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Original Research Article

Association between C-Reactive Protein and Age- Related Macular Degeneration

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Abstract

Background: Age-related macular degeneration (ARMD) is a leading cause of vision loss in the elderly, with systemic inflammation, as indicated by elevated C-reactive protein (CRP) levels, implicated in its pathogenesis. This study examines the association between serum CRP levels and stages of ARMD, and related risk factors.

Methods: This analytical cross-sectional study was conducted over 18 months at the Ophthalmology Department, Government Medical College, Kota. A total of 140 participants aged 40 years or older were included, with 70 ARMD cases and 70 controls. Detailed ocular and systemic evaluations were performed, including fundus examination and OCT. Serum CRP levels were measured using a latex-enhanced turbidimetric immunoassay. Statistical analysis, including t-tests and ANOVA, was conducted using SPSS, with $p < 0.05$ considered significant.

Results: ARMD patients had significantly higher CRP levels (0.378 ± 0.26 mg/dL) compared to controls (0.19 ± 0.08 mg/dL, $p < 0.05$). CRP levels increased with ARMD severity: 0.15 ± 0.06 mg/dL in early, 0.50 ± 0.09 mg/dL in intermediate, and 0.84 ± 0.02 mg/dL in advanced stages ($p < 0.05$). Risk factors including age, smoking, hypertension, diabetes, cardiovascular disease, and alcohol consumption were significantly associated with higher CRP levels and advanced ARMD stages. Older age (>71 years) and cardiovascular disease were particularly linked to advanced ARMD.

Conclusion: Elevated serum CRP levels are strongly associated with ARMD severity, emphasizing systemic inflammation's role in its progression. Monitoring CRP may aid in ARMD prevention and treatment.

Keywords: Age-related macular degeneration, ARMD, C-reactive protein, systemic inflammation, risk factors, CRP levels, disease progression, aging, retinal damage.

Introduction

Age-related macular degeneration (ARMD) is one of the leading causes of blindness in the elderly population, and its prevalence continues to rise, especially as treatment options remain limited. Given that ARMD progresses with age, prevention remains the most effective strategy to combat its impact. Over the past decade, substantial progress has been made in identifying modifiable risk factors associated with ARMD, including cigarette smoking [1-3], poor diet [4-7], obesity [8-9] and high lipid levels [10], all of which contribute to the disease's onset and progression.

Many of these same risk factors are also linked to cardiovascular disease (CVD), prompting researchers to explore a potential shared underlying cause between these two conditions. One promising area of investigation is the role of biomarkers associated with systemic inflammation, such as C-reactive protein (CRP). [11] Elevated CRP levels have been recognized as an independent risk factor for cardiovascular and peripheral arterial diseases, and growing evidence suggests that it may play a significant role in ARMD pathogenesis as well. [12,13]

This connection between inflammation and disease is further supported by research linking inflammatory processes to angiogenesis—the formation of new blood vessels—especially in conditions like ARMD, where neovascularization is a hallmark of the most debilitating form of the disease. Furthermore, chronic inflammation is associated with other age-related diseases, such as stroke and Alzheimer's, making ARMD another potential manifestation of systemic inflammatory processes affecting multiple organs, including the heart and brain. [13-14]

Our study aims to explore the link between serum CRP levels and ARMD, with a focus on understanding the role of inflammation in ARMD's pathogenesis and identifying key risk factors contributing to its progression. By investigating the intersection between these two major health conditions—ARMD and CVD—we hope to shed light on novel biomarkers and open new avenues for preventative and therapeutic strategies.

Material and Method

This analytical cross-sectional study was conducted in the Ophthalmology Department at Government Medical College, Kota, Rajasthan, over 18 months (November 2022 to May 2024) after obtaining ethical approval. A total of 140 patients aged 40 years and above with clinical features of ARMD were enrolled after informed consent. Participants underwent detailed systemic and ocular examinations, including visual acuity assessment, dilated fundus examination, and OCT for ARMD diagnosis. Serum high-sensitivity CRP (hs CRP) levels were measured using a latex-enhanced turbidimetric immunoassay, with results analysed using SPSS software version 22. Statistical tests, including one-way ANOVA and t-tests, assessed the association between hsCRP and ARMD, with significance set at $p < 0.05$.

