Diabetes Mellitus
Diabetic Retinopathy

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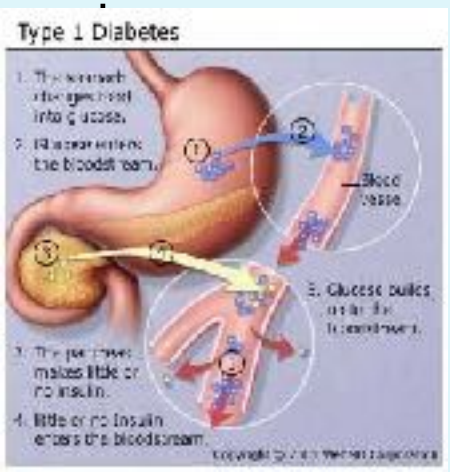
David A. Faris, M.D.
1219 Johnson Avenue
Bridgeport, West Virginia

Diabetes Mellitus

- Type I
  - Previously called “juvenile-onset diabetes” or “insulin-dependent diabetes”
  - Often begins in childhood
  - An autoimmune condition – the body attacks its own pancreas (beta cells) with antibodies
  - The damaged pancreas doesn’t make insulin
  - Often genetic – otherwise, cause is
  - Treatment with insulin

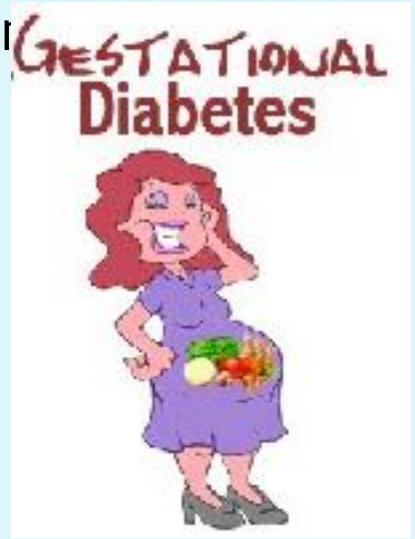


Diabetes Mellitus

- Type II
  - Previously called “adult-onset diabetes” or “non-insulin-dependent diabetes”
  - With obese/overweight/inactive children, more teens are now developing Type II DM
  - Often milder than Type I
  - Two scenarios – the pancreas produces an inadequate amount of insulin, or the body’s cells are resistant to the insulin
  - Causes – often obesity & inadequate exer

Diabetes Mellitus

- Gestational Diabetes
  - Triggered by pregnancy – with no previous history of DM
  - 2 – 10% of pregnancies
  - Usually resolves after pregnancy
  - 10% of women with gestational diabetes later develop Type II DM
  - Risk to mother – damage to heart, kidney, r
  - There are risks for the fetus
    - Abnormal weight gain before birth
    - Breathing problems at birth
    - Higher obesity/diabetes risk later in life



“Normal” Blood Glucose Levels

- Fasting (8 hours after eating)
  - <100 milligram/deciliter (mg/dl)
- Postprandial (2 hrs) –
  - <140 mg/dl – age 50 and younger
  - <150 mg/dl – ages 50 -60
  - <160 mg/dl – age 60 and older
- Random – 80 – 120 mg/dl

Hemoglobin A1c

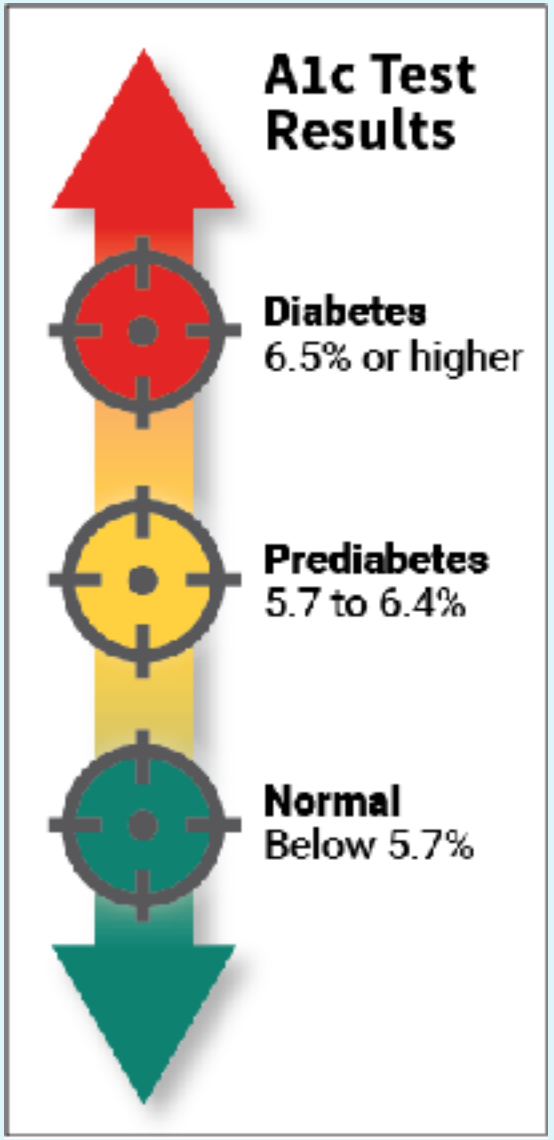
- Blood glucose binds to hemoglobin
- HbA1c (glycated hemoglobin or glycohemoglobin) measures how much glucose is bound – reflects past 3 months (because RBC's life span is about 4 months)
- 4.0% to 5.6% - Normal
- 5.7% to 6.4% - Pre-diabetic
- 6.5% - Diabetes
- ADA recommends < 7.0%
- Test every 3 months & no less that 2X/year

Blood Glucose - Diabetes

- Two consecutive fasting blood glucose tests >126 mg/dl
- Any random blood glucose >200mg/dl
- Any A1c > 6.5

A1c and Blood Sugar

A1c (%)	Average Blood Sugar (mg/dL)
4	68
5	97
6	126
7	152
8	183
9	212
10	240
11	269
12	298
13	326
14	355



Diabetes Mellitus Symptoms

- Frequent urination (polyuria)
- Increase thirst (polydipsia)
- Increased hunger (polyphagia)
- Weight loss
- Less often – blurry vision, headache, fatigue, itchy skin/skin rashes (diabetic dermadromes)
- Symptoms develop more rapidly with Type I and much more slowly, or subtle, or absent, with Type II

Diabetes Mellitus Treatment/Prevention

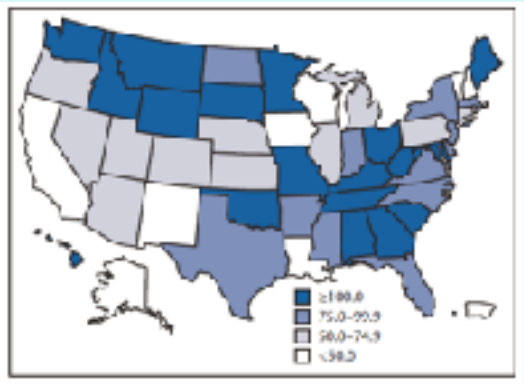
- Blood glucose levels - monitoring
- Hemoglobin A1c monitoring
- Healthy diet
- Daily exercise
- Normal body weight
- Avoid use of tobacco
- Control blood pressure
- Control BG - (Sometimes) taking insulin (Type I or II) or other oral hypoglycemic agents (Type II)
- Treat hyperlipidemia

Diabetes Mellitus
Primary Prevention

- For each 1% reduction in A1c
  - Reduction in all risks from DM -21%
  - Reduction in deaths -21%
  - Reduction in myocardial infarctions -14%
  - Reduction in all microvascular comp. -37%
- Improvements in glycemic control between 1998 & 2010 have leveled off
- Median HbA1c – 6.9%
- 1 in 7 with DM have HbA1c > 9%

Diabetes Mellitus Epidemiology

- 1985 – 30 million (worldwide)
- 2015 – 415 million (8.3% of population)
- 2015 – 30.3 million in US (9.4% of population)
- 2017 – 451 million (triple since 2000)
- (2045 – 693 million – if current trends continue)
- 90% - Type 2
- Men:women – same
- DM doubles a person's risk of early death
- Global costs estimated at $850 billion/year



Diabetes Mellitus
Races at Higher Risk

- African American
- Hispanic
- Native Alaskan
- American Indian
- Pacific Islander
- Asian

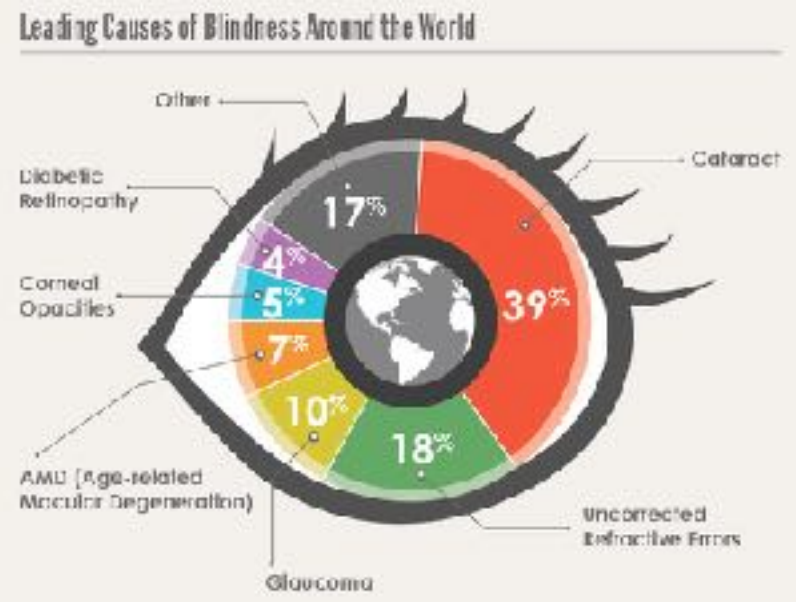
Diabetic Eye Disease

- Diabetic Retinopathy (DR) – the most common cause of vision loss among people with diabetes and the leading cause of vision impairment and blindness among working-age adults
- Diabetic Macular Edema (DME) – Secondary to DR – a swelling in the macula
- Cataract – 2-5 times more likely in diabetics

  Also develops at an earlier age
- Glaucoma – double the risk in diabetics

Diabetic Retinopathy
Social Impact

- Contributes 4.6% to the 37 million cases of world blindness (1.7million people)
- **Most common cause of bilateral severe visual loss in working age group in USA**



Diabetic Retinopathy Epidemiology

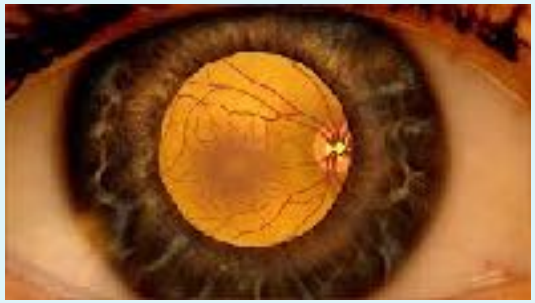
- 33% of all diabetics have DR
- 7.5% of all diabetics have PDR
- DR/DME/PDR higher rate in Type I vs. Type II
- 10% of all diabetics have vision-threatening DR/DME
- Leading cause of vision loss – ages 20-74
- Duration of DM is a risk factor – Almost 100% of Type I will eventually develop DR

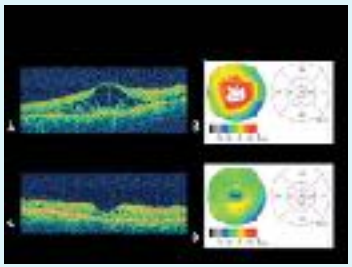
Diabetic Retinopathy Risk Factors

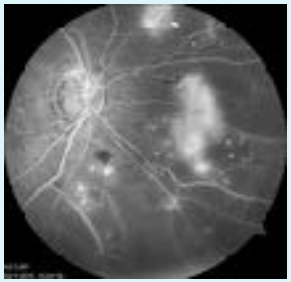
- Diabetes mellitus
- Blood glucose control/HgA1c
- Length of time with DM
  - After 20 years – Type I - 100% - some degree of DR
    of diabetes Type II – 60% - some degree of DR
- Family History
- Pregnancy
- Hypertension
- Hyperlipidemia
- Obesity
- Smoking
- Sedentary lifestyle

