A Discussion of AMD and Statins

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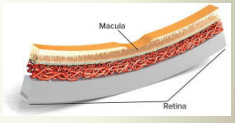
Midwest Optometric Society



Age-Related Macular Degeneration
Review

- Affects over 150 million people worldwide
- Leading cause of vision loss in developed countries
- Prevalence increasing due to increased life expectancy
- Worldwide projected cost of vision loss due to AMD in 2020 is predicted to be approx. $392 billion
- Prevalence:
  - Dry (85%)
  - Wet (15%)
- Genetics vs Environmental factors

Risk Factors Associated with AMD

- Age
- Smoking
- Family history
- Gender
- Race
- UV exposure
- Diet
- Obesity
- Hypertension
- Eye color

Current Treatment Options for AMD

- Wet AMD(15%)
  - Injections with angiogenesis inhibitors (VEGF)
  - Photodynamic Therapy
  - Laser surgery
- PROBLEM:
  - Disease and loss of vision may progress despite treatment
  - Sustainability

Current Treatment Options for AMD

- Dry AMD(85%)
  - Early and Intermediate stage
    - Vitamin supplementation (AREDS)
    - Lifestyle/Environmental
- Problem:
  - Prevention vs treatment?
  - Science on supplementation still controversial
  - No form of treatment available (advanced stage)

****Lack of effective treatment available for non-exudative AMD(85%)**

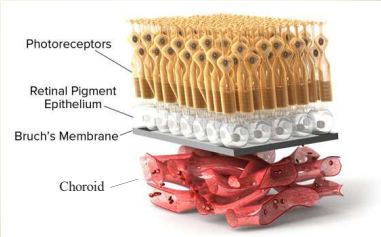
Pathogenesis of AMD

6 Major Pathways

1. Age
2. Lipid and lipoprotein metabolism and transport
3. Inflammation and immunity
4. Extracellular matrix and cell adhesion
5. Angiogenesis
6. Cellular stress and toxicity

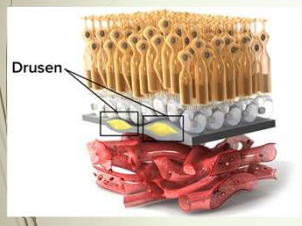
Adapted from Miller JW. Age-related Macular Degeneration-Piecing the Puzzle: The LXIX Edward Jackson Memorial Lecture. Amer J Ophthal 2013; 155, 1-35. e13

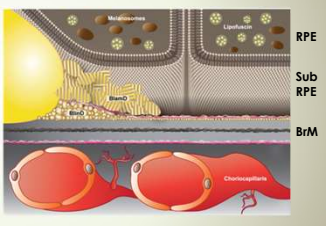
Normal Macular Structure



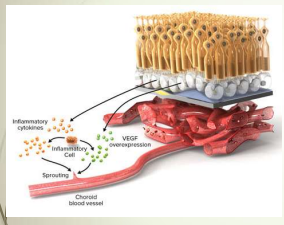
Dry AMD

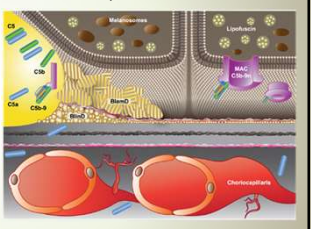
Lipid Transport and Metabolism



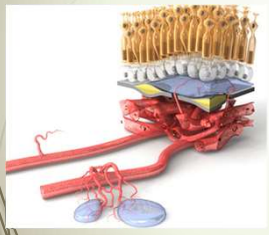


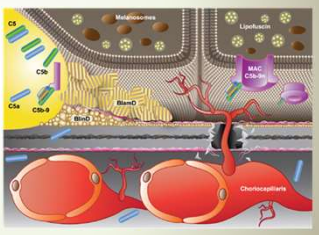
Progression of Dry AMD
Inflammation and Immunity



