New Frontiers in the Detection & Management of Diabetic Retinopathy

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A. Paul Chous, OD

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These affiliations will not affect the content of this presentation

Objectives
- Epidemiology & Demographic Trends
- What IS Diabetic Retinopathy
- What’s New for Detecting Diabetic Retinopathy
- Assaulting Diabetic Retinopathy
- Prevention & Optometry’s Role

Worldwide Statistics

- 1 billion will have diabetes by 2050
- Highest increases in diabetes & prediabetes in Asia and Sub-Saharan Africa

International Diabetes Federation, 2015; www.diabetesatlas.org

2017 CDC Diabetes Statistics

- 30.3 million Americans
- 7.2 million undiagnosed
- 84.1 million have prediabetes
- 1.4 million legally blind from DR

National Diabetes Statistics Report 2017
US Centers for Disease Control & Prevention

Increasing Prevalence of Diabetes Over Time

Improvements in therapies and medical management over time are factored in
Diabetic Retinopathy

- Threatening diabetic retinopathy
  - Native American ethnic groups
  - Macular edema (DME) is the biggest cause of vision loss
- Improving blood glucose & blood pressure control lowers the risk of diabetic retinopathy and its progression
  - Disease duration most important risk factor
- No level of average blood glucose is totally protective against diabetic retinopathy


Blue Things

- Worldwide diabetes prevalence is now 483 million
- Undiagnosed
- Five million deaths attributable to diabetes in 2017 – half of these were in patients < 60 yo
- You or the person next to you almost certainly has or soon will have diabetes or prediabetes

Cost of Diabetes to the US Economy

- $327 Billion in 2017
  - $92 Billion in lost productivity
  - 1 in 4 health care dollars
- Up from $245 Billion in 2012
- 26% increase after adjusting for inflation

Diabetes Care. 2018 May;41(5):917-928

US PROJECTED FUTURE PREVALENCE OF DIABETES

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>1 in 10</td>
</tr>
<tr>
<td>2050</td>
<td>1 in 3 to 5</td>
</tr>
</tbody>
</table>

Significant increase in prevalence of total diagnosed and undiagnosed diabetes in adults in the US over the next 40 years.

Mean Estimate: 100 million Americans by 2050

Ocular Affects of Diabetes

- Diabetes can produce any of the following ophthalmic manifestations
  - Refractive changes
  - Ocular surface disease
  - Glaucoma and cataracts
  - Diabetic vitreopathy
  - Cranial nerve palsies
  - Deficits in visual function
  - Retinal vascular occlusion
  - Diabetic retinopathy

Diabetes and DR affect more than visual acuity
**What IS Diabetic Retinopathy?**

Two distinct but inter-related processes

- Microvascular disease detected by **observation** of vascular abnormalities
- Retinal neuro-degeneration with loss/derangement of neural elements including ganglion cell bodies, nerve fiber layer, and photoreceptors causing **loss of visual function**

Jackson GR, Scott IU, Quillen DA, Walter UE, Gardner TW. Inner retinal-visual dysfunction is a sensitive marker of non-proliferative diabetic retinopathy. *Journal of Ophthalmology* 2012;96:699-703

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**Diabetic Retinopathy (& diabetes writ large) is a Neurovascular Disease**

- **Retinal Neurodegeneration**
  - Loss of ganglion cell bodies
  - Glial reactivity
  - Neural apoptosis

- **Retinal Vasculopathy**
  - Microaneurysms
  - Capillary non-perfusion
  - Neovascularization

- **Generalized Neurodegeneration**
  - Peripheral nerves
  - Autonomic nervous system
  - Brain

- **Generalized Vasculopathy**
  - Renal
  - Heart
  - Brain

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**Early Detection of Diabetes-Induced Retinal Vascular & Neural Dysfunction**

- Careful dilated fundus exam, including the periphery
- OCT and OCTA
- Multi-spectral Imaging/FAF
- Widefield Retinal Imaging
- Macular pigment optical density
- ERG/VEP
- Contrast sensitivity
- Threshold Color Contrast Vision
- Threshold perimetry (FDT)

