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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 (AMD) is the leading cause of irreversible visual impairment among the elderly, worldwide affecting 30-50 million individuals. Inflammation is now increasingly thought to be a key risk factor for AMD. The association of CRP with AMD has been reported in only a few studies, with somewhat inconsistent results. The present study was undertaken to determine the association between AMD and serum CRP levels.
Methods: A total of 53 patients diagnosed of any form of AMD fulfilling inclusion and exclusion criteria were included. A 5 mL sample of venous blood (non-fasting) was collected to determine serum high-sensitivity CRP levels (hsCRP). Different stages of AMD and serum hs CRP level were compared using one-way ANOVA test and calculated p value <0.05 was considered as statistically significant. Comparison between the two groups, one with risk factor and one without risk factor was performed using student-t test and calculated p value <0.05 was considered statistically significant.
Results: Out of 53 patients 21 were having early AMD, 21 were having intermediate AMD and 11 were having advanced AMD. The mean serum hs CRP level was 0.14±0.05 mg/dL, 0.20±0.09 mg/dL and 0.28±0.08 mg/dL in early, intermediate and advanced AMD respectively. When statistically analysed the difference of mean serum hs CRP level among the three groups was found to be statistically significant.
Conclusions: Type of AMD influence the baseline hsCRP level. Smoking and diabetes are associated with higher baseline serum hsCRP in all stages of AMD.

Keywords: Age-related macular degeneration (AMD), C-reactive protein, Choroidal neovascular membrane, Drusen, Geographical atrophy, hsCRP

INTRODUCTION

Age-related macular degeneration (AMD) is a common, chronic, progressive degenerative disorder of the macula that affects older individuals and features loss of central vision as a result of abnormalities in the photoreceptor/retinal pigment epithelium/Bruch's membrane/choroidal complex often resulting in geographic atrophy and/or neovascularization.

It is the leading cause of irreversible visual impairment among the elderly, worldwide affecting 30-50 million individuals, and its consequences are increasing because treatment options are limited.[1-6] Prevention remains the main approach for decreasing the occurrence of this leading cause of blindness.

There are two basic types of AMD-dry/atrophic and wet/exudative. The dry or non-exudative from involves

both atrophic and hypertrophic changes in the retinal pigment epithelium (RPE) underlying the central macula as well as drusen deposition beneath the RPE. This type is more common (85-90%), but visual acuity is usually not drastically affected.

The wet exudative form of AMD, in which pathologic choroidal neovascular membranes (CNV) develops under the retina, leak fluid and blood, and ultimately causes a blinding disciform scar. Approximately 10-20% of patients with non-exudative AMD progress to exudative form, which is responsible for most of the estimated 1.75 million cases of advanced AMD in United States. It is also responsible for approximately 90% of severe vision loss by AMD. By definition, advanced atrophy (i.e. geographic atrophy) and/or the presence of CNV membranes were required for the diagnosis of AMD and exudative form.[3]

There are a number of classifications of AMD in the literature. The AREDS was a prospective multicenter randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors for age-related cataract and AMD. The effects of antioxidant vitamins and minerals on these two ocular conditions were studied.[7]

The classification of AMD that was taken in this study is from the AREDS.[7]

Inflammation is now increasingly thought to be a key risk factor for AMD.[8-10] The major acute phase reactant, C - reactive protein (CRP), is present in human serum at low levels under normal conditions, but can be markedly elevated in inflammatory conditions.[11] The association of CRP with AMD has been reported in only a few studies, with somewhat inconsistent results.[8-10] In light of the evidence linking inflammation and AMD, it is of interest to determine whether CRP levels and other markers of inflammation are predictive of AMD. Thus, the present study was undertaken to determine the association between AMD and serum CRP levels.

METHODS

The study was conducted in the Department of Ophthalmology, Assam medical college and Hospital, Dibrugarh, Assam, India for a duration of 1 year from July 2017 to June 2018. Ethical clearance was taken from institutional ethics committee.

Inclusion criteria

- Diagnosed cases of AMD,
- Age group > 40years,
- Minimum vision ≥ perception of light.

Exclusion criteria

- Patients below 40 years of age,
- Minimum vision ≤ perception of light,
- Significant media opacity,
- Patient already treated with either laser photocoagulation or intravitreal anti-VEGF or any other mode of treatment.