Diabetic Retinopathy Diagnosis

- Visual Acuity
- IOP
- (Gonioscopy)
- Dilated fundus
- Photos/OCT/RSFA

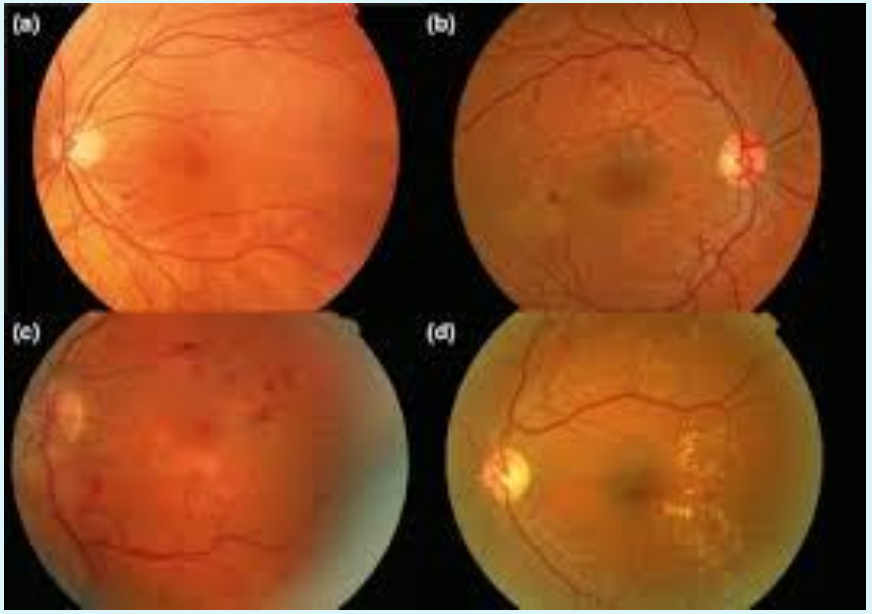






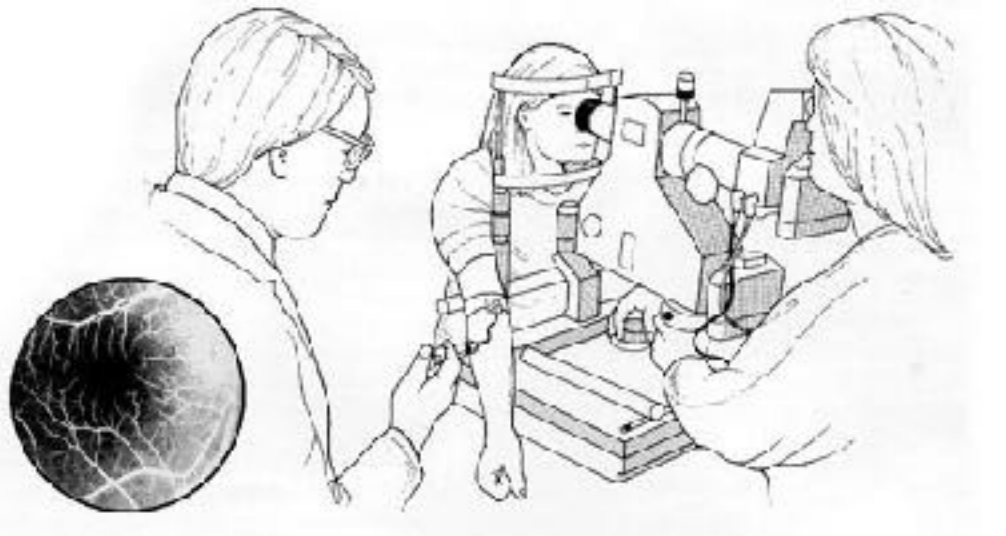
Diabetic Retinopathy Diagnostic

- Fundus Photography



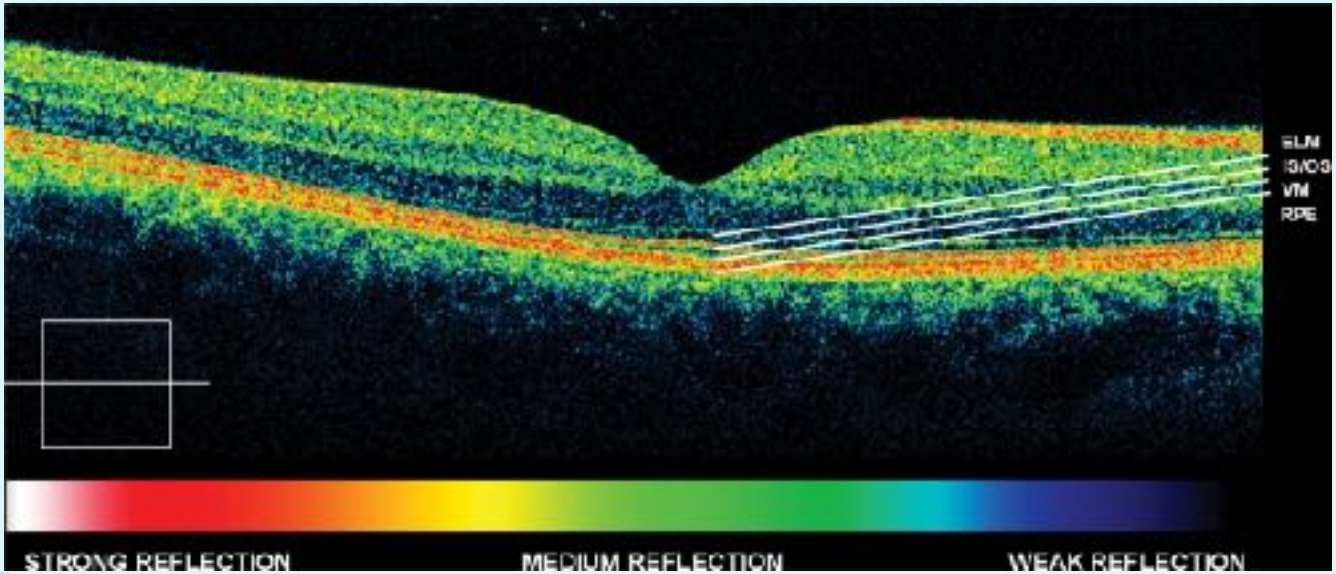
Diabetic Retinopathy Diagnostic

- Fluorescein Angiography (RSFA) – Fluorescein dye in injected into the bloodstream. Within 12-14 seconds, the dye flows through the retinal vasculature



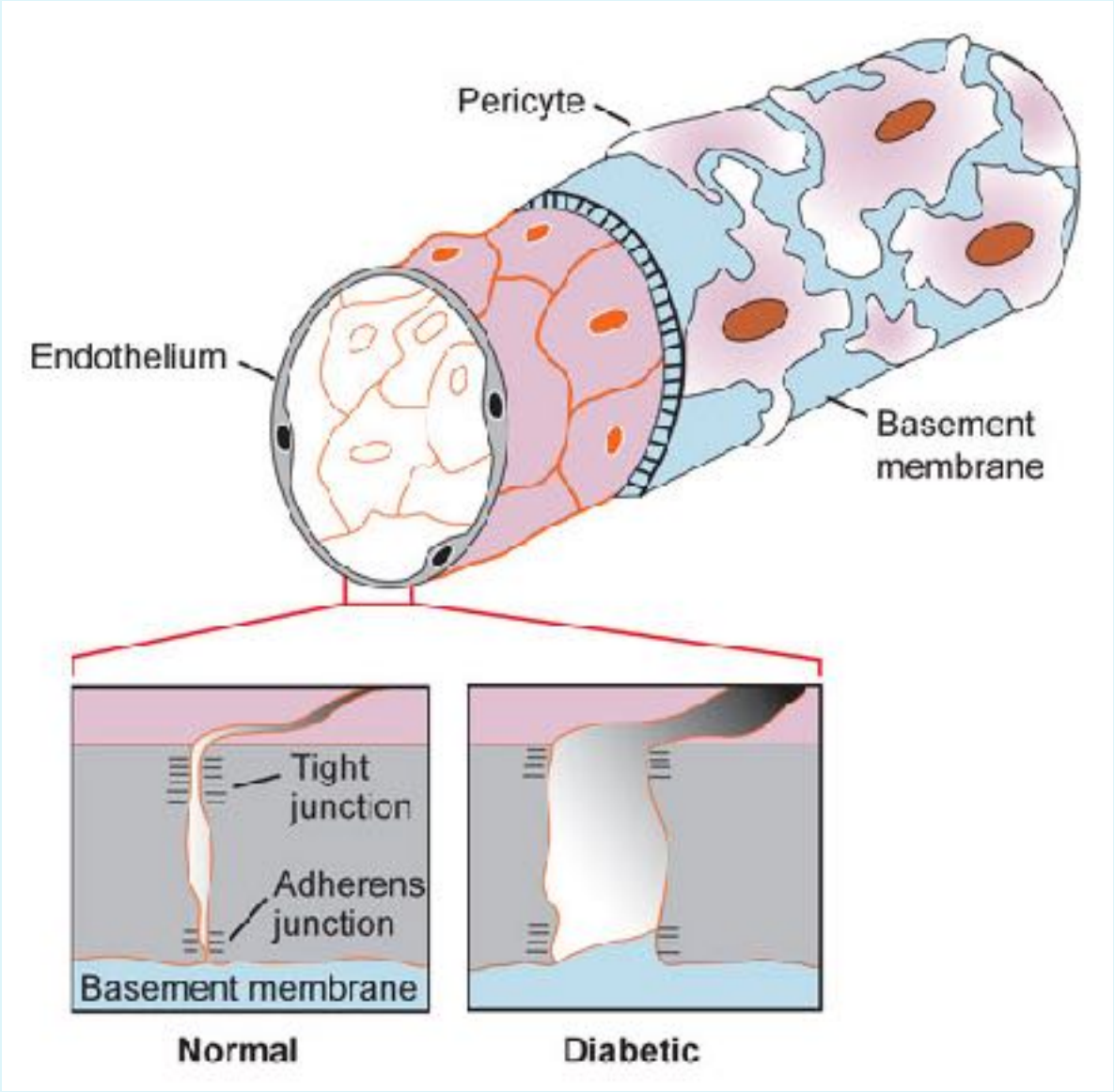
Diabetic Retinopathy Diagnostic

- OCT – Optical Coherence Tomography – light waves used to take a ultrahigh resolution cross-section of tissue – often the macula – so that the distinctive layers can be viewed

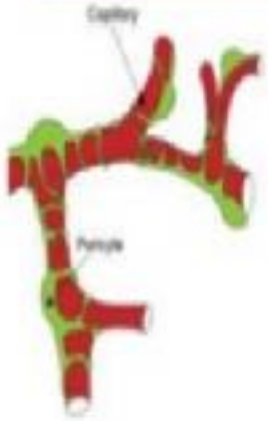


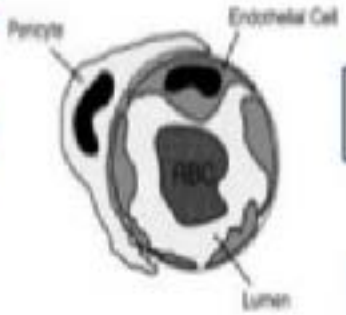
Diabetic Retinopathy

- Progressive dysfunction of the retinal blood vessels – specifically, the retinal capillaries
- Caused (primarily) by chronic hyperglycemia


Pericyte
Endothelium
Basement membrane
Tight junction
Adherens junction
Basement membrane
Normal
Diabetic

Degeneration and loss of pericytes → Capillary wall weakening

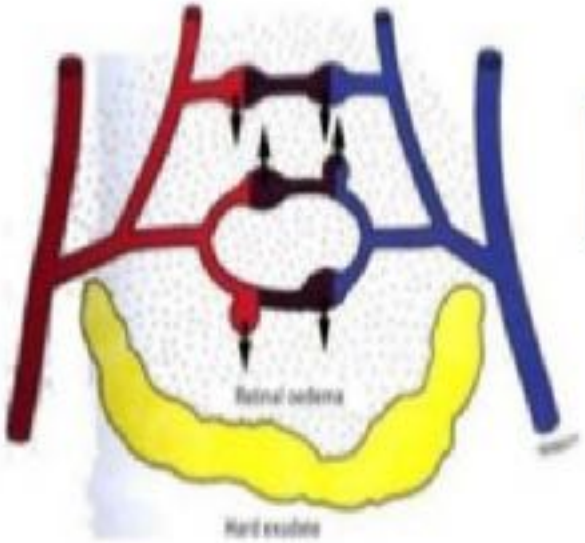




Capillary wall weakening → Plasma leakage → Retinal edema → Hard exudate (Circinate pattern)

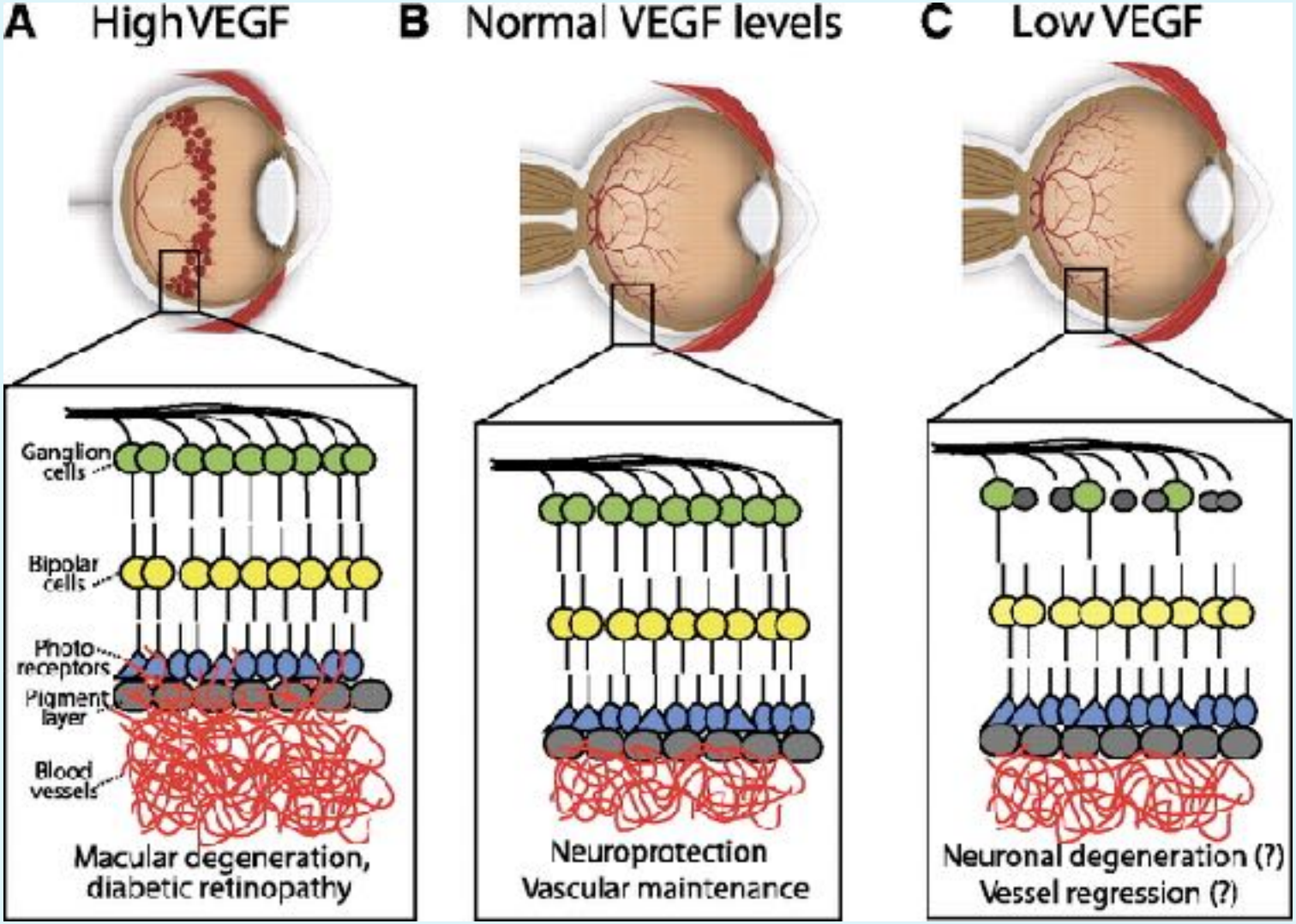
Capillary wall weakening → microaneurysm

microaneurysm → Intraretinal hemorrhage



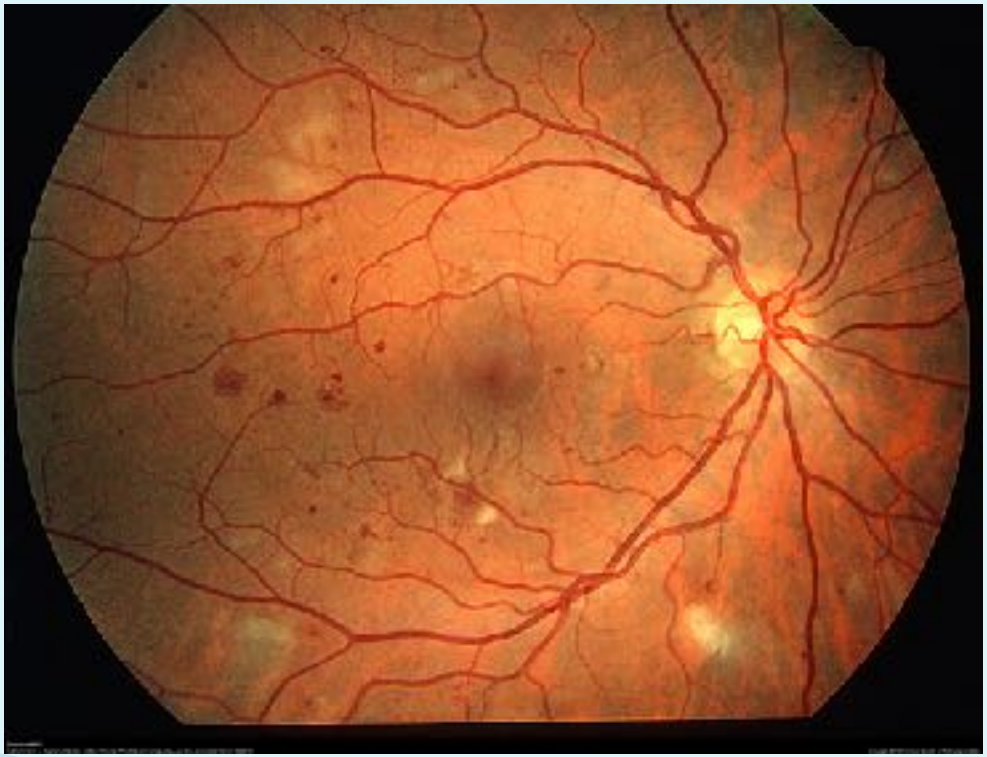
VEGF
Vascular Endothelial Growth Factor

- A signal protein/growth factors
- Produced by cells that stimulate the formation of blood vessels
- Part of the system that restores oxygen supply to tissue when blood circulation is inadequate


A High VEGF
B Normal VEGF levels
C Low VEGF
Ganglion cells
Bipolar cells
Photo receptors
Pigment layer
Blood vessels
Macular degeneration, diabetic retinopathy
Neuroprotection
Vascular maintenance
Neuronal degeneration (?)
Vessel regression (?)

