Age-related Macular Degeneration Update

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Financial Disclosures
- Honoraria
  - Review of Optometry
  - Optometric Management
  - Maculogix
- Paid Advisory Board Member
  - Zeiss
  - EyePromise/Zeavision
  - Genentech
  - Regeneron

Financial Disclosures
- Proprietary Interests
  - None
- Consulting Fees
  - Zeiss
  - EyePromise/Zeavision
- Stockholder: Zeavision

E-Newsletter
QUESTIONS?

Course Goals

- To provide clinically useful information about AMD
- Prevention
- Early diagnosis
- Treatment and management

AMD Beyond the Post Pole

Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2

Amitha Domalpally, MD, Traci E. Clemons, PhD, Ronald P. Danis, MD, Srinivas R. Sadas, MD, Catherine A. Cukras, MD, PhD, Cynthia A. Toth, MD, Thomas R. Friberg, MD, Emily Y. Chew, MD

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Bob Marley
get up, stand up

optometricretinasociety.org
What are the four primary retinal pigments?

- Lutein and Zeaxanthin – found in the macula’s sensory layers
- Melanin – found in the RPE
- Lipofuscin – found in the RPE

Xanthophylls and AMD

- Lutein, zeaxanthin, and their metabolites help form the macular pigment.
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants and blue light screening compounds

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The Importance of Macular Pigment

- Filters blue light
- Acts as an antioxidant by quenching free radicals
- Provides support to sensory retina

Macular Pigment Optical Density (MPOD)

Heterochromatic Flicker Photometry (HFP)

Risk assessment, early detection and monitoring of AMD

- Macular Pigment Optical Density (MPOD)

Test Results

Macular Pigment Optical Density (du)

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<td>0.10-0.30</td>
<td>0.30-0.50</td>
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MPOD is the IOP for AMD

MPOD Summary

- Macular Pigments are important photoprotectants and antioxidants
- Low MPOD is a modifiable AMD risk factor
- Increasing MPOD improves visual function
- Measuring MPOD is fast, affordable, accurate, important
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About AMD

“Dry”

“Wet”

Drusen, RPE clumping, RPE atrophy

CNVM

“Dry” ARMD = 85-90% of all cases

“Wet” ARMD = 10-15% of all cases (90% of all cases of severe vision loss)

Drusen are the earliest clinically detectable ophthalmoscopic sign of AMD. **

Mixed Drusen

20% of eyes with dry AMD eventually convert to Wet AMD. **
Advanced Atrophic AMD

Advanced Neovascular AMD

Fundus Biomicroscopy

Both Wet and Dry (Advanced x 2)

**The “gold standard” for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients is Fluorescein Angiography.**

Statement of The Problem

- The AMD “Epidemic”
- AMD is the leading cause of blindness in individuals over the age of 50 in the developed world.

The Burden of Disease

Prevalence of Ocular Diseases
- Glaucoma: 4 million
- Diabetic Retinopathy: 5 million
- Intermediate AMD: 8 million

1. Age-Related Eye Disease Study 1 data

Epidemiology
- 2004 data: 15 million affected in the US
- 2012: 17 million
- 2016: 20 million
- Distribution (age)
  - 55–64: 17% of Caucasians have AMD
  - 65–74: 26%
  - >75: 42%


AMD: A Changing Environment
- How will these dramatic changes and projections impact your practice?

What is AMD?
- AMD is a heterogeneous disorder affecting the RPE/Bruch’s membrane/choriocapillaris complex.
- Early disease is classically characterized by minor vision loss associated with focal or diffuse sub-RPE debris and changes in RPE pigmentation.
- Late, advanced disease is characterized by severe vision loss associated with extensive RPE atrophy with or without the sequelae of choroidal neovascularization.


What is AMD?
- Continuum of Normal Aging and Disease
- Degenerative changes are observed in maculae of most elderly persons to some degree.
Terminology

- **Age Related Maculopathy (ARM)**
  - age related changes in central retina
  - Examples: drusen, RPE disturbances

- **Age Related Macular Degeneration (AMD)**
  - retinal status when vision deteriorates

What is AMD?

