

Slide 1

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San Antonio

Course # 113

Emerging Trends in AMD

Joe Pizzimenti, OD

Please Silence All Mobile Devices.

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Slide 2

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Disclosure statements:
No financial relationships to disclose

All relevant relationships have been mitigated.

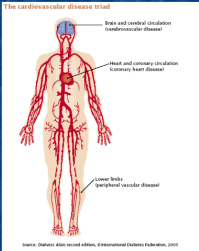
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Slide 3

Emerging Trends in AMD

The cardiovascular disease triad



Source: Diabetes Atlas second edition, International Diabetes Federation, 2005

Joseph J. Pizzimenti, OD, FAAO

Slide 4

Course Goals

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



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.

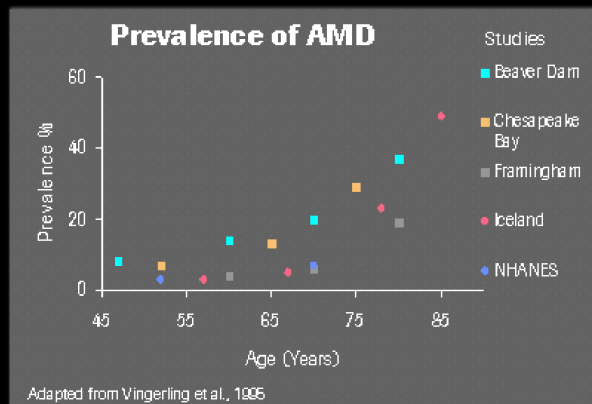


What is AMD?

- 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).

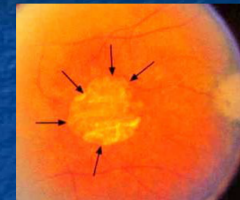
■ Zarbin MA. Age-related macular degeneration: review of pathogenesis. Eu. J Ophthalmol. 1998;199–206.

Epidemiology



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

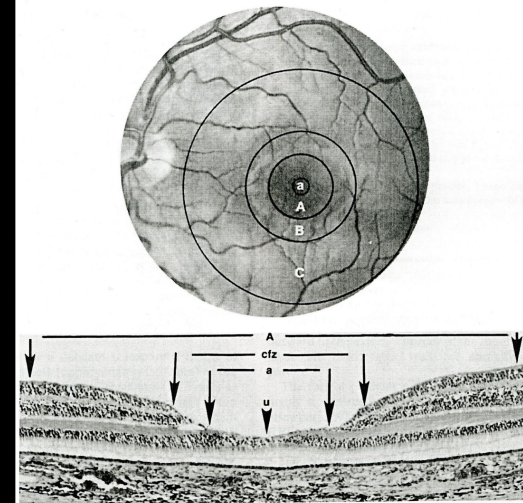
- Patients, loved ones, caregivers, medical community.
- Consequences may be:
 - Physical
 - Social- isolation
 - Economic
 - Psychological- depression



The AMD “Epidemic”

How should we as optometrists respond?

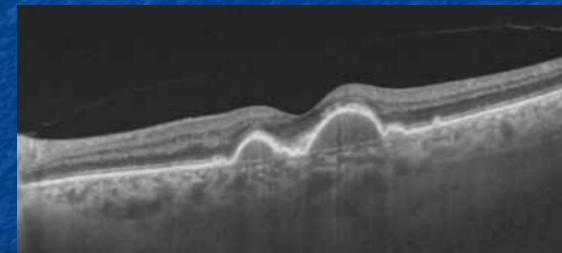
Prevention
Early Diagnosis
Early Intervention
Improved Visual Outcomes



Mixed Drusen



OCT of Soft Drusen



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

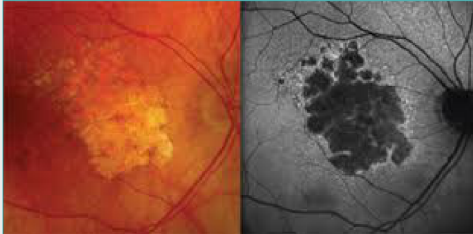
Pathobiology of AMD

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



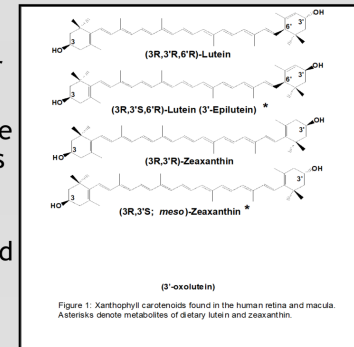
What are the four primary retinal pigments?

- Zeaxanthin
- Lutein
 - along w/their metabolites, L & Z are found in the macula's sensory layers
- Melanin – found in the RPE
- Lipofuscin – found in the aging RPE



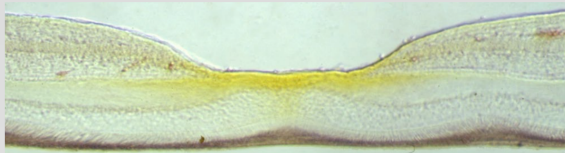
Xanthophylls and AMD

- 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.



