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Advances in Diabetes and Thyroid Disease 2013
Joslin Diabetes Center
Harvard Medical School

“Ocular complications in diabetes are frequent, distressing and destined to become one of the challenging problems of the future”
Howard Root, MD—Joslin’s The Treatment of Diabetes Mellitus, 1935.

Program Overview
Diabetic retinal complications
• Impact and burden
• Diagnosis and retinal findings
• Current management
• Telemedicine approaches
Prevalence of Diabetic Complications

![Graph showing the prevalence of diabetic complications](image)

Centers for Disease Control and Prevention, 2008

Global Projections for the Diabetes Epidemic: 2011-2030

![Graph showing global projections for diabetes epidemics](image)


Global need for retinopathy evaluation

Based on current estimates

3 million eyes will need to be evaluated at the minimum per day by 2030

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Global need for retinopathy evaluation


Development of Diabetic Retinopathy


1 in 2 will need laser in their lifetime

Development of Diabetic Retinopathy


~30%

1 in 3 will need laser in their lifetime

Initial Ophthalmologic Examination Schedule

<table>
<thead>
<tr>
<th>Diabetes Type</th>
<th>Recommended First Examination</th>
<th>Minimum Routine Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Within 3–5 years after diagnosis of diabetes or once patient is 10 years of age or older</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2</td>
<td>At time of diagnosis of diabetes</td>
<td>Yearly</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Prior to conception and during the first trimester</td>
<td>Physician discretion pending</td>
</tr>
</tbody>
</table>

*Abnormal findings necessitate more frequent follow-up

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Other Considerations

1. Initiation of intensive glycemic control in long standing poor controlled patients
2. Initiation of an intensive exercise regimen
3. Cataracts
   - Glare and night vision
   - Related to glycemic levels
   - 2x higher risk in diabetes patients compared to age matched individuals
4. Refractive error
   - May fluctuate with glycemic levels

Clinical Stages of DR

ETDRS Levels

<table>
<thead>
<tr>
<th>ETDRS Level</th>
<th>Retinopathy Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>DR Absent</td>
</tr>
<tr>
<td>14/15</td>
<td>DR Questionable</td>
</tr>
<tr>
<td>20</td>
<td>Microaneurysms only</td>
</tr>
<tr>
<td>35</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>43</td>
<td>Moderate NPDR</td>
</tr>
<tr>
<td>47</td>
<td>Moderately Severe NPDR</td>
</tr>
<tr>
<td>53</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>61</td>
<td>Mild PDR</td>
</tr>
<tr>
<td>65</td>
<td>Moderate PDR</td>
</tr>
<tr>
<td>71/75</td>
<td>High Risk PDR</td>
</tr>
<tr>
<td>90</td>
<td>Cannot determine</td>
</tr>
</tbody>
</table>

*ETDRS: Early Treatment Diabetic Retinopathy Study; DR: diabetic retinopathy; NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy*
International Clinical Diabetic Retinopathy and Diabetic Macular Edema Scale

<table>
<thead>
<tr>
<th>Level of Diabetic Retinopathy</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Microaneurysms only</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>More than microaneurysms, but less than severe NPDR</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Any of the following: 20 intraretinal hemorrhages in each four retinal quadrants, definite DME in one or more retinal quadrants, and no PDR</td>
</tr>
<tr>
<td>PDR</td>
<td>One or more of the following: neovascularization, vitreous/preretinal hemorrhages</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of DME Findings</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DME apparently absent</td>
<td>No apparent retinal thickening or HEs in the posterior pole</td>
</tr>
<tr>
<td>DME apparently present</td>
<td>100 DME; some retinal thickening or HEs in the posterior pole, but distant from center of the macula</td>
</tr>
<tr>
<td></td>
<td>Moderate DME; retinal thickening or HEs approaching the center, but not involving the center</td>
</tr>
<tr>
<td></td>
<td>Severe DME; retinal thickening or HEs involving the center of the macula</td>
</tr>
</tbody>
</table>

Comparison of International and ETDRS levels of retinopathy

<table>
<thead>
<tr>
<th>International Classification</th>
<th>ETDRS Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>Levels 10: DR absent</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Level 20; mild NPDR</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>Levels 35, 43, 47; mod. NPDR</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Levels 53A-E; sev.-v.sev. NPDR</td>
</tr>
<tr>
<td>Proliferative DR</td>
<td>Levels 61, 65, 71, 75, 81, 85; PDR</td>
</tr>
</tbody>
</table>