- Cell Death and Functional Loss *
  - Only in some individuals do age-related changes progress to this stage

- Transition From “Normal Aging” to Disease?
  - Loss of Visual Acuity
  - Funduscopic Appearance
  - Measurable Loss of Functional Vision *

The 4 Seasons of AMD

- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization

Stages of AMD

- Early AMD
- Intermed. AMD
- Advanced AMD
- CNV
- GA

Classification of AMD

- **Non-exudative (atrophic, “dry”)**
  - Can be performance-degrading
  - Majority of AMD cases

- **Exudative (neovascular, hemorrhagic, “wet”)**
  - Choroidal NV – devastating to central VA
  - Minority of AMD cases
  - Majority of vision loss

Dry AMD is the new Wet AMD.
The AMD “Epidemic”
*How should we as optometrists respond?*

Prevention
Early Diagnosis
Early Intervention
Improved Visual Outcomes

A recent review of the **global prevalence** of AMD shows that the number of people with AMD in 2020 is projected to be 196 million, which will increase to 288 million in 2040.

**Intermediate Stage AMD**

- AREDS Category 3
  - Extensive intermediate drusen (63-124µ diameter)
  - At least one large druse (>125µ)
  - Geographic atrophy not involving the foveal center

**Soft drusen**: Large, ill-defined, and confluent

**Unfavorable prognostic signs leading to CNVM, GA:**

- Soft, large, confluent drusen
- Reticular (pseudo) drusen*
- Focal hyperpigmentation
- Disciform lesion in the fellow eye
- Older age
- Poor dark adaptation*
It would be naïve to assume that only 6 vitamins/nutrients are important in retinal health.

A Rod-centric Model of Disease

- In maculae of healthy, young adults, rods outnumber cones by 9:1.
- Therefore, the macula may be described as cone-enriched but rod-dominated.
- In AMD, central rods die first, followed shortly by the nearby cones.

Beyond AREDS: broad-spectrum antioxidant AREDS 2 Plus formulae

**Supplement Facts**

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<td>HPLC tested for impurities</td>
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<td>Total (as Cholesterol)</td>
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A Rod-centric Model of Disease

Patients with pre-AMD often complain of difficulty with activities performed at night and under low illumination (e.g., driving, reading).

Early Detection of Degenerative Change in “Subclinical AMD” or “Pre-AMD”

- DA measures the time for retinal adaptation after exposure to a light stimulus.
- Poor DA is a functional manifestation of early disease.
- Rod intercept (RI) is analogous to A1C.

Dark Adaptation (RI) is the A1C for AMD

QUESTIONS?

AdaptDx Pro

- Eye tracking technology automatically aligns with the eye to capture an accurate measurement of dark adaptation function.
- Interactive LCD screen
- On-board technician, Theia™, guides patients through the test.
- Powered by artificial intelligence.

Imaging the Macula

Invasive Methods
Fluorescein Angiography (FA)

- FA answers the question: is the blood-retinal barrier intact?

The “gold standard” for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients.

Conversion to Exudative AMD

- **20% of dry (non-exudative) AMD eyes progress to wet (exudative) AMD,**

**Indocyanine green (ICG) is a dye that is used as an alternative to fluorescein.**

Indocyanine Green Angiography

- Clinical CNVM Case

Common Causes of CNV

- **Exudative AMD**
- Ocular Histoplasmosis
- High Myopia
- Angioid Streaks
- Choroidal Rupture
- Chronic CSC (less common)
CNV Variants

Polypoidal Choroidal Vasculopathy (PCV)

Retinal Angiomatous Proliferation (RAP)

Advanced AMD

Defined as either:
- Geographic atrophy (GA)
  - Atrophy of the RPE and/or photoreceptors, CC
  - "End-stage" non-exudative (dry) AMD
- Choroidal neovascularization (CNV)
  - Exudative "wet"

80-90% of advanced AMD cases are due to CNV.
CNVM Size and Progression

Average size CNV lesion @
diagnosis 3000-3300 μm

Growth = ~10-20 μm/day
Too large, too late

Olsen, TW Ophthalmology Feb. 2004

Retina Quiz: CNV Tx

Which of the following is the main advantage of Photodynamic therapy (PDT) over traditional laser photocoagulation?