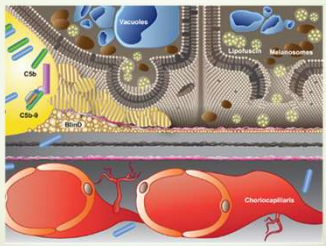


Pathogenesis of Wet AMD
Angiogenesis

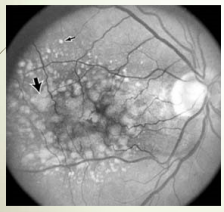


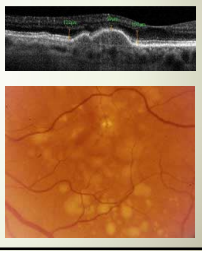


Progression of AMD
Advanced Atrophic AMD

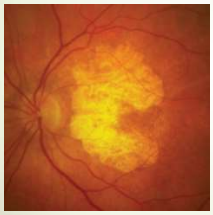
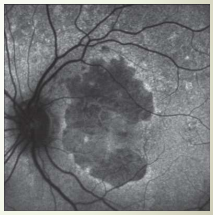


Intermediate-Late Stage Dry AMD
Discrete and Large Confluent Drusen
Drusenoid Pigment Epithelial Detachments

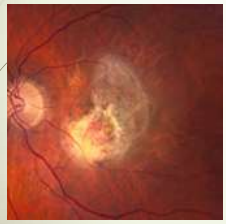
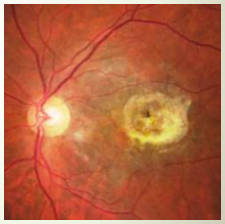




Late-Stage Dry AMD
Geographic Atrophy

Late-Stage Wet AMD
Disciform Scar

Link Between Cardiovascular Disease and AMD

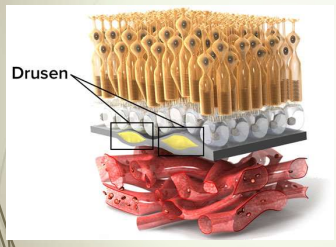
Cardiovascular Risk Factors Associated with AMD Development and Progression[1,2]

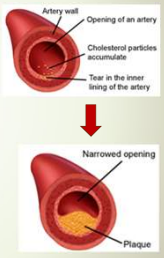
- Smoking
- Hypertension
- Serum lipid levels
- Shared susceptibility genes

1 Yip, J.L., Khawaja, A.P., Chan, M.P. et al. Cross sectional and longitudinal associations between cardiovascular risk factors and age related macular degeneration in the EPIC-Norfolk eye study. PLoS One. 2015; 10: e0132565

2 Miller, J.W. Age-related macular degeneration revisited—piecing the puzzle: the LXIX Edward Jackson memorial lecture. Am. J. Ophthalmol. 2013; 155: 1–35 e13

Dry AMD and Atherosclerosis

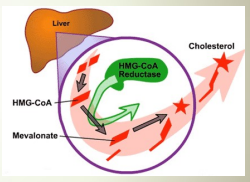




Could Statin Treatment Have an Affect on AMD Status or Progression?

Statins

- Inhibit HMG-CoA reductase
- Reduces cholesterol synthesis
- Increase liver LDL receptor levels
- Decrease serum LDL, triglycerides
- Increase serum HDL
- Antioxidant properties



Epidemiological Studies Involving Statins and AMD

- Gehlbach et al., 2015: "…evidence is insufficient to conclude if statins have a role in preventing, delaying the onset, or progression of AMD."
- Guymer et al., 2013: "…a small placebo-controlled study …suggested that 40mg of simvastatin may slow the progression of early/intermediate AMD…"
- Vanderbeek et al., 2013: "…found that statin use for more than a year was associated with increased hazard for neovascular AMD"
- Klein et al., 2014: "over a 20-year follow-up period did not show a significant association between lipid levels or lipid pathway genes with the incidence or progression of AMD"

Limitations of Previous AMD/Statin Studies

- Large heterogeneity of AMD
- Lack of standardization of statin dosage
- Lack of standardization of lipophilicity
- Small samples sizes
- Retrospective biases

High Dose Statin Cardiovascular Studies

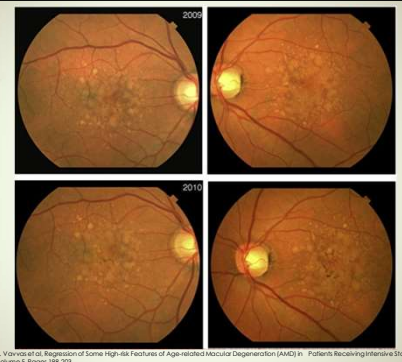
- PROVE-IT Study
- REVERSAL Trials
- ASTEROID Trials
- Others