Diagnosed cases of systemic inflammatory diseases. In this hospital-based observational study, consecutive patients above 40 years of age with clinical features suggestive of AMD attending the outpatient department and retina clinic of the Ophthalmology department of the Assam medical college and hospital were included. All patients underwent thorough clinical evaluation including history, general and local ophthalmological examination. Best corrected visual acuity (log MAR decimal) was recorded for each patient. Based on the history and examination, important risk factors were identified. Cases with no improvement of visual acuity or little improvement were dilated with mydriatic-cycloplegic eye drops. After full dilatation of pupil, usually 5-15 minutes after instillation of mydriatic-cycloplegic eye drop, fundus examined initially with direct ophthalmoscope (Heine Beta 200S LED) followed by Indirect Ophthalmoscope (Heine) using 20 D lens and slit lamp examination with ±78D/90D lens was performed. Cases identified with the fundus findings suggestive of AMD were separated and by a digital fundus camera (Zeiss VISUCAM- 500 fundus camera) the fundus photographs were taken. Fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) was done wherever needed. Based on the pathological hallmark of AMD i.e. drusen, their size/shape, presence/absence of pigmentary epithelium changes and neovascular changes, AMD was graded into early, intermediate and advanced AMD according to AREDS8 under the guidance of retina expert. A 5 mL sample of venous blood (non-fasting) was collected to determine serum hs CRP with the method named particle enhanced turbidmetric immunoassay (PETIA).

Statistical analysis

All data was tabulated and was in the form of percentage and/or mean ± SD. Different stages of AMD and serum hs CRP level were compared using one-way ANOVA test and calculated p value <0.05 was considered as statistically significant. Comparison between the two groups, one with risk factor and one without risk factor was performed using student-t test and calculated p value <0.05 was considered statistically significant.

RESULTS

In the age group 41-50 years all the cases were of early AMD (7 cases). In the age group 51-60 years there were equal number of early and intermediate AMD cases. (7 cases in each group). No advanced AMD case was in the age group 41-50 years and 51-60 years. However, in the age group 61-70 years, maximum number of cases were of intermediate AMD (11 cases). But in the age group more than 71 years, no early AMD cases seen. Moreover,

in this age group number of advanced AMD cases was even more than the intermediate AMD (5 cases and 3 cases respectively). The mean age of the patients was 62.89±8.87 years. The mean age of the male patients was 62.63±10.87 years and the female patients was 63.15±6.74 years respectively. The difference between the two groups was not statistically significant (Figure 1).

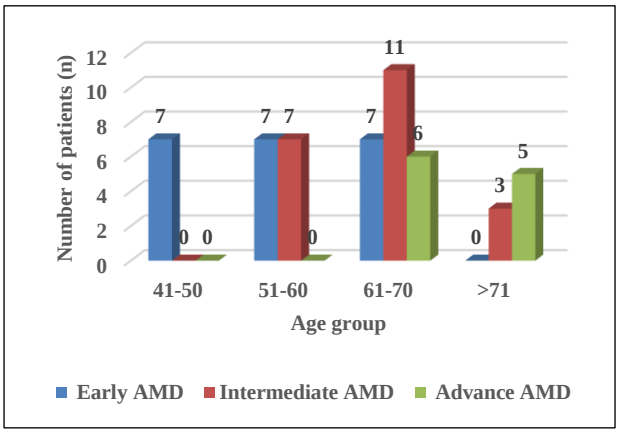

Figure 1: Age distribution of AMD patients.

Out of 53 patients 27 were males (50.94%) and 26 were females (49.06%). In males 10 patients were having early AMD, 8 patients were having intermediate AMD and 9 patients were having advanced AMD. In females 11 patients were having early AMD, 13 patients were having intermediate AMD and 2 patients were having advanced AMD.

Out of 106 eyes, maximum number of eyes i.e. 44 eyes (41.51%) were having vision of 0.6 - >0.3 (equivalent to Snellen's 6/24 - >6/12), 22 eyes (20.75%) were having visual acuity of 0.8 - >0.6 (equivalent to Snellen's 6/36 - >6/24) (Figure 2).