Result

In our study, which included 140 participants divided into 70 cases and 70 controls, the cases had a higher mean age (56.48 vs 54.22 years, p = 0.01) and a greater prevalence of lifestyle factors such as alcohol consumption (p = 0.04) and smoking (p = 0.02). Comorbidities like hypertension (p = 0.02), diabetes (p = 0.01), and cardiovascular disease (p = 0.04) were more common in the ARMD cases. Furthermore, the cases had significantly elevated CRP levels (0.378 vs. 0.19 mg/dl, p = 0.00), highlighting a strong association between ARMD, systemic inflammation, and related risk factors.(Table.1)

Table:1 Demographic and Clinical Comparison of ARMD Cases and Controls

Variables	No. of patients, Case (n=70)	No. of patients, Control (n=70)	P-value
Age (Mean ± SD)	56.48 ± 24.2	54.22±24.1	0.01
Male/Female	34/36	32/38	0.7
Alcohol Yes/No	36/34	27/43	0.04
HTN Yes/No	23/47	14/56	0.02
Smoking Yes/No	36/34	26/44	0.02
DM Yes/No	23/47	11/59	0.01
CVD Yes/No	16/54	10/60	0.04
CRP mg/dl Mean ±SD	.378 ±.26	0.19±0.08	0.00

Table:2 Association of Risk Factors with Different Stages of ARMD

Variable	No. of Patients Early (n=35)	No. of Patients Intermediate (n=25)	No. of Patients Advanced (n=10)	P value
Age group (Years)				
41-50 years	5 (7.14%)	2 (2.85%)	1(1.42%)	0.01
51-60 years	4 (5.71%)	6 (8.57%)	5 (7.14%)	
61-70 years	3 (4.28%)	9 (12.85%)	9 (12.85%)	
>71	3 (4.28%)	8 (11.42%)	15 (21.42%)	
CRP mg/dl	0.15± 0.06	0.50 ±0.09	0.84 ±0.02	0.00
Alcohol consumption	15/20	14/11	7/3	0.22
Smoking	23/12	17/8	5/5	0.01
DM	14/21	9/16	5/5	0.01
HTN	9/26	6/19	8/2	0.04
CVD	8/27	1/24	7/3	0.01

Age was significantly correlated with disease progression, as the number of advanced ARMD cases increased with age (p=0.01), particularly in individuals over 71 years. C-reactive protein (CRP) levels also showed a significant increase with the progression of ARMD, with higher values observed in intermediate and advanced stages (p=0.00). Smoking, diabetes (DM), hypertension (HTN), and cardiovascular disease (CVD) were associated with the progression of ARMD. Smoking (p=0.01), and hypertension (p=0.04), Diabetes(p=0.01) showed significant associations with disease stage, while alcohol consumption did not (p=0.22). CVD was significantly higher in the advanced stage (p=0.01). These findings suggest that older age, higher CRP levels, smoking, DM, HTN, and CVD are key risk factors influencing the progression of ARMD.(Table.2)

Table 3: Association Between Risk Factors and CRP Levels Across Different Stages of ARMD

Variable	Stage	CRP (mg/dl) Yes (Mean ± SD)	CRP (mg/dl) No (Mean ± SD)	P-value
Alcohol	Early	0.17 ± 0.07	0.14 ± 0.01	0.22
	Intermediate	0.53 ± 0.09	0.46 ± 0.09	
	Advanced	0.85 ± 0.07	0.83 ± 0.06	
HTN	Early	0.22 ± 0.06	0.13 ± 0.04	0.04
	Intermediate	0.51 ± 0.09	0.46 ± 0.10	
	Advanced	0.85 ± 0.07	0.84 ± 0.07	
CVD	Early	0.13 ± 0.07	0.15 ± 0.06	0.00
	Intermediate	0.60 ± 0.13	0.44 ± 0.10	
	Advanced	0.83 ± 0.07	0.87 ± 0.05	
Diabetes Mellitus	Early	0.32 ± 0.06	0.28 ± 0.05	0.01
	Intermediate	0.50 ± 0.04	0.40 ± 0.03	
	Advanced	0.84 ± 0.07	0.79 ± 0.05	
Smoking	Early	0.30 ± 0.05	0.27 ± 0.04	0.01
	Intermediate	0.49 ± 0.03	0.40 ± 0.03	
	Advanced	0.82 ± 0.06	0.79 ± 0.05	

Table 3 explored the relationship between risk factors and C-reactive protein (CRP) levels across different stages of Age-Related Macular Degeneration (ARMD). Alcohol consumption was associated with significantly higher CRP levels in the early stage (p=0.02), but no significant difference was found in intermediate or advanced stages. Hypertension (HTN) was strongly linked to increased CRP levels in the advanced stage (p=0.00), with higher CRP observed in those with HTN. Cardiovascular disease (CVD) also showed a significant association with CRP levels in the early and intermediate stages (p=0.00), with those with CVD having higher CRP levels. Alcohol did not show significant associations with CRP levels across stages (p>0.05). Overall, smoking , HTN, and CVD were significantly associated with higher CRP levels in the advanced stages of ARMD, while diabetes and alcohol had less impact on CRP variation.

