Diabetic Retinopathy: An Update for Diabetes Educators

A. Paul Chous, M.A., O.D., F.A.A.O.
Private Practice - Tacoma, WA
Specializing in Diabetes Eye Care & Education

A. Paul Chous, MA, OD, FAAO
- Author of Diabetic Eye Disease: Lessons From a Diabetic Eye Doctor (Fairwood Press, 2003)
- Web columnist for www.dLife.com and www.diabetesincontrol.com
- Optometric representative to the National Diabetes Education Program of the NIH
- Winner of American Diabetes Association’s Distinguished Public Service Award in 1998
- T1DM x 45 years

Disclosures
I am or have been a consultant for, been on advisory boards of, or spoken on behalf of:
- Bausch & Lomb, Freedom Meditech, GlaxoSmithKline, Kestrel, Kowa, LifeMed Media, Prodigy Diabetes Care, Risk Medical Solutions, Vision Service Plan, ZeaVision

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Diabetes-Related Eye Diseases
- “Diabetic Eye Disease” refers to ocular pathologies more commonly seen in patients with diabetes
- All of these conditions are attributable, at least in part, to chronic hyperglycemia

Ocular Diseases Associated With Diabetes
- Cataract
- Keratopathy
- Efferent Cranial Neuropathy
- Glaucoma
- Ischemic Optic Neuropathy
- Retinal Vascular Occlusion
- Diabetic Retinopathy

Cataract
CN VI Palsy
Corneal Disease
Chronic hyperglycemia unleashes a progressive cascade of events:
- Endothelial pericyte loss
- Retinal Ganglion Cell (RGC) death
- Increased vascular permeability
- Capillary closure
- Release of vasoproliferative factors
- Neovascularization, fibrovascular vitreo-retinal adhesions, vitreous hemorrhage

Another American becomes legally blind from diabetic retinopathy every 24 minutes.
No independent tracking of irreparable vision loss from other eye diseases commonly associated with diabetes (retinal vascular occlusion, AION, glaucoma).
Realistic accounting might increase the toll from 12-24 thousand to 30,000+ cases per year.

Most patients develop DR over time:
- 60% at 10 yrs
- 90% at 20 yrs
Old statistics from WESDR – may be improving with better metabolic management.
Minimizing the severity of DR is the key to preventing vision loss.
DR Lesions

- **Microaneurysms**: balloon-like outpouchings of normal retinal capillaries
- **Intra-retinal Hemorrhage**: from faulty capillaries
- **Hard exudates**: protein and fat leakage
- **Intra-retinal swelling**: causes macular edema (DME)
- **Cotton Wool Spots**: infarcted retinal nerve fibers
- **Vein Beading**: signal ischemia
- **IRMA**: precursors to abnormal new blood vessel
- **Neovascularization** of optic nerve or retina or iris
- **Vitreous hemorrage**: vision loss
- **Traction retinal detachment**: vision loss

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**Retinopathy Lesions**

- Microaneurysms (MA)
- Dot & Blot Hemorrhages
- Hard Exudates
- Retinal Thickening
- Cotton Wool Spots
- Vein Beading
- Intra-retinal Microvascular Abnormalities (IRMA)
- Neovascularization (of disk, retina or iris/angle) – Proliferative Diabetic Retinopathy

**Which of these cause severe vision loss?**
What’s The Most Common Symptom of DR and/or DME?

- A. I see spots before my eyes (vitreous floaters)
- B. I see flashes of light before eyes (photopsia)
- C. I am having trouble reading street signs
- D. No symptoms whatsoever

3 Types of DR

- **Non-proliferative DR (NPDR):** no neovascularization; typically no symptoms; most common form of DR
- **Proliferative DR (PDR):** neovascularization of the optic ‘disk’ (NVD) or elsewhere on the retina (NVE); often no Sx unless retinal detachment or vitreous hemorrhage → total blindness
- **Diabetic Macular Edema (DME):** fluid damages photoreceptors → vision loss but not total blindness; may occur in isolation or with NPDR or PDR

Staging of Diabetic Retinopathy

- No Apparent DR: no retinal findings
- Mild NPDR: microaneurysms only
- Moderate NPDR: > ‘mild’ but < ‘severe’
- Severe NPDR: > 20 hemorrhages in 4 quads or definite vein beading in 2+ quads or IRMA in 1+ quads (4-2-1 rule)
- PDR: definite NVD or NVE and/or VH/PRH

Staging of Diabetic Macular Edema

- DME Absent: no retinal thickening or hard exudates in the posterior pole
- DME Present: some retinal thickening or hard exudates in the posterior pole
  - Mild DME: RT or HE in the posterior pole but distant from the macula
  - Moderate DME: RT or HE approaching but not involving the macular center
  - Severe DME: RT or HE involving the center of the macula
Macular Edema

- 3 evidence-based criteria for Tx
  - Thickening <1/3DD from center of macula
  - Heme/exudate with thickening of adjacent retina <1/3dd from center of macula
  - Thickening >1dd size within 1dd center