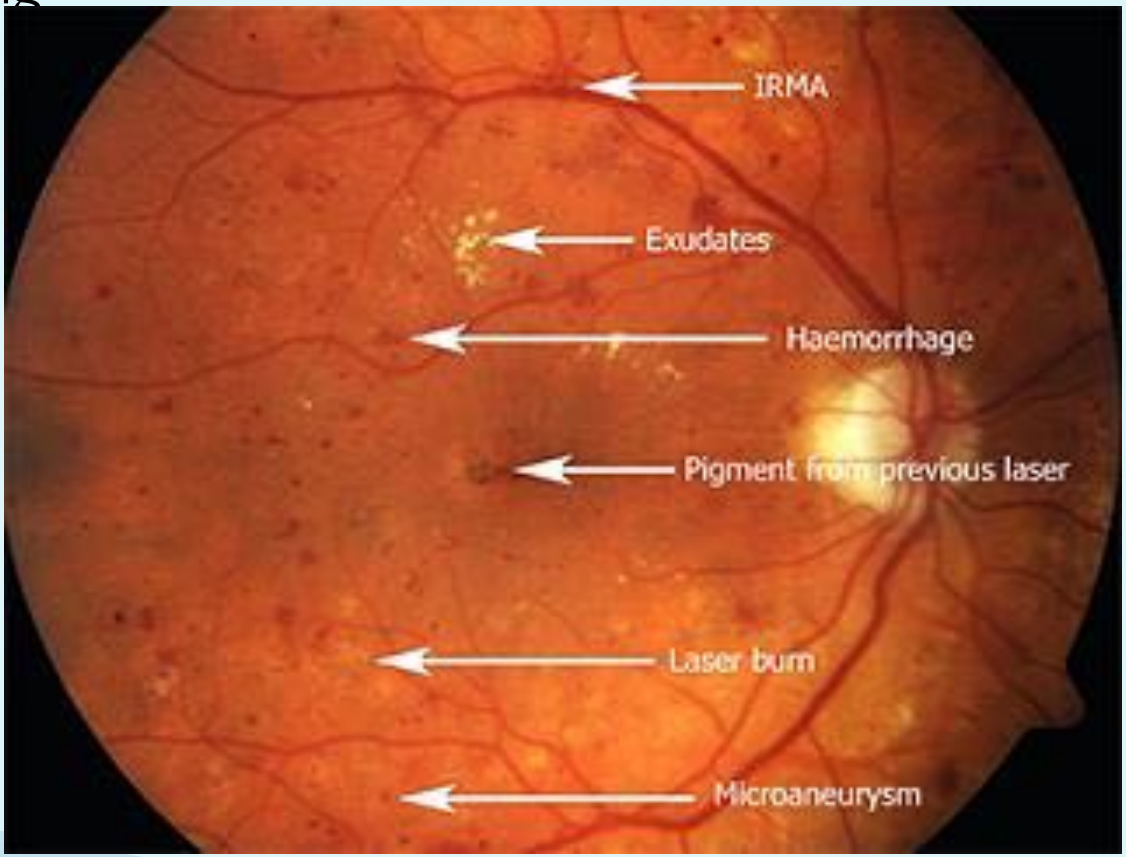
Diabetic Retinopathy Definitions

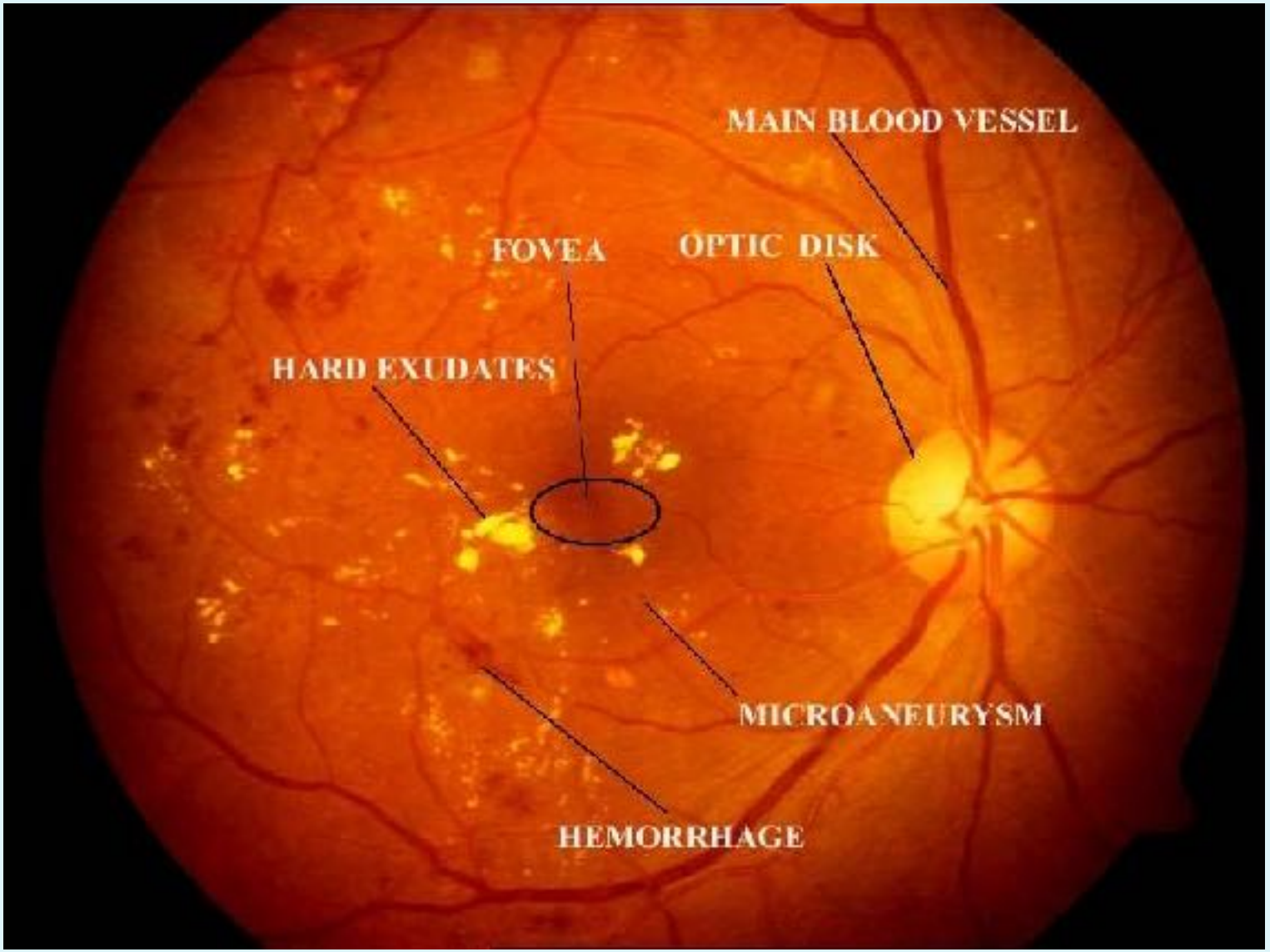
- Non-proliferative Diabetic Retinopathy (NPDR) – formerly known as “background diabetic retinopathy” – the early stage of DR with mild symptoms



Diabetic Retinopathy Definitions (NPDR)

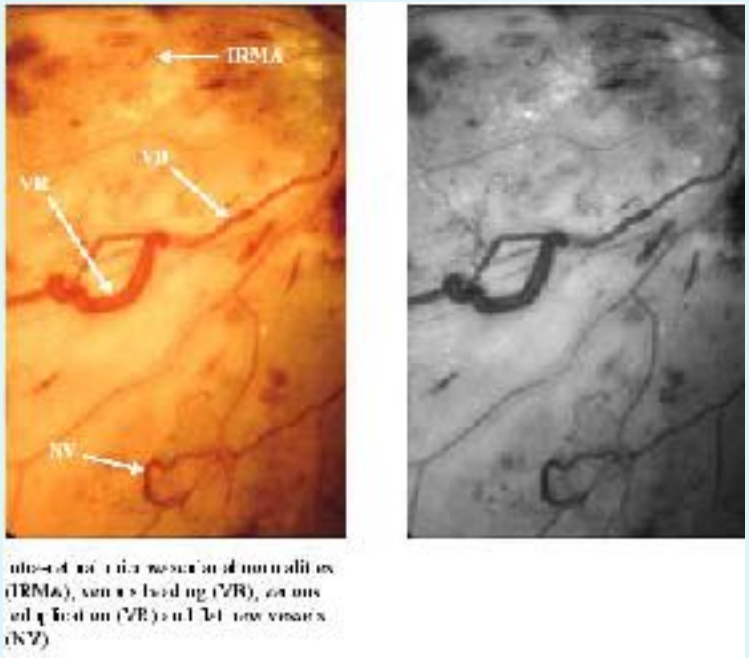
- Microaneurysm MA – small balloon-like swelling in the retinal blood vessels
- Hemorrhages - bleeding
- Exudates – leakage of protein and lipids from the damaged retinal blood vessel




MAIN BLOOD VESSEL
FOVEA
OPTIC DISK
HARD EXUDATES
MICROANEURYSM
HEMORRHAGE

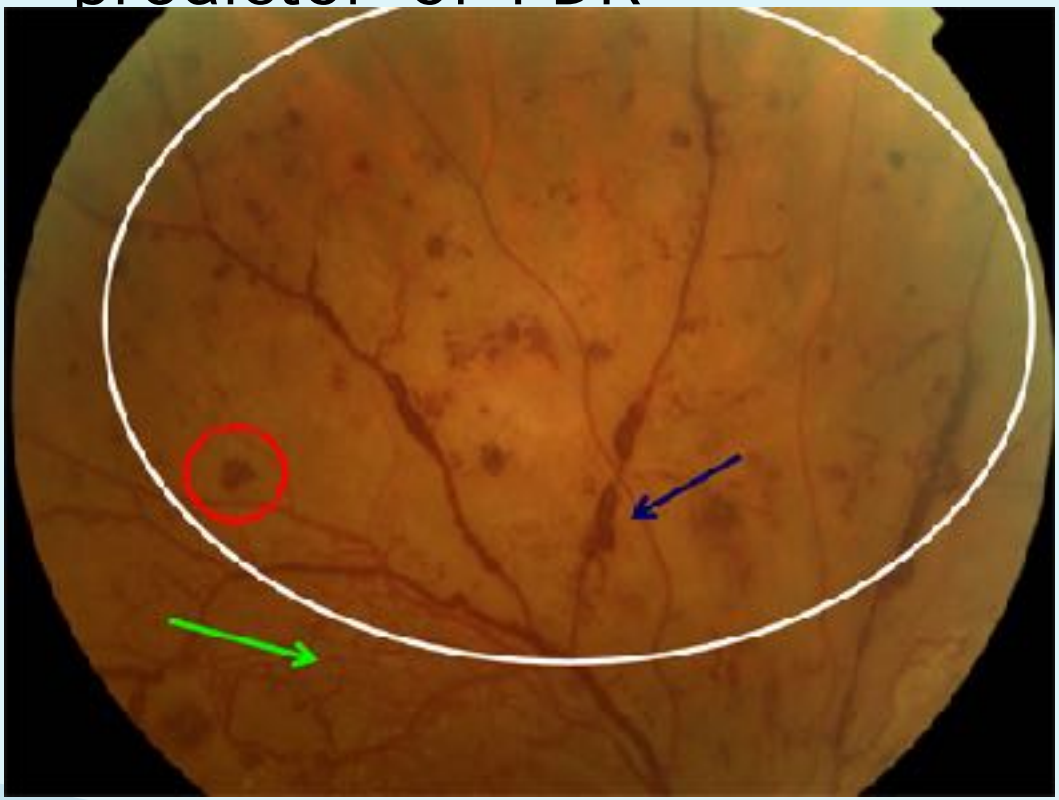
Diabetic Retinopathy Definitions (NPDR)

- Cotton wool spots/soft exudates – fluffy white patches – from damage to the nerve fiber – accumulations of axoplasmic material
- IRMA – IntraRetinal Microvascular Abnormalities – shunt vessels



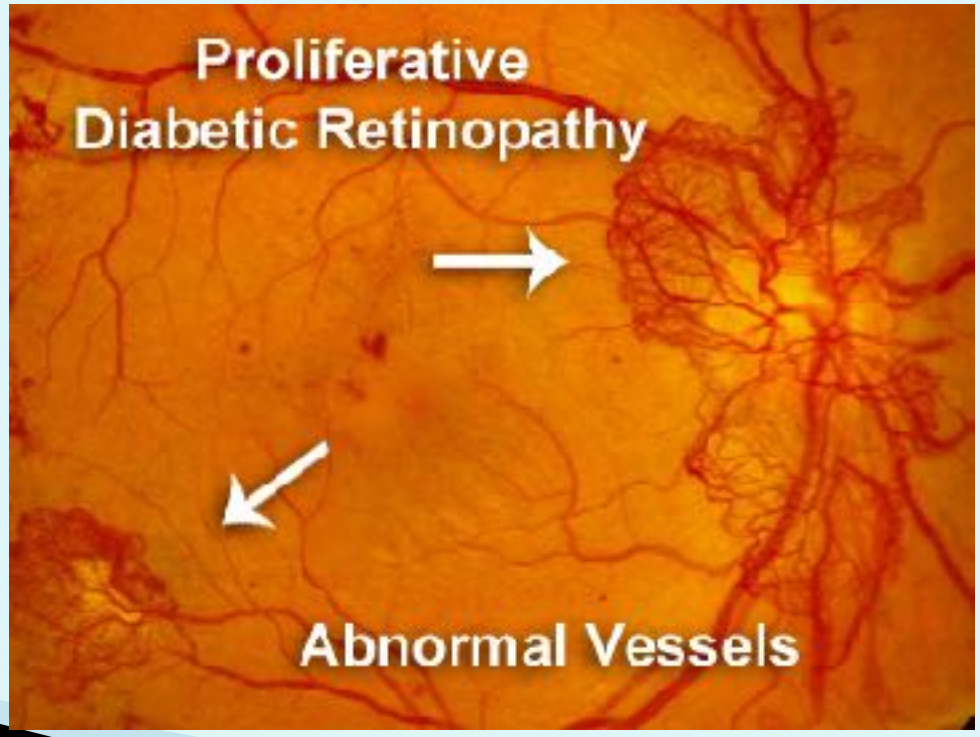
Diabetic Retinopathy Definitions (Advanced NPDR)

- Venous Beading – occur adjacent to areas of retinal non-perfusion – reflect increasing retinal ischemia – predictor of PDR