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**Peripheral DR**

- Predominantly peripheral diabetic retinopathy lesions (PPL) significantly associated with increased non-perfusion, risk of progression and 80% more Hm/Hm detected with UWF imaging than SSFP

- DRCR.net Procool AA is attempting to confirm the predictive value of PPL and association with other diabetes comorbidities
Importance of the Retinal Periphery in DR

- Study at Joslin showed that patients with predominantly peripheral DR lesions (PPL) were significantly more likely to progress (3.2X) and develop PDR (4.7X) \( p = 0.005 \)
  
  Ophthalmology. 2015 May;122(5):949-56.

- Patients with PPL had significantly more ischemia on UWF angiography
  
  Ophthalmology. 2015 Dec;122(12):2465-72

- Compared to standardized seven-field stereo photos (ETDRS standard), UWF suggested a more severe level of DR in 10% of cases
  
  Ophthalmology. 2013 Dec;120(12):2587-95

- DRCR.net Protocol AA will evaluate the predictive value of UWF imaging on ocular/systemic endpoints (study completion in 2020)

UWF Imaging is available from Eidon, Optos and Zeiss

Comparison of Optos California & Zeiss Clarus 500

- 46 eyes with a single image capture
- Good consistency regarding DR grading
- Optos device imaged a mean of 465 DD versus a mean 243 DD with Clarus (200 vs 133 degrees)
- 85% of Optos versus 7% of Clarus images showed obscured areas within the 7 ETDRS fields \( p < 0.001 \)
- No evaluation of observed area outside the 7 ETDRS fields


FAF imaging detects significantly more microaneurysms than does standard color photography \( p < 0.016 \)


Key Point for Optometry

- DME is the leading cause of vision loss from diabetes
**sdOCT** is great for monitoring DME, response to therapy & detection of subclinical DME

Up to 30% of DME is undetected by stereo funduscopy and these patients are 3X more likely to develop CSME. Ophthalmologica. 2013;230(4):201-6.

**OCTA**

- Optical coherence tomography angiography
- 64,000 sequential B-scans/sec allows visualization of vascular perfusion
- Fast, dye-less, no iatrogenic risk
- Allows visualization of subclinical microaneurysm formation, capillary non-perfusion, neovascularization at the vitreoretinal interface


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**Patient with T1DM x 10 years**

20/15 Vision  Minimal NPDR on clinical exam

**OCTA shows DR NOT seen on clinical exam**

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**OCTA Findings Linked to DR Progression**

- 57 eyes with mild/moderate/severe NPDR and PDR = retrospective analysis
- Increased FAZ, and both decreased vessel density and flow area in the DCP were highly associated with worsening DR severity (p < 0.01)

*ARVO 2017*

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**OCTA Identifies Pre-Clinical DR**

- Parafoveal vessel density in the choriocapillaris, superficial and deep capillary plexi of diabetes subjects is significantly reduced compared to controls
  
  *Acta Diabetol. 2018 May;55(5):469-477*

- Density normals > DM sans DR > DM with DR
- OCTA showed ma and nonperfusion in 11%/28% of patients without clinical DR
Retinal Diabetic Neuropathy (RDN):Detecting Neuro-degeneration with OCT

OCT Imaging
- Nerve fiber layer
- Ganglion cell layer
- Inner plexiform
- Outer plexiform
- Outer nuclear
- External limiting
- Photoreceptor IS/OS
- Retinal pigment epithelium

Retinal diabetic neuropathy (RDN) manifested on optical coherence tomography as significant thinning of the retinal nerve fiber layer and ganglion cell and inner plexiform layers.


