• Clinical Research •

Systemic C-reactive protein levels in patients with geographic atrophy stratified by sex

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Abstract

● **AIM:** To determine the differences in levels of systemic C-reactive protein (CRP) in patients with geographic atrophy (GA) and sex-based differences in CRP levels.

● **METHODS:** Blood samples from patients with GA and controls were collected in a prospective age-related macular degeneration (AMD) registry from August 2014 to June 2021. AMD was confirmed using multimodal imaging and the Beckman and Consensus of Atrophy Meeting criteria for GA. High-sensitivity serum CRP levels were measured using an automated nephelometer. A non-parametric (rank-based) linear regression model was fit with an interaction between sex and GA.

● **RESULTS:** There were 97 GA patients and 139 controls, with females comprising 55% and 66% of each cohort, respectively. There is no difference in CRP between cases and controls, with a median (interquartile range) of 1.2 (0.6-2.6) mg/L in GA patients versus 1.3 (0.8–2.9) mg/L in controls (P=0.52). Although females had higher CRP levels compared to males in both the GA and control groups, this difference did not reach statistical significance after adjustment for multiple comparisons.

● **CONCLUSION:** There is no significant difference in systemic CRP levels between GA cases and controls.

● **KEYWORDS:** age-related macular degeneration; C-reactive protein; geographic atrophy; multimodal retinal imaging

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of progressive vision loss among older adults in developed, high-income countries. It is estimated that 300 million individuals will be affected by the disease by 2040[1]. Geographic atrophy (GA) is the advanced non-neovascular form of AMD affecting 5–6 million people globally. GA is characterized by the loss of photoreceptors, outer retinal layers, and retinal pigment epithelial (RPE) causing progressive and irreversible loss of central vision[2]. There are multiple pathways involved in the pathogenesis of GA, including complement activation[3], inflammation[4], drusen formation[5], and oxidative stress of the retina[6]. Current treatments to prevent GA progression are limited. There is, however, recent Food and Drug Administration approval for a complement inhibiting drug and there are other clinical trials in various phases investigating several drugs that have shown promising results in the form of attenuation of the progression of GA[7-10]. Most of the established research has focused on the contribution of local inflammatory events to the pathogenesis of AMD[3-6]. Our group has specifically investigated the role of systemic inflammation in AMD. We have thus far described a role for systemic inflammatory biomarkers such as the select complement system[11], cytokines[12], and chemokines in AMD[13]. We are now expanding our research to study the role of systemic levels of C-reactive protein (CRP) in patients with GA. CRP is an acute-phase reactant and a systemic inflammatory biomarker produced by hepatocytes. CRP is produced in response to infection or tissue inflammation and is stimulated by interleukin-1, interleukin-6, and tumor necrosis factor[14]. Histopathological studies have shown that the monomeric form of CRP can activate the local complement

cascade in the RPE, thereby creating an environment with local chronic inflammation which leads to the formation of drusen[15-16]. Chronic activation of this complement system leads to progression into atrophy[17]. Although the involvement of local CRP in the pathogenesis of AMD is widely accepted, prior investigations into the role of systemic CRP in AMD have resulted in conflicting results. Some authors have suggested a pattern of higher levels of systemic CRP in AMD[18-22], while other authors have found no relationship between CRP levels and AMD[23-26]. Regarding sex-based differences in inflammatory biomarkers of AMD, our group has investigated sex-related altered levels of complement factors[27] and regulated upon activation, normal T cell expressed and secreted (RANTES)[28] in AMD. To our knowledge, sex-based differences in systemic CRP levels have not been studied specifically in GA. Thus, the primary aim of this study was to determine if there are differences in levels of CRP in a cohort of patients with GA carefully characterized using multimodal imaging compared with controls without AMD. The secondary aim was to elucidate the understudied area of systemic CRP levels by sex in AMD patients with GA and control patients without AMD.

