Tight Blood Glucose and Blood Pressure (BP) Control for Prevention and Management of Diabetic Retinopathy (DR)

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Presentation Outline

• DR Overview
  – Risk factors
  – Characteristics
  – Complications

• Prevention
  – Primary care provider role
  – Risk factor management
  – Referral and screening recommendations

• Supporting evidence for tight BP and diabetes control

• Intervention
  – Laser photocoagulation
  – Vitrectomy

• Roundtable Discussion
DR Overview

• Leading cause of blindness in the working-age population
  – Vision to 20/200 or worse in 50% of patients within 5 yrs of proliferative diabetic retinopathy (PDR) onset
  – Complications can have sudden and severe effects on visual acuity
• Affects retinal vessels

DR Overview

• Two categories
  – PDR
  – Nonproliferative (NPDR)
• Asymptomatic unless
  – Macular edema/ischemia
  – Vitreous hemorrhage
  – Retinal detachment
  – Neovascular glaucoma

American Academy of Ophthalmology (AAO). Available at:
DR Risk Factors

- Diabetes duration
- Hyperglycemia
- Hypertension
- Hyperlipidemia
- Nephropathy (microalbuminuria)
- Pregnancy
- Smoking
- Cataract surgery

ADA. *Diabetes Care*. 2005;28(suppl 1):S4-S87.
# International Clinical DR Disease Severity Scale

<table>
<thead>
<tr>
<th>Proposed Disease Severity</th>
<th>Dilated Ophthalmoscopy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Microaneurysms (MAs) only</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>More than just MAs, but less than severe NPDR</td>
</tr>
</tbody>
</table>
| Severe NPDR               | No signs of PDR + any of the following:  
                             • >20 intraretinal hemorrhages in each of 4 quadrants  
                             • Venous beading in ≥2 quadrants  
                             • Intraretinal microvascular anomalies in ≥1 quadrant |
| PDR                       | ≥1 of the following:  
                             • Neovascularization  
                             • Vitreous or preretinal hemorrhage |

NPDR

• Levels of severity: mild, moderate, severe
• Severity correlates with probability of progression to PDR
• Early physiologic changes
  – Increased capillary permeability
  – Leakage of fluid into the retina
  – Macular thickening
  – Closure of retinal capillaries
  – Macular ischemia
  – Vision loss

Mild NPDR

- Clinical features:
  - Dot and blot hemorrhages (Hs)
  - Microaneurysms (MAs)
- Little threat to vision
- Follow-up every 6-12 months


Moderate NPDR

• Clinical features
  – Increased Hs/MAs
  – Intraretinal microvascular abnormalities (IRMAs)
  – Venous beading (VB) and looping
  – Cotton-wool spots (CWS)

• Follow-up every 4-6 months

Severe NPDR

• Clinical features
  – Hs/MAs in all 4 quadrants
  Or
  – VB in 2 quadrants
  Or
  – IRMAs in 1 quadrant
• High risk of PDR
• Follow-up every 2-4 months

PDR

- Proliferation of fragile new vessels
- Neovascularization of the disk (NVD) or elsewhere (NVE)
- Attempt to supply oxygenated blood to ischemic retina
- Activated endothelial cells migrate, grow on posterior surface of vitreous gel


High-risk PDR

- Increased risk of severe vision loss
- Clinical features
  - NVD >1/3 disc diameter
  - NVD with vitreous or preretinal H
  - NVE >1 disc area with vitreous or preretinal H

DME

• Consequence of DR at any stage
• Physiologic changes
  – Blood–retinal barrier breakdown
  – Extracellular fluid accumulation and/or hard exudate deposition
• Focal, diffuse, or ischemic
• Visual acuity loss, impaired color vision, metamorphopsia
• Clinically significant ME (CSME)
  – Involves or threatens fovea
  – Endangers central vision
  – Macular laser treatment


Porta M, Bandello F. Diabetologia. 2002;45:1617-1634.
Complications of Severe PDR

• Tractional retinal detachment
  – Fibrotic NV and posterior gel surface pull on retina and cause detachment
  – Leads to severe vision loss

• Vitreous hemorrhage
  – Fragile NV tears and bleeds

• Neovascular glaucoma
  – NV on iris and trabecular meshwork
  – Causes elevated pressure, pain, blindness

AAO. Available at: http://www.medem.com/MedLB/article_detailb.cfm?article_ID=ZZZL4RFEH4C&sub_cat=112.
Images: 1CMSP. Available at: Available at:http://www.cmsp.com/cmsp/vlb5d03/imagepreview?stockno=Z031-Z-157.
3Courtesy of Thomas Ciulla, MD, PC.
DR Prevention: Role of the Primary Care Physician

• Identify patients at risk for DR
• Educate patients about DR consequences
• Coordinate risk factor management
  – Hyperglycemia
  – Hypertension
  – Hyperlipidemia
• Refer for screening and treatment
• Be aware of the role of laser photocoagulation and surgical intervention

O’Shea JG, Infeld DA. Available at: http://medweb.bham.ac.uk/easdec/screening_review.html.
# DR Prevention and Early Treatment: Screening and Exam Recommendations

<table>
<thead>
<tr>
<th>Diabetes Type</th>
<th>First Exam</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>5 yrs after onset</td>
<td>Annually</td>
</tr>
<tr>
<td>Type 2</td>
<td>At diagnosis</td>
<td>Annually</td>
</tr>
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</table>
| Prior to pregnancy (type 1 or type 2) | Prior to conception or early in the first trimester | • No DR to moderate NPDR: every 3-12 months  
• Severe NPDR or worse: every 1-3 months |

ADA. *Diabetes Care*. 2005;28(suppl 1):S4-S87.