Inner retinal thinning in Diabetes

• Inner retinal thinning (both ganglion cell-IPL AKA ‘ganglion cell complex’ and RNFL)
  – “Retinal Diabetic Neuropathy” (RDN)
  – 4-10X increased risk of cardiac autonomic neuropathy
  – CAN increases risk of MI, stroke, death 2-3 fold

Diabetes & RDN Affect Visual Function

- Snellen visual acuity is a 150+ yr old test that does not always reflect real world visual function
- DM/DR also impair: color perception, contrast sensitivity, visual field sensitivity & dark adaptation


Color Vision Deficits

• 40% of DM patients with no ophthalmoscopically detectable retinopathy have acquired color vision deficits
• Selective loss of S-cone function predominates – S-cone paucity & heightened phototoxicity

Chromatic Contrast Threshold is a Marker of RDN

• Chromatic visual disturbance in association with retinal diabetic neuropathy precedes clinical diabetic retinopathy in 55% of patients
• 55%-65% of patients with diabetic retinopathy have color vision defects
• Blue-yellow deficiency is found in almost 90% of patients with diabetic retinopathy
dyschromatopsia

ChromaContrast is a Marker of Diabetes Retinopathy

Computer-assisted extended color vision testing determines the type of color vision defect and the severity of the diabetes-induced dyschromatopsia.
Full-Field Flicker ERG to Dx Severe DR

- Delayed implicit time (≥ 36 milliseconds) detected any DR and severe NPDR/PDR with 84% and 89% sensitivity, respectively compared to retinal specialist exam
  - 48 control and 118 diabetes eyes (Japan)
  - Hand-held non-mydriatic flicker ERG
  - Non-mydriatic


RETeval ERG is a hand-held device that measures visual function using a full-field electroretinogram testing protocol

Other OD-Friendly Tests

- Frequency Doubling Perimetry and Contrast sensitivity progressively distinguish DM and worsening DR from age-matched subjects without DM

- Macular Pigment is reduced in patients with DM and is inversely associated with DR severity
  - Retina. 2015 Sep;35(9):1808-16

- Several RCTs show that carotenoid + antioxidant supplementation improves visual function in DM and DR
  - Br J Ophthalmol. 2015 Feb;50(2):227-34

Macular Pigment

- MPOD is lower in patients with diabetes and lower still in patients with increasing severity of DR
- Macular pigment is inversely associated with visual function in many studies
  - Molecules. 2017 Apr 20;22(4). pii: E610
- ECPs should measure and optimize MPOD in our patients with and at-risk for diabetes
**Treatment & Management Goals**

- Delay the development of diabetes
- Delay the development of diabetic retinopathy
- Arrest or slow the worsening of DR
- Refer for treatment of sight-threatening disease (PDR/Center-involved DME)

**The philosophers have only interpreted the world, in various ways; the point, however, is to**

**Karl Marx - Theses on Feuerbach, 1845**

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**IMPACT OF INTENSIVE THERAPY OF DIABETES: Summary of Major Clinical Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Microvascular Risk</th>
<th>Blood Glucose Reality</th>
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</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>DCCT/EDIC*</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>-</td>
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<tr>
<td>ADVANCE</td>
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<tr>
<td>VADT</td>
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**Initial Trial**

**Long-Term Follow-Up**

**Metabolic Memory**

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**Good Control Does NOT Eliminate Risk of Severe DR**

- 10 year risk of PDR and/or CSME in a newly dx patient with A1c = 6.5% and BP = 120/80 is nearly 4%
- With mild NPDR, the 10 yr risk is 8.4%

*Diabetologia. 2011 Oct;54(10):2525-32*

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**Blood Glucose Reality**

- Many patients never or rarely check their glucose
- Many patients never get A1c < 7% within the first 5 years - when tight glucose control is most effective at preventing DR

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**Is HbA1c the Best Predictor of DR Risk?**

- Disease duration and HbA1c thought to be most predictive YET....
- Analysis of DCCT/EDIC data shows that mean A1c during the studies accounted for a mere 6-11% of DR risk!
- Moreover, the Joslin “Gold Medlist” study showed little correlation between development of sight-threatening DR and A1c in patients with T1DM > 50 years......

