IHS Division of Diabetes
Advancements in Diabetes Seminar

Clinical Advancements in Diabetes Eye Care

Mark B. Horton, OD, MD
Director, IHS/JVN Teleophthalmology Program
Diabetes Mellitus in Indian Country

Endemic nature of diabetes paralleled by diabetic eye disease
## Ocular Complications of DM (1 of 3)

<table>
<thead>
<tr>
<th>Ocular Tissue</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lids</td>
<td>Xanthelasma, Blepharitis</td>
</tr>
<tr>
<td>Orbit</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Keratitis, Epithelial erosions, Keratitis</td>
</tr>
<tr>
<td>Iris</td>
<td>Poor dilation, Rubeosis</td>
</tr>
<tr>
<td>Lens</td>
<td>Transient refraction changes, Cataract (and ↓ surgical outcomes)</td>
</tr>
<tr>
<td>Retina</td>
<td>Retinopathy/Maculopathy, Retinal vein occlusions, Retinal artery occlusions, Ischemic syndromes</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Papillopathy, Ant Isch Optic Neuropathy, Glaucoma</td>
</tr>
<tr>
<td>Cranial Nerves</td>
<td>3rd, 4th, 5th, 7th CN palsies</td>
</tr>
<tr>
<td>CNS</td>
<td>CVA associated vision loss</td>
</tr>
</tbody>
</table>
## Ocular Complications of DM (2 of 3)

<table>
<thead>
<tr>
<th>Ocular Tissue</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lids</td>
<td>Xanthelasma, Blepharitis</td>
</tr>
<tr>
<td>Orbit</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Keratitis, Epithelial erosions, Keratitis</td>
</tr>
<tr>
<td>Iris</td>
<td>Poor dilation, Rubeosis</td>
</tr>
<tr>
<td>Lens</td>
<td>Transient refraction changes, Cataract (and ↓ surgical outcomes)</td>
</tr>
<tr>
<td>Retina</td>
<td>Retinopathy/Maculopathy, Retinal vein occlusions, Retinal artery occlusions, Ischemic syndromes</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Papillobathy, Ant Isch Optic Neuropathy, Glaucoma</td>
</tr>
<tr>
<td>Cranial Nerves</td>
<td>3rd, 4th, 5th, 7th CN palsy</td>
</tr>
<tr>
<td>CNS</td>
<td>CVA associated vision loss</td>
</tr>
</tbody>
</table>
# Ocular Complications of DM (3 of 3)

<table>
<thead>
<tr>
<th>Ocular Tissue</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lids</td>
<td>Xanthelasma, Blepharitis</td>
</tr>
<tr>
<td>Orbit</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Keratitis, Epithelial erosions, Keratitis</td>
</tr>
<tr>
<td>Iris</td>
<td>Poor dilation, Rubeosis</td>
</tr>
<tr>
<td>Lens</td>
<td>Transient refraction changes</td>
</tr>
<tr>
<td></td>
<td>Cataract (and ↓surgical outcomes)</td>
</tr>
<tr>
<td>Retina</td>
<td><strong>Retinopathy/Maculopathy</strong></td>
</tr>
<tr>
<td></td>
<td>Retinal vein occlusions</td>
</tr>
<tr>
<td></td>
<td>Retinal artery occlusions</td>
</tr>
<tr>
<td></td>
<td>Ischemic syndromes</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Papillopathy, Ant Isch Optic Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Cranial Nerves</td>
<td>3\textsuperscript{rd}, 4\textsuperscript{th}, 5\textsuperscript{th}, 7\textsuperscript{th} CN palsy</td>
</tr>
<tr>
<td>CNS</td>
<td>CVA associated vision loss</td>
</tr>
</tbody>
</table>
Diabetic Retinopathy (DR) (1 of 2)

- Virtually all diabetics eventually have DR.
- Diabetic Retinopathy is the leading cause of new blindness in working age adults.
- Blindness due to diabetes can be eliminated by timely Dx and Tx.

Half of AI/AN population with DM does not get timely Dx and Tx.
Diabetic Retinopathy (DR) (2 of 2)

DR blindness is nearly preventable by adhering to accepted standards of care and established best practices.

