

Course Goals

- To provide clinically useful information about AMD
- Systemic approach
 - Prevention
 - Early diagnosis
 - Treatment and management
 - **Nutrition**



AN INCREASE OF LONGEVITY IS **NOT NECESSARILY** ASSOCIATED WITH HEALTHY AGING.

Unhealthy (sick) longevity may be the most serious public health issue of the 21st century.

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.

■ Klein R, Klein BEK, Linton KLP. Prevalence of age-related maculopathy. *Ophthalmology*. 1992;99:933-943.



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 (GA) with or without the sequelae of macular neovascularization (MNV).

■ Zatzin MA. Age-related macular degeneration: review of pathogenesis. *Eu. J Ophthalmol*. 1998;199-206.

Classification of AMD

- **Non-neovascular, aka “dry”**
 - Non-exudative, atrophic
 - Can be performance-degrading
 - Majority of AMD cases
- **Neovascular, aka “wet”**
 - Exudative, hemorrhagic
 - **MNV** –devastating to central vision
 - Minority of AMD cases
 - Majority of vision loss



The Burden of Disease



The Burden of Severe Vision Loss in AMD

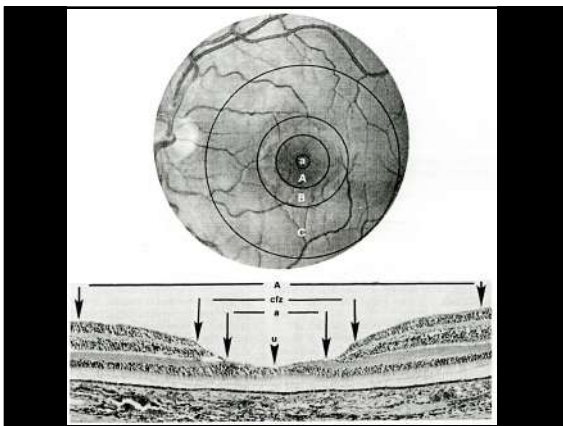
- Patients, loved ones, caregivers, medical community.
- Consequences may be:
 - Physical
 - Social- isolation
 - Economic
 - Psychological- depression



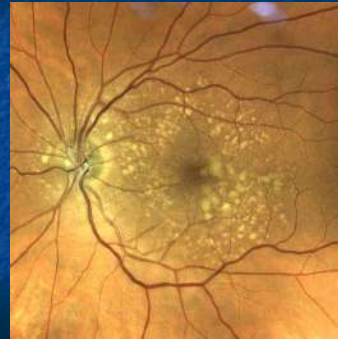
The AMD “Epidemic”

How should we as optometrists respond?

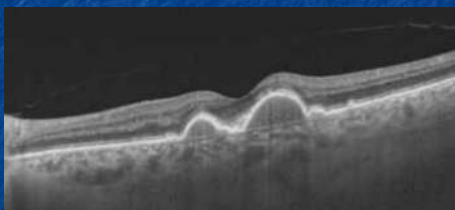
- Prevention
- Early Diagnosis
- Early Intervention
- Improved Visual Outcomes



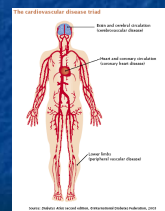
Mixed Drusen



OCT of Soft Drusen



Emerging Trend: AMD as a Systemic Disease



AMD Risk Factors

- Non-modifiable
 - Age
 - Heredity
 - Sex (F>M)
 - Pigmentation
 - Race
 - Iris color
- Modifiable
 - Smoking
 - Cardiovascular disease
 - Blood lipid status
 - Hypertension
 - Alcohol consumption
 - Light exposure (UV, blue)
 - Nutrition
 - Obesity
 - Low MPOD
 - Poor dark adaptation

Macular Degeneration

Pathobiology of AMD

- Aging of the photoreceptors and RPE/Bruch
- Genetic component
- Environmental stress
 - Lifestyle/nutrition
 - Light-initiated oxidative damage



QUESTIONS AND ANSWERS



Email me at pizzimen@uiwtx.edu

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.



