Ocular Manifestations in Diabetes

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Disclosures and Special Request

Paid consultant for:

- Alcon Pharmaceuticals, Bausch and Lomb, Carl Zeiss Meditec, Merck Pharmaceuticals, NiCox, SARCcode

Special Request:

Interactive remotes don’t work on your TV, so please don’t take them home! 😊

Commitment to change:

- write down three things that you “learned” from this presentation that you can incorporate into your practice to improve patient care
- revisit these points a month from now, again in 3 months and 6 months and see if you have adopted them
- make a commitment to change how you care for patients!
Overview

• Definition of diabetes
• Diabetic effects on ocular structures
• Diabetic retinopathy
  – Classification of diabetic retinopathy
  – Treatment and management options
Diabetic Classification

- Classification: IDDM vs Type 1 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)
Type 1 Diabetes

- 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
    - Example: Type 1 diabetes develops more often in winter than summer and is more common in places with cold climates.
- Characterized by an almost total lack of insulin
  - due to destruction of the pancreatic B-cells
  - presentation is usually acute (polyuria and polydipsia)
- Complications (e.g. retinopathy) uncommon before puberty and usually present after 10 years duration
- Mortality is increased over general population
Diabetes

Complications of Chronic Hyperglycemia

- Retinopathy
  - Macular edema
  - Capillary nonperfusion
  - Angiogenesis
  - Hemorrhage
  - Glaucoma

- Stroke

- Heart disease
  - Atherosclerosis
  - Endothelial dysfunction
  - Hypertension
  - Dystlipidemia
  - Procoagulant state
  - Antifibrinolytic state
  - Vascular inflammation

- Nephropathy
  - Damaged glomeruli
  - Hyperfiltration
  - Renal damage

- Peripheral neuropathy
  - Nerve damage
  - Ulceration
  - Necrosis

- Autonomic neuropathy
  - Nerve damage
  - Gastrointestinal dysfunction
  - Genitourinary dysfunction

American Diabetes Association Position Statements. Diabetes Care 2004; 27
28.5% Diabetic retinopathy (DR) in patients 40 years of age or older

≈13% Diabetic macular edema (DME) in patients with DR

8.5% Stroke in patients 35 years of age or older

20.4% Cardiovascular disease in patients 35 years of age or older

33.4% Diabetic nephropathy in diabetes patients

≈60% to 70% Diabetic neuropathy in diabetes patients
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

• Most Type 2 diabetics are:
  – more obese then the background population
    • Obesity on the rise:
      – increased consumption of high calorie diets,
      – changes in lifestyle,
      – lack of exercise.
  – present with insidious symptoms of polyuria, polydipsia and blurred vision
Type 2 Diabetes

– Genetic predisposition to Type 2 stronger than 1
– at least 90% of the total diabetic population
– mortality and morbidity increased with uncontrolled blood pressure and lipid levels.
  • other risk factors include alcohol consumption and smoking.
– Blue Mountain Eye Study indicated that greatest risk factors were:
  • increased blood sugar levels,
  • increased blood pressure,
  • elevated lipid levels, and
  • duration of diabetic condition
Blood Sugar

• Throughout a 24 hour period blood sugar typically maintained between 70-145
  – Diabetes is diagnosed with a fasting BS of \( \geq 126 \) or an A1c value of \( \geq 6.5 \)

• Hypoglycemia is typically defined as plasma glucose 70 or less
  – patients typically become symptomatic of hypoglycemia at 50 or less
# Diagnostic Test For Diabetes