- Identify all patients with DM
- Control confounding factors and co-morbidities
- Diagnose level of DR yearly
- Apply timely treatment
Diabetic Retinopathy

Clinical Management

Primary Care Diabetes Team
+
Ophthalmologist / Optometrist

Systemic control
Timely (Early?) diagnosis
Timely (Early?) treatment
Diabetic Retinopathy

*Standard of Care*

Minimum standard - annual eye examination

- **ADA** American Diabetes Association
- **AAO** American Academy of Ophthalmology
- **AOA** American Optometric Association
- **VHA** Veteran’s Health Administration
- **DoD** Department of Defense
- **HEDIS** Health Plan Employer Data and Information Set
Diabetic Retinopathy (1 of 4)

- Non-proliferative DR (NPDR)
  - Intraretinal hemorrhages (H)
  - Microaneurysms (MA)
  - Venous beading (VB)
  - Shunt vessels (IRMA)
- Proliferative DR (PDR)
  - Neovascularization (NVD/NVE)
  - Vitreous Hemorrhage (VH)
  - Retinal detachment (RD)
- Diabetic macular Edema (DME)
  - Fluid accumulation
  - Hard exudates (HE)
# Diabetic Retinopathy (2 of 4)

**International DR Disease Severity Scale**

<table>
<thead>
<tr>
<th>DR Severity Level</th>
<th>Retinal Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DR</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Micro aneurysms only</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>&gt; Just MA, but &lt; severe NPDR</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>&gt; 20 intra-retinal hemorrhages in 4 quad</td>
</tr>
<tr>
<td></td>
<td>Venous beading in 2 or more quad</td>
</tr>
<tr>
<td></td>
<td>Prominent IRMA in 1 or more quad</td>
</tr>
<tr>
<td></td>
<td>No PDR</td>
</tr>
<tr>
<td>PDR</td>
<td>Neovascularization</td>
</tr>
<tr>
<td></td>
<td>Vitreous Hemorrhage</td>
</tr>
</tbody>
</table>
Diabetic Retinopathy (3 of 4)

International DR Disease Severity Scale

<table>
<thead>
<tr>
<th>DR Severity Level</th>
<th>Retinal Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular Edema-not clinically significant</td>
<td>Retinal edema or lipids not threatening the macula</td>
</tr>
<tr>
<td>Macular Edema-clinically significant (CSME)</td>
<td>Retinal edema or lipids threatening the macula</td>
</tr>
</tbody>
</table>
## Diabetic Retinopathy (4 of 4)

**Standard of Care**

**AAO Preferred Practice Guidelines**

<table>
<thead>
<tr>
<th>DR severity</th>
<th>CSME</th>
<th>f/u (mths)</th>
<th>Laser Tx</th>
<th>Focal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal NPDR</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild-Moderate NPDR</td>
<td>No</td>
<td>6-12</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2-4</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>No</td>
<td>2-4</td>
<td>Maybe</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2-4</td>
<td>Maybe</td>
<td>Usually</td>
</tr>
<tr>
<td>Low Risk PDR</td>
<td>No</td>
<td>2-4</td>
<td>Maybe</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2-4</td>
<td>Maybe</td>
<td>Usually</td>
</tr>
<tr>
<td>High Risk PDR</td>
<td>No</td>
<td>3-4</td>
<td>Usually</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3-4</td>
<td>Usually</td>
<td>Usually</td>
</tr>
</tbody>
</table>
FARSITED Protocol
Retinal Imaging

Mild nonproliferative DR
Moderate nonproliferative DR Severe nonproliferative DR

Proliferative DR
Proliferative DR
Diabetic macular edema
Diabetic Eye Exam and Tx
Standards of Care

No Retinopathy  Mild NPDR  NPDR  Early PDR  HR PDR  Severe PDR

DCCT / UKPDS
Control BP, Glucose

ETDRS
Timing of Tx, Tx DME effective

DRS
Laser Tx Effective

DRVS
Vit effective
Diabetic Retinopathy

Diabetes Control and Complication Trial (DCCT) 1983-1993

- DM I
- Standard control vs Intensive control
  - A1c 9.0 vs 7.9
  - Glucose levels qid
  - Insulin qid or pump
  - Diet and exercise
Diabetic Retinopathy (1 of 2)

Impact of Intensive DM control

Cumulative %

- No Baseline Retinopathy
- Std Control

76% reduction in risk of developing progressive retinopathy

Intensive tx

Study Years

0 1 2 3 4 5 6 7 8 9
Diabetic Retinopathy (2 of 2)

Impact of Intensive DM control

Mild to Moderate Retinopathy

- Std Control
- Intensive tx

cumulative %

Study Years
Diabetic Retinopathy

*Intensive Glucose Control – mild to mod DR*

- 54% reduction in progression of DR
- 47% reduction in development of severe NPDR or PDR
- 59% reduction in need for laser surgery
Microvascular Complications