Evidence: Benefits of Glycemic Control

- United Kingdom Prospective Diabetes Study (UKPDS)
  - Type 2 diabetes
  - Tight control (oral agents or insulin) vs conventional treatment
  - Tight control reduced the risk of diabetic retinopathy progression by 21%
  - Tight control reduced the risk of retinal photocoagulation by 29%

Evidence: Benefits of Glycemic Control

- Diabetes Control and Complications Trial (DCCT)
  - Type 1 diabetes
  - Tight (intensive insulin) vs conventional treatment
    - 76% risk reduction (RR) in DR development
    - 54% RR in DR progression

- Tight glycemic control is an effective medical treatment to slow onset and progression of DR

Evidence: Benefits of BP Control

• UKPDS (Report No. 38)
  – Tight (T) vs less tight (LT) BP control
  – 37% reduction in DR progression
  – 47% RR in visual acuity deterioration

• Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID)
  – Normotensive type 1 diabetes patients
  – Trend (not significant) toward reduced retinopathy progression

Evidence: Benefits of BP Control

- Appropriate Blood Pressure Control in Diabetes (ABCD)
  - Type 2 diabetes patients with hypertension, intensive vs moderate BP control
  - Also, normotensive type 2 diabetes patients, antihypertensive agents (AHA) vs placebo
  - 5 yrs
  - Hypertensive group: no difference in DR progression
  - Normotensive group: DR progression less frequent among AHA-treated

UKPDS 69: Hypertension in Diabetes Study (HDS)

• Primary objective: Determine the relationship between tight BP control and DR in type 2 diabetes patients
  – DR considered apart from nephropathy and neuropathy
  – Endpoints: photocoagulation, vitreous hemorrhage, specific lesions, retinopathy progression, vision loss

UKPDS 69: Study Demographics

- HDS participants comprised of a subset of UKPDS participants
  - Newly diagnosed type 2 diabetes patients
  - Exclusion criteria (for UKPDS):
    - Retinopathy requiring photocoagulation
    - Malignant hypertension
    - Ketonuria
    - MI in the previous year
    - Current angina or heart failure
    - >1 vascular episode
    - Elevated serum creatinine
    - Uncorrected endocrine abnormality
    - Occupation prohibiting insulin therapy
    - Life-threatening or systemic illness
UKPDS 69: Study Demographics

- N = 1,148
- 54% male
- 56.4 ± 8.1 yrs of age
- Enrollment based on mean of 3 BPs at consecutive clinic visits
  - 160/90 mm Hg if not on antihypertensive therapy
  - 200/85 mm Hg if treated for hypertension
UKPDS 69: Study Design–Treatment Protocol

• Tight BP control (T group; n = 758)
  – Goal BP <150/85 mm Hg
  – ACE inhibitor (captopril; n = 400) OR
  – β blocker (atenolol; n = 358)
  – Additional agents considered if goal BP was not attained on maximum allocated therapy drug

• Less tight BP control (LT group; n = 390)
  – Goal BP <200/105 mm Hg
  – Avoiding therapy with ACE inhibitors or β blockers
UKPDS 69 Study Design: DR Assessment

- Retinal color photography, ophthalmoscopy, and visual acuity at UKPDS enrollment and every 3 yrs thereafter
  - 1.5, 4.5, and 7.5 yrs after randomization
- Annual direct ophthalmoscopy
- Lesions (MA, hard exudates, CWS) assessed
- Progression graded using modified ETDRS scale
- Ocular endpoints: photocoagulation, vitreous hemorrhage, cataract extraction, vision loss (acuity and blindness)

UKPDS 69: Safety and BP Endpoints

• No reported adverse events
• Among patients with 9-year follow-up data:
  – Significantly better BP control in T group
    • $P < 0.001$
    • T group mean = 144/82 mm Hg
    • LT group mean = 154/87 mm Hg

UKPDS 69: Outcomes (T vs LT)

• Fewer DR lesions*
  – MAs, hard exudates, CWSs
  – Significantly lower in T group at 4.5 and 7.5 yrs
  – $P < 0.05$ for each

• Slower DR progression*
  – Fewer in T group deteriorated 2 steps or more on ETDRS scale
  – $P < 0.002$ and $P < 0.001$ at 4.5 and 7.5 yrs, respectively

*No difference between captopril and atenolol.
UKPDS 69: Outcomes (T vs LT)

- Lower photocoagulation rate*
  - Most due to maculopathy
  - 37% RR in T group ($P = 0.03$)

- Vision loss
  - Lower risk of blindness in 1 eye in T group ($P = 0.046$)
  - 47% lower risk of acuity deterioration in T group ($P = 0.004$)

*No difference between captopril and atenolol.
Intervention

• If DR progresses despite glycemic and BP control…
  – Intervention
    • Laser photocoagulation
    • Vitrectomy

• Potential future interventions?
  – Intraocular injections
  – Oral agents
Laser Photocoagulation

- Delivered through a slit-lamp via a corneal contact lens

**PDR**
- Panretinal (PRP; scatter)
- Palliative
- Destroys ischemic retinal tissue
- Seals, shrinks, and prevents growth of abnormal vessels
- AEs: ↓night, color, peripheral vision; exacerbate existing DME

**DME**
- Focal for focal DME
- Grid for diffuse or ischemic DME
- Cauterizes leaking MAs
- Allows absorption of fluid, hard exudates

Image courtesy of NEI, NIH

Vitrectomy

- To remove vitreous hemorrhage
- To treat or prevent retinal detachment
- Outpatient procedure
- Usually combined with PRP

Summary

• DR is progressive and a leading cause of blindness
• DR risk factors include hyperglycemia and hypertension
• Tight glycemic and BP control decrease risks of DR development and progression
• If all else fails, surgical intervention may prevent further vision loss