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# Serum High Sensitive - C Reactive Protein Levels in Type 2 Diabetes Mellitus -A Case Control Study

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors SVK and GSK designed the study, wrote the protocol and supervised the work. Authors SVK and MR carried out all laboratories work and performed the statistical analysis. Author GSK managed the analyses of the study. Authors SVK and GSK wrote the first draft of the manuscript. Author MR managed the literature searches and edited the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** The process of inflammation induces hepatic synthesis of various acute phase proteins such as high sensitivity C-reactive protein (hs-CRP) which is believed to play a role in insulin resistance. Higher incidence of type-2 diabetes mellitus has been observed with high levels of hs-CRP.
**Objectives:** The present case control study was under taken to 1. Find the serum hs-CRP levels in type 2 DM patients, 2. Find the serum hs-CRP levels in healthy controls, 3. Compare hs-CRP level

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between type 2 DM patients and healthy control subjects, 4. Find correlation between HbA1c and hs-CRP in type 2 DM patients and 5. Find the optimum cut-off value for hs-CRP for type 2 DM
**Materials and Methods:** The study was conducted on type 2 DM subjects from Jan 2015 to February 2016. The FBS, PPBS, HbA1c and hs-CRP was estimated. SPSS software was used for statistical analysis. Pearson's correlation coefficient was used to show the correlation.
**Results:** The biochemical parameters FBS, PPBS, HbA1c and hs-CRP levels were increased in cases compared to controls. The p value was 0.0001 for all the parameters, which is highly significant. There is a positive correlation between the HbA1c and hs-CRP. The area under the ROC curve for serum hs-CRP values at various cut-off was 0.797 and the best cut-off of serum hs-CRP levels greater than 3.86 mg/L.
**Conclusion:** The hs-CRP was higher in healthy controls of this ethnic group. hs-CRP levels were high in type 2 diabetes mellitus, which correlated with HbA1c. Routine screening for hs-CRP in diabetes patients can be done with best cut-off value of 3.86 mg/L.

*Keywords: Type 2 diabetes mellitus; serum hs-CRP.*

## ABBREVIATIONS

*hs-CRP : High sensitivity C-reactive protein*
*DM : Diabetes mellitus*
*CVD : Cardiovascular diseases*
*HbA1c : Glycated haemoglobin*
*FBS : Fasting blood sugar*
*PPBS : Post prandial blood sugar*
*IFG : Impaired fasting glucose*
*IGT : Impaired glucose tolerance*
*ROC : Receiver operating characteristic*

## 1. INTRODUCTION

Diabetes mellitus (DM) consists a group of metabolic disorders that share common phenotype of hyperglycemia [1]. India has the highest number of type 2 DM individuals worldwide, with a prevalence of 11.6% in urban populations [2,3]. Cardiovascular diseases (CVD) like myocardial infarction, ischaemic stroke and peripheral arterial obstructive disease are the most prevalent cause of death in type 2 DM patients [4,5,6]. Asian Indians are known to be at a high risk for type 2 DM, CVD, and metabolic syndrome [7,8].

In type-2 DM, insulin resistance is the primary event, followed by increasing degree of β-cell dysfunction [9]. Chronic, systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome, and type 2 DM [10]. The process of inflammation induces hepatic synthesis of various acute phase proteins such as serum ferritin and high sensitivity C-reactive protein (hs-CRP), which is believed to play a role in insulin resistance as well as atherosclerosis [11]. Serum levels of hs-CRP have been found to be a strong predictor for increased cardiovascular disease risk associated with type 2 DM. Higher incidence of type 2 DM has been observed with high levels of hs-CRP [10,12].

These high-sensitivity assays help quantify low grades of systemic inflammation, in the absence of overt systemic inflammatory or immunologic disorders [13]. The hs-CRP provide a sensitive marker of increased inflammatory activity in the arterial wall [14,15]. The hs-CRP is the measurement of CRP level with greater accuracy. The lower limit of its measurement is 0.01 mg/L and the measurement is more than 100 times as sensitive than CRP measurement (lower limit 5 mg/L). On the basis of data obtained from population based studies, the American Heart Association/Centres for Disease Control working group on markers of inflammation in CVD has classified serum hs-CRP levels <1, 1–3 and >3 mg/L as low-, intermediate-, and high-risk groups for global CVD, respectively [16]. There is no enough data of serum hs-CRP level in normal non-diabetic people, but in some studies have shown that Asian people have comparatively higher (17%) level of CRP [17,18,19]. Elevated levels of hs-CRP have been observed in Indians [20-22].

