

Serum high sensitive - C reactive protein levels in type 2 diabetes mellitus -A case control study

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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 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

Material 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 3.86mg/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.

Key words: Type 2 Diabetes Mellitus, Serum hs-CRP

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. MATERIAL 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 ($r = 0.10$) (Figure 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 (mg/dl)	Cases	49	202.4±89.8	8.73	0.0001 HS**
	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

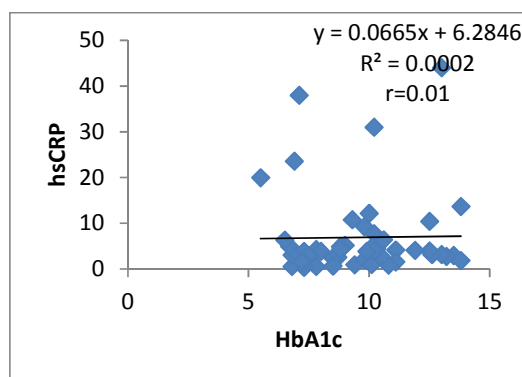
HbA1c: Glycated Haemoglobin

hs-CRP: High sensitive C- reactive protein

NS*: Not significant

HS **: Highly significant

Fig1. 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 figure 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.

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

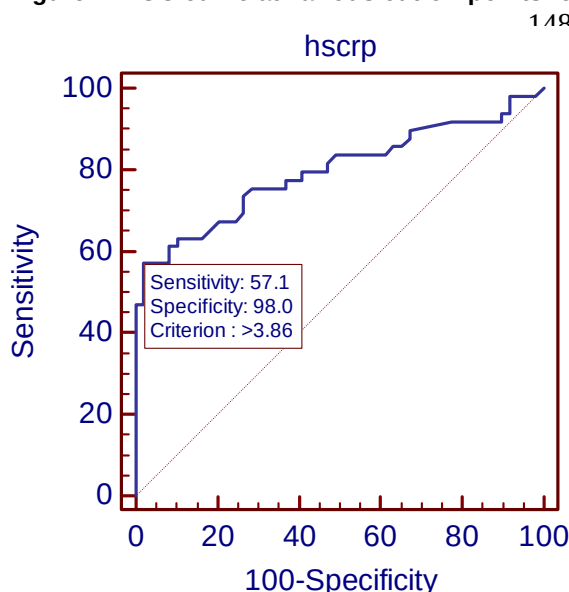
ROC curve: Rreceiver operating characteristic curve

CI: Confidence limits

+LR: Positive likelihood ratio

-LR: Negative likelihood ratio

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



4. DISCUSSION

Kamath DY et al. 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[13]. 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 was 1.8 ± 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

