



Treatment of Diabetic Retinopathy

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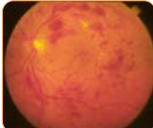

Disclosures

- Off-label use of certain medications will be discussed
- I have no financial disclosures related to this talk



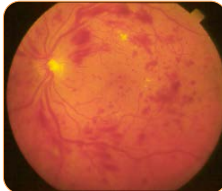

Introduction

- 16 million Americans have diabetes
 - Only 50% know they have the disease
- After 20 years, retinopathy in
 - 99% Type 1
 - 60% Type 2
 - Leading cause of blindness
 - working-age adults
- More common in African and Mexican Americans
- Severity depends on
 - Duration, age, sugar and blood pressure control, lipid levels


Introduction

- 1/3 of diabetic patients
 - Never been examined
- 1/3 who need treatment
 - proliferative diabetic retinopathy
 - clinically significant diabetic macular edema
 - have not seen an ophthalmologist or optometrist within 2 years


Screening Guidelines

- Retinopathy
 - profound implications for vision and quality of life
 - effective treatments are available
 - timely screening is of critical importance
- The American Academy of Ophthalmology:
 - Type 1 Diabetics
 - screening 5 years after diagnosis, and yearly thereafter
 - Type 2 Diabetics
 - yearly screening starting at the time of diagnosis



Screening

- Initial intensive systemic treatment
 - may worsen retinopathy, need close follow up
- Pregnancy
 - women should be seen prior to conception
 - early in the first trimester



Symptoms

- Blurred vision
- Distortion
- Difficulty with night vision or reading
- Floaters



Etiology

- Diabetes is a microvascular disease
 - Heart, kidneys, brain, peripheral nerves, eye
- Retina has small arterioles and venules that are affected
- Damage to the small vessels leads to
 - leakage, bleeding, and new abnormal blood vessel formation



Etiology

- Precise cause unknown
 - Decompensation of vascular endothelium, pericytes implicated
 - Growth factors (VEGF, TNF) and cytokines play a role
 - Inflammation implicated



Classification of Retinopathy

National Eye Institute in the 1970's and 1980's established these grading systems

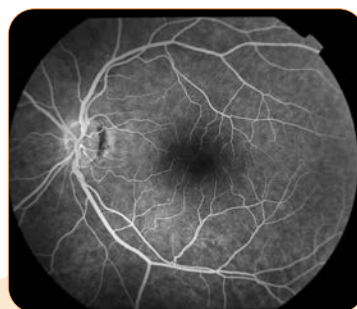
- Non-proliferative (background) diabetic retinopathy (NPDR)
 - early stage
- Proliferative Diabetic Retinopathy (PDR)
 - late stage
- Diabetic macular edema (CSME)
 - May be present at any level



Normal Retina



Normal Angiogram

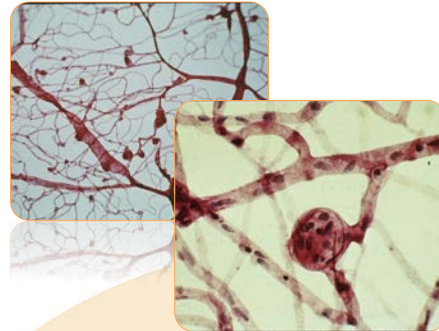


Non-proliferative Diabetic Retinopathy

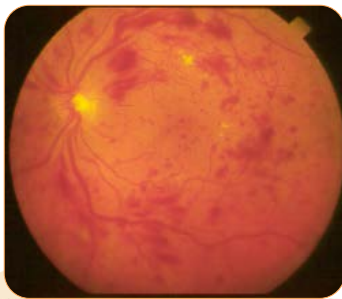
- Characterized by:
 - Dot and blot hemorrhages
 - Microaneurysms
 - Cotton wool spots
 - Venous beading
 - Hard exudates
 - Edema