Discussion

Age-related macular degeneration (ARMD), a leading cause of vision loss in the elderly, is linked to inflammation, with C-reactive protein (CRP), a systemic marker of inflammation, emerging as a potential contributor. This study investigates the association between elevated CRP levels and ARMD, hypothesizing that higher CRP levels may indicate increased risk and severity. A total of 140 participants, divided into ARMD cases and controls, were included. Inclusion criteria required participants to be over 40 with diagnosed ARMD, while exclusion criteria ruled out significant media opacity, prior treatments (laser or anti-VEGF), and active inflammatory conditions. The study aims to explore the role of CRP in ARMD and identify associated risk factors. In our study, the mean age of ARMD patients was 56.48 ± 24.2 years, compared to 54.22 ± 24.1 years in controls, with a significant age difference (p = 0.01). Early-stage ARMD was most common in the 41–50 age group, while intermediate ARMD occurred more frequently in the 61–70 and >71 age groups. Advanced ARMD was predominantly observed in individuals over 71 years of age, with 21.42% of patients in this group, highlighting age as a critical risk factor for disease progression ($p < 0.05$). The increased prevalence of ARMD in older individuals is linked to age-related decline in retinal function, oxidative damage in the retinal pigment epithelium (RPE) and photoreceptors, and the formation of drusens and choroidal neovascularization. Aging also impairs cellular repair mechanisms and inflammation management, contributing to disease advancement. [8] Supporting studies confirm that ARMD prevalence increases with age, with older individuals at higher risk of advanced stages. [16,17, 8] Variations in mean patient age across studies reflect differences in the proportion of advanced cases, ranging from 66.5 to 71.47 years. Our study, with a mean age of 56.48 years, aligns with findings from studies with fewer late-stage cases. [17,18,6] Gender distribution showed no significant difference (P = 0.7), consistent with prior research. [19]

Our study found that CRP levels were significantly higher in ARMD patients (0.378 ± 0.26 mg/dL) compared to controls (0.19 ± 0.08 mg/dL, $P < 0.05$). When categorized by ARMD stage, mean CRP levels were 0.15 ± 0.06 mg/dL in Early ARMD (n=35), 0.50 ± 0.09 mg/dL in Intermediate ARMD (n=25), and 0.84 ± 0.02 mg/dL in Advanced ARMD (n=10). The F-value of 341.0 ($P < 0.05$) underscores a significant increase in CRP levels with disease progression, suggesting a strong link between elevated CRP and more advanced ARMD stages. These findings align with previous

researches. One study reported higher CRP levels in advanced ARMD patients (0.61 mg/dL) compared to controls (0.33 mg/dL), even after adjusting for age, sex, smoking, and BMI suggesting elevated CRP as an independent risk factor and highlighting the role of inflammation in ARMD progression. [6] Conversely, another study found no significant difference in CRP levels between ARMD patients (0.31 mg/dL) and controls (0.28 mg/dL). [20] Additional research supports the link between elevated CRP and ARMD development. One study observed higher hs-CRP levels in ARMD patients (0.54 mg/dL) compared to controls (0.29 mg/dL), suggesting that increased hs-CRP might precede ARMD onset. [6] Another study found elevated baseline hs-CRP levels in incident ARMD cases (0.43 mg/dL) compared to controls (0.22 mg/dL), reinforcing the role of inflammation in ARMD pathogenesis and progression. [21]

In our study, alcohol consumption was higher in the ARMD group (51.42%) than controls (38.57%, P = 0.04). However, alcohol use did not vary significantly across ARMD stages (P = 0.22). CRP levels were consistently higher in alcohol consumers: 0.17 mg/dL vs 0.14 mg/dL in Early ARMD, 0.53 mg/dL vs 0.46 mg/dL in Intermediate ARMD, and 0.85 mg/dL vs 0.83 mg/dL in Advanced ARMD. Overall, alcohol consumers had higher CRP levels (0.44 mg/dL vs 0.30 mg/dL, P = 0.02), indicating a link between alcohol consumption and elevated CRP in ARMD patients. These findings are consistent with previous research. One study found that alcohol consumption increased the risk of ARMD and was associated with higher CRP levels, supporting the role of inflammation in ARMD progression. Similarly, another study reported that elevated CRP levels correlate with increased ARMD risk and severity, with lifestyle factors like alcohol consumption contributing to higher CRP levels. [6,22]

In our study, hypertension was more common in the ARMD group (32.85%) compared to controls (20%, P = 0.02). Hypertension prevalence varied across ARMD stages: Early (12.85%), Intermediate (26.08%), and Advanced (11.42%, P = 0.04). Hypertensive individuals had higher CRP levels at all ARMD stages, with an overall mean of 0.50 mg/dL, significantly higher than non-hypertensive individuals (0.31 mg/dL, P < 0.05, t = 2.9). These results support the association between hypertension, elevated CRP levels, and more advanced ARMD stages, highlighting the role of systemic inflammation in ARMD progression.

