Study of Highly Sensitive C - Reactive Protein (hs-CRP) In Type 2 Diabetes Mellitus and Its Correlation with Glycosylated Hemoglobin

Authors
Shyam Murari Garg, Sudhir Maan, PD Gupta, Himanshu Devender Kumar*, Kshitiz D Vashista, Anish Gupta, Neeraj Gupta
Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana, India 133207
*Corresponding Author
Himanshu Devender Kumar
Email: himanshu.parashar86@gmail.com

Abstract
Background: Diabetes mellitus is one of the leading causes of morbidity and mortality. Studies have shown that hs-CRP is associated with insulin resistance, type 2 diabetes and higher HbA1C levels. This study was done to evaluate the correlation of hs-CRP with HbA1C.
Objectives: The aim of this study is to determine the serum high sensitive C- Reactive Protein (hs-CRP) in patients with type 2 diabetes mellitus and to correlate with HbA1C levels.
Materials and Methods: In this study 50 patients aged above 18 years with type 2 diabetes mellitus were enrolled and subjected to detailed history and examination. In all patients hs-CRP with HbA1C were measured.
Results: In our study population 79% had hs-CRP levels ≥3.0 and 21% had hs-CRP levels <3.0. It concludes that higher prevalence of increase of hs-CRP in subjects with Type 2 diabetes. We found no statistically significant correlation among them except with duration of DM.
Conclusion: This study strongly warrants future investigations that probe the role of genetic variants and other environmental factors that influence the elevation of hsCRP levels in this high-risk group.
Keywords: HbA1C, hs-CRP, Type 2 diabetes mellitus.

Introduction
Diabetes is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate, and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extracellular hyperglycemia which results in tissue damage and chronic vascular complications in both types I and II Diabetes Mellitus.1,2

Previous studies have shown that hs-CRP is associated with insulin resistance, type 2 diabetes, and higher HbA1c levels. A recently retrospective observed the hs-CRP levels correlated with HbA1c levels. Mean HbA1c levels were
significantly higher in patients who had hs-CRP levels of 1 mg/L or more.\(^1\) In the year 2015 Chinese study was also revealed through multivariate stepwise regression analysis that indicated that HbA1c correlated with hs-CRP.\(^2\) A Turkish study also reported a positive correlation between serum hs-CRP and HbA1c.\(^3\) Chronic inflammation plays an important role in the development and progression of late complications of diabetes. C-reactive protein (CRP), an acute phase reactant, is a highly sensitive marker of inflammation. Its level rises dramatically during an inflammatory process.\(^4\) CRP has a long half-life, affordability of estimation, and stability of its levels with no circadian variation, and therefore is one of the best markers of vascular inflammation.\(^5\) CRP has been found to be associated with disorders like DM, cardiovascular disorders, metabolic syndrome, Rheumatoid Arthritis, renal failure, etc.\(^6,7,8\) The serum high sensitivity CRP (hsCRP) level is higher in patients with Type 2 diabetes than in normal subjects and plays an important role in the development and progression of Type 2 DM.\(^9\) India is having the highest number of T2D individuals worldwide, with a prevalence of 11.6% in urban populations.\(^10,11\) Furthermore, Asian Indians are known to be at a high risk for T2D, CVD, and metabolic syndrome.\(^12,13\) Although elevated levels of hs-CRP have been observed in expatriate adult Indians\(^14\) and adolescents residing in India\(^15\), data on adult individuals residing in India are scanty. Therefore, the present study was designed to study the correlation of hs-CRP levels with HbA1c in type II subjects in MMU Mullana.

Materials and Methods
The present study was conducted at M.M. Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. Fifty patients were taken from OPD or indoor wards of the department of medicine. All the patients fulfilled the inclusion/exclusion criteria into the study after obtaining written informed consent. All patients were subjected to detailed history and systemic examination. In every patient routine biochemical investigations were sent along with hsCRP and HbA1C. The result was compiled using SPSS and appropriate statistical tests were used.