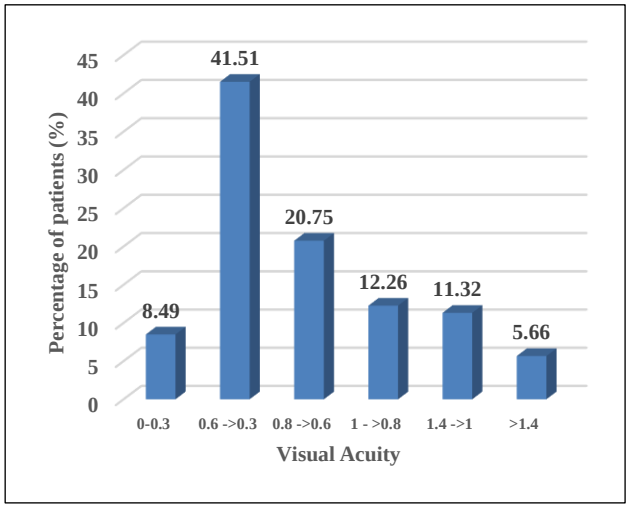

Figure 2: Visual acuity (log MAR).

Authors found all bilateral cases. Of all 53 patients 18 (33.96 %) patients were former or current smokers, 19 (35.84 %) patients were hypertensive, 12 (22.64 %) patients were diabetic and 5 (9.43 %) patients were having evidence of cardiovascular disease. When categorized into different groups of severity of AMD, out of 18 smokers, 7 were having advanced AMD, 6 patients were having intermediate AMD and 5 patients were having early AMD. Advanced AMD was more in smokers (7 cases) as compared to non-smokers (4 cases) but these findings was not seen in early and intermediate AMD group (Figure 3).

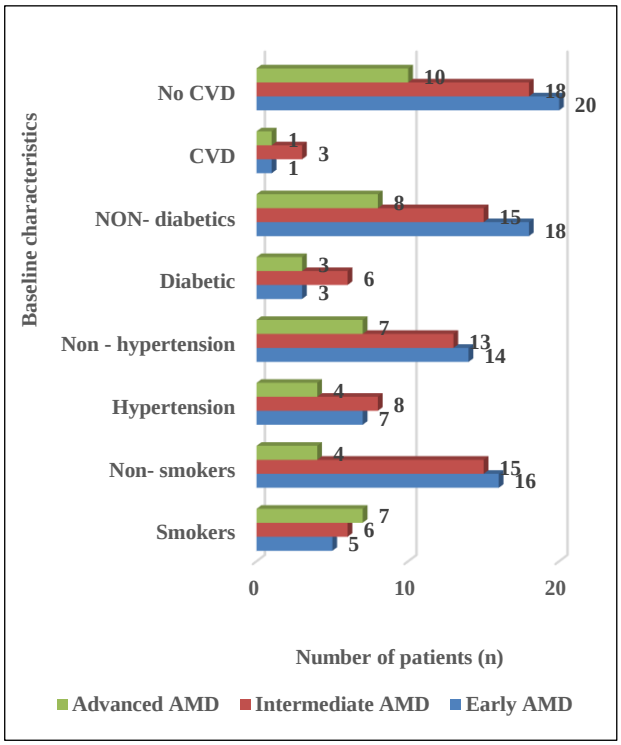

Figure 3: Distribution of baseline characteristics by different stages of AMD.

Out of 19 hypertensive patients 7 were having early AMD, 8 were having intermediate AMD and 4 were having advanced AMD respectively. Out of 12 diabetic patients 3 were having early AMD, 6 were having intermediate AMD and 3 were having advanced AMD respectively. Out of 4 patients with evidence of cardiovascular disease, 1 was having early AMD, 3 were having intermediate AMD and 1 was having advanced AMD respectively. (Figure 3).

The mean serum hsCRP level in early AMD group was 0.14±0.05 mg/dL, in intermediate AMD was 0.20±0.09 mg/dL and in advanced AMD was 0.28±0.08 mg/dL respectively. When statistically analysed the difference of mean serum hsCRP level among the three groups (by one-way ANOVA test), the difference was found to be statistically significant (p value <0.0001). The mean serum hsCRP level was significantly higher in intermediate AMD as compared to early AMD and in advanced AMD as compared to early and intermediate AMD (Table 1).

Table 1: Relation of CRP (mean value in mg/dl) with different stages of AMD.

Serum hs CRP mean (mg/dL)	Early AMD	Intermediate AMD	Advanced AMD
	0.14±0.05	0.20±0.09	0.28±0.08
p value	<0.0001 (extremely significant)		

*Values were compared by one-way ANOVA test.