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)

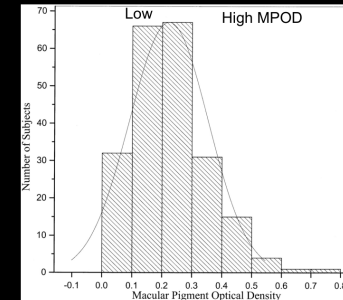
Heterochromatic Flicker Photometry (HFP)

Risk assessment, early detection and monitoring of AMD

- Macular Pigment Optical Density
- MPOD



Macular Pigment Optical Density (du) ranges from 0.0-1.0



- 217 healthy subjects (79 men, 138 women) were recruited from the Phoenix metropolitan area (age range = 17–92 years).
- The average MPOD was 0.22 ± 0.13 .
 - Investigative Ophthalmology & Visual Science May 2000, Vol.41, 1492-1497.

MPOD is the IOP
for
AMD

The Macula & Beyond: Value of MPOD

- AMD
- MacTel
- Type 2 DM, DR
- Obesity, smoking, heart dx
- Neurodegenerative disease
 - MS
 - Cognition including early AD
- Eye and brain development

- Demmig-Adams B, López-Pozo M, Stewart JJ, Adams WW III. Zeaxanthin and Lutein: Photoprotectors, Anti-Inflammatories, and Brain Food. *Molecules*. 2020; 25(16):3607. <https://doi.org/10.3390/molecules25163607>
- Gazzolo D, Picone S, Galero A, Bellettato M, Montrone G, Riccobene F, Lista G, Pellegrini G. Early Pediatric Benefit of Lutein for Maturing Eyes and Brain—An Overview. *Nutrients*. 2021; 13(9):3239. <https://doi.org/10.3390/nu13093239>
- Retina. September 2015 - Volume 35 - Issue 9 - p 1808-1816doi: 10.1097/IAE.0000000000000551
- Investigative Ophthalmology & Visual Science April 2018, Vol.59, 1828-1835. doi:https://doi.org/10.1167/iovs.17-22656
- Olivia M. Rifai, Sarah McGrory, Cason B. Robbins, Dilraj S. Grewal, Andy Liu, Sharon Fekrat, Thomas J. MacGillivray, The application of optical coherence tomography angiography in Alzheimer's disease: A systematic review, *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 10.1002/dad2.12149, 13, 1, (2021).

Benefits of Supplementation with Dietary Xanthophyll Carotenoids for People WITH OR WITHOUT AMD at Any Age

- Ocular structural and visual function development
- Ocular health and visual performance enhancement
- Brain development/health and cognitive performance
- Preserve retinal/macular health by improving MPOD, physiology
- Preserve cognitive health
- Preserve systemic vascular health (DM, CV)
- Blue light protection

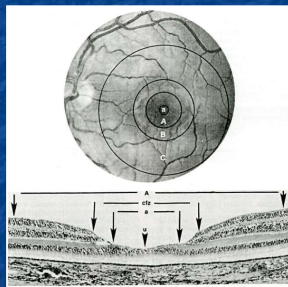
MPOD Summary

- Macular Pigments are important photo-protectants and antioxidants.
- Low MPOD is a modifiable AMD risk factor.
- Increasing MPOD improves visual function and has additional health benefits.
- Measuring MPOD is fast, affordable, accurate, important.

[Vision Res. 2010 Mar 31; 50\(7\): 716–728.](#)

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.



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).

Mangione CM, Gutierrez PR, Lowe G, Orav EJ, Seddon JM
Influence of age-related maculopathy on visual functioning and health-related quality of life. Am J Ophthalmol. 1999;128:45–53.

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

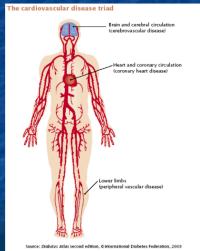


QUESTIONS AND ANSWERS



Email me at pizzimen@uiwtx.edu

Emerging Trend: AMD as a Systemic Disease



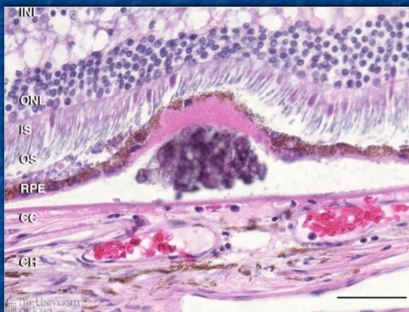
AMD and Drusen

- AMD is a disease resulting from poor "Waste Management".



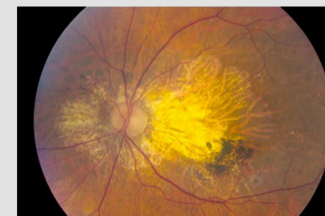
- Drusen are "pockets of inflammation"
 - Recent investigations show that proteins associated with inflammation and immune-mediated processes are prevalent in drusen.

Drusen

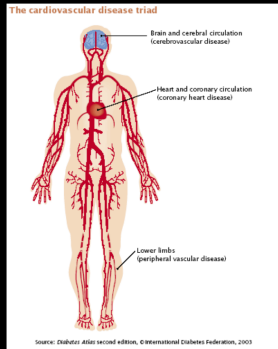


Drusen is the earliest clinically detectable feature of AMD.**

AMD: a sick eye in a sick body?



