

## Ocular Manifestations in Diabetes

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## Overview

- “New” Evidence Based Clinical Practice Guidelines for Diabetes
- Definition of diabetes
- Diabetic effects on ocular structures
- Diabetic retinopathy
  - Classification of diabetic retinopathy
  - Treatment and management options



## What is Evidence-Based Practice?

- Decision-making using the best clinical research evidence available, in conjunction with individual clinical experience and patient preferences
- Takes into account risk and benefits of clinical decisions
  - ▶ For more information or to see the Guidelines, please visit: [www.aoa.org/evidence](http://www.aoa.org/evidence)



## Diabetic Classification

- Classification: IDDM vs Type1 and NIDDM vs Type 2 and Type 1.5
- Type 1 diabetes previously known as IDDM:
  - describes patients’ who cannot survive without insulin replacement
- Type 2 diabetes previously NIDDM:
  - describes patients’ who can survive without insulin replacement for at least 6 months after diagnosis of diabetes is made
- Type 1.5: LADA (Latent Autoimmune Diabetes in Adults)



## Blood Sugar

- Throughout a 24 hour period blood sugar typically maintained between 70-140 mg/dL (3.9-7.8 mmol/L)
- Fasting Plasma Glucose or Fasting Glucose Test:
  - Fasting means after not having anything to eat or drink (except water) for at least 8 hours before the test.
  - Diabetes is diagnosed at fasting blood glucose of greater than or equal to 126 mg/dl HbA1c levels depend on the blood glucose concentration



## Blood Sugar

- HbA1c:
  - higher the glucose concentration in blood, the higher the HbA1c.
    - HbA1c are not influenced by daily fluctuations in the blood glucose concentration but reflect the average glucose levels over the prior six to eight weeks
      - useful indicator of how well the blood glucose level has been controlled in the recent past and may be used to monitor the effects of diet, exercise, and drug therapy on blood glucose in diabetic patients.



### Pre-Diabetes

- Risk state of high chance of developing diabetes

Test	Results	Designation
Fasting Plasma Glucose (FPG)	100-125 mg/dL 5.6-6.9 mmol/L	Impaired Fasting Glucose (IFG)
Oral Glucose Tolerance Test (OGTT)	140-199 mg/dL 7.8-11.0 mmol/L	Impaired Glucose Tolerance (IGT)
A1C	5.7%-6.4% 6.0%-6.4%	USA Canada



### Pre-Diabetes

- Conversion to diabetes ranges from 50-70% (depending on study and country)
  - Chinese population reported >90%
- 13% of mothers with gestational diabetes developed diabetes after pregnancy compared to 1% of mothers without gestational diabetes



### Type 1 Diabetes

- Autoimmune disease with a combination of:
  - Genetic factors (6% risk with sibling vs 0.4% general population)
  - Immunologic factors
  - Environmental factors (viruses/nutrition)
- In most cases of type 1 diabetes individuals inherit risk factors from both parents
  - thought to be more common in whites because whites have the highest rate of type 1 diabetes
  - most people who are at risk do not get diabetes so environmental triggers are thought to be necessary



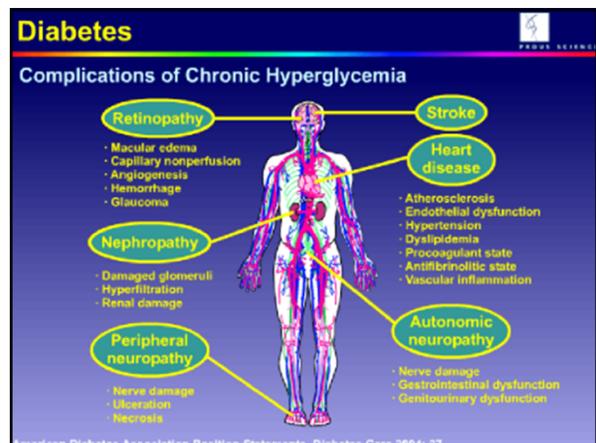
### Type 1 Diabetes

- Characterized by an almost total lack of insulin
  - due to autoimmune destruction of the pancreatic B-cells
  - presentation is usually acute (polyuria and polydipsia)
  - patients thought to become hyperglycemic and symptomatic at 40-50% B-cell loss (previously estimated at 80% loss)



### Type 1 Diabetes

- Complications (e.g. retinopathy) uncommon before puberty and usually present after 10 years duration
- Mortality is increased over general population
- For expectant mothers with type 1 diabetes, tight control of glucose that begins before conception lowers the risk of birth defects, miscarriage, and newborn death to a range that is close to that of the general population.



