The Posterior Segment in Diabetes

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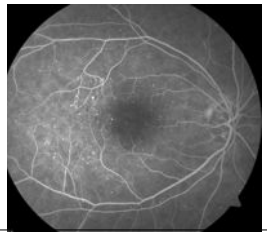
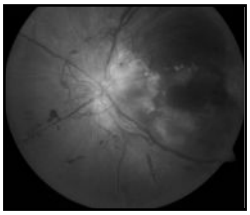
Course Goal

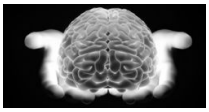
- To provide useful clinical information about current standards in the treatment and management of diabetes and diabetic retinopathy.



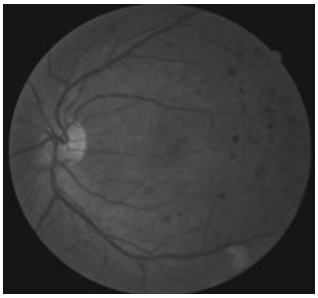
- **The eye does not exist in isolation. It is an extension of the brain/CNS.**
- **The anatomy of the eye is structured to serve the retina.**
- **Primary reason for dilation is to detect systemic disease.**



The eye is the only part of the body where neurological and vascular tissues can be viewed directly.



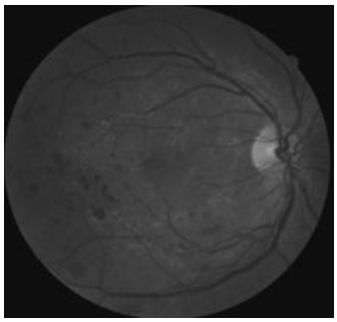
The Posterior Segment in Diabetes Mellitus



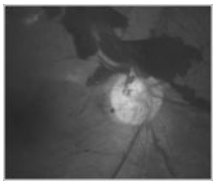
Statement of the Problem

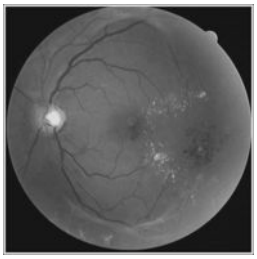
- Diabetes and diabetic retinopathy (DR) is the leading cause of blindness in the working population in the western world.
- As the number of people living with type 2 DM is on the rise, eye care providers are seeing more and more DR.
- The obesity epidemic is driving these alarming increases.

Fellow eye of same patient



32 yo WM



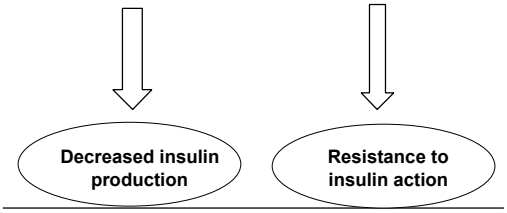


- 5 ft 8 in tall, 265 lbs
- "sees red" OD
- Type 2 DM x 3 yrs
- Recent Dx. Obstructive Sleep Apnea

Diabetes Mellitus

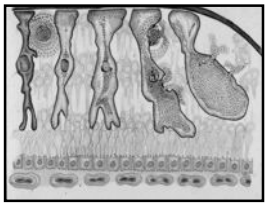
- The inability of the body to use and store sugar properly, resulting in high blood sugar levels.
  - Type 1 (5-10%): previously called juvenile-onset or insulin-dependent.
    - beta cell destruction and absolute insulin deficiency
  - Type 2 (90-95%): previously termed adult-onset or non insulin-dependent.
    - insulin resistance with relative insulin deficiency.

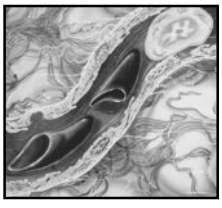
Diabetes is a disease of impaired insulin action



DM/DR is Inflammation

- **Leukocytes, once inside retinal tissue, secrete a variety of inflammatory substances such as TNF and VEGF.**
- **These released mediators increase vascular permeability and stimulate more mediators to enhance the inflammatory reaction.**

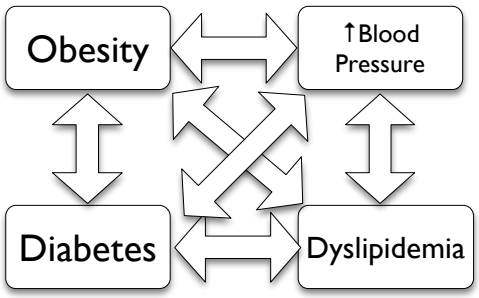




Diabesity

- M_____ S_____ is characterized by central (abdominal) obesity, dyslipidemia, raised blood pressure, and insulin resistance.
- *"Diabesity"*
  - Up to 97% of type 2 caused by excessive weight
  - Obesity = Increased weight caused by excess accumulation of fat.

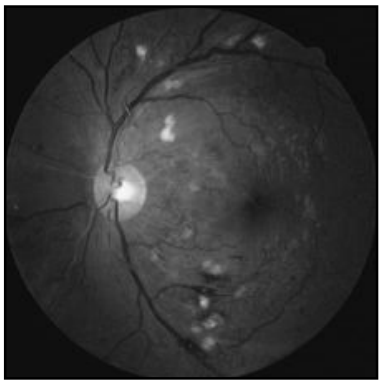
Metabolic Syndrome



*3 or more are diagnostic of Metabolic Syndrome:

- waist circumference:
  Men — > 40 inches
  Women — > 35 inches
- triglycerides ≧150 mg/dL
- HDL cholesterol:
  Men — <40 mg/dL
  Women — <50 mg/dL
- BP ≧130/85 mmHg
- FPG ≧100 mg/dL

45 y/o BM



Hb A1C = 9.8%

Sleep Apnea w/ No CPAP use

Anemia = 8 Hb

Albuminuria>300

BP = 150/90

Smoker

Gum Disease

Vitamin D deficiency

EPIDEMIOLOGY

- DM is 7th leading cause of death in the US
- > 25 million people with DM, costing $132 billon

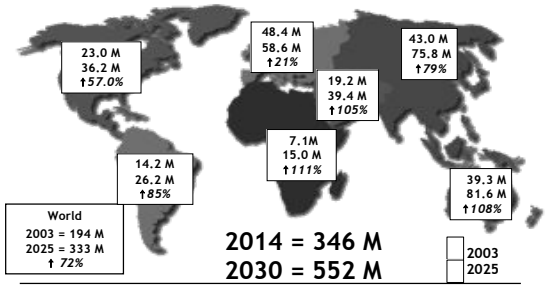
  75 million have pre-diabetes
- DM is leading cause of new blindness, lower limb amputation and renal failure
- DM => a 2-4 fold increased risk of CV disease

Diabetes Mellitus

- Increasing Prevalence in the United States (CDC Data)

	2003	2005	2007	2010
▪ Age 20 yrs or older	8.7%	9.6%	10.7%	11.3%
▪ Age 60 yrs or older	18.3%	20.9%	23.1%	26.9% (≥65)

The Future



Diabetes Atlas Committee. *Diabetes Atlas 2nd Edition:* IDF 2003

Diabetic Retinopathy: Epidemiology

- 28.5% of Americans with DM over 40 yrs of age have DR
  - 4.1 million
  - 6 million by the year 2020
- DR Prevalence increases with:
  - Duration of diabetes
  - Patient age
- Most common cause of blindness in young Americans (20-64 yrs).

- JAMA. 2010 Aug 11;304(6):649-56. doi: 10.1001/jama.2010.1111.
  Prevalence of diabetic retinopathy in the United States, 2005-2008.

What We Already Know

- DR is a microvascular disease.
- Proliferative DR (PDR) characterized by new vessel formation in the retina and optic disc as a result of hypoxia, microangiopathy, and capillary occlusion.
- Tractional RD, CSME, and NVG may result in severe vision loss.

Diabetic Retinopathy: Epidemiology

- WESDR
  - Wisconsin Epidemiologic Study of Diabetic Retinopathy
- After 20 yrs of Diabetes
  - 99% type 1 DM will have retinopathy
  - 60% type 2 DM will have retinopathy
- Limitation: primarily white patients of northern European descent

Questions and Comments?