- Current treatment: Grid/Focal laser; Intravitral injection of anti-VEGF drugs (Avastin/Lucentis)

DR – some real numbers

- Pooled analysis from almost 23k with DM
  - 34.6% prevalence for any DR
  - 6.96% for PDR
  - 6.81% for DME
  - 10.2% for Vision Threatening DR (PDR and/or DME)
  - All DR end points increased with DM duration, A1c & BP
  - Higher in people with T1DM compared w T2DM

- Worldwide: 93M w DR, 17M PDR, 21M DME, 28M VTDR


Managing Diabetic Retinopathy

Out, damned spot!
Out, I say! - Macbeth

Management of DR

- Prevention of Diabetes!
- Delay onset of DR by optimizing metabolic control, patient education and adherence to the treatment plan
- Annual dilated eye exams
- Laser and/or intravitreal injections for STR as indicated

Blood Glucose Control

Meta-analysis of the DCCT and UKPDS shows that:

Each 10% Reduction in HbA1c Lowers the Risk of DRT Progression By 43%

This linear reduction in risk holds for HbA1c between 5% and 8%

Drugs. 2010 Dec 3;70(17):2229-45.

The DCCT 20 Years Later

Intensive control of T1DM lowered the risk of DR 58% and nephropathy by 64% after 30 years
The risk of CV events was lowered by 36%
After 30 years of T1DM, <1% of pts assigned to intensive control during the DCCT suffered VA worse than 20/40, ESRD or amputation

Arch Intern Med 2009;169(14): 1307-16
Highlights from The ‘Big’ DR Studies

PRP reduces risk of severe vision loss (< 20/800) from PDR by 50-65% (DRS/ETDRS)
Focal laser reduces risk of doubling the visual angle by 50% in CSME (ETDRS)
Aspirin has no effect on PDR/VH (ETDRS)
Vitrectomy is indicated for non-clearing vitreous hemorrhage and tractional RD of the macula (DRVS)

Lucentis versus Laser for Vision loss from CSME (20/40 to 20/200 BCVA)
Percent achieving ≥ 20/40 ETDRS acuity at 12 months:
- Lucentis – 53%
- Lucentis + Laser – 44.9%
- Laser alone – 26.3%
**Benefit of Lucentis maintained at 3 years**
No increased MI or CVA with Lucentis

What’s Best for DME?
anti-VEGF treatments are superior to macular laser for VA and retinal thickening
BUT...need repeat injections & costs more money
Bevacizumab (Avastin™) + Laser most cost-effective comparing laser, steroid, Lucentis, Avastin or any combination

ACEIs/ARBs & Retinopathy
Vasotec® (enalapril) and Cozaar® (losartan) reduced the risk of DR progression by 65% and 70% in T1DM
Captopril reduces DR progression 40% and DME 30% in T2DM

Should these agents become standard treatment of DR?
-prils and –sartans may lower DR Risk of Progression
**Lipid Agents & Retinopathy**

**Simvastatin + Fenofibrate therapy** lowers the risk of DR progression by 35% (and need for laser by 31%) compared to simvastatin alone in pts with T2DM and high cardiovascular risk (n = 2856) \(^1\) Consistent with FIELD Study showing reduced progression of DR and need for laser Tx \(^2\)

*Lancet 2007 370(9600):687-97*

Add-on Fenofibrate lowers risk of DR progression in T2DM

**TZDs & DME**

- Retrospective cohort study of 103K+ T2DM patients suggests use of rosiglitazone or pioglitazone more than doubled the risk of DME (3x risk with concomitant insulin use – attenuated by ASA and especially ACEI use)

*Arch Intern Med. 2012 Jul 16;172(13):1005-11*

**More to Retinopathy than Retinopathy**

- Retinopathy predicts CV mortality and coronary heart disease (CHD)\(^1\)
- PDR>NPDR=no retinopathy in likely CVD and CHD mortality, and women>men, especially in NPR
- In women, PDR yields nearly 5x risk of CHD death!
- Independent of smoking, HTN, Cholesterol, HDL, duration or control of DM or proteinuria
- Retinopathy predicts stroke rate\(^2\)
- Those with DR have 2.34x risk for ischemic stroke

2. *Cheung et al. Stroke. Feb 2007*

**Risk Factors For Diabetic Retinopathy**

**Established**
- Disease duration
- HbA1c
- Disease sub-type
- Gender
- HTN
- Microalbuminuria

**Emerging**
- Obesity
- Sleep apnea
- Vitamin D insufficiency
- Vit B12 deficiency
- Carotenoid imbalance

**Can We Predict Who is Going to Develop Sight-threatening Diabetic Retinopathy?**

**Obstructive Sleep Apnea Syndrome**

- OSAS is independently associated with risk of DR and its progression

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PDR Risk Goes Up With:
- Higher HbA1c: each 1 pt increase in pts with NPDR raises PDR risk 14%
- Non-healing limb ulcers increased risk of PDR by 54%
- Diabetic Kidney Disease increases risk of PDR by 29%

Is it Important Prevent Blood Glucose Spikes?
- AKA “Post-prandial Hyperglycemia” or “Glycemic excursions”