Microaneurysms



NPDR



NPDR



Very Severe NPDR




NPDR

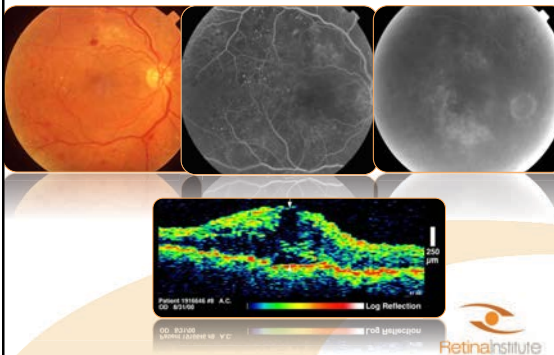

- NPDR affects vision by:
 - Macular Ischemia
 - Lack of oxygen reaching retina
 - Loss of capillaries supplying the fovea
 - Macular edema
 - Leakage causing swelling

Diabetic Macular Edema

- Diabetic macular edema is the **leading cause of vision loss in diabetics**
 - Vessels around the fovea (central vision) leak
 - Leakage seen on fluorescein angiography
 - Increased thickness seen on ocular coherence tomography (OCT)


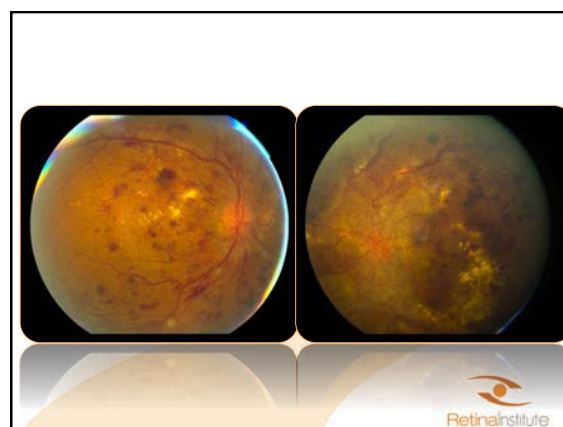
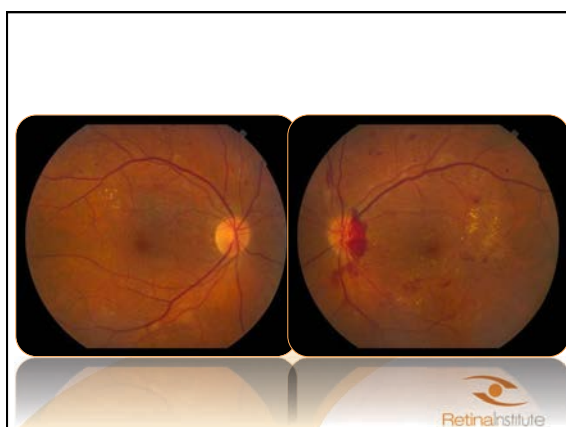


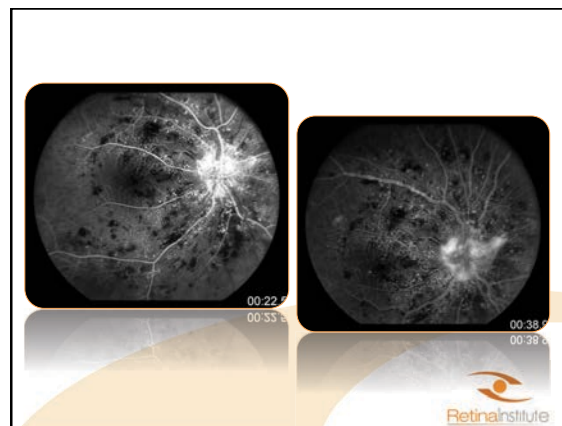
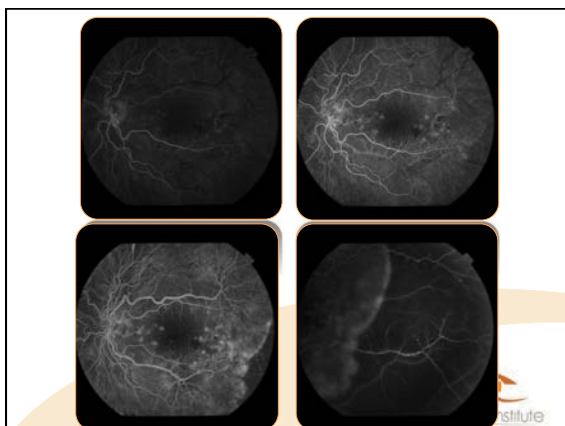
Diabetic Macular Edema