The mean serum hsCRP level in non-diabetic patients was 0.13±0.05 mg/dL in early AMD group, 0.18±0.08 mg/dL in intermediate AMD group and 0.28±0.1 mg/dL in advanced AMD group respectively. However, the overall mean serum CRP level in non-diabetic patients was 0.18±0.09 mg/dL. The mean serum hs CRP level in diabetic patients was 0.19±0.03 mg/dL in early AMD group, 0.27±0.09 mg/dL in intermediate AMD group and 0.29±0.03 mg/dL in advanced AMD group respectively. However, the overall mean serum CRP level in diabetic patients was 0.25±0.08 mg/dL. Moreover, the difference between the mean serum hs CRP level between the diabetic and non-diabetic patients was statistically significant (p value 0.0189) (Table 2). The mean serum hsCRP level in non-smokers was 0.14±0.03 mg/dL in early AMD group, 0.17±0.07 mg/dL in intermediate AMD group and 0.25±0.05 mg/dL in advanced AMD group respectively. However, the overall mean serum hsCRP level in non-smokers was 0.16±0.07 mg/dL.

Table 2: Relation of C-reactive protein (mean value in mg/dl) with different stages of AMD and diabetes.

Type of AMD	Without diabetes (n=41)	With diabetes (n=12)	P value
Early AMD	0.13±0.05 (18)	0.19±0.03 (3)	0.0189
Intermediate AMD	0.18±0.08 (15)	0.27±0.09 (6)	
Advanced AMD	0.28±0.1(8)	0.29±0.03 (3)	
All cases	0.18±0.09	0.25±0.08	

*Values were compared by student-t test.**n= number of patients.

The mean serum hsCRP level in smokers was 0.17±0.06 mg/dL in early AMD group, 0.28±0.09 mg/dL in intermediate AMD group and 0.30±0.09 mg/dL in advanced AMD group respectively. However, the overall mean serum hsCRP level in smokers was 0.26±0.1 mg/dL. Moreover, the difference between the mean serum hsCRP level between the smokers and non-smokers was extremely statistically significant (p value <0.0001) (Table 3).

Table 3: Relation of C-reactive protein (mean value in mg/dl) with different stages of AMD and smoking.

Type of AMD	Never smoked (n=35)	Former or current smokers (n=18)	p value
Early AMD	0.14±0.03 (16)	0.17±0.06 (5)	<0.0001 (extremely significant)
Intermediate AMD	0.17±0.07 (15)	0.28±0.09 (6)	
Advanced AMD	0.25±0.05 (4)	0.30±0.09 (7)	
All cases	0.16±0.07	0.26±0.1	

*Values were compared by student-t test. **n= number of patients

Table 4: Relation of C-reactive protein (mean value in mg/dl) with different stages of AMD and hypertension.

Type of AMD	Non-hypertensive (n=34)	Hypertensive (n=19)	P value
Early AMD	0.14±0.05 (14)	0.14±0.04 (7)	0.1170 (>0.05) not significant
Intermediate AMD	0.18±0.07 (13)	0.24±0.11 (8)	
Advanced AMD	0.26±0.09 (7)	0.32±0.06 (4)	
All cases	0.18±0.08	0.22±0.1	

*Values were compared by student-t test. **n= number of patients

Table 5: Relation of C-reactive protein (mean value in mg/dl) with different stages of AMD and CVD.

Type of AMD	No CVD (n=48)	with CVD (n=5)	P value
Early AMD	0.14±0.05 (20)	0.18 (1)	0.6072 (>0.05) Not significant
Intermediate AMD	0.20±0.1 (18)	0.22±0.04 (3)	
Late AMD	0.28±0.09 (10)	0.31 (1)	
All cases	0.19±0.09	0.23±0.5	