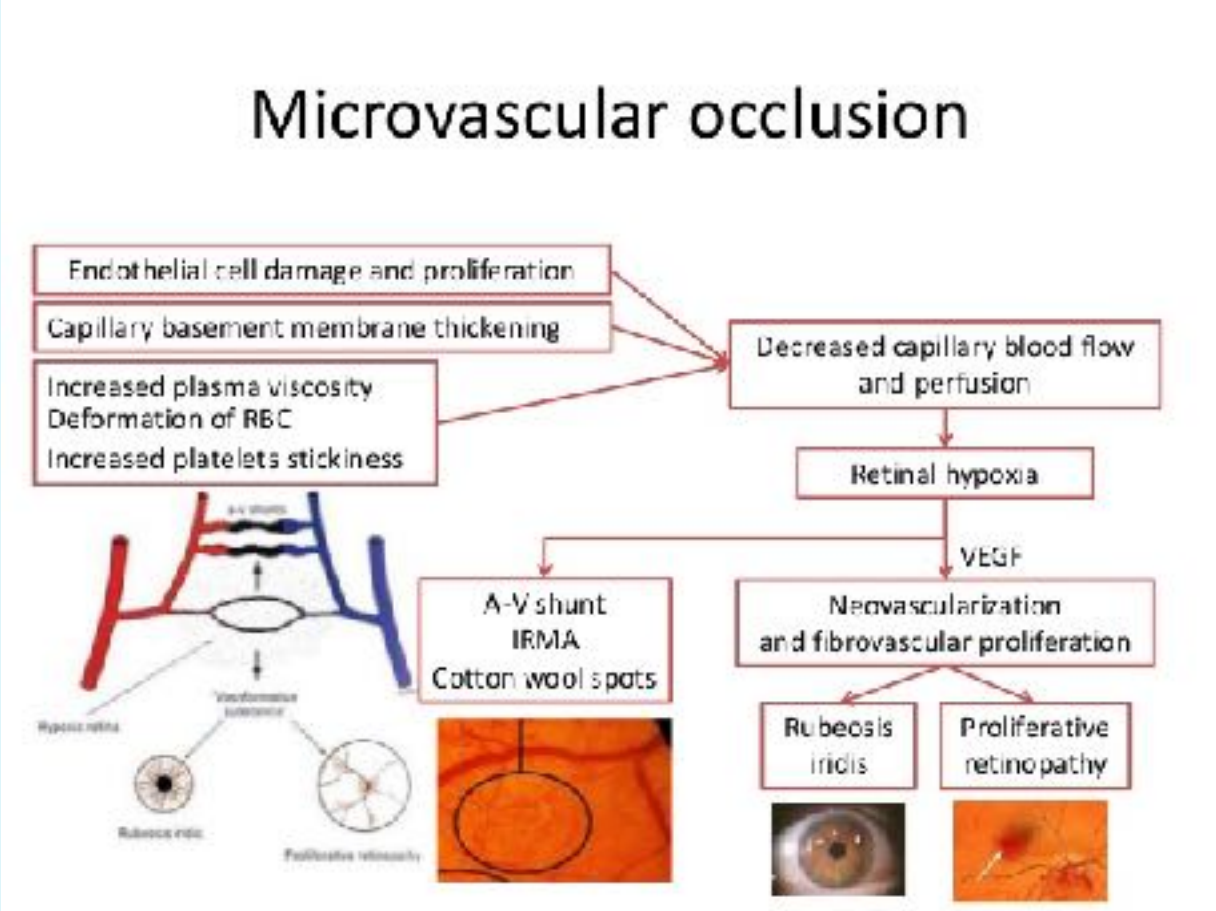


Diabetic Retinopathy Definitions

- Proliferative Diabetic Retinopathy (PDR) – more advanced DR with new & fragile blood vessels which make leak blood



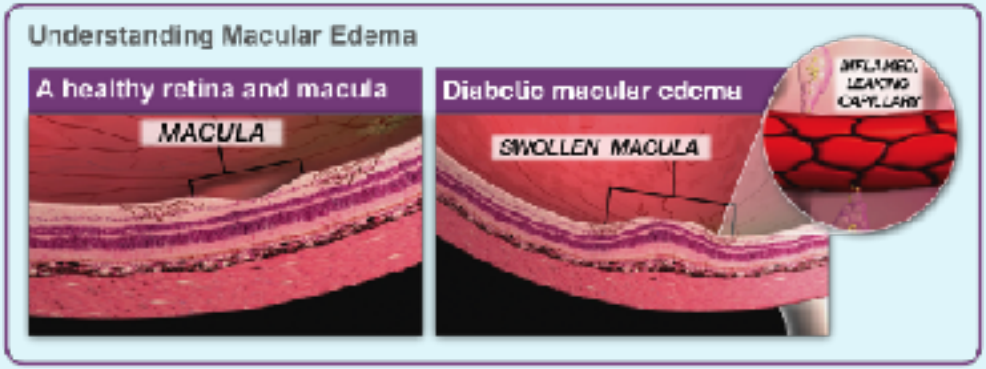
Proliferative Diabetic Retinopathy Pathology

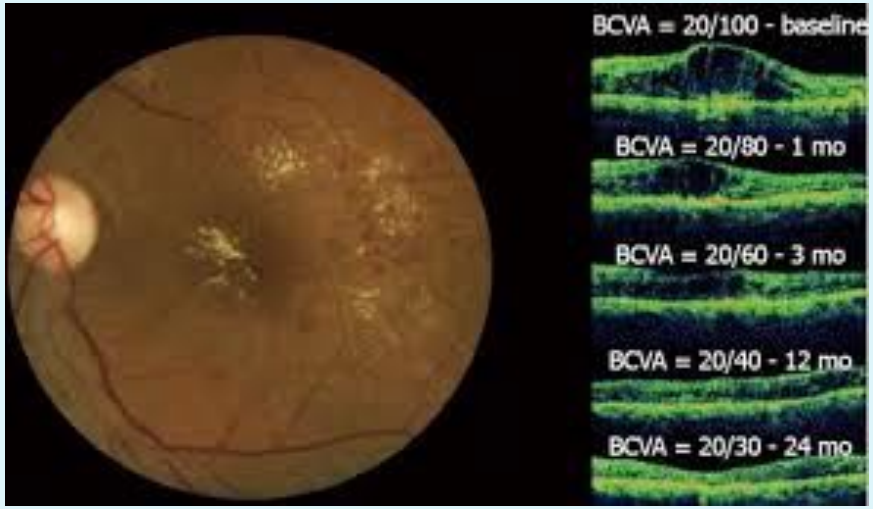


Diabetic Macular Edema

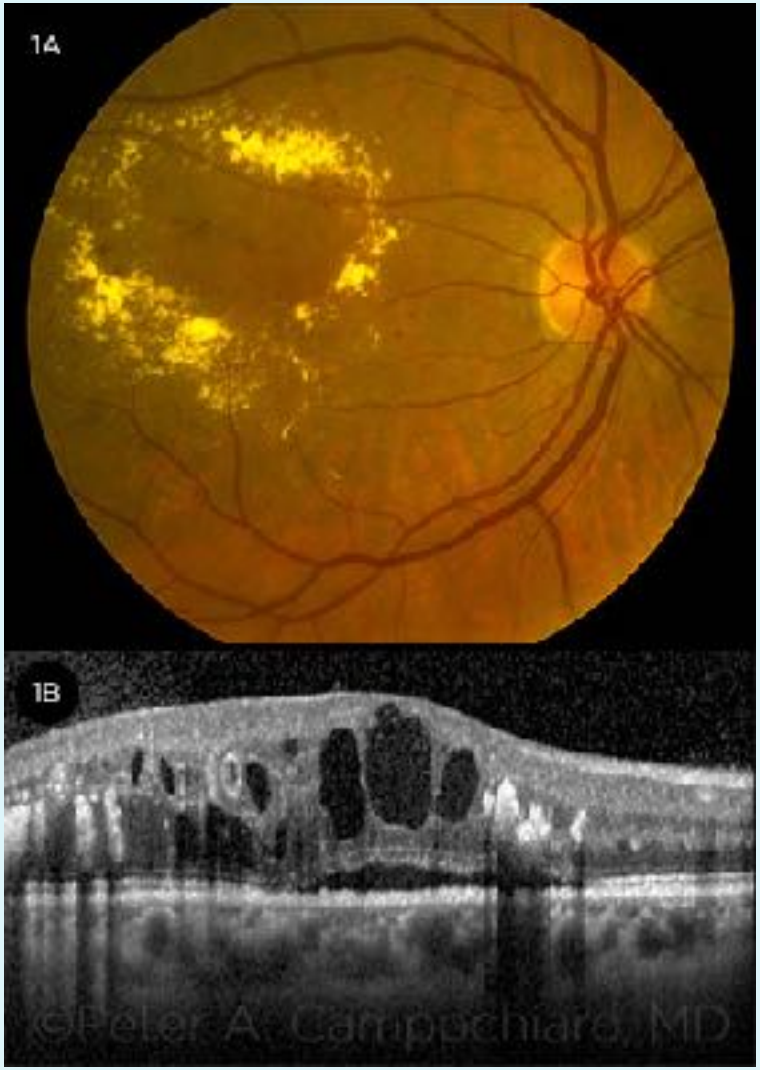
Diabetic Macular Edema

- Damaged retinal vessels leak in 10% of diabetics
- Can occur at any stage of DR

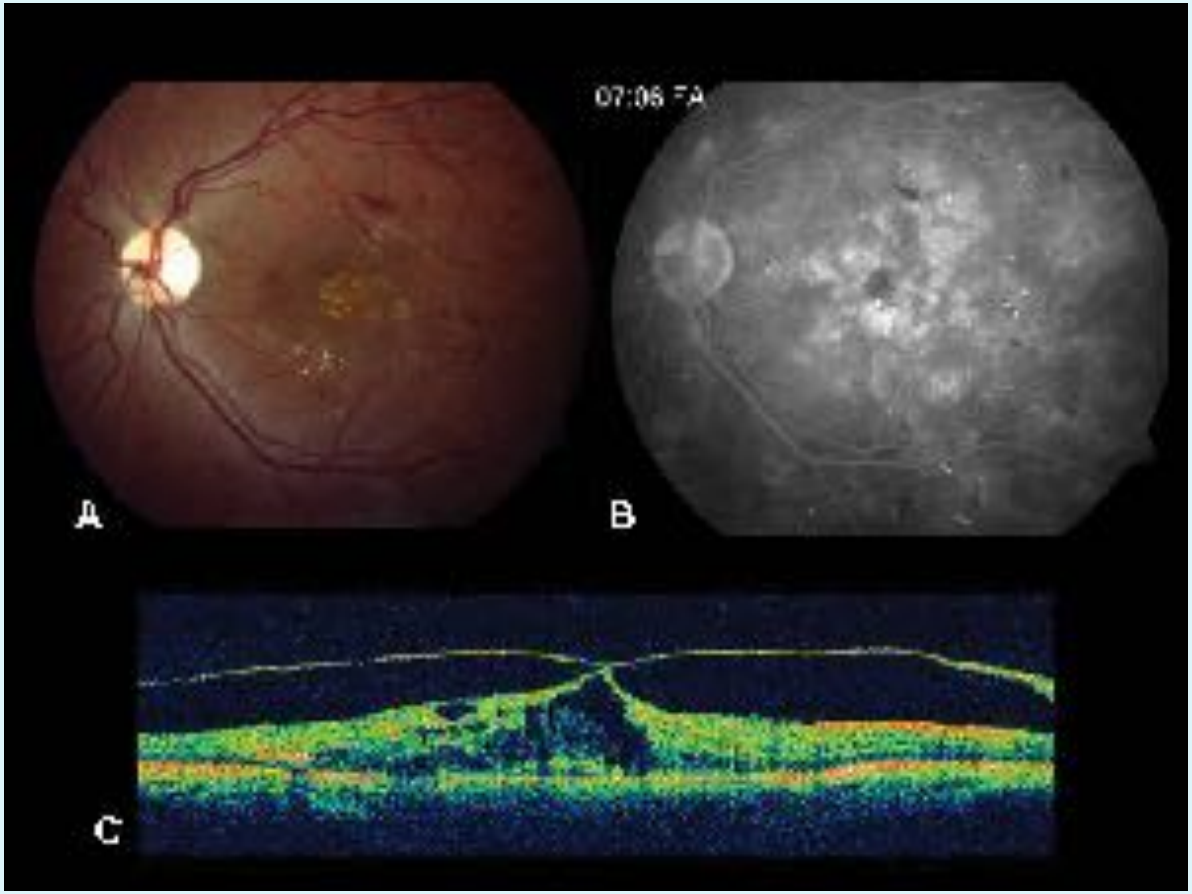




Diabetic Macular Edema - OCT



Diabetic Macular Edema - RSFA



Diabetic Macular Edema

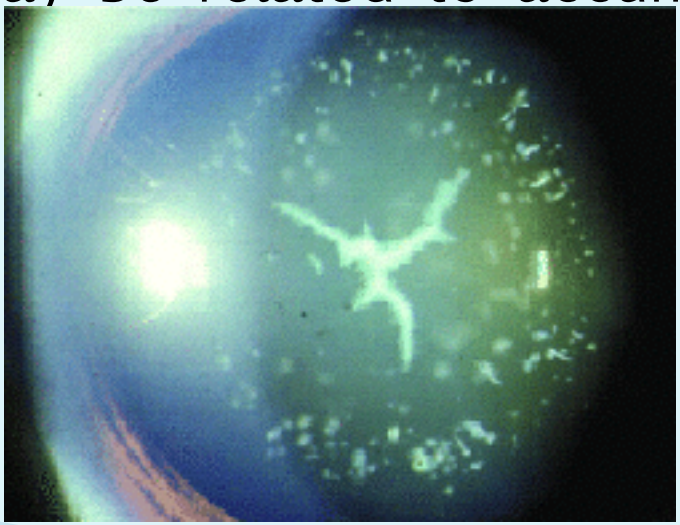
- Blurred vision and darkened or distorted images

Diabetic Retinopathy Classification (ETDRS)

- 1. No Diabetic Retinopathy
  - Blurry vision secondary to BG >200
  - Glucose in eye converted to sorbitol
  - Sorbitol in lens increases osmotic pressure
  - Influx of water into the lens
  - Myopic shift

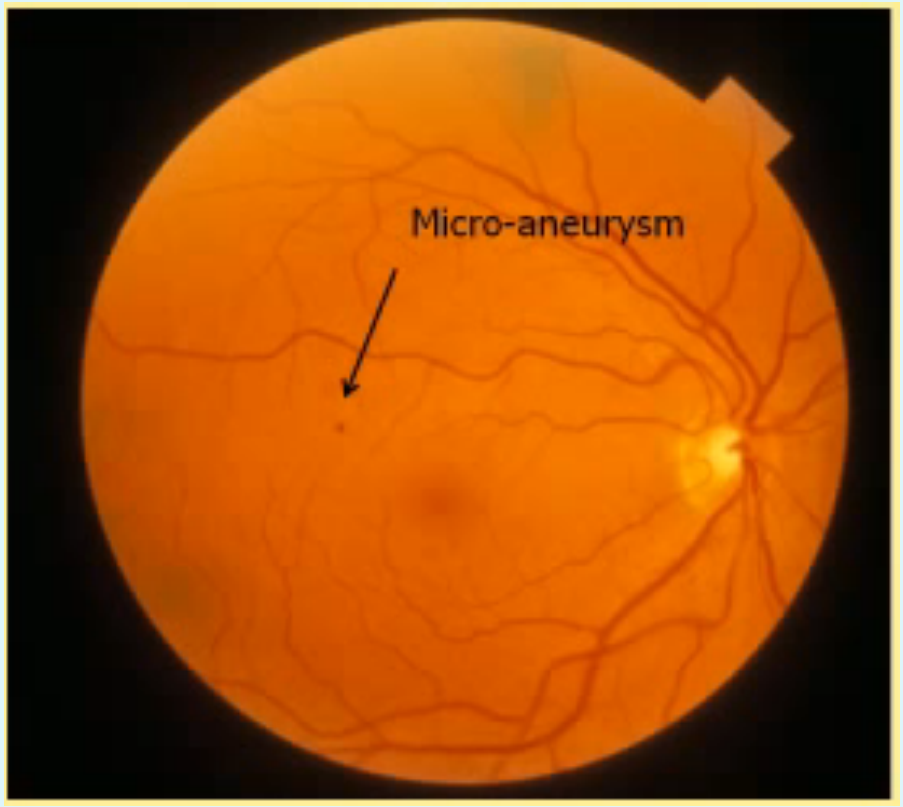
Diabetic Retinopathy Classification (ETDRS)