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Results</th>
<th>Confirmation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Plasma Glucose (FPG)</strong></td>
<td>&gt;126 mg/dL suggest DM</td>
<td>Confirm by repeat test on different day</td>
</tr>
<tr>
<td></td>
<td>100-125 mg/dL prediabetes</td>
<td></td>
</tr>
<tr>
<td><strong>Random Plasma Glucose</strong></td>
<td>≥ 200 mg/dL in setting of symptoms indicates DM</td>
<td>Confirm with FPG or OGTT performed on another day</td>
</tr>
<tr>
<td><strong>2-h oral glucose tolerance test (OGTT)</strong></td>
<td>≥200 mg/dL diagnostic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>140-199 mg/dL prediabetes</td>
<td></td>
</tr>
<tr>
<td><strong>Glycosylated hemoglobin:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBA1c</td>
<td>≥6 but &lt;6.5-prediabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥6.5 diabetic</td>
<td></td>
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<tr>
<td></td>
<td><strong>HbA1c is a better predictor of DR than FPG Diabetes Care 2009 November; 32(11): 2027-32</strong></td>
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</tbody>
</table>
Assumptions About Type 2 Diabetes: Disease Progression

Evolution and remission is a continuum within individuals

Pro-Diabetes Factors:
- Obesity
- Inactivity
- Pro-diabetes medications
- Diet
- Aging
- Other medical diagnoses

Anti-Diabetes Factors:
- Lean weight
- Active
- Anti-diabetes Rx
- Diet

Normal Blood Glucose (Genetic Diabetes)

Pre-Diabetes

30-40%

Diabetes
Risk Factors for Type 2 Diabetes

• Age > 45 yrs
• 1st degree relative with type 2 DM
• AA, Hispanic, Asian, Pacific Islander or Native-American heritage
• History of gestational DM
• Overweight, especially abdominal obesity
• Cardiovascular disease, hypertension, dyslipidemia or other metabolic syndrome condition
too much food, with too much animal fat

not enough exercise

one set of genes inherited from parents make you hungry

other set of genes inherited from parents make islet cells in pancreas wear out early; cannot make enough insulin

another set of genes causes greater insulin resistance

overweight: need extra insulin as body becomes 'resistant'

fatty deposits in pancreas cause even more damage

Result

body needs more insulin but cannot produce it

type 2 diabetes
## Oral Drug Therapies for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Biguanides (metformin)</td>
<td>Suppresses glucose production and improves insulin sensitivity</td>
</tr>
<tr>
<td>Sulfonylureas (glimperpiride, glipizide, glyburide, acetohexamide, etc)</td>
<td>Increases pancreatic secretion of insulin</td>
</tr>
<tr>
<td>Thiazolidinediones (rosiglitazone and pioglitazone)</td>
<td>Increases sensitivity to insulin</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Reduces GI carbohydrate absorption</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Increases pancreatic secretion of insulin</td>
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# Recommendations for Management

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<table>
<thead>
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<tbody>
<tr>
<td><strong>A1c</strong></td>
<td>Twice yearly if controlled, if not every 3 mo</td>
<td>&lt;7%, and as close to 6% as possible</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td>Annually unless control not achieved</td>
<td>LDL&lt;100 mg/dL, HDL&gt;40 mg/dL, Triglycerides&lt;150</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>Every visit, monthly until control reached</td>
<td>&lt;130/80 mm Hg</td>
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HbA1c

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

<table>
<thead>
<tr>
<th>HbA1c test score</th>
<th>MEAN BLOOD GLUCOSE mg/dL</th>
<th>mmol/L</th>
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<tbody>
<tr>
<td>14.0</td>
<td>380</td>
<td>21.1</td>
</tr>
<tr>
<td>13.0</td>
<td>350</td>
<td>19.3</td>
</tr>
<tr>
<td>12.0</td>
<td>315</td>
<td>17.4</td>
</tr>
<tr>
<td>11.0</td>
<td>280</td>
<td>15.6</td>
</tr>
<tr>
<td>10.0</td>
<td>250</td>
<td>13.7</td>
</tr>
<tr>
<td>9.0</td>
<td>215</td>
<td>11.9</td>
</tr>
<tr>
<td>8.0</td>
<td>180</td>
<td>10.0</td>
</tr>
<tr>
<td>7.0</td>
<td>150</td>
<td>8.2</td>
</tr>
<tr>
<td>6.0</td>
<td>115</td>
<td>6.3</td>
</tr>
<tr>
<td>5.0</td>
<td>80</td>
<td>4.7</td>
</tr>
<tr>
<td>4.0</td>
<td>50</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Very rough estimation: like converting kg to pounds: approx 2.2
Alternatives to Medications

