Diabetic Retinopathy

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Disclaimer

- PI for Genetech sponsored clinical trial using ranibizumab (Lucentis) for treatment of diabetic macular edema, ARMD and other retinal vascular diseases.

Acknowledgment

- Several of the slides used in this presentation come from slide sets prepared for diabetes education by:
  - Pennsylvania Diabetes Association
  - American Academy of Ophthalmology

Off label medications

- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Pegaptanib (Macugen)
- Triamcinolone (Triessence, Kenalog)
- Dexamethasone
Objectives

- Review the risk factors, presentations and clinical manifestations of DR
- Review current treatment options, goals and outcomes
- Review screening and management roles played by non-ophthalmologic physicians

1976 Diabetic Retinopathy Study

- Demonstrated effectiveness of panretinal photocoagulation for proliferative retinopathy

Pre-1974

- Blindness
- Pituitary ablation

Late 1970’s – Early 1980’s

- Refinement of laser procedures
- Development of vitreo-retinal microsurgical instrumentation and procedures
<table>
<thead>
<tr>
<th><strong>1982</strong></th>
<th><strong>2009</strong></th>
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<tbody>
<tr>
<td><strong>Early Treatment Diabetic Retinopathy Study</strong></td>
<td><strong>Diabetic Retinopathy remains one of the most significant complications of diabetes and continues to be the leading cause of blindness</strong></td>
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<tr>
<td>• Demonstrated effectiveness of focal photocoagulation for macular edema</td>
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| **2005** | **First use of VEGF inhibitors** |
Diabetic Retinopathy

- Early detection and early treatment are crucial for the prevention of blindness

A 66 year old woman presents with decreased vision in her right eye. What additional information is important? What will you do to evaluate and manage her complaint?

A 35 year man, 25 year Hx of IDDM, previously visually asymptomatic with 20/20 vision, now presents with sudden onset of floaters.

58 year old woman
CC: gradual blur of vision, getting worse for 6 months
PMH: NIDDM 11 years, HgbA1C = 8.7
BP 158/90
Va: 20/80 OD, 20/25 OS
Who Gets Retinopathy?

Factors include
- Age of onset
- Duration of disease
- Degree of control
- Hypertension

Age of Onset and Duration

Prior to age 30
- Duration less than 5 years
  - 17% have some retinopathy
  - Macular edema unusual, PDR rare
- Duration greater than 15 years
  - 98% have some retinopathy
  - Approximately 1/3 have macular edema
  - Approximately 1/3 have PDR

After age 30
- Duration less than 5 years
  - 29% have some retinopathy
  - Macular edema unusual, PDR 2%
- Duration greater than 5 years
  - 78% have some retinopathy
  - Approximately 28% have macular edema
  - Approximately 16% have PDR
DCCT and UKPS

- Intense glucose control reduced rates of progression of retinopathy
- Blood Pressure control reduced progression of retinopathy

Diabetes Control and Complications Trial

- Intensive glucose control
- No baseline retinopathy
  - 76% reduction in the risk of developing significant retinopathy

Diabetes Control and Complications Trial

- Intensive glucose control
- Mild to moderate retinopathy
  - 54% reduction in progression
  - 47% reduction in development of severe NPDR or PDR
  - 56% reduction in need for laser surgery
### Hypertension and Diabetes

- There is a positive correlation between elevated systolic blood pressure and the development of exudative complications of retinopathy.

### Pathophysiology Known

- VEG-F
  - Stimulates proliferation of new vessels
  - Increases vascular permeability
  - Has pro-inflammatory activity
- PEDF
  - Decreases in DR
  - Inhibits neovascularization

### Pathophysiology Known

- Hyperglycemia > loss of pericytes
- Loss of pericytes > loss of capillary endothelia and capillaries
- Loss of capillaries > hypoxia and ischemia
- Hypoxia > release of VEGF
- Decrease PEDF

### Other Possible Mechanisms

- Aldose reductase: glucose to sorbitol causing osmotic cell damage
- Protein Kinase C upregulates VEGF, enhanced by hyperglycemia
- Reactive oxygen species causes oxidative damage – increased VEGF
- Growth hormone plays permissive role for VEGF, reduction in GH prevents neovascularization
Classification and Lesions of Diabetic Retinopathy

- NonProliferative Diabetic Retinopathy (NPDR)
- Proliferative Diabetic Retinopathy (PDR)

Early NonProliferative Diabetic Retinopathy

- Microaneurysms
- Hard exudates
- Intraretinal hemorrhages
- Macular edema*
Advanced NonProliferative Diabetic Retinopathy

- Cotton wool spots
- IntraRetinal Microvascular Abnormalities (IRMA)
- Venous Bleeding
Advanced NonProliferative Diabetic Retinopathy

- High risk of imminent PDR
- No immediate treatment
- Patient needs re-evaluated in 2-4 months
**Proliferative Diabetic Retinopathy**

- Signs of NPDR including macular edema
- Neovascularization of disc (NVD) or retina (NVE)
- Vitreous hemorrhage
- Fibrous proliferation with retinal detachment
What Causes Vision Loss?

