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Increased Systemic C-Reactive Protein Is Associated With Choroidal Thinning in Intermediate Age-Related Macular Degeneration

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Purpose: C-reactive protein (CRP) and decreased choroidal thickness (CT) are risk factors for progression to advanced age-related macular degeneration (AMD). We examined the association between systemic levels of CRP and CT in patients with intermediate AMD (iAMD).

Methods: Patients with iAMD in the Colorado AMD Registry were included. Baseline serum samples and multimodal imaging including spectral domain–optical coherence tomography (SD-OCT), fundus photography, and autofluorescence were obtained. Medical and social histories were surveyed. CT was obtained by manual segmentation of OCT images. High-sensitivity CRP levels were quantified in serum samples. Univariate and multivariable linear regression models accounting for the intrasubject correlation of two eyes were fit using log-transformed CT as the outcome.

Results: The study included 213 eyes from 107 patients with a mean age of 76.8 years (SD, 6.8). Median CT was 200.5 µm (range, 86.5–447.0). Median CRP was 1.43 mg/L (range, 0.13–17.10). Higher CRP was associated with decreased CT in the univariate model ($P = 0.01$). Older age and presence of reticular pseudodrusen (RPD) were associated with decreased CT ($P < 0.01$), whereas gender, body mass index, and smoking were not associated with CT. Higher CRP remained significantly associated with decreased CT after adjustment for age and RPD ($P = 0.01$).

Conclusions: Increased CRP may damage the choroid, leading to choroidal thinning and increased risk of progression to advanced AMD. Alternatively, CRP may be a marker for inflammatory events that mediate ocular disease. The results of this study further strengthen the association between inflammation and AMD.

Translational Relevance: Increased CRP is associated with choroidal thinning, a clinical risk factor for AMD.

Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness worldwide.[1] The pathophysiology underlying development of AMD is multifactorial.[2] Previous studies have linked cardiovascular disease and its risk factors, such as cigarette smoking, obesity, and hypertension, to the development and progression of AMD.[1–4]

C-reactive protein (CRP) is an evolutionarily conserved inflammatory marker that has been established as an independent risk factor for cardiovascular disease and AMD.[2] Seddon et al.[5] found higher levels of CRP in patients with intermediate and advanced AMD compared with normal controls in the Age-Related Eye Disease Study cohort.[6] This effect was independent of smoking and body mass index (BMI). In a longitudinal study of an independent cohort, Seddon et al.[7] further reported that higher levels of

baseline CRP were associated with progression of intermediate AMD to advanced stages.

The mechanism of the effect of higher CRP on AMD is unclear but may be related to its effects on the choroid. Prior studies have shown that CRP increases vascular resistance in the ophthalmic artery in patients with treatment-naïve exudative AMD.[8] Increased levels of monomeric CRP (mCRP), the proinflammatory breakdown product of pentameric CRP, has also been found in the choroidal vessels of donor eyes of patients with AMD.[9] Higher levels of mCRP have also been found in donor eyes of patients with the homozygous Y402H single-nucleotide polymorphism in the gene encoding complement factor H, which has been shown to increase risk for AMD.[10,11]

Previous studies have identified biomarkers for the progression of AMD on spectral domain–optical coherence tomography (SD-OCT), including morphological type of drusen, height and width of the drusen and the retinal pigment epithelium–drusen complex, presence of pigmentary hyperreflective material in the retina, and subsidence of the outer plexiform layer (OPL) and inner nuclear layer (INL).[12–15] Several studies have reported decreased choroidal thickness (CT) in patients with early AMD, as well as advanced atrophic and neovascular AMD.[16–21] In a study by Fan et al.,[17] patients with decreased subfoveal CT at baseline were more likely to develop advanced macular atrophy at 18-month follow-up. However, to our knowledge, there have been no studies examining the relationship between CRP and OCT biomarkers in AMD.

The focus of recent research from our department has been the contribution of systemic inflammation to AMD, and the department has had several works published in this area.[22–24] In this study, we aimed to examine the relationship between CRP and OCT markers of AMD in a cohort of patients with intermediate AMD (iAMD).

