

## A COMPARATIVE STUDY OF HIGH SENSITIVITY C-REACTIVE PROTEIN (HS-CRP) AND GLYCEMIC MARKERS IN TYPE 2 DIABETES MELLITUS

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### ABSTRACT

**Objective:** To determine the relationship between high sensitivity CRP (hs-CRP) and glycemic markers in samples of individuals with diabetes.

**Study Design:** Cross sectional study.

**Place and Duration of Study:** Fatima Memorial Hospital Lahore, from Feb to Aug 2019.

**Methodology:** Consecutive patients aged 18-65 years coming for screening of diabetes mellitus (DM) were included. Blood sample for plasma glucose and glycated hemoglobin (HbA1c), high sensitivity CRP (hs-CRP) were analyzed.

**Results:** Total 93 subjects were included, out of which 42 (45.2%) were males and 51 (54.8%) were females with the mean age of  $48.3 \pm 12$  years and  $42.6 \pm 14$  years respectively. Median concentration of hs-CRP in males and females was 0.7 (IQR1.2) mg/L and 0.6 (IQR1.4) mg/L ( $p$ -value=0.844) respectively. A significant positive correlation was observed between hs-CRP levels, HbA1c with  $r=0.205$  ( $p=0.05$ ) and fasting plasma glucose (FPG) with  $r=0.225$  ( $p=0.03$ ). However, no significant relationship was found between hs-CRP and age, BMI, waist circumference and systolic blood pressure (SBP) and diastolic blood pressure (DBP), cholesterol, LDL-cholesterol, triglycerides (TG), HDL-cholesterol.

**Conclusion:** HbA1c and fasting plasma glucose is significantly associated with hs-CRP. This implies a significant relation between inflammation and glycemic markers. This leads to the conclusion that patients with diabetes and high hs-CRP need further evaluation, follow-up and therapy for inflammation compared to those with low hs-CRP.

**Keywords:** High-sensitivity C-reactive protein, Diabetes mellitus, HbA1c, Metabolic syndrome.

**How to Cite This Article:** Imran SB, Khawaja S, Taj S, Khanum A, Ahmed Q. A Comparative Study of High Sensitivity C-Reactive Protein (HS-CRP) And Glycemic Markers in Type 2 Diabetes Mellitus. *Pak Armed Forces Med J* 2021; 71(5): 1651-1655. doi: <https://doi.org/10.51253/pafmj.v71i5.4918>

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### INTRODUCTION

There is well-documented evidence that inflammation plays an important role in atherosclerosis and is one of the vital risk factors in the development of cardiovascular diseases (CVD).<sup>1,2</sup> There are many systemic markers available for the diagnosis of inflammation, among them high-sensitivity C-reactive protein (hs-CRP) is considered a promising marker. In comparison to numerous other biomarkers that reveal the pathophysiology of inflammation and insulin resistance, hs-CRP assessment is economical, standardized and widely available. Many studies have reported a strong relationship between hs-CRP and coronary heart disease (CHD) even in non-diabetic population.<sup>3-5</sup> On the other hand patients with type 2 diabetes have shown significantly increased risk for developing CHD and majority of them die with CHD.<sup>6</sup> The risk of major cardiovascular events in patients with type 2 diabetes without history of CHD is comparable with the non-diabetic patients with history of chronic heart disease. High

levels of hs-CRP have been associated with the development of CHD in diabetes.<sup>7</sup> However, there are only few studies that show the relation of hs-CRP with the level of glycemic control in patients with diabetes and very little is known about this in Asian-Pakistani population-a high risk population.

Furthermore, elevated levels of hs-CRP can also lead to the development of the metabolic syndrome. Studies show that adding hs-CRP to the definition of metabolic syndrome will increase its predictive power for the diagnosis of cardiovascular disease (CVD) and diabetes mellitus.<sup>8</sup> Metabolic syndrome is a group of risk factors that can lead to CVD and DM so the question arises whether hs-CRP be added to the definition of metabolic syndrome or not? Therefore, we determined the association of hs-CRP levels with glycemic markers in patients with diabetes.

### METHODOLOGY

This was a cross sectional study conducted in department of Pathology, Fatima Memorial Hospital Lahore, from February to August 2019. The study was conducted after taking approval from institution's ethics review committee (FMH-01-2020-IRB-720-M).