Systemic Conditions that May Exacerbate DR

- Elevated serum lipids (dyslipidemia)
- Hypertension
- Carotid artery occlusive disease
- Advanced diabetic renal disease
- Sleep Apnea
- Anemia
- Pregnancy
- Obesity

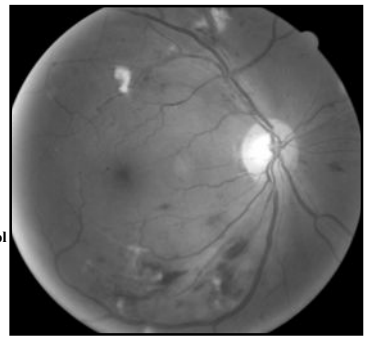
Hypertension

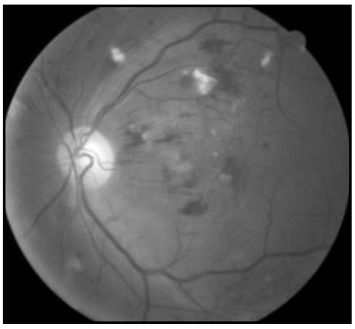
54 year old

+ Diabetes

+ HTN

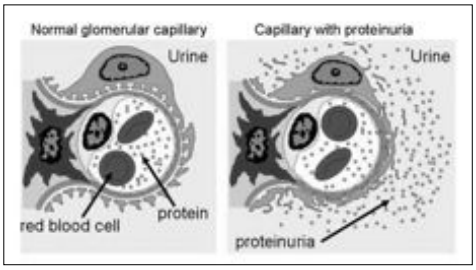
+ Cholesterol



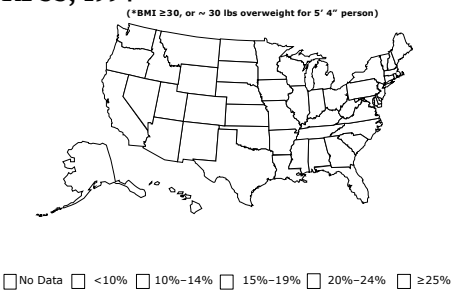


Diabetic Nephropathy

Hydrostatic Pressure = moves fluid out
Osmotic Pressure = keeps fluid in

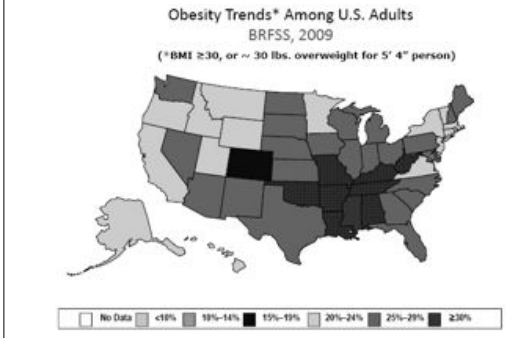


Obesity Trends* Among U.S. Adults BRFSS, 1994

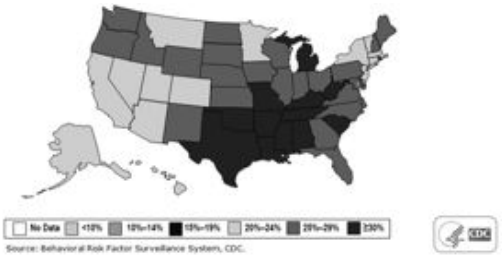


Body Mass Index

- World Health Organization (WHO) Classification
  - For adults, Grade 1 (simply called overweight) is a BMI of 25-29.9 kg/m2.
  - Grade 2 (commonly called obesity) is a BMI of 30-39.9 kg/m2.
  - Grade 3 (commonly called severe obesity) is a BMI greater than or equal to 40 kg/m2.



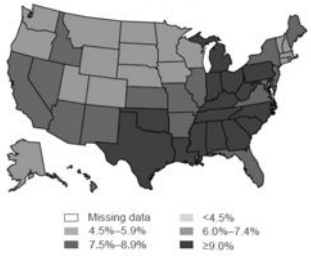
Obesity trends-2012



"Diabesity Belt"

Age–Adjusted Prevalence of Diagnosed Diabetes
Among U.S. Adults

2010



The Pathology of Obesity

Skin	**Yeast Infections, Gout, DJD**
Endocrine	**Polycystic Ovarian Syndrome, low testosterone, high estrogen**
Heart	**Heart Attack, Stroke, CHF**
Pulmonary	**Sleep Apnea**
GI	**Gallstones, GERD**
Urinary	**Incontinence**
Gyno	**Abnormal menses, Infertility**
Neuro	**Depression, memory problems**
Cancer	**Breast cancer, colon, prostate, bladder and esophagus**
Post-Op	**Pulmonary embolism**

Complications of Excess Weight

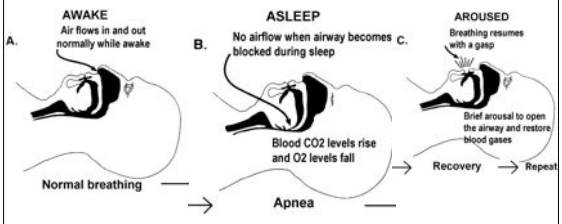
Obstructive Sleep Apnea Syndrome (OSA)

What We Already Know

- Type 2 DM is the most highly associated systemic complication of obesity. *
- Sleep Apnea Syndrome and DR
  - 12 million American adults have OSA.
  - It is often found in patients with obesity, diabetes and/or cardiovascular disease.
  - OSA may aggravate DR, secondary to nocturnal hypertension and hypoxemia.

Systemic Complications of OSA

- HTN
- Type 2 DM
- Congestive Heart Failure
- Coronary Artery Disease
- Atrial Fibrillation
- OSA is an independent RF for stroke.*



Impaired blood flow in OSA

Ocular Complications of OSA

- Changes in eyelid tissue
  - Floppy eyelid syndrome (FES)
- Changes in cornea
  - K-conus
- Changes in the optic nerve
  - The glaucomas
    - open angle (OAG)
    - normal tension (NTG)
  - Non-arteritic anterior ischemic optic neuropathy (NAION)
- Changes in retina: DR, HR, RVO

CPAP: "Up your nose with a rubber hose!"

Sleep Apnea and DR

- DME
  - Higher prevalence of DME
  - Recurrence rate higher
  - Unresponsive to Anti-VEGF
- PDR
  - Higher prevalence of PDR
  - Worsening of PDR
- Improvement of DME, PDR w/CPAP

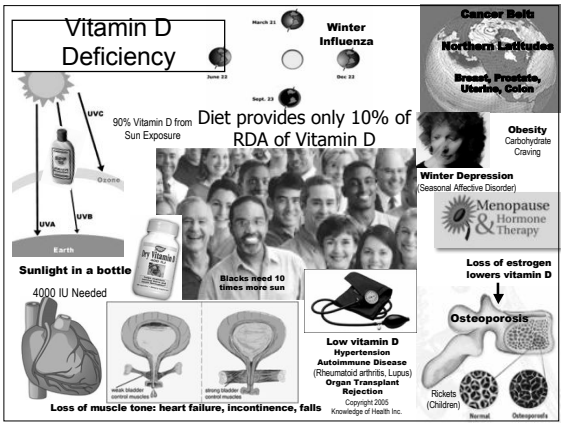
CPAP Therapy

www.austinoms.com/sleep_apnea.htm

Cigarette Smoking, Ocular & Vascular Disease

- Increased arteriolar stiffness (sclerosis)
- Increased Vascular Endothelial Growth Factor (VEGF) production
- Development/worsening of DR
- Development/worsening of AMD

DM + Smoking = Blindness



- For people aged one to 70 years, the RDA is at least 600 IU.
- For people over 70, RDA is at least 800 IU

Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health[10]	
<12ng/mL	Deficiency, leading to rickets in infants and children and osteomalacia in adults
12-20ng/mL	Inadequate for bone and overall health in healthy individuals
>20ng/mL	Adequate for bone and overall health ←
>50ng/mL	Potential adverse effects

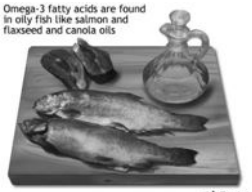
Sources of Vitamin D	
Non-fat fortified milk	1 cup per day
Fish: salmon, tuna, sardines, mackerel, herring	at least three servings per week
"Sensible sunlight"	Five to 15 minutes, two to five times per week
Vitamin D3 supplements	1,000 IU per day

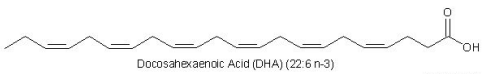
Dietary Vitamin D:
Cod Liver Oil, Sockeye Salmon

- Modulation of cell growth
- Neuromuscular and immune functions
- Reduction of inflammation*
- Vitamin D may moderate cardiac and vascular disease, and reduce proteinuria.

Omega-3s (EPA and DHA)

- **Decreases insulin resistance**
- **Decrease depression**
- **Prevents cardiac arrhythmias**
- **Increases telomere length**
- **1000 mg to 4000 mg / daily**





Docosahexaenoic Acid (DHA) (22:6 n-3)

Figure by RMB

Questions and Comments

Screening for Diabetes & Pre-Diabetes

- Consider testing if person is:
  - Overweight or obese with additional risk factor for diabetes (e.g. smoking, HTN)
  - Age 45 or older
- **Obtain: A1C <u>or</u> FPG <u>or</u> 2-hour plasma glucose post 75g OGTT**
- Repeat testing every 3 years if results are normal
- In patients with increased risk, identify and treat other CVD risk factors

American Diabetes Association. Diabetes Care 2010; 33;(Suppl1).