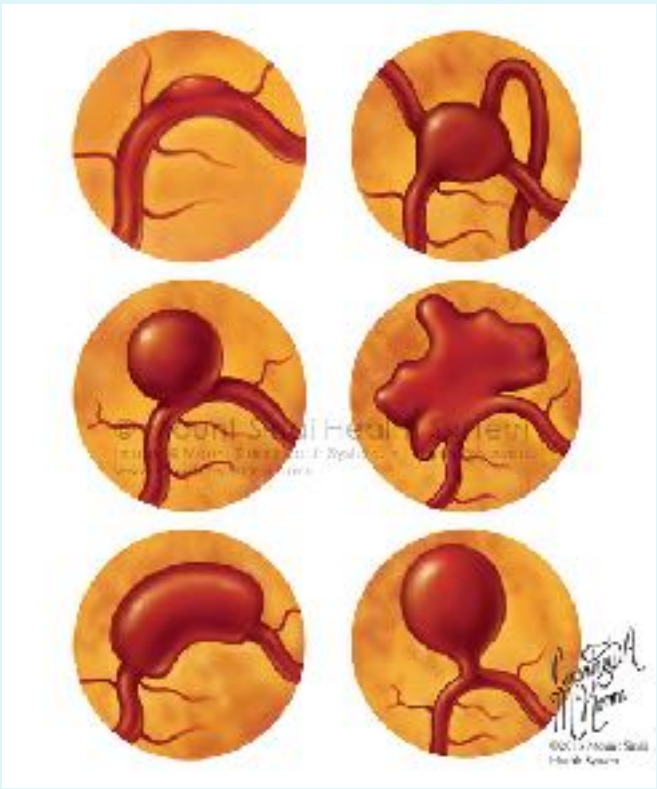
- 1. No Diabetic Retinopathy
  - Cataract – snowflake
  - Typically in young people with uncontrolled DM
  - Normal NSC develop at an earlier age in diabetics
  - May be related to accumulation of sorbitol in lens



Diabetic Retinopathy Classification (ETDRS)

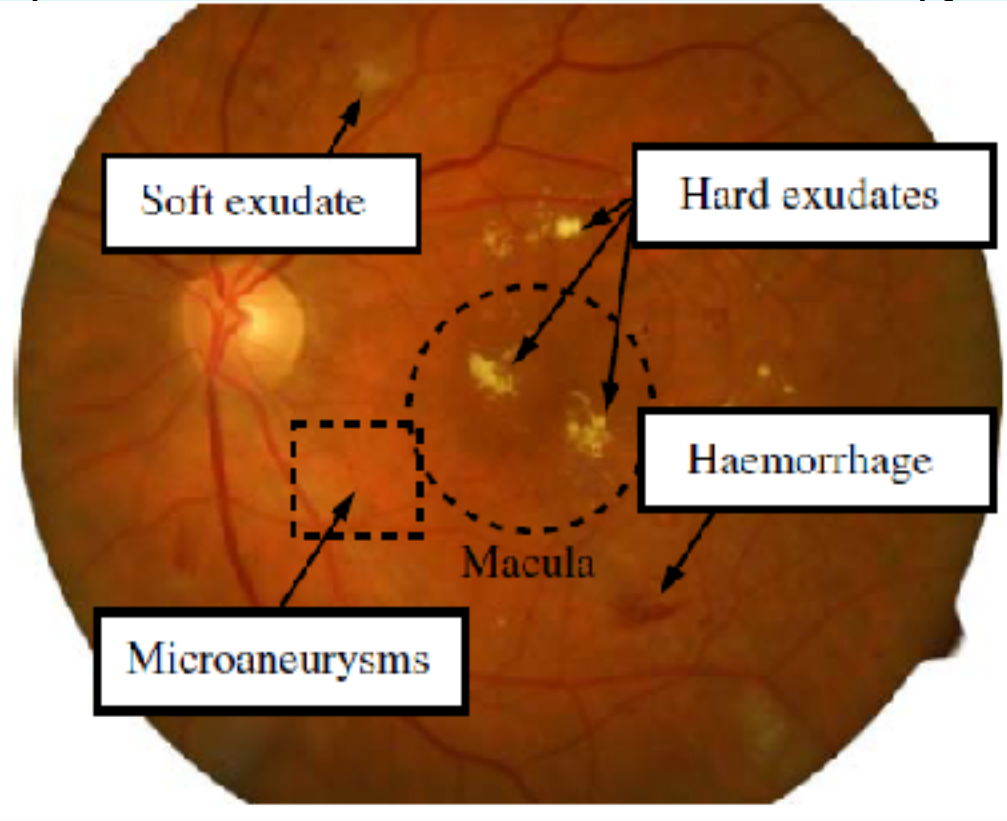
- 2. Very Mild NPDR – Microaneurysms only





Diabetic Retinopathy Classification (ETDRS)

- 3. Mild NPDR – MA plus exudates, cotton wool spots, and/or mild retinal hemorrhages

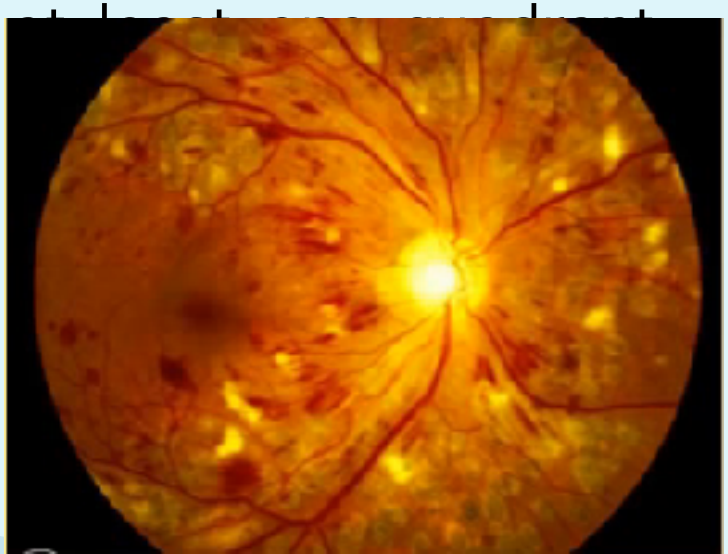


Diabetic Retinopathy Classification (ETDRS)

- 4. Moderate NPDR – MA plus mild IRMA or moderate retinal hemorrhages

Diabetic Retinopathy Classification (ETDRS)

- 5. Moderately Severe NPDR
  - More extensive IRMA, severe retinal hemorrhages, or venous beading in one quadrant
- 6. Severe NPDR
  - Severe retinal hemorrhages in four quadrants or venous beading in at least two quadrants, or moderately severe IRMA in



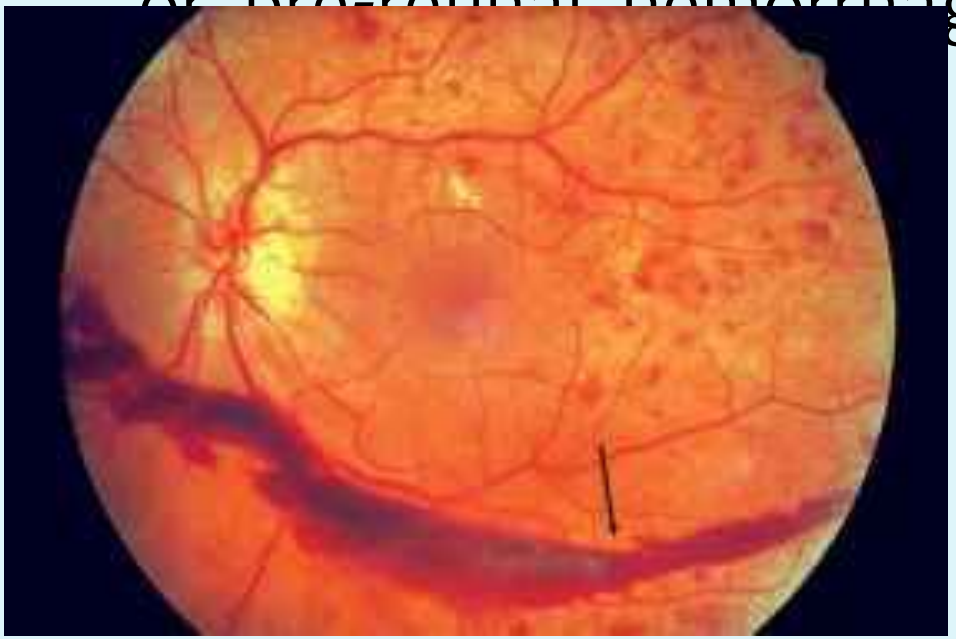
Diabetic Retinopathy Classification (ETDRS)

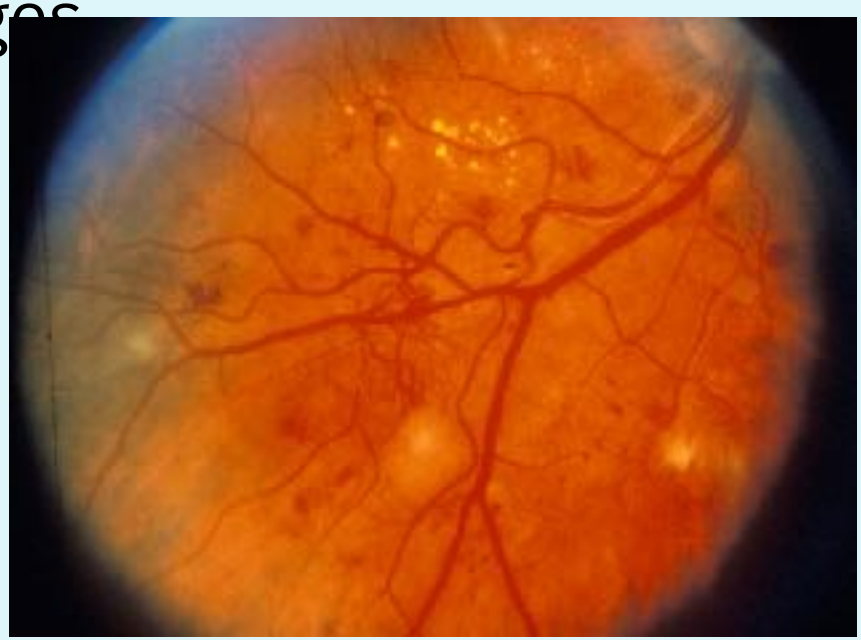
- 7. Mild PDR – Neovascularization, but mild

Figure 4. Fundus photograph and accompanying fluorescein angiogram in the early to mid phase in a patient with more advanced (high risk) proliferative retinopathy.

Diabetic Retinopathy Classification (ETDRS)

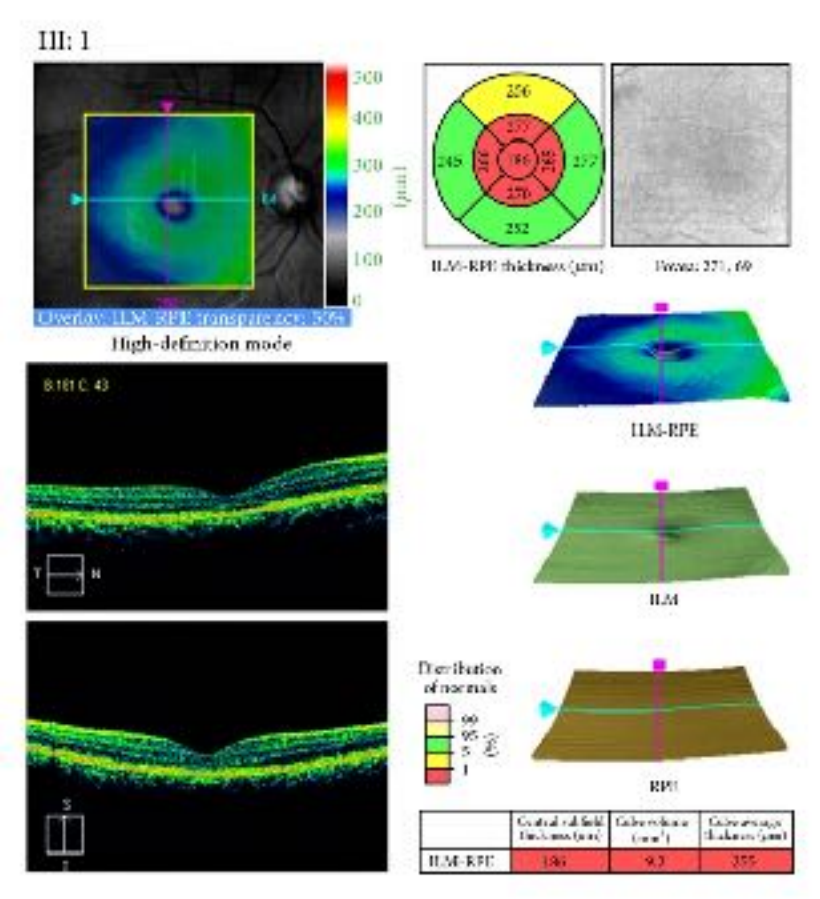
- 8. Moderate PDR
- 9. High Risk PDR – NVD with/without vitreous or pre-retinal hemorrhages





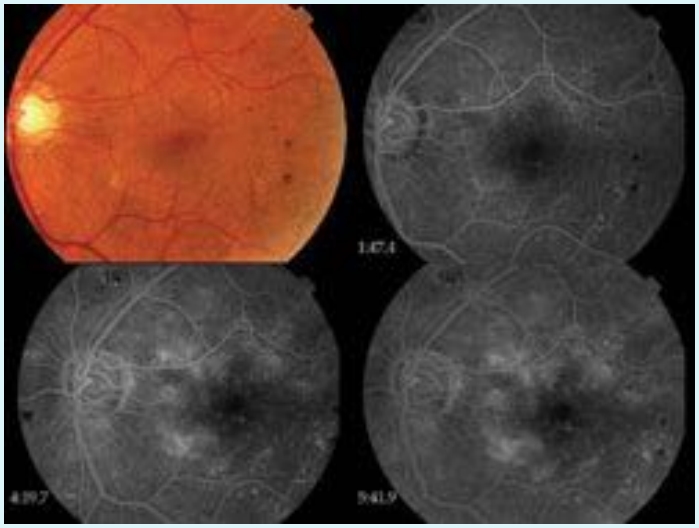
Diabetic Macular Edema Classification (ETDRS)