*Diabetes Care. 2011 Apr;34(4):968-974*
**Why HbA1c Isn’t the Whole Story**

- Doesn’t reflect glucose variability or the burden of acute hypoglycemia

  ![The Many Faces of a 7% A1c](image)

- US spent $1.25 billion in 2009 on hospitalizations for severe hypoglycemia

  [J Med Econ. 2016 Sep;19(9):852-7.]

**Glucose Spikes Increase DR Risk**

- T1DM patients > 10 years (n = 23)

- Continuous glucose monitoring (DexCom) showed same A1c but dramatic increase in glucose spikes > 400 mg/dl in subjects with moderate-severe NPDR (no difference if > 350 or 250)
  - 1 spike/2.6 days in those with NPDR
  - 1 spike/9.9 day in those without

  [ARVO. May 7, 2017]

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**The Perils of Transient Hyperglycemia**

- A 6 hour episode of elevated glucose (> 190 mg/dl) results in a 6-day massive increase in mitochondrial reactive oxygen species AFTER blood glucose is totally normalized

- High ROS persist for 2 weeks before normalizing

- ROS are the driving force underlying DR

- These glycemic excursions are often too short to be captured by mean glycemia (HbA1c)

  [Diabetes. 2015 Sep;64(9):3273-84.]

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**Pathophysiology**

- Blood vessel damage in diabetes is mediated by four distinct biochemical pathways driven by mitochondrial production of ROS

  ![Intracellular Glucose & FFAs](image)

  ![Mitochondria](image)

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**The Four Pathways**

- Polyol
- Hexosamine
- Protein Kinase C (PKC)
- Advanced Glycation Endproducts (AGEs)

  Each of these pathways depends on over-production of reactive oxygen species (O₂⁻) by mitochondria exposed to excess glucose and/or free fatty acids

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**Glucose Metabolism**

- Glucose → Polyl Pathway
- Glucose-6-phosphate
- Fructose-6-phosphate → Hexosamine Flux
- Glyceraldehyde-3-phosphate → Protein Kinase C
- ATP + 1,3 Diphosphoglycerate → Advanced Glycation Endproducts
Post-Prandial Hyperglycemia

- So what do we do?
- More research needed in humans
- Optimize HbA1c
- Try to minimize duration of episodic hyperglycemia > 190 that may be too brief to be captured by HbA1c
- Minimize blood glucose spikes > 400
- Increase the glucose time-in-range

A 10-minute walk after the evening meal lowered glucose 22% more than a 30-minute walk before any meal

CGM & TIR

- Continuous glucose monitoring (CGM) systems capture real-time data and allow measurement of glucose time-in-range (TIR)
  - < 70, 70-180, > 180 mg/l
  - DexCom Clarity & Medtronic Sugar IQ apps measures TIR in tandem with their CGMs
- A 10% decrease of TIR results in a 61% increased risk of retinopathy incidence & 2-step ETDRS progression

Beyond HbA1c in diabetes: it is time to look at other outcomes; ADA Scientific Sessions - June 24, 2018, Orlando, FL

CGM Updates

- Continuous glucose monitoring systems
- Constant biofeedback regarding current blood glucose and trend

- CMS requires insulin use and intensive glucose management with 4 home blood glucose measurements/day

Practical Implications of TIR

- Moderate NPDR T1DM x 10 years
- HbA1c = 7% TIR = 60% (14.4 hours)
- To achieve a 40% reduction in risk of progressing to STDR, he could:
  - Reduce HbA1c to 4.1%
  - Increase TIR to 73.6% (17.6 hours)

Biggest Benefit When HbA1c Is Already Lower and TIR is also LOW
Dexcom CLARITY® Weekly Summary
San Nov 26, 2017 - Sat Dec 2, 2017

Time in Range
87%

Target Range Settings:
Daytime (7:15 AM - 11:00 PM): 70 – 140 mg/dL
Nighttime (11:00 PM - 7:15 AM): 70 – 140 mg/dL

Medtronic Sugar IQ Predictive Resopne App

Medtronic Sugar IQ with Watson—A cognitive computing-based diabetes management solution (16-OR).

