

Increased Systemic C-Reactive Protein (CRP) Associated with Choroidal Thinning in Intermediate Age-Related Macular Degeneration (AMD)

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Disclosures

- The purpose of this study was to examine association between systemic CRP and OCT biomarkers of AMD progression
- I have no relevant disclosures.
- Thank you to the co-authors:
 - Dr. Alan Palestine
 - Dr. Naresh Mandava
 - Dr. Anne Lynch
 - Dr. Jennifer Patnaik
 - Dr. Marc Mathias
 - Dr. Brandie Wagner

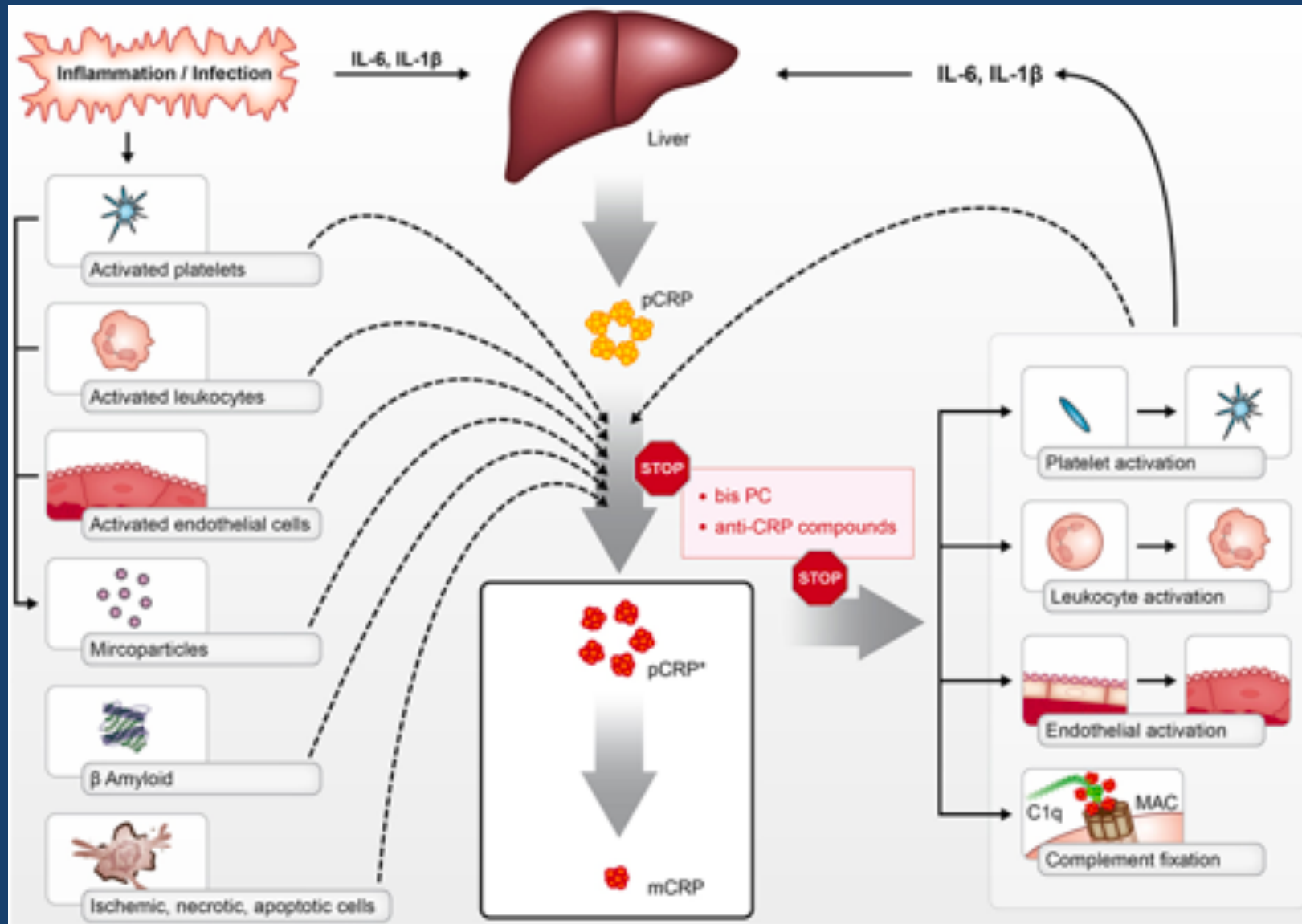
Summary

- Higher systemic CRP is associated with choroidal thinning in patients with intermediate AMD
- Qualitative OCT markers (presence of conical drusen, presence of pigmentary hyperreflective foci, subsidence of OPL and INL) were not associated with CRP
- Supports the hypothesis that high levels of CRP results in damage in the choroid