*ETDRS: Early Treatment Diabetic Retinopathy Study; DR: diabetic retinopathy; NPDR: nonproliferative diabetic retinopathy; proliferative diabetic retinopathy

Standard Photos for DR Grading

Std Photo 2A

Std Photo 6B

Std Photo 10A (enlarged for detail)

Std Photo 8A

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Standard Photo 10A

*enlarged to show details

No Apparent Diabetic Retinopathy

- No clinical signs of DR
- Early changes in retinal blood flow
- Nondiabetic changes and complications may be present

Mild Nonproliferative DR

- At least one microaneurysm
- Criteria not met for more severe levels of Diabetic Retinopathy

PDR (1 yr.): 5% HR-PDR (5 yr.): 15%
Moderate Nonproliferative DR

- H/Ma > standard photo 2A in 1-3 retinal quadrants or
- Soft exudate, venous beading, or IRMA definitely present
- Criteria not met for more severe levels of DR

Standard Photo 2A

PDR (1 yr.): 12-27%  HR-PDR (5 yr.): 33%

Severe NPDR

The 4-2-1 Rule

- H/Ma > standard 2A in all 4 retinal quadrants or
- Venous beading (VB) in 2 or more retinal quadrants or
- IRMA > standard 8A in at least 1 retinal quadrant
- Criteria not met for more severe levels of DR

PDR (1 yr.): 52%  HR-PDR (5 yr.): 60%

Proliferative Diabetic Retinopathy

- H/Ma > standard photo 2A in 1-3 retinal quadrants or
- Soft exudate, venous beading, or IRMA definitely present
- Criteria not met for more severe levels of DR
Progression from PDR to NPDR

Clinically Significant Macular Edema

- Macular edema that involves or threatens the fovea
- CSME can be present with any level of DR

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Diabetic Retinopathy

The Science Behind the Care

- Diabetic Retinopathy Study (DRS): 1971-1975
- Early Treatment DRS (ETDRS): 1979-1990
- Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC): 1983-Present
- United Kingdom Prospective Diabetes Study (UKPDS): 1977-1999

ETDRS Results

Early Scatter Laser Photocoagulation:
- Small reduction in risk of severe visual loss
- Benefit of early treatment more pronounced for patients with type 2 DM or patients with type 1 DM of long duration

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Focal Laser Photocoagulation

ETDRS Results

**Focal laser photocoagulation for CSME:**
- Decreased risk of moderate visual loss
- Caused occasional moderate visual gain
- Decreased retinal thickening

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Focal Laser Photocoagulation

ETDRS Results
650 mg aspirin/day:
- Did not alter progression of retinopathy
- Did not increase risk of vitreous hemorrhage
- Did not affect vision
- Did not alter rate of CE

DCCT Results—Type 1 DM: Primary Prevention
Intensive Blood Glucose Control
- 27% Reduction in Development of DR
- 78% Reduction in 3-step Progression of diabetic retinopathy
DCCT Results—Type 1 DM: Secondary Intervention

Intensive Blood Glucose Control
- 54% reduction in 3-step DR progression
- 47% reduction in PDR and severe NPDR
- 56% reduction in photocoagulation
- 23% reduction in macular edema

UKPDS Summary—Type 2 DM

Intensive blood glucose control resulted in:
- 29% reduction in need for laser
- 17% reduction in 2-step progression of DR
- 24% reduction in need for cataract extraction
- 23% reduction in vitreous hemorrhage
- 16% reduction in legal blindness
- Continued benefit after 10 years despite convergence of A1C levels after 1 year

Pars Plana Vitrectomy

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**Intravitreal Pharmacologic Therapy**

- Anti-VEGF – Avastin, Lucentis, Macugen, Eyelea
- Steroids – triamcinolone, dexamethasone, fluocinolone implants
- Vitreolysis - microplasmin

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**Laser-Ranibizumab-Triamcinolone Randomized Clinical Trial for DME:**

**Study Objective**

Evaluate efficacy and safety of 0.5-mg intravitreal ranibizumab plus prompt (within 1 week) or deferred laser (≥24 weeks), or 4-mg intravitreal triamcinolone plus prompt (within 1 week) laser, in comparison with sham plus prompt laser for treatment of diabetic macular edema
Mean Change in Visual Acuity* at Follow-up Visits