Proliferative Diabetic Retinopathy

- With time, NPDR can progress to PDR:
 - New blood vessel formation
 - On the optic nerve head (NVD)
 - Elsewhere (NVE)
 - Vitreous hemorrhage
 - Tractional retinal detachment



Treatment of Diabetic Retinopathy

- Systemic Treatment of Patient
 - Internist
- Ocular Treatment
 - Ophthalmologist
 - Retina Specialist



Effect of Systemic Conditions on Retinopathy

- Blood sugar control is the **cornerstone** of diabetes management
 - **Diabetes Control and Complications Trial**
 - Randomized, Controlled Trial of Type 1 Diabetes
 - Intensive sugar control reduced both the frequency and severity of retinopathy, nephropathy, and neuropathy
 - Intensive group had a HgbA1c of 7.2% vs. 9.1% in the conventional treatment group
 - During start of intensive treatment, can have initial worsening of retinopathy, needs closer follow up




- **United Kingdom Prospective Diabetes Study**
 - Randomized, controlled trial for Type 2 diabetes
 - Intensive treatment - goal was fasting glucose of 110 mg/dL
 - Conventional control was diet; medications added when symptoms developed or fasting glucose > 270 mg/dL



- Intensive treatment achieved HbA1c of 7.0% vs. 7.9% in conventional group
- **29% reduction** in the need for laser treatment
 - For every **1% point decrease in HbA1c**, there is a **35% decrease** in risk of microvascular complications




- UKPDS also compared tight **blood pressure** control (<150/85) vs. less tight control (<180/105)
 - Tight BP control led to a **35% decrease in laser treatments** and **47% reduced risk of losing 3 lines of visual acuity** at 7.5 years.
- Control of blood pressure also very important




Early Treatment of Diabetic Retinopathy Study

- ETDRS data demonstrate that increase in **plasma lipids** leads to **increase in hard exudate** and this increases risk of acuity loss
 - Control cholesterol levels
- **Aspirin** use has not been shown to be helpful or harmful in retinopathy




American Diabetic Association Guidelines

- Goals:
 - **HbA1c: less than 7%**
 - fasting glucose of less than 120
 - Can modify by patient
 - Young and healthy 6-6.5%
 - Older with higher risk of hypoglycemia 7.5%
 - Blood pressure: systolic less than 130 mm Hg, diastolic < 85 mm Hg
 - Daily exercise and diet management



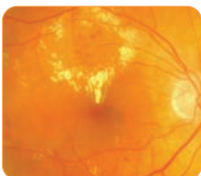

Treatment of NPDR

- Systemic Control
 - Blood sugar
 - Blood pressure
 - Lipid levels
- Ocular Treatments



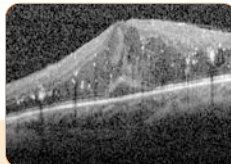

Diabetic Macular Edema

- Difficult to treat
- Most common cause of legal blindness (<20/200) for Americans less than 65 yo