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Received: 05 May 2020; revision received: 05 Oct 2020; accepted: 19 Oct 2020

Consecutive sampling technique was used. Sample size was calculated as a minimum sample size of 85 was selected using 5% level of significance 95% confidence interval, 8% margin of error and 16.98% prevalence of type II diabetes mellitus.

**Inclusion Criteria:** All the subjects aged 18-65 years who were referred for screening of diabetes, at the Clinical Laboratory of FMH were included in the study, after informed consent.

**Exclusion Criteria:** Subjects who were taking medications affecting glucose or HbA1c level were excluded from the study. Subjects with recent history (15 days) of inflammation or sepsis were also excluded from this study.

Demographic details weight, height, waist circumference, smoking history and family history of diabetes were recorded on a preformed questionnaire. Blood samples were collected for HbA1c and glucose. Samples for fasting plasma glucose (FPG) were collected after a minimum of 8 hours of fasting. Whole blood HbA1c was analyzed by immunoassay method (NGSP certified and traceable to the DCCT reference method) on Cobas c311 chemistry analyzer (Roche). Cutoffs for HbA1c were normal  $\leq 5.7\%$ , prediabetes 5.7-6.4%, and diabetic  $\geq 6.5\%$ .<sup>9,10</sup> Plasma glucose was measured by hexokinase method on Cobas c311 chemistry analyzer (Roche). Cutoffs for FPG were, normal  $< 100$  mg/dl, prediabetes 100-125 mg/dl and diabetic  $\geq 126$  mg/dl. System performance was assessed using three levels of quality control i.e. low, medium and high. Levels of hs-CRP  $< 1$ , 1-3, and  $> 3$  mg/L have been defined as lower, moderate, and higher cardiovascular risk.

Subjects were labeled normal weight, overweight and obese according to the criteria proposed for Asian populations by International Association for the Study of Obesity and International Obesity Task Force of World Health Organization (WHO) 2001.<sup>11,12</sup> Out of 93 patients, metabolic syndrome parameters HDL-Cholesterol and Triglyceride (TG) were available only for 37 patients.

Normality of the continuous/quantitative variables was assessed by Kolmogorov Smirnov test. Mean  $\pm$  SD or Median (IQR) were reported for quantitative variables depending upon the distribution. Frequency (%) for the categorical variables was reported. Before the application of all the inferential statistics, assumptions were checked, and appropriate tests were applied according to the situation. Continuous variables by gender were compared using independent sample t-test/Mann Whitney U. Data was stratified according

to the hs-CRP categories (low, average, high risk) and DM (Diabetic, Non-diabetic and Impaired). Gender, Hs-CRP and DM category wise comparison with categorical demographic variables was done by Fisher's Exact Test/Chi square/likelihood test. Continuous variables by hs-CRP and DM category was compared by ANOVA/Kruskal Wallis H Test. Pearson correlation coefficients/spearman's rank correlation (*p*-value) and partial correlation coefficient were calculated to assess the association of hs-CRP with demographic data and laboratory parameters.

## RESULTS

A total of 93 patients were included, out of which 42 (45.2%) were males and 51 (54.8%) were females with the mean age of  $48.3 \pm 12$  years and  $42.6 \pm 14$  years respectively as shown in Table-I. The mean weight of males and females was  $81.0 \pm 12.3$ kg,  $72.9 \pm 15$  kg (*p*-value=0.007) and mean waist in males and females  $37.5 \pm 3.9$  cm,  $33.3 \pm 4.9$  cm (*p*-value=0.0001) respectively. Median concentration of hs-CRP in males and females was 0.7 (IQR1.2) mg/L and 0.6 (IQR1.4) mg/L (*p*-value=0.844) respectively. Males had higher fasting blood glucose, HbA1c, TG and LDL cholesterol as compared to female with mean in male and females being  $105 \pm 26.6$  mg/dL,  $101 \pm 26$  mg/dL (*p*-value=0.480), 6.1% (IQR1.10), 5.9% (IQR 0.80) (*p*-value=0.139), mean  $172 \pm 77$  mg/dL,  $142 \pm 69$  mg/dL (*p*-value=0.252), mean  $110 \pm 36$  mg/dL,  $103 \pm 39$  mg/dL (*p*-value=0.57) respectively. While females had higher BMI, cholesterol and HDL-cholesterol compared to males with mean of females and males being  $28.4 \pm 6.5$  mg/dL,  $27.3 \pm 5.7$ mg/dL (*p*-value=0.39),  $173 \pm 32$  mg/dL,  $169 \pm 36$  mg/dL (*p*-value=0.76),  $43.5 \pm 8.0$  mg/dL,  $38 \pm 6.4$  respectively (*p*-value=0.05) as shown in Table-II.