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

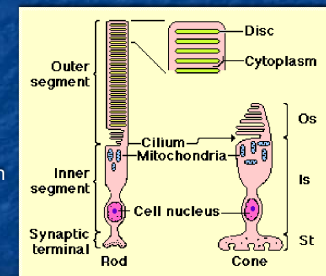
The 4 Seasons of AMD

- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization

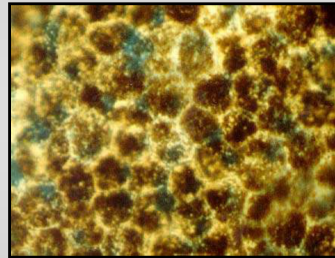
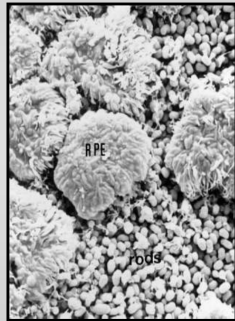


Normal Retinal Metabolism

- Outer segment discs of rods and cones are transported to RPE for metabolism
- Discs are engulfed into RPE and fuse with lysosomes, where they are digested
- Undigested residual bodies remain as **lipofuscin**
 - These are the real troublemakers! *



Abnormal Retinal Metabolism

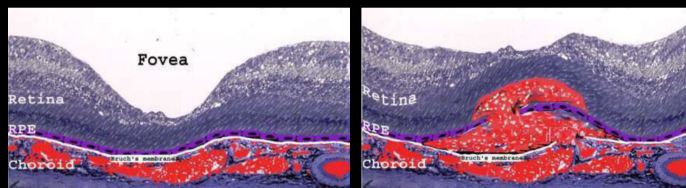


Lipofuscin accumulates in the aging RPE

Reactive Oxygen Species (ROS)

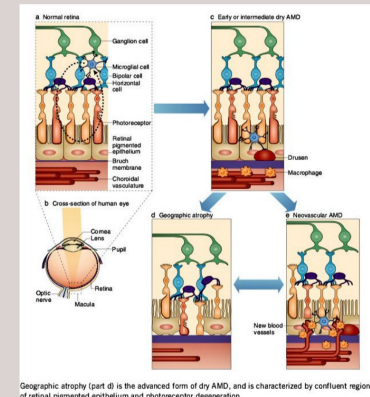
- ROS are the byproducts of oxygen metabolism.
 - Free radicals
 - Hydrogen peroxide
 - Singlet oxygen
- The retina/macula is particularly susceptible to **oxidative stress** because of its high O₂ consumption and exposure to visible light.

Wet AMD Pathology



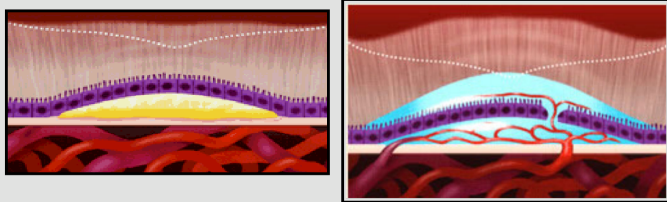
~20% of eyes w/dry AMD ultimately convert to wet AMD.*

Pathways in AMD Pathogenesis

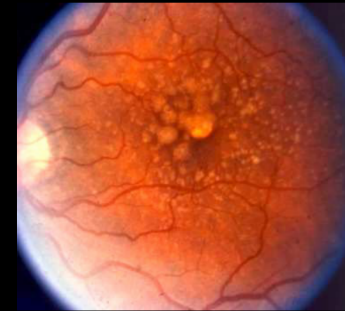


Pathogenesis of CNVM

- Breaks in Bruch's Theory
 - Diffuse thickening of Bruch's w/soft drusen
 - Predisposes Bruch's to breaks
 - New BV's from CC grow and proliferate



Advanced AMD starts out like this:



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

Intermediate Stage AMD

• AREDS Category 3



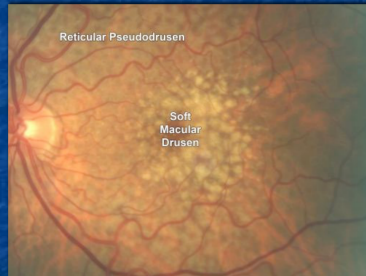
- Extensive intermediate drusen (63-124 μ diameter)
- At least one large druse (>125 μ)
- Geographic atrophy not involving the foveal center

Unfavorable prognostic signs leading to CNVM, GA:

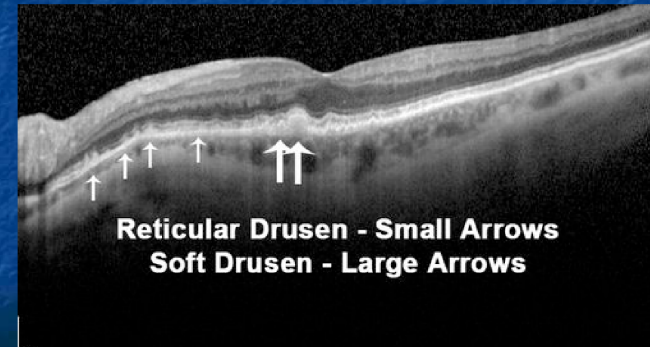
- Soft, large, confluent drusen
- Reticular (pseudo) drusen*
- Focal hyperpigmentation
- Disciform lesion in the fellow eye
- Older age
- Poor dark adaptation*

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.

