Diagnosis and Treatment of Diabetic Retinopathy

Learning Objectives
Identify who would benefit from seeing an eye care professional.

Describe and identify the levels of diabetic retinopathy.

Have a better understanding of the current management of advanced diabetic eye disease.

Disclosure to Participants

Notice of Requirements For Successful Completion
Please refer to learning goals and objectives
Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

Conflict of Interest (COI) and Financial Relationship Disclosures:
Presenter: Blake Cooper, MD, FACS – No COI/Financial Relationship to disclose

Non-Endorsement of Products:
Accredited status does not imply endorsement by AADE, ANCC, ACPE or CDR of any commercial products displayed in conjunction with this educational activity

Off-Label Use:
Participants will be notified by speakers if any product used for a purpose other than for which it was approved by the Food and Drug Administration.

Personal Objectives
Recognize the importance of diabetic retinopathy as a public health problem.

Realize that diabetic retinopathy is a leading cause of (preventable) blindness.

Understand landmark clinical trials and the role of eye care professionals in the treatment of a patient with diabetes.
What is the Retina?

The retina is a multilayered, light sensitive neural tissue lining the back of the eye.

Light is focused onto and stimulates the retina which then transmits information to the brain through the optic nerve.

The macula is a highly sensitive area in the center of the retina, responsible for reading, recognizing faces and executing other activities that require fine, sharp vision.
Diabetic Retinopathy

Progressive dysfunction of the retinal blood vessels caused by chronic hyperglycemia.

It can be a complication of type 1 or 2 diabetes.

Initially, patients are asymptomatic, if not treated though they will develop visual loss and possible blindness.

Diabetic Retinopathy

30 million known diabetics
40-45% have some level of retinopathy
Leading cause of blindness in Americans aged 25-65
Accounts for 12% of new blindness
Diabetic patients 25 times more likely to go blind
Will blind 25,000 Americans this year
90% of blindness could be prevented
Half of patients receive appropriate eye care

Risk Factors

Duration of diabetes
Poor control of Diabetes
Hypertension
Nephropathy
Obesity and hyperlipidemia
Smoking
Pregnancy
WISCONSIN EPIDEMIOLOGIC STUDY of DIABETIC RETINOPATHY

Duration + A1C = retinopathy

DR at 20 years
- 99% of type 1
- 60% of type 2

Blindness at 20 years
- 1.6% if dx >30 yrs of age
- 3.6% if dx <30 yrs of age

Symptoms
Asymptomatic in early stages of the disease

As the disease progresses symptoms may include:
- Blurred vision
- Floaters
- Fluctuating vision
- Distorted vision
- Dark areas in the vision
- Poor night vision
- Impaired color vision
- Partial or total loss of vision

Pathogenesis
Prolonged hyperglycemia is the major etiologic agent in all of the microvascular complications of diabetes, including diabetic retinopathy.

Breakdown of endothelial tight junctions
Increase in Vascular Endothelial Growth Factor (VEGF)
- a significant angiogenic protein
- potent vaspermeability factor
Increase of Advanced Glycation Endproducts (AGEs)

Pathways of Visual Loss

Diabetes
- Preclinical Changes
  - Background DR
  - Proliferative DR
- Microvascular Leakage
- Microvascular Occlusion
- Clinically Significant Macular Edema
- Neovascular Glaucoma
- Vision Loss

AADE16
- Pericyte Loss
- Endothelial Cell loss
- Blood-retina barrier breakdown

Microvascular Leakage

Microvascular Occlusion

NPDR & CSDME

Microvascular Occlusion

DME CSDME Central Involving Macular edema

Microvascular Occlusion
Stages of Diabetic Retinopathy

• No BDR
• NPDR
  - Mild
  - Moderate
  - Severe
• PDR

DME
VMT/ERM
VH
TRD
NVI

8/12/2016
PDR

Vitreous Hemorrhage U/S

PDR FA

Epiretinal Membrane

Vitreous Hemorrhage

TRD
Why is macula so important?

- It is responsible for central vision.
- DME may be asymptomatic at first.
- As edema moves into the macula, patients lose the ability to read and recognize faces.