Intensive Glucose Control and End Organ Dz
Diabetic Retinopathy
Epidemiology of Diabetes Interventions and Complications (EDIC) 1994-2003 (Slide 1 of 2)

- DCCT Cohort
- Long term effects of conventional vs intensive DM treatment
- Nephropathy, microvascular, and cardiovascular complications
Diabetic Retinopathy

Epidemiology of Diabetes Interventions and Complications (EDIC) 1994-2003 (Slide 2 of 2)

• Long term benefits of improved control
• Metabolic memory
  – Effects of control are sustained even after some slippage in the degree of control
  – Once the processes leading to MV complications are initiated, they are self-perpetuating
Diabetic Retinopathy

UK Prospective Diabetes Study (UKPDS) (1977-1997) (1 of 2)

- DM II
- Standard glucose control (A1C 7.9%) vs Intensive glucose control (A1C 7.0%)
- Standard BP control (154/87) vs Tight BP control (144/82)
Diabetic Retinopathy

*UKPDS* (2 of 2)

- 34% reduction in DR progression
- 25% reduction in need for laser surgery
- BP control as important as glucose control for lowering risk for DR (<130/85)
Diabetic Retinopathy

*UK Prospective Diabetes Study (1977-1997/2007)*

- **Legacy effect of glucose control**
  - Differences in A1c levels disappeared within one year of trial completion.
  - Intense tx group continued to experience significant reductions in MV disease, MI, and all-cause mortality as compared to conventional tx group.

- **No legacy effect for intensive BP control**
Diabetic Retinopathy

Confounding Factors for DR

• Control
  – Blood Pressure- 130/85
  – Blood Glucose- A1c 6.5%-7.0% (↑ risk of compl)
  – Blood lipids

• Decrease risk of DR development
• Decrease risk of DR progression
• Decrease need for laser surgery
Diabetic Retinopathy

Pathophysiology of Vision Loss (1 of 2)

Hyperglycemia

Vision Loss

Moderate

Severe
Diabetic Retinopathy

Pathophysiology of Vision Loss (2 of 2)

- Hyperglycemia
  - Endothelial damage
  - Rheologic changes
  - Oxidative stress
  - Inflammation

- Capillary Occlusion

- Angiogenic Cascade

- Neovascularization

- Vascular permeability

- Retinal edema

- CSME
  - Moderate

Vision Loss
  - Severe

- Vitreous Hemorrhage Scarring

- Retinal Detachment

28
Vision Loss From Diabetes

Vitreous Hemorrhage

Macular Edema

Traction Retinal Detachment
Diabetic Retinopathy
Current Ophthalmic Treatment

• Proliferative DR (PDR)-
  – Laser photocoagulation (PRP)
Visual Acuity Less than 20/800

Proliferative Diabetic Retinopathy

Years after PDR Dx

Event Rate (%)
Diabetic Retinopathy

Current Ophthalmic Treatment (1 of 3)

Diabetic Macular Edema (DME)- Intravitreal injections
Diabetic Retinopathy
Anti-VEGF and Steroids for DR

• Lucentis (Genetech) $1,200/dose
• Eylea (Regeneron) $1,850/dose
• Avastin (Genetech) $60/dose
• Ozurdex (Allergan) $1,300/dose 3-4 months
• Iluvien (Alimera Sciences) $8,800/dose 36 months
Diabetic Retinopathy

Current Ophthalmic Treatment (2 of 3)

Vitreous hemorrhage/Retinal Detachment

Vitrectomy (PPV)
Diabetic Retinopathy- PDR / VH / RD

*Vitrectomy*

- Remove vitreous hemorrhage
- Allow laser treatment
- Repair retinal detachment
Diabetic Retinopathy
*Primary Care Management of DR*

- ~ 50% reduction in the prevalence of DR among AI/AN over the past two decades:
  - NPDR 17.7%
  - PDR 2.3%
  - DME 2.3%
  - STR 4.2%
- Similar reduction in prevalence of diabetes-related ESRD over the same period, which aligns temporally with SDPI implementation.
Diabetic Retinopathy

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) 2005

• 78% reduction of progression among pts with pre-existing retinopathy
• 31% reduction in need for treatment (progression to sight threatening DR)

Diabetic Retinopathy

Action to Control Cardiovascular Risk in Diabetes (ACCORD) 2010

• 36% reduction of progression (all cases)
• 78% reduction of progression (mild NPDR)
Fenofibrate
Mechanism of Action