## Type 1 Diabetes Treatment

- The new HbA1c target of less than 7.5% across all pediatric age groups
- The adult HbA1c target of less than 7%
  - Less stringent A1C goals (such as <8%)
    - history of severe hypoglycemia,
    - limited life expectancy,
    - advanced microvascular or macrovascular complications,
    - and extensive comorbid conditions and in those with longstanding diabetes in whom the general goal is difficult to attain



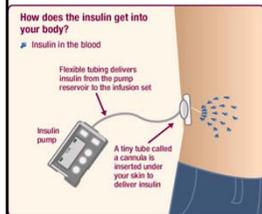
## Continuous Glucose Monitoring



- tiny sensor inserted under the skin to check glucose levels in tissue fluid
- transmitter sends information about glucose levels via radio waves from the sensor to a pagerlike wireless monitor
- must check blood samples with a glucose meter to program the devices



## Insulin Pumps



- deliver rapid- or short-acting insulin 24 hours a day through a catheter placed under the skin
- Delivers 24 hour insulin, boluses at meals, better A1C control, eat whenever, fewer low blood sugar episodes
- Patients still need to check BS before/after meals



## Type 2 Diabetes



- Combination of:
  - failure of pancreatic B-cells to secrete sufficient amounts of insulin to meet metabolic needs and
  - insulin resistance at the cellular level
- strong association of insulin resistance with obesity and physical activity
  - genetic predisposition to Type 2 stronger than 1
    - 1 parent with Type 2: 30-40% risk
    - 2 parents with Type 2: 70% risk



## Type 2 Diabetes



- at least 90% of the total diabetes population
- patients present with insidious symptoms of polyuria, polydipsia and blurred vision
- Most Type 2 patients are:
  - more obese than the background population
    - obesity on the rise:
      - increased consumption of high calorie diets,
      - changes in lifestyle,
      - lack of exercise (inactivity)



## Type 2 Diabetes

- historically a disease of adults (>45) but has been on the rise in children
  - most cases of pediatric type 2 diabetes occur in obese or overweight individuals, with body mass index (BMI) frequently above the 85th percentile
  - mortality and morbidity increased with uncontrolled blood pressure and lipid levels
    - 80% of Type 2 patients die from CV complications
    - **Smoking is considered an additional significant risk factor and all patients should be educated to quit smoking**



## Type 2 Diabetes

– Blue Mountain Eye Study indicated that greatest risk factors for complications secondary to diabetes are:

- increased blood sugar levels,
- increased blood pressure,
- elevated lipid levels, and
- duration of diabetes



## Diagnostic Test For Diabetes

Fasting Plasma Glucose (FPG)	≥126 mg/dL suggest DM 100-125 mg/dL prediabetes	Confirm by repeat test on different day
Random Plasma Glucose	≥ 200 mg/dL in setting of symptoms indicates DM	Confirm with FPG or OGTT performed on another day
2-h oral glucose tolerance test (OGTT)	≥200 mg/dL diagnostic 140-199 mg d/L prediabetes	
Glycosylated hemoglobin: HbA1c	≥5.7 but <6.5-prediabetes ≥6.5 diabetic	HbA1c is a better predictor of DR than FPG <i>Diabetes Care 2009 November; 32(11): 2027-32</i>

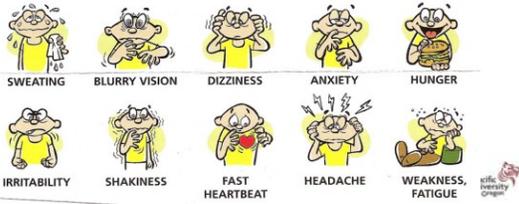


## Blood Sugar

- Hypoglycemia is typically defined as plasma glucose 3.9 mmol/L (70 mg/dL) or less
  - patients typically become symptomatic of hypoglycemia at 2.8 mmol/L

### 1 Recognize Symptoms Early

No matter how carefully you manage diabetes with insulin, hypoglycemia (low blood sugar) may still develop very quickly. Symptoms include:



## Action Item

- Optometrists should have a rapid-acting carbohydrate (glucose gel or tablets, sugar-sweetened beverage or fruit juice) in their offices for use with a diabetes patient who experience acute hypoglycemia during an eye examination



## Hypoglycemia

Always have a rapid-acting carbohydrate in the office (juice, sugared soda, glucose gel) for pts on meds that can cause low blood glucose....



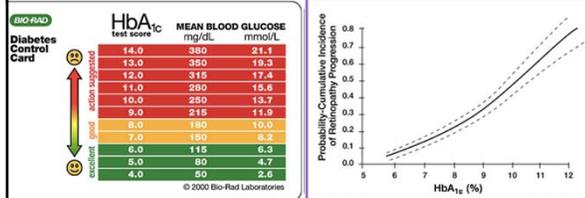
## Recommendations for Management

- A: A1c:** <7.0 for most non-pregnant adults  
<8.0 for adults with limited life expectancy, history of hypoglycemia or advanced CVD  
<6.5 for recent diagnosed or long life expectancy
- B: Blood Pressure:** <140/90 (USA) or 130/80 (Canada)
- C: cholesterol:** All patients with diabetes (age 40-75 years) with LDL-C 70-189 mg/dl, without any evidence of CVD should receive statin therapy
- D: Drugs:** to reduce CVD (e.g. statins, blood pressure, aspirin)
- E: Exercise:** regular aerobic and resistance training proper nutrition and weight management
- S: Smoking:** smoking cessation



## HbA1c

- Mean Plasma Glc=(A1c x 35.6) - 77.3



Very rough estimation: like converting kg to pounds:  
apprx 2.2

## Type 2 Diabetes

### Clinical Pearl:

Patient education to all patients with diabetes must include:

1. Importance of good blood sugar control and minimizing daily fluctuations
2. Importance of good blood pressure control <140/90 USA (130/80 Canada)
3. Importance of good lipid control
4. Cessation of smoking