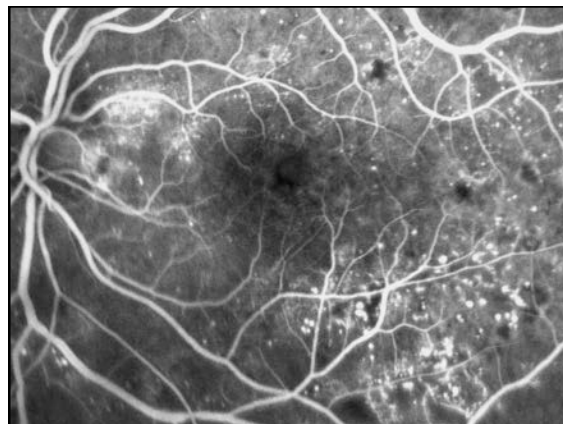
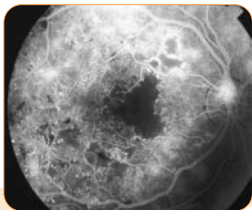
Photoreceptor cell death

- Edema and subretinal fluid
 - prevents flow of oxygen and glucose from choroidal circulation
 - death of photoreceptors
- Integrity of photoreceptor layer as well as ELM more predictive of BCVA than foveal thickness

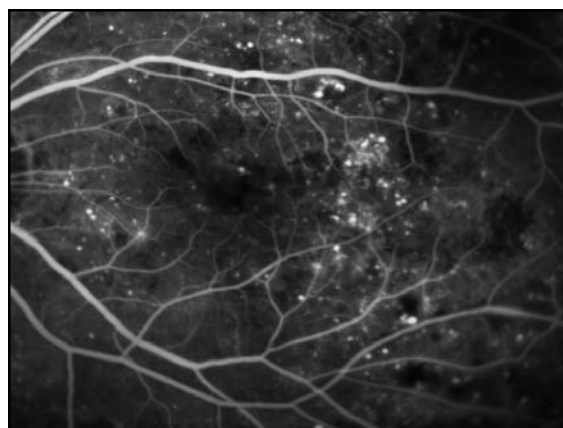
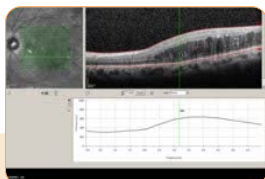
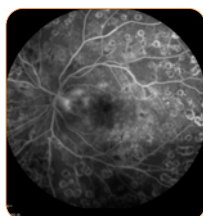



DME complications

- There is a time dependent relation between length of DME and photoreceptor cell death
- This explains why slow resolution of DME can result in decreased vision
- Need Aggressive Treatment, even if vision minimally reduced



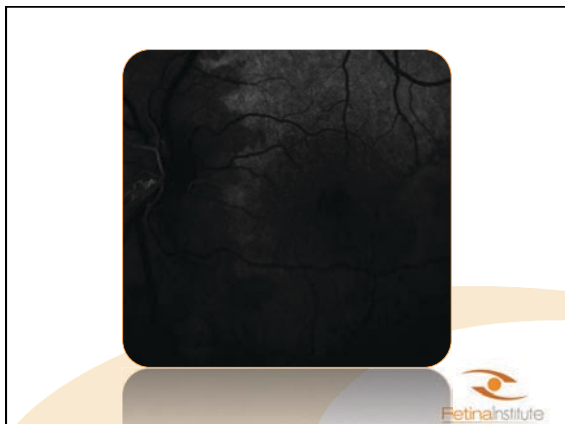
Microaneurysms and DME



Fluorescein Angiography

- Still the **gold standard** in diagnosis
- OCT very good for follow-up exams
- OCT does not replace fluorescein angiography





Treatment for DME

1. Laser - Focal and/or PRP laser
2. Steroids - intravitreal or subtenons
3. Anti-VEGF Agents - antibodies (Avastin/ Lucentis) or VEGF trap (Eylea)
4. Surgery - Vitrectomy to release vitreous or glial traction on the retina

Treatment for DME

- Multiple treatment modalities may improve success
- Especially for advanced cases of DME