FDA-approved Pseudo-Closed Loop Available in 2018

Medtronic 670 G

Vinegar Battles Glucose Spikes

- Vinegar improves insulin sensitivity in IR subjects
- 2 Tbsp vinegar consumed before a 75g CHO meal prevented post-prandial glucose spikes in pts with T1DM and reduced AUC BG by 20%
  - Acetic acid delays gastric emptying and enhances glycogen replention
  Diabetes Care. 2010 Feb;33(2):e27

Super-fast-Acting Insulins

- Fiasp – fast-acting insulin aspart
  (Novolog with niacinamide adjuvant forms insulin monomer to penetrate SC fat more rapidly)
- 29 point 1-hour reduction in post-prandial glucose; 12 point reduction at 2 hours
  Diabetes Technol Ther. 2017 Jan 1; 19(s1): 25-33
- 0.15% drop in HbA1c
  Diabetes Metab. 2017 Jan 1.

Available in US March 2018

Fast-Acting Insulin Aspart

- Monomeric Aspart (Novolog, Novo Nordisk)
- Much more rapid onset of action

Fast-Acting Insulin Aspart (Novolog, Novo Nordisk)

- Much more rapid onset of action

What do we know about faster aspart via s.c. injection in T1D (PK/PD)?

- 29 point 1-hour reduction in post-prandial glucose; 12 point reduction at 2 hours
- 0.15% drop in HbA1c
- Much more rapid onset of action
**Fenofibrate** – oral therapy to prevent progression of DR

- Approved first-line therapy for mild-moderate NPDR in Australian adults with T2DM
  - NNT = 14 for prevention of CSME or PDR

*Ophthalmic Epidemiol. 2014 Oct;21(5):307-17*

- Fenofibrate significantly decreases multiple inflammatory cytokines in patients with DR (VEGF, IL1B, LpPLA2)

*Medicine (Baltimore). 2017 Aug;96(31):e7671*

**Brimonodine and Somatostatin Retard Neurodegeneration**

- BID combination eyedrop in 700+ with T2DM followed fo 2 years v. placebo (EuroCondor Trial)
- Those with multifocal electroretinogram abnormalities at baseline had less evidence of neurodegeneration by mfERG (p < 0.01)

**Di V Fu S (DiVFuSS)**

- 6 month placebo-controlled RCCT of adults with T1DM or T2DM > 5 years
- With and without retinopathy
- Daily use of a novel, multi-component nutritional supplement
- CSF, MPOD, color vis., macular perimetry, OCT, A1c, lipids, 25(OH) vit. D, TNF-α, hsCRP, DPNS score

*B r J Ophthalmol. 2016 Feb;100(2):227-34*

**Test Formula**

- Zeaxanthin & Lutein
- Benfotiamine
- Alpha Lipoic Acid
- Vitamin D
- Vitamins C & E
- Mixed Tocopherols/ Tocotrienols
- Resveratrol
- Green Tea
- Curcuminoids
- N-Acetyl Cysteine
- Grape Seed Extract
- CoQ10
- Zinc Oxide
- EPA/DHA
- Pycnogenol
- Vitamin B12

**Animal model of DR**

- DiVFuSS formula prevents mtDNA damage, normalizes ROS and VEGF, and prevents retinal capillary apoptosis

