Diabetes-Related Eye Disease: Bridging the Gap in Care

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• 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

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  – Presenter: Blake Cooper, MD – Speaker’s Bureau: Novo Nordisk

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  – Participants will be notified by speakers to any product used for a purpose other than for which it was approved by the Food and Drug Administration.
Learning Objectives

• Identify who would benefit from seeing an eye care professional.

• Describe and identify the levels of diabetes-related retinopathy.

• Have a better understanding of the current management of diabetes-related eye disease.
Personal Objectives

- Recognize the importance of diabetes-related retinopathy as a public health problem.
- Realize that diabetes-related retinopathy is a leading cause of (preventable) blindness.
Retina

- pigment epithelium
- rods
- cones
- horizontal cells
- bipolar cells
- amacrine cells
- ganglion cells
- inner limiting membrane
- retina pigment epithelium

Light
Retinal Diagnostic Tests

- Fundus Photography
- Fluorescein Angiography (FA)
- Optical Coherence Tomography (OCT)
- Ocular Ultrasonography
- Electroretinography (ERG)
Wide Field Imaging
Normal OCT
Diabetes-Related 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 may be asymptomatic, if not treated though they may develop visual loss and possible blindness.
Diabetes-Related Retinopathy

A leading cause of visual loss globally

Patients with diabetes are 25 times more likely to go blind

Only half of patients receive appropriate eye care

90% of blindness could be prevented
Risk Factors

- Duration of diabetes
- Glycemic Level
- Hypertension
- Nephropathy
- Obesity and hyperlipidemia
- Smoking
- Pregnancy
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
Pathology

1. Basement membrane thickening
2. Endothelial cell damage
3. R. B. C. changes
4. Platelet stickiness increased

Occlusion

Leakage

Loss of pericytes
Disease progression pathways

- Diabetes
  - Preclinical changes
  - Background DR
    - Preproliferative DR
      - Proliferative DR
        - Vitreous hemorrhage and/or
          - Retinal detachment and/or
            - Neovascular glaucoma
          - Neovascular glaucoma
      - Clinically significant macular edema
        - Vision loss

Microvascular leakage

Microvascular occlusion

DR, diabetes-related retinopathy.
Microvascular Leakage (Center Involving Macular Edema)
Microvascular Occlusion (Macular Ischemia)
Microvascular occlusion
Microvascular occlusion
No Background Diabetes-Related Retinopathy
Microaneurysms

Mild Nonproliferative Diabetes-Related Retinopathy
Moderate Nonproliferative Diabetes-Related Retinopathy

- Hard exudates
- Microaneurysm
- Flamed shaped hemorrhage
Venous beading

Severe Nonproliferative Diabetes-Related Retinopathy
Neovascularization
Hard exudates
Cotton wool spot
Proliferative Diabetes-Related Retinopathy
Blot hemorrhage
Proliferative Diabetes-Related Retinopathy
Proliferative Diabetes-Related Retinopathy

FA, fluorescein angiography.
Vitreous Hemorrhage
Traction Retinal Detachment
Traction Retinal Detachment
Increasing retinal ischemia setting the stage for proliferative changes

**Background retinopathy**
- Retinal/macular edema (maculopathy)
- Dot & blot hemorrhages
- Microaneurysms
- Flame shaped hemorrhages

**Preproliferative retinopathy**
- Macular edema (maculopathy)
- Hard exudates
- Cotton wool spots

**Proliferative retinopathy**
- Intraretinal microvascular abnormalities
- Venous changes
- Macular edema (maculopathy)
- Traction retinal detachment
- Vitreous hemorrhage