- Sham+prompt laser
- Ranibizumab+prompt laser
- Ranibizumab+deferred laser
- Triamcinolone+prompt laser

* Values that were ≥30 letters were assigned a value of 30

Primary outcome time point

Mean Change in Visual Acuity* at Follow-up Visits

- Sham+prompt laser
- Ranibizumab+prompt laser
- Ranibizumab+deferred laser
- Triamcinolone+prompt laser

≥10 Letter Improvement in Visual Acuity at Follow-up Visits

- Sham+prompt laser
- Ranibizumab+prompt laser
- Ranibizumab+deferred laser
- Triamcinolone+prompt laser

P values for the difference in proportion of ≥10 letter improvement in visual acuity from sham+prompt laser at the 52-week visit:
- Ranibizumab+prompt laser vs sham+prompt laser: <0.001
- Ranibizumab+deferred laser vs sham+prompt laser: <0.001
- Triamcinolone+prompt laser vs sham+prompt laser: =0.16

≥10 Letter Worsening in Visual Acuity at Follow-up Visits

- Sham+prompt laser
- Ranibizumab+prompt laser
- Ranibizumab+deferred laser
- Triamcinolone+prompt laser

P values for the difference in proportion of ≥10 letter worsening in visual acuity from sham+prompt laser at the 52-week visit:
- Ranibizumab+prompt laser vs sham+prompt laser: <0.001
- Ranibizumab+deferred laser vs sham+prompt laser: =0.001
- Triamcinolone+prompt laser vs sham+prompt laser: =0.75
Cardiovascular or Cerebrovascular Events According to Antiplatelet Trialists’ Collaboration through 2-Years

<table>
<thead>
<tr>
<th></th>
<th>Sham n = 530</th>
<th>Ranibizumab n = 375</th>
<th>Triamcinolone n = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-fatal cerebrovascular accident-ischemic or hemorrhagic (or unknown)</td>
<td>6%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Vascular death (from any potential vascular or unknown cause)</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Any APTC event</td>
<td>12%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*N = Number of Study Participants. Study participants with 2 study eyes are assigned to the non-sham group. Multiple events within a study participant are only counted once per event. ‡One participant had a non-fatal myocardial infarction and a non-fatal stroke (only counted once in the any cardiovascular event row). †Four of the vascular deaths in the sham group, 1 of the vascular deaths in the ranibizumab group, and 1 of the vascular deaths in the triamcinolone group were from an unknown cause.

Summary: Intravitreal Ranibizumab

- Intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser had superior VA and OCT outcomes compared with focal/grid laser treatment alone
  1. ~50% of eyes had substantial improvement (≥10 letters) while ~30% gained ≥15 letters
  2. Less than 5% loss substantial visual acuity loss (≥10 letters)

Intravitreal antiVEGF injections are now the standard of care for center involved diabetic macular edema causing visual impairment.

AntiVEGF intravitreal injections

- Available antiVEGF agents for intravitreal injections:
  - Pegaptanib (Macugen)
  - Ranibizumab (Lucentis)
  - Bevacizumab (Avastin)
  - Aflibercept (Eyeltra)

- Dose administered (0.05 mL) given monthly
  - ~400 times less than the intravenous dose
  - Average of 8 injections in the first year

- Main ocular risks - 0.1% per injection, 1% per patient
  - Serious eye infection (endophthalmitis)
  - Retinal detachment
  - Vitreous hemorrhage

- Most common adverse events
  - Conjunctival irritation
  - Subconjunctival hemorrhage

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Vision Loss From PDR
- Vitreous Hemorrhage
- Traction Retinal Detachment

Vision Loss From PDR
- Vitreous Hemorrhage
- Traction Retinal Detachment

Vision Loss From DME
Fundus Photograph
- Normal foveal depression
- Intraretinal cysts

OCT Image
Effective Evidence Based Treatment

- Diabetes Control and Complications Trial (DCCT)
- United Kingdom Prospective Diabetes Study (UKPDS)
- Diabetic Retinopathy Study (DRS; 1971-1975)
- Early Treatment Diabetic Retinopathy Study (ETDRS; 1973-1991)
- DRCR.net Intravitreal Ranibizumab or Triamcinolone in Combination with Laser for DME

Outcomes at Beetham Eye Institute, Joslin Diabetes Center, 2006 – 2009
(N = 13,746 patients)

