

## ASSOCIATIONS BETWEEN DIABETIC RETINOPATHY AND PLASMA LEVELS OF HIGH-SENSITIVE C-REACTIVE PROTEIN

Dipti Lunaviya<sup>1</sup>, Mitalkumari G Patel<sup>1</sup>, Pradip Poriya<sup>2</sup>, Vishakhabahen Dabhi<sup>3</sup>

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**Corresponding Author:**

Dr. Vishakhabahen Dabhi,  
Email: dr.abc2306@gmail.com

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<sup>1</sup>Assistant Professor, Department of Ophthalmology, GMERS Medical College and Hospital, Junagadh, Gujarat, India

<sup>2</sup>Senior resident, Department of Ophthalmology, GMERS Medical College and Hospital, Junagadh, Gujarat, India

<sup>3</sup>Assistant Professor, Department of Ophthalmology, Nootan Medical College and Research Centre, Visnagar, Gujarat, India

### Abstract

**Background:** The high-sensitivity test for CRP (hs-CRP) is a key indicator of subclinical and chronic inflammation. Diabetic Retinopathy is associated with markedly increased serum hs-CRP levels, particularly in older individuals with longer disease durations. **Materials and Methods:** This cross sectional study was carried out among 100 patients of Type 2 DM. Detailed medical history, complete ophthalmic examination was performed for each patient. Fasting blood glucose (FBG), postprandial blood glucose (PPBG), glycosylated hemoglobin (HbA1c), and hsCRP were estimated. **Result:** As age increases, hs-CRP level also increases ( $p = 0.03$ ). Patients with duration of diabetes more than 40 years had higher hs-CRP (3.34 mg/l) than patients with less than 20 years of DM (2.67 mg/l). HbA1c had significant positive correlation with hs-CRP ( $r = 0.532$ ,  $p = 0.04$ ). The hs-CRP value in PDR (7.63 mg/l) was significantly higher than NPDR (mild – 1.98 mg/l, moderate – 2.71 mg/l, severe - 4.42 mg/l) as well as higher than patients without DR (0.87 mg/l) and  $p$  value was 0.01. **Conclusion:** This study revealed that severe grades of DR had significantly higher level of hs-CRP compared to milder grade of DR. The hs-CRP serves as an important prognostic marker of chronic inflammation and severity of DR.

## INTRODUCTION

Diabetic retinopathy (DR), major microvascular complication of diabetes mellitus (DM), is a one of the main cause of vision loss. DR patients have a 25 times higher risk of blindness than non-diabetics.<sup>[1]</sup> Proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) are two types of DR.<sup>[2]</sup> About 50% of individuals with very severe NPDR progress to PDR in the natural course within a year. Although the precise sequence of events in the pathophysiology of DR is still unknown, several studies suggest that aberrant metabolic pathways, oxidative stress, inflammation, and microvascular blockage are major contributors.<sup>[3,4]</sup> C-reactive protein (CRP) is a prototypical acute-phase protein and predominantly expressed in hepatocytes in response to infection, inflammation, or tissue injury.<sup>[5]</sup> The high-sensitivity test for CRP (hs-CRP) is a key indicator of subclinical and chronic inflammation since it can detect low (even 0.3 mg/L) and persistent CRP levels.<sup>3</sup> hs-CRP elevation can be utilised to predict increased cardiovascular risk in

diabetes patients in addition to conventional cardiovascular risk factors.<sup>[6]</sup>

It is believed that type 2 DM, metabolic syndrome, and insulin resistance are all caused by persistent low-grade inflammation, which is demonstrated by raised hs-CRP.<sup>[7]</sup> Potentially, hyperglycemia can boost CRP production. Large-scale research has been done on the potential relationships between CRP and DR, although the findings are still controversial. Numerous investigations have shown that the existence of DR is associated with markedly increased serum CRP and hs-CRP levels in both DM types, particularly in older individuals with longer disease durations. This suggests that CRP level more than 3 mg/L may be recognised as an independent risk factor for the development of DR.<sup>[8-10]</sup>

Beyond blood glucose levels, emerging risk factors including hs-CRP are becoming more significant as predictors of vascular events. hs-CRP levels have been demonstrated in many studies to be the indicators of atherosclerosis.<sup>[11]</sup> Therefore, this study aims at assessment of hs-CRP levels and its correlation with severity of diabetes mellitus retinopathy.