Macula

Fovea

Why is macula so important?
- It is responsible for central vision.
- DME may be asymptomatic at first.
- As edema moves into the macula, patients lose the ability to read and recognize faces.

Treatment Options

NPDR without macular edema -
1. Observation
2. Control Risk Factors

Macular edema -
1. Intravitreal VEGF inhibitor +/- Steroid
2. Focal/Grid laser photocoagulation
3. Vitrectomy with membrane peeling
4. Control Risk Factors

Focal Laser

**Early Photocoagulation for Diabetic Retinopathy**

*ETDRS Report Number 9*

Focal laser reduces risk of visual loss by 50%

*Ophthalmology 1991; 98: 766-785*
Focal Laser

DME

MICROVASCULAR LEAKAGE

- Impairment of endothelial tight junctions
- Loss of pericytes
- Weakening of capillary walls
- Elevated levels of vascular endothelial growth factor (VEGF)

Vascular Endothelial Growth Factor

- Promotes vascular growth and permeability
- Elevated levels of circulating VEGF in conditions with retinal ischemia
- Levels are not reduced with Focal laser
Diabetic Macular Edema

Intravitreal Injections

The Diabetic Retinopathy Clinical Research Network
Dedicated to multicenter clinical research of diabetic retinopathy, macular edema and associated conditions

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY018817

Priority Initiatives
Involvement of community-based practices, as well as “academic” or university-based centers.
Collaborate with industry to facilitate investigations and pursue opportunities otherwise not possible and to do so in a manner consistent with the Network’s dedication to academic integrity and optimal clinical trial performance.
DRCR.net Status
(as of 1/6/14)

<table>
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<th>Total</th>
<th>(Community &amp; Academic Centers)</th>
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DRCR Network Completed Protocols
(as of 2/12/14)

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<th>Protocol</th>
<th># of Subjects</th>
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<td>I: Laser-Ranibizumab-Triamcinolone Study for DME</td>
<td>691</td>
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<tr>
<td>J: Laser-Ranibizumab-Triamcinolone Study for DME + PRP</td>
<td>333</td>
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<tr>
<td>K: The Course of Response to Focal Photocoagulation for DME</td>
<td>128</td>
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<td>L: Autorefraction and E-ETDRS Measurements in DME</td>
<td>490</td>
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<td>N: Intravitreal Ranibizumab for Vitreous Hemorrhage from PDR Study</td>
<td>261</td>
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<td>O: Comparison of Time Domain OCT &amp; Spectral Domain OCT in DME</td>
<td>1183</td>
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<tr>
<td>P: Pilot Study of Individuals with DME Undergoing Cataract Surgery</td>
<td>68</td>
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<tr>
<td>Q: Individuals with Diabetes without DME Undergoing Cataract Surgery</td>
<td>317</td>
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<td>R: NSAIDs in Eyes with Non Central Involved DME</td>
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Background

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections of either aflibercept (Eylea), bevacizumab (Avastin), or ranibizumab (Lucentis) are effective in treating DME.

The relative efficacy and safety of these agents within a head-to-head study were unknown prior to the results of this trial.

Medicare allowable charges:
- Aflibercept (2.0 mg): $1961
- Bevacizumab (repackaged 1.25mg): $67
- Ranibizumab (0.3 mg): $1189

Treatment Schedule
Through 1 Year (q4 weeks)

Repeat injections at every 4-week visit if eye "improved" or "worsened".

Otherwise, defer injections if either:
- Visual acuity 20/20 or better and OCT CST "normal" or,
- At or after 24 weeks, visual acuity and OCT stable after 2 consecutive injections

Resume injections if VA or OCT worsened

Focal/grid laser: initiated at or after 24 weeks only if persistent DME not improving after at least 2 injections

*Improved/worsened defined as:
- ≥ 5 letter change (~1 Snellen line) from last injection, or,
- ≥ 10% CST change on OCT from last injection

The Diabetic Retinopathy Clinical Research Network

Protocol T
Comparative Effectiveness Study of Aflibercept, Bevacizumab, or Ranibizumab for DME

Supported through a cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817

Mean Change in Visual Acuity Over 2 Years

* P-values adjusted for baseline visual acuity and multiple comparisons
Mean Change in Visual Acuity Over 1 Years

Baseline Visual Acuity 20/32 to 20/40

Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity 20/50 or Worse

Mean Change in OCT CST Over 2 Years

DME Treatment: anti-VEGF

DME Treatment: Laser

Discussion

Vision gains (from baseline) were seen with all three drugs at 2 years, with reduced number of injections and lasers in year 2.