To monitor the glycemic status, the glycated haemoglobin (HbA1C) has several advantages over fasting blood sugar (FBS) and oral glucose tolerance test, including greater convenience (fasting not required), greater pre-analytical stability, and less day-to-day perturbations during stress and illness [23]. As we searched the literature, we could find only one original research article [24] on optimal cut-off value for hs-CRP in DM.

Hence the present case control study was under taken to

1. Find the serum hs-CRP levels in type 2 DM patients,
2. Find the serum hs-CRP levels in healthy controls,
3. Compare hs-CRP level between type 2 DM patients and healthy control subjects,
4. Find correlation between HbA1c and hs-CRP in type 2 DM patients and
5. Find the optimum cut-off value for hs-CRP for type 2 DM.

## 2. MATERIALS AND METHODS

The study was conducted on type 2 DM subjects attended the OPD at Hanagal Shri Kumareshwara hospital, Bagalkot. The study was approved by S.Nijalingappa Medical College ethics committee. Informed consent was obtained from all the participants. The study was conducted from Jan 2015 to February 2016. The type 2 DM patients diagnosed on the basis of WHO criteria, irrespective of duration and treatment were selected for the study. Age and sex matched control were selected for the study.

Patients with diabetic complications, any infection, chronic renal failure and other systemic conditions were excluded from the study. Pregnant women were also excluded from the study.

Under aseptic precautions 5 ml of fasting sample was collected. The fasting blood glucose (GOD, POD method), hs-CRP (Particle enhanced immunoturbidimetric method) were estimated (kits supplied by Transasia and Euro Diagnostic Systems Chennai), using semiautomatic analyser Statfax 3300. The glycated haemoglobin, was estimated by Nycocard reader method. Post prandial blood sugar (PPBS) was also estimated.

### 2.1 Statistical Analysis

Statistical package for social science (SPSS for window version; SPSS, 11.5 Inc, Chicago IL) software was used for statistical analysis. Pearson's correlation coefficient was used to show the correlation between the HbA1c and hsCRP in type 2 DM. All the results were expressed as mean±SD.

## 3. RESULTS

Totally 99 participants were enrolled in the study, out of which 49 were cases and 50 were controls, maximum age group was between 41-50 years (34%), followed by 51-60 years of age (31%). 61 were male and 38 were female participants. Among cases, 26 were male and 23 were female. In controls, 35 were male and 15 were female.

There was no significant difference in age between cases and controls. There was statistically significant increase in all the biochemical parameters viz FBS, PPBS, HbA1c and hs-CRP levels in cases as compared to controls. The *P* value was 0.0001 for all the parameters, which is highly significant (Table 1). There is a positive correlation between the HbA1c and hs-CRP levels, but it is not statistically significant (r = 0.10) (Fig. 1).

**Table 1. Biochemical parameters in cases and controls**

| | Group | No | Mean±SD | t | *P* |
|---|---|---|---|---|---|
| Age (years) | Cases | 49 | 55.1±10.1 | 0.47 | 0.63 NS* |
| | Controls | 50 | 56.0±9.2 | | |
| FBS | Cases | 49 | 202.4±89.8 | 8.73 | 0.0001 HS** |
| (mg/dl) | Controls | 50 | 90.9±9.6 | | |
| PPBS (mg/dl) | Cases | 49 | 293.1±115.0 | 10.8 | 0.0001 HS** |
| | Controls | 50 | 116.4±13.5 | | |
| HbA1c % | Cases | 49 | 9.6±2.2 | 12.68 | 0.0001 HS** |
| | Controls | 50 | 116.4±13.5 | | |
| hs-CRP (mg/L) | Cases | 49 | 6.9±9.3 | 3.90 | 0.0001 HS** |
| | Controls | 50 | 1.8±1.0 | | |

*FBS: Fasting blood sugar*
*PPBS: Post prandial blood sugar*
*HbA1c: Glycated Haemoglobin*
*hs-CRP: High sensitive C- reactive protein*
*NS*: Not significant*
*HS **: Highly significant*