## MATERIALS AND METHODS

This cross sectional study was carried out among 100 patients of Type 2 DM who admitted at the Department of Ophthalmology and Department of General Medicine after getting approval from an institutional ethics committee. Patients with end-stage renal disease, acute or chronic infections, patients taking medications, which affect CRP levels, patients with ocular media opacity in both eyes that may prevent thorough fundus examination, patients with other degenerative lesions of the fundus, and pregnant women were all excluded from the study. Each patient underwent a detailed medical history, general physical examination and complete ophthalmic examination. Fundus evaluation was performed using direct and indirect ophthalmoscopy. DR can be divided into non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) and non proliferative diabetic retinopathy are further divided into mild, moderate, severe and very severe diabetic retinopathy.<sup>[2]</sup> Laboratory investigation was performed to determine the levels of fasting blood glucose (FBG), postprandial blood glucose (PPBG), glycosylated hemoglobin (HbA1c), and urine albumin excretion. Estimation of serum hs-CRP levels was done in vitro using flex reagent cartridge on the dimension clinical chemistry system.

### Statistical Analysis

Collected data was entered and analysed in the Micro soft Excel version 2016. Qualitative variables were expressed as frequencies and percentages, and quantitative variables as mean with standard deviation (SD) or median with 10th–90th percentile. Association between the qualitative variables was evaluated using the Chi-square test. A comparison of quantitative data between two groups and more than two groups were performed using the student t-test

and ANOVA test respectively. Correlation between quantitative data was analysed with spearman correlation coefficient (r). A p value of < 0.05 was considered as statistically significant.

## RESULTS

In this study 100 patients with long term DM were included. Majority of the diabetic patients were in 51 to 70 year age group (58.0%) followed by < 51 years (31.0%) and > 70 years (11.0%). Mean age was 58.32 ± 7.23 years. Out of 100 patients, 58.0% were males. About 62.0% were smokers. Overweight and obesity were found in 47.0% and 29.0%. Mean BMI was 28.65 ± 6.78 kg/m<sup>2</sup>. [Table 1]

More than half of patients had 21 to 40 years duration of DM. Mean duration of DM was 23.23 ± 8.73 years. Out 100 patients, 43.0% had no diabetic retinopathy. NPDR was reported in 46.0% patients (mild – 16.0% patients, moderate – 14.0% patients, severe – 16.0% patients). PDR was detected in 11.0% patients. Mean HbA1c was 8.45 ± 2.02 %. Mean hsCRP was 3.12 ± 0.78 mg/l. [Table 2]

As age increases, hs-CRP level also increases (p – 0.03). Patients with duration of diabetes more than 40 years had 3.34 mg/l hs-CRP, patients with 31-40 years of DM had 3.08 mg/l hs-CRP and patients with less than 20 years of DM had 2.67 mg/l hs-CRP. Smoking have also effect on hs-CRP level. Smokers had higher hs-CRP (1 to 20 pack per year – 2.87 mg/l hs-CRP and > 20 pack per year – 3.65 mg/l hs-CRP) than non smoker (0.58 mg/l hs-CRP, p-0.01). HbA1c had significant positive correlation with hs-CRP (r- 0.532, p - 0.04). The hs-CRP value in PDR (7.63 mg/l) was significantly higher than NPDR (mild – 1.98 mg/l, moderate – 2.71 mg/l, severe - 4.42 mg/l) as well as higher than patients without DR (0.87 mg/l) and p value was 0.01. [Table 3]

**Table 1: Characteristics of study participants (n-100)**

Characteristics	Frequency	Percentage (%)
Age (years)		
< 51	31	31.0%
51 to 70	58	58.0%
>70	11	11.0%
Mean ± SD (Median)	58.32 ± 7.23, (55.34)	
Gender		
Male	58	58.0%
Female	42	42.0%
Smoking (pack per year)		
0	38	38.0%
1 to 20	36	36.0%
> 20	26	26.0%
BMI (kg/m <sup>2</sup> )		
Underweight	5	5.0%
Normal	19	19.0%
Overweight	47	47.0%
Obese	29	29.0%
Mean ± SD (Median)	28.65 ± 6.78 (28.23)	