Patients were categorized into low, moderate and high cardiovascular risk groups is shown in the Tables-III & IV.

The mean age of low cardiovascular risk group was  $44 \pm 13.8$  years, the mean age of average cardiovascular risk group was  $48 \pm 14.8$  years, whereas the mean age of high cardiovascular risk group was  $43 \pm 12.8$  years with more females in high risk group i.e., 9 (9.7%) compared to males i.e., 5 (5.4%). It was observed that patients in high cardiovascular risk category had higher mean BMI ( $29.2 \pm 3.7$ ) kg/m<sup>2</sup> and higher mean waist ( $36.6 \pm 4.3$ ) cm. Out of total 47 obese patients, 10 were in high risk category whereas no one with normal waist were present in high risk category.

High cardiovascular risk group patients also had higher FPG with median 105 (IQR47.2) mg/dL and

## High Sensitivity C-Reactive Protein and Glycemic Markers

**Table-I: Demographic details of study population.**

Variables	Patients with Diabetes	Impaired Diabetes	Individuals Without Diabetes	p-value
Age (years)	48.5 ± 11.5	48.5 ± 14.2	34.9 ± 10.6	<0.001
<b>Gender</b>				
Male	14 (15.1%)	19 (20.4%)	9 (9.7%)	0.549
Female	12 (12.9%)	25 (26.9%)	14 (15.1%)	
<b>Body Mass Index (BMI)</b>				
Normal	4 (4.3%)	6 (6.5%)	6 (6.5%)	0.705
Overweight	10 (10.8%)	14 (15.1%)	6 (6.5%)	
Obese	12 (12.9%)	24 (25.8%)	11 (11.8%)	
Waist Circumference (cm)	34.69 ± 4.48	36.136 ± 5.68	34.174 ± 3.92	0.182
Hypertensive	7 (7.5%)	16 (17.2%)	2 (2.2%)	0.053
Blood pressure (BP): Systolic (mm Hg)	122.5 (30)	120 (27.5)	120 (10)	0.275
Blood pressure (BP): Diastolic (mm Hg)	80 (15.75)	80 (10)	80 (5)	0.103
<b>Smoking</b>				
Yes	8 (8.6%)	5 (5.4%)	6 (6.5%)	0.104
No	18 (19.4%)	39 (41.9%)	17 (18.3%)	
<b>Family History of Diabetes Mellitus</b>				
Yes	16 (17.2%)	30 (32.3%)	11 (11.8%)	0.267
No	10 (10.8%)	14 (15.1%)	12 (12.9%)	

Continuous variables with normal distribution are presented in form of Mean ± SD, Continuous variables with non-normal distribution are presented in form of Median (IQR), Categorical variables are presented in form of n (%).

**Table-II: Biochemical variables of study population.**

Variables	Patients with Diabetes	Impaired Diabetes	Individuals Without Diabetes	p-value
High Sensitivity C-Reactive Protein (hs-CRP) (mg/L)	0.83 (4.94)	0.66 (1.20)	0.46 (0.85)	0.267
Fasting Plasma Glucose (FPG) (mg/dL)	130 ± 32.7	96 ± 12.5	84 ± 6.2	<0.001
HbA1c(%)	6.8 (0.75)	6 (0.5)	5.2 (0.5)	<0.001
Total Cholesterol (TC) (mg/dL)	176 ± 46.1	170 ± 29.5	165 ± 30	0.972
Triglycerides (TG) (mg/dL)	196 ± 72.7	148 ± 73.7	138 ± 73.6	0.136
High Density Lipoprotein Cholesterol (HDL-C) (mg/dL)	39 ± 8.1	39 ± 6.0	43 ± 9.6	0.754
Low Density Lipoprotein Cholesterol (LDL-C) (mg/dL)	105 ± 42.0	109 ± 35.7	106 ± 37.4	0.954

**Table-III: Demographic details of study population in cardiovascular disease (CVD) risk groups on the basis of hs-CRP levels.**