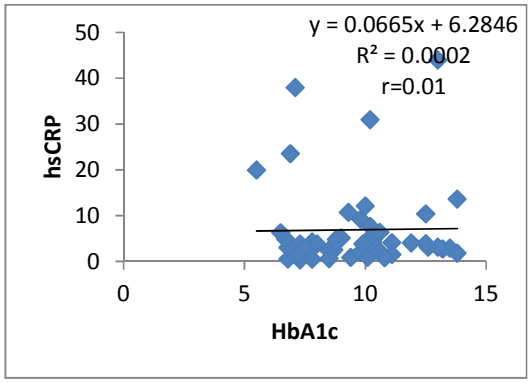


**Fig. 1. Correlation between HbA1c and hsCRP**

The area under the receiver operating characteristic (ROC) curve for serum hs-CRP values at various cut-off was 0.797(95% confidence interval, 0.705-0.871; *P* < 0.0001) as shown in Fig. 2. Sensitivity and specificity of hs-CRP levels in diabetes at various cut-off values is shown in Table 2. A maximum sensitivity of 57.14% and specificity of 98.0% were achieved in diabetes at the best cut-off of serum hs-CRP levels greater than 3.86 mg/L.

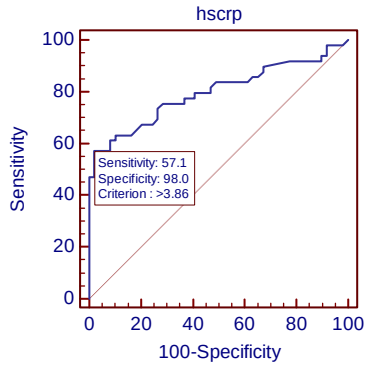


**Fig. 2. ROC curve at various cut-off points for hs-CRP**

## 4. DISCUSSION

Kamath DY et al. [13] in their review of total 24 studies, control group patients in at least 13 (54.2%) studies had hs-CRP levels in the intermediate to high risk group level (>1 mg/L), indicating that the basal concentration of hs-CRP is high in Indians. An analysis of the control arm of the various studies derives a mean hs-CRP value of 1.88 mg/L. In the current study also the hs-CRP level in controls was1.8±1.0 mg/L. Similar results have been found among Asian Indians living in the United Kingdom, where Indians were found to have 17 per cent higher CRP values compared with Europeans [21]. A study in Bangladesh by Fazlul Haque et al. showed that the mean hs-CRP level of healthy people was 0.39 mg/L which was within normal range and below the level of mild risk for cardiovascular disease(<1 mg/L) [19].

A recent meta-analysis including 18 prospective studies demonstrated that high baseline CRP levels are associated with future type 2 DM [25]. Festa et al. demonstrated that people who developed DM had higher baseline serum CRP levels than those who did not develop DM. There was a linear increasing trend in the incidence of DM as the baseline CRP quartile increased [26]. In Pizarra prospective study, people with baseline hs-CRP ≥3 mg/L developed DM [27]. Mahajan et al. [28] in a study reported that hs-CRP is an independent predictor of type 2 diabetes mellitus (OR, 1.66; 95% CI, 1.21 – 2.28, *P*=0.002). All these findings support the chronic low-grade inflammation hypothesis in the development of DM.

Gohel MG and Chacko AN [10] in their study showed statistically significant increase in concentration of hs-CRP in type 2 DM compared to healthy persons. Amanullah S et al. [29] showed significant increase of hs-CRP in subjects with type 2 DM. Tutuncu Y et al. demonstrated a linear increasing trend for hs-CRP levels from normal glucose tolerance through impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and new DM [24,30]. Yuan G et al. in the year 2006, found that in comparison with controls serum hs-CRP was significantly increased in IGT and type-2 DM group (*P*<0.001), although there was no significance between the IGT and type-2 diabetes mellitus [10]. The study on gestational diabetes by Rosy N et al. [31] found that, hs-CRP was significantly increased in gestational DM patients (9.56 mg/L) compared to control group (2.19 mg/L). Fazlul Haque et al. [19] found that The mean hs-CRP of type- 2 diabetic patients was 1.13 mg/L which was significantly higher than that of the normal healthy people (0.39 mg/L) (*P*<0.01). Plasma hs-CRP level in type-2 DM patients was about 3 times higher than normal people. The current study is also in accordance with previous studies. But in the current study mean hs-CRP in type 2 DM patients was 6.9±9.3 mg/L and it was significantly higher (*P*<0.0001) compared to controls (1.8±1.0 mg/L). Even though the current study and Fazlul Haque et al. study was done in

same ethnic (continent) group, but still there is a big difference in values of hs-CRP, hence studies may be required, to standardize the estimation technique and method.