### Inclusion Criteria
- Age above 18
- Type 2 diabetes mellitus

### Exclusion Criteria
- Gestational diabetes
- Cardiovascular abnormalities (IHD, RHD)
- On anti-inflammatory drugs
- No history of RA arthritis
- No history of acute infections (UTI, URTI)
- No history of chronic infection like HBV, HCV
- No history of collagen vascular disease like SLE

### Results

#### Table 1: Descriptive analysis of Age Group in study population (n=100)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-35</td>
<td>11</td>
<td>11.00%</td>
</tr>
<tr>
<td>36-50</td>
<td>43</td>
<td>43.00%</td>
</tr>
<tr>
<td>51-65</td>
<td>33</td>
<td>33.00%</td>
</tr>
<tr>
<td>66 and above</td>
<td>13</td>
<td>13.00%</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td><strong>50.97±13.4</strong></td>
<td></td>
</tr>
</tbody>
</table>

Descriptive analysis of Age Group in study population shows the maximum number of samples in the age group of 36-50 years, a mean age 50.97 years, a maximum age of 89 years and the lowest age of 18 years.

#### Figure 1: Pie chart of Age Group distribution in study population (n=100)
In our study 74% are male and 26% are female that were enrolled.

**Figure 2:** Bar chart of Gender distribution in study population (N=100)

![Gender Distribution Chart](image1.png)

In our study population maximum patients had HbA1c levels more than 9.6; 45%, mean Hba1c levels was 9.86, maximum of 19.90 and a minimum level of 4.90.

**Figure 3:** Bar chart of HbA1c levels distribution in study population (N=100)

![HbA1c Levels Chart](image2.png)

In our study population, 79% had hs-CRP levels ≥3.0 and 21% had hs-CRP levels <3.0.

**Figure 4:** Pie chart of hs-CRP distribution in study population (N=100)

![hs-CRP Pie Chart](image3.png)

Maximum 59 (59%) patients had diabetic from less than 5 years.

**Figure 5:** Pie chart of Duration of Diabetics Mellitus distribution in study population (n=100)

![Duration of DM Pie Chart](image4.png)
Table 6: Descriptive analysis of BMI category in study population (n=100)

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;23</td>
<td>9</td>
<td>9.00%</td>
</tr>
<tr>
<td>≥23</td>
<td>91</td>
<td>91.00%</td>
</tr>
</tbody>
</table>

91% of the study population had a BMI ≥ 23 and 9% had a BMI < 23. Mean BMI of the study population is 25.64 with lowest BMI recorded was 22.50 and highest BMI recorded was 29.70.

Figure 6: Bar chart of BMI category distribution in study population (n=100)

Table 7: Descriptive analysis for FBS in study population (n=100)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± STD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>95% for ( \exp(B) ) Lower</th>
<th>95% for ( \exp(B) ) Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>205.27±50.23</td>
<td>192</td>
<td>141.00</td>
<td>379.00</td>
<td>195.30</td>
<td>215.24</td>
</tr>
</tbody>
</table>

In our study population we achieved a mean FBS 205.27, maximum FBS recorded is 379, and minimum FBS recorded is 141.

Figure 7: showing values of FBS obtained in study population (n=100)

Scattered diagram

Table 8: Association of HS CRP category with Age Group of study population (N=100)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HS CRP Category</th>
<th>Chi-Square</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 (n=79)</td>
<td>&lt;3 (n=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-35</td>
<td>7 (8.9%)</td>
<td>3.243</td>
<td>0.355</td>
</tr>
<tr>
<td>36-50</td>
<td>33 (41.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>27 (34.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 and above</td>
<td>12 (15.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In our study, there was no relation between hs-CRP and Age group (p>0.05)

Figure 8: association with hs-CRP with age group of study population (n=100)

Table 9: Association of HS CRP with Gender of study population (n=100)