## Type 1.5 (Latent Autoimmune Diabetes in Adults [LADA])

- LADA is a type 1 diabetes which shows slow progression to insulin dependence
- Patients present as an adult who is not insulin dependent at diagnosis and is usually treated as a type 2
- LADA is an autoimmune condition unlike type 2 and can be distinguished from type 2 by blood tests for antibodies

## Type 1.5 (Latent Autoimmune Diabetes in Adults [LADA])

- Potentially 11-13% of 18-45 years old patient with type 2 diabetes are actually LADA and require insulin therapy
  - approximately 20% of all Type 2 DM patients
- Currently, most patients with LADA are treated according to the guidelines for type 2 diabetes.
- Early studies have suggested that LADA patients should possibly begin treatment with insulin within one year of diagnosis

## Action Item: Pregnancy and Diabetes

- Women with pre-existing diabetes who are planning pregnancy or who become pregnant should have a comprehensive eye exam prior to the planned pregnancy or during the first trimester, with follow up exams every trimester of pregnancy.

## Gestational Diabetes

- Commonly occurs during 2<sup>nd</sup>/3<sup>rd</sup> trimester
  - 5-10% of pregnancies
- Higher prevalence among Black, Hispanic, American Indian populations
- Risk factors:
  - Obesity
  - FHx of Type 2 diabetes
- **Not associated with development of retinopathy**
  - \*35-60% chance of developing Type 2 DM 10-20 years postpartum



### How Does Diabetes Affect the Pregnant Body?

- Increased risk of **development or progression of diabetic retinopathy**:
  - Exact mechanism unknown
  - Usually **mild, temporary**
    - Regresses to normal several months post-delivery
  - Grading is the same as for non-pregnant patients
- Increased risk of **macular edema**
  - With or without proliferative retinopathy
  - Postpartum regression
  - May not resolve
    - Possible long-term vision loss



### EXTRAOCULAR AND OCULAR EFFECTS OF DIABETES



### Case

- 42 BM (truck driver)
- CC: pain OD when he wakes up in the morning, has happened several times before and seems to be occurring more often
- PMHX: diabetes for 15 years
  - states well controlled, LBS 150 (2 days ago) range is 120-160, doesn't know last A1C, LME was 6 months ago
  - HTN- 15 years and well controlled
  - CVD- taking aspirin to help manage
- Meds: metformin, Lasix, baby aspirin
- Social Hx: patient is an occasional smoker



### Entrance Skills

- BCVA: 20/20 with correction
- PERRL
- EOMS: FROM
- CVF: FTFC
- Amsler: - metamorphopsia OD, OS

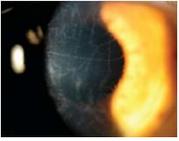


### Lids

- Xanthelasmas reported to occur more frequently secondary to elevated serum lipid levels and may reflect poor diabetic control.
- Composed of foamy, lipid-laden xanthoma cells clustered around blood vessels and adnexal tissue within the superficial dermis
- Treatment includes surgical excision, CO2 ablation and topical trichloroacetic acid. Recurrence is common.



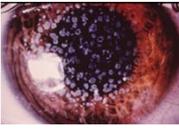
### Corneal Dystrophies



Lattice Dystrophy



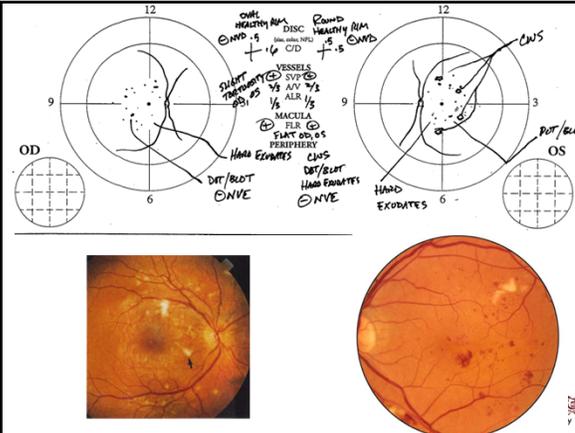
Avellino Dystrophy



Granular Dystrophy



EBMD

### Extraocular Muscles

- Palsies associated with diabetes are not common but they are characteristic.
- Diabetes is one of the more frequent etiologies of an acquired palsy where the onset of sudden diplopia is the main symptom.
- Basic pathology is occlusion of blood supply to the nerves.
- The 3rd, 4th and 6th nerves are affected, though uncertain which is more commonly affected (3rd and 6th frequently cited).



### Cranial Nerves: Reason to Perform

- Increased ability to make correct diagnosis:
  - E.g. third nerve palsy secondary to diabetes (common problem)
    - Check cranial nerves on both sides to be sure problem is isolated and not missing a more serious cause.
- Increased ability to refer patient to correct health care provider
- Possible health care cost containment



### Sixth Nerve Palsy

- Likely most common nerve affected
- Patients often experience horizontal diplopia in primary gaze as well when looking towards the affected side.
- Fresnel prisms highly effective in treating patients to resolve diplopia during the affected time.




### Third Nerve Palsy

- Less common
- If affected:
  - unable to elevate,
  - depress or
  - adduct (eye is down and out)
- Upper lid ptosis maybe present but unlike other 3rd never lesions, the pupil is spared.




## Fourth Nerve Palsy

- Rarely affected
- Difficult to diagnose a 4th nerve palsy in isolation because of the adopted head tilt and vertical diplopia
- 4th nerve more commonly affected in trauma patients.