Lima et al. [32] in their study on hs-CRP in type 2DM and/or high blood pressure, showed high plasma hs-CRP levels and a positive, significant correlation with type 2DM and high blood pressure cases (r = 0.25, *P* = 0.02). However, no correlation was obtained for the isolated diseases. Another finding they observed was hs-CRP levels did not correlate significantly with only one disease, i.e., type 2DM or high blood pressure. These data suggest a concomitant action of these two diseases in the occurrence of an increase in the inflammatory process that is reflected by an increase in hs-CRP levels. Hence they concluded that hypertensive patients with type 2 DM, but not those with either hypertension or type 2 DM, were observed to have higher levels of hs-CRP, a circulating inflammatory marker, than normal subjects.

**Table 2. Criterion values and coordinates of the ROC curve**

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI | +LR | -LR |
|---|---|---|---|---|---|---|
| >=0.4 | 100 | 92.7 - 100.0 | 0 | 0.0 - 7.1 | 1 | |
| >0.4 | 97.96 | 89.1 - 99.9 | 2 | 0.05 - 10.6 | 1 | 1.02 |
| >0.5 | 97.96 | 89.1 - 99.9 | 8 | 2.2 - 19.2 | 1.06 | 0.26 |
| >0.6 | 93.88 | 83.1 - 98.7 | 8 | 2.2 - 19.2 | 1.02 | 0.77 |
| >0.68 | 93.88 | 83.1 - 98.7 | 10 | 3.3 - 21.8 | 1.04 | 0.61 |
| >0.7 | 91.84 | 80.4 - 97.7 | 10 | 3.3 - 21.8 | 1.02 | 0.82 |
| >0.8 | 91.84 | 80.4 - 97.7 | 22 | 11.5 - 36.0 | 1.18 | 0.37 |
| >0.9 | 89.8 | 77.8 - 96.6 | 32 | 19.5 - 46.7 | 1.32 | 0.32 |
| >0.97 | 87.76 | 75.2 - 95.4 | 32 | 19.5 - 46.7 | 1.29 | 0.38 |
| >1 | 85.71 | 72.8 - 94.1 | 34 | 21.2 - 48.8 | 1.3 | 0.42 |
| >1.19 | 85.71 | 72.8 - 94.1 | 36 | 22.9 - 50.8 | 1.34 | 0.4 |
| >1.2 | 83.67 | 70.3 - 92.7 | 38 | 24.7 - 52.8 | 1.35 | 0.43 |
| >1.4 | 83.67 | 70.3 - 92.7 | 50 | 35.5 - 64.5 | 1.67 | 0.33 |
| >1.6 | 81.63 | 68.0 - 91.2 | 52 | 37.4 - 66.3 | 1.7 | 0.35 |
| >1.7 | 79.59 | 65.7 - 89.8 | 52 | 37.4 - 66.3 | 1.66 | 0.39 |
| >1.88 | 79.59 | 65.7 - 89.8 | 60 | 45.2 - 73.6 | 1.99 | 0.34 |
| >1.89 | 77.55 | 63.4 - 88.2 | 60 | 45.2 - 73.6 | 1.94 | 0.37 |
| >2.09 | 77.55 | 63.4 - 88.2 | 64 | 49.2 - 77.1 | 2.15 | 0.35 |
| >2.1 | 75.51 | 61.1 - 86.7 | 64 | 49.2 - 77.1 | 2.1 | 0.38 |
| >2.3 | 75.51 | 61.1 - 86.7 | 72 | 57.5 - 83.8 | 2.7 | 0.34 |
| >2.4 | 73.47 | 58.9 - 85.1 | 74 | 59.7 - 85.4 | 2.83 | 0.36 |
| >2.76 | 69.39 | 54.6 - 81.7 | 74 | 59.7 - 85.4 | 2.67 | 0.41 |
| >2.8 | 67.35 | 52.5 - 80.1 | 76 | 61.8 - 86.9 | 2.81 | 0.43 |
| >2.9 | 67.35 | 52.5 - 80.1 | 80 | 66.3 - 90.0 | 3.37 | 0.41 |
| >2.96 | 65.31 | 50.4 - 78.3 | 82 | 68.6 - 91.4 | 3.63 | 0.42 |
| >3 | 63.27 | 48.3 - 76.6 | 84 | 70.9 - 92.8 | 3.95 | 0.44 |
| >3.11 | 63.27 | 48.3 - 76.6 | 90 | 78.2 - 96.7 | 6.33 | 0.41 |
| >3.12 | 61.22 | 46.2 - 74.8 | 90 | 78.2 - 96.7 | 6.12 | 0.43 |
| >3.14 | 61.22 | 46.2 - 74.8 | 92 | 80.8 - 97.8 | 7.65 | 0.42 |
| >3.2 | 57.14 | 42.2 - 71.2 | 92 | 80.8 - 97.8 | 7.14 | 0.47 |
| **>3.86 *** | **57.14** | **42.2 - 71.2** | **98** | **89.4 - 99.9** | **28.57** | **0.44** |
| >4 | 46.94 | 32.5 - 61.7 | 98 | 89.4 - 99.9 | 23.47 | 0.54 |
| >4.02 | 46.94 | 32.5 - 61.7 | 100 | 92.9 - 100.0 | | 0.53 |
| >44 | 0 | 0.0 - 7.3 | 100 | 92.9 - 100.0 | | 1 |