<table>
<thead>
<tr>
<th>Gender</th>
<th>HS- CRP</th>
<th>Chi Square</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>≥3 (n=79)</td>
<td>58 (73.42%)</td>
<td>16 (76.19%)</td>
</tr>
<tr>
<td>Female</td>
<td>&lt;3 (n=21)</td>
<td>21 (26.58%)</td>
<td>5 (23.80%)</td>
</tr>
</tbody>
</table>

In our study, hs-CRP levels were found to be independent of Gender (p>0.05)
Table 10: Association of hs-CRP with Duration of Diabetics of study population (n=100)

<table>
<thead>
<tr>
<th>Duration of Diabetics Mellitus</th>
<th>hs-CRP</th>
<th>Chi-Square</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 years</td>
<td>≥3(n=79)</td>
<td>6.801</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>&lt;3(n=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10 years</td>
<td>42</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>≥11 years</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

In our study hs-CRP levels were found to be significant with increasing duration of DM (p>0.05)

Figure 10: Association of hs-CRP with Duration of Diabetics of study population (n=100)

Table 11: Association of hs-CRP with HBA1C category of study population (n=100)

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>hs-CRP</th>
<th>Chi-Square</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.5</td>
<td>4 (5.06%)</td>
<td>2 (9.52%)</td>
<td></td>
</tr>
<tr>
<td>6.6-7.5</td>
<td>8 (10.12%)</td>
<td>6 (28.57%)</td>
<td></td>
</tr>
<tr>
<td>7.6-8.5</td>
<td>14 (17.72%)</td>
<td>4 (19.04%)</td>
<td>6.222   0.183</td>
</tr>
<tr>
<td>8.6-9.5</td>
<td>14 (17.72%)</td>
<td>2 (9.52%)</td>
<td></td>
</tr>
<tr>
<td>≥9.6</td>
<td>39 (49.36%)</td>
<td>7 (33.33%)</td>
<td></td>
</tr>
</tbody>
</table>

In our study hs-CRP levels were found to significant with increasing levels of HbA1c (P>0.05)

Figure 11: Association of hs-CRP with HbA1c levels of study population (n=100)

Discussion

In the present study diabetic patients were older with mean 50.97±13.4 years and the majority 74% being male as similar to study done by Amanullah S et al16 Reported mean age of 51 years of diabetic subjects. In the prospective study done by Sasidharan A et al17 enrolled 50 patients in the study, there were 36 (78%) males and 14 (28%) female patients. The minimum age was 34 years old and maximum age was 75 years old which is similar to the present study. 91% of the study population had a BMI ≥ 23 and 9% had a BMI < 23. Mean BMI of the diabetic population is 25.64 with lowest BMI recorded was 22.50 and highest BMI recorded was 29.70.
This was further confirmed by the study done by Ni Mhurchu et al.\textsuperscript{18}. Eric and John\textsuperscript{19} and NHANES\textsuperscript{20} the report indicates that most adults with diagnosed diabetes were overweight or obese, the prevalence of overweight or obesity was 85.2\% and the prevalence of obesity was 54.8\%. Cosin Aguilar et al\textsuperscript{21} from this study state that the obese patients showed the higher prevalence of diabetes.

Elevated hs-CRP levels frequently cluster with well-established risk factors of T2DM such as obesity and insulin resistance.\textsuperscript{22} Therefore, we extensively evaluated the effect of markers of these conditions on hsCRP levels. BMI and WC were observed to be the dominant contributors of hsCRP levels here. These observations reiterate the role of obesity as a major determinant of hs-CRP levels in this population. Similar observations have been previously made by Forouhi NG et al where they found obesity as a major determinant of hs-CRP levels in healthy expatriate South Asians.\textsuperscript{23}

In our study population, 79\% had hs-CRP levels ≥3.0 and 21\% had hs-CRP levels <3.0. It concludes that higher prevalence of increase of hs-CRP in subjects with Type 2 diabetes. Studies on western populations have shown low-grade systemic inflammation to be one of the mechanisms by which known risk factors such as obesity, smoking, and Hypertension promote the development of diabetes mellitus as studies conducted by Pradhan et al.\textsuperscript{24} 2001; Pfutzner and Forst.\textsuperscript{25} However, there are few studies of hs-CRP in Asian Indians, a very high-risk group for diabetes as reported by Mohan et al.\textsuperscript{1} 2003 and Mohan et al.\textsuperscript{27}