**Mean Change/SD in visual function measures, serum lipids, hsCRP, TNF-α, glycohemoglobin, foveal thickness and symptoms of diabetic peripheral neuropathy with 95% p-Values**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Suppl v. Plac</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Color Error Score</td>
<td>-20.55±24.37</td>
<td>+7.5±22.01</td>
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<tr>
<td>S-2 MD (d)</td>
<td>+2.78±9.83</td>
<td>-0.75±0.98</td>
</tr>
<tr>
<td>MPOD (du)</td>
<td>+0.09±0.05</td>
<td>-0.01±0.03</td>
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<tr>
<td>LDL-C (mg/dl)</td>
<td>-7.61±16.08</td>
<td>+0.82±10.15</td>
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<tr>
<td>HDL-C (mg/dl)</td>
<td>+3.82±6.24</td>
<td>-1.61±5.31</td>
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<tr>
<td>TGs (mg/dl)</td>
<td>-10.46±28.48</td>
<td>+2.39±11.56</td>
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<tr>
<td>hsCRP (mg/L)</td>
<td>-2.14±3</td>
<td>-0.28±1.83</td>
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<tr>
<td>TNF-α (pg/ml)</td>
<td>+0.76±5.04</td>
<td>+0.56±2.79</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.1±0.4</td>
<td>+0.1±0.4</td>
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<tr>
<td>Foveal Thickness</td>
<td>2.66±11.25 m</td>
<td>0.34±3.48 m</td>
</tr>
<tr>
<td>DPNSS</td>
<td>-30.7%</td>
<td>+10.7%</td>
</tr>
</tbody>
</table>

**Mean glucose of study animals = 1100 mg/dl**

**Nut Metab (Lond). 2014 Jan 30;11(1):8.**
Long-Chain Omega-3 PUFA

• PrediMed Trial comparing Mediterranean-type diet supplemented with extra virgin olive oil or tree nuts versus AHA diet against CV events in patients with T2DM (n=3482)
• Primary trial halted early because both Med diets were significantly superior, especially for stroke prevention
• Subjects consuming > 500 mg daily long-chain-ω3PUFA were 48% less likely to develop STR over 6 yrs compared to those consuming < 500 mg (p=0.001)

How Far Out of the Barn Must the Horse Be to Start Treatment?

Evidence-based Tips for Minimizing Diabetic Retinopathy

• Don’t get diabetes/Don’t get prediabetes
• Get HbA1c as low as safely possible a quickly as possible after Dx; keep BP < 140/90
• Limit post-prandial hyperglycemia < 5 hours
• Consume at least 500mg LCω3PUFA/day
• Increase fiber & macular pigment
• Consider a science-based nutritional supplement for DR

Prevalence of DR in the US

Approximately 8 million (26%) of people with diabetes have DR
• 5.8 million are diagnosed
• 2.3 million have DME

When to Refer?

• It depends on your comfort level
• My Answer:
  • When the patient needs treatment of DR/DME
  • With unexplained VA loss
  • When I am unsure of the diagnosis
  • When the patient has chronic, sub-optimal metabolic control or is receiving decidedly sub-optimal care; frequent hypoglycemia; kids

Sight-threatening DR – Must Refer
**ETDRS:** Early Treatment Diabetic Retinopathy Study

Risk for Progressing to PDR in 1 yr

- Mild NPDR: 5%
- Moderate NPDR: 12%
- Severe NPDR: 52%
- Very Severe NPDR: 72%

It is key to identify patients with severe NPDR for referral.

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**When to Worry About NPDR**

- The 4-2-1 Rule
  - Hmg/MA
  - Venous Beading
  - IRMA

Per ETDRS

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**Anti-VEGF Therapy for NPDR**

- Lucentis is now approved to treat any level of DR with or without DME
- Eylea is expected to receive similar approval

- Significant improvements in DR severity, especially in those with moderately severe or worse NPDR (DRSS Level 47+)

- ETDRS severity level 47: multiple intra-retinal hemorrhages in two or more quadrants, any vein beading, any prominent IRMA

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**Diabetic Retinopathy Severity Score (DRSS) Example of 2-Step Improvement**

- Severe NPDR DRSS Level 53 (Level 6)
- Moderate NPDR DRSS Level 43 (Level 4)

- Severe retinal hemorrhages in 4 quadrants, or
- Venous beading in ≥2 quadrants, or
- Moderately severe intraretinal microvascular abnormalities (IRMA) in ≥1 quadrant