When initial visual acuity loss is mild, on average there is still little difference in visual acuity between all three drugs.

At worse levels of initial visual acuity aflibercept was more effective at improving visual acuity versus bevacizumab, but not ranibizumab.
HIGH-RISK PROLIFERATIVE DIABETIC RETINOPATHY
At risk for serious vision loss
Any combination of three of the following findings
- Presence of vitreous or preretinal hemorrhage
- Presence of new vessels (neovascularization, NV)
- Location of NV on or near the optic disc
- Moderate to severe extent of new vessels

Pan Retinal Photocoagulation (PRP)

Photocoagulation Treatment of Proliferative Diabetic Retinopathy
Clinical Application of Diabetic Retinopathy Study (DRS) Findings, DRS Report Number 8

PRP reduces risk of visual loss by 50%
Ophthalmology 1991; 88; 583-600

The Diabetic Retinopathy Clinical Research Network

Protocol S
Prompt PRP vs. Ranibizumab + Deferred PRP for PDR Study
Supported through a cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14229, EY14230, EY19807
Background
Panretinal photocoagulation (PRP) has been the treatment for PDR over last 4 decades
- Substantially reduces risk of severe vision loss, but . . .
- Inherently destructive
- Peripheral visual field loss
- Night vision loss
- Exacerbation of pre-existing DME
- Not perfect: 5% severe vision loss (scored than 50/200 at 2 consecutive visits) despite PRP
- Anti-VEGF, when given for DME, decreases risk of diabetic retinopathy worsening and increases chance of improved retinopathy level

Primary Question
Is visual acuity using ranibizumab for PDR not worse than treatment with PRP at 2 years?
Non-inferiority margin of 5 letters

Secondary Question
Are there potential benefits of ranibizumab on:
- Vision throughout follow-up (area under the curve)
- Peripheral vision
- Macular edema
- Incidence of vitrectomy

Complications of PDR

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab Group (N = 191)</th>
<th>PRP Group (N = 203)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Any retinal detachment</td>
<td>6%</td>
<td>10%</td>
<td>0.05</td>
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<tr>
<td>Neovascular glaucoma</td>
<td>2%</td>
<td>3%</td>
<td>0.50</td>
</tr>
<tr>
<td>Iris neovascularization</td>
<td>1%</td>
<td>1%</td>
<td>0.96</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>27%</td>
<td>34%</td>
<td>0.09</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>4%</td>
<td>15%</td>
<td>&lt; 0.001</td>
</tr>
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</table>

Discussion
DRCR.net Protocol S (PRP vs. Ranibizumab for PDR):
- Treatment with 0.5-mg ranibizumab met primary non-inferiority outcome for VA being no worse than PRP
- Summary of Ranibizumab group results vs. PRP:
  - Superior mean visual acuity over course of 2-years (area under the curve analysis)
  - Superior mean visual field outcomes
  - Decreased occurrence of vitrectomies
  - Decreased development of central involved DME
- PRP rarely given for failure or futility of ranibizumab
Steroid Agents

Intraocular steroids

Dexamethasone Implant

Recently approved by FDA for DME
Bio-erodible
Duration ≤6 months
Ozurdex MEAD Study Group 2014:
1048 eyes; 20/50-20/200; CRT ≥300μ; 3-year study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>15 letter improvement</th>
<th>Mean Δ CRT (μ)</th>
<th>Cataract</th>
<th>Glaucoma Surgery</th>
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<tr>
<td>Sham injection</td>
<td>3.1%</td>
<td>NS</td>
<td>51%</td>
<td>0.5%</td>
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<tr>
<td>Fluo 0.2 μg/d</td>
<td>33%</td>
<td>NS</td>
<td>82%</td>
<td>4.4%</td>
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<tr>
<td>Fluo 0.5 μg/d</td>
<td>32%</td>
<td>NS</td>
<td>89%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