** Criterion corresponding with highest Youden index*
*ROC curve: Rreceiver operating characteristic curve*
*CI: Confidence limits*
*+LR: Positive likelihood ratio*
*-LR: Negative likelihood ratio*

Gohel MG and Chacko AN also found a significant positive linear relationship between hs-CRP and HbA1C [10]. Li et al. [33] also found similar results, hs-CRP was positively correlated with HbA1c. Amanullah S et al. [29] concluded that low HbA1c was strongly related to negative hs-CRP levels. A prospective study on the Type 2 DM subjects suggested a decrease in hs-CRP levels with a decrease in HbA1c [34]. Tutuncu Y et al study found a positive correlation between hs- CRP levels and all glycaemia and insulin resistance parameters [24]: it also showed that among people with new DM, the highest hs-CRP levels were obtained in those identified with the HbA1c criterion. As they showed a positive correlation between hs-CRP and HbA1c, it has been reported that people with DM with poorer glycaemic control had higher CRP levels [35]. Wu and co-workers reported that high levels of hs-CRP were correlated with high levels of HbA1c and FPG in men [36]. In the current study also there was a positive correlation between hs-CRP and HbA1c, but the correlation was not statically significant.

Tutuncu Y et al. [24] estimated the optimal cut-off for hs-CRP and area under curve with 95%CIs for DM for each of the three diagnostic methods separately. They reported the optimum cut-off point hs-CRP for HbA1c 6.5% and over was 2.9 mg/L in women with a 65% sensitivity and 64%specificity and 2.0 mg/L in men with a 60%sensitivity and 62% specificity, and the area under curve for hs-CRP to detect new DM was found in women and men when using HbA1c (women: 0.700; men: 0.656). den Engelsen et al got the cut-off point for hs CRP for metabolic syndrome, at 3 mg/L, the sensitivity and specificity were 72% and 37%; at this point positive predictive value and negative predictive value were 42% and 67% [37], Tutuncu Y et al. [24] conclude that, an hs-CRP level ≥1.8 mg/L generally detects more than half of the people with new DM.

In the current study, the area under the ROC curve for serum hs-CRP values at various cut-off was 0.797 (95% confidence interval, 0.705-0.871; *P*<0.0001). A maximum sensitivity of 57.14% and specificity of 98.0% were achieved in diabetes at the best cut-off of serum hs-CRP levels greater than 3.86 mg/L.

However, hs-CRP is decreased by factors such as moderate alcohol consumption, excessive exercise, weight loss, and medications such as statin, fibrate, and niacin [38]. These factors may be encountered frequently and hence accuracy of making conclusions based on the hs-CRP levels is controversial [39]. These are the limitations present study the other limitation were small sample size, duration of diabetes was not considered for the study. Further studies are required with large sample size, so that hs-CRP can be used as glycemic control parameters.

## 5. CONCLUSION

The hs-CRP was higher in healthy controls of this ethnic group, who are at the risk of developing DM and CVD (Intermediate risk). hs-CRP levels were high in type 2 DM who are also at high risk of developing CVD, which correlate with HbA1c. Thus, routine screening for hs-CRP concentration in diabetes patients can be done to assess risk of CVD and the glycemic control in type 2 DM, with best cut-off value of 3.86 mg/L.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Institutional Ethics Committee of S. N. Medical College Bagalkot, Karnataka, India.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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