Background

- Age-related macular degeneration is a multifactorial disease – genetics, environmental risk factors all play a role
 - AMD shares risk factors with cardiovascular disease - such as obesity, hypertension, smoking
- Seddon et al. 2004 showed increased systemic (CRP) associated with increased risk for intermediate and advanced AMD in AREDS cohort
- Follow up Seddon et al. 2005 study showed baseline higher CRP (highest vs lowest quartile) associated with progression of AMD (RR 2.10, controlled for BMI, smoking, cardiovascular variables) in intermediate AMD

What is CRP?



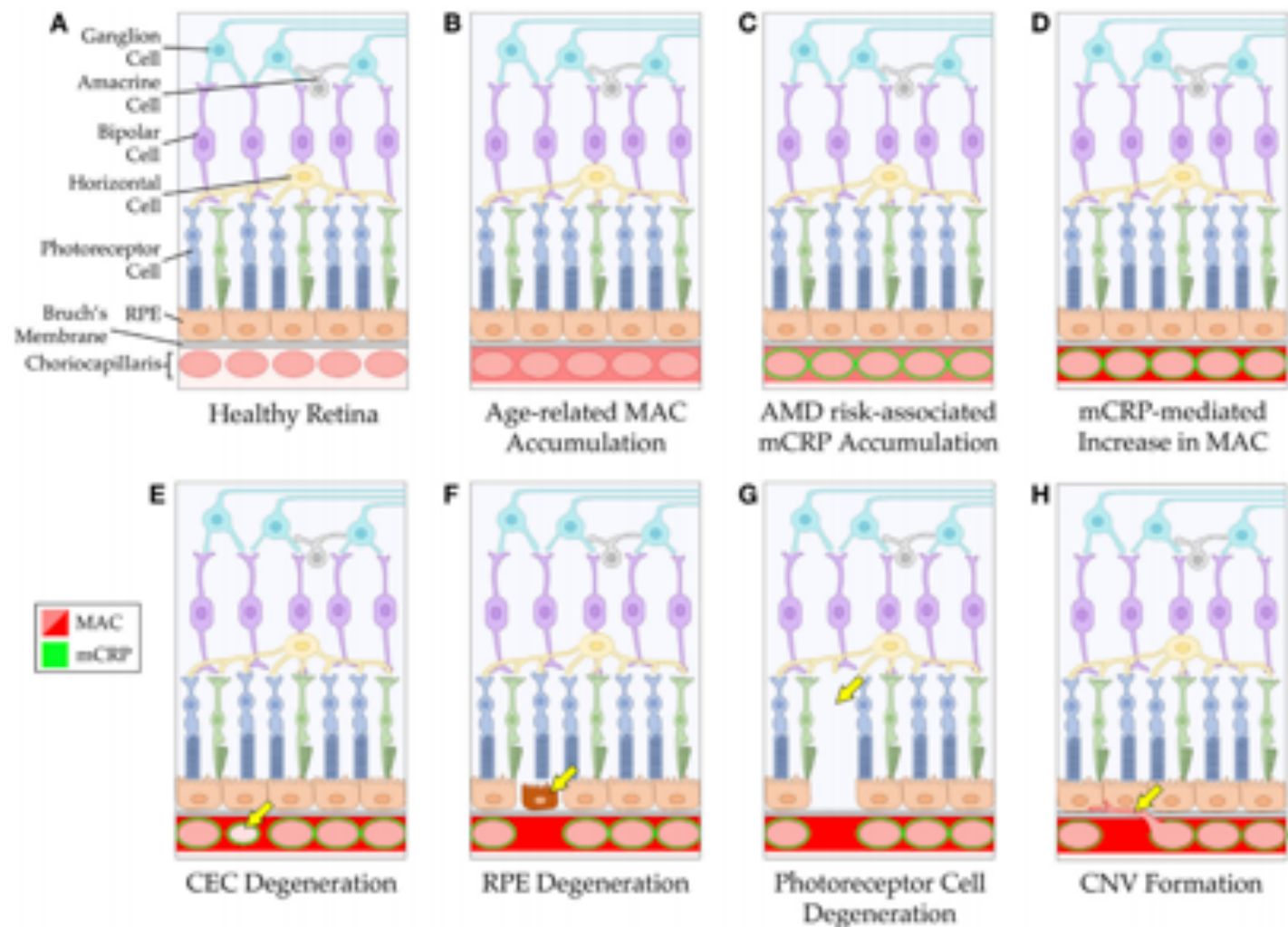
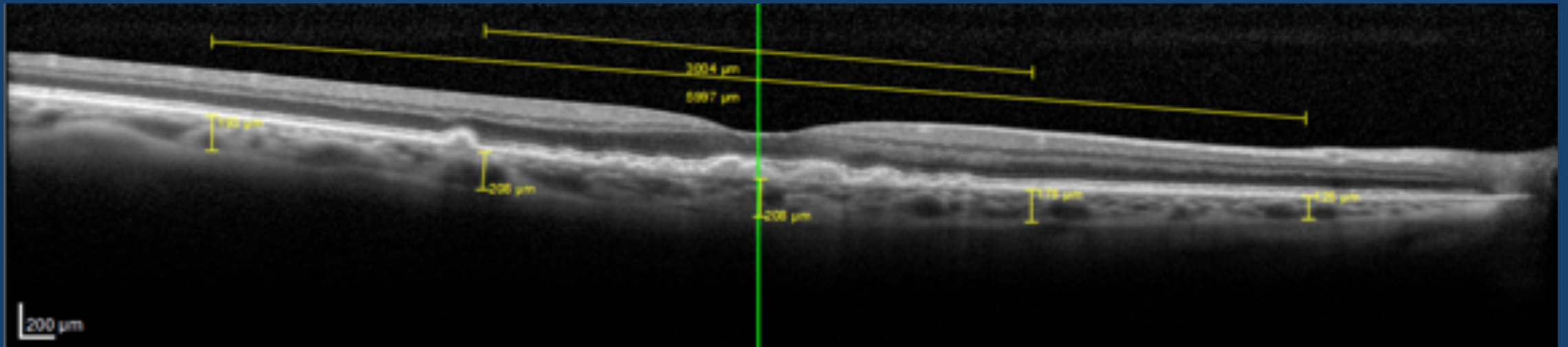