- a. Lower cost for PDT
- b. More scar tissue formation in PDT
- c. Less scar tissue formation in PDT *
- d. PDT uses a “hotter” laser

Antiangiogenic Drugs:
VEGF Inhibitors

VEGF binds to receptor

~30% showed improved VA in
ANCHOR, MARINA
New Therapy with a Fraternal Name: Brolucizumab

- Humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A.
- Phase III data from the HAWK and HARRIER trials.
- May allow for an extended interval between intravitreal injections for CNV, thus reducing the treatment burden.

Brolucizumab

Figure 1. Brolucizumab may allow for an extended interval between intravitreal injections for CNV lesions, as revealed with Direct OCT/CHIP with Angiography (from).

AMD and Drusen

- AMD is a disease resulting from poor “Waste Management”.
- Drusen are “pockets of inflammation”
  - Recent investigations show that proteins associated with inflammation and immune-mediated processes are prevalent in drusen.

Drusen

Drusen is the earliest clinically detectable feature of AMD.**

AMD: a sick eye in a sick body?

Figure 1. Hypothetical Common Inflammatory Pathway

- Three Key Retinal Disease Factors
  - Inflammation
  - Angiogenesis
  - Vascular Leakage

MCP-1 = Monocyte chemoattractant protein-1

MCP-1 = Monocyte chemoattractant protein-1

Common Pathway

- IL-6
- IL-8
- MCP-1
- VEGF

BRVO: Branch retinal vein occlusion
CRVO: Central retinal vein occlusion
Other retinal inflammatory diseases
Parallel Worlds: Heart Disease and AMD

- Diet – Low fruit/vegetable consumption increases risk of AMD and CVD
- Obesity and physical inactivity
- C-reactive protein (elevated)
  - Inflammatory marker
- Homocysteine (elevated)
- Omega-3 EFA may be beneficial for AMD patients
- Cholesterol (elevated)
- Serum Iron – Increased amounts may increase AMD and CVD

Optical Coherence Tomography

OCT uses low-coherence interferometry to obtain real-time, cross-sectional histology of live tissue (virtual biopsy).
The earliest clinically detectable feature of AMD is Drusen.

Reticular (Pseudo)drusen (RPD)
- Seen as a reticular pattern of small yellow-white lesions often in the superior macula. RPD are a high-risk sign for advanced AMD.

Presence of RPD is a consistent risk factor for progression to both atrophy and CNV.
- IS/OS C-scan
- B-scan

Spectral Domain OCT shows CNV
- **Current commercially available Spectral Domain OCT is capable of obtaining 3-5 um resolution**
Vitreomacular Adhesion in AMD

- May hasten progression/conversion from dry to wet disease.

Key Point

New CNV typically shows increased retinal thickness on OCT due to fluid leakage

WHAT IS ENHANCED DEPTH OCT IMAGING?

- EDI-OCT
- Enhanced-depth imaging (EDI) OCT modifies the standard technique of image acquisition to better reveal the structural details of the choroid.

EDI SHOWS DEEPER INTRAORBITAL ON, LAMINA, C/S JXN

OCT Structural Changes: FV Scar
ORT is a feature of photoreceptor rearrangement after retinal injury.
Functional Testing in AMD

• Benefits of early detection and treatment of neovascular AMD are evident from both clinical trials and “real-world” outcome studies.
• There has been rapid evolution in the sophistication and utility of visual function testing; in particular preferential hyperacuity perimetry (PHP).
• Sensitive and specific home monitoring is available for patients at risk for exudative disease.

Structure and Function

• OCT and PHP work synergistically

Case

• 81 Year old Female with a history of arthritis.
• 7 year history of injections with Avastin or Lucentis
• PMH: AMD OU, Cataracts OU
• OcHx: Injections for Wet AMD in OD
Ophthalmic Exam

- VA:
  - OD: 20/400
  - OS: 20/80
- IOP:
  - OD: 11
  - OS: 12
- SLE:
  - OD: NS +1
  - OS: NS + 1
- DFE:
  - RPED OD and Geographic Atrophy OS

After Switching to Eylea

- VA 20/400
- VA 20/50

Another RPED example

OD Comparison

- 7 Years of Avastin and Lucentis
  - 20/400
- 2 Injections of Eylea
  - 20/50

VA 20/50

VA 20/25

Six mon s/p IV Lucentis x 6
Autofluorescence (FAF)

- **Principle**
  - When stimulated with light in the blue range, lipofuscin granules emit yellow fluorescence.
  - Patterns of fundus autofluorescence may predict which cases will progress more quickly.

Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites

Reduced degradation of cellular debris leads to the accumulation of lipofuscin, toxic vitamin A metabolites.

Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites

Autofluorescence

Fundus Autofluorescence
Wet AMD
Multi-Modality Imaging

- Color photography
- Infrared
- Red-free
- FAF
- Fluorescein Angiography
- Indocyanine Green Angiography
- OCT/OCT-A

Simultaneous FAF and OCT

Geographic Atrophy
- FAF shows areas of hypo-autofluorescence in GA
- OCT outlines the corresponding photoreceptor dropout

Imaging

Adaptive Optics
AMD Risk Factors

- Non-modifiable:
  - Age
  - Heredity
  - Sex
  - Pigmentation
  - Race
  - Iris color

- Modifiable:
  - Smoking
  - Cardiovascular disease
  - Blood lipid status
  - Hypertension
  - Alcohol consumption
  - Light exposure (UV, blue)
  - Nutrition
  - Obesity

Epidemiology

- Inherited variation in the complement factor H gene is a major risk factor for drusen.
- A single-nucleotide polymorphism (SNP) in the promoter region of HTRA1 (a serine protease gene on chromosome 10q26) is a major risk factor for Wet AMD.

Genetics and AMD

- DeWan, A. Science, November 2006: Vol. 314. no. 5801, pp. 989 - 992

Adapted from Wingertling et al. 2005
Genetics and AMD

Naturally occurring variations conferring AMD risk

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Smoking interacts with CFH Gene variants to increase AMD risk by 5X compared with genetically similar nonsmokers.


Cigarette Smoking, Ocular & Vascular Disease

- Increased arteriolar stiffness (sclerosis)
- Increased Vascular Endothelial Growth Factor (VEGF) production
- Development/worsening of DR
- Development/worsening of AMD

AMD GeneAssociations

- Mutations in the TIMP3 gene
- Metalloprotease inhibitor 3 gene
- Two variants involved in the HDL cholesterol pathway.
- Human hepatic lipase (LIPC) and cholesterol ester transfer protein (CETP).

Proceedings of the National Academy of Sciences (4/2010)

Johanna Seddon, MD (Tufts U)

“Don’t smoke; follow a healthful diet rich in dark green leafy vegetables and low in fat; eat fish a few times a week; maintain a normal weight and waist size; exercise regularly; and control blood pressure and cholesterol.”

“Anyone with signs of intermediate-level macular degeneration in both eyes or advanced macular degeneration in one eye should also take dietary supplements that contain lutein, zeaxanthin, vitamin C, vitamin E, and zinc.”

It would be naïve to assume that only 6 vitamins/nutrients are important in retinal health.
The Complement Cascade: Inflammation

A BMI over 30 increases AMD risk by 2.5X.

Example of Genomics

Nutritional Factors

Key AMD-associated Genes

AREDS 1 and 2

AREDS 1 Grading Scale

1. No drusen or a few small drusen.
2. Pigment abnormalities or non-extensive small or intermediate drusen.
3. Extensive intermediate drusen or any large drusen or non-central atrophy.
4. Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovascularization or geographic atrophy).
Is There a Strategy?
- USDA Food Triangle/My Plate
- 5+ daily portions of fruits & veggies
- at least 1 dark green, leafy veg (spinach, kale)
- Low saturated/trans fat, low cholesterol
- Antioxidant for at risk patients
- L and Z
- CV Dx
- Physical Activity
- Low WL Blue, UV protection

USDA Replaces Food Pyramid

Behavior Modification
- Physical activity
- Fish consumption
- Greens
- Smaller portions
- Alcohol in moderation
- Nutritional supplements
- Blocking blue light from reaching retina

Behavior Modification
- Sedentary lifestyle
- Smoking
- Excess Alcohol
- High BMI
- HTN, Cholesterol
- Diet low in fish, green veggies

Conclusions
- AMD is on the rise.
- We must take proactive steps on behalf of our patients.

Prevention
Early Diagnosis
Early Intervention
Improved Visual Outcomes
Thank you!

Joe

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