Materials and Methods

Colorado AMD Registry

The study cohort is a subset of patients with iAMD from the Colorado AMD Registry, which has been previously described in detail.[25] In brief, patients with AMD who were seen at the UCHealth Sue Anschutz-Rodgers Eye Center were eligible to be included in the AMD registry. Patients underwent an institutional review board–approved informed consent for review of medical history, collection of blood samples, and multimodal imaging, including color fundus photography (CFP), fundus autofluorescence, near-infrared reflectance, and SD-OCT. Patients with active ocular inflammation or pre-existing severe retinal disease or who required panretinal photocoagulation or anti–vascular endothelial growth factor for indications other than AMD were excluded from the registry. All images were reviewed by two vitreoretinal specialists and then categorized using the classification described by Ferris et al.[26] Specifically, iAMD was defined as the presence of at least one large drusen or any AMD-related pigment abnormalities in a setting of multiple medium drusen and a lack of other etiology for pigment abnormalities. Reticular pseudodrusen (RPD), as previously described by other authors, were considered to be present if they were evident on at least two imaging modalities.[27–31] RPD appear as confluent deep retinal lesions in a ribbon-like network on CFP, as hyporeflectant lesions in a mildly hyperreflectant background on near-infrared reflectance, as hypoautofluorescent lesions in mildly hyperautofluorescent background on fundus autofluorescence, and as hyper-reflective material in the outer retinal layer anterior to the RPE on SD-OCT.[27–31] Methods for the collection of epidemiological data in this registry are described elsewhere.[25] Risk factors included in the dataset were age, gender, family history of AMD, BMI, and smoking. Blood samples were collected at time of imaging. Serum was isolated by allowing the blood to coagulate for 30 minutes to 2 hours. The samples were then centrifuged at 3000 revolutions per minute in a cooled (4°C) centrifuge for 10 minutes. Samples were pipetted into aliquots and stored in a –80°C freezer.

Study Cohort

Patients included in this iAMD cohort underwent a second imaging review that specifically excluded patients with other retina comorbidities ($n = 5$) and unilateral RPD ($n = 4$). Five eyes from this dataset were excluded due to lack of OCT imaging. The final dataset included 107 patients.

Measurement of CRP

Serum samples collected at the time of image acquisition were assayed for CRP.[22,25] High-sensitivity CRP assays were performed using the automated BN II System nephelometer (Siemens Healthineers, Malvern, PA).

Measurement of CT

SD-OCT images were reviewed by a single reviewer (RCC). A random sample of 20 eyes (9.4%) was

reviewed by another grader (NM). Scans for each eye were imported into ImageJ (National Institutes of Health, Bethesda, MD) from HEYEX software. The choroid was manually segmented focusing on the 6 mm centered on the fovea using the "polygon" tool in both horizontal and vertical scans. The outer border of the hyperreflective line of the retinal pigment epithelium–Bruch's membrane and the inner border of the hyporeflective line between choroid and sclera were chosen as the boundaries of the choroid. CT was obtained by dividing the segmented area by 6 mm. Average CT was obtained by averaging measurements from horizontal and vertical scans when both were available.

Measurement of Qualitative OCT Measures

Qualitative OCT measures associated with progression to advanced AMD were identified from prior literature.[13–15] OCT measures included C-type conical debris, defined as conical-shaped drusen with at least three focal, well-circumscribed hyperreflective cores within the drusen; subsidence of the OPL and INL layer, defined as focal areas of disruption in the ellipsoid zone and external limiting membrane with increased signal transmission below Bruch's membrane; pigmentary hyperreflective foci in the neurosensory retina that were more reflective than the RPE band; and broad drusenoid pigment epithelial detachment with horizontal width greater than 375 µm (three times the width of large drusen). Qualitative OCT measures were described for each patient as present or absent.

Statistical Analysis

Descriptive statistics included means and associated standard deviation for normally distributed continuous variables and medians and ranges or interquartile ranges for continuous variables that were not normally distributed. Basic frequencies and percentages were used to summarize categorical variables. Among the 20 records measured by the two graders, the median percent difference between the two graders and the Pearson's correlation coefficient were calculated. We examined the association of CRP with binary variables of qualitative OCT measures using the Wilcoxon rank-sum test. CT and CRP were log base e transformed to reduce skewness. Univariate associations were assessed using a linear regression with generalized estimating equations to account for the intrasubject correlation of having two eyes included in the analysis. Associations between CT and CRP with other potential confounders such as gender, age, BMI, smoking, and RPD were evaluated. Finally, multivariable linear regression was used to assess the relationship between CT and CRP (both natural log transformed), adjusted for significant factors of age and RPD. A sensitivity analysis was also performed in which the CT measures from both eyes of patients were averaged, and only one record was included for each patient. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

This study included 213 eyes of 107 patients. Table 1 describes characteristics of the cohort. The average age was 76.8 years, and about two-thirds of patients were female. Median CT was 200.5 µm (range, 86.5–447). Measurements between the two graders were very similar, with a median absolute percent difference of 5.5% and a Pearson correlation coefficient of 0.96 ($P < 0.0001$), indicating excellent correlation. Median CRP was 1.43 mg/L (0.13–17.10). Out of the 107 patients, 39 had bilateral reticular pseudodrusen.