• Not related to lipid effects.
• Treat early in the course of DR, but precise timing is not determined.
• Possible collateral benefits to other microvasculopathic end organ processes:
  – Renal
  – Peripheral neuropathy
• High patient safety.
Fenofibrate

Patient Safety

• Long history of fenofibrate use for dyslipidemia with good safety record.
• Theoretical risk of interaction with statins not a realized risk with fenofibrate (0.12% incidence) in contrast to gemfibrozil (5%).
• Well tolerated in both FIELD and ACCORD, with and without statins:
  – .5% vs .8% serious ADE (placebo : fenofibrate)
Fenofibrate

Clinical Use

• On label use for DR in Australia and other countries
• DM clinical practice guidelines:
  – Canadian Diabetes Association, 2016: “Though not recommended for CVD prevention or treatment, fenofibrate, in addition to statin therapy, may be used in patients with type 2 diabetes to slow the progression of established retinopathy.”
  – American Diabetes Association, 2017: “… collaboration between the ophthalmologists (eye care providers) and the medical physician to consider this treatment for people affected with diabetic retinopathy.”
Diabetic Retinopathy
Primary Care Treatment with Fenofibrate

• Treat early in the course of DR.
  – Treat by PCP without specialty referral
  – Reduced need for difficult and costly travel to subspecialty eye care

• Naturally incorporated into a primary care-based teleophthalmology-DR program for combined benefits of pt recruitment, DR Dx, and treatment.
Diabetic Retinopathy
Possible Early Fenofibrate DR Tx Best Practice in IHS
Diabetic Retinopathy

Failure to Meet Standard of Care

40%-60% of patients fail to receive needed treatment to prevent vision loss due to diabetic retinopathy.
Half of AI/AN population with DM does not get timely Dx and Tx (1 of 2)

“Every system is perfectly designed to achieve the results it gets.”

Donald Berwick
Director CMS
CEO, IHI
Half of AI/AN population with DM does not get timely Dx and Tx (2 of 2)

A DR surveillance program limited to conventional eye exams by eye doctors has not been an effective public health approach for this problem in Indian Country or elsewhere.
Diabetic Retinopathy
Surveillance Best Practices

• This is not a problem with eye doctors
  – Patients with an asymptomatic chronic condition
  – Inconvenient examination
• A primary care diabetes management problem
  – Programs that depend upon appointed visits to an eye doctor usually fail standard of care for 40%-50% of DM patients
• Must be smarter than the disease
• Must understand the patient
Telemedicine-DR: A better tool to address this universal public health problem

- **VHA**
  - 1.3 million veterans with DM (25%)
  - 400 Tmed-DR deployments / 500,000 annual exams

- **UK**
  - ~2.9 million with DM
  - 2.1 million annual tmed DR exams
  - 2014 - For the first time in 5 decades of survey, DR is no longer the leading cause of new blindness among working age adults in UK

DR Surveillance Methods (1 of 2)

• GPRA element #6 - annual DR exam
• Qualifying examinations:
  – Dilated Exam by optometrist or ophthalmologist
  – 7 standard field stereoscopic 35mm slides using ETDRS methodology
  – Photographic method validated to EDTRS
DR Surveillance Methods (2 of 2)

• GPRA element #6 - annual DR exam
• Qualifying examinations:
  – Dilated Exam by optometrist or ophthalmologist
  – 7 standard field stereoscopic 35mm slides using ETDRS methodology
  – Photographic method validated to EDTRS
Indian Health Service-Joselin Vision Network (IHS-JVN)

Teleophthalmology Program

• Reduce vision loss through timely Dx and Tx using telemedicine in the primary care setting
• Centrally funded
• Clinical operation since 2001
Joslin Vision Network (JVN)

- Quick and painless
  - Low level illumination
  - No pupil dilation
- Non-invasive
- Interleaved with other patient encounter events
- Validated
JVN Physical Components

JVN Image Acquisition Station

- Retinal Image Acquisition by certified imager in primary care clinic
- Demographics harvested from RPMS
- Hx supplemented
- Patient Education
- Data transmission
  - Images
  - Health Summary
JVN Physical Components

JVN Diagnostic Workstation

- Image analysis
- Automated diagnosis with reader validation
- Automated documentation
ETDRS Standard 30° Fields

ETDRS 7 standard 30-degree fields
First Year Experience of UWFI in IHS-JVN

- 25,635 patients: 17,526 NMFP, 8109 UWFI
- Reduction in ungradable rate (3-4%)
- 2X increase in rate of diagnosed DR
- More severe level of DR in 9%
- Reduction in unnecessary referral in ~ 4,000 pts/yr
JVN Validation Studies