<table>
<thead>
<tr>
<th>BCVA median (Q1, Q3)</th>
<th>20/20 (20/16/20/20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter Change in BCVA, mean (SD)</td>
<td>-0.2 (7)</td>
</tr>
<tr>
<td>20/200 or better</td>
<td>99% (13,651)</td>
</tr>
<tr>
<td>20/40 or better</td>
<td>94% (12,980)</td>
</tr>
<tr>
<td>20/20 or better</td>
<td>79% (12,980)</td>
</tr>
<tr>
<td>61% with DR, 17% with PDR, 22% with DME, 6% with CSME</td>
<td></td>
</tr>
</tbody>
</table>

Discrepancies in Access to Eye Care

- 285,000,000 individuals with diabetes
- 160,000 ophthalmologists

- 54% increase in diabetes population
- < 2% growth in the number of ophthalmologists
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Preservation of Vision in Diabetic Retinal Disease

Percent of Diagnosed Diabetes Patients Who Said They had a Dilated Eye Exam in the Past Year

Unawareness of Retinopathy by DR severity

Telemedicine Approach

- Brings exam to patient
- Within cultural context
- Flexible timing
- Avoid dilation
- Combined with education
- Apply disease management
- Facilitate clinical trials

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Joslin Vision Network: Validated Telemedicine Program for DR

- Digital stereoscopic images
- Undilated pupils
- Image/data storage
- EMR interface
- Clinical Level of DR
- Non DM retinal findings
- Does not replace comprehensive eye exam

JVN Nonmydriatic Digital Imaging Fields

>2,000,000 retinal images to date

JVN vs. ETDRS Seven Standard Fields
Joslin Diabetes Center
Advances in Diabetes and Thyroid Disease 2013
Preservation of Vision in Diabetic Retinal Disease

48/M, DM1 x 31 yrs. A1c 8.9
Patient self reported last eye exam 2 years ago with mild retinopathy
Nonmydriatic 200 degree images

Peripheral new vessels >1/2DA beyond ETDRS fields

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Telemicine Study: Methods

- 2 patient cohorts imaged by JVN protocol by certified imagers
  - NMFP protocol (Topcon MW6s camera):
    - November 1, 2011 to March 31, 2012
    - 3298 eyes of 1649 patients
  - UWFI protocol (Optos P200MA):
    - April 1, 2012 to November 1, 2012
    - 4308 eyes of 2154 patients

Results

7606 eyes of 3803 subjects were evaluated

<table>
<thead>
<tr>
<th></th>
<th>NMFP (N = 1649)</th>
<th>UWFI (N = 2154)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years)</td>
<td>53.6</td>
<td>54.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Duration of DM (mean in years)</td>
<td>13</td>
<td>13.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender (%, female)</td>
<td>43.4</td>
<td>43.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Minority (%)</td>
<td>18.9</td>
<td>19.5</td>
<td>0.70</td>
</tr>
<tr>
<td>Insulin Use (%)</td>
<td>62.8</td>
<td>63.2</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Identification of Eyes with DR and VTDR

UWFI: ultrawide field imaging, NMFP: nonmydriatic fundus photography, DR: diabetic retinopathy, VTDR: Vision threatening diabetic retinopathy
Evaluation of Peripheral Lesions
(1622 eyes, 502 with DR)

14% of subjects had HMA outside ETDRS Standard Fields

Median Image Evaluation Time
(N=3,803 subjects)

Medina Image Evaluation Time (minutes)

UWFI: ultrawide field imaging, NMFP: nonmydriatic fundus photography

Ungradable Image Rate
(N=7,606 eyes)

UWFI: ultrawide field imaging, NMFP: nonmydriatic fundus photography, DR: diabetic retinopathy, DME: diabetic macular edema

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Summary

• There is a global need for diabetes eye care
• Evidence based treatment of diabetes eye disease is remarkably effective in reducing the risk for severe visual loss
• Treatment for diabetic retinopathy complications include control of systemic factors, appropriate and regular ophthalmic follow-up, laser photocoagulation, intravitreal injections and vitrectomy surgery

Summary (continued)

• Intensive, multidisciplinary evidence-based diabetes eye and medical care can result in excellent visual outcomes
• Identification of patients at risk for visual loss early leads to long-term prevention of visual complications and the preservation of vision
• Telemedicine approaches to systematic diabetic retinopathy evaluation may have the potential to achieve this

Thank you