AMD is an Immune-mediated Disease Process

Clinical Medicine
Part of THE LANCET Discovery Series

Submit Article | Log in | Register

HP0021 | 10.1016/j.ophico.2015.09.002

Patients with MPNs and retinal drusen show signs of complement system dysregulation and a high degree of chronic low-grade inflammation

Charlotte Linking | 10.1016/j.ophico.2015.09.002 | 10.1016/j.ophico.2015.09.002

Published: December 26, 2015 | DOI: 10.1016/j.ophico.2015.09.002

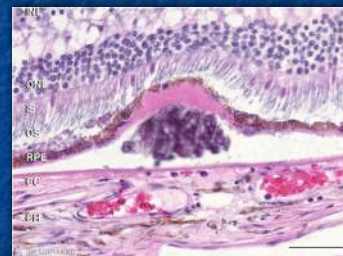
Information for Authors

Summary

Background

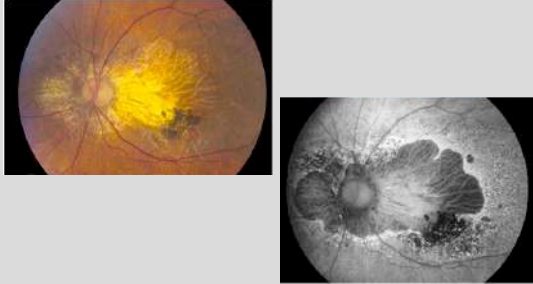
The hematopoietic stem cell disorders, myeloproliferative neoplasms (MPNs), are characterized by chronic low-grade inflammation (CLG). Recently, we observed that patients with MPNs have an increased prevalence of drusen and age-related macular degeneration (AMD), and drusen prevalence correlated with higher CLG. We hypothesize that MPNs may represent a novel model of disease.

Drusen

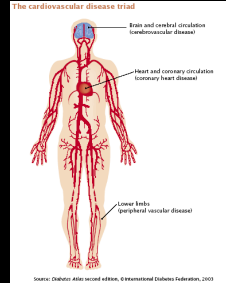


Drusen is the earliest clinically detectable feature of AMD.**

AMD: a sick eye in a sick body?



AMD and Cardiovascular (Heart) Disease



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

The 4 Seasons of AMD

- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization



Advanced AMD starts out like this:



Large, ill-defined, and confluent soft drusen**

Intermediate Stage AMD

• AREDS Category 3



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

Unfavorable prognostic signs leading to MNV, GA:

- Soft, large, confluent drusen
- **Reticular (pseudo) drusen***
- Focal hyperpigmentation
- Disciform lesion in the fellow eye
- Older age
- **Poor dark adaptation***

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.

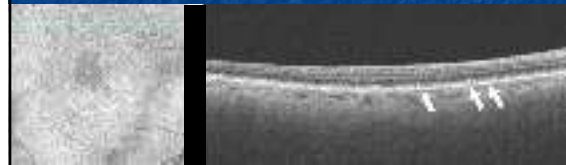


Reticular (Pseudo)drusen

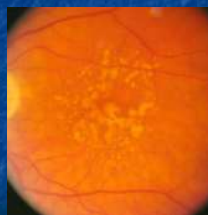


Reticular (Pseudo)drusen

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



Emerging Trend: Dry AMD is the New Wet



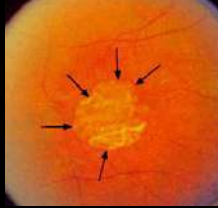
Evidence-based Advice for Patients

AREDS-Established Risk Factors to Advanced AMD

- Increased risk for NV AMD: smokers, Caucasians
- Increased risk for CGA: smokers, those with a higher body mass index (AREDS-19)
- Higher intake of omega-3 long-chain polyunsaturated fatty acid (LCPUFA) and fish: associated with decreased likelihood of having NV AMD (AREDS-20)
- Higher dietary intake of lutein/zeaxanthin: associated with decreased likelihood of having NV AMD and GA (AREDS-22)
- Omega-3 LCPUFA intake: associated with a decreased risk of progression from bilateral drusen to CGA (AREDS-23)

Age-Related Eye Disease Study Research Group. Control Clin Trials. 1992;13(6):573-602.

Prevention and treatment of GA remains an unmet need.