There were no associations between CRP and any qualitative OCT biomarker (Table 2). Table 3 describes the relationship between CT and CRP and potential confounders. CT was significantly associated with CRP (parameter estimate ± SE, –0.07 ± 0.03; $P = 0.01$) (Fig.). This relationship remained and was more highly significant in the sensitivity analysis with only one record per patient and the average CT included in the model (–0.07; $P = 0.0002$). Age was significantly associated with CT (–0.01 ± 0.004; $P < 0.01$) but not CRP ($P = 0.37$). Presence of RPD was associated with CT (–0.16 ± 0.05; $P < 0.01$), but not with CRP ($P = 0.58$). Gender, BMI, and smoking were not associated with CT ($P > 0.05$ for all). C-reactive protein remained significantly associated with CT after adjustment for age and presence of RPD (–0.07 ± 0.03; $P = 0.01$).

Table 1. Characteristics of the Intermediate AMD Cohort ($N = 107$)

Characteristic	
Female gender, *n* (%)	73 (68.2)
Family history of AMD, *n* (%)	
None	52 (48.6)
Yes	36 (33.6)
Uncertain	19 (17.8)
Smoking, *n* (%)	
Never	51 (47.7)
Ever smoke (current/former)[a]	56 (52.3)
Age (yr), mean (SD)	76.8 (6.8)
BMI ($n = 102$), mean (SD)	26.4 (4.9)

[a]Includes two current smokers and 54 former smokers.

Table 2. Binary OCT Measures and CRP Among the Intermediate AMD Cohort

	Patients, *n*	CRP, Median (Interquartile Range)	*P* (Wilcoxon Rank-Sum Test)
Subsidence of OPL/INL			0.62
Present in either eye	10	0.94 (0.56–8.08)	
Absent	97	1.45 (0.75–2.46)	
Conical drusen			0.82
Present in either eye	6	0.85 (0.56–9.83)	
Absent	101	1.45 (0.72–2.46)	
Broad drusenoid pigment epithelial detachment			0.62
Present in either eye	58	1.36 (0.72–3.57)	
Absent	49	1.45 (0.65–2.25)	
Pigmentary hyperreflective foci			0.77
Present in either eye	29	1.46 (0.65–3.95)	
Absent	78	1.43 (0.72–2.43)	

Table 3. Univariate and Multivariable Associations Between Average CT With CRP and Potential Confounders ($N = 213$)

	CT (Natural Log Transformed)	
	Parameter Estimate (SE)	*P*
Univariate Analysis		
CRP (log base e; mg/L)	–0.07 (0.03)	0.01
Age (yr)	–0.01 (0.004)	<0.01
Female gender	0.06 (0.06)	0.27
BMI as continuous variable (kg/m^2)	–0.01 (0.01)	0.18
RPD*	–0.16 (0.05)	<0.01
Ever smoked	–0.02 (0.05)	0.71
Multivariable Analysis[a]		
CRP (log base e; mg/L)	–0.07 (0.03)	0.01

[a]Multivariable analysis adjusted for age and RPD.

Because these data are natural log transformed, this parameter estimate can be interpreted as for every 1% increase in CRP CT decreased by 0.07%.

Discussion

In this study, we examined the association between CRP, an established risk factor for AMD, and OCT biomarkers previously found to confer higher risk for progression to advanced AMD. To the authors' knowledge, this is the first study to describe the association between systemic CRP and choroidal thinning on OCT in patients with intermediate AMD.