Case Report

- 63yo wm with hx dry AMD/AREDS supple
- Presented for second opinion due to deteriorating vision
- Baseline VA 20/25 OU w distortion
- Fundus: Extensive large confluent soft drusen w pig alterations
- SD-OCT: Significant drusenoid PEDs w distortion of overlying RPE/photo

- Plan: Continue AREDS supple, monitor fundus/VA
- 1 year Results: VA decreased to 20/30 OU, increased distortion

1 Demetrios G. Vavvas et al. Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment. EBioMedicine, March 2016, Volume 5, Pages 198-203



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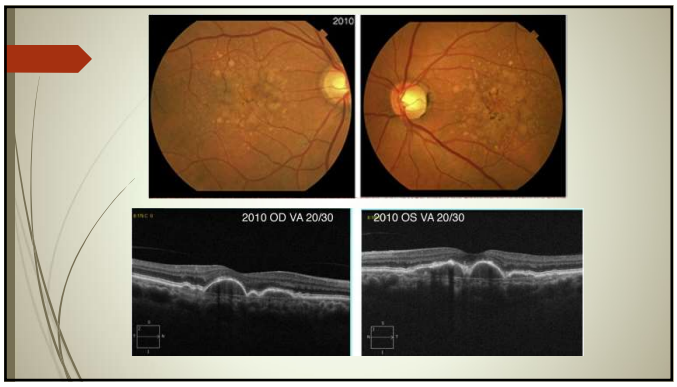
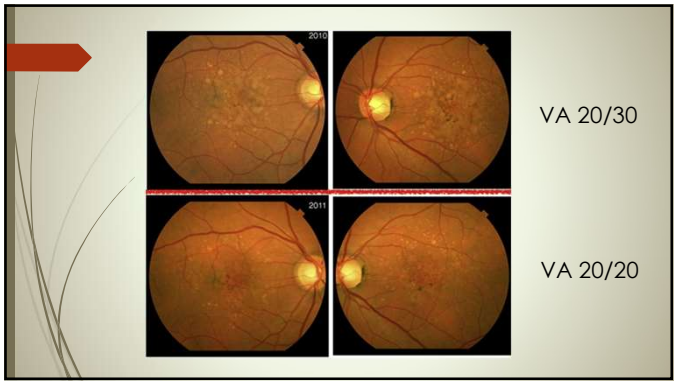
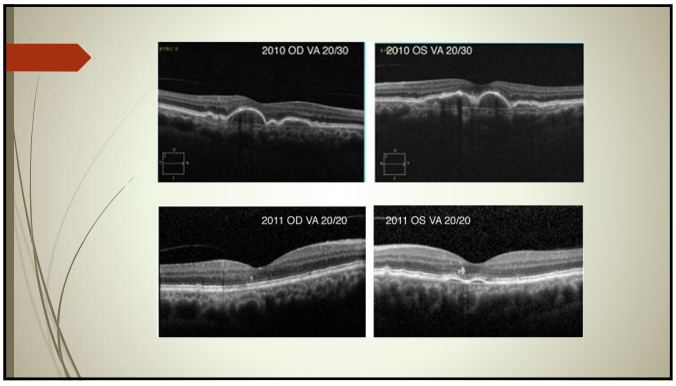


New Treatment Plan

Initial Case Report

- High-dose Atorvastatin
- 10mg/day initial dose gradually increased to 80mg/day over 9 mos
- Results reported 6 mos after reaching target dose





Pilot Study[1]

Mass Eye and Ear, Boston, USA
University of Crete, Heraklion, Greece

- Objective: To study the effects of **high-dose statins**, similar to those showing regression of atherosclerotic plaques, in AMD
- Design: Multicenter clinical study of 26 patients. Pts received 80 mg of atorvastatin daily and were monitored at baseline and every 3 months with best corrected VA, fundus photographs, OCT, and blood work
- Enrollment Criteria: >50 years of age, diagnosis of AMD and presence of large soft confluent drusen (drusenoid PED's); no or minimal GA; no choroidal neovascularization