Diagnostic Criteria for Pre-Diabetes & Diabetes

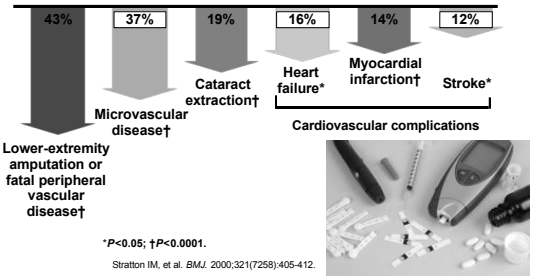
	A1C	Fasting Plasma Glucose Test (FPG)	2-Hour Oral Glucose Challenge
Acceptable	≤5.6%	Below 100 mg/dl	Below 140 mg/dl
Pre-Diabetes	5.7% - 6.4%	100-125 mg/dl (IFG)	140-199 mg/dl (IGT)
Diabetes	≥ 6.5%	126 mg/dl or above	200 mg/dl or above

American Diabetes Association. Diabetes Care 2010; 33;(Suppl.1):S11-61.

Even small reductions in A1C levels significantly reduce the risk for long-term complications.

UKPDS: 1% A1C Decrease & Reduced Risk of Complications

The UK Prospective Diabetes Study (UKPDS)



*$P<0.05$; †$P<0.0001$.

Stratton IM, et al. *BMJ.* 2000;321(7258):405-412.

MACROVASCULAR COMPLICATIONS

Coronary artery disease
- Heart attacks

Peripheral vascular disease
- Limb Amputations

Cerebral vascular disease
- Strokes ----->

Renal vascular disease
- Renal failure and dialysis

Diabetic Retinopathy: Pathogenesis

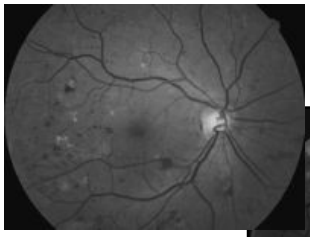
- Extended exposure to hyperglycemia leads to biochemical and physiologic changes that ultimately cause vascular endothelial damage
- Loss of pericytes
- Basement membrane thickening
  - Compromises lumen (leading to non-perfusion)
  - Decompensation of endothelial barrier function

Diabetic Retinopathy: Pathogenesis

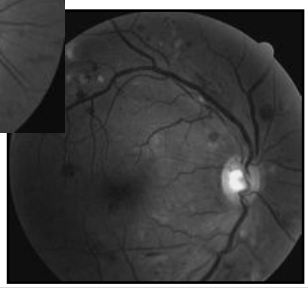
- Several hematologic and biochemical abnormalities correlate with prevalence and severity of DR.
  - Increased platelet adhesiveness
  - Increased erythrocyte aggregation
  - Abnormal serum lipids
  - Defective fibrinolysis
  - Upregulation of VEGF
  - Abnormalities in whole blood viscosity

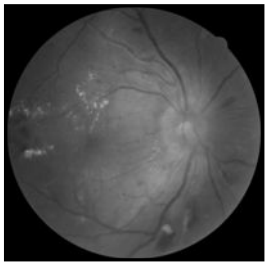
Diabetic Retinopathy: Pathogenesis

- Vision Loss
  - Capillary Leakage
    - macular edema
  - Capillary Occlusion
    - macular ischemia
    - diabetic papillopathy
  - Sequelae from ischemia-induced neovascularization
    - vitreous hemorrhage
    - traction retinal detachment
    - neovascular glaucoma



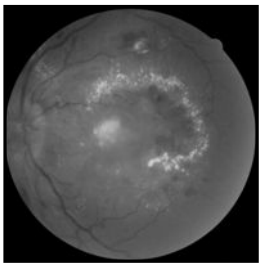
Non- Proliferative Diabetic Retinopathy

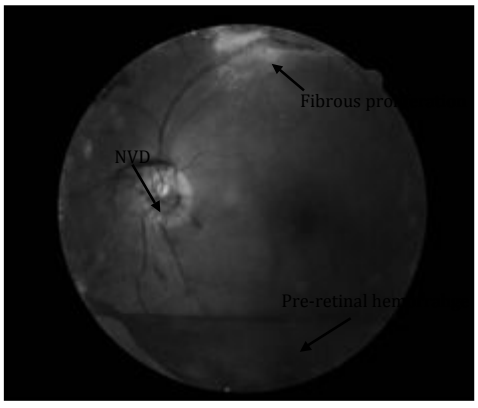


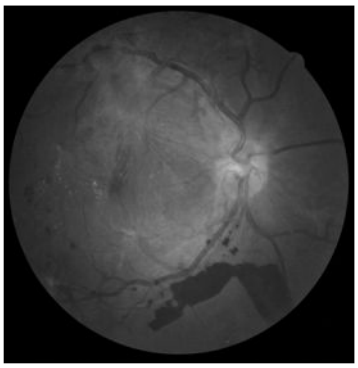


Diabetic Macular Edema

Diabetic Papillopathy



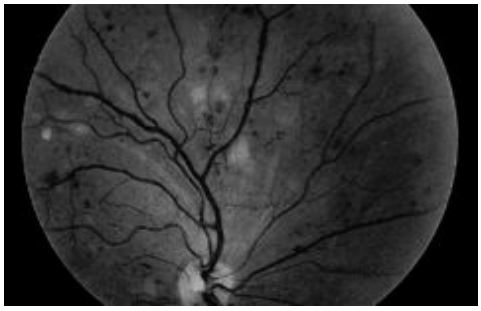




Non Proliferative Diabetic Retinopathy (NPDR)

- Microaneurysms
- Dot-and-blot intraretinal hemorrhages
- Cotton wool spots
- Hard exudates
- Venous beading
- Intraretinal microvascular abnormaities (IRMA)

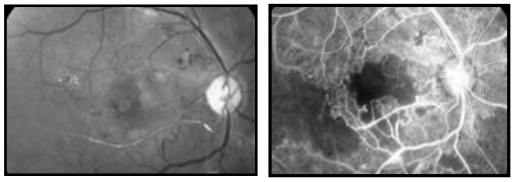
NPDR



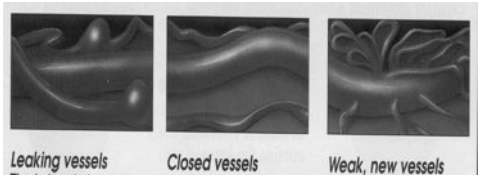
Severe NPDR

- 4-2-1 rule (any one)
  - 4 quadrants of intraretinal hemorrhages and microaneurysms
  - 2 quadrants of venous beading
  - 1 quadrant of IRMA
    - 15% chance of progression to High Risk PDR in 1yr
- Very severe NPDR
  - Any two of the above
    - 45% chance of progression to High Risk PDR in 1yr

Enlargement of FAZ to more than 1000 microns correlates with decreased vision/foveal ischemia



Vascular Changes in DR



Proliferative Diabetic Retinopathy (PDR)

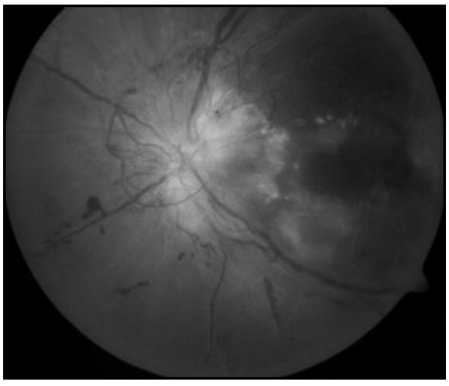
- Extraretinal fibrovascular proliferation that extends beyond the ILM
- New vessels evolve in three stages
  - Fine new vessels with minimal fibrous tissue
  - Increase in size and fibrous component
  - Regression of vessels with residual fibrovascular proliferation along the posterior hyaloid scaffold
- Neovascularization can occur in the retina, on the optic nerve head, or in anterior segment (iris, angle)

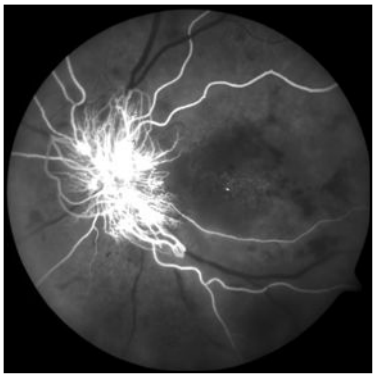
Proliferative Diabetic Retinopathy

- NVI: Neovascularization of the iris
- NVA: Neovascularization of the angle
- NVD: Neovascularization of the disc
- NVE: Neovascularization elsewhere

Diabetic Retinopathy: Classification of PDR

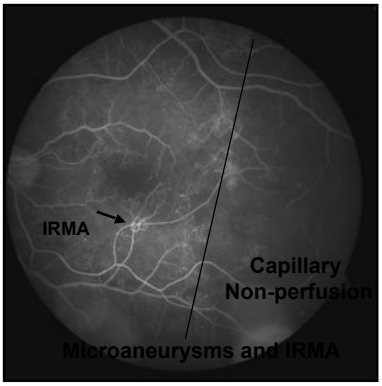
- DRS Classification of High Risk Characteristics
  - Any NVD with vitreous hemorrhage
  - NVD ≥ 1/4 to 1/3 DA (with or without vitreous hemorrhage)
  - NVE ≥ 1/2 DA with vitreous hemorrhage
  - Or, any 3 of the following 4 findings:
    - Presence of vitreous heme or preretinal heme
    - Presence of new vessels
    - Location of new vessels on or near the optic disc
    - Moderate to severe extent of new vessels