• The Diabetes Prevention Program (DPP)
  – lifestyle modification lowers the risk of developing Type 2 DM in high-risk patients vs. metformin
  – E.g. walking 150 minutes per week

• The DPP Ten Years Out:
  – 38% reduced risk of with lifestyle modification
  – 17% reduced risk with metformin

• Exercise was twice as effective as drug!
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])

• Diagnosed by presence of pancreatic auto-antibodies such as glutamic acid decarboxylase (GAD) antibodies

• LADA is primarily classified as type 1 diabetes

• Compared to a person with type 2 diabetes, a LADA patient maybe:
  – younger and thinner and
  – usually insulin deficient rather than insulin resistant
  – there is often a family history of autoimmune conditions
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 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
EXTRAOCULAR AND OCULAR EFFECTS OF DIABETES
Orbit (Cellulitis)

- Diabetic more prone to infection and thus are predisposed to acute orbital cellulitis (normally of bacterial origin)
- Orbitorhinomucormycosis is the most dreaded form
  - caused by bread mold
  - develops in patients with severe acidosis and poor metabolic control
Lids

- Ptosis from isolated 3rd nerve palsies and is the result of neuropathy due to microangiopathy. The levator is especially sensitive to chronic hypoxia and thus develops a ptosis.
  - pupils are usually normal,
  - degree of lid closure is influenced by duration of diabetes,
  - more prevalent in Type 1, and
  - ptosis usually recovers within a few weeks.

- Xanthelasmas reported to occur more frequently secondary to elevated serum lipid levels and may reflect poor diabetic control.
Ptosis
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
IOP’s and Glaucoma

• Mean IOP’s in diabetes is higher than the mean for general population

• Clinical observation has demonstrated an increased prevalence of glaucoma in diabetics — though debatable due to the possibility that this is a result of increased observation of diabetics

• Demonstrated that diabetics with glaucoma are more likely to develop field loss and therefore a more difficult disease to manage and need to maintain lower IOP’s than non-diabetics.
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.
Juvenile Diabetic Cataract vs Adult Cortical Cataract

**Juvenile Cataract**
- Typically seen in Type 1 diabetics of young age, rarely seen in Px over the age of 30
- Snowflake variety, with an overlapping network of vacuoles
- Bilateral in presentation
- Rarely affect vision

**Adult Cataract**
- Typically seen in Type 2 diabetics and are similar to senile cortical cataracts except appear early in life
- There is an increased rate of development of the cataracts,
  - I.e. they mature more rapidly in diabetic patients than in the normal population.
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 6-10 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 (Acular qid or newer Xibrom or Nevanac)
- 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 diabetic patients
  – CME that results in diabetics is often much more difficult to treat

• Recommend pre-treating diabetic patients with Acular/Xibrom/Nevanac and throughout post-op treatment
Diabetes and Diabetic Retinopathy

• Diabetes and diabetic retinopathy remains one of the leading causes of blindness and new blindness cases in the US

• Retinopathy increases with duration of the diabetic condition.
  – Poor control and additional systemic conditions (hypertension) may exacerbate the retinopathy.
  – Target BP met only 38% of patients, increasing by 65% chance of needing laser Tx
  – Importance of BP control known but rarely achieved
Diabetic Retinopathy

• Closely related to the duration of the diabetic disease
• 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

• VEGF: vascular endothelial growth factor is crucial in pathophysiology of DR
  – Enhances vascular permeability and key inducer of angiogenesis
  – Increased in patients with CSME, directly correlates with breakdown of blood-retinal barrier
  – Experimental injection of VEGF in healthy eyes induces diabetic-related ocular pathologies
Diabetic Retinopathy Signs

• Microaneurysms
• Retinal edema
• Hard exudates
• Cotton wool spots
• Intraretinal microvascular abnormalities (IRMA)
• Vitreous heme
• Neovascularization (NVE, NVD, NVI)
Microaneurysms
Hemorrhages-Pre-retinal
Hemorrhages-Nerve Fiber Layer
Hard Exudates
Cotton Wool Spots
Intraretinal Microvascular Abnormalities (IRMA)
Vitreous Hemorrhage
Neovascularization of the Disc-NVD
Neovascularization of the Iris-NVI
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