## Cornea

- Patients with diabetes have decreased corneal sensitivity which is part of the peripheral neuropathy
  - due to inactivation of the corneal nerves (trigeminal and their branches)
- Evidence to demonstrate an abnormal basement membrane. All combine to increase:
  - RCE,
  - slow wound healing,
  - neurotrophic ulceration and
  - defective re-epithelialization

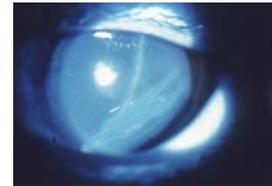


## Cornea-Neurotrophic Ulcer



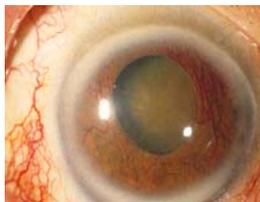
## Cornea-Poor Wound Healing

- Not normally a problem, but does pose a problem under stress situations
- CL wear needs to be carefully evaluated:
  - not an absolute contraindication but extra caution indicated



## Iris Neovascularization

- Major complication is iris neo (rubeosis)
- Neo develops either at pupillary frill or in the anterior angle which later spreads across iris surface
- Possible development of peripheral anterior synechiae which blocks drainage and leads to increased IOP and neovascular glaucoma.



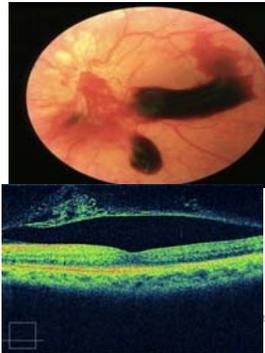
## Pupils

- Pupil reactivity is generally sluggish
- Excessive miosis or failure to dilate normally in the dark
- Poor dilation due to poor response to mydriatic agents such as tropicamide:
  - may need to use more than one drop and use of phenylephrine
- Pupillary dysfunction closely related to duration of diabetes and likely linked to both neuropathic and myopathic etiology



## Vitreous

- Increase syneresis and liquefaction
- The vitreous provides the support framework for the development of neovascular complexes.



## Lenticular Changes: Dynamic Alterations

- Changes in shape of the lens and its refractive index result in changes or fluctuations in refractive error and variable vision
- 20-40% of patients report vision changes when first diagnosed
- Sorbitol pathway results in water being drawn into the lens which results in changes in lens curvature, thickness and refractive index
- Both myopic and hyperopic shifts have been recorded, though we typically associate myopic shifts with diabetics.



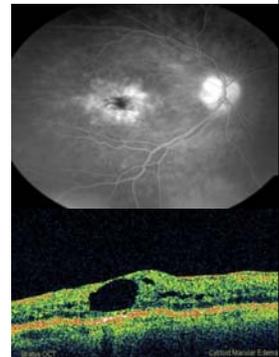
## Cystoid Macular Edema (CME)

- Primary complaint is decreased vision
- Occurs after any type of ocular surgery though probably most commonly observed after cataract surgery
  - Peak incidence is about 4-6 weeks post surgery and the incidence increases with surgical complications such as iris prolapse, vitreous prolapse and vitreous loss



## CME

- Critical signs:
  - Irregularity and blurring of the FLR
  - Foveal thickening with or without small intraretinal cysts
  - FA often shows early leakage and late macular staining
    - Classically in a flower-petal or spoke-wheel pattern
  - Note the central cyst of fluid on OCT



## CME: Treatment

- Most resolve spontaneously in 6 months
- Topical NSAID for 6 weeks (Ilevro or Prolensa)
- Consider Diamox 500 mg daily
- Other forms of treatment with unproven efficacy:
  - Systemic NSAIDs (eg indomethacin 25 mg po tid for 6 weeks)
  - Topical steroids (eg Pred Forte qid for 3 weeks then taper for 3 weeks)
  - Systemic steroids (prednisone 40 mg daily for 5 days then taper over 2 weeks)
  - Subtenon's steroid injection



## CME and Diabetes

- Increased prevalence of CME in patients with diabetes
  - CME that results in diabetes patients is often much more difficult to treat
- Recommend pre-treating patients with diabetes with Ilevro/Prolensa and throughout post-op treatment



### Diabetic Retinopathy

- Closely related to the duration of the diabetes
- Evolution of the retinopathy is variable and hard to predict
- Retinopathy expected in 20% of patients after 10 years and 80% by 20 years
- Females tend to be affected more than males
- 5-10% of patients develop advanced sight threatening retinopathy
- Differences in development between Type 1 and 2



### Diabetic Retinopathy

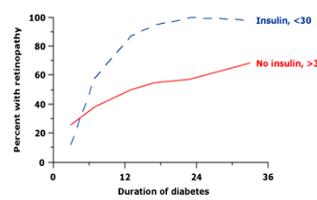
- Almost 61% have some manifestation of diabetic eye disease
- Leading cause of new blindness in U.S. for 20-74 y.o.
  - 12% of all new cases of blindness per year
- Risk of blindness about 25 X greater in DM
  - Primarily due to diabetic retinopathy
- Early intervention lessens risk and severity of vision loss
- 50-65% have not had a DFE in the previous year