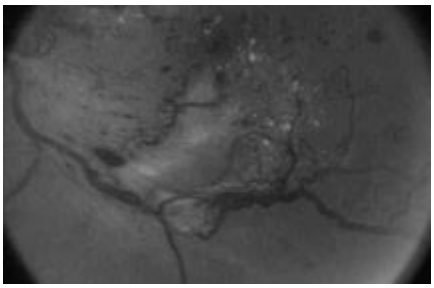


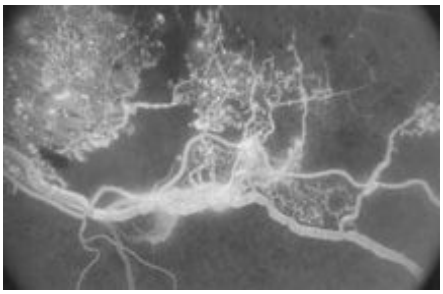


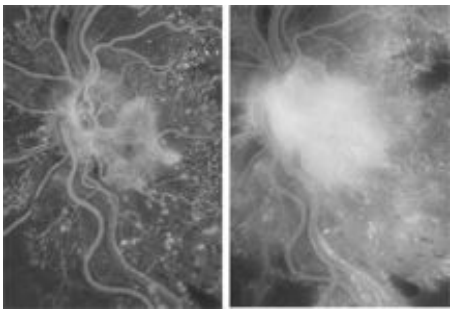
PDR

- Associated with increased risk of:
  - Heart Attack
  - Stroke
  - Kidney Failure
  - Amputation
  - Death









Questions and Comments?

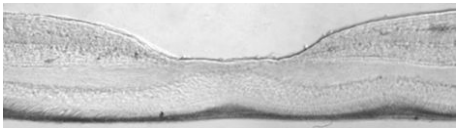
Novel Ocular Biomarkers for Diabetes

Macular Pigment Optical Density (MPOD)

Crystalline Lens Autofluorescence (CLA)

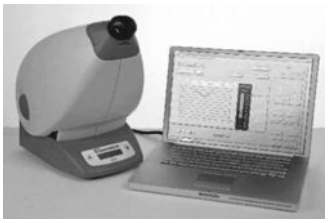
The Importance of Macular Pigments

- Serum levels of lutein and zeaxanthin are inversely associated with type 2 DM and impaired glucose metabolism.[1]
- A recent study showed that type 2 patients—with or without retinopathy—had reduced MPOD compared to non-diabetic patients. In addition, researchers observed an inverse correlation between MPOD and HbA1c levels. [2]



1. Davies NP, Morland AB. Color matching in diabetes: optical density of the crystalline lens and macular pigments. Invest Ophthalmol Vis Sci. 2002 Jan;43(1):281-9.
2. Lima VC, Rosen RB, Maia M, et al. Macular pigment optical density measured by dual-wavelength autofluorescence imaging in diabetic and nondiabetic patients: a comparative study. Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5840-5.

MPOD--HFP with QuantifEye

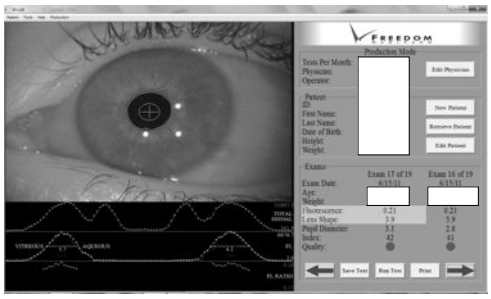


Crystalline Lens Autofluorescence (CLA)

- CLA identifies elevated advanced glycosolated end-products (AGEs)—a biomarker highly correlated to glycemic status—prior to early DM complications.
- Subjects with poor long-term glycemic control had significantly higher levels of lens AGEs compared to age-matched healthy controls.

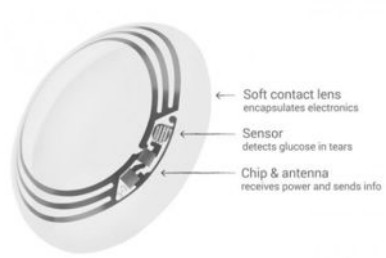
Yu NT, Krantz BS, Eppstein JA, et al. Development of a noninvasive diabetes screening device using the ratio of fluorescence to Rayleigh scattered light. J Biomed Opt. 1996 Jul;1(3):280-8.
Sparrow JM, Bron AJ, Brown NA, Neil HA. Autofluorescence of the crystalline lens in early and late onset diabetes. B J Ophthalmol. 1992 Jan;76(1):25-31.

CLA with ClearPath DS-120



A clinician plots the fluorescence ratio (.21) and age (45) on X/Y axis of data chart

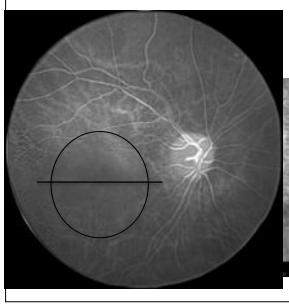
Google Glucose Smart CL

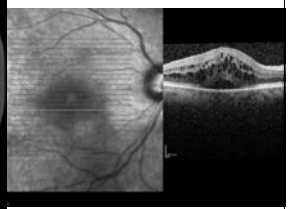


Diabetic Retinopathy-Multi-Spectral Image

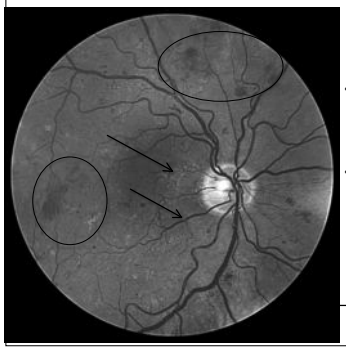
Oxy/Deoxy Hemoglobin

- Macular edema centrally is evidenced by the elevated blurry area (red circle)
- CME is confirmed with OCT





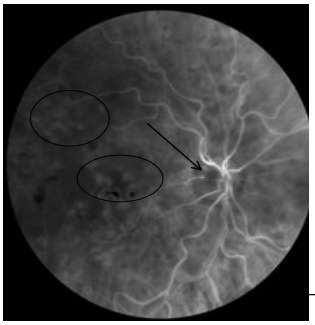
Diabetic Retinopathy



MSI Yellow

- Intraretinal blot hemorrhages are hyporeflective and seen throughout the posterior pole (circles)
- A broad area of epiretinal membrane is also seen (arrows)

Diabetic Retinopathy

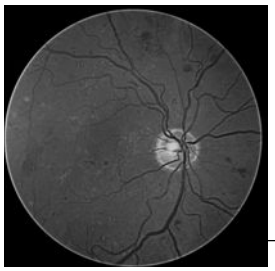


MSI Oxy/Deoxy Hemoglobin

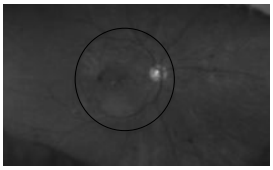
- Reveals a hyporeflective (dark) optic nerve consistent with ischemia (arrow)
- Atrophic scars from focal laser treatment are evident (circles)

Diabetic Retinopathy

Color MSI Image



Color Wide Field



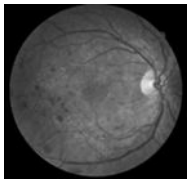
Diabetic Retinopathy: Optometry's Role

- Prevention
- Comprehensive workup and annual DFE
- Early detection
- Proper consultation and referral
- Vision Rehabilitation

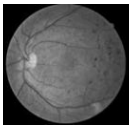
Structure and Function in DR

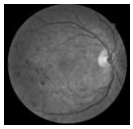
Indications for Visual Field Testing

- Glaucoma
- Neural Loss/Neuro Eye Disease
- **Retinal Disease**
- Functional Testing