*Ultrawide Field Imaging (UWFI)*

- Predominately Peripheral DR Lesions
  - 3.2x risk for progression of DR
  - 4.7x risk for PDR
50% increase in DR surveillance and laser treatments
Diabetic Retinopathy

Cost Effectiveness

IHS/JVN is both less costly and more effective for:

- Detecting DR
- Identifying IHS patients who require laser tx
- Preventing severe vision loss

Diabetic Retinopathy Surveillance

IHS-JVN Teleophthalmology Program

96 Fixed/Hybrid sites + 13 Portable Sites in 25 States

- Phoenix, AZ
- Sacaton, AZ
- Polacca, AZ
- Pinon, AZ
- San Carlos, AZ
- Salt River, AZ
- Ft. Yuma, AZ
- Whiteriver, AZ
- Sells, AZ
- Tuba City, AZ
- Tucson, AZ
- Parker, AZ
- Peach Springs, AZ
- San Xavier, AZ
- Kayenta, AZ
- Chinle, AZ
- Flagstaff, AZ
- Inscription House, AZ
- Navajo Mountain, AZ
- Elko, NV
  - Goshute, NV
  - Ely, NV
  - Duckwater, NV
- Owyhee, NV
- Reno Sparks, NV
- Fallon, NV
- Claremore, OK
- Wewoka, OK
- Eufaula, OK
- Okmulgee, OK
- Oklahoma City, OK
- Tahlequah, OK
- Lawton, OK
- Carnegie, OK
- Miami, OK
- Anadarko, OK
- Portland, OR
- Warm Springs, OR
- Salem, OR
- Cow Creek, OR
- Klamath, OR
- Pendleton, OR
- Nespelem, WA
- Yakima, WA
- Walla Walla, WA
- Tacoma, WA
- Fort Hall, ID
- Lapwai, ID
- Plummer, ID
- Pine Ridge, SD
- Rosebud, SD
- Rapid City, SD
- Sisseton, SD
- Wagner, SD
- Eagle Butte, SD
- Spirit Lake, ND
- Ft. Yates, ND
- Belcourt, ND
- Ft. Peck, MT
- Ft. Belknap, MT
- Crow Agency, MT
- Lame Deer, MT
- Browning, MT
- Ft. Washakie, WY
- Red Lake, MN
- Cass Lake, MN
- White Earth, MN
- Lawrence, KS
- Mayetta, KS
- Shiprock, NM
- Santa Fe, NM
- Albuquerque, NM
- Mesilla, NM
- Crown Point, NM
- Jicarilla, NM
- San Fidel, NM
- Dallas, TX
- Winnebago, NE
- Hayward, WI
- Mt Pleasant, MI
- Oneida, NY
- Charlestown, RI
- Fairbanks, AK
- Bristol Bay, AK
- Ketchikan, AK
- Metlakatla, AK
- Rock Hill, SC
- Cherokee, NC
- U&O, UT
- Presque Isle, ME
- Indian Island, ME
- Philadelphia, MS

Portable Deployments
- Alaska- EAT, APIA
- North Carolina
- Oklahoma- Redbird
- Sam Hider Jay
- Arizona- Supai
- Nevada- Schurz, Loveloc
- Yerington
- Maine- Littleton, Princeton, Pleasant Point
IHS/JVN Experience

IHS-JVN Exams 2000-2016

Cumulative Exams

Annual Exams

Program Year


183 1001 1262 1624 3018 3756 4547 5532 5830 8091 10984 11546 11910 14825 16245 19184 22914

0 10000 20000 30000 40000 50000 60000 70000 80000 90000 100000 110000 120000 130000 140000 150000 160000 170000 180000 190000 200000 210000 220000 230000 240000

0 2000 4000 6000 8000 10000 12000 14000 16000 18000 20000 22000 24000
Clinical Outcome

IHS DR Exam Rate pre/post JVN Ramp-up

[Graph showing the DR Exam Rate comparison pre-JVN and post-JVN with data points and trend lines.]
Best Practices:

Strategy for Preventing Vision Loss due to DM

- Patient Education
- Control confounding factors:
  - Glucose
  - Lipids
  - BP
  - Smoking
- Fenofibrate ??
- Annual DR exams for timely DX and Tx
Thank you;

Questions?

Mark B. Horton, OD, MD
Director, IHS/JVN Teleophthalmology Program

mark.horton@ihs.gov
602 820-7654