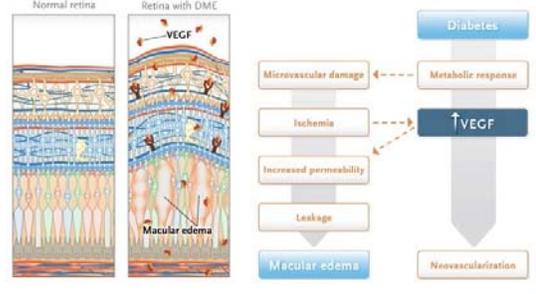
### Diabetic retinopathy

– Risk Factors:

- **Duration of diabetes!**
- Associated conditions
  - Poor glycemic control!
  - Dyslipidemia
  - Hypertension
  - Smoking
  - Pregnancy




### VEGF and DME/Neo




### Diabetic Retinopathy Signs

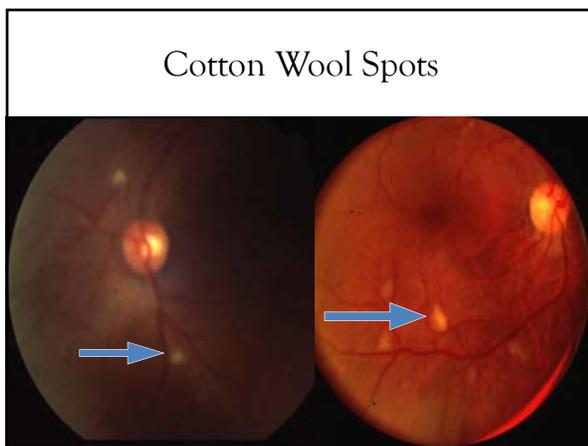
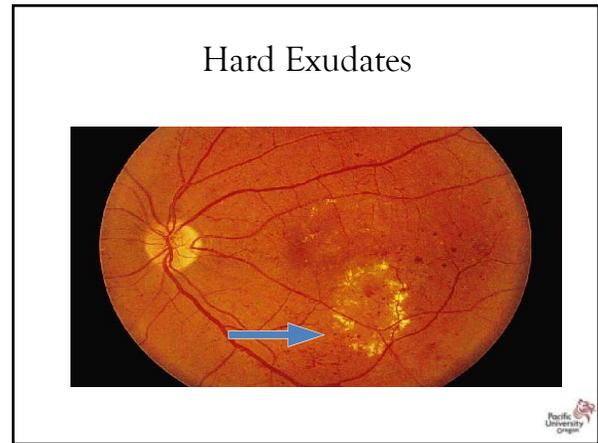
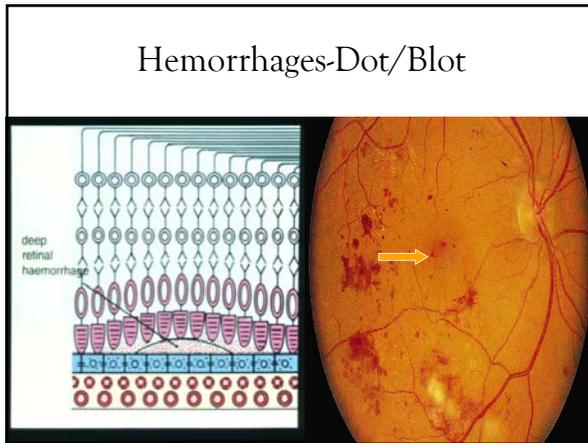
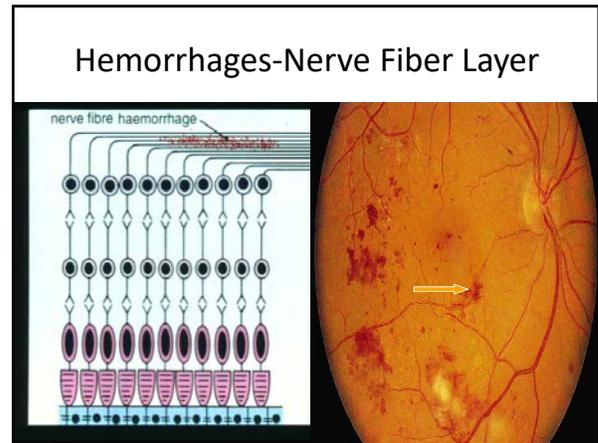
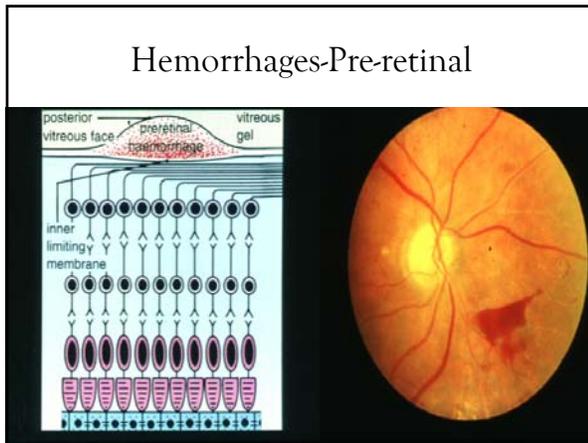
- Microaneurysms
- Retinal edema
- Hard exudates
- Cotton wool spots
- Venous beading
- Intraretinal microvascular abnormalities (IRMA)
- Vitreous heme
- Neovascularization (NVE, NVD, NVI)

• Important to make sure you LOOK for all of these and document pertinent negatives