*Values were compared by student-t test. **n= number of patients

The mean serum hsCRP level in non-hypertensive patients was 0.14±0.05 mg/dL in early AMD group, 0.18±0.07 mg/dL in intermediate AMD group and 0.26±0.09 mg/dL in advanced AMD group respectively. However, the overall mean serum hsCRP level in non-hypertensive patients was 0.18±0.08 mg/dL. The mean serum hsCRP level in hypertensive patients was 0.14±0.04 mg/dL in early AMD group, 0.24±0.11 mg/dL in intermediate AMD group and 0.32±0.06 mg/dL in advanced AMD group respectively. However, the overall mean serum hsCRP level in hypertensive patients was 0.22±0.1 mg/dL. Moreover, the difference between the mean serum hsCRP level between the hypertensive and non-hypertensive patients was not statistically significant (p value 0.1170) (Table 4).The mean serum hsCRP level in patients without evidence of CVD was 0.14±0.05 mg/dL in early AMD group, 0.20±0.1 mg/dL in intermediate AMD group and 0.28±0.09 mg/dL in advanced AMD group respectively. However, the overall mean serum hsCRP level in patients without evidence of CVD was 0.19±0.09 mg/dL. The mean serum hsCRP level in patients with evidence of CVD was 0.18 mg/dL in early AMD group, 0.22±0.04 mg/dL in intermediate AMD group and 0.31 mg/dL in advanced AMD group respectively. However, the overall mean serum CRP level in patients with evidence of CVD was 0.23±0.5 mg/dL. Moreover, the difference between the mean serum hsCRP level between the patients with and without CVD was not statistically significant (p value 0.6072) (Table 5).

DISCUSSION

In present study we found that higher baseline level of serum hsCRP in advanced AMD as compared to early and intermediate AMD, and in intermediate AMD as compared to early AMD. When authors analysed the level among these three groups the difference was found to be statistically significant. Seddon JM et al, demonstrated higher serum CRP level in advanced AMD than no AMD.[8] After adjustment for age, sex, and other variables, including smoking and body mass index, CRP levels were significantly associated with the presence of intermediate and advanced stages of AMD.[8] They suggested that elevated CRP level was an independent risk factor for AMD and may implicate the role of inflammation in the pathogenesis of AMD. Seddon JM et al, But the association was not exist in the later study by McGwin G et al, Debra A et al, had shown that higher level of hsCRP may precede the development of AMD.[8-10] In Rotterdam study (2007) the researchers had found that higher baseline level of serum hsCRP level was associated with incident AMD cases.[12]

In present study the maximum number of AMD patient were in the age group 61-70 years, as most of the cases were of early and intermediate AMD. The mean age of the patient was 62.89±8.87 years. Mean age of the male patients was 62.63±10.87 years and for female patients was 63.15±6.74 respectively. There was no significant difference in the age between the sexes. In the study by Seddon JM et al. (2004) the mean age of the patient was 69 years. This was may be due to a greater number of advanced AMD cases.[8] Colak et al, demonstrated in their study, the mean age of the patients with AMD was 71.47±7.02 years.[13] It was higher than in present study because in their study maximum number of patients were of advanced AMD. In the study by Boey PK et al, the mean age of the patients was 66.5±9.77 years, which was quite similar to present study, this may be due to a smaller number of late AMD cases in their study.[14]

The number of male patients was almost similar to the number of female patients but when authors performed the sex distribution in different stages of AMD, authors found that there was almost similar number of cases in early and intermediate AMD in the both sexes, but number of advanced AMD cases were higher in males than females. This was may be due to the greater number of smokers in males which is considered to be risk factor for development of advanced AMD.

In present study the Mean±SD of baseline serum hsCRP value was 0.14±0.05 mg/dL, 0.20±0.09 mg/dL and 0.28±0.08 mg/dL in early, intermediate and advanced AMD respectively. The difference among these three groups was statistically significant (p value <0.0001), indicating that higher baseline serum hsCRP was increased significantly as authors proceed from early to advanced AMD group. Seddon JM et al, in their study categorized the patient into no, early, intermediate and advanced AMD and compared the median CRP value in the interquartile range (because of large number of patients) and demonstrated difference between the median value for the most advanced maculopathy group 4 (3.4mg/L) and the median for maculopathy group 1 (2.7 mg/L) was statistically significant (P=.02).[8] However McGwin G et al, in their study found that median CRP levels among those with AMD (1.76 mg/l) were similar to those without AMD (1.77 mg/l). CRP levels were categorized into quartiles and compared between those with and without AMD.[9] Relative to those in the lowest quartile (0.07-0.93 mg/l), the odds ratios (OR) in the higher quartiles, adjusted for demographic, lifestyle, and health related characteristics were increased but not statistically significant. Colak E et al, in their study by logistic regression analysis revealed a weak but significant association between AMD occurrence and CRP values, and particularly between AMD and CRP values higher than 3 mg/l (p = 0.016).[13] They found that the type of AMD did not influence the CRP values since no difference was found between the AMD groups. These findings might be the result of nonhomogeneous distribution of AMD pathology, because the majority of patients had an advanced form of the disease, and very few had the early and intermediate stages of AMD.