Focal Laser for CSME

- **Early Treatment of Diabetic Retinopathy Study**
 - Purpose of treatment is to slow the rate of vision loss
 - Use argon laser to photocoagulate leaking microaneurysms
 - Treatment decreases severe vision loss by 50%
 - Some had modest visual improvement

CSME

(1) Any retinal edema within 500 μm of the center of the fovea

(2) Hard exudates within 500 μm of the center of the fovea if associated with adjacent areas of retinal thickening

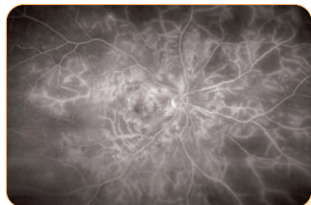
(3) Retinal edema >1 disc area in size and within 1 disc diameter of the center of the fovea

Focal laser complications

- Paracentral scotomata
- Loss central vision
- Decreased color vision

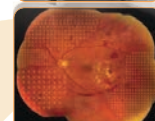
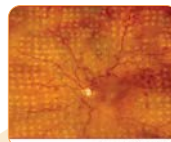
PRP for DME

- Addresses peripheral retinal ischemia which causes elevated VEGF
 - PRP can cause resolution of DME as seen in cases of florid PDR
- VEGF levels related to DME



Advances in Laser - PASCAL

- PASCAL multispot laser
- semi-automated laser



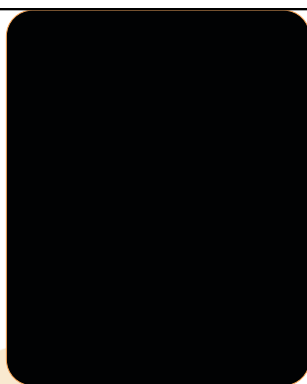
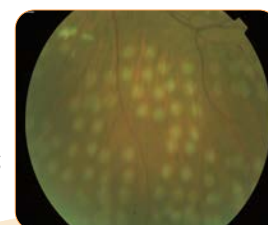
PASCAL Advantages

- Less pain
 - decreased thermal diffusion into the choroid
- Reduced energy per laser shot (1/5) as pulse duration 20 millisecc PASCAL vs. 200 milliseconds
- Reduced expansion of laser spot (430 microns versus 310 microns at 3 mos when using 200 micron laser spot). Study with 60 pts comparing eyes same patient



PASCAL LASER

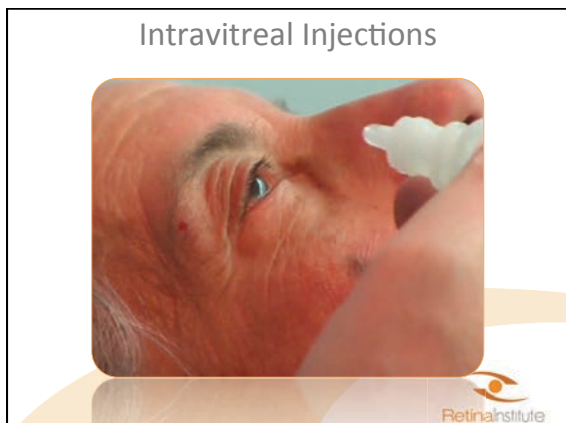
- Greater uniformity and less visual field loss sensitivity using HVF 30-2
- Less Losses in night vision
- 3X less time consuming for the patient