Variables	Low Risk	Average Risk	High Risk	p-value
Age (years)	44 ± 13.8	48 ± 14.8	43 ± 12.8	0.470
<b>Gender</b>				
Male	28 (30.1%)	9 (9.7%)	5 (5.4%)	0.742
Female	32 (34.4%)	10 (10.8%)	9 (9.7%)	
Body Mass Index (BMI) (kg/m <sup>2</sup> )	27.7 ± 6.9	27.7 ± 4.9	29.2 ± 3.7	0.695
<b>Body Mass Index (BMI)</b>				
Normal	12 (12.9)	4 (4.3)	-	0.130
Overweight	2 (22.6%)	5 (5.4%)	4 (4.3%)	
Obese	27 (29%)	10 (10.8%)	10 (10.8%)	
Waist (cm)	35.5 ± 5.3	33.6 ± 3.8	36.6 ± 4.3	0.193
Hypertensive	12 (12.9%)	8 (8.6%)	5 (5.4%)	0.128
<b>Smoking</b>				
Yes	9 (9.7%)	5 (5.4)	5 (5.4)	0.192
No	51 (54.8%)	14 (15.1%)	9 (9.7%)	

higher HbA1c levels with median 6.6 (IQR 2.0) %, whereas total cholesterol, TG and LDL-cholesterol were high in average cardiovascular risk group compared to high cardiovascular risk group. Comparison between two groups is shown in the Table-V.

The median hs-CRP levels were high in diabetic group while no statistically significant difference was

seen in hs-CRP levels between diabetic, pre-diabetic and non-diabetic groups.

Among 93 patients, metabolic syndrome parameters were available only for 37 patients among those, metabolic syndrome was present in n=17, out of which 4 (%) were diabetic, 11 (29.7%) were pre-diabetic and 2 (5.4%) were non-diabetics. Metabolic syndrome was

absent in 20 out of which 7 (18.9%) were diabetics, 8 (21.6%) were pre-diabetic, 5 (13.5%) were non-diabetics. Patients with metabolic syndrome had median hs-CRP of 0.77 (IQR 1.62) and for non-metabolic syndrome it was 0.69 (IQR 1.27). There was no significant difference in the hs-CRP levels in patients with metabolic syndrome and non-metabolic syndrome.

A significant positive correlation was observed between hs-CRP levels, HbA1c with  $r=0.205$  ( $p=0.05$ ) and FPG with  $r=0.225$  ( $p=0.03$ ). However, no significant relationship was found between hs-CRP and age, BMI, waist circumference and SBP and DBP, cholesterol, LDL-cholesterol, TG, HDL-cholesterol.

also reported a statistically significant positive correlation between hs-CRP and HbA1c with  $r=0.22$ ,  $p$ -value  $=0.001$ . As we shown a positive correlation between hs-CRP, FPG and HbA1c, it has been reported that patients with diabetes who had poorer glycemic control had higher hs-CRP levels.<sup>19</sup> The results of the present study favor the finding that among diabetic population, higher levels of glycemic markers i.e. FPG and HbA1c correlates well with significantly higher hs-CRP levels. Based on these findings we suggest that the inflammation may not only be associated with development of diabetes, but also associated with poor glycemic control once diabetes is established. Poor

**Table -IV: Biochemical variables of study population in cardiovascular disease risk groups on the basis of hs-CRP levels.**

Variables	Low Risk	Average Risk	High Risk	p-value
Fasting plasma glucose (FPG)(mg/dL)	93 (21.25)	98 (22)	105 (47.2)	0.034
HbA1c(%)	5.9 (0.80)	6.1 (0.90)	6.6 (2.0)	0.105
Triglycerides (TG)(mg/dL)	145 ± 56	192 ± 99	131 ± 12.5	0.110
High Density Lipoprotein Cholesterol (HDL)(mg/dL)	38.7 ± 5.2	42 ± 9.3	43 ± 11.3	0.436
Low Density Lipoprotein Cholesterol (LDL)(mg/dL)	104 ± 35	112 ± 41	109 ± 41	0.847
Total Cholesterol (TC) (mg/dL)	165 ± 30	177 ± 40	171 ± 38.2	0.695

**Table-V: Comparison of diabetic groups with low, medium and high-risk cardiovascular disease groups based on hs-CRP levels.**