PARTICIPANTS AND METHODS

Ethical Approval This study was conducted using data from an AMD registry housed in the Division of Ophthalmic Epidemiology, Department of Ophthalmology at the University of Colorado School of Medicine. Details of this registry are described elsewhere[29]. In brief, patients with AMD and healthy controls without AMD who attend the Sue-Anschutz Rodgers Eye Center are eligible to be included in this registry. The registry is approved by the Colorado Multiple Institutional Review Board (COMIRB approval number: 14-0470) and conforms with the Declaration of Helsinki. Informed consent was obtained from the subjects.

Study Population Patients between 55 and 99 years of age who have AMD in one or both eyes and can provide consent are eligible for inclusion in the registry. Controls are patients recruited from our cataract surgery clinics who do not have any AMD on review of multimodal imaging. Controls are enrolled one month after their cataract surgery. Exclusion criteria for involvement in the registry include terminal illness, active ocular or systemic inflammatory conditions, prior intravitreal anti-vascular endothelial growth factor injections, pan-retinal photocoagulation, diabetic retinopathy, central and branch retinal vein occlusion with macular damage, central serous chorioretinopathy, full-thickness macular hole, macula-off retinal detachment, intraocular tumors, macular dystrophy, macular telangiectasia, history of corneal transplant, drusen unrelated to AMD, current systemic cancer treatment, use of ocular or systemic immunosuppressants, and severe cognitive impairment or advanced dementia.

All patient data and image review forms are entered into a secure web-based Research Electronic Data Capture (REDCap) database[30]. Epidemiological data studied as a part of this pecific study included age, smoking history, family history of AMD, abnormal lipid panel, body mass index (BMI), and ocular and systemic medication use. Recruitment into the registry is ongoing, and for this study, we used data from patients recruited between August 2014 and June 2021.

Measurement of Visual Acuity In this study, all visual acuity measurements for patients were obtained in a clinical setting using Snellen visual acuity testing at a distance, representing the habitual acuity at the time of enrollment. These measurements were converted to logMAR values for statistical analysis. Both eyes of each patient were included in the study, with the better-seeing eye defined as the one with the lower logMAR value, and the worse-seeing eye as the one with the same or higher logMAR value.

Blood Collection and Processing Blood samples were collected at the time of enrollment, and each sample was allowed to coagulate between 30min and 2h to isolate the serum. The samples were then spun in a refrigerated centrifuge (-4°C) at 3000 rotations per minute, for 10min. The serum samples were then pipetted into aliquots and stored in an 80°C freezer before being transferred to the biorepository for long-term storage.

Measurement of CRP High-sensitivity serum CRP assays were performed at the Clinical Translational Core Laboratory, located at Children's Hospital Colorado, using the automated II System nephelometer (Siemens Healthineers, Malvern, PA, USA). The lower limit of detection for this assay was 0.007 mg/L, all the values obtained for this study were above this threshold. Each of the samples underwent duplicate testing and were considered acceptable if their coefficient of variance was below 15%, indicating low variability between the two measurements.

Image Review For patients enrolled in the registry, imaging was performed using either the Eidon True Color Confocal Scanner (iCare Spa, Vantaa, Finland) or the Topcon TRC-50DX (Topcon, Tokyo, Japan) to capture 50- or 60-degree color fundus photographs centered on the fovea (field 2). Additionally, 60-degree fundus autofluorescence images were obtained with the Heidelberg Spectralis (Heidelberg Engineering Inc., Germany), employing an automatic real-time (ART) function set at 50, also centered on the fovea. For high-resolution imaging, the Heidelberg Spectralis was utilized to capture both horizontal and vertical enhanced depth imaging (EDI) line scans (6 mm/30 degrees/ART 100) and 49-line cube scans (6 mm/30 degrees/ART 9), with the scans centered on the fovea.

