Course Description

Because of complex structure of the eye with its multitude of different tissue types, many systemic diseases affecting different tissues types can also show ocular findings. The eyes, though this mirroring of the body, can give important clues to underlying systemic diseases, both clinically manifested and occult, in our patients. In this presentation, systemic diseases that commonly affect the eyes are presented, along with recommend work-up, traditional medical management, and supplemental/nutritional management.

Learning Objectives

• To list the systemic diseases that most commonly affect the eyes.
• To review clinical manifestations, both ocular and systemic, of the more common systemic diseases that affect the eyes.
• Discuss medical management, including both the strengths and weakness of current treatments.
• Review evidence of how supplements and nutrition can impact the management and course of the different systemic diseases presented.

Common Systemic Diseases with Ocular Findings

1. Diabetes mellitus
2. Hypertension
3. Atherosclerosis
4. AIDS
5. Grave’s Disease
6. Sarcoidosis
7. Systemic lupus erythematosus
8. Arthritis
9. Sickle cell disease
10. Multiple sclerosis
11. Cancer

Traditional vs. Complementary vs. Alternative vs. Integrative Health

Diabetes mellitus (DM)

Prevalence - 26 million in the United States → 8.3% of the population
79 million → pre-diabetes

Mortality - diabetes listed as underlying cause on 71,382 death certificates and as a contributing factor on additional 160,022 death certificates → contributed to a total of 231,404 deaths in 2007 (2011 National Diabetes Fact Sheet)
Complications
Heart disease and stroke – risk of either is 2 to 4X vs. non-diabetic
High blood pressure
Kidney disease – DM leading cause of kidney failure
Neuropathy – up to 70% of diabetics
Amputation – 60% non-traumatic lower limb
Blindness - leading cause new cases blindness adults 20–74 yo
- examples of common ocular findings in DM

Labs
1. Fasting Plasma Glucose (FPG)
   >126 mg/dL suggests DM
   100-125 mg/dL pre-diabetes
   *(confirm with repeat test different day)*
2. Causal Plasma Glucose
   > 200 mg/dL with symptoms → DM
   *(confirm with FPG or OGTT different day)*
3. 2-hr oral glucose tolerance test (OGTT)
   >200 mg/dL → dm
   140-199 mg d/L pre-diabetes
4. Glycosylated hemoglobin: A1C
   >6.5 → DM
   >6.0 but <6.5 → pre-diabetes

Which lab is best predictor of diabetic retinopathy :

![Image of graph showing sensitivity and specificity of A1C and FPG](image)
*(Diabetes Care 2009 November; 32: 2027-32)*

Medication Classes for Type-2 DM based on mechanism of action
Biguanides → Suppress glucose production/improve insulin sensitivity
Sulfonylureas and Meglitinides → Increases pancreatic secretion of insulin
Thiazolidinediones → Increases sensitivity to insulin
Alpha-glucosidase inhibitors → Reduce GI carbohydrate absorption
Insulin → moves glucose from bloodstream into cells
ACP Clinical Practice Guidelines Type-2 DM

<table>
<thead>
<tr>
<th>Dietary Supplements (with best evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium picolinate</td>
</tr>
<tr>
<td>increases insulin-responsive glucose transport (GLUT4)</td>
</tr>
<tr>
<td>enhances tyrosine phosphorylation insulin receptor</td>
</tr>
<tr>
<td>dosage → 200-1000 mcg daily in divided doses</td>
</tr>
<tr>
<td>Note: some multivitamins use chromium chloride, which is poorly absorbed</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Magnesium</th>
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<tbody>
<tr>
<td>increases insulin sensitivity and secretion</td>
</tr>
<tr>
<td>forms of magnesium</td>
</tr>
<tr>
<td>dosage → 360 mg daily</td>
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<table>
<thead>
<tr>
<th>Botanicals</th>
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<tbody>
<tr>
<td>Cinnamon – true cinnamon (Cinnamomum verum) vs (Cinnamomum cassia)</td>
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<tr>
<td>American ginseng</td>
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<tr>
<td>Bitter melon</td>
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**Hypertension (HTN)**

Prevalence - 76.4 million ≥20 yo in United States → approximately 30% of adults
- increasing incidence in children

Mortality – increases risk for heart disease and stroke, the first and third leading causes of death in the United States
Complications
- Heart attack or stroke
- Heart failure
- Kidney failure
- Aneurysm
- Dementia