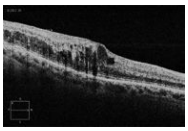


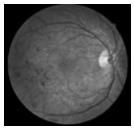
48 y/o WM with Diabetic Retinopathy

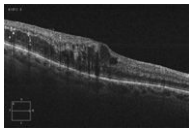


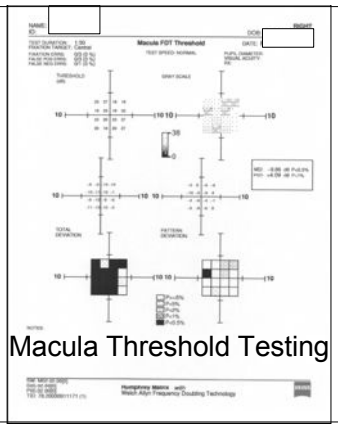


Macular Edema



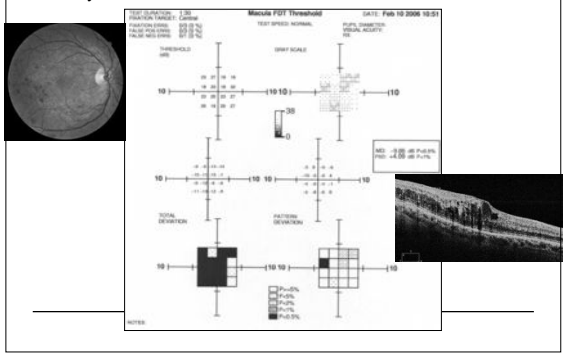




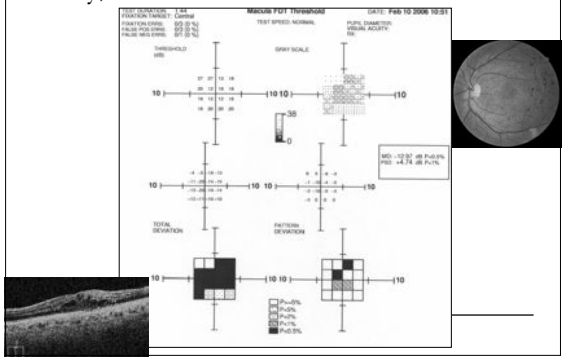


Macula Threshold Testing

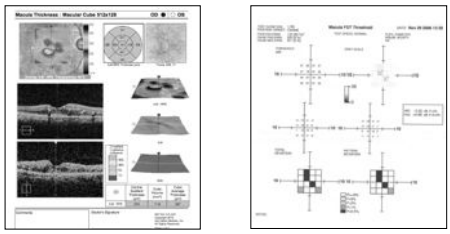
48 y/o WM with DME OD



48 y/o WM with DME OS



Clinical Case of Patient RW: Integrating Structure and Function



FDT Macula Threshold Testing

Co-management

- A cooperative effort between individuals who participate in the patient's care
  - Optimizing patient management
- Critical factors
  - Continuous communication
  - Clear guidelines for referral and consultation
  - Periodic review of the patient's progress

Diabetic Retinopathy: Treatment

- Systemic Medical and Nutritional Management
  - Glycemic control
  - Hypertension control
  - Lipids
- Ocular Treatment
  - Panretinal Laser Photocoagulation
  - Focal/Grid Macular Laser Treatment
  - Pharmaceutical Treatment
  - Combined Pharmaceutical Treatment and Laser
  - Surgery

Diabetic Retinopathy: Systemic Medical Management

- Intensive glycemic control associated with decreased risk of newly diagnosed DR and reduced progression of existing retinopathy.
  - Diabetes Control and Complications Trial (DCCT)
    - Type 1
  - United Kingdom Prospective Diabetes Study (UKPDS)
    - Type 2

Diabetic Retinopathy: Systemic Medical Management

- DCCT
  - Intensive glycemic control versus conventional treatment
    - Reduced development of DR by 76% and progression by 54%
    - Reduced progression of NPDR to severe NPDR, PDR
    - Reduced DME
    - Reduced need for Focal/Grid laser and PRP
    - Reduced risk of neuropathy by 60%; nephropathy by 54%

Diabetic Retinopathy: Systemic Medical Management

- UKPDS
  - Control of hypertension
    - Reduced progression of retinopathy
    - Reduced loss of vision
    - Reduced other microvascular complications

Diabetic Retinopathy: Systemic Medical Management

- Asymmetric carotid artery occlusive disease
  - Mild or moderate may have protective effect (perhaps due to diminished effect of HTN on retina)
  - Severe may lead to proliferative disease as part of ocular ischemic syndrome
- Pregnancy associated w/worsening of DR
  - Although improvement seen after delivery, treatment should not be delayed.

Questions and Comments?

Diabetic Retinopathy Study (DRS)

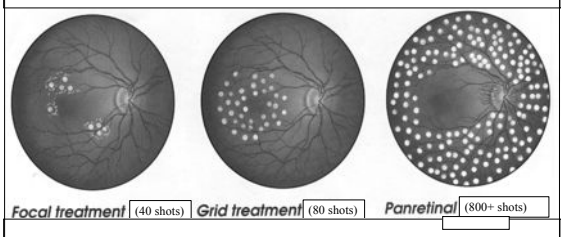
Study question: Is photocoagulation (argon or xenon arc) effective for treating DR?

Eligibility: PDR or bilateral severe NPDR, with visual acuity 20/100 or better in each eye.

Randomization: 1742 participants. One eye randomly assigned to photocoagulation (argon or xenon arc) and 1 eye assigned to no laser.

Outcome variable: Visual acuity less than 5/200 for at least 4 months.

Results: Photocoagulation (argon or xenon arc) reduces risk of severe vision loss compared with no treatment. Treated eyes with high-risk PDR achieved the greatest benefit.

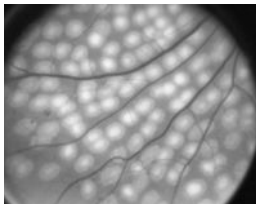


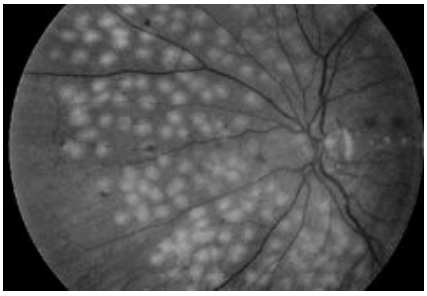
DRS/ETDRS Panretinal Laser

≥ 1200 shots

500 micron spots

½ burn apart



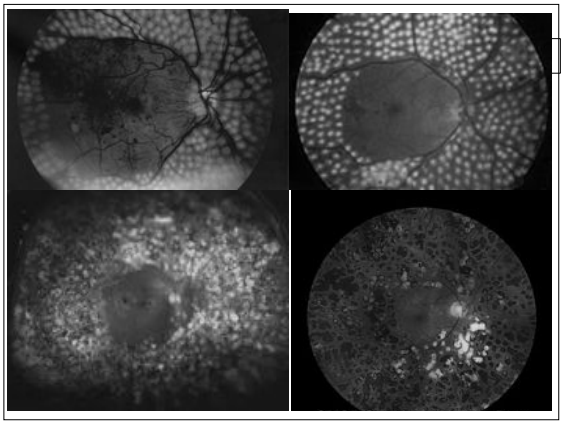


DRS

- PRP reduced risk of severe visual loss (SVL) by 50% over 5 years
  - Subjects w/High Risk PDR had greatest benefit

DRS

- PRP Adverse effects
  - Vitreous Hemorrhage
  - Tractional Retinal Detachment (TRD)
  - Combined TRD and Rhegmatogenous RD
  - Decreased
    - Night vision
    - Color vision
    - Contrast sensitivity
    - Peripheral vision
- Transient adverse effects
  - Loss of accommodation
  - Loss of corneal sensitivity
  - Photopsias



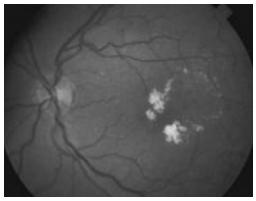
PDR: Surgery (Vitrectomy)

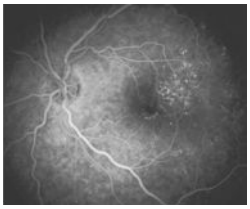
- Indications
  - Dense, non-clearing VH (6wks – 3mo)
  - TRD (macula involving or threatening)
  - Combined TRD and Rhegmatogenous RD
  - Diffuse DME associated with posterior hyaloid traction
  - Significant recurrent VH despite max PRP
  - Anterior segment NV with media opacity
  - Dense premacular subhyaloid hemorrhage

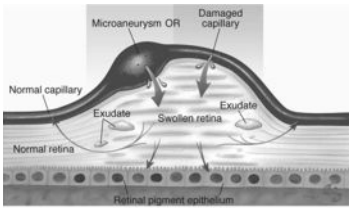
Diabetic Retinopathy Vitrectomy Study (DRVS)

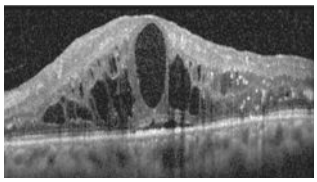
- Prospective, randomized trial
- Early (1-6 mo) vs. late (1 yr after onset) vitrectomy for VH related to PDR
- Early PPV clearly better for type 1 DM
- Type 2 DM showed no advantage of early vitrectomy
- These results no longer strictly adhered to
  - Usually 6 wks to 3 mon with early PPV if no prior PRP

Diabetic Macular Edema









Early Treatment Diabetic Retinopathy Study (ETDRS)

Study questions:
Is photocoagulation effective for treating DME?
Is photocoagulation effective for treating diabetic retinopathy?
Is aspirin effective for preventing progression of diabetic retinopathy?

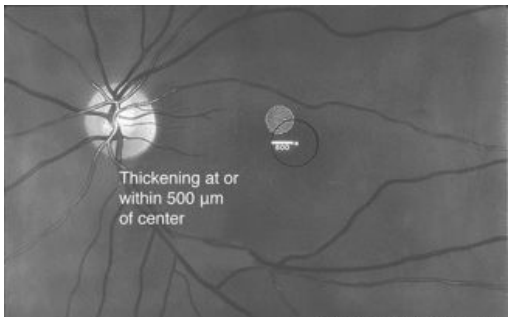
Aspirin use results:
Aspirin use did not alter progression of diabetic retinopathy.
Aspirin use did not increase risk of vitreous hemorrhage.
Aspirin use did not affect visual acuity.
Aspirin use reduced risk of cardiovascular morbidity and mortality.