### Microaneurysms



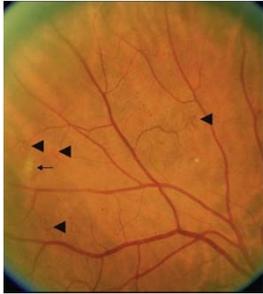


### Intraretinal Microvascular Abnormalities (IrMA)

- shunt vessels and appear as abnormal branching or dilation of existing blood vessels
  - not commonly found around the disc
- either new vessel growth within the retina or remodeling of pre-existing vessels
  - they appear deeper in the retina and have blurrier edges

### Intraretinal Microvascular Abnormalities (IrMA)

- stimulated by hypoxia bordering areas of capillary nonperfusion
  - they usually occur adjacent to cotton wool spots



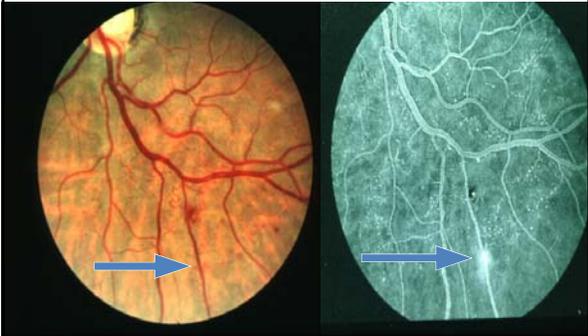
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### Vitreous Hemorrhage



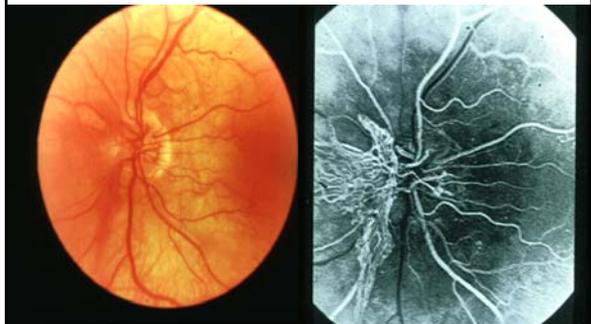
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### NVE



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### Neovascularization of the Disc-NVD



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### Neovascularization of the Iris-NVI



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### Categorization

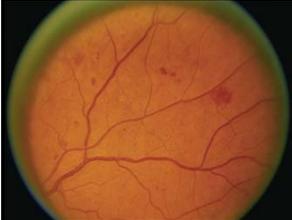
- Two broad categories exist in DR:
  - non-proliferative and proliferative
- Within non there non-PDR (NPDR) there exists three stages:
  - mild, moderate and severe with the addition of very severe NPDR
- Within PDR you have high risk factors

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**Table 1. Classification of Diabetic Retinopathy**

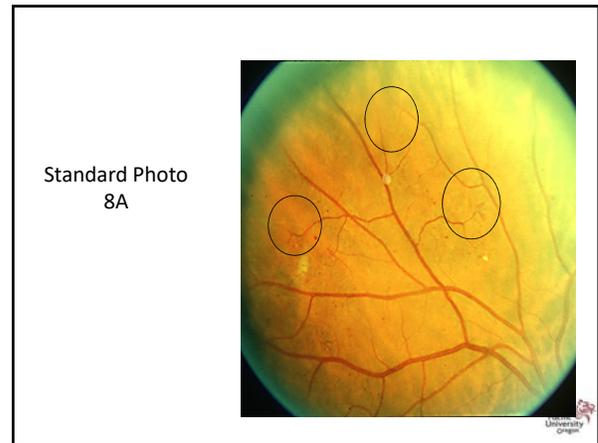
Form/Category	Characteristics
<b>Nonproliferative Diabetic Retinopathy (NPDR)</b>	
Mild NPDR	At least one retinal microaneurysm
Moderate NPDR	Hemorrhage/microaneurysm $\geq$ ETDRS standard photograph 2A, and/or soft exudates (cotton wool spots), venous beading, and intraretinal microvascular abnormalities (IRMA) definitely present
Severe NPDR "4:2:1 rule"	Hemorrhage/microaneurysm $\geq$ ETDRS standard photograph 2A in all 4 retinal quadrants, or Venous beading in at least 2 quadrants, or IRMA $\geq$ ETDRS standard photograph 8A in at least 1 quadrant
Very Severe NPDR	$\geq 2$ Criteria for severe NPDR in the absence of frank neovascularization