**Table 2: Diabetic profile of patients (n-100)**

Characteristics	Frequency	Percentage (%)
Duration of DM (years)		
< 20	36	36.0%

21 to 40	52	52.0%
> 40	12	12.0%
Mean $\pm$ SD	23.23 $\pm$ 8.73	
Grade of retinopathy		
No Retinopathy	43	43.0%
Mild NPDR	16	16.0%
Moderate NPDR	14	14.0%
Severe NPDR	16	16.0%
PDR	11	11.0%
Diabetic profile		
FBS (g/dl)	198.23 $\pm$ 15.67	
PPBS (g/dl)	287.12 $\pm$ 13.43	
HbA1c (%)	8.45 $\pm$ 2.02	
hsCRP (Mean $\pm$ SD, Range)	3.12 $\pm$ 0.78 (0.31 to 35.43)	

**Table 3: Association of hs-CRP with other variables**

Variable	Median	10 <sup>th</sup> to 90 <sup>th</sup> Percentile	p value
Age			
< 50	1.98	0.31 to 7.66	0.03
51 to 70	2.72	0.43 to 15.76	
>70	3.55	0.32 to 33.4	
Gender			
Male	3.32	0.31 to 29.23	0.89
Female	3.01	0.34 to 33.32	
Duration of DM			
< 20	2.67	0.31 to 18.23	0.08
31 to 40	3.08	0.34 to 23.34	
> 40	3.34	0.35 to 33.78	
Correlation with hs-CRP	r-0.231, p value- 0.07		
Smoking (Pack per year)			
0	0.58	0.32 to 3.45	0.01
1 to 20	2.87	0.43 to 19.65	
> 20	3.65	0.54 to 35.43	
Grade of retinopathy			
No Retinopathy	0.87	0.31 to 7.22	0.01
Mild NPDR	1.98	0.52 to 12.66	
Moderate NPDR	2.71	0.42 to 21.32	
Severe NPDR	4.42	0.32 to 25.67	
PDR	7.63	0.32 to 34.23	
HbA1c (%)			
< 5.7	1.23	0.26 to 7.43	0.03
5.71 to 6.40	1.72	0.45 to 15.64	
6.41 to 8.00	2.98	0.34 to 22.34	
> 8.0	3.33	0.56 to 33.45	
Correlation with hs-CRP	r-0.532, p value- 0.04		

## DISCUSSION

Since inflammation is a major contributor to the development of DR, treatment strategies including corticosteroids and anti-vascular endothelial growth factor have been found to be successful in slowing its progression.<sup>[12,13]</sup> Patients with diabetes and those who have major vascular problems have higher levels of hs-CRP, a marker of inflammation. As a result, it is thought to be a marker for vascular and cardiovascular disorders. The severity of retinopathy is positively correlated with serum hs-CRP levels.<sup>[14]</sup> In the current study, we assessed the degree of DR together with the level of hs CRP.

### Characteristics of patients with DR

In developing countries, the majority of people with diabetes are in the 5th to 6th decade. In the present study, mean age was 58.32  $\pm$  7.23 years. There were 58 % males, 62.0% smokers, 29.0% obese. Similar age distribution was reported in the study of Gupta R et al,<sup>[15]</sup> (53.46 $\pm$ 12.01 years), and Laursen et al,<sup>[16]</sup>

(58.7  $\pm$  12.01 years). Male predominance was also reported in these studies (Laursen et al - 67.4%, Nail M et al - 62.7%).<sup>[16,17]</sup>

In the present study, prevalence of DR was 57.0%. NPDR was reported in 46.0% patients (mild – 16.0% patients, moderate – 14.0% patients, severe – 16.0% patients) and PDR in 11.0% patients. Mean duration of DM was 23.23  $\pm$  8.73 years. Majority of the patients had poor glycaemic control (mean HbA1c was 8.45  $\pm$  2.02 %). In the study of Laursen et al,<sup>[16]</sup> prevalence of DR was 83.6%. About 19.4% had mild NPDR, 11.0% had moderate NPDR, and 53.2% had PDR. Mean duration of diabetes was higher as compared to other studies (43 years). Nail M et al,<sup>[17]</sup> reported 65.3% prevalence of DR. About 24.0% patients had mild NPR, 40.0% patients had moderate NPDR, whereas only 1.3% patient had severe NPDR. The prevalence and severity of DR differ across studies. This could be because of variation in duration of DM and glycaemic control among DM patients