• Within PDR you have high risk factors
# NPDR

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Occasional MA’s, dot blots or exudates</td>
<td>Document and f/u in 6-12 mo</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hemes and/or Ma’s, CWS in 3-4 fields</td>
<td>Increased risk of PDR, f/u in 3-6 months</td>
</tr>
<tr>
<td>Severe</td>
<td>Large hemes, CWS and venous beeding in 2 quads, IRMA present</td>
<td>&gt;50% progress to PDR. Follow closely and consider retina</td>
</tr>
</tbody>
</table>
Non-proliferative Diabetic Retinopathy-NPDR
Clinically Significant Macular Edema (CSME)

• Also referred to in the literature 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 of center of fovea
Clinically Significant Edema - CSME (DME)
CSME (DME): Cirrus OCT
CSME (DME) Treatment

• Focal/grid laser treatment has been gold standard and decreases proportion of patients who develop significant loss of vision (blindness) by 50% over 5 years.

• Oxygen theory proposed mechanism of action.
  – Coagulation of RPE and adjacent photoreceptors results in decreased O2 consumption with no change in O2 diffusion from choroid.
  • results in increased O2 tension in retina and decreased VEGF production and subsequent decreased vascular permeability.
Focal/Grid Photocoagulation
CSME (DME) Treatment: Steroids

• Additional treatment options for CSME include Triamcinolone (kenalog) injections (implantable options in clinical trials)
  – Demonstrated ability to completely resolve CSME
  – Effect is temporary (6-9 months)
  – Complications include:
    • 40% develop secondary OHTN
    • 1-2% develop medically uncontrollable IOP
    • 15-20% develop surgical cataracts
    • 1:1000 post-op infectious endophthalmitis
VEGF and DME

Normal retina

Retina with DME

Microvascular damage
Ischemia
Increased permeability
Leakage
Macular edema

Diabetes
Metabolic response

↑VEGF

Neovascularization
CSME (DME) Treatment: anti-VEGF

- **Ranibizumab (lucentis) for Edema of the Macula in Diabetes (READ-2)**
  - during a span of 6 months, ranibizumab injections had a significantly better visual outcome than focal/grid laser treatment in patients with DME. *Ophthalmology* 2009 Nov; 116(11): 2175-81

- Intravitreal ranibizumab (lucentis) with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula. *(Ophthalmology 2010;117:1064–1077)*
Aug. 10, 2012: FDA approves Lucentis to treat diabetic macular edema

• The drug’s safety and effectiveness to treat DME were established in two clinical studies involving 759 patients who were treated and followed for three years.
  – patients were randomly assigned to receive monthly injections of Lucentis at 0.3 milligrams (mg) or 0.5 mg, or no injections during the first 24 months of the studies
  – after 24 months, all patients received monthly Lucentis either at 0.3 mg or 0.5 mg

• Results:
  – 34-45% of those treated with monthly Lucentis 0.3 mg gained at least three lines of vision compared with 12-18% of those who did not receive an injection.
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
Proliferative Diabetic Retinopathy - PDR
PDR
Recent Patient
Pan Retinal Photocoagulation
New DR ICD-9 Codes (as of October 1st, 2005)

• 362.03 NPDR NOS (no other symptoms)
• 362.04 Mild NPDR.
• 362.05 Moderate NPDR.
• 362.06 Severe NPDR. (4-2-1 rule)
• 362.07 Diabetic macular edema
• 362.02 PDR
• Remember these codes must be linked up to your 250 codes!
Resources

• Basic tutorial on diabetes:
  – Canadian Diabetes Association (www.diabetes.ca) “Living with Diabetes”
  – American Diabetes Association (www.diabetes.org) “All About Diabetes”

• More health care professionally related sites:
  – www.diabetes.ca:80/for-professionals/
  – www.diabetesincontrol.com
  – www.presentdiabetes.com