- Microaneuysms, plus
- Mild IRMAs, or
- Moderate retinal hemorrhages

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**PANORAMA Phase 3 52 Week Data**

- Aflibercept (Eylea) Q8 or Q16 weeks for moderately severe to severe NPDR sans DME
- 80%/65% achieved 2-step DRSS improvement
  - p < 0.0001
- VTC (PDR/ASneo) reduced 82-85%
- CI-DME reduced 68-74%

Regeneron Press Statement, October 25, 2018
Why some people with DR are Lost to Follow-up (LTFU)

- A study from San Francisco looked at risk for non-compliance
- 209 patients mean age 58yo w A1c 8.5
- 46% of patients attended <80% of f/u
- Risk factors for missing f/u:
  - Foot involvement OR 2.4
  - Foot/kidney OR 3.7
  - Major depressive disorder OR 2.1
  - MediCal or SF Health insurance. OR 5.01/6.79


Emerging Treatments for DR/DME

- Combined Anti-VEGF & Angiopoetin-2 Blockade → Farcimab™
- Tyrosine Kinase (TIE-2) Activation
  - Subcutaneous injection improves DR and DKD
  - Aerpio Therapeutics
- Adenoviral-Associated Vector Gene Therapy
  - Intravitreal
  - Sub-RPE

Activated Tie-2 promotes vascular stability
Tyrosine Protein Kinase Receptor

VEGF + ANG-2 Blockade - RESULTS

Farcimab compared to Lucentis:
- 3.6 more letters gained
- More gain 1+ to 3+ lines
- More have a >2 step DRSS improvement
AT 24 WEEKS

Subcutaneous TIE-2 Activator

- TIME-2b study
- Aerpio Therapeutics AKB-9778
- 167 subjects with moderate to severe NPDR
- 1 or 2 subcutaneous injections/day
- Early data shows improvement of DR severity and renal function: study completion 06/2019

Subcutaneous Injection for DR

Percentage of Patients with a ≥ 2 Step Improvement in DRSS from Baseline

![Graph showing subcutaneous injections for DR]
Adenoviral-Associated Vector Gene Therapy Produces Aflibercept

Key Points
- Diabetes causes both vascular and neuronal damage within the retina
- Multiple technologies can help us detect both
- WE CAN DO MORE than simply monitor patients for the development of sight-threatening retinopathy
- Therapies for advanced DR save vision
- Preventing diabetes is the best way to prevent ocular complications

Evidence-Based Tips To Avoid Diabetes
- Exercise 30 minutes each day (soon after waking) & minimize added sugars
- Eat a predominantly plant based diet including a variety of fruits and vegetables and more vegetables
- Minimize processed meats
- Drink coffee or tea
- Sleep > 8 hours per night and < 8 hours
- Get your serum vitamin D > 40 ng/ml
- Don’t smoke
- Live away from smog
- Breast Feed
- Turn down the thermostat
- Reduce Light at Night
- Fast if you’re obese

Reversing T2DM

Patient PK
- 52 yo male - T2DM x 2 years - no DR
- Metformin + Januvia® (sitagliptin)
- A1c 6.6% at Dx, lowered on meds but now 7.4% and placed on insulin (Lantus®) QHS
- BMI 38 at Dx and now 40 kg/m²
- We discussed options, including alternate daily fasting (ADF) combined with Paleo-type low carb diet on ‘feeding days’

PK 6 months later
- 35 lbs weight loss (BMI = 30 Kg/m²)
- A1c now 5.4% and has discontinued insulin and Januvia
- PK reports increased energy, libido and clearer thinking
- “This was the best thing I’ve ever done”
Why ODs Should Be on The Diabetes Care Team

- We are often gatekeepers into the health care system for many patients
- Diabetes and diabetic retinopathy are largely preventable conditions and ODs do a fabulous job educating our patients
- DM and DR cases continue to climb
- Our countries, communities, other HCPs and patients need us

Thank You!