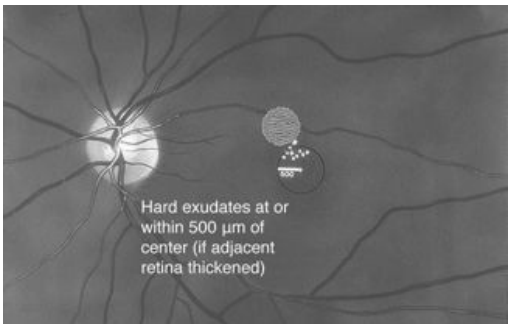
Early scatter photocoagulation results:
Early scatter photocoagulation resulted in a small reduction in the risk of severe vision loss (<5/200 for at least 4 months).
Early scatter photocoagulation is not indicated for eyes with mild to moderate DR
Early scatter photocoagulation may be most effective in patients with type 2 diabetes.

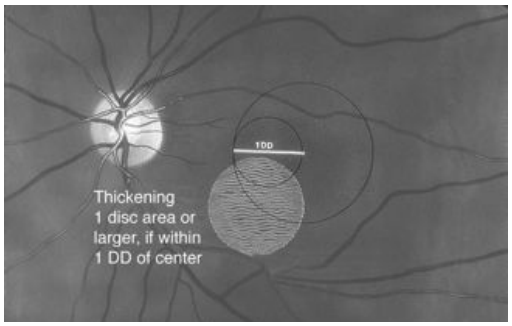
Macular edema results:
Focal photocoagulation for DME decreased risk of moderate vision loss
Focal photocoagulation for DME increased chance of moderate vision gain
Focal photocoagulation for DME reduced retinal thickening.

Diabetic Macular Edema

- Clinically Significant Macular Edema (CSME)
  - ETDRS classification



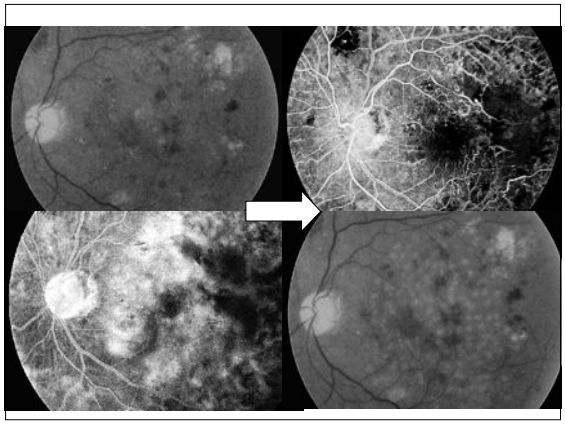


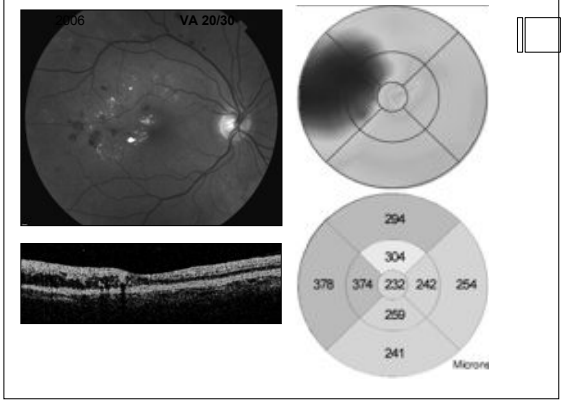


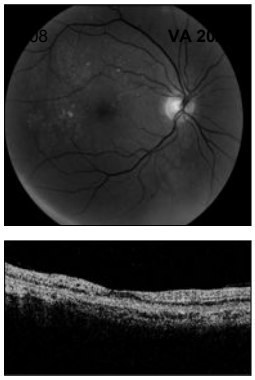
ETDRS Outcomes for CSME

Three Year Analysis			
	Immediate Tx (N=105)	Deferral of Tx (N=215)	P Value
SUCCESS			
% ≥ 10 Letter Improvement	26.7%	11.2%	0.0006
% ≥ 15 Letter Improvement	11.4%	5.1%	0.06
FAILURE			
% ≥ 10 Letter Worsening	21.9%	46.5%	<0.0001
% ≥ 15 Letter Worsening	16.2%	36.7%	0.001

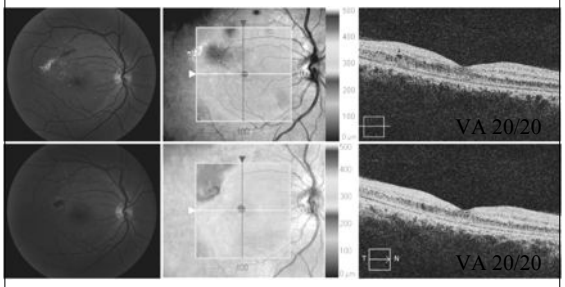
(VA ≤ 20/32)
Eyes With Definite Center Thickening, Less Severe Retinopathy



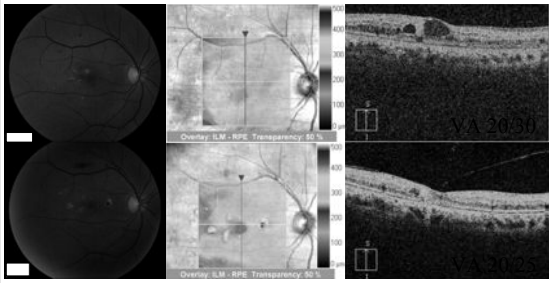




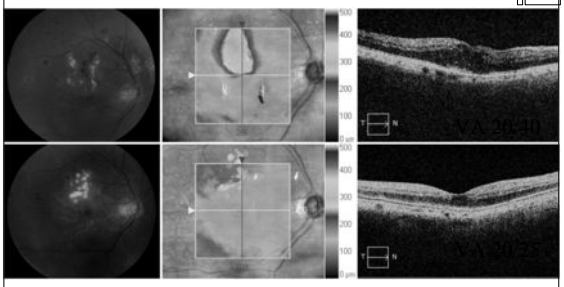
Before laser: Tx 20/20?



1year s/p focal/grid laser



Two years s/p focal/grid laser



Two years s/p focal/grid laser

Table 5-1 Focal Laser Photocoagulation: Adverse Effects and Complications

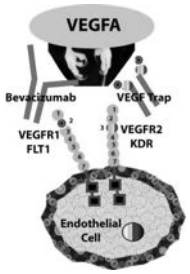
Paracentral scotomata
Transient increase of edema/decrease in vision
Choroidal neovascularization
Subretinal fibrosis
Photocoagulation scar expansion
Inadvertent foveolar burns

Modified from Kim JW, Al E. Diabetic retinopathy. In: Regillo CD, Brown GC, Flynn HW Jr, eds. *Vitreoretinal Disease: The Essentials*. New York: Thieme; 1999:147.

CSME: Laser Treatment

- Pre-Tx clinical features associated with poorer visual outcome after laser for DME:
  - Diffuse macular edema with foveal involvement
  - Diffuse fluorescein leakage
  - Macular ischemia
  - Hard exudates in fovea
  - Marked CME

Questions and Comments?



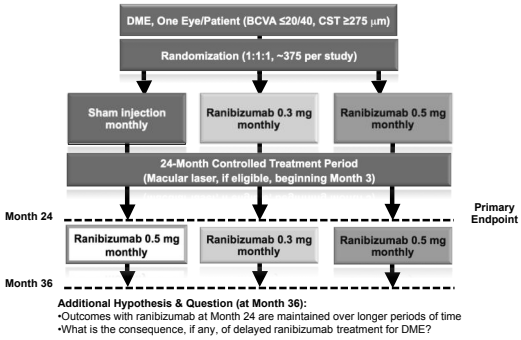
DME: Anti-VEGF Therapy

- **READ** - Ranibizumab for Edema of the mAcula in Diabetes
- **RESOLVE** - Safety and Efficacy of Ranibizumab in Diabetic Macular Edema with Center Involvement
- **RESTORE** – Efficacy and Safety of Ranibizumab in Patients with Visual Impairment Due to Diabetic Macular Edema
- **RISE/RIDE** – A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to DM
- **DRCR.net Protocol I** – Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema
- **BOLT** – Intravitreal Bevacizumab Or Laser Therapy in the Management of Diabetic Macula Edema
- **VIVID/VISTA –** Intravitreal Aflibercept for Diabetic Macula Edema

Diabetic Macular Edema anti-VEGF Treatment

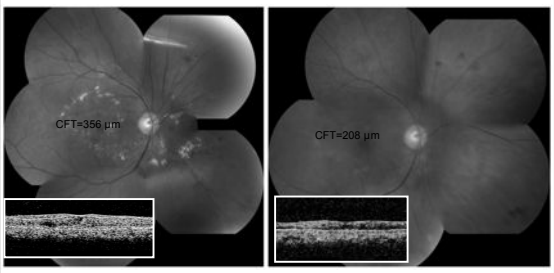
- RIDE & RISE

RIDE & RISE Study Design

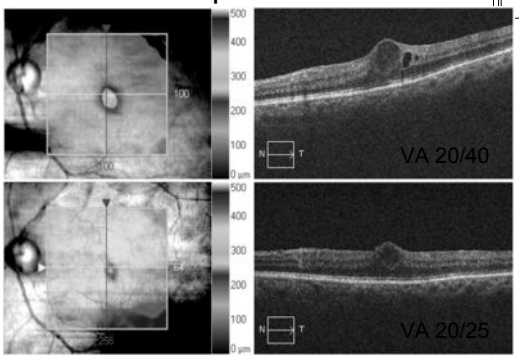


Additional Hypothesis & Question (at Month 36):
- Outcomes with ranibizumab at Month 24 are maintained over longer periods of time
- What is the consequence, if any, of delayed ranibizumab treatment for DME?