FIGURE 1 | Schematic of mCRP-associated age-related macular degeneration (AMD) pathogenesis. The healthy retina and choriocapillaris is depicted in **(A)**. With advancing age, the membrane attack complex (MAC) accumulates around the vessels of the choriocapillaris **(B)**. In individuals with an increased genetic risk for AMD (via the *CFH* Y402H polymorphism), mCRP accumulates around the vessels of the choriocapillaris **(C)**, and this may lead to increased complement activation and subsequent elevation in MAC levels in the tissue **(D)**. The mCRP- and/or MAC-mediated changes to the tissue environment may result in CEC death and degeneration of the choriocapillaris **(E)**. Loss of the vessels of the choriocapillaris can cause dysfunction and degeneration of the RPE **(F)**, and eventually the photoreceptor cells **(G)**. Alternatively, loss of choriocapillaris vessels can lead to choroidal neovascularization formation **(H)**. RPE, retinal pigment epithelium; CEC, choroidal endothelial cell; CNV, choroidal neovascularization.

Methods

- Colorado AMD Registry
 - Cross-sectional
 - Subset of 109 patients with intermediate AMD by Ferris criteria as determined by two vitreoretinal specialists
 - Biomarker data: high sensitivity CRP assay
 - Medical/social history: age, gender, BMI, smoking
 - Baseline imaging including SD-OCT, red-free, fundus autofluorescence, and color fundus photos
 - Two patients excluded for lack of high quality OCT imaging
- All patients reviewed for OCT markers for progression of AMD as identified in previous literature

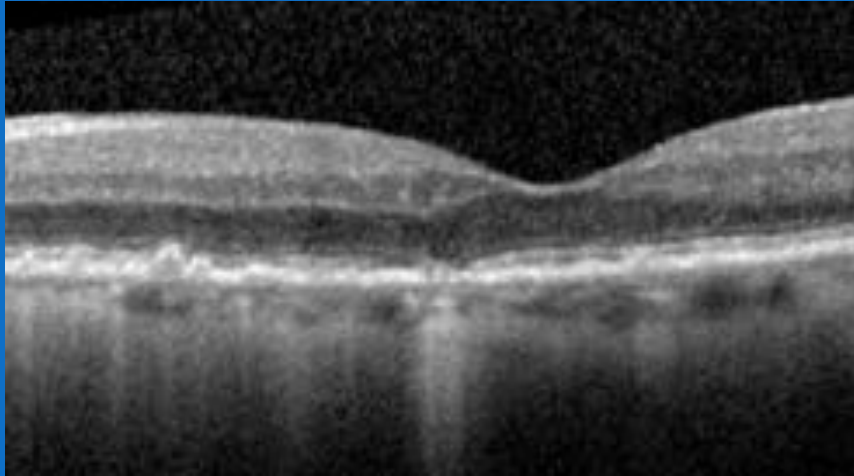
OCT Markers: Quantitative



- Choroidal Thickness (Keenan et al.)
 - average of horizontal and vertical cuts of central 6mm centered on fovea
- Maximum drusen height (DeSisternes et al.)
 - measured directly in Heidelberg Explorer

OCT Markers: Qualitative

- Qualitative markers
 - Broad drusenoid PED (> 375 micrometers)
 - Type of drusen (conical drusen) (Veerappan et al.)
 - Presence of pigmentary hyperreflective foci (Christenbury et al.)
 - Subsidence of OPL and INL (Wu et al.)



Subsidence of OPL and INL

- Disruption of Ise and RPE band
- Break in ELM
- Increased signal transmission below Bruch's Membrane

Statistical analysis

- Spearman correlation used for continuous variables
- Wilcoxon rank sum tests used for binary variables
- Choroidal thickness and CRP log transformed to reduce skewness
- Linear modeling with estimating equations used to account for intra-subject correlation of fellow eyes
- Confounders (gender, age, BMI, smoking, RPD) assessed using linear regression
- Multivariable linear regression to assess relationship between choroidal thickness and CRP, accounting for confounders

Table 1. Characteristics of the intermediate AMD cohort, N=107.

| | n (%) |
|-------------------------------|-------------------------------|
| Female Gender | 73 (68.2%) |
| Family history of AMD | |
| None | 52 (48.6%) |
| Yes | 36 (33.6%) |
| Uncertain | 19 (17.8%) |
| Smoking | |
| Never | 51 (47.7%) |
| Ever smoke (current/former)* | 56 (52.3%) |
| | n (standard deviation) |
| Age (years) | |
| Mean | 76.8 (6.8) |
| Body Mass Index, n=102 | |
| Mean | 26.4 (4.9) |

*Includes two current smokers and 54 former smokers.

Table 2. Univariate and multivariable associations between average choroidal thickness with CRP and potential confounders.

| | Average Choroidal thickness (natural log transformed) | |
|-------------------------------------|---|-----------------|
| | Parameter Estimate (SE) | p-value |
| | Univariate Analysis | |
| CRP (log (base e) mg/L) | -0.07 (0.03) | 0.01 |
| Age (years) | -0.01 (0.004) | <0.01 |
| Female Gender | 0.06 (0.06) | 0.27 |
| BMI as continuous (kg/m2) | -0.01 (0.01) | 0.18 |
| Reticular Pseudodrusen (RPD) | -0.16 (0.05) | <0.01 |
| Ever Smoked | -0.02 (0.05) | 0.71 |
| | Multivariable Analysis* | |
| CRP (log (base e) mg/L) | -0.07 (0.03) | 0.01 |

*Multivariable analysis adjusted for age and RPD.

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