158 Haque et al. showed that the mean hs-CRP level of healthy people was 0.39 mg/L which was
 159 within normal range and below the level of mild risk for cardiovascular disease(<1mg/L)[19].
 160 A recent meta-analysis including 18 prospective studies demonstrated that high baseline CRP
 161 levels are associated with future type 2 DM [25]. Festa et al. demonstrated that people who
 162 developed DM had higher baseline serum CRP levels than those who did not develop DM.
 163 There was a linear increasing trend in the incidence of DM as the baseline CRP quartile
 164 increased [26]. In Pizarra prospective study, people with baseline hs-CRP ≥ 3 mg/L developed
 165 DM [27]. Mahajan et al [28] in a study reported that hs-CRP is an independent predictor of
 166 type 2 diabetes mellitus (OR, 1.66; 95% CI, 1.21 – 2.28, $P=0.002$). All these findings support
 167 the chronic low-grade inflammation hypothesis in the development of DM.
 168 Gohel MG and Chacko AN in their study showed statistically significant increase in
 169 concentration of hs-CRP in type 2 DM compared to healthy persons [10]. Amanullah S et al.
 170 showed significant increase of hs-CRP in subjects with type 2 DM [29]. Tutuncu Y et al.
 171 demonstrated a linear increasing trend for hs-CRP levels from normal glucose tolerance
 172 through impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and new DM
 173 [24,30]. Yuan G et al in the year 2006, found that in comparison with controls serum hs-CRP
 174 was significantly increased in IGT and type-2 DM group ($P<0.001$), although there was no
 175 significance between the IGT and type-2 diabetes mellitus [10]. The study on gestational
 176 diabetes by Rosy N et al. found that, hs-CRP was significantly increased in gestational DM
 177 patients (9.56mg/L) compared to control group (2.19mg/L) [31]. Fazlul Haque et al found that
 178 The mean hs-CRP of type- 2 diabetic patients was 1.13 mg/L which was significantly higher
 179 than that of the normal healthy people (0.39 mg/L) ($P<0.01$). Plasma hs-CRP level in type-2
 180 DM patients was about 3 times higher than normal people [19]. The current study is also in
 181 accordance with previous studies. But in the current study mean hs-CRP in type 2 DM
 182 patients was 6.9 ± 9.3 mg/L and it was significantly higher ($P<0.0001$) compared to controls
 183 (1.8 ± 1.0 mg/L). Even though the current study and Fazlul Haque et al. study was done in
 184 same ethnic (continent) group, but still there is a big difference in values of hs-CRP, hence
 185 studies may be required, to standardize the estimation technique and method.
 186 Lima et al. in their study on hs-CRP in type 2DM and/or high blood pressure, showed high
 187 plasma hs-CRP levels and a positive, significant correlation with type 2DM and high blood
 188 pressure cases ($r = 0.25$, $P = 0.02$). However, no correlation was obtained for the isolated
 189 diseases. Another finding they observed was hs-CRP levels did not correlate significantly with
 190 only one disease, i.e., type 2DM or high blood pressure. These data suggest a concomitant
 191 action of these two diseases in the occurrence of an increase in the inflammatory process that
 192 is reflected by an increase in hs-CRP levels. Hence they concluded that hypertensive patients
 193 with type 2 DM, but not those with either hypertension or type 2 DM, were observed to have
 194 higher levels of hs-CRP, a circulating inflammatory marker, than normal subjects [32].
 195 Gohel MG and Chacko AN also found a significant positive linear relationship between hs-
 196 CRP and HbA1c [10]. Li et al also found similar results, hs-CRP was positively correlated
 197 with HbA1c [33]. Amanullah S et al. concluded that low HbA1c was strongly related to
 198 negative hs-CRP levels [29]. A prospective study on the Type 2 DM subjects suggested a
 199 decrease in hs-CRP levels with a decrease in HbA1c [34]. Tutuncu Y et al study found a
 200 positive correlation between hs- CRP levels and all glycaemia and insulin resistance
 201 parameters [24]: it also showed that among people with new DM, the highest hs-CRP levels
 202 were obtained in those identified with the HbA1c criterion. As they showed a positive
 203 correlation between hs-CRP and HbA1c, it has been reported that people with DM with poorer
 204 glycaemic control had higher CRP levels [35]. Wu and co-workers reported that high levels of
 205 hs-CRP were correlated with high levels of HbA1c and FPG in men [36]. In the current study
 206 also there was a positive correlation between hs-CRP and HbA1c, but the correlation was not
 207 statically significant.
 208 Tutuncu Y. et al.[24] estimated the optimal cut-off for hs-CRP and area under curve with
 209 95%CIs for DM for each of the three diagnostic methods separately. They reported the
 210 optimum cut-off point hs-CRP for HbA1c 6.5% and over was 2.9 mg/L in women with a 65%
 211 sensitivity and 64%specificity and 2.0 mg/L in men with a 60%sensitivity and 62% specificity,
 212 and the area under curve for hs-CRP to detect new DM was found in women and men when
 213 using HbA1c (women: 0.700; men: 0.656). den Engelsen et al got the cut-off point for hs
 214 CRP for metabolic syndrome, at 3mg/L, the sensitivity and specificity were 72% and 37%; at
 215 this point positive predictive value and negative predictive value were 42% and 67% [37],
 216 Tutuncu Y et al conclude that, an hs-CRP level ≥ 1.8 mg/L generally detects more than half of
 217 the people with new DM [24].

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 3.86mg/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

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.

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List of 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