In the present study, we evaluated the association between hs-CRP and risk factors like age, gender, duration of DM and Hba1c. We found no statistically significant correlation among them except the duration of DM, we document the association of hs-CRP levels with glycemic control in North Indian adults. The CRP levels are significantly increased in diabetics. In this study, a strong correlation is present between CRP and a host of other variables such as age, BMI, waist circumference, waist-hip ratio, systolic and diastolic blood pressure, serum triglyceride, family history of diabetes, physical inactivity, use of antihypertensive drugs, and hormonal replacement therapy. However, a strong positive correlation exists between CRP and risk of developing diabetes in women.\textsuperscript{19}

These results are also in agreement with previous studies, Bhavita Patel\textsuperscript{28}, in their study; the lowest levels of hsCRP were found in normal patients and were lower in comparison to obese-diabetics. On univariate analysis, hs-CRP was found to be significantly increased in patients with diabetes mellitus (p < 0.021) and those with abnormal waist circumference (p<0.003).

In the recent study, Geetha Bhaktha et al\textsuperscript{29} reported a high level of Hs-CRP in diabetic subjects when compared to normal individuals. hs-CRP failed to show any correlation with BMI, FBS, and HbA1c. Diabetes is considered as an inflammatory disease hence they observed an increase in the hs-CRP level in diabetes than in the normal. Since the vascular complication was totally absent hs-CRP failed to show any correlation with BMI, FBS, and HbA1c which is similar to the present study.

After adjustment of mean insulin among men and women, it was found that there is a concomitant increase in HbA1c level with CRP as reported by Wu T et al.\textsuperscript{30} King et al. found a strong correlation between HbA1c levels and CRP. Besides, they also found that CRP levels were associated with HbA1c levels.\textsuperscript{31} The difference in results in the present study from the previous literature may be due to only inclusion criteria and design of the study. Anubha Mahajan et al\textsuperscript{32} aimed to assess the association of hs-CRP with T2D and to determine its correlates in North Indians of Indo-European origin. They demonstrate the association of low-grade systemic inflammation, as indicated by elevated hs-CRP levels, with T2D in North Indian population which is similar to the present study.
Roopakala MS et al enrolled 50 DN patients in the age group of 50-60 years with more than ten years of duration of diabetes were recruited for the study and 25 age-and-sex-matched healthy subjects were included in this study as controls. The hsCRP levels showed a positive correlation with HbA1c in DN. These results suggest that estimation of serum hs-CRP levels and aiming at good glycemic control help in early intervention and prevention of further complications in diabetic patients.  

Ajay Meshram et al stated that Anthropometric parameters found to be high in diabetic subjects compared with non-diabetic subjects. The high hs-CRP levels in diabetic subjects were also observed. The results concluded that hs-CRP has a strong association with diabetic individuals. The magnitude of this association, however, seems to be strongly affected by the presence or absence of T2D.  

Over the years, accumulating evidence suggests that hs-CRP may be associated with an increased risk of future cardiovascular events in otherwise healthy individuals. The advantages of this study include the systematic recruitment of subjects and rigorous assessment of different parameters traits. Given the marked difference in the levels of anthropometric and biochemical parameters between urban and rural set-ups, samples have been obtained from a well-defined population, representing a single ethnic group inhabiting urban locales. Nevertheless, our study is limited by its cross-sectional design, which precludes conclusions regarding the cause and effect relationships. This study strongly warrants future investigations that probe the role of genetic variants and other environmental factors that influence the elevation of hsCRP levels in this high-risk group.

Reference
10. Kang ES, Kim HJ, Ahn CW. Relationship of serum high sensitivity C-reactive