**Complications of proliferative change; sight threatening**
- Rubeosis iridis neovascular glaucoma

**Physical/anatomical effects of diabetes**

**Progression of retinopathy**
### Screening for diabetes-related retinopathy

**EXAMPLE: RECOMMENDED SCREENING PROGRAM, ADA GUIDELINES**

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with type 1 diabetes</td>
<td>Initial dilated and comprehensive eye examinations within 5 years of diabetes onset</td>
</tr>
<tr>
<td>Adults with type 2 diabetes</td>
<td>Initial dilated and comprehensive eye examinations at the time of diabetes diagnosis</td>
</tr>
<tr>
<td>No evidence of retinopathy for one or more annual eye examination</td>
<td>Consider examinations every 1-2 years</td>
</tr>
<tr>
<td>Any evidence of retinopathy present</td>
<td>Subsequent dilated retinal examinations for type 1 or type 2 repeated at least annually</td>
</tr>
<tr>
<td>Retinopathy progressive or sight-threatening</td>
<td>More frequent dilated retinal examinations are recommended</td>
</tr>
</tbody>
</table>

PATIENTS WITH DIABETES

- 72% without DR
- 24% with DR (not vision threatening)
- 4% with DR (vision threatening)

With Retinopathy:
- 83% Unaware of Eye Disease
- 78% Unaware of Eye Disease
- 50% No Routine Eye Exams
Retinopathy Screening

Age-Adjusted % U.S. Adults with Diagnosed Diabetes

Behavioral Risk Surveillance System, CDC Division of Diabetes Translation
Reasons why patients do not receive annual eye exams

**Patient* barriers**
- No need**: 39.7%
- Cost/lack of insurance: 32.3%
- Other: 21.5%
- No eye doctor, no transportation, or could not get appointment: 6.4%

**Provider barriers**
- Understanding the importance
- Lack of specific referral (e.g., specific eye care specialist or specific request/patient information)
- Keeping the referral appointment

*Patients diagnosed with diabetes who are not receiving annual eye exams
**Consisted of "have not thought of it" and "no reason to go"
Chou et al. Diabetes Care 2014;37:180–8;
Treatment options

- NPDR without macular edema
  - 1. Observation
  - 2. Control risk factors

- Macular edema
  - 1. Intraocular VEGF inhibitor +/- steroid
  - 2. Focal/grid laser photocoagulation
  - 3. Vitrectomy with membrane peeling
  - 4. Control risk factors
Center Involving Macular Edema

Elevated levels of VEGF are not reduced by Focal laser
Center Involving Macular Edema

- Mild NPDR: 3%
- Moderate-Severe NPDR: 38%
- PDR: 71%
Focal laser reduces risk of visual loss by 50%

Ophthalmology 1991; 98; 766-785
Center Involving Macular Edema
Focal laser
Focal laser
Focal laser
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 (VEGF)

• Promotes vascular growth and permeability
• Elevated levels of circulating VEGF in conditions with retinal ischemia
• Levels are not reduced with focal laser
Microvascular Damage and Diabetes-Related Retinopathy

Retinal Hypoxia

↑ VEGF-A
Possibly Other Mediators

↑ Permeability
↑ Neovascularization

Vascular Leakage

Center Involving Retinopathy

Optical Coherence Tomography (OCT) Images

Normal retina

Retina with Center Involving Retinopathy
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
Change in visual acuity over 2 years

104-week treatment group comparison*:
- Aflibercept vs. bevacizumab $P = 0.02$
- Aflibercept vs. ranibizumab $P = 0.47$
- Ranibizumab vs. bevacizumab $P = 0.11$

* $P$-values adjusted for baseline visual acuity and multiple comparisons
Intravitreal injections
Preparation
PDR
Pan retinal photocoagulation (PRP)

Photocoagulation Treatment of Proliferative Diabetic Retinopathy

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

THE DIABETIC RETINOPATHY STUDY RESEARCH GROUP

PRP reduces risk of visual loss by 50%

Ophthalmology 1991; 88; 583-600
Panretinal photocoagulation (PRP)
Post pan-retinal photocoagulation
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 EY14231, EY14229, EY018817
Intraocular steroids
Treatment options