Fluocinolone Implant

Recently approved by FDA for DME
Non-responders; Duration ≤3 years
FAME Study 2012:
953 eyes; failed FLT; 20/50-20/400; CRT ≥250μ; 3-year study

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<th>Treatment</th>
<th>15 letter improvement</th>
<th>Mean Δ CRT (μ)</th>
<th>Cataract</th>
<th>Glaucoma Surgery</th>
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<tbody>
<tr>
<td>Sham injection*</td>
<td>21%</td>
<td>NG</td>
<td>51%</td>
<td>0.5%</td>
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<td>Fluo 0.2 μg/d</td>
<td>33%</td>
<td>NG</td>
<td>82%</td>
<td>4.8%</td>
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<td>Fluo 0.5 μg/d</td>
<td>32%</td>
<td>NG</td>
<td>89%</td>
<td>8.1%</td>
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*Treatment Options

Vitreous Hemorrhage -
1. Pan-retinal photocoagulation
2. Vitrectomy with laser photocoagulation
3. Intraocular VEGF inhibitor

Traction Retinal Detachment -
1. Observation if not involving the macula
2. Vitrectomy with membrane dissection

Dexamethasone Implant

Vitrectomy results in improved vision in patients with persistent vitreous hemorrhage
Arch. Ophthalmol. 1985; 103:1644-1652

Pars Plana Vitrectomy

Early Vitrectomy for Severe Vitreous Hemorrhage in Diabetic Retinopathy
Two-Year Results of a Randomized Trial
Diabetic Retinopathy Vitrectomy Report 2
THE DIABETIC RETINOPATHY VITRECTOMY STUDY RESEARCH GROUP
PM 53yo WF - Vision 20/20

PM 53yo WF Vision CF@6in

Pars Plana Vitrectomy

27g Vitrectomy
27g Vitrectomy

CM 46yo AAM
Vision HM@6in

1 Month Post Op
Vision 20/25

5 months later
Vision 20/200

CM 46yo AAM
Vision CF@1FT

5 months later
Vision LP
2 months Post Op
Vision 20/70

Bottom Line
Treatments work best before vision is lost
Many patients are diagnosed only after vision is lost
Vision loss is a late symptom of diabetic eye disease

Post Op - Under SO
Vision HM

Bottom Line
How you can prevent visual loss
• Control patient risk factors
• Insist patients get yearly dilated eye exams

PreOp
PostOP

RECOMMENDED EYE EXAMINATION SCHEDULE

<table>
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<tr>
<th>Diabetes Type</th>
<th>Recommended Time of First Examination</th>
<th>Recommended Follow-up</th>
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<tr>
<td>Type 1</td>
<td>Until the age of 15 or 5 years after diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2</td>
<td>At time of diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Pregnancy (Type 1 or type 2)</td>
<td>Prior to conception and early in the 3rd trimester</td>
<td>No retinopathy to mild nonproliferative diabetic retinopathy (NPDR) every 3 months, moderate NPDR or worse every 1-3 months.</td>
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</table>
EYE EXAM

- Performed by an ophthalmologist or an optometrist – both specialists in the exam of the eye.
  - This usually means that you will have drops put into the eye to open or enlarge the central black area of the eye, the pupil, allowing the doctor to better see the nerves and blood vessels in the back of the eye.
- An examination through a non-dilated pupil is not acceptable because many areas of the retina cannot be visualized without pupil dilation.
- Retinal photography through a non-dilated pupil with the photographs being read by an ophthalmologist is only acceptable as a screening tool. If retinopathy is discovered on a retinal photograph, an examination through a dilated pupil is necessary.

Learning Objectives

- Identify who would benefit from seeing an eye care professional.
- Describe and identify the levels of diabetic retinopathy.
- Have a better understanding of the current management of advanced diabetic eye disease.

QUESTIONS?

blakecooper@kcretina.com