### Association between hs-CRP and Diabetes

It is believed that hyperglycemia is a key factor in the development of the tissue damage that results in diabetes complications. According to Brownlee, intracellular hyperglycemia has the power to trigger a number of harmful pathways that might result in oxidative stress, defective gene transcription, and changes in circulating proteins. Intracellular hyperglycemia, among other things, causes the synthesis of advanced glycosylated endproduct precursors. Production of growth factors and inflammatory cytokines may result from this. PDR could be caused by growth factors such vascular endothelial growth factor, and people with DR have been reported to have higher than average levels of inflammatory cytokines. As a result, it is possible to anticipate a rise in inflammatory indicators and/or endothelial dysfunction markers, which could make them useful as a substitute for DR markers. As hs-CRP is a well-known inflammatory marker it would be expected to be elevated in patients with poor glycemic status.<sup>[16]</sup>

In the present study, mean hs-CRP was  $3.12 \pm 0.78$  mg/l. hs-CRP level was higher in older patients (> 70 years - 3.55 mg/l, 51 to 70 - 2.71 mg/l, < 50 - 1.98 mg/l,  $p = 0.03$ ) and smokers (> 20 pack per year - 3.65 mg/l v/s non smoker - 0.58 mg/l,  $p = 0.01$ ). HbA1c had significant positive correlation with hs-CRP ( $r=0.532$ ,  $p = 0.04$ ). The present study found that as the severity of diabetic retinopathy worsened, there was a corresponding increase in the hsCRP level. (Patients without DR - 0.87 mg/l, mild NPDR - 1.98 mg/l, moderate NPDR - 2.71 mg/l, severe NPDR - 4.42 mg/l, PDR - 7.63 mg/l,  $p = 0.01$ ). Our findings are compatible with findings of other studies.<sup>[3,16]</sup>

In the study of Laursen et al,<sup>[16]</sup> it was observed that hs-CRP levels were higher in older patients and smokers. There was an association between higher hs-CRP levels and a longer duration of DM. Furthermore, there was a trend of increasing hs-CRP levels with the severity of DR. Highest plasma levels of hs-CRP were 2.6 times more likely to have PDR than patients with the lowest plasma levels of hs-CRP (odds ratio: 2.59; 95% CI: 1.09–6.12).

In the study by Chaudhari H et al,<sup>[3]</sup> the PDR group had the highest blood levels of hs-CRP (6.68 mg/L), followed by the Pre PDR group (3.2 mg/L), and the Border line DR group (1.56 mg/L). In patients with T2DM, hs-CRP levels were found to significantly correlate with DR. Additionally, hs-CRP was found to substantially ( $p < 0.005$ ) positively correlate with age, duration of DM, FBG, PPBG, and HbA1c levels. In the study of Sajjanshetty A et al,<sup>[6]</sup> hs-CRP >3mg/dl was reported in all very severe (n=2, 100%) and severe cases (n=8, 100%). hs-CRP 1 to 3mg/dl was noted in 35 patients (87.5%) having moderate DR and 5 patients (16.7%) of mild DR. hs-CRP < 1 mg/dl was observed in 25 patients (83.3%) of mild DR, 5 patients (12.5%) of moderate DR, 3 patients (15.0%) with no DR.

Gupta R et al,<sup>[15]</sup> observed a positive linear correlation of hsCRP with duration of diabetes ( $r=0.20$ ;  $p=0.044$ ) and HBA1C ( $r = 0.0507$ ;  $p<0.0001$ ). Gopinath et al,<sup>[18]</sup> who demonstrated the co-relation of inflammatory process and metabolic control in the pathogenesis of DR and diabetic macular edema as indicated by hs-CRP and HbA1c. Higher hs-CRP levels were discovered in type 1 diabetes patients with NPDR and PDR among 543 individuals in a nested case-control trial of the EURODIAB research compared to patients without DR.<sup>[19]</sup>

### CONCLUSION

This study revealed that severe grades of DR had significantly higher level of hs-CRP compared to milder grade of DR. hs-CRP was also significantly associated with age, smoking and poor glycaemic control. The hs-CRP serves as an important prognostic marker of chronic inflammation and severity of DR.

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