• Vitreous hemorrhage
  – 1. Pan-retinal photocoagulation
  – 2. Vitrectomy with laser photocoagulation
  – 3. Intraocular vascular endothelial growth factor (VEGF) inhibitor

• Traction retinal detachment
  – 1. Observation if not involving the macula
  – 2. Vitrectomy with membrane dissection
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

Vitrectomy results in improved vision in patients with persistent vitreous hemorrhage

Arch Ophthalmol. 1985; 103 1644-1652
Pars plana vitrectomy
Severe NPDR

PM 53yo WF
Vision 20/20
PM 53yo WF
Vision CF@6in
27g Vitrectomy
27g Vitrectomy
27g Vitrectomy
s/p PPV/MP/EL

1 Month Post Op
Vision 20/25
CM 46yo AAM
Vision HM@6in
PDR/VH

CM 46yo AAM
Vision HM @ 6 in
5 months later
Vision 20/200
5 months later
Vision LP
s/p PPV/MP/EL

2 months Post Op
Vision 20/70
s/p PPV/MP/EL/SO

Post Op - Under SO Vision HM
• Treatments work best before vision is lost

• Many patients are diagnosed only after vision is lost

• Vision loss is a late symptom of diabetes-related eye disease

Bottom line
How you can prevent visual loss

• Control risk factors
• Have yearly dilated eye exams

Bottom line
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.
Early Worsening of Diabetes-Related Retinopathy in the Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial Research Group

• The magnitude, but not the rapidity, of the reduction in HbA1c during the first 6 months of intensive treatment was an important risk factor for EW

• Retinopathy progression between the baseline and 4-year visits was no greater even in intensively treated patients who experienced EW than in conventionally treated patients who did not experience EW

• No case of EW was associated with serious visual loss in the DCCT
Early Worsening of Diabetes-Related Retinopathy in the Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial Research Group

- If retinopathy is at or past the moderate nonproliferative stage - Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6 to 12 months thereafter seems appropriate for such patients.

- In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if hemoglobin A1c is high.
Diabetes-Related Retinopathy and the Effect of Pregnancy

• Pregnancy is associated with increased risk of development and progression of diabetes-related retinopathy (DR).

• Although pregnancy does not have any long term effect on DR, progression of retinopathy changes occur in 50%-70% of cases.

• The greatest risk of worsening occurs during the second trimester and persists as long as 12 months postpartum.
Diabetes-Related Retinopathy and the Effect of Pregnancy

• The other factors found to be associated with its progression include duration of the diabetes, severity of retinopathy at conception, hyperglycemia, anemia and progression of coexisting hypertension.

• Laser photocoagulation should be promptly instituted in all cases of severe non-proliferative retinopathy and should not be delayed till the patient develops early proliferative changes.

• Euglycemia before and during pregnancy can help prevent this increase in the progression and serious vision loss.
Anti-VEGF Crunch

• Anti-VEGF crunch is an infrequent complication following intravitreal injection of anti-VEGF agents.

• Occurs in patients with tractional retinal detachment secondary to fibrovascular traction in proliferative retinopathy.

• The condition results from regression of the vascular component of fibrovascular proliferation and a concurrent increase in fibrosis, resulting in worsening retinal traction.
Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group

N Engl J Med 2010; 363:233-244

• Intensive blood sugar control reduced the progression of diabetes-related retinopathy compared with standard blood sugar control.

• Combination lipid therapy with a fibrate and statin also reduced disease progression compared with statin therapy alone.

• Intensive blood pressure control provided no additional benefit to patients compared with standard blood pressure control.
Important Articles

1. Early Photocoagulation for Diabetic Retinopathy: ETDRS Report # 9; Ophthalmology 1991; 98; 766-785
3. Photocoagulation Treatment of Proliferative Diabetic Retinopathy: DRS Report # 8; Ophthalmology 1991; 88; 583-600
QUESTIONS?
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