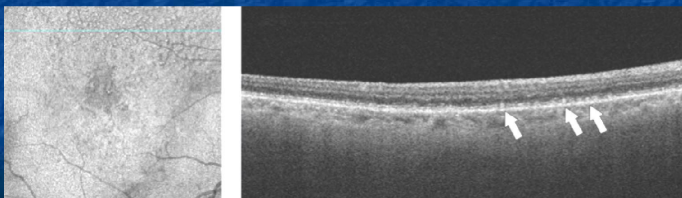


Reticular (Pseudo)drusen



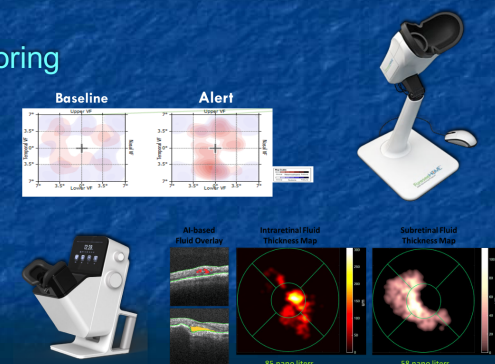
Reticular (Pseudo)drusen

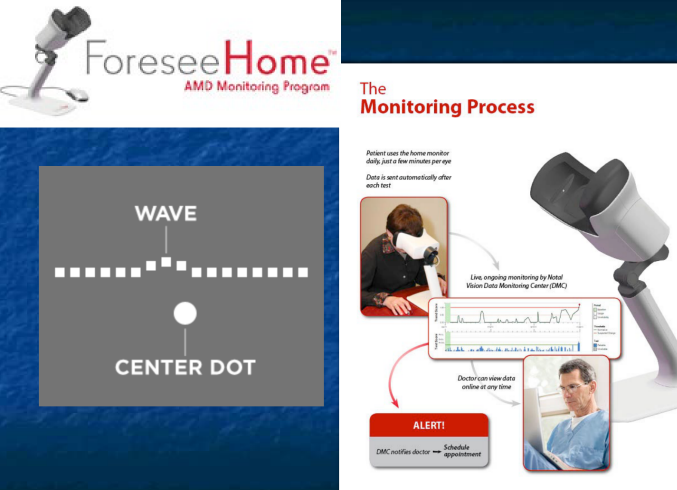
- Presence of RPD is a consistent risk factor for progression to both atrophy and CNV
- IS/OS C-scan B-scan



Emerging Trend

- Home monitoring
- PHP
- OCT





ForeseeHome™
AMD Monitoring Program

The Monitoring Process

Patient uses the home monitor daily, just a few minutes per eye. Data is sent automatically after each test.

Live, ongoing monitoring by Retinal Vision Data Monitoring Center (DMC)

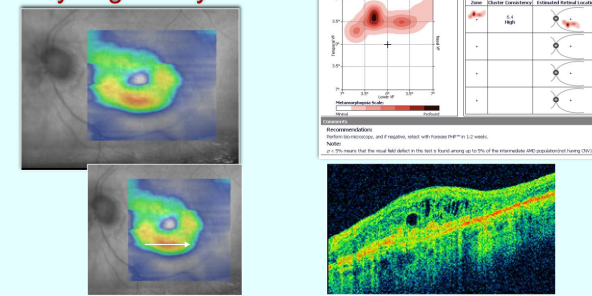
Doctors can view data online at any time.

ALERT!
DMC notifies doctor → Schedule appointment

Diagram showing the patient using the device, data being sent to the DMC, and the doctor viewing the data online.

Structure and Function

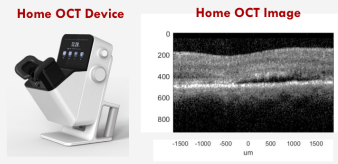
OCT and PHP work synergistically



Diagrams illustrating the structure and function of the retina, showing the relationship between OCT (Optical Coherence Tomography) and PHP (Peripapillary Hemodynamics) in monitoring AMD.

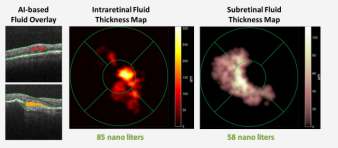
Home OCT for Monitoring Therapy of nAMD Between Visits

- Monitoring of intra- and subretinal fluid based on daily patient self-imaging
- Easy-to-use, patient-operated device
- Takes less than one minute per eye
- AI algorithm analyzes images on cloud
- Remote diagnostic clinic, provider of monitoring program, reports changes meeting physician-selected fluid volume thresholds to referring physician
- 24/7 physician access to all data



Home OCT Device

Home OCT Image



AI-based Fluid Overlay

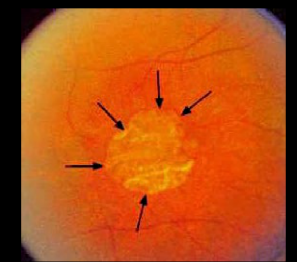
Intraretinal Fluid Thickness Map

Subretinal Fluid Thickness Map

85 nano liters

58 nano liters

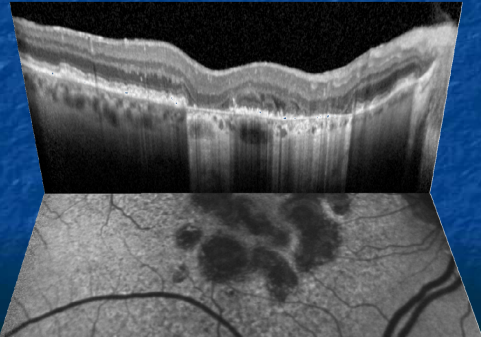
Prevention and treatment of GA remains an unmet need.