A1c Variability Matters!
- 5 year cumulative incidence of laser Tx for DR in 1459 T1DM pts with highest (19%) vs lowest (10%) A1c variability controlling for mean A1c, duration, BP, kidney status, gender – 70% increase risk of PDR in hi SD group

STR Risk Calculator
- Risk calculator for STR (PDR and/or CSME) based on a few simple inputs
  - DM sub-type, gender, age, HbA1c, BP, presence and severity of NPDR
- Excellent predictive accuracy when compared to outcomes from the Danish Diabetes Cohort (n=5199 followed for 20 yrs)

C-reactive Protein & CSME
- Blood samples from 1441 DCCT subjects
- Analyzed for ICAM, TNF-a and hsCRP
- Highest quartile of hsCRP linked to 83% increased risk of CSME vs lowest quartile

Q: How effective in a diverse, multicultural society?
If our patient can reduce HbA1c to the AACE Target of 6.5% the 10 year risk of developing sight-threatening retinopathy drops to 19.8%, or by 39%.

www.Retinarisk.com

Gold Medalists
Time/Metabolic Control may not be the only enemy...

"Medalists": h/o T1DM x 50yrs
42.6% did not have PDR, and those without had little progression of DR after first 17yrs
With little to no correspondence to A1c
Diabetes Care. 2011 Apr;34(4):968-74

Key Message

Most blindness and severe visual impairment caused by diabetic retinopathy is preventable with good diabetes self-management, regular dilated eye examinations and timely treatment

Diabetes & DR 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

Diabetes Med. 2011 Jul;28(7):865-71
BJO 1996;80: 209-13
KWS 1999; 389: 1819-24
It may be time to develop, test and educate ECPs, PCPs & the public about an AREDS-2 type multi-component supplement for patients with diabetes and diabetic retinopathy.

Beyond AREDS: is there a place for antioxidant therapy in the prevention/treatment of eye disease?

**Diabetes Visual Function Supplement Study (DiVFuSS)**
- 6 month placebo-controlled RCCT of adults with T1DM or T2DM ≥ 5 years
- With and without retinopathy
- Daily use of a multi-component nutritional supplement (lutein, zeaxanthin, D, C, E, 2n, curcumin, benfotamine, Pycnogenol, lipoic acid, NAC, resveratrol, grapeseed extract, green tea, O-3 FAs, CoQ10)
- Contrast sensitivity, color vis., macular perimetry, OCT, A1c, lipids, 25(OH) vit. D, TNF-a, hsCRP, DPNS

Presented at ARVO 2013, Seattle IOVS, awaiting publication.
Subject Characteristics (n = 46)
- 31-79 yo (mean = 56 yrs)
- 25 with NPDR & 21 with no DR
- 18 T1DM & 28 T2DM
- HbA1c range 5.8 to 9.3% (mean 7.4%)  
  Mean A1c in those with DR = 7.8%
  Mean A1c in those with no DR = 7.1%
- Diabetes duration 5-52 years (mean 21.2 yrs)
  Mean 23.4 years in those with DR
  Mean 14.7 years in those with no DR

DiVFuSS Unmasked Data
\[ \Delta \text{from baseline} \quad \text{Supplement versus Placebo} \]
- Contrast: +31% -20%
- Color Error Score: -50% -2%
- 5-2 MD: +1.1 dB +0.17 dB
- hsCRP: -72% +10%
- HbA1c: -4% +2.5%
- OCT mean NFL: unchanged in both groups
  
  For contrast, color, visual field, hsCRP, p < 0.02

Summary of Early Findings in Human Subjects
- DiVFuSS formula improved visual function, including contrast sensitivity, visual field sensitivity and color perception
- DiVFuSS formula significantly reduced hsCRP and DPN scores

Getting Patients to Buy In to Good Diabetes Self-Management
- YOU are the experts
- Here are my thoughts as a patient & a provider........

Good Public Health and Economics
Suggest that we should...
- Make it “cheap” to practice good self care & incentivize good health habits
- Screen for and manage depression
- Educate and re-educate patients
  - Diabetes doesn’t cause complications. Poorly controlled diabetes causes complications
My Experience

- Scare tactics generally don’t work, if at all, until patients have lost something
- Scare tactics and threats aren’t conducive to good relationships
- Building a relationship works

“If you want to tell someone the truth, first make them laugh. Otherwise they will kill you.”
- Oscar Wilde

Getting Patients To Buy In

- Use humor
- Tell patients about your personal or family experiences with diabetes
- Criticize behaviors, not the person
- Use patient Handouts & Digital Imaging
- Conference with the patient & family
- As a last resort for men, the risk of impotence can be a very strong motivator

“Get your facts first, then you can distort them as you please”

The Most Important Message A Health Care Professional Can Convey To Other Members of the Diabetes Care Team...

“The only way to keep your health is to eat what you don’t want, drink what you don’t like, and do what you’d rather not.”

Various research indicates that men think about sex 6-8 seconds.
Thank You!

A. Paul Chous, MA, OD, FAAO
dr.chous@diabeticeyes.com