36 mos s/p ranibizumab x 36

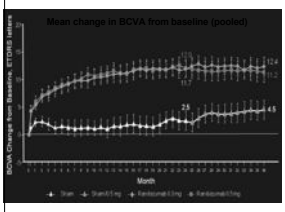


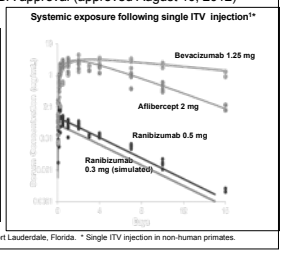
One month s/p ranibizumab x 1



Rationale for 0.3 mg Ranibizumab in DME

- Both doses demonstrated similar rapid, sustained efficacy in DME through Month 36
- Fewer AEs potentially related to systemic VEGF inhibition with 0.3 mg in DME
- DME patients often more medically complex than those w/o DME
- Bilateral treatment rates higher in DME patients
- 0.3 mg dose provides best balance of efficacy with lower potential systemic exposure
- Genentech, Inc. recommended 0.3 mg for FDA approval (approved August 10, 2012)





1. Tuomi L, et al. Paper 4178: 2012 ARVO Annual Meeting; May 6-10, 2012; Fort Lauderdale, Florida. * Single ITV injection in non-human primates.

A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema

24-Month Data: Report 3

Ranjan Rajendram, MD, FRCOphth; Samantha Fraser-Bell, PhD, FRANZCO; Andrew Kaines, FRANZCO; Michel Michaelides, MD, FRCOphth; Robin D. Hamilton, DM, FRCOphth; Simona Degli Esposti, MD; Tunde Peto, MD, PhD; Catherine Egan, FRANZCO; Catey Bunce, DSc; Richard David Leslie, MD, FRCP; Philip G. Hykin, MD, FRCOphth

- This study's results support longer term use of intravitreal bevacizumab for persistent center-involving CSME.

***Arch Ophthalmol*. 2012;130:972-979.**

BOLT Study: Bevacizumab for DME Visual Acuity and OCT at 2 Years

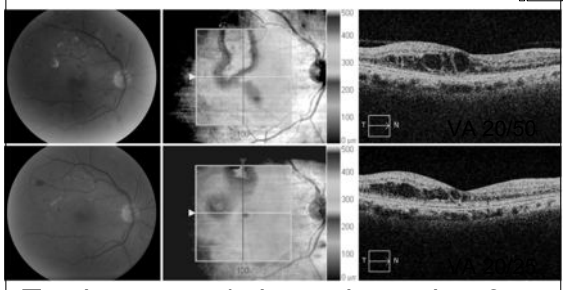
Outcome	Laser N=28	Bevacizumab N=37
Median Change in BCVA (letters)	+2.5	+9*
Mean Change in retinal thickness (microns)	-118	-146**

***P*=0.005 ****P*=0.001**

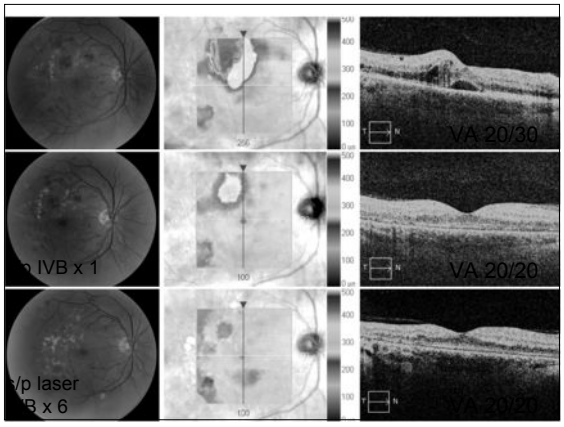
Median of 13 bevacizumab injections (9 in year 1 and 4 in year 2)

Median of 4 laser treatments (3 in year 1 and 1 in year 2)

***Arch Ophthalmol*. 2012;130:972-979.**



Twelve mon s/p bevacizumab x 8



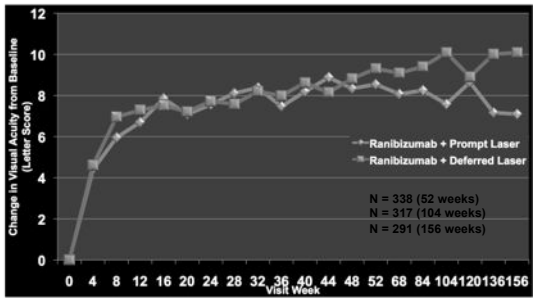
The Diabetic Retinopathy Clinical Research Network

Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt vs Deferred Laser Treatment:

3-year Randomized Trial Results

Visual Acuity

Mean Change in Visual Acuity at Follow-up Visits



Change in Visual Acuity*

Change in Visual Acuity (letters)**	Ranibizumab + Immediate Laser N = 144	Ranibizumab + Deferred Laser N = 147	Estimated Difference (B vs. C) (95% CI) [P-Value]
2-years (Estimated Means)	**+7.2**	**+9.0**	**-1.8 (-3.6 to +0.1) [*P* = 0.06]**
3- Years (Estimated Means)	**+6.8**	**+9.7**	**-2.9 (-5.4 to -0.4) [*P* = 0.02]**

*Visits occurring between 980 and 1204 days from randomization were included as 3 year visits
**truncated to ± 30 letters, based on longitudinal analyses adjusting for baseline VA

Study Conclusions

- Focal/grid laser performed at the initiation of intravitreal ranibizumab is no better, and possibly worse, than deferring laser for at least 24 weeks in eyes with DME involving the fovea and vision impairment.

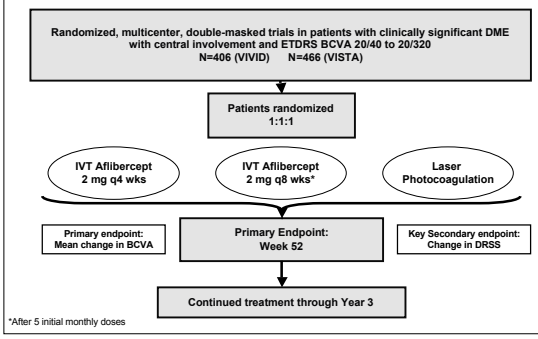
VIVID DME

Intravitreal Aflibercept Injection for Diabetic Macular Edema

Primary Results

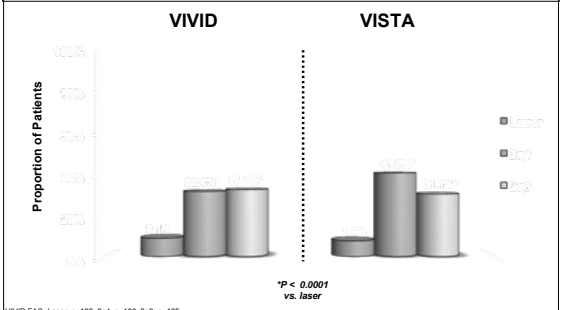
VISTA DME

Study Design



*After 5 initial monthly doses

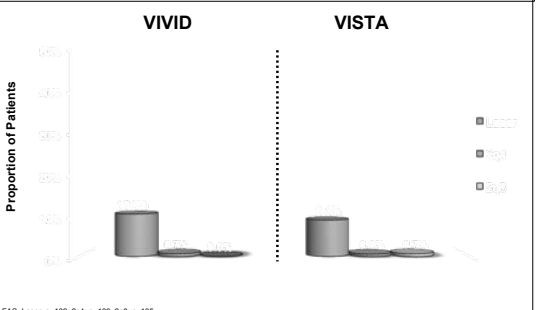
Proportion of Patients Gaining ≥ 15 Letters



*P < 0.0001 vs. laser

VIVID FAS- Laser: n=132; 2q4: n=136; 2q8: n=135
VISTA FAS- Laser: n=154; 2q4: n=154; 2q8: n=151
Compared to baseline; LOCF

Proportion of Patients Losing ≥ 15 Letters



VIVID FAS- Laser: n=132; 2q4: n=136; 2q8: n=135
VISTA FAS- Laser: n=154; 2q4: n=154; 2q8: n=151
Compared to baseline; LOCF

Questions and Comments?