This may soon change thanks to innovations such as complement inhibition.

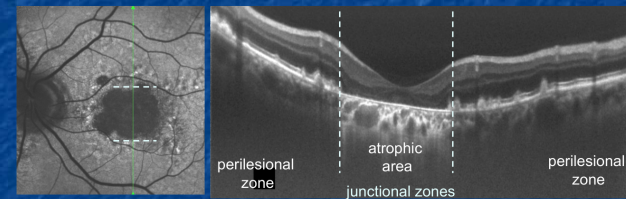
FAF + OCT in GA

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



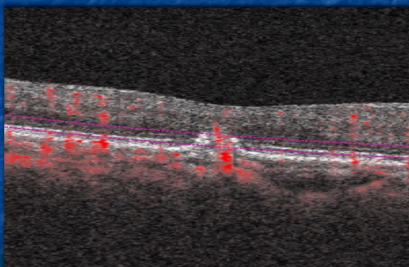
Simultaneous FAF and OCT

Geographic Atrophy



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

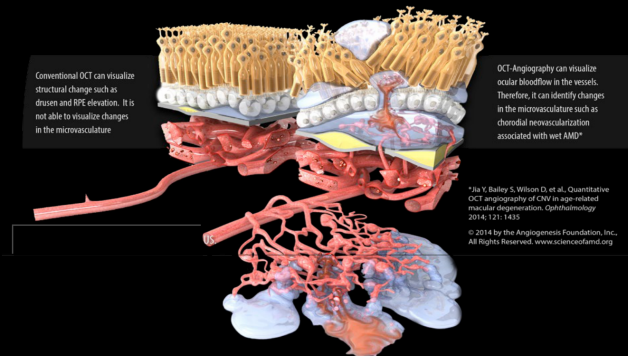
Emerging Trend: OCTA

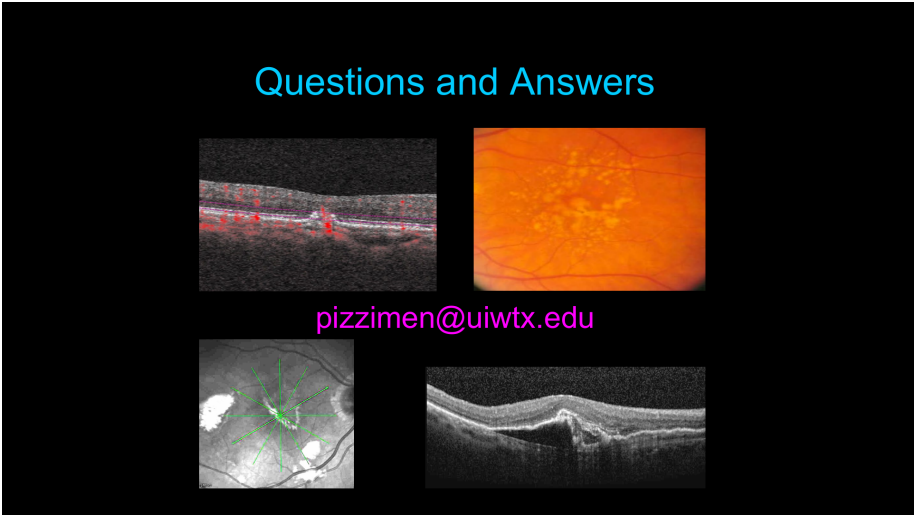
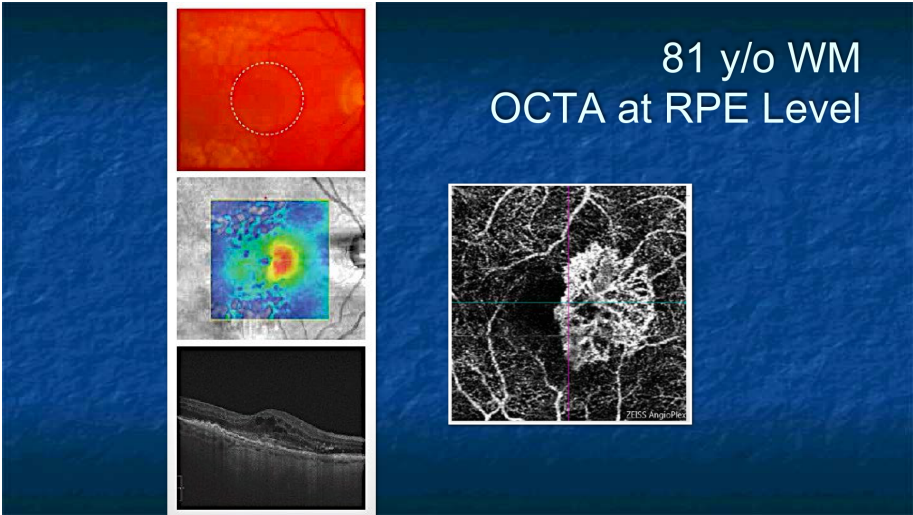
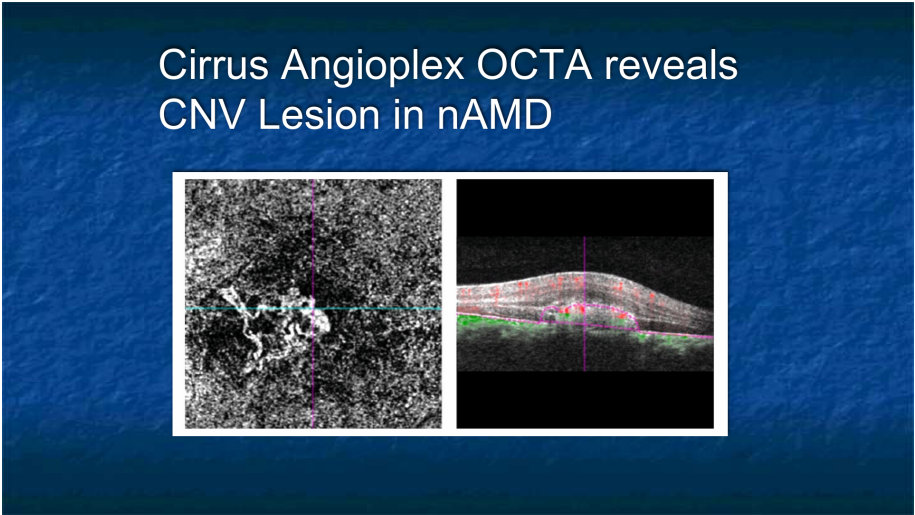
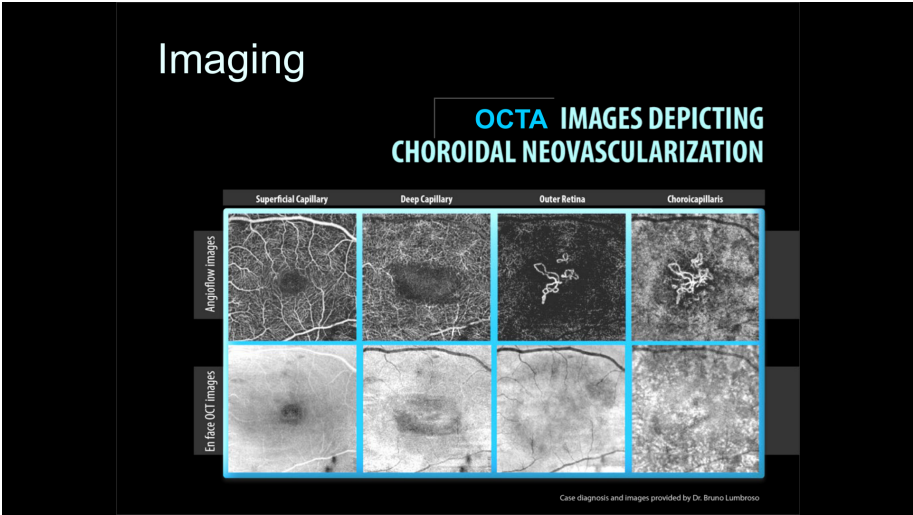