Micropulse Laser Treatment

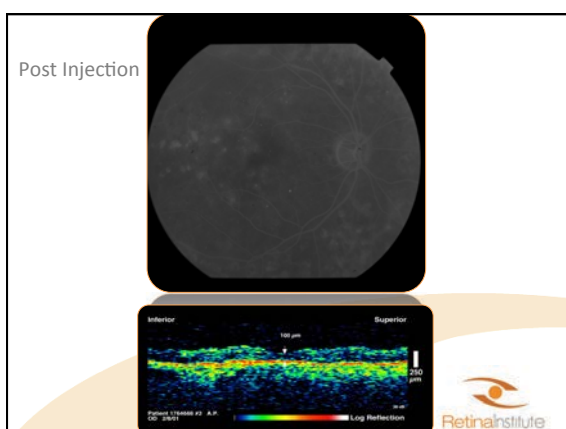
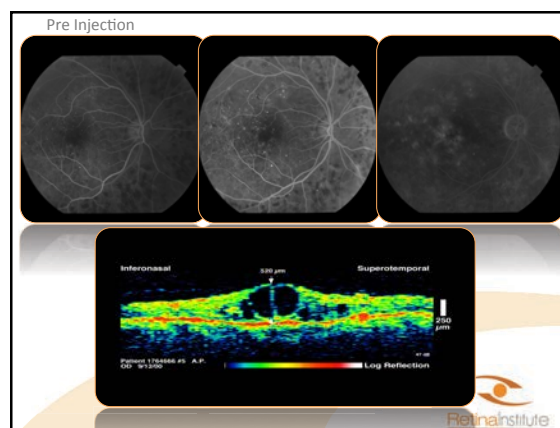
- 810 nm Subthreshold Micropulse diode laser
- Subthreshold: not visible on slit lamp biomicroscopy exam or on the FA
- Case reports have shown success in DME cases resistant to anti-VEGF injections and conventional focal laser






Intravitreal Kenalog Injection

- Steroid injection to reduce edema
 - Acts by reducing cytokines and inflammation
 - Impressive results in patients refractory to laser
 - 90% have improvement of edema
 - 60% have improvement in vision



Ozurdex


- A phase 3, multicenter, masked, randomized, sham-controlled, 3-year trial
- Patients randomized to:
 - Sham (needleless applicator) (n = 328)
 - OZURDEX® (dexamethasone intravitreal implant) 0.7 mg (n = 328)
- Specified treatment interval: no more than approximately every 6 months
- Evaluations performed at baseline, every 45 days during year 1, and every 3 months during years 2 and 3

Ozurdex 

**All Randomized Patients:
Visual Acuity Outcomes at Month 39¹**


Measurement	OZURDEX® (n = 328)	Sham (n = 328)	Estimated difference (95% confidence interval) [CI]
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	19.5% (64)	10.7% (35)	8.8% (3.4%, 14.3%)
Patients losing ≥ 15 letters in BCVA (n)	13.7% (45)	10.7% (35)	3.0% (-2.0%, 8.1%)
Mean change in BCVA (letters) (SD) ^a	2.2 (15.88)	0.8 (12.72)	1.3 (-0.9, 3.4)

^aStandard deviation.



Iluvien®

- ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg
- Approved by the FDA (9/26/14)
- Indicated for the treatment of diabetic macular edema (DME)
 - Patients who have been previously treated with a course of corticosteroids
 - AND did not have a clinically significant rise in intraocular pressure.



Iluvien®



- Intravitreal implant of fluocinolone acetonide
- First DME treatment to deliver 36 months of continuous, low-dose corticosteroid with a single injection



RetinaInstitute



Avastin for DME

- Reports estimate effects last up to 6 weeks
- Multiple treatments needed
- Quickly becoming a very popular treatment for center involved DME


Anti-VEGF treatments: Lucentis

- READ results at 6 mos showed lucentis alone (22% 3 line improvement 6 mos tx period) to improve vision more than focal laser or combined treatment(8%)
- READ study 2 yr preliminary results show about half as many injections needed when laser done in combined approach

DRCR

- Lucentis/prompt focal laser
 - 2x as effective when assessing improvements vs. laser alone
 - 30% vs. 15% in producing 3 lines of vision gain
 - 50% vs 28% at least 2 lines improvement
 - 3x less likely to lose 2 lines vision than laser alone or kenalog plus prompt focal laser
 - 4% vs. 13%, 14% for 2 line vision loss