Standard Photo 2A



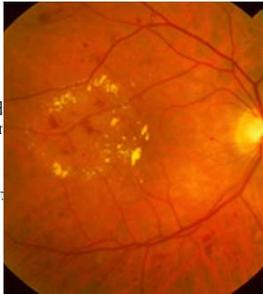
Standard Photo 8A



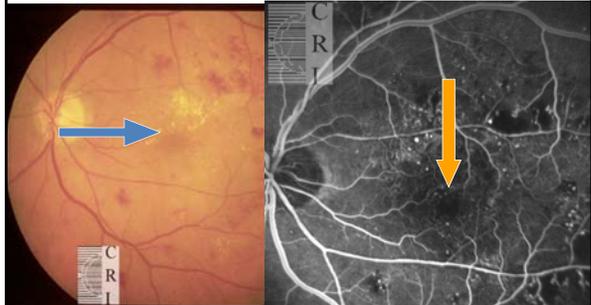
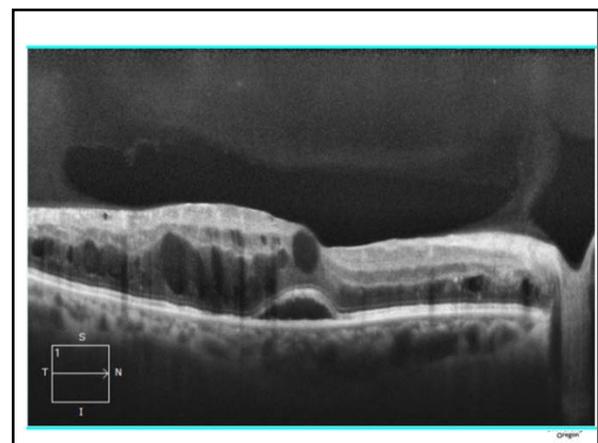
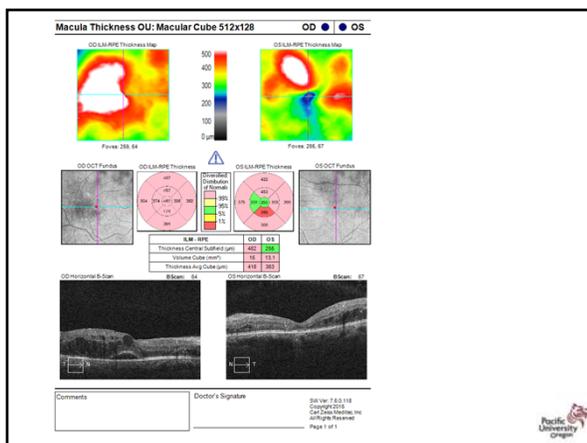


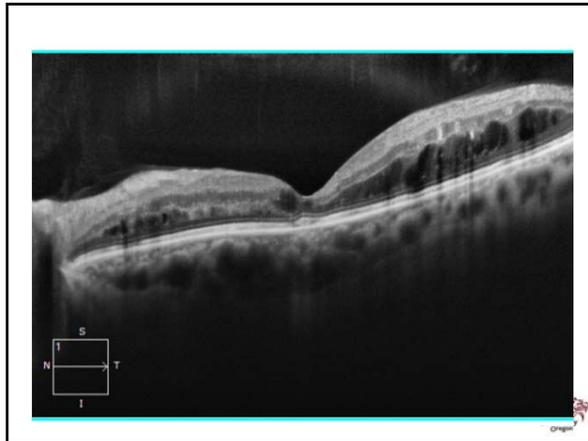
### Clinically Significant Macular Edema (CSME)

- Also referred to as diabetic macular edema (DME)
- Consists of 3 clinical signs:
  - Hard exudates with associated retinal thickening within 1/3rd DD of center of fovea
  - Edema (retinal thickening) within 1/3rd DD of center of fovea
  - Edema of 1 DD within 1 DD center of fovea



### Clinically Significant Edema-CSME (DME)



### Treatment of CSME

- Recommend all eyes with CSME and reduced vision be treated
  - Standard of care: intravitreal anti-VEGF with focal laser photocoagulation if needed
    - Afibercept (Eyelea®) 2 mg
    - Ranibizumab (Lucentis®) 0.3 mg
    - Bevacizumab (Avastin®) 1.25 mg (off-label)
  - Intravitreal injections: Loading dose 1 inj/m then q 2 m
  - ↑ VA compared to grid laser alone for at least 3 years
  - Defer grid laser for 24 weeks → 50% don't need laser



### Risk of PDR

Current level of DR	PDR at 1 year	HR PDR at 1 year	HR PDR at 5 years
Mild NPDR	5%		15%
Mod NPDR	12%–27%	1.2%–8.1%	33%
Severe NPDR	52%	14.6%	60%–75%
Very Severe NPDR	75%	45%	75%
Non HR PDR	--	--	75%
High Risk PDR	25-40% develop severe vision loss in 2 years if untreated		



### Referral Criteria

- Refer within 2 - 4 weeks
  - Macular edema
  - Severe or very severe NPDR which may be treated if risk factors
    - » Hx of PDR or poor vision in fellow eye, poor DM control, risk of being lost to follow up,
    - » renal disease, pregnancy
  - Early (Non-high-risk) PDR
- Refer within 24 - 48 hours
  - High risk PDR or Vitreous heme