When authors grouped people into diabetic and non-diabetic, authors found that baseline serum hsCRP was significantly higher in diabetic group (0.25±0.08 mg/dL) as compared to non-diabetic group (0.18±0.09 mg/dL) (p

value <0.05). Boey PY et al, in their study demonstrated no association was found between CRP and AMD.[14] After subjects were stratified by diabetes status, the data showed that higher CRP was associated with any AMD in 2385 persons without diabetes (multivariate-adjusted odds ratio (OR), 1.73; 95% confidence interval (CI), 1.03-2.91, comparing the 4th versus the 1st quartiles of CRP).[14] However in their study, fraction of late AMD cases was very low as compared to present study. In present study the serum hsCRP level was higher in advanced AMD irrespective of diabetes status, and 1/3rd of the patients with advanced AMD were diabetic.[14] Further study will be required to check whether diabetes status is associated with high serum CRP independent of AMD.

Smoking is considered a strong risk factor for the development of AMD.[15-21] But the question arises whether it influence the serum CRP level in AMD patients. In present study total number of smokers was 18 out of 53 (5 in early, 6 in intermediate and 7 in advanced AMD). Number of smokers was higher in advanced AMD (7 out of total 11 advanced AMD cases). In present study the Mean±SD value of baseline serum hsCRP was 0.16±0.07 mg/dL and 0.26±0.1 mg/dL in non-smokers and smokers with AMD respectively, and when smoking status was categorized in relation to different stages of AMD, the serum hsCRP level was higher in smokers in each stage of AMD as compared to non-smokers. The difference between the two groups was statistically significant (p value <0.0001). Seddon JM et al, (2004) in their study calculated the relative risk of developing AMD in smokers with high serum CRP.[8] They found a trend for an increased risk for intermediate and advanced AMD with higher levels of CRP in smokers (OR, 2.16; 95% CI, 1.33-3.49) and those who never smoked (OR, 2.03; 95% CI, 1.19-3.46) with the highest level of CRP.[8] In their study they concluded that highest level of CRP appeared to increase the risk of AMD independent of smoking.[8] However McGwin G et al, found when the data are stratified according to smoking status that, the unadjusted ORs suggested no significant relation between AMD and CRP for either never or ever smokers.[9] Following adjustment for demographic and medical characteristics, for never smokers all of the ORs are increased yet the only significant association was observed for the 3rd quartile (OR 1.65; 95% CI 1.01 to 2.69). This was may be due to the smaller number of advanced AMD cases in their study.

In present study there was no significant difference was found in hsCRP level in patients of AMD with and without hypertension and in patients of AMD with and without evidence of CVD, with p value >0.05. This may be due to the fact that many factors associated with AMD are also related to cardiovascular disease.[22] One of these factors is C-reactive protein (CRP), a marker of systemic inflammation, which has been shown to be an independent indicator of risk for cardiovascular and peripheral arterial disease.[23,24] Further studies will be needed to evaluate the level of CRP in the patients with evidence of CVD and hypertension.

CONCLUSION

In the present study authors have detected high baseline serum hsCRP level in patient with intermediate and advanced AMD as compared to early AMD. The baseline serum hsCRP level was increased as authors proceeded from early to advanced AMD. Type of AMD influence the baseline hsCRP level. Smoking also influence the baseline serum hsCRP level in all stages of AMD. Smoking is associated with higher baseline serum hsCRP. Diabetes is also associated with higher baseline serum hsCRP in all stages of AMD. Evidence of CVD and presence of hypertension was also associated with high baseline serum hsCRP level in all stages of AMD, but the difference was not statistically significant.

It has been confirmed from the literature that the pathological hallmark of AMD i.e. drusen is composed of many components of inflammation including CRP, present study further supports the hypothesis that inflammation has role in the pathogenesis for the development of AMD. Although a role of inflammation and innate immunity/complement dysregulation in AMD is now established, a direct role for CRP in AMD causation remains a topic of research and debate, and further studies will be required to find out the role of CRP in AMD causation.

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