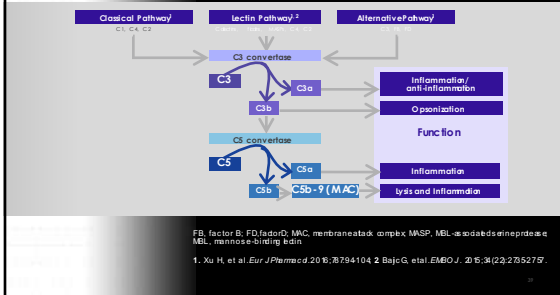


This is changing thanks to innovations such as **complement inhibition**.

Complement Inhibition

- As of February 17, 2023, there is one approved therapy for GA and several are under investigation.
 - Pegcetacoplan (Syfovre) is indicated for the treatment of GA secondary to dry AMD.
 - A targeted C3 inhibition therapy that works by regulating excessive activation of the complement cascade, which could lead to the onset and progression of diseases.
 - A 15 mg/ml dose to be administered by intravitreal injection once every 25 to 60 days into each affected eye to reduce the progression of GA.

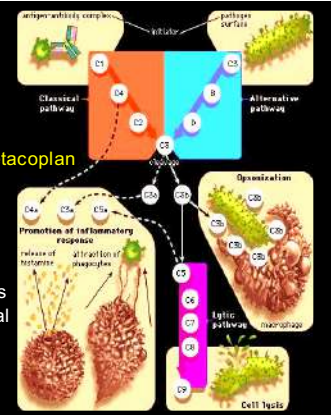
Dysregulated activation of the complement system can lead to inflammation and cell death and may be central to GA pathogenesis¹



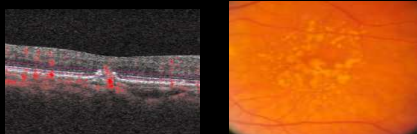
The Complement Cascade: Inflammation

*Pegcetacoplan

avacincaptad pegol (ACP) is investigational



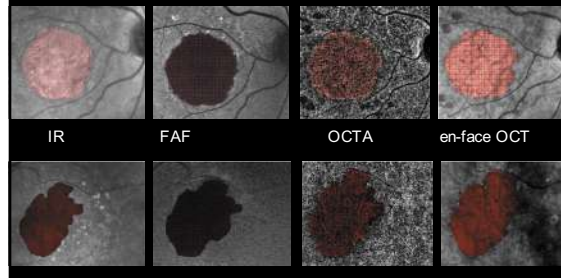
Questions and Answers



pizzimen@uiwtx.edu



Emerging Trend: Multimodal Imaging (MMI)



FAF + OCT in GA

Offers a new perspective of the structure-function relationship within the retina

Simultaneous FAF and OCT

Geographic Atrophy

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

Emerging Trend: OCTA

THE ARRIVAL OF OCT-ANGIOGRAPHY (OCTA)

A new way of visualizing ocular bloodflow in the vessels—identifies retinal microcirculation using the intrinsic motion of blood cells in the vessel

- Enables immediate assessment of microcirculation in ocular diseases with unprecedented microvascular detail

Conventional OCT can visualize structural changes such as drusen and RPE atrophy, but not able to visualize changes in the microvasculature

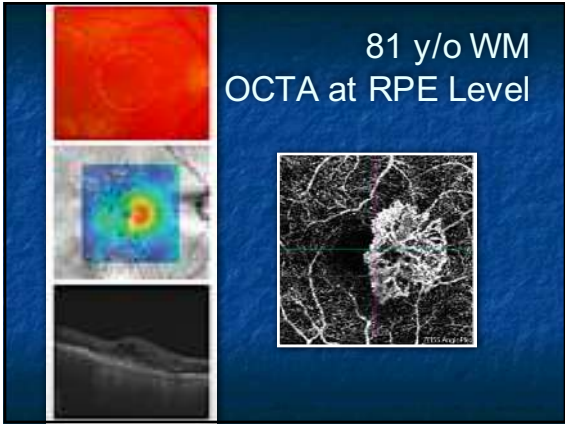
OCT Angiography can visualize ocular bloodflow in the vessels. However, it is unable to image in the microvasculature such as choroidal neovascularization associated with wet AMD

© 2014 by The Association for Research in Vision and Ophthalmology. All Rights Reserved. www.iovjournal.org

Imaging

OCTA IMAGES DEPICTING CHOROIDAL NEOVASCULARIZATION

Cirrus Angioplex OCTA reveals CNV Lesion in nAMD



Emerging Trend: Home Monitoring

The Monitoring Process

- 1. Patient uses handheld device to monitor vitreous wave.
- 2. Data is transmitted to the Monitoring Center (MC).
- 3. MC analyzes data and sends alerts to caregiver.