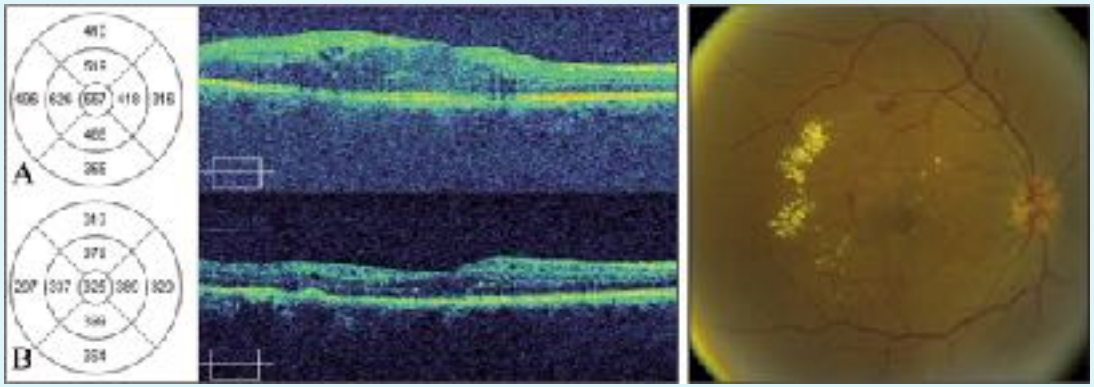
- No apparent DME



Diabetic Macular Edema Classification

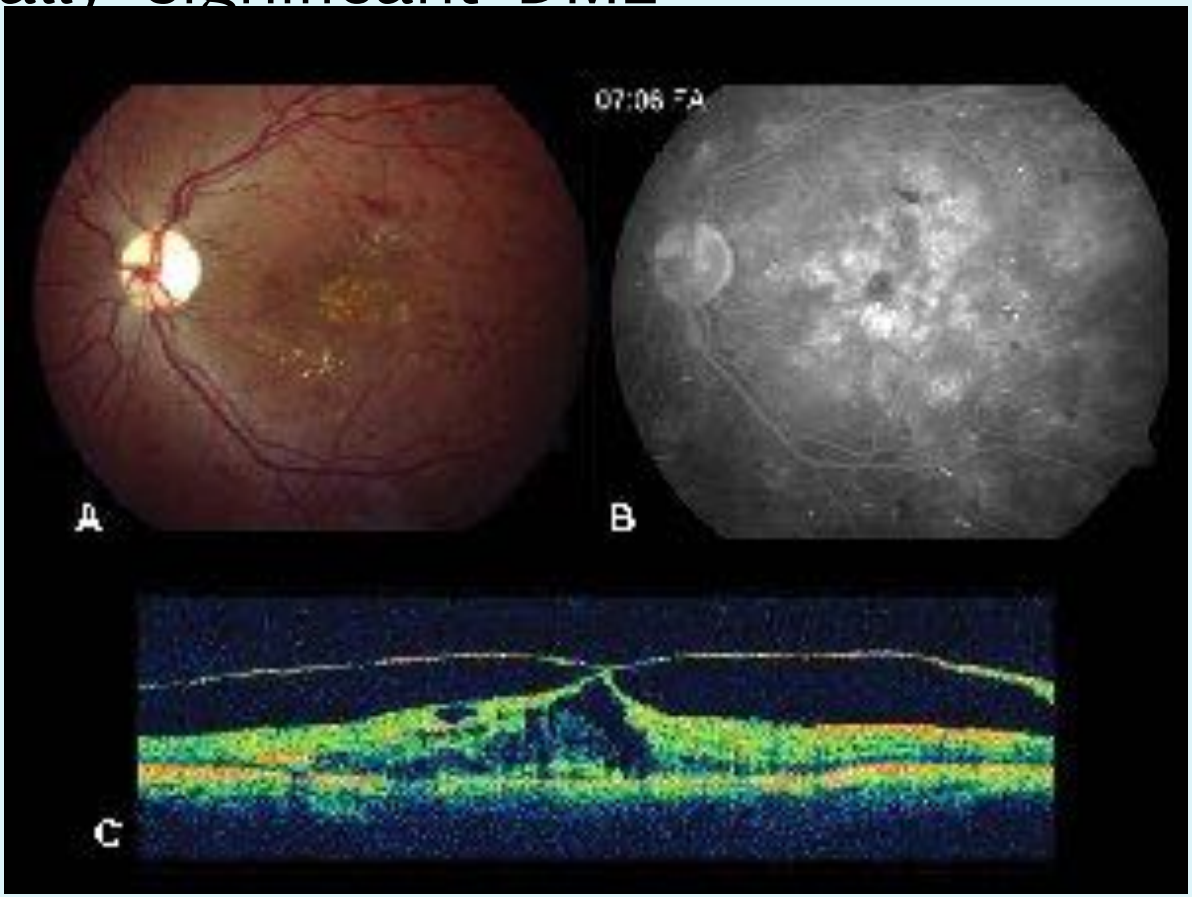
- DME apparently present – some thickening of retina/macula with some Hard Exudates close to the macula





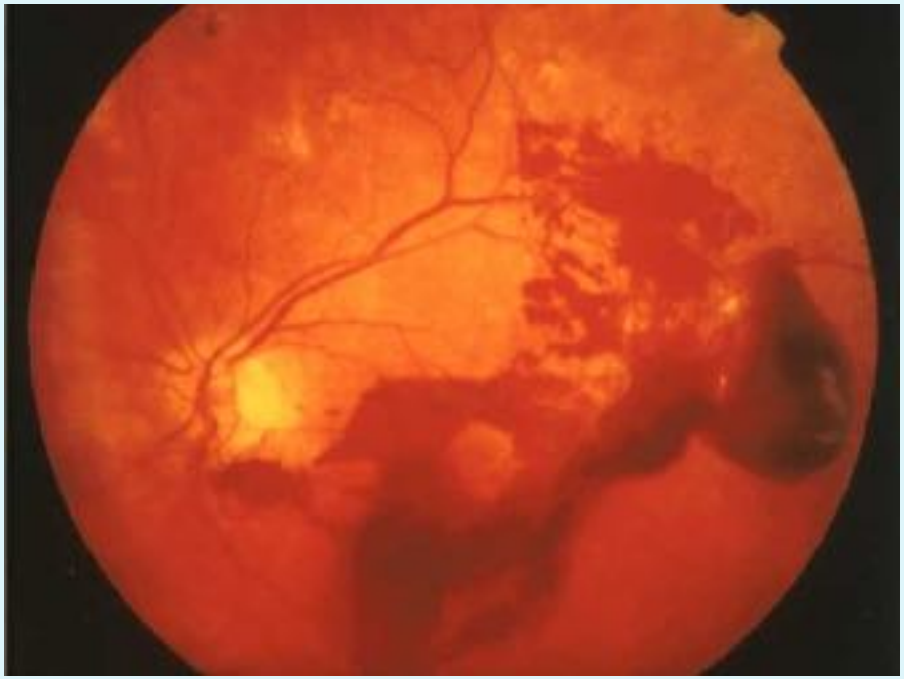
Diabetic Macular Edema Classification

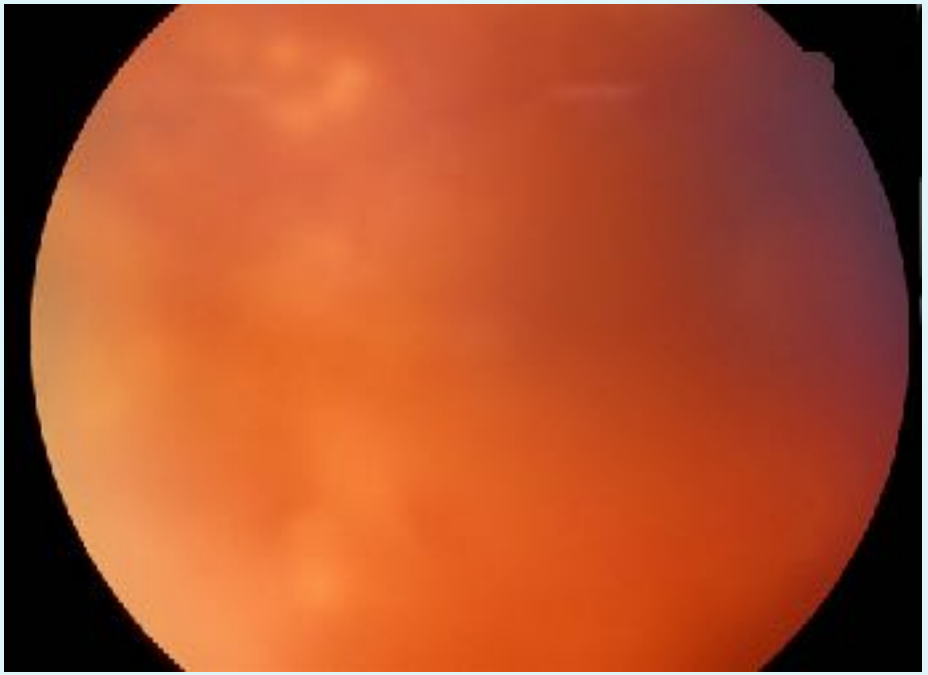
- Clinically significant DME



Advanced Diabetic Retinopathy

- Vitreous Hemorrhaging





Advanced Diabetic Retinopathy

- Ischemic Maculopathy – narrowed or blocked retinal vessels secondary to diabetic-related damage

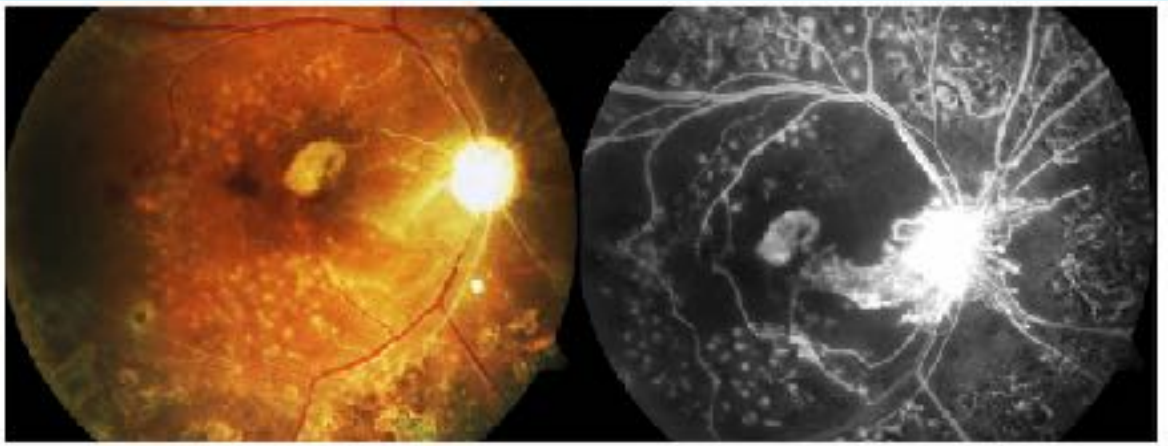
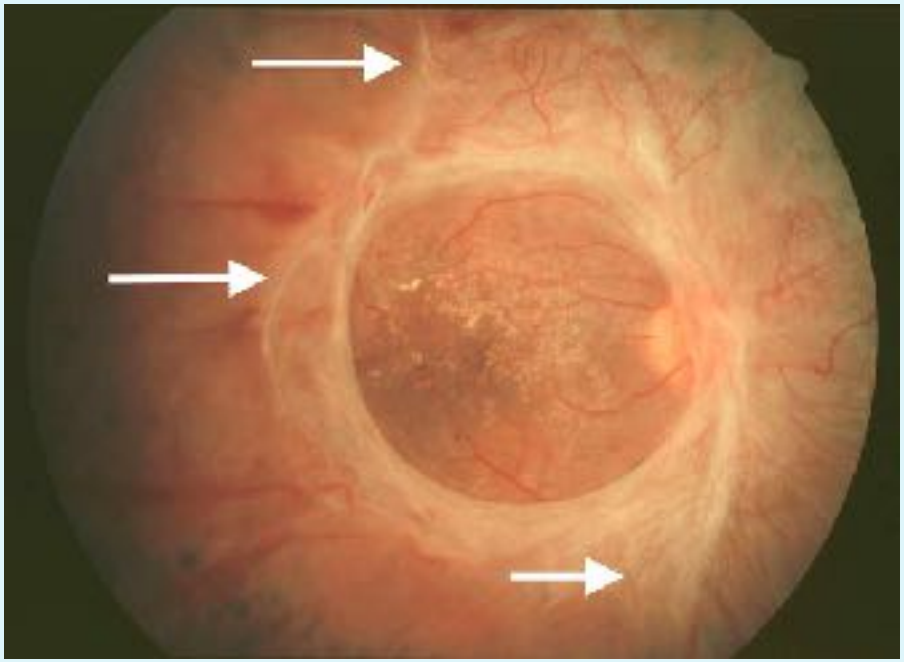
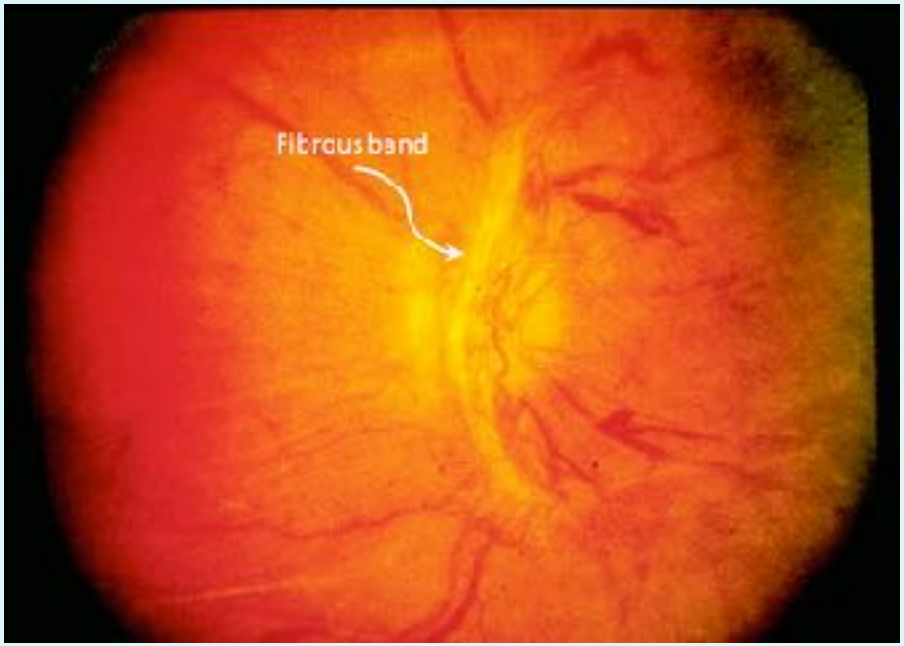


Figure 5. Advanced proliferative diabetic retinopathy with associated ischemic maculopathy. Note the laser scars form panretinal laser photocoagulation, including areas of focal grid laser treatment within the macula. The extensive capillary dropout represents end-stage diabetic retinopathy. Although additional laser may arrest the proliferative changes, very little vision remains secondary to the obliteration of the inner retinal vasculature.