1 Demetrios G. Vavvas et al. Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment. EBioMedicine, March 2016, Volume 5, Pages 198-203

Results of Pilot Study

Mass Eye and Ear, Boston, USA
University of Crete, Heraklion, Greece

- 26 subjects enrolled with 3 discontinuing because of cramps (1), muscle aches (1), and hair loss (1)
- 23 subjects completed a minimum follow-up of 12 mos (avg 16 mos)
- 10 of 23 subjects showed significant regression of drusen deposits (8 showing almost complete regression)
- Responders showed avg VA gain of 3 letters
- Avg time to respond was 11.7 mos (range 3-22 mos)

Results of Pilot Study

Mass Eye and Ear, Boston, USA
University of Crete, Heraklion, Greece

- Previously drusenoid PED regression has been accompanied by atrophy and vision loss
- In this Pilot Study we observed regression of drusen and drusenoid PEDs with vision gain and without atrophy
- No cases progressed to neovascular AMD

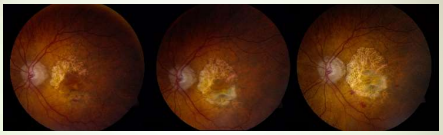
Characteristics of Responders vs Non-Responders

	All	Responders	Non-Responders	
	(n=23)	(n=10)	(n=13)	
Age	68.1 ± 6	70.6 ± 6.2	66.2 ± 5.5	p= 0.08137
Hypertension	10	5/10	5/13	Fisher 0.685018
Initial Cholesterol	208 ± 34.9	210 ± 33.4	207 ± 37.4	p = 0.859484
(total chol mg/dL)				
Last Cholesterol	147 ± 31	161 ± 34.2	136 ± 24.4	p = 0.057162
Chol. Reduction	−62 ± 35	−49 ± 31.2	−71 ± 35.9	p = 0.140764
Eye Vitamins	14	7/10	7/13	Fisher 0.669269
Vitamin D Use	5	3/10	2/13	Fisher 0.635117
Fish Oil Use	5	2/10	3/13	Fisher 1
Aspirin Use	7	3/10	4/13	Fisher 1
Initial VA (letters)	77.6 ± 8.3	74.2 ± 9.9	80.2 ± 6	p = 0.089024
Last VA (letters)	77.7 ± 8.4	77.5 ± 10.3	77.9 ± 7.1	p = 0.908481
VA gain (loss)		+3.3	-2.3	p = 0.061144

Possible Mechanism of Action of Hi-Dose Statins in AMD

- Reduction of local and systemic lipid production
- Increase viability of macrophages
- Reducing oxidative damage
- Reduce inflammatory cytokines, VEGF

Drusen Reduction in AMD



- Spontaneous regression
- Drusen reduction in late stage disease
- Laser trials (PTAMD)
- Complement inhibitor 5 trial

Limitations of Pilot Study

- Open label, non-randomized
- Small, homogeneous sample size
- Short time period (avg 1.5 yrs)
- Possibility of spontaneous reduction of drusen w/o atrophy
- How long will effects last?
- How long should statins be administered?
- Other dosages? Statin types? AMD types?

Future Studies With Statins

- Should take into account genotype and phenotypes
- Stages of AMD
- Dosing
- Lipophilicity and potency of statin
- Larger, randomized

Translation of Scientific Data to Optometric Practice When Evaluating Non-Exudative AMD

Risk assessment

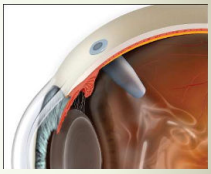
- Genetic and environmental risk factors
- Genetic profiling and testing
- Risk factors
- Clinical evaluation of hi-risk characteristics
- Dark adaptation(Maculogix)
- Cholesterol status?

Translation of Scientific Data in Optometric Practice When Evaluating Non-Exudative AMD

- Supplementation
  - AREDS II
  - Zinc?
  - Omega-3s?
- Smoking cessation
- Dietary considerations/BMI
- UVA/UVB protection
- Statin discussion with hi-risk patients and primary physicians?

Future Research of AMD Treatments

- Angiogenesis
  - Port delivery systems
- Neuroprotection
- Biology
  - Lampalizumab(Phase 3)
- Improvements in phenotyping and classification



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