CRP is an acute-phase reactant produced by the liver in response to proinflammatory cytokines; it is also a mediator of inflammation.[32] In local tissues, systemic pentameric CRP dissociates into its monomeric form, mCRP, which activates the classical complement pathway through its interaction with complement protein C1q.[33] It also binds to complement factor H (CFH), which then downregulates the alternative complement pathway.[32] Specific CFH polymorphisms, such as the Y402H variant, have been associated with increased risk for AMD.[32] The downregulatory effect of CRP is impaired in these at-risk polymorphic CFH variants.[32]

Extensive evidence within the cardiovascular disease literature shows that increased CRP contributes to atherogenesis by locally activating the complement pathway, releasing proinflammatory cytokines, promoting endothelial dysfunction, and impeding lipid uptake by macrophages.[34] Cardiovascular disease and AMD share multiple proinflammatory risk factors, including smoking, obesity, and lipid levels.[5] Therefore, CRP may also function similarly in the pathogenesis

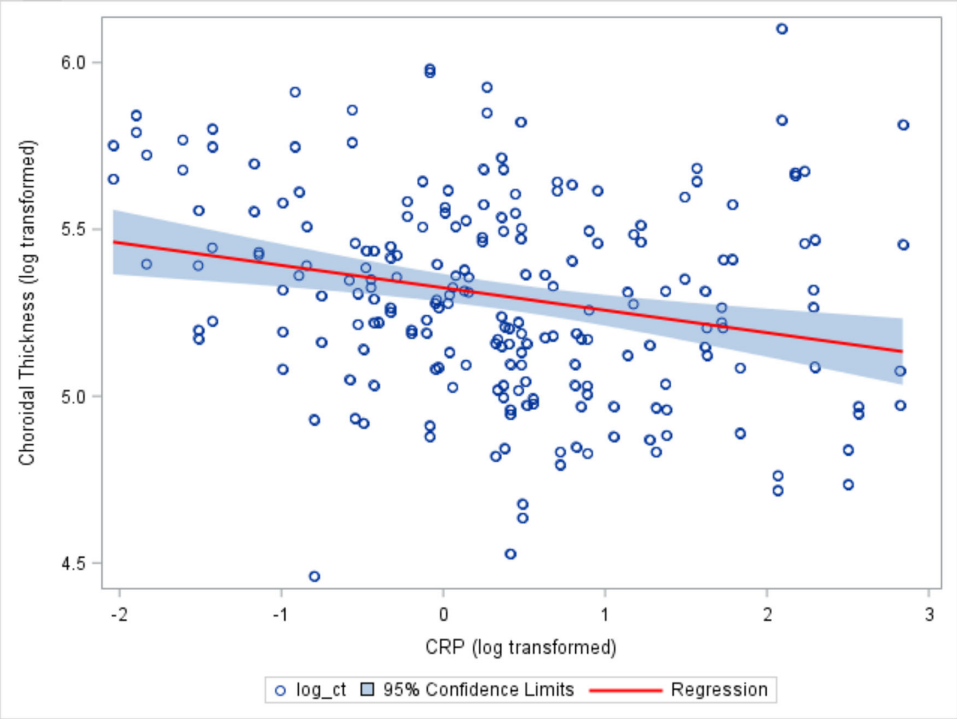

Figure. Plot of average CT (natural log transformed) and CRP (natural log transformed) for both eyes. Parameter estimate of –0.07 (±0.03 SE) of negative association between CT and CRP ($P = 0.01$).

of AMD through its effects on localized inflammation. Seddon et al.[5] first established increased systemic CRP as a risk factor for intermediate and advanced AMD. In 2005, Seddon et al.[7] further found higher baseline CRP as a risk factor for progression of intermediate to advanced AMD. Subsequent studies on CRP in AMD demonstrated that CRP predominantly accumulates in the choroid and RPE. In donor eyes of patients with the high-risk Y402H polymorphism, CRP was found in increased levels in the choroid compared with those with low-risk Y402.[11] Follow-up studies similarly demonstrated increased staining of mCRP in the choriocapillaris and Bruch's membrane in patients with the Y402H polymorphism.[10] In donor eyes, CFH decreases mCRP-induced upregulation of interleukin-8, with significantly greater effect in non–high-risk CFH variants than in the high-risk Y402H variant.[11] mCRP also directly increases choroidal endothelial cell migration and monolayer permeability and upregulates proinflammatory gene expression in human RPE–choroid tissue in vivo, which has previously been implicated in AMD.[10,35] Immunostaining of donor eyes of patients with early and wet AMD has shown increased CRP and decreased complement factor H (FH) staining in choroidal vessel walls.[9] In all, these findings suggest that CRP-mediated activation of choroidal inflammation plays a role in the development of AMD.