DaVinci Study: VEGF TRAP Phase II results

- Monthly injections superior to bi-monthly injections
 - 2mg each month did better than 2mg monthly for 3 months and then every 2 months or prn arms
- Higher dosing of medicine more effective .5mg versus 2mg



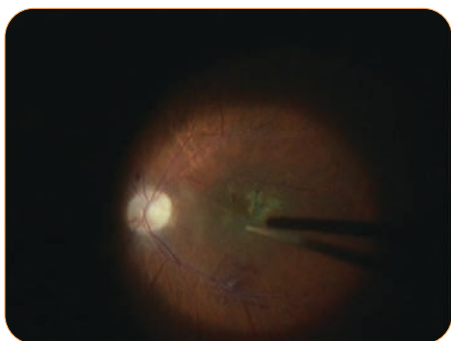
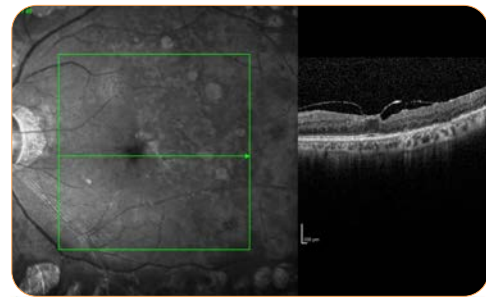
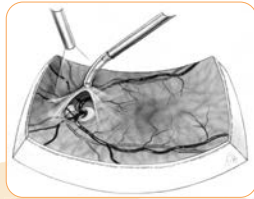
DRCR Protocol T

- Bevacizumab vs Ranibizumab vs Afibercept in treatment of DME
- Results:
 - All 3 are effective at treating DME
 - When visual loss is mild, no significant difference at 1 year of treatment
 - With worse presenting vision, aflibercept more effective than other 2 at improving vision

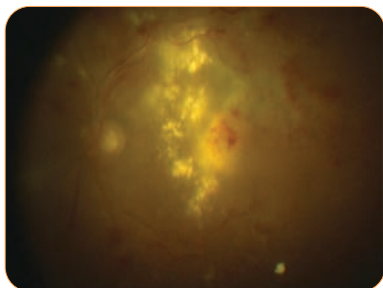


Vitrectomy for DME

- There have been several small randomized controlled clinical trials examining vitrectomy for DME and none have shown a significant benefit
- Limit to cases where there is clinical or OCT findings of VMT

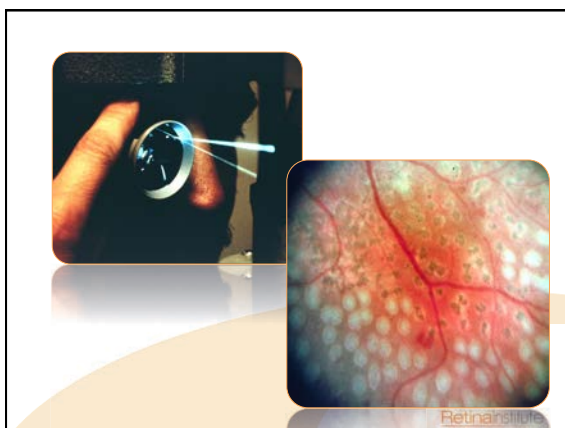


Resection of Lipid in Fovea



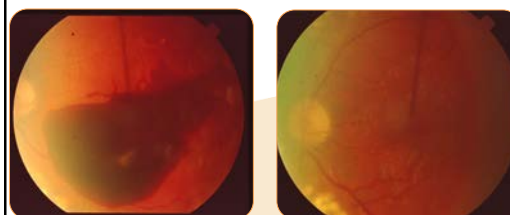
Treatment of PDR

- Panretinal laser photocoagulation
 - Apply laser to entire midperipheral fundus
 - Works by decreasing Growth Factors
 - Reduces risk of severe vision loss by 50%
 - Complications usually mild
 - transient discomfort
 - decreased night vision
 - decreased peripheral vision