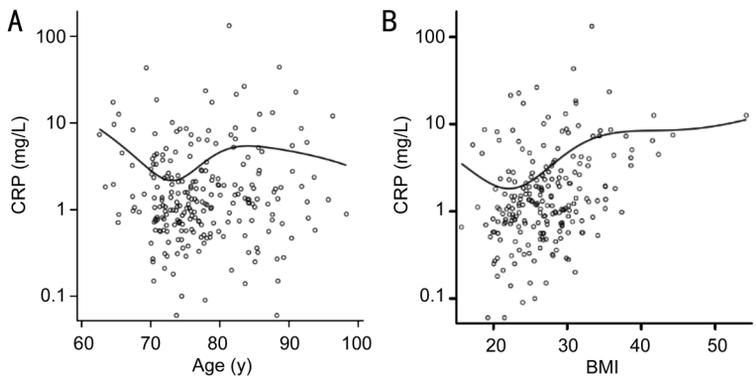

Figure 1 Correlation between systemic CRP levels and age (A), CRP levels and BMI (B) for geographic atrophy patients CRP: C-reactive protein; BMI: Body mass index.

Patients were initially classified as having GA associated with AMD based on the Classification of Atrophy Meetings (CAM) criteria: 1) loss of outer retinal layers, 2) loss of the RPE, 3) choroidal hypertransmission measuring at least 250 μm in patients diagnosed with AMD without any other retinal conditions[31]. Most patients underwent multimodal imaging annually, though follow-up intervals varied for some individuals. To ensure accurate AMD classification, two vitreoretinal specialists independently reviewed the images upon registry enrollment, and any disagreements were resolved by a third reviewer.

Statistical Analysis Two-sample *t*-test to analyze continuous variables and χ^2 test or Fisher's exact test for categorical variables were used, as appropriate. A regression model was applied to examine the relationship between CRP, sex, and GA. Levels of CRP were fit with a regression model using a rank transformation that included an AMD classification by sex interaction and age, BMI and laboratory batch effects as covariates. Additionally, we performed a sensitivity analysis to adjust for variables that were significantly associated with the study groups and CRP levels, including age, BMI and batch effect. Least square means were used to analyze pairwise comparisons for all sex by study group comparisons. To account for multiple comparisons, *P*-values were adjusted using the Tukey-Kramer method. Spearman correlation coefficient was used to find the association between CRP and covariates. Non-parametric statistics were used due to the skewness of the CRP values. A sensitivity analysis was included after randomly imputing missing BMI values for the model that included BMI as a covariate. All statistical analysis was conducted using SAS version 9.4 from The SAS Institute in Cary, NC, USA. $P<0.05$ is considered statistically significant.

RESULTS

All patients with available samples were included in this study, resulting in 97 patients with GA and 139 control patients without AMD. In Table 1, we present a comparison of the demographic characteristics and selected comorbidities between GA cases and controls. The GA group included 53 females (55%) while the control group included 92 females (66%). The GA group had a significantly higher mean age and a higher rate of family history of AMD compared to the control group ($P<0.01$ for both). Additionally, the GA group had significantly higher rates of treated hypertension ($P<0.01$) and kidney disease ($P=0.04$) than the control group. The median logMAR for the better-seeing eye in GA AMD patients was 0.30 [interquartile range (IQR): 0.10 to 0.54], compared to 0.10 (IQR: 0.00 to 0.18) in controls, with a statistically significant difference ($P<0.01$). Similarly, for the worse-seeing eye, GA AMD patients had a median logMAR of 0.70 (IQR: 0.40 to 1.00), whereas controls had a median of 0.18 (IQR: 0.10 to 0.30), also showing a statistically significant difference ($P<0.01$).

There was no significant difference in CRP levels between GA cases and controls with a median IQR of 1.2 (0.6–2.6) mg/L in cases versus 1.3 (0.8–2.9) mg/L in controls ($P=0.52$). We found no significant relationship between CRP and GA ($P=0.13$) following adjustment for age, BMI, and laboratory batch effect. The result was not changed when repeating the analysis after imputing the missing 16 BMI values as a sensitivity analysis. Following adjustment for age alone, we found no significant relationship between CRP and GA ($P=0.09$).