Ocular
- Chronic hypertensive vascular changes
- Acute hypertensive retinal changes
- Acute hypertensive choroidopathy
- Acute hypertensive optic neuropathy

Staging systems for hypertensive retinopathy

Blood pressure stages

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>120/80-139/89</td>
<td>Lifestyle modifications</td>
</tr>
<tr>
<td>Stage 2</td>
<td>140/90-159/99</td>
<td>Medication (Diuretics)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>160/100-179/109</td>
<td>Medication (Beta-blockers, ACE inhibitors)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>180/110+</td>
<td>Hospitalization</td>
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</tbody>
</table>

→ why you should measure BP on both arms
→ elevated BP and dilation – when should you not dilate

Medication Classes for Hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| Diuretics | • HCTZ (hydrochlorothiazide)
• Lasix (Furosemide)
• Trandolapril + HCTZ (Valz, Maxzide) |
| Increase sodium & water excretion by kidneys |
| Beta-adrenergic blockers | • propranolol
• metoprolol (Lopresor)
• atenolol (Tenormin) |
| Decrease cardiac output & peripheral vascular resistance |
| Alpha-adrenergic blockers | • captopril (Capoten)
• enalapril (Vasotec)
• lisinopril (Prinivil, Zestril) |
| Block an enzyme in the kidneys
This...
- reduces vasoconstriction
- stimulates water excretion |
| Calcium channel blockers | • verapamil (Calan)
• nifedipine (Procardia)
• amlodipine (Norvasc, Lotrel) |
| Prevent entry of calcium into cardiac and smooth muscle cells
This...
- results in vasodilation,
- which lowers blood pressure |
| Alpha-adrenergic blockers | • doxazosin (Cardura)
• terazosin (Hytrin)
• prazosin (Minipress) |
| Cause vasodilation
This...
- decreases blood pressure |
**Dietary Supplements**

**Folic acid**
- cofactor for nitric oxide synthase
- dosage → 1000 ug daily in females, males possible cancer risk with high dose

**Vitamin D**
- inverse relationship between plasma 25-hydroxy vit. D and HTN risk
- dosage → studies mixed, dosage for HTN not established

**Vitamin C**
- high dosages can reduce BP by about 5 mmHg
- dosage → 500 mg daily

**Magnesium**
- involved in activation of calcium activated potassium channels
- dosage → 360 mg daily

**Cocoa**
- increases production of nitric oxide (NO)
- dosage → 3 oz. dark chocolate

**Omega-3 fatty acids**
- best source from cold water fish
- dosage → as high as 3 grams in studies, bleeding of concern at that level

**Grave’s Disease**

Prevalence - 13 million in United States (~50% dx’ed)
- most common cause of hyperthyroidism in the United States

Complications (systemic)
- Cardiac problems including heart failure
- Thyroid crisis - rapid heartbeat, fever, and worsening of all sx’s → fatal if not tx’ed

Ocular
- Female:Male, 3:1 fourth/fifth decades Autoimmune, can be unrelated thyroid status
- IgG orbital/extraorbital antigen Increased serum IgE Increased edema and orbital volume Lymphocytic/plasmacytic infiltration EOM fibrosis

Grave’s Ophthalmopathy/TED correlation not 100% between ophthalmopathy & thyroid hormone status:
- Hyperthyroid >50% pts Hyperthyroid at Dx TED
- Euthyroid (most of remaining pts)
- many go on to develop hyperthyroidism existing subtle thyroid dysfunction
- Hypothyroid (MUST ASK ABOUT PRIOR TX!)
  - most had radio-I\(^{131}\) tx for hyperthyroid, rare cases of primary hypothyroid

Exposure Keratitis
- Dry eye very common complaint: eyelid dysfunction, proptosis, loss of Bell’s phenomenon with restrictive myopathy
- Untreated can lead to ulceration and perforation

EOM Involvement
- present in up to 80% of patients
- typically IR>MR>LR>SR
- forced duction + (may be neg. early in disease)
- rare cases of muscle paresis
Optic Neuropathy
5% Grave’s patients
most do not have marked proptosis or optic nerve head changes
insidious onset
worse/more progressive in smokers
decreased VA, color vision, APD(<50% pts)