### PDR

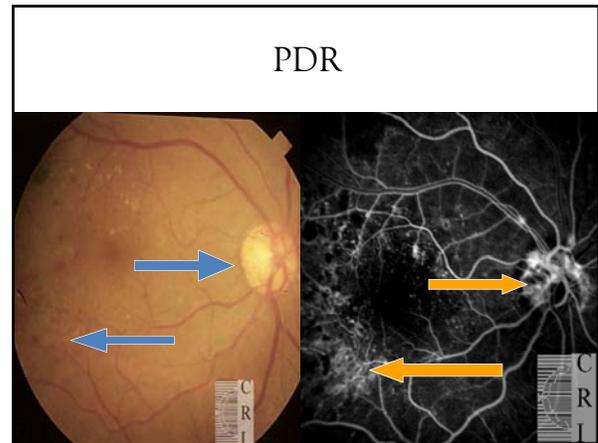
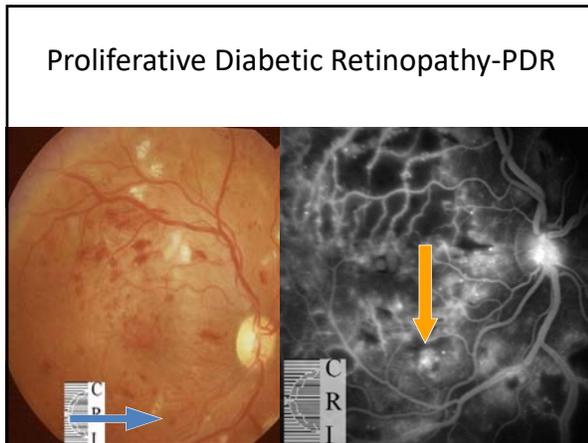
- Hallmark sign is any neovascularization: NVI, NVE or NVD
- Common patient presenting symptom is blurry vision secondary to vitreous heme
- Concern of tractional retinal detachment secondary to fibrotic proliferation
- Management is retinal consult for possible PRP, vitrectomy, and new anti-VEGF injection.
  - Alternative to vitrectomy for vitreous heme is Vitrase (hyaluronidase) which liquifies the vitreous heme.



### High Risk PDR

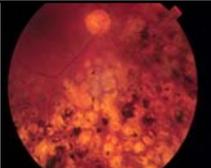
- High risk PDR is characterized by the following:
  - NVD > 1/4 to 1/3 disc area
  - Any NVD with a preretinal or vitreous hemorrhage
  - Moderate to severe NVE with a vitreous or preretinal hemorrhage
  - Any NVI





### Treatment of PDR

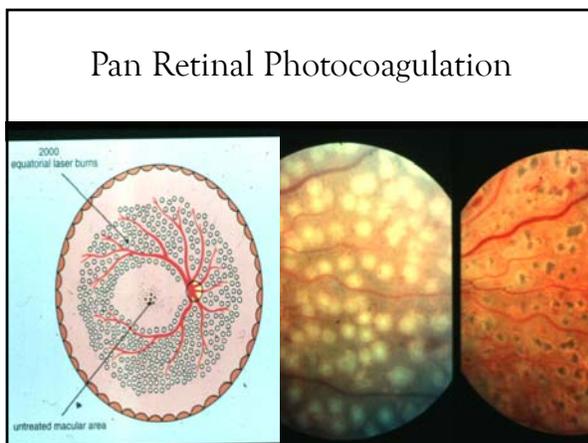
- Panretinal photocoagulation
  - Laser absorbed by RPE
  - 1200 to 2400 burns
  - Placed in scatter pattern on retina to reduce NV (spare macula)
  - Reduced risk of severe vision loss at 6 years by 50% in Diabetic Retinopathy Study
  - Regression of NV occurs in 30 – 55% of eyes
  - Follow q 2- 4 months




### Panretinal photocoagulation (PRP) indications

- High risk PDR including NVD indirectly
- Rubeosis (NVI) with or without glaucoma (indirectly)
- Non-high risk PDR (occasionally)
- Widespread retinal ischemia and capillary non perfusion





### Treatment of PDR

- Lucentis effectively treats PDR
- The Diabetic Retinopathy Clinical Research Network enrolled 305 participants with proliferative diabetic retinopathy in one or both eyes to randomly receive Lucentis or laser therapy.
- Laser group:
  - 50% required more than one treatment of laser
  - No improvement in VA
  - Significant loss of side vision and 28% developed DME



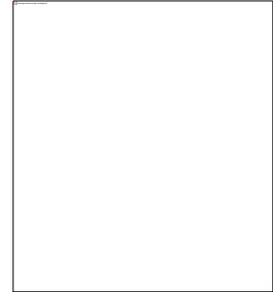
## Lucentis for PDR

- Lucentis group:
  - Injection once a month for three months or until retina stabilized
  - No loss of side vision
  - Improvement of half of line of VA over two years and only 9% developed DME
- Lucentis appears to be a safe alternative versus PRP for PDR
- Patients will be followed for 5 years



## Diabetic Papillopathy

- Visual acuity is often normal or only mildly abnormal.
- Visual fields may be normal or demonstrate a slightly enlarged blind spot;



## Diabetic Papillopathy

- Fundusoscopic examination demonstrates optic disc swelling, often with hyperemia and a striking dilation of the inner optic disc vasculature
- may be unilateral or bilateral; when bilateral, the involvement may be simultaneous or sequential



## Diabetic Papillopathy

- Macular edema is a frequent comorbid finding, occurring in 70 to 100 percent of patients
- If bilateral, then papilledema needs to be eliminated
- no treatment is required or recommended for patients



## Resources

- Basic tutorial on diabetes:
  - Canadian Diabetes Association ([www.diabetes.ca](http://www.diabetes.ca)) "Living with Diabetes"
  - American Diabetes Association ([www.diabetes.org](http://www.diabetes.org)) "All About Diabetes"
- More health care professionally related sites:
  - [www.diabetes.ca:80/for-professionals/](http://www.diabetes.ca:80/for-professionals/)
  - [www.diabetesincontrol.com](http://www.diabetesincontrol.com)
  - [www.presentdiabetes.com](http://www.presentdiabetes.com)