THE ARRIVAL OF OCT-ANGIOGRAPHY (OCTA)

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

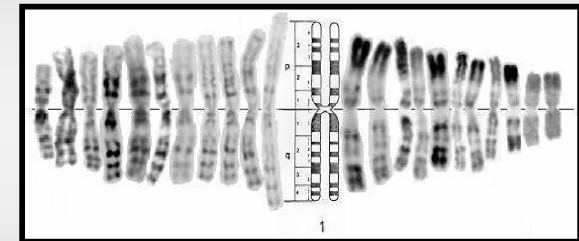




Emerging Trend: Genetics and Genomics



Genetics: ARMD-1



Chromosome 1
Region Displayed: 1q25-q31

Genetics and AMD

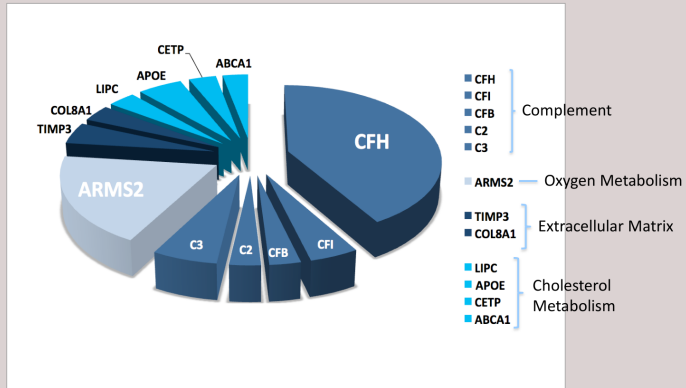
- Inherited variation in the **complement factor H gene** is a major risk factor for drusen.
- A single-nucleotide polymorphism (SNP) in the promoter region of **HTRA1** (a serine protease gene on chromosome 10q26) is a major risk factor for **nAMD**.
 - DeWan, A. Science, November 2006:Vol. 314. no. 5801, pp. 989 - 992

Genetics and AMD

Naturally occurring variations conferring AMD risk

Marker	Allele	Odds Ratio	Freq
CFH	H1+H3 (risk)		0.202
	Average	>15	0.495
	(H2+H4)		0.303
C3 rs2230199	G (risk)	2.6	0.18
	C		0.83
ARMS2 rs10490924	T (risk)	8.2	0.17
	G		0.83
Smoking	Current (risk)	3.14	0.17
	Never		0.55
mt A4917G	G (risk)	2.2	0.09
	A		0.90

Key AMD-associated Genes



Example of Genomics



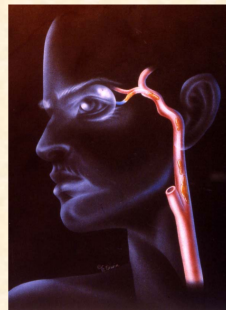
Smoking interacts with CFH Gene variants to increase AMD risk by 5X compared with genetically similar nonsmokers.