Emerging Trend

- Home monitoring
- PHP
- OCT

Structure and Function

■ OCT and PHP work synergistically

Parameter	Value
Central Thickness (µm)	340
Macular Volume (mm³)	11.5
Subfoveal Thickness (µm)	120
Superotemporal Thickness (µm)	110
Superonasal Thickness (µm)	100
Inferotemporal Thickness (µm)	110
Inferonasal Thickness (µm)	100

TREATMENT OF NEOVASCULARAMD

CNV ---> FV Scar

1980's – Thermal Laser Photocoagulation

- Very few patients suitable for treatment*
- High recurrence rate (~50%)**

Extrafoveal

Juxtafoveal

Subfoveal with post-laser scar

* Freund KB, Yannuzzi LA, Sorenson JA. Am J Ophthalmol 1993; 115:796-791
** Macular Photocoagulation Study Group. Arch Ophthalmol 1990; 108:625-631

2000 – Photodynamic Therapy (PDT)

****Advantage of PDT: less scarring than thermal laser****
 FDA-approved only for patients with subfoveal predominantly classic angiographic subtype

Predominantly classic
25%

Minimally classic
35%

Occult with no classic
40%

****PDT scars less than thermal laser****

75% with no FDA-approved therapy

Is AMD a Systemic Disease?

The cardiovascular disease triad

Heart and vascular disease
Heart and brain disease

Three Key Retinal Disease Factors

COMMON PATHWAY

IL-6 IL-8 MCP-1 VEGF

↓

BRVO Other retinal inflammatory diseases CRVO

Adapted from Vitorius et al.

MCP-1 = Monocyte chemoattractant protein-1

Angiogenesis

Environmental factors¹ (hypoxia,² pH)
 Growth factors, hormones¹ (EGF, bFGF, PDGF, IGF-1, IL-1 α , IL-6, estrogen)

VEGF-A binding and activation of VEGF receptor³

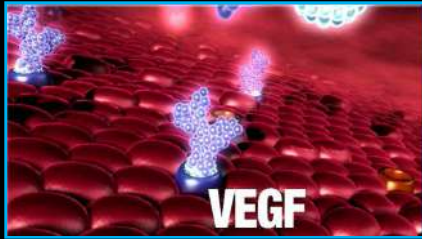
↓

Endothelial cell activation³

VEGF-A = vascular endothelial growth factor A; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; PDGF = platelet-derived growth factor; IGF = insulin-like growth factor; IL = interleukin.
 1. Dvorak HF. J Clin Oncol 2002;20:488-2. Aiello LP, et al. Arch Ophthalmol 1995;113:1538.
 3. Ferrara N, et al. Nat Med 2003;9:669-4. Griffioen AW and Moilem G. Pharmacol Rev 2003;55:207.



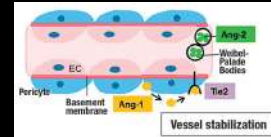
Antiangiogenic Drugs: VEGF Inhibitors



VEGF binds to receptor

Faricimab

- Bi-specific Ab that targets the VEGF and angiotensin pathways.
 - VEGF and Ang-2 inhibitor
- There are 2 ligands, Ang-1 and Ang-2, and they both affect the Tie2 receptor. This receptor is critical for the stability of vascular tissue.
- In nAMD, Ang-2 is upregulated. This competes with the Ang-1-Tie2 signaling, causing vascular endothelial tight junction breakdown, as well as increased inflammation and MNV.



Faricimab

- Phase 3 studies TENAYA and LUCERNE evaluated faricimab in nAMD.
- Both studies achieved visual outcomes with faricimab that were non-inferior to those of aflibercept (Eylea, Regeneron) injections q8wks.
- Also approved for DME.



Behavior Modification

- Physical activity
- Fish consumption
- Greens and plant-based
- 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, and it has systemic comorbidities and implications.
- Diet, nutrition, lifestyle matter.
- We must take proactive steps on behalf of our patients.

QUESTIONS AND ANSWERS



Email me at pizzimen@uiwtx.edu



Thank you!

Joe