Management of Diabetic Retinopathy

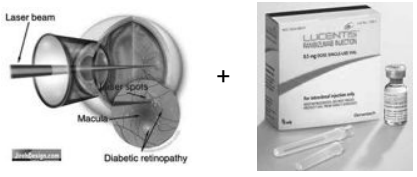
- In 2005, we had a major paradigm shift in AMD treatment.
  - From ablative therapy to pharmacotherapy.
  - Anti-VEGF injections improve the visual acuity rapidly and sustain visual acuity gains.
- This same paradigm shift is happening in DR, but at a slower pace.

Management of DR: The Future

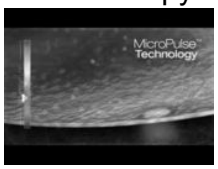
- Will there still be a role for laser in DR?
- Probably. In DM/DR, VEGF production is continuous.
  - Using pharmacotherapy alone will mean sustained injections for the rest of the patient's life.
  - Diabetic Retinopathy Clinical Research Network (DRCR) is evaluating combination therapy.

Management of DME

- Recently, laser out-performed intravitreal Kenalog.
- Laser + Lucentis out-performed laser alone.



Micropulse Laser Therapy for DME



- Sub-visible, tissue-sparing photocoagulation.
- MPL technology "chops" a continuous-wave beam into a train of repetitive short pulses.

Emerging Treatments for DME

- Dexamethasone Drug Delivery System
  - OZURDEX (intravitreal implant) 0.7mg (Allergan)
  - Intraocular, biodegradable implant
  - Approved for treatment of persistent ME in RVO

Diabetic Macular Edema: Steroid Therapy

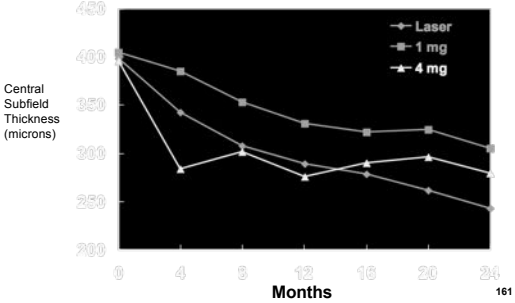
- **DRCR.net Protocol B**
- **DRCR.net Protocol I**
- **MEAD -** Macular Edema: Assessment of Implantable Dexamethasone (Ozurdex) in DME

DRCR Network: Protocol B

- **840 eyes (693 subjects) from 88 clinical sites**
- **Treatment Groups**
  - **Intravitreal Triamcinolone Acetonide**
    - **Laser: N = 330**
    - **1 mg: N = 256**
    - **4 mg: N = 254**

Ophthalmology 2008; 115:1447-1459 (PROTOCOL B)
MONOTHERAPY with LASER vs IVTA

Median Central Subfield Thickness in Laser and IVTA Treated Eyes



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DRCR Network Protocol B: Subgroup Analysis

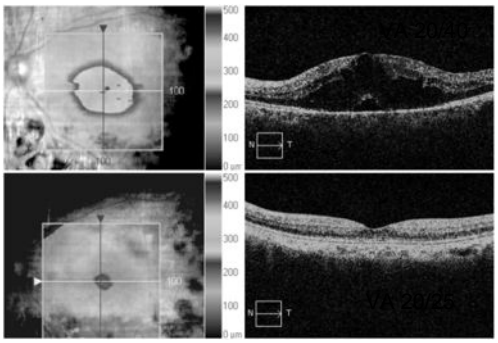
Baseline Data

2 Year Data

Baseline Va	# Eyes Laser, 1 mg, 4 mg			≥10-Letter Worsening (%)			≥10-Letter Improvement (%)		
				Laser	1mg	4mg	Laser	1mg	4mg
20/32 - 20/63	189	149	149	23	28	33	23	17	16
$20/63^{-1}$ - $20/200^{+1}$	129	94	92	12	24	26	43	33	39
$20/200 – 20/320^{-1}$	12	13	13	17	15	0	42	46	77

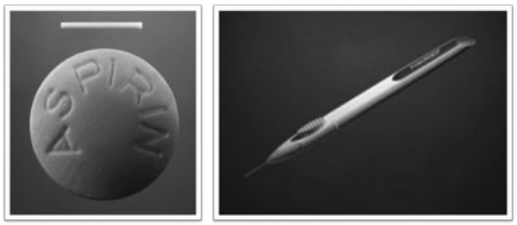
Table 5. Change in Visual Acuity at 2-Year Primary Outcome among Subgroups

Ophthalmology 2008; 115:1447-1459

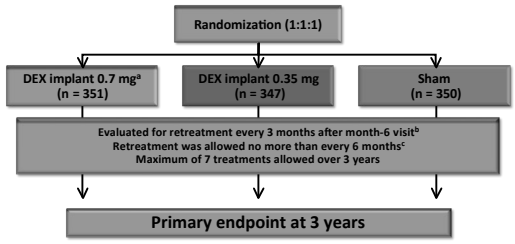


Five mon s/p IVTA x 1

Dexamethasone Implant



MEAD Study Design

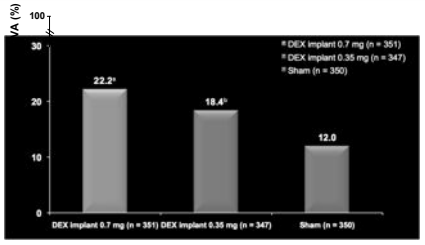


[a] FDA-approved dose.
[b] Every 1.5 months from month 6 to month 12.
[c] Eligibility criteria for retreatment: residual retinal edema (CRT > 175 µm).

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

Primary Outcome Measure: ≥ 15-Letter Gain at End of Study

Results After 3 Years

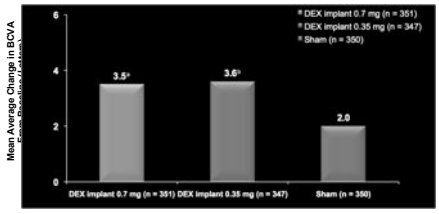


[a]*P* < .001 vs sham. [b]*P* = .018 vs sham.

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

Mean Average Change in BCVA During the Study

Results During the 3-Year Study



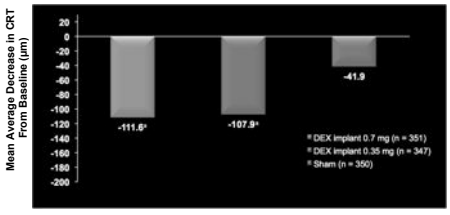
[a]*P* = .023 vs sham. [b]*P* = .019 vs sham.

Results During the 3-Year Study

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

Decrease in Central Subfield Retinal Thickness From Baseline was Significantly Greater With DEX Implant 0.7 mg versus Sham

Decrease From Baseline in Central Subfield Retinal Thickness During Study



[a]*P* < .001 vs sham.

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

Percentage of Phakic Patients With Cataract AEs or Surgery at Any Time During Study

- The incidence of cataract-related AEs increased after the first study year
- Most cataract surgeries were performed between 18 and 30 months

Patients With a Phakic Study Eye at Baseline	Incidence During the Study (%)
Cataract-related AE	
DEX implant 0.7 mg	67.9
DEX implant 0.35 mg	64.1
Sham	20.4
Cataract surgery	
DEX implant 0.7 mg	**59.2**
DEX implant 0.35 mg	52.3
Sham	7.2

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

IOP Safety Parameters in Study Eyes

- Overall, 36% of DEX implant 0.7-mg patients and 5.1% of sham patients had AEs related to elevated IOP or glaucoma during the study

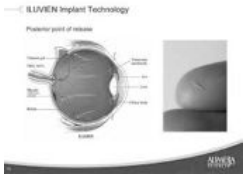
Parameter	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
IOP at any visit during the study, % (n)			
IOP ≥ 25 mm Hg	32.0 (111)	27.4 (94)	4.3 (15)
IOP ≥ 35 mm Hg	6.6 (23)	5.2 (18)	0.9 (3)
Increase of IOP ≥ 10 mm Hg from baseline	27.7 (96)	24.8 (85)	3.7 (13)
Use of IOP-lowering medication, % (n)	41.5 (144)	37.6 (129)	9.1 (32)

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

DEX Implant Provides Rapid and Durable Treatment Benefit in DME

1. Boyer et al. *Ophthalmology*. 2014. doi: 10.1016/j.ophthal.2014.04.024.

MEAD Conclusions



DME Treatment Paradigm

- Focal/grid laser
  - Non-center involved DME with good VA
- Anti-VEGF therapy
  - Center-involved DME with VA loss
- Steroids
  - Pseudophakia
  - Refractory DME

Conclusions

- Type 2 DM is on the rise for all ages.
- Obesity and sleep disordered breathing are among several contributing factors.
- DR is a microvascular disease.
- Traditional treatment of DR works, but…
- With pharmacotherapies, the treatment paradigm is shifting, for the better!

Take Home Message on DM/DR

• Diabetic Retinopathy is exacerbated by many concomitant conditions.

• Control of the systemic aspects of the disease improves both systemic and ocular health.

• Understand how Diabetic Retinopathy relates to the overall systemic health.

Thank you!

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