Laboratory Testing (Don’t need for ocular dx...do to r/o systemic involvement)
TSH -single best test
Hyperthyroidism → low TSH
Hypothyroidism → high TSH
T4 - most is bound to proteins → order free T4 instead (direct measurement T4)
T3
RT3 – reverse T3 (consider for hypothyroid cases)

When to order antibody studies?
TSH receptor antibodies (TRAb)
TSH stimulating antibodies (TSAb)
Thyroid-Stimulating Immunoglobulins (TSI)

Imaging Studies (For ocular dx)
CT imaging → study of choice in most places...why it may change in the future
–EOM enlargement sparing tendinous insertions
–orbital fat increased some patients
–occasional lacrimal gland enlargement
–optic nerve compression at apex
Ultrasonography
–no ionizing radiation
–measurement of enlarged EOM’s
–DDx of other causes of enlarged EOM’s
MRI → when indicated, what I learned from a recent case

Treatment
Anti-thyroid drugs → blocks the binding of iodine
Methimazole
Propylthiouracil (PTU) → not used as 1st med because of possible liver failure and death
Radioactive iodine-131 (RAI)
slow working over months
increases risk of TED (15-20%) both short-term and long-term, can steroid tx help?
hypothyroidism incidence rate up to 80%
Thyroidectomy
young patients and pregnant patients
suspicious nodules or suspected cancer, large goiter, concurrent TED

EOM Treatment
prisms
surgery after stable for 6 months
–recessions only
–adjustable sutures
prednisone if congestion/early
radiation tx: if congestion
Optic Neuropathy Treatment
STAT Treatment!
vision loss can be severe to (NLP)
prednisone 100 mg po/dy immediately
–if improved surgery may not be needed
posterior orbital decompression
–must be done prior to muscle surg.
radiation tx
–if not at fibrotic stage and without sig. visual loss

Dietary Supplements
Selenium → for mild TED
improved quality of life measure, reduced ocular involvement, slower progression of
orbitopathy
dosage → 100 mcg twice daily
Additional treatments including accupuncture, meditation, and various mind/body
therapies have been shown to provide comfort in patients with Grave’s disease. Caution
to reduce excess dietary iodine (cow’s milk, bread, seafood, iodized table salt, etc.), and
management of celiac disease if present.

Sickle cell disease
Prevalence - 2 million with sickle cell trait United States
1 in 500 African-Americans and 1 in 1,200 Hispanic-Americans born with
sickle cell disease
Cause characterized by the genetically determined presence of an abnormal type of
hemoglobin in the RBC’s
- hemoglobin S (valine sub. for glutamic acid)
- hemoglobin C (lysine sub. for glutamic acid)
- thalassemia (decrease rate synthesis of the α or β hemoglobin polypeptide chain)
Types
AS (sickle-cell trait)
- mildest form and requires severe hypoxia to produce sickling
SS (sickle-cell disease or anemia)
- causes severe systemic complications and severe hemolytic anemia
- mild and often asymptomatic ocular findings WHY?
SC (sickle-cell C disease) and S-thal (thalassemia)
- mild systemic anemia
- severe ocular complications
8-10% American blacks have some form of hemoglobinopathy
AS.......80%
S-thal...10%
SS.......4%
SC.......1% to 2%
Complications
acute painful episodes last hrs to dys in bones and chest (SS)
repeated vasoocclusion episodes damages the heart, liver, bone, spleen, and
kidneys (SS)
sickle cell trait (AS) are usually hematologically normal, but acute painful episodes can occur with vigorous exertion, poor physical condition, heat, dehydration, asthma, or at high altitudes. Increased hemoglobin F levels if increased associated with more benign clinical course.

Labs

1. Sickledex: in-office screening for sickle cell
2. Electrophoresis → required to confirm the diagnosis and determine which type of disease is present

Family pedigree can also be useful

Ocular

(Primary affects retina)
comma or "S"- shaped capillary segments in the bulbar conj.
focal iris atrophy
anterior segment ischemia/necrosis

Non-proliferative retinopathy: (follow pt at this disease stage)
venous tortuosity
black sunburst
- localized pigmented lesions in fundus periphery secondary to old intraretinal or subretinal hem.
- represents reactive RPE hyperplasia
salmon-patches
- peripheral intraretinal hemorrhages
- resolved → small retinoschisis cavity w shining crystals or black sunburst
angiod streaks

Proliferative sickle retinopathy: (follow until Stage 3)
occurs in retinal periphery at junction of perfused (posterior) and non-perfused (peripheral) retina