Advanced Diabetic Retinopathy

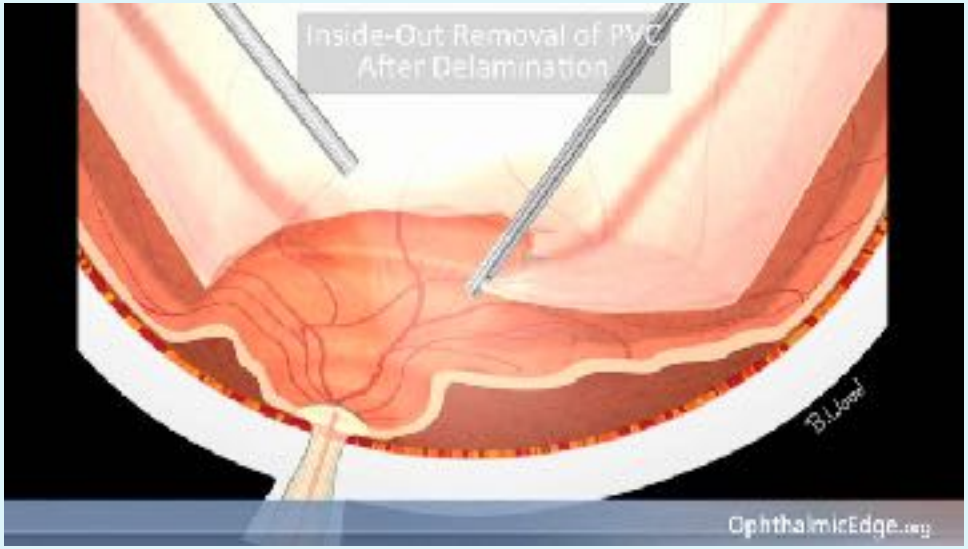
- Fibrinous Disease





Advanced Diabetic Retinopathy

- Tractional Retinopathy

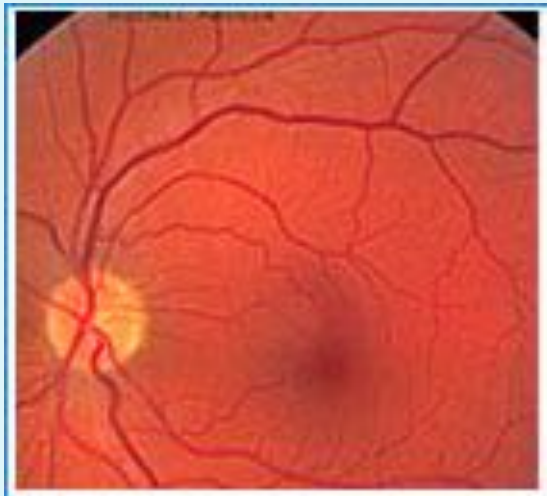


Advanced Diabetic Retinopathy

- Rubeosis Iridis/Neovascular Glaucoma

Diabetic Retinopathy
Differential Diagnosis

Macular degeneration



A healthy retina.

A retina showing "dry" macular degeneration with deposits, called drusen.

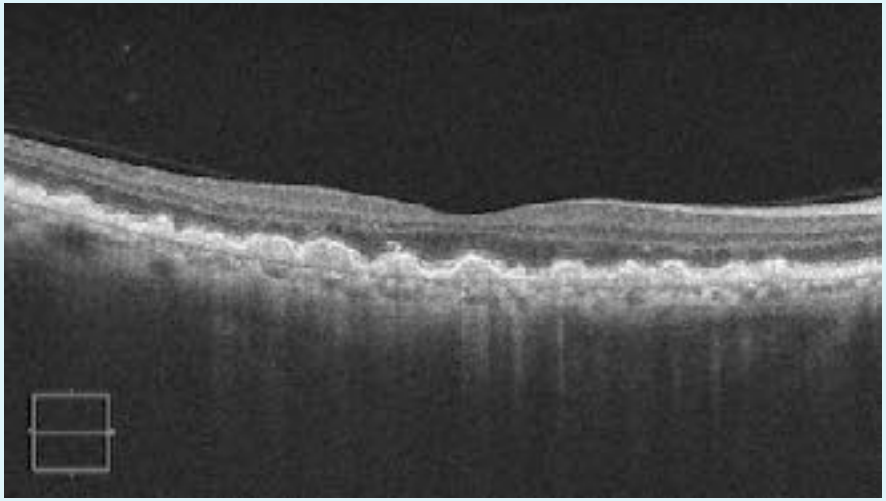
"Wet" macular degeneration revealing scarring and hemorrhaging on the retina.

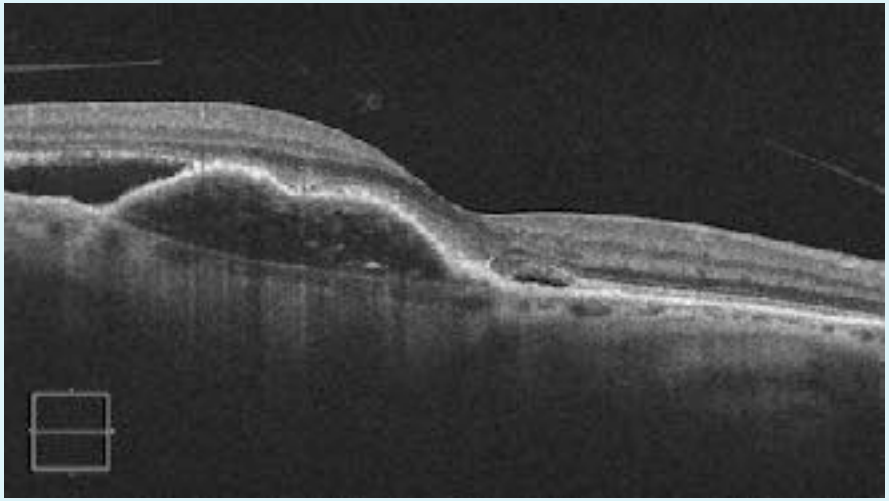
Diabetic Retinopathy Differential Diagnosis

- Macular degeneration – fluorescein angiography

Diabetic Retinopathy Differential Diagnosis

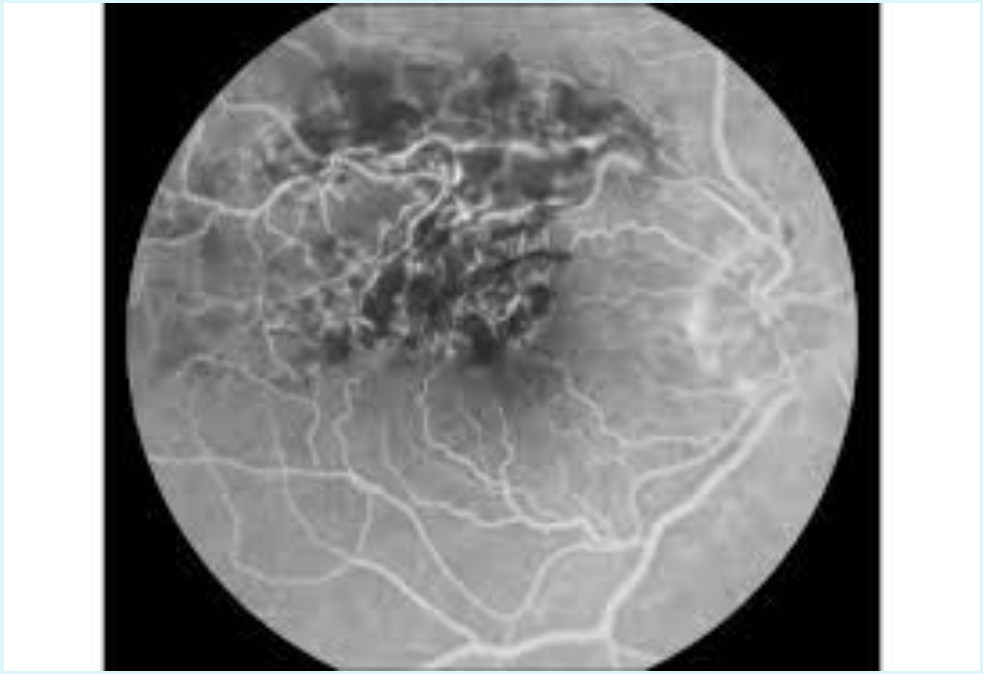
- Macular degeneration - OCT





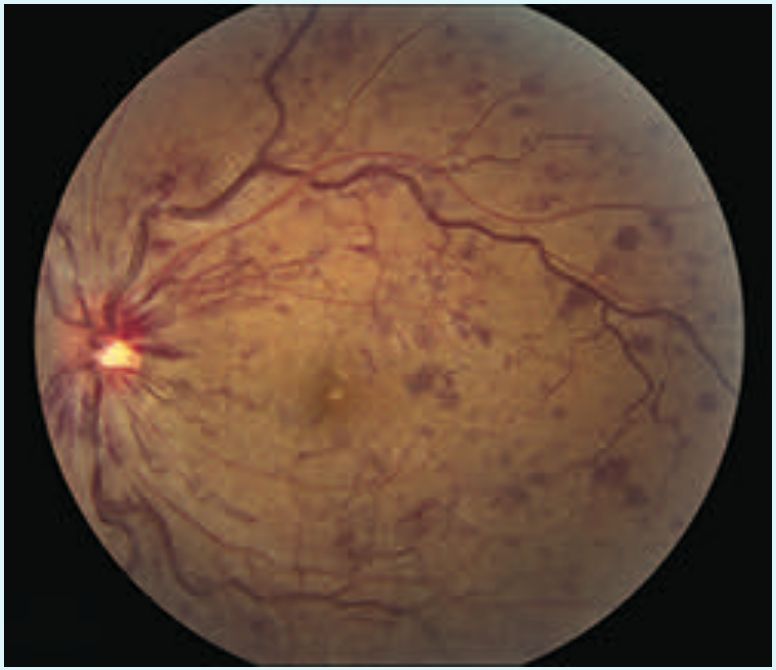
Diabetic Retinopathy Differential Diagnosis