Am J Epidemiol. 2009 March 1; 169(5): 633–641.

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 Gene Associations

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

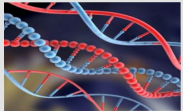
● Proceedings of the National Academy of Sciences (4/2010)

Example of Genomics

A BMI over 30 increases
AMD risk by 2.5X.

Clinical & Experimental
Ophthalmology

Celebiler et al., J Clin Exp Ophthalmol 2012, 3:5



**IS AMD A NUTRITION-RESPONSIVE
DISEASE?**

AMD and Nutrition



"The **AREDS 1 Study** resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by **25%** at 5 years."

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland

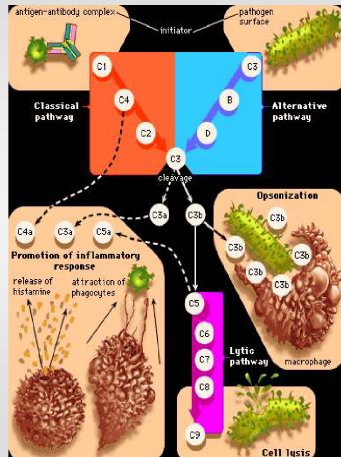
Johanna Seddon, MD (Tufts U)

"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."

The Complement Cascade: Inflammation



AREDS 2



AREDS 1 and 2 Formulations

- Vitamin C: 500 mg*
- Vitamin E: 400 IU*
- Beta-carotene: 15 mg (May be listed on the label as "25,000 IU vitamin A as beta-carotene") (eliminated)
 - Why?
- Zinc oxide: 80 mg (40 mg)
 - Why?
- Copper: 2 mg (needed to prevent Cu deficiency caused by high dosage of zinc)*
- Lutein & Zeaxanthin (10 mg & 2 mg)
- Omega-3 fatty acids (1 gram)

Study Subjects: AREDS 1 vs AREDS 2

- | | |
|---------------------------|---|
| ● All stages of AMD | ● More advanced stage |
| ● Average age = 69 | ● average age = 74 |
| ● 67% took Centrum (no L) | ● 89% taking Centrum Silver (w/minimal L) |
| ● Varied diets | ● diet high in carotenoids and vegetables |
| ● Varied serum L and Z | ● higher serum L and Z |

These differences could impact the ability to detect a more significant reduction in progression!

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. 1999;20(6):573-600.

QUESTIONS?



pizzimen@uiwtx.edu

It would be naïve to assume that only 6 vitamins/nutrients are important in retinal health



Emerging Trend: "Superfoods"

In AMD Prevention and Management



Dietary Sources of Lutein/Zeaxanthin



Dietary Lutein and Zeaxanthin: Eggs have high bioavailability



Lutein



Lutein



LUTEINofta
Gocce

Integratore alimentare a base di LUTEINA e ZEAXANTINA.

LUTEINofta® gocce è indicato nel caso di aumentato fabbisogno o di diminuito apporto con la dieta dei suoi componenti. LUTEINofta® gocce può essere utile, in particolare, per favorire la protezione della retina verso lo stress ossidativo.

INGREDIENTI
Olio di girasole, Aroma, Antiossidante: vitamina E (dl- α -tocoferolo E 307), Luteina e zeaxantina in olio di cartamo (antiossidante: dl- α -tocoferolo).

INFORMAZIONI NUTRIZIONALI	
	per dose 2,5 ml
Luteina	0,14 mg
Zeaxantina	0,006 mg
	0,5 ml 100 ml

Zeaxanthin



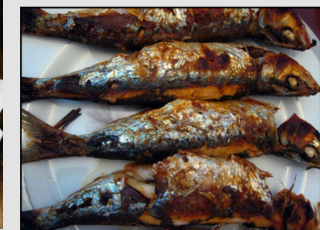
Dietary Zeaxanthin: Gogi Berry



Benefits of Supplementation with Dietary Xanthophyll Carotenoids for People **WITH OR WITHOUT** AMD at Any Age