Regarding the relationship between CRP and other co-variates, we found CRP levels were not associated with age ($r=0.02$, $P=0.75$; Figure 1A), smoking ($P=0.78$), logMAR for the worse-seeing eye ($r=0.15$, $P=0.15$), logMAR for the better-seeing eye ($r=0.18$, $P=0.07$), treated hypertension ($P=0.57$), or family history of AMD ($P=0.11$). However, CRP levels were associated with sex ($P=0.01$) and BMI ($r=0.32$, $n=220$, $P<0.01$; Figure 1B) as a continuous variable.

In the final stage of the analysis, we examined levels of CRP with a group by sex interaction (Figure 2). The unadjusted interaction was not significant ($P=0.47$), however, females in the GA group had higher levels of CRP compared with males, although this was not statistically significant after adjustment

Table 1 Clinical characteristics of study groups

Parameters	GA AMD (*n*=97)	Controls (*n*=139)	*P*
Sex, female	53 (55%)	92 (66%)	0.07
Age, y, mean (SD)	82.3 (7.0)	74.2 (4.7)	<0.01
Hispanic ethnicity	5 (5%)	6 (4%)	0.35[a]
logMAR of the better-seeing eye, median (IQR)	0.30 (0.10, 0.54)	0.10 (0.00, 0.18)	<0.01
logMAR of the worse-seeing eye, median (IQR)	0.70 (0.40, 1.00)	0.18 (0.10, 0.30)	<0.01
Family history of AMD			<0.01[a]
None	56 (58%)	106 (77%)	
Yes	28 (29%)	26 (19%)	
Uncertain	13 (13%)	6 (4%)	
BMI, mean (SD)	26.7 (5.0) *n*=84	27.3 (5.6) *n*=136	0.36
BMI categories			0.08[a]
Underweight (<18.5)	1 (1%)	3 (2%)	
Normal (18.5 to <25)	29 (35%)	51 (38%)	
Overweight (25 to <30)	39 (46%)	42 (31%)	
Obese (≥30)	15 (18%)	40 (29%)	
Smoking			0.16[a]
Never	39 (40%)	72 (52%)	
Current	2 (2%)	2 (1%)	
Former	56 (58%)	64 (46%)	
History			
Treated hypertension	71 (73%)	75 (54%)	<0.01
Abnormal lipids	72 (74%)	106 (76%)	0.72
Kidney disease	17 (18%)	12 (9%)	0.04
Peripheral vascular disease	10 (10%)	21 (15%)	0.14
Cardiac disease	41 (42%)	42 (30%)	0.06
Diabetes	15 (15%)	18 (13%)	0.58
Patient reported current medication use			
Aspirin	48 (49%)	64 (46%)	0.60
NSAIDS	15 (15%)	26 (19%)	0.52
Cholesterol-lowering drugs	8 (8%)	6 (4%)	0.27[a]

P-values were obtained from Chi-square for categorical variables and *t*-test for continuous variables unless noted otherwise. [a]*P*-value were calculated from Fisher's exact test. SD: Standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs; IQR: Interquartile range; GA: Geographic atrophy; AMD: Age-related macular degeneration; BMI: Body mass index.

for multiple comparisons (Table 2). This significance only changed slightly (*P*=0.07) following adjustment for age, BMI, and laboratory batch effects.

DISCUSSION

In our study, we did not find a significant difference in levels of serum CRP in patients with GA compared to controls without AMD. In both GA cases and controls, levels of CRP were higher in females compared to males, although not statistically different after multiple comparisons adjustment.