- Macular edema can occur in NPDR or PDR
- Vitreous hemorrhage PDR
- Traction Retinal Detachment PDR
### Diabetic Maculopathy Includes

| • Macular edema (retinal swelling) |
| • Lipid exudation (hard exudates) |
| • Ischemia (capillary nonperfusion) |

### When is Maculopathy Treated?

| • Retinal edema within 1/3 disc diameter from the center of the fovea |
| • Hard exudate within 1/3 DD associated with edema |
| • Edema greater than 1 DD in area within 1 dd from fovea |

### What Are Symptoms of Maculopathy?

| • None |
| • Gradual progressive loss of central vision |
| • Vision is “smeared”, “oily”, “filmy”, “scum”, “dirty glasses” |
| • Central scotoma |

### How do We Treat Macular Edema?

| • Treatment guided by Fluorescein angiography |
| • Focal laser coagulation of microaneurysms |
| • Grid laser to areas of retinal edema and non-perfusion |
### Results of Treatment for Macular Edema

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>50% reduction in rate of vision loss</td>
<td>50%</td>
</tr>
<tr>
<td>20% improved vision</td>
<td>20%</td>
</tr>
<tr>
<td>60% stable vision</td>
<td>60%</td>
</tr>
<tr>
<td>20% will show progressive vision loss in spite of treatment</td>
<td>20%</td>
</tr>
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### What are Symptoms of Proliferative Diabetic Retinopathy?

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>None</td>
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<tr>
<td>Floaters and cobwebs</td>
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<tr>
<td>Rapid dramatic vision loss</td>
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<td>Visual field loss</td>
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When is Proliferative Diabetic Retinopathy Treated?

- Pan Retinal Photocoagulation for High Risk PDR:
  - NVD
  - NVD or NVE with preretinal bleeding
- Vitrectomy for non-clearing vitreous hemorrhage or TRD

Pan Retinal Photocoagulation (PRP)

- Outpatient procedure
- 1000-2000 laser burns
- 1 to 3 sessions
- Side effects:
  - Decreased night vision
  - Decreased peripheral vision
  - Decreased central vision
POST PHOTOCOAGULATION

Eye with vitreous hemorrhage before vitrectomy

Fiberoptic illumination
Infusion Line
Suction/Cutting tip
### Results of Treatment for Proliferative Diabetic Retinopathy

- Laser reduces risk of severe vision loss by 60%
- Vitrectomy restores pre-hemorrhage vision in 85% and allows completion of treatment with laser
- Vitrectomy restores vision in 65% for repair of TRD

### Medical Management

#### Hgb A1C < 7.0
- Good Glucose control
  - Both DCCT and UK study show reduction in ocular complications

### Emerging Therapy

- VEG-F inhibitors – off label, in clinical trial
  - Macugen (pegaptanib) PDR, CSDME
  - Lucentis (ranibizumab) CSDME, CRVO, BRVO
  - Avastin (bevacizumab) CSDME, PDR, NVG, CRVO
- Intra-vitreal steroid injection – off label, in clinical trial
  - Triamcinolone CRVO, BRVO, CSDME
  - Dexamethasone CRVO, BRVO, PDR, CSDME

### Medical Management

#### Hypertension
- A significant risk factor for development and progression of retinopathy
- Systolic < 130 mmHg
- Risk reduction similar for ACE inhibitors or other agents (Beta-blockers)
Renal Disease may aggravate retinal edema.

Role of dialysis in regard to stabilizing retinopathy is not clear (many have already had laser).

Heparin – increased risk of bleeding.

Medical Management

Renal Disease

- Renal disease may aggravate retinal edema
- Role of dialysis in regard to stabilizing retinopathy is not clear (many have already had laser)
- Heparin – increased risk of bleeding

Medical Management

Lipid Abnormality

- Increased retinal exudation with:
  - Elevated serum cholesterol
  - Elevated triglycerides
  - Manage lipid abnormalities

Medical Management

Anemia

- Frequently overlooked
- Significant effects on retina
- Hgb < 12gms = 2x risk for retinopathy
- Increased risk of macular edema

Medical Management

Anemia

- Low hematocrit is an independent risk factor for developing PDR and severe vision loss
- Frequently related to renal disease and associated lack of erythropoietin production
- Correction reduces retinal exudation and edema
### Medical Management

#### Medication FAQs

- Aspirin – no increase in severity or frequency of hemorrhage
- ASA did decrease death from Cardiovascular disease by 17%
- Anti-oxidants - ? Benefit of Vitamins C, E, beta-carotene

#### Screening Criteria

- Pregnancy: discuss risk before conception
  - Existing retinopathy may worsen
  - Retinopathy may develop
  - Retinal evaluation before conception or in first trimester

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### Medical Management

#### When to refer?

- Situations requiring referral
  - [✓] Macular edema
  - [✓] NVD/NVE
  - [✓] Vitreous bleeding
  - [✓] Sudden unexplained vision loss

#### Screening Criteria

- Diabetes Dx < age 30:
  - [✓] Annual ophthalmologic exams beginning 5 years after diagnosis
  - [✓] Ophthalmoscopy by PCP at other intervals
Medical Management

Screening Criteria

• Diabetes Dx > age 30:
  ✓ Annual ophthalmologic exams beginning at the time of diagnosis
  ✓ Ophthalmoscopy by PCP for signs at other intervals

Final Comment

• Team Event: patient, ophthalmologist and physician managing diabetes.
• With good team play, the prognosis for maintaining functional sight is good