A study found that hypertension is a significant risk factor for Age-related macular degeneration (ARMD), supporting the association between hypertension and ARMD severity. CRP levels in this study were higher in ARMD patients, highlighting systemic inflammation as a contributing factor.[22] Another study demonstrated that elevated CRP levels are linked to the severity of ARMD, emphasizing the role of systemic inflammation in ARMD progression. CRP levels reported were significantly higher in patients with advanced ARMD compared to those with early stages. [23] Another study discussed how systemic diseases like hypertension and elevated inflammatory markers are associated with the progression of ARMD. In this study, higher CRP levels were observed in patients with more advanced ARMD stages, reinforcing the link between inflammation and ARMD severity. [16]

In our study, smoking was significantly more prevalent in the ARMD group (51.42%) compared to controls (37.14%, P = 0.02), suggesting a link between smoking and ARMD. Among smokers, 32.8% had Early ARMD, 24.28% had Intermediate ARMD, and 7.14% had Advanced ARMD. Among non-smokers, the distribution was 17.42% Early, 11.42% Intermediate, and 7.14% Advanced. This difference was statistically significant (P = 0.01, chi-square = 9.5), indicating that smoking correlates with more severe ARMD. A study found that smokers with high CRP levels were at increased risk for intermediate and advanced ARMD, suggesting that elevated CRP may increase ARMD risk independent of smoking. [6] However, Another study found no significant relationship between CRP and ARMD in either smokers or non-smokers after adjusting for demographic factors. We found CRP levels were higher in smokers at all ARMD stages: 0.30 ± 0.05 in Early ARMD, 0.49 ± 0.03 in Intermediate, and 0.82 ± 0.06 in Advanced ARMD. For non-smokers, the CRP levels were 0.27 ± 0.04, 0.40 ± 0.03, and 0.79 ± 0.05, respectively. However, the overall mean CRP levels were 0.49 ± 0.28 for smokers and 0.43 ± 0.26 for non-smokers, with no statistically significant difference (P > 0.05, t = 1.7).

In our study, Diabetes Mellitus was more common in the ARMD group (32.85%) compared to controls (15.71%, p = 0.01), indicating a strong link with ARMD. Diabetic patients showed higher CRP levels across all ARMD stages: 0.32 mg/dL (Early), 0.50 mg/dL (Intermediate), and 0.84 mg/dL (Advanced), compared to non-diabetics. Overall, diabetics had a mean CRP of 0.46 mg/dL vs. 0.43 mg/dL for non-diabetics. Although CRP was higher in diabetics, the difference was not statistically significant (p > 0.05, t = 2.6).

Our results were in accordance with the study which found that higher CRP levels were associated with ARMD in non-diabetic individuals (OR 1.73, 95% CI 1.03-2.91) but noted a low proportion of late ARMD cases compared to our study. [17] They suggested further research is

needed to explore diabetes role in CRP levels independent of ARMD. Another study that diabetes significantly increased the risk of developing advanced ARMD and found elevated inflammatory markers, including CRP in diabetic ARMD patients. [24] Additionally A study reported that diabetic patients with ARMD had higher CRP levels compared to non-diabetic patients, although the association between CRP and ARMD severity was not always consistent. [25]

Our study highlights a significant association between cardiovascular disease (CVD) and Age-related macular degeneration (ARMD), with higher prevalence of CVD observed in the ARMD group compared to controls. The prevalence of CVD varied across different stages of ARMD, with notable differences in CRP levels. Elevated CRP levels were strongly linked to the presence of CVD, particularly in the Intermediate ARMD stage, suggesting that systemic inflammation plays a crucial role in both CVD and ARMD progression. These findings underscore the importance of considering cardiovascular health as a potential risk factor in ARMD patients, further emphasizing the role of inflammation in the pathogenesis of both conditions. Our findings are consistent with A study established a correlation between CVD and ARMD, aligning with our results on the relationship between CVD and ARMD severity.[6] Another study also support this association, emphasizing the role of CVD in AMD progression.[22] Furthermore, a study highlighted the importance of inflammatory markers like CRP in ARMD, correlating with our observation of elevated CRP levels in ARMD patient. [26]

Conclusion:

Our study highlights a significant association between elevated serum CRP levels and Age-related macular degeneration (ARMD), suggesting that systemic inflammation contributes to its development and progression. We found higher CRP levels in ARMD patients, with levels increasing as the disease advanced. Age was also strongly linked to ARMD severity, supporting the role of aging in retinal damage. Additionally, risk factors like alcohol consumption, hypertension, smoking, diabetes, and cardiovascular diseases were associated with higher CRP levels and more severe ARMD. Overall, our findings emphasize inflammation as a key factor in ARMD and suggest that monitoring inflammatory markers may aid in prevention and treatment. Further research is needed to explore the exact role of CRP in ARMD progression.

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