CRP is an acute-phase reactant generated by the liver. Elevated levels are observed during inflammation and infection[14]. CRP has been considered a marker for age-related systemic conditions including coronary artery disease[32], stroke[33], Alzheimer's disease (AD)[34], atherosclerosis[35], cancer[36], and schizophrenia[37]. Several authors have found an association between CRP and age-related ocular conditions such as AMD[18-22]. However, we did not find this relationship, which is consistent with a number of prior studies[23-26]. Our study demonstrated that CRP levels did not exhibit an association with GA, which is consistent with the findings from Klein *et al*[23] who studied a cohort of 188 cases with intermediate and advanced AMD (neovascular AMD and GA) from the Beaver Dam Eye Study cohort. It is noteworthy that our results are also aligned with the findings of a systematic review and Meta-analysis of studies on serum CRP in AMD which demonstrated that patients with GA did not have significantly different CRP levels than controls[38]. Our results are, however, not in keeping with the findings by Seddon *et al*[18] who analyzed 547 cases of

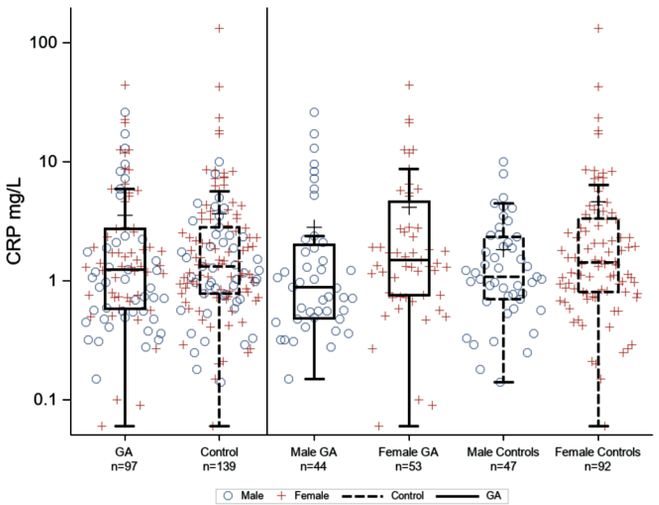

Figure 2 Box and whisker plot showing CRP levels for GA patients and controls stratified by sex The box extends to the 25th and 75th percentiles, the line represents the median. Individual colored circles/plus points illustrate the observed values. Y-axis tick marks are displayed on a log(10) scale. Male patients are represented by blue circles and female patients are represented by red plus signs. CRP: C-reactive protein; GA: Geographic atrophy.

Table 2 Sex stratification for CRP in GA versus controls mg/L

Sex	GA AMD	Controls	P^a
Male	0.9 (0.5–2.0)	1.1 (0.7–2.4)	0.86
Female	1.4 (0.8–2.8)	1.4 (0.8–3.3)	0.99
P^b	0.13	0.50	

Reported *P*-values were adjusted for multiple comparisons using Tukey-Kramer method. [a]Comparing study groups for males and females separately; [b]Comparing males and females within each study group. CRP: C-reactive protein; GA: Geographic atrophy; AMD: Age-related macular degeneration.

advanced (neovascular AMD and GA) and intermediate AMD compared with 383 controls that included patients with early stages of AMD, from two eye centers within the Age-Related Eye Disease Study (AREDS). The investigators of that study found higher serum CRP levels in this highest CRP quartile between the advanced forms of AMD. Similarly, Krogh Nielsen *et al*[20] in a prospective cohort study of 42 GA cases and 27 controls demonstrated that CRP levels in GA were higher when compared with controls. We suggest that reasons for the differences between these studies may include differences in underlying demographics and clinical characteristics of the cohorts, sample size, measurement methods for CRP, and the definition of cases and controls. The use of multimodal imaging in our contemporary study cohort may also have contributed to the differences as these older studies used only color fundus photography to grade and phenotype AMD cases[39].