STAGES:
Stage 1- peripheral arteriolar occlusion
Stage 2- peripheral arteriovenous anastomoses
Stage 3- proliferative lesions have a "sea fan" configuration, with feeding arterioles and draining venules
Stage 4- hemorrhage from neovascularization
Stage 5- rhegmatogenous or tractional RD

Treatment

Supportive - avoid situations that precipitate sickling episodes: low O2, infections, cold exposure, physical exertion, acidosis, and dehydration
PO hydroxyurea with acute/recurrent pain crises → increases hemoglobin F levels
Avoid CAI’s (Acetazolamide) in glaucoma patients
Prophylactic tx has not been shown to be effective in preventing neovas.
- monitor until stage II
- scatter laser tx (i.e. PRP) for neo
- standard vitrectomy/RD surg. (↑ risk ant. seg. ischemia)
- What about anti-VEGF?

Dietary Supplements

Folic acid
involved in erythropoiesis to reduce the degree of anemia
dosage → 1 mg daily
Magnesium

reduce

erhrocyte dehydration w possible reduction of acute pain episodes
dosage \( \rightarrow 540 \text{ mg daily} \) (final dosage still to be established)

L-arginine

works as a vasodilator by increasing NO levels, typically low in patients with SS
dosage \( \rightarrow 2 \text{ g to 8 g daily} \) in divide dose (final dosage still to be established)

Omega-3 fatty acids

increases fluidity of RBC membranes
dosage \( \rightarrow 1 \text{ gram daily} \) (final dosage still to be established)

Zinc

increases the oxygen-carrying capacity of RBC, reduces cell damage
dosage \( \rightarrow 220 \text{ mg three times daily} \)

**Multiple sclerosis (MS)**

Prevalence - 350,000 in United States

varies by location increasing the farther from the equator in either hemisphere

Types 4 clinical patterns:

![Graph of disability over time for different clinical patterns of MS](image)

(Neurology 1996;46:907-911)

Complications

Fatigue
Loss of mobility (spasticity)
Bowel and urinary dysfunction
Cognitive issues/depression
Paralysis (typically in the legs)
Ocular – INO/BINO, palsies, ON, uveitis, CNS field loss

Imaging

Magnetic resonance imaging (MRI)

T1-weighted (is contrast needed?)
T2-weighted w FLAIR
Diffusion-weighted

OCT

NFL loss even in the absence of clinically evident optic neuritis with the
degree of NFL loss correlated with the duration of the disease

Recent review paper (2011) online:

Risk of MS  Longitudinal Optic Neuritis Study
Predictors of developing MS:
- initial MRI with signal abnormalities
  [BEST PREDICTOR]
- optic neuritis in fellow eye
- vague, nonspecific neurologic symptoms
- prior paresthesias
- pain on eye movement (retrobulbar)
- female
- Caucasian
- <30 yo at presentation (young)

Treatment

Dietary Supplements
Omega-3 and/or omega-6 fatty acids
  studies have been mixed on results
B12 and magnesium
  may help with motor function loss
  blood levels should be measured for dosing guidance
Vitamin D
  preventive in action, at high dosages can reduce number relapses
  dosage → 1000-2000 IU daily, study to reduce relapses used 14,000 IU daily
N-acetylglucosamine (GlcNAc)
  inhibited the growth and function of abnormal T-cells in mouse model similar to
  what is seen in the autoimmune dysfunctions of MS patients
  dosage → still to be established
Reduce saturated-fat in diet
  reducing saturated-fat decreased sx’s of MS
  incidence of MS lower in populations that have limited saturated-fat diets

Video Presentation TEDxTalks
  Dr. Terry Wahls - used diet to help manage her MS and get out of her wheelchair
Good Websites for additional information on complementary medicine:

1. University of Maryland Medical Center
   http://www.umm.edu/altmed/

2. National Center for Complementary and Alternative Medicine
   http://nccam.nih.gov/

3. Natural Standard - provides high-quality, evidence-based information about complementary and alternative medicine including dietary supplements and integrative therapies, some aspects require subscription or library access
   http://www.naturalstandard.com/

4. Natural Medicines Comprehensive Database - “Unbiased, Scientific Clinical Information on Complementary, Alternative, and Integrative Therapies”, some aspects require subscription or library access
   http://naturaldatabase.therapeuticresearch.com/