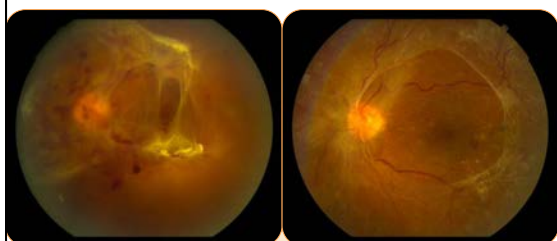
Surgery

- Vitreous hemorrhage
 - Neovascularization may bleed into vitreous
 - May clear spontaneously over 2 to 3 months
 - If persists, can surgically remove blood and abnormal membranes, apply laser/steroids

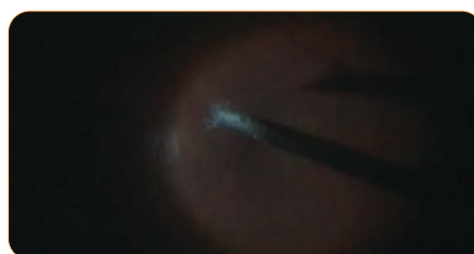


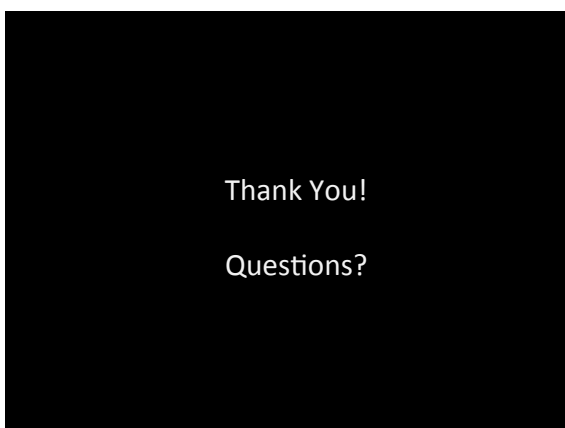
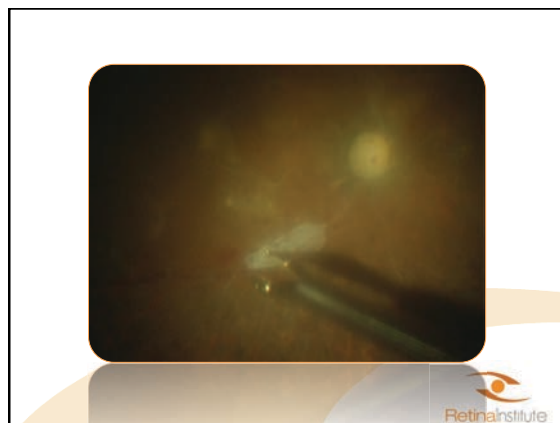
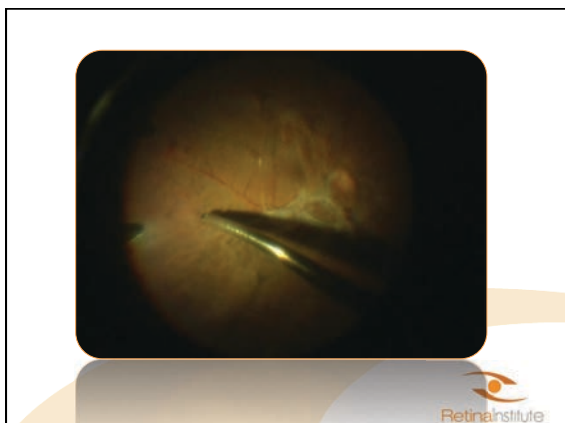
Surgery

- Traction Retinal Detachment
 - New vessels
 - Pull on retina causing detachment
 - Surgically remove the membranes
 - relieve traction
 - apply laser to decrease stimulus for further membrane formation



Vitrectomy for Diabetes





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