We propose several mechanistic explanations for our finding of no significant difference in levels of CRP between cases of GA and controls. We hypothesize that levels of serum CRP are low in the early stages of AMD and increase in the intermediate stages, potentially leading to progression into atrophy, followed by a decline once the disease's most advanced stages manifest, especially in older age groups. Researchers have established that despite chronic inflammation being linked with aging, the relative importance of inflammation and inflammatory biomarkers often declines in older adults[40-41]. This may be attributed to a decreased hepatic synthetic capacity due to physical aging[42], decrease or internalization of serum interleukin-6 receptors[43], decrease in toll-like receptor surface expression[44], or due to the administration of statins and anti-inflammatory drugs[45], thereby leading to a potential decline in serum CRP levels in the older population. Our hypothesis is also supported by studies from several authors[23,46] who demonstrated that higher CRP levels in intermediate AMD were related to progression to advanced AMD. Additionally, our hypothesis is also supported by comparative research[47-48] from investigators in the field of AD research where serum CRP follows a progression in which it is increased in early stages prior to AD manifestation followed by a decline in serum CRP in the older age group with cerebral atrophy[49-51]. While we hypothesize that systemic CRP levels may change throughout AMD progression, this interpretation is based solely on cross-sectional data. Further longitudinal studies are needed, including studies in different population cohorts, to verify this hypothesis.

Our study observed a trend toward higher CRP levels in females compared with males in both the GA and control groups, with a greater magnitude seen in the GA group. Although this difference was not statistically significant after adjustment for multiple comparisons, it is consistent with other findings from our group showing elevated systemic inflammatory biomarkers in females with AMD. This finding is aligned with other results from our group where we found that females with AMD exhibited higher levels of systemic inflammatory biomarkers such as select complement factors[27] and the chemokine RANTES compared with males[28]. These findings are also supported by Lakoski *et al*[52] who studied the Multiethnic Study of Atherosclerosis (MESA) cohort and found that women exhibited significantly higher levels of CRP compared with male study participants. This statistically significant result remained after excluding women who were undergoing hormone replacement therapy from the cohort. It is well-established that sex-based differences are found in certain diseases including diabetes mellitus[53], cardiovascular disease[54], depression[55], autoimmune disorders[56], and ocular conditions[57]. There are several explanations for these differences between males and females including racial and ethnic differences, lifestyle risk factors, psychosocial risk

factors, changes that happen during pregnancy and menopause, and sex hormone-dependent signaling[53-58]. Furthermore, sex-specific and X-linked gene expression may modulate the immune system in women, rendering them more susceptible to autoimmunity[59]. Indeed, ocular conditions such as primary open angle glaucoma, dry eye disease, thyroid eye disease, and AMD occur more frequently in females[60]. Moreover, as previously reported, one specific imaging biomarker, reticular pseudodrusen, a specific subtype of drusen found in macular degeneration, is more commonly found in females[61-62].

There are some limitations to this study including the small sample size and a single-point measurement of systemic CRP which restricts the ability to infer temporal changes in CRP levels throughout AMD progression. Controls were recruited from cataract surgery clinics, which may introduce selection bias. However, all controls were rigorously reviewed by retina specialists to ensure they had no evidence of AMD based on multimodal imaging. Another limitation of this study is the absence of measurements for sex-related risk factors, such as the hormonal status of the patients, which has been suggested by several authors to play a role in the aging process and the immune system[57-58]. We recognize that both the lack of hormonal status data and the recruitment of controls from a surgical clinic setting may impact the generalizability of our findings and should be explored further in future longitudinal studies. Nevertheless, our study has notable strengths, including meticulous data abstraction, careful phenotyping of disease using multimodal imaging, and the diligent handling and storage of blood samples.

In conclusion, we have demonstrated no significant difference in levels of CRP in patients with GA compared with controls. We also found that the levels of CRP differed by sex. In the future, our plan is to expand upon this research by studying a larger cohort with longitudinal blood samples taken at various stages of AMD, including early, intermediate, and late stages, with further consideration of sex-related effects. By gaining insight into the differences in inflammatory markers in male and female patients, we hope to provide direction for future intervention and treatment strategies aimed at addressing this visually debilitating eye disease.

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