In acute inflammatory states, such as in acute uveitis flares in lupus, Behçet's disease, and spondyloarthropathies, CT increases.[36] However, in chronic inflammation, chronic ischemia may lead to atrophy and fibrosis, resulting in choroidal thinning.[36] A similar process may occur in AMD. Histopathological studies in eyes with AMD have shown reduced submacular large choroidal vessel density compared with controls.[37] OCT analyses similarly show a decreased choroidal vascular index (CVI), the proportion of choroid comprised of intraluminal space, in patients with AMD.[38] Loss of choriocapillaris under intact RPE predates development of drusen and enlargement of geographic atrophy.[39,40] Choroidal thinning has also been associated with both early and late AMD in multiple studies, although the magnitude of thinning is increased in late AMD compared with early or intermediate AMD.[16,20,21] Sigler et al.[21] examined 150 eyes of 150 patients with early AMD (large drusen without pigmentary changes) and intermediate AMD (drusen with pigmentary or RPE changes but without geographic atrophy) and found significantly decreased CT in both groups. Chung et al.[16] similarly found decreased CT in patients with early AMD and with

advanced neovascular AMD. Importantly, multiple studies have suggested that decreased CT and CVI are associated with progression to late AMD. Govetto et al.[18] found that CT in eyes with neovascular AMD was significantly thinner compared with fellow eyes with non-neovascular AMD. A subanalysis based on groups of non-neovascular AMD showed larger differences in CT when neovascular AMD was compared with earlier stages of non-neovascular AMD, suggesting that the choroid undergoes progressive thinning with advancing disease.[18] Fan et al.[17] reported that decreased baseline subfoveal CT in intermediate AMD was associated with increased risk for development of macular atrophy. In 2019, Keenan et al.[41] described increased CT and CVI in patients with intermediate AMD without late AMD in the fellow eye but not in those with late AMD in the fellow eye, suggesting that changes in CVI are biphasic, with initial increase and subsequent decrease in patients at higher risk for progression in AMD. Accordingly, our data support the concept that increased CRP may be a marker and mediator for inflammation within the choroid in AMD. When combined with the studies discussed above, it may be that chronic inflammation results in choroidal thinning and increased risk for progression of AMD.

It is interesting to note that patients with a genetic predisposition to AMD may already demonstrate baseline choroidal thinning. For example, in a population-based study of healthy Korean older adults, a high-risk CFH variant was associated with choroidal thinning.[42] Although CFH may be an independent risk factor, it may also reflect the differential effect of CRP on the choroid in high-risk CFH variants. Future studies are necessary to elucidate how the effect of CRP on choroidal thinning is modified by high-risk genetic alleles.

Alternatively, CRP may be a marker for underlying systemic disease that may increase risk for AMD and affect CT independently. In one study in patients with cardiovascular disease, which shares common risk factors with AMD, CT was significantly decreased compared with controls.[43] Higher levels of systemic CRP have also been found in other diseases of aging, such as Alzheimer's, which has also been associated with choroidal thinning.[44,45] It is important to note, however, that although CRP and choroidal thinning are both associated with aging the relationship between CRP and choroidal thinning in AMD remained after adjusting for age in this study.

There are several limitations to this study. Imaging in this study was done using SD-OCT without enhanced depth imaging OCT (EDI-OCT), which has a smaller depth of field and poorer visualization of the choroid compared with SD-OCT with EDI-OCT. However, prior studies have shown good correlation between successful choroidal measurements on SD-OCT without and with EDI-OCT.[46] In addition, we were able to determine the choroid–sclera junction in at least one eye of all patients who had OCT imaging in this study. Given that AMD is a disease with thin choroid, we feel that SD-OCT is less of a limitation in quantifying CT. Within the limits of a cross-sectional study and because of the small sample size, we were not able to analyze whether increased CRP and choroidal thinning were associated with higher risk for progression of AMD. Although we evaluated for possible confounders such as age, BMI, gender, smoking, and presence of RPD, we were unable to evaluate other established effectors of CT, such as axial length. Notably, axial length has not been previously associated with CRP and would not be expected to be a confounder.[47] Finally, the small sample size in this study may have limited the evaluation of qualitative OCT features.

In conclusion, to our knowledge, this is the first study to suggest a relationship between CRP and choroidal thinning on OCT in patients with iAMD, lending support to the hypothesis that chronic inflammation is crucial to the pathogenesis of AMD. Further research is needed to elucidate the role of inflammation in progression of AMD and to investigate the application of antiinflammatory agents in its treatment.

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