		Diabetes Mellitus (DM) categories		
		Patients with diabetes	Individuals without diabetes	Impaired
High Sensitivity C-Reactive Protein Hs-CRP category	Low Risk cardiovascular disease group	14 (15.1%)	17 (18.3%)	29 (31.2%)
	Average Risk cardiovascular disease group	5 (5.4%)	4 (4.3%)	10 (10.8%)
	High Risk cardiovascular disease group	7 (7.5%)	2 (2.2%)	5 (5.4%)

## DISCUSSION

Hs-CRP is an inflammatory marker; it plays a significant role in the development of insulin resistance (IR). Many studies have suggested that inflammation is linked with insulin resistance that plays a vital role in the pathogenesis of type 2 diabetes mellitus as well as in atherosclerosis.<sup>13,14</sup> Conversely, hyperglycemia by itself may induce inflammation and contribute in the development of complications in patients with diabetes.<sup>15</sup> Studies have shown that hs-CRP levels are higher in patients with diabetes.<sup>16</sup> Tutuncu *et al*, reported a positive correlation between hs-CRP levels and with other glycemic and insulin resistance parameters.<sup>17</sup> In this cross-sectional study the association of hs-CRP with other metabolic markers such as FPG, HbA1c, TC, LDL-cholesterol, HDL-cholesterol, TG and BMI were evaluated. Similar study was done by Mahajan *et al*, they reported median hs-CRP levels in diabetic patients 2.68 mg/dL, which was significantly higher compared to non-diabetics 1.58 mg/dL ( $p$ -value  $\leq 0.0001$ ).<sup>18</sup>

We also found a significant positive correlation between hs-CRP levels and HbA1c ( $r=0.205$ ) ( $p$ -value  $=0.05$ ) and FPG ( $r=0.225$ ) ( $p$ -value  $=0.03$ ). Mahajan *et al*,

glycemic control further leads to inflammation. Better glycemic control may lower inflammation and consequently reduce the risk of cardiovascular events. As inflammation leads to hyperglycemia, then management of inflammation may help improve glycemic control. The findings of this study further support the relation between glycemic control and systemic inflammation in patients with diabetes.

In our study we observed that patients in high cardiovascular risk group (hs-CRP  $>3$ mg/L) were of younger age with mean age  $43 \pm 12.8$  years, their median FPG was 105 (IQR47.2) mg/dL which fall into impaired diabetic category and they had higher median HbA1c levels 6.6 (IQR 2.0) % as compared to average and low cardiovascular group. So, this could be said that patients who have elevated hs-CRP at younger age are more prone to develop cardiovascular disease early as compared to patients who have low levels of hs-CRP at same age.

Elevation of hs-CRP at younger age is like a double-edged sword, one causes the development of diabetes and other is responsible for atherosclerosis. In our study, we found that patients with raised hs-CRP

had impaired FPG and higher HbA1c levels further analysis showed that they also had raised LDL-cholesterol and TC. Diagnosing the patients at younger age group by analyzing hs-CRP levels especially in high-risk population could be beneficial in prevention and early treatment of diabetes and atherosclerosis which decreases the risk for cardiovascular disease. Similar study done by Effoe *et al*, who did age-stratified analysis, they found out that the association of hs-CRP with diabetes is stronger in patients at younger than 45 years compared with those older than 45 years.<sup>20</sup> Gupta *et al*, observed premature CVD in less than 45 years of age, the majority of them (80.8%) had high hs-CRP levels with only few (3.8%) having hs-CRP levels within the normal limits (<1 mg/L) (*p*-value 0.00).<sup>21</sup>

There was no significant difference seen in hs-CRP levels in patients with metabolic syndrome and non-metabolic syndrome. This may be due to the fact that metabolic syndrome parameters were available only in 37 (39.7%) patients, it was the limitation of our study. Furthermore, this study was conducted at single institute with a small sample size. The strength of the study was a strict inclusion criterion of patients and completion of study on time.

#### CONCLUSION

This study reveals that higher levels of glycemic markers are significantly associated with increased levels of hs-CRP. The results suggest note worthy relationship between inflammation and glycemic control in diabetic population. It can be important to realize that newly diagnosed patients with diabetes with high levels of hs-CRP need more intensive therapy than those with low levels of hs-CRP.

**Conflict of Interest:** None.

#### Authors' Contribution

SI: Designed, conception, planning and execute the study, SK: Data entry, data interpretation, preparation of data, ST: Data entry, data interpretation, preparation of data, AK: Statistical analysis, QA: Critical review.

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