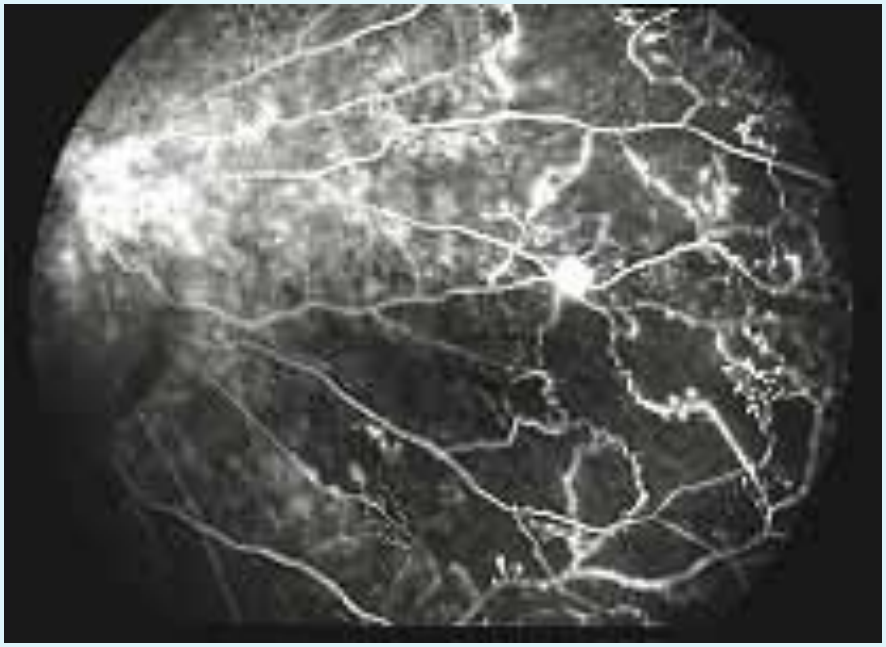
- BRVO



Diabetic Retinopathy Differential Diagnosis

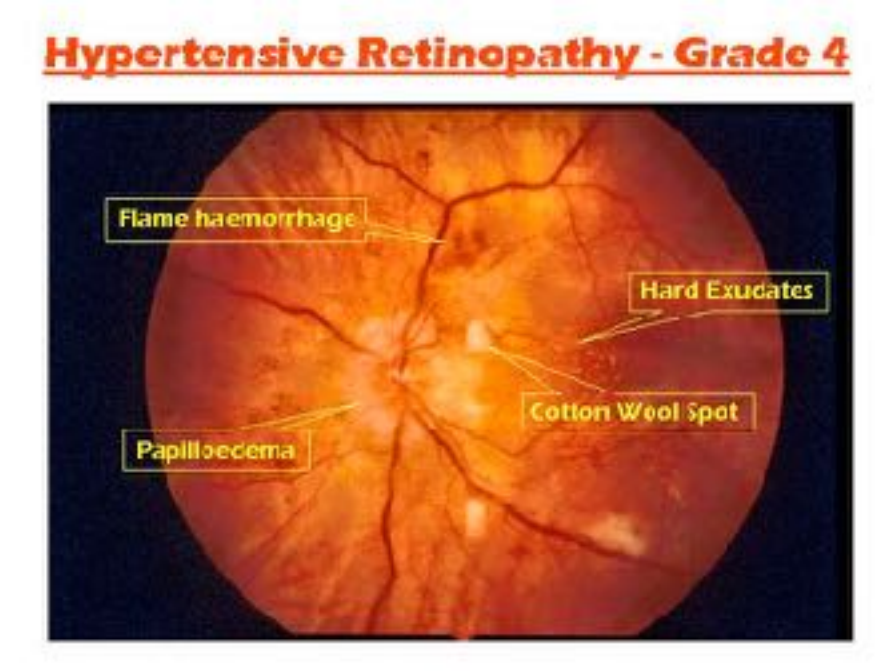
- CRVO

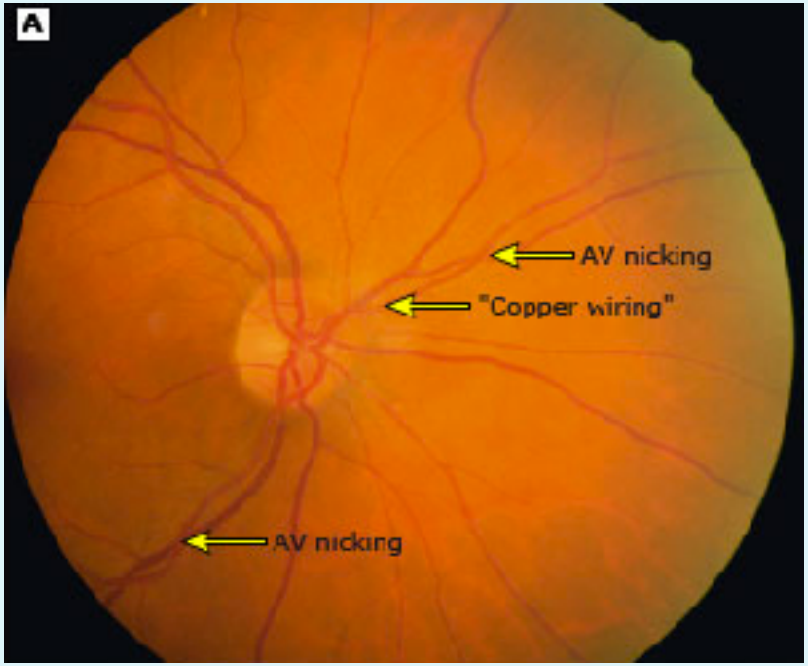




Diabetic Retinopathy Differential Diagnosis

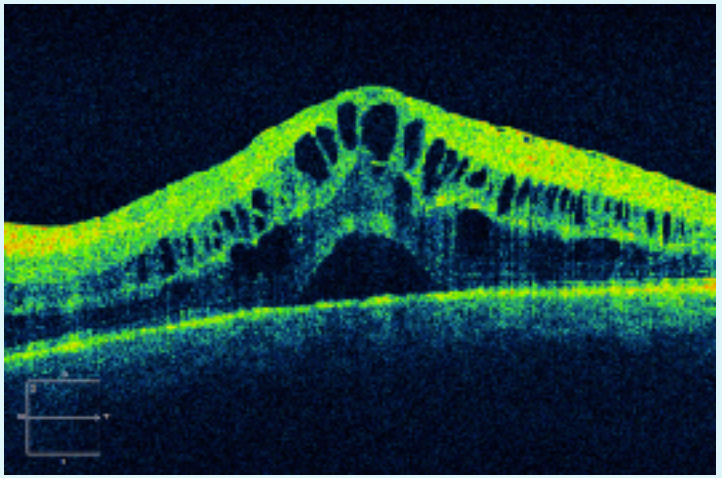
- Hypertensive Retinopathy

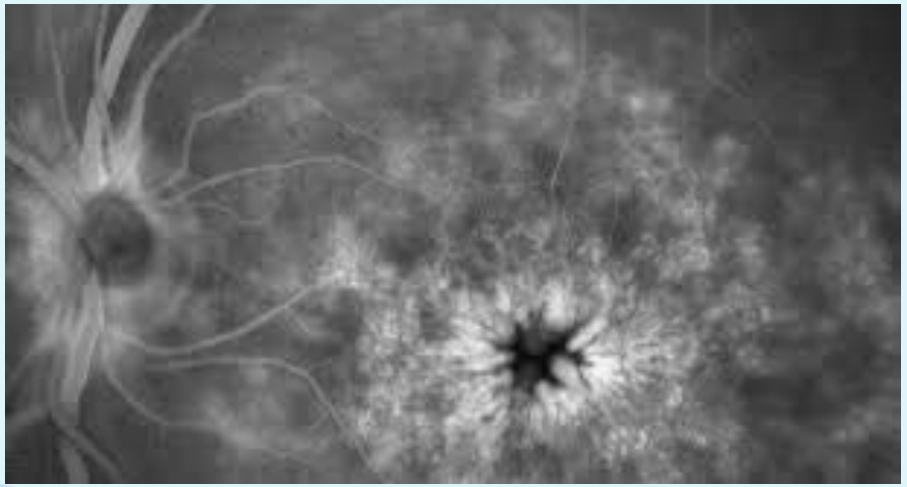




Diabetic Retinopathy Differential Diagnosis

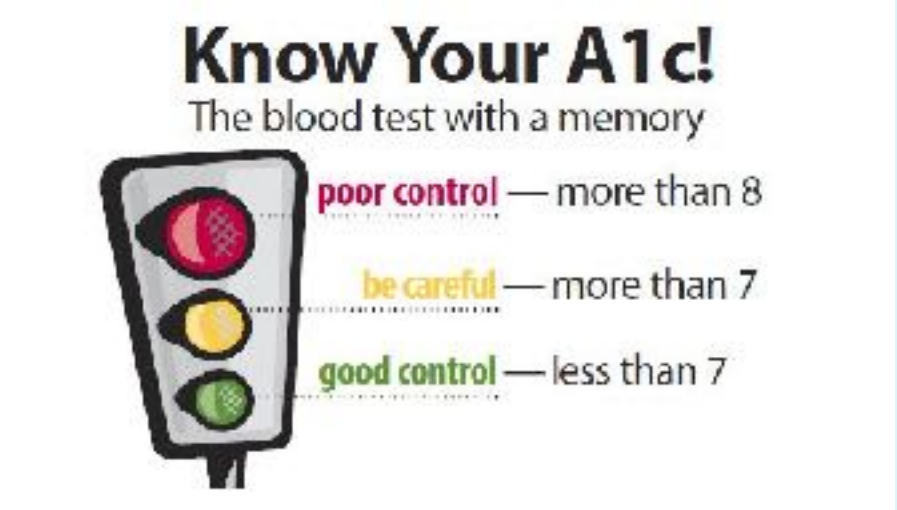
- CME





Diabetic Retinopathy Treatment

- Observation
- Regular eye exams
- Strict glycemic control – **90% of disease prevented by simple BG control and regular eye exams**
- Blood pressure control
- Blood lipid control
- Stop smoking
- Intake less sugar
- Weight control
- Stay physically active



Diabetic Retinopathy/DME Treatment

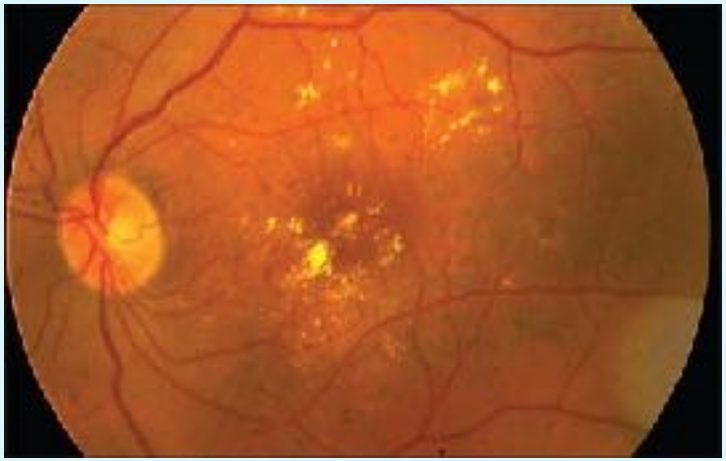
- Increased incidence of DM secondary to obesity (WV led nation with 37.7% obesity rate)
- Associated increase incidence of DR/DME
- DME resolves spontaneously in 35% after 6 months
- Anti-vascular endothelial growth factor VEGF has drastically changed the treatment of DME
- Intracameral steroids also play an important roll in treating DME

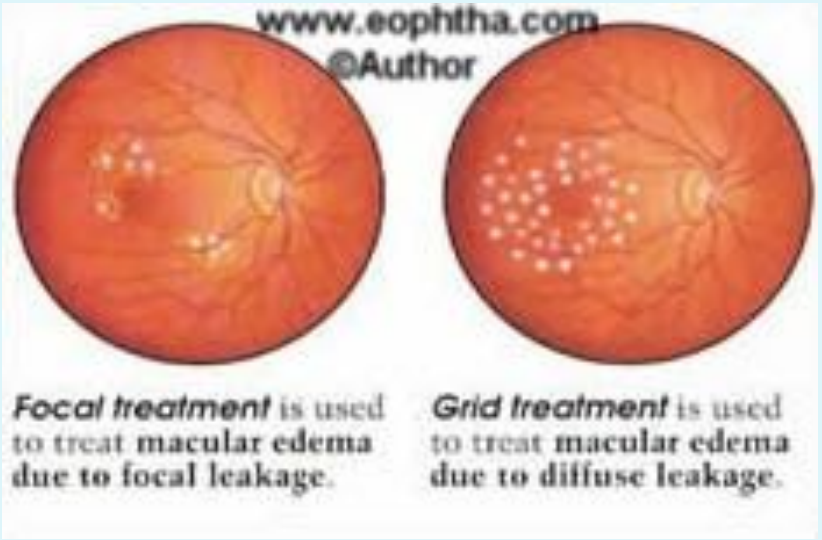
Diabetic Retinopathy/DME Treatment

- The ETDRS showed that focal laser was effective in treating eyes with DME
- Laser became the gold standard in treating DME
- ETDRS showed long-term improvement in VA following laser
- Focal for specific areas of leakage & grid for diffuse leakage

Diabetic Retinopathy Treatment

- Argon laser – focal/grid
  - Significant visual improvement is unlikely/uncommon
  - Seals leaking blood vessels – per the RSFA
  - Avoid FAZ





Diabetic Retinopathy/DME Treatment

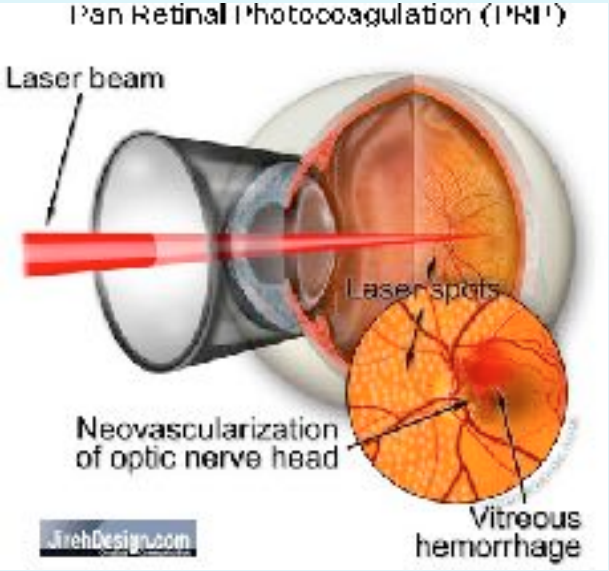
- Laser damages the retina
- Laser scars can enlarge
- Laser can cause SRNVM (damage to Bruch's membrane)
- **Intravitreal steroids & anti-VEGF are now so effective that grid laser is generally used only in cases of DME unresponsive to the intravitreal medications**

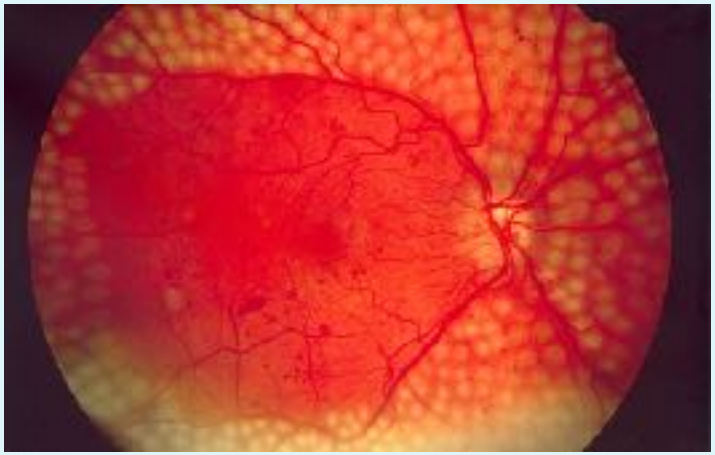
Diabetic Retinopathy/DME Treatment

- Argon laser – PanRetinal Photocoagulation – PRP
- Used to treat PDR
- 1600 to 2000 burns in peripheral retina – usually divided into two treatments
- Reduce the area of the retina that needs oxygen/ reduces oxygen demand – leads to decrease in NV
- Avoid fovea
- Causes decreased peripheral vision, night vision, and color vision
- Treat DME before doing PRP – if possible

Diabetic Retinopathy/PDR Treatment

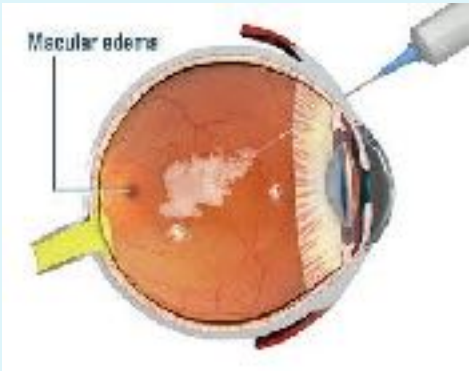
- PRP





Diabetic Retinopathy/DME Treatment

- Triamcinolone – into vitreous cavity – decreases macular edema & improve vision
- Effects last up to 3 - 6 months
- More effective following cataract surgery
- Complications – cataract, steroid-induced glaucoma, retinal detachment, endophthalmitis
- Better outcome than macular laser grid treatment



Diabetic Retinopathy/DME Treatment

- VEGF (vascular endothelial growth factor)
  - Ocular VEGF
    - Increases in DM/DR
    - Causes breakdown of blood-retinal barrier
    - Leads to DME/PDR

- Anti-VEGF
  - Injected into the eye
  - Reduce the growth of new blood vessels and decrease edema/DME
  - Repeated every 4 -8 weeks
  - Potential complications – endophthalmitis, retinal detachment, glaucoma, ? Risk of strokes

Diabetic Retinopathy/DME Treatment

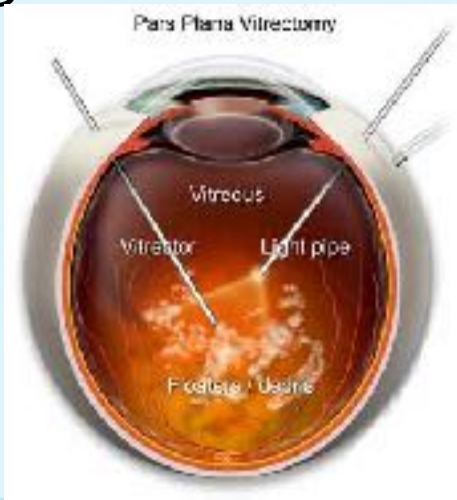
- Anti-VEGF drugs
  - Avastin – bevacizumab – much less expensive – not approved by FDA for intravitreal use
  - Lucentis – ranibizumab
  - Eylea - aflibrcept

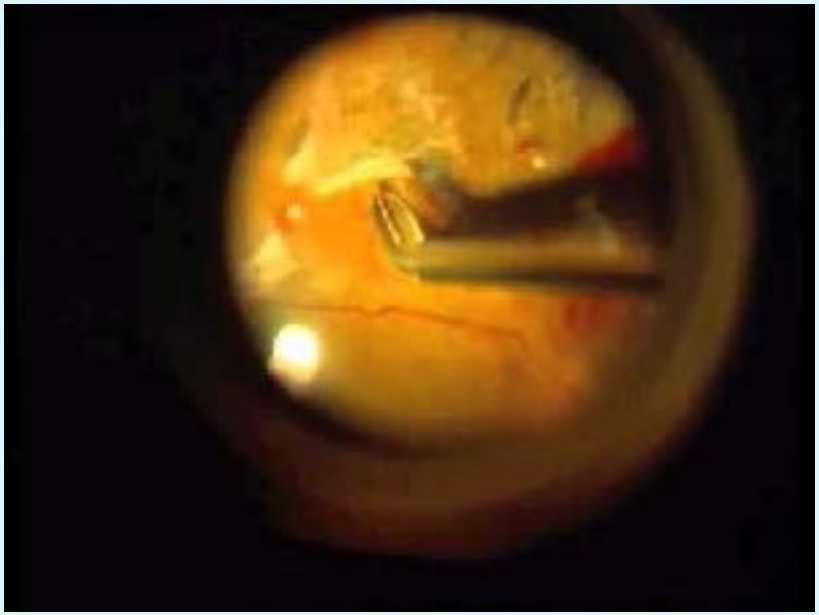
Diabetic Retinopathy/DME Treatment

- Intravitreal anti-VEGF
- Studies and experience are defining the most efficacious treatment with anti-VEGF drugs for the treatment of DR & DME

Diabetic Retinopathy/DME Surgical Treatment

- Vitrectomy – for blood in vitreous
- Vitrectomy with membrane peeling for fibrinous changes in vitreous/retina
- Early vitrectomy effective for significant hemorrhages or traction





Conclusion

Diabetic Retinopathy is the most common cause of vision loss among people with diabetes, and a leading cause of blindness among working-age adults

The most important preventive measure is good blood glucose control along with low-glucose diet, weight loss, staying physically active, good BP control, and

SMOKING!

Conclusion (cont)

90% of diabetic eye disease can be prevented simply by proper regular eye exams, timely treatment, and good blood glucose control!