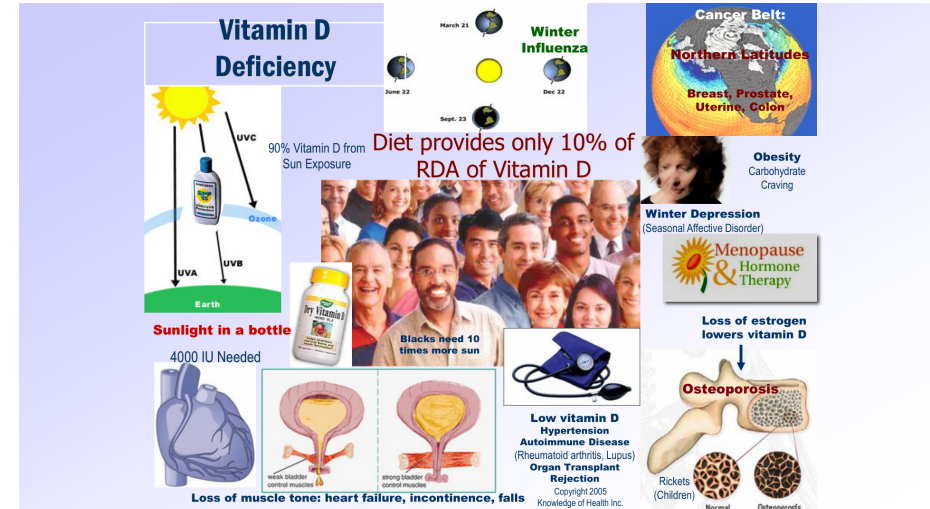
- Ocular structural and visual function development
- Ocular health and visual performance enhancement
- Brain development/health and cognitive performance
- Preserve retinal/macular health by improving MPOD, physiology
- Preserve cognitive health
- Preserve systemic vascular health (DM, CV)
- Blue light protection

Essential Fatty Acids (AMD, CVD, Stroke)



Dietary Vitamin D: Cod Liver Oil, Sockeye Salmon

- Modulation of cell growth
- Neuromuscular and immune function
- Reduction of inflammation



- For people aged one to 70 years, the RDA is at least 600 IU.
- For people over 70, RDA is at least 800 IU

Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health¹⁰

<12ng/mL	Deficiency, leading to rickets in infants and children and osteomalacia in adults
12-20ng/mL	Inadequate for bone and overall health in healthy individuals
>20ng/mL	Adequate for bone and overall health ←
>50ng/mL	Potential adverse effects

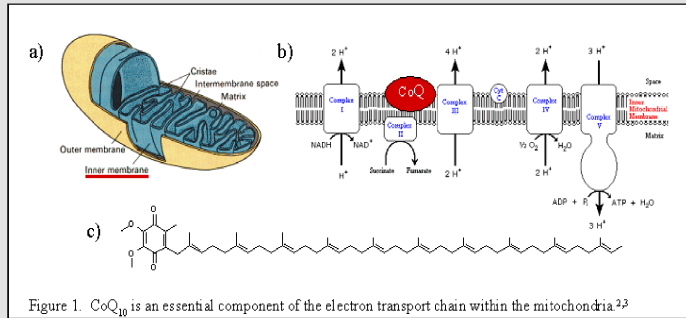
Sources of Vitamin D

Non-fat fortified milk	1 cup per day
Fish: salmon, tuna, sardines, mackerel, herring	at least three servings per week
"Sensible sunlight"	Five to 15 minutes, two to five times per week
Vitamin D3 supplements	1,000 IU per day

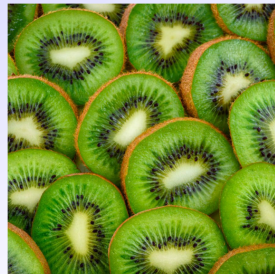
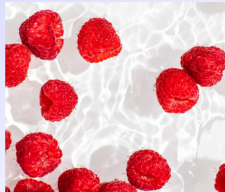
Phototrop Study

- Improvement of Visual Function and Fundus Alterations in Early AMD Treated With a Combination of Acetyl-L-Carnitine, n-3 Fatty Acids, and CoQ10
 - Feher, et.al.
 - *Ophthalmologica*:2005;219:154-166
- 160 early AMD subjects randomized to Tx and controls
- 12 months
- VFMD, foveal sensitivity
- ETDRS VA, fundus exam
- All 4 parameters showed statistically significant improvement
- Principle: improved mitochondrial lipid metabolism

CoQ10

Flavonoids are Anti-oxidants,
CA Fighters

B-carotene, L, and Z



Not-so-guilty Pleasures

- Walnuts favorably affect cholesterol levels, reduce risk of heart disease.
- Dark chocolate, red wine are rich in antioxidants.
- Resveratrol enhances circulatory health (blood flow) and may have benefits in certain types of cancer.



Folic Acid, B₆, B₁₂

- Folic Acid, Pyridoxine, and Cyanocobalamin Combination Treatment and Age-Related Macular Degeneration in Women: The Women's Antioxidant and Folic Acid Cardiovascular Study

- William G. Christen, ScD; Robert J. Glynn, ScD; Emily Y. Chew, MD; Christine M. Albert, MD; JoAnn E. Manson, MD
- *Arch Intern Med.* 2009;169(4):335-341.

Folic Acid, B₆, B₁₂ in Foods



Folic Acid, B₆, B₁₂

- 5442 female health care professionals 40 years or older with pre-existing CV disease
- Randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo.
- After an average of 7.3 years of treatment and follow-up, there were **55 cases of AMD in the combination treatment group and 82 in the placebo group** (relative risk, 0.66; 95% confidence interval, 0.47-0.93 [$P = .02$]).

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, and it has systemic comorbidities and implications.
- Diet, nutrition, lifestyle matter.
- We must take proactive steps on behalf of our patients.



Thank you!

Joe