

**Research Article**

## **High – Sensitivity C - reactive protein is associated with Traditional Cardiovascular Risk Factors in Indians with Type 2 Diabetes Mellitus**

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### **Abstract**

**Background:** India is experiencing twin epidemic of type 2 diabetes mellitus and cardiovascular diseases imposing huge toll on healthcare system. In type 2 diabetes 65-80% deaths occur due to cardiovascular disease whose etiology cannot be explained by chronic hyperglycemia, dyslipidemia and traditional cardiac risk factors. To improve risk stratification serum high-sensitivity C- reactive protein estimation is an adjunct to other risk factors.

**Study design:** O.P.D. based Cross sectional study.

**Method:** 100 patients of type 2 diabetes and 100 healthy controls were selected and demographic data and anthropometric measures recorded. Fasting blood samples were assayed for serum lipid profile and high-sensitivity C- reactive protein.

**Result:** In study group we observed clustering of multiple cardiac risk factors age, family history of cardiovascular disease in first degree relatives, obesity, smoking, and hypertension. Serum high-sensitivity C- reactive protein is raised significantly ( $p < 0.001$ ) in cases compared to controls and shows positive association with body mass index ( $r = 0.531$ ), waist: hip ( $r = 0.497$ ), total cholesterol ( $r = 0.523$ ), triglycerides ( $r = 0.621$ ), low density lipoprotein ( $r = 0.432$ ) while negative correlation with high density lipoprotein ( $r = -0.54$ ).

**Conclusion:** Identification and management of subclinical atherosclerosis by serum high-sensitivity C- reactive protein assay and traditional risk factors remain at cornerstone in patients of type 2 Diabetes Mellitus.

**Keywords:** Type 2 Diabetes Mellitus, high-sensitivity C- reactive protein, lipid parameters, traditional cardiac risk factors.

### **1. Introduction**

Diabetes mellitus, a well recognized independent traditional risk factor for cardiovascular disease is characterized by absolute or relative deficiency of Insulin leading to progressive worsening of glycemic control. A wealth of epidemiologic data show that the prevalence of Type 2 Diabetes Mellitus (T2DM) is rising at an alarming rate virtually in each and every developed and developing country. This explosive rise in the prevalence of T2DM and its complications

represent the greatest health care challenge facing the world today<sup>1</sup>. T2DM, a worldwide health crisis emerged as a major growing health problem imposing socioeconomic burden is an important cause of mortality and morbidity from cardiovascular disease (CVD) accounting for 65-80% of deaths in them<sup>2</sup>. The current NCEP III guidelines recommend treating patients of T2DM as coronary artery disease equivalents. It is associated with two to fourfold excess risk of coronary heart disease, higher post infarction fatality rate and sudden cardiac death<sup>3</sup>. Diabetic patients are likely to die from first event of acute myocardial infarction compared to their non-diabetic counterparts<sup>4</sup>. Also patients of T2DM present with premature and silent acute myocardial infarction due to insulin resistance and dyslipidemia. Moreover CVD occurs two to three decades earlier in diabetics with high mortality within first year after AMI<sup>5</sup>.

India is experiencing rapidly escalating epidemics of both T2DM and CVD. India has the highest number of T2DM patients in the world and it is predicted that by 2025 India will have more than 60 millions diabetic patients with largest burden of cardiovascular disease in the world.<sup>6</sup> The prevalence of coronary heart disease (CHD) in T2DM is 21.4% as compared to 9.1% in persons with normal glucose tolerance and 14.9% in impaired glucose tolerance. Indians have been shown to have high risk of developing premature CHD one to two decades earlier.<sup>7</sup> T2DM itself is a strong risk factor for CVD as Insulin Resistance or its deficiency leads to disturbances in glucose and lipoprotein metabolism triggering atherogenesis. Presence of T2DM with long exposure to multiple cardiac risk factors exaggerates cardiovascular risk 2 to 4 times. High prevalence of cardiovascular diseases in T2DM is not only contributed by dyslipidemia or chronic hyperglycemia, but clustering of multiple cardiac risk factors compounds the cardiovascular risk. The cause of higher prevalence of CHD in T2DM is multifactorial which include obesity, smoking, physical inactivity, hypertension, dyslipidemia, poor glycemic control, hypercoagulability.<sup>8</sup>

CVD is in part an inflammatory process; C - reactive protein (CRP) has been widely investigated in context of atherosclerosis and subsequent vascular events. Multiple epidemiological and interventional studies have been reported mild elevation of high – sensitivity C – reactive protein (hs-CRP) associated with future cardiovascular risk. Chronic low grade systemic inflammation plays a major role in pathophysiology of both T2DM as well as atherosclerosis.<sup>9</sup> CRP is a liver derived protein from Pentraxin family composed of five 23 KDa subunits with plasma half life about 18 hours. It is an acute phase reactant protein now understood to be a mediator and marker of atherothrombotic disease.<sup>10</sup>

Rinkoo Dalan and associates observed significantly higher hs-CRP concentrations in Indians compared to the Chinese in both the diabetic and nondiabetic individuals after adjustment for the various demographic, metabolic, and therapeutic variables.<sup>11</sup> In various studies prevalence of cardiac risk factors has been studied in T2DM patients.<sup>12, 13, 14</sup> But to our knowledge there is scarcity of data about association of serum hsCRP with multiple cardiac risk factors in Indian individuals with T2DM.

To improve global risk prediction, we hypothesized that increased levels of serum hsCRP are associated with various traditional cardiac risk factors in patients with T2DM. Present study was planned to assess traditional modifiable and nonmodifiable cardiac risk factors in T2DM and to study their association with serum hsCRP level which is an independent proinflammatory cardiac risk marker. This will help the clinicians to target high risk population for therapeutic lifestyle change to minimize twin epidemic of DM and CVD.

## 2. Material and Methods

Present cross sectional study was conducted in the Department of Biochemistry at Government Medical College, Aurangabad Maharashtra in India as per the guidelines of Institutional Ethical Committee. 100 patients of T2DM attending Diabetic O.P.D. were selected as cases and 100 healthy age and sex matched nondiabetic controls. Patients with the history of cardiovascular disease, acute systemic illness, liver diseases, chronic obstructive pulmonary disease, arthritis, patients on oral contraceptive pills and hormone replacement therapy were excluded from study group. A standard questionnaire was designed to record demographic data and personal habits including age, sex, other co morbid conditions, history of CVD in first degree relatives, duration of T2DM, history of medication and any complication. Details of smoking history, alcohol use, physical activity, social class were recorded. Systolic and diastolic blood pressures were recorded for all subjects.

For anthropometric measurements, we recorded weight (kilograms), height (centimeters), waist circumference (centimeters), hip circumference (centimeters). Then we calculated body mass index (BMI) as weight (kilograms)/ height (meters<sup>2</sup>) as a measure of obesity and waist: hip ratio as an index of abdominal adiposity. All the study subjects were recalled after overnight fast for assessment of biochemical parameters.

**2.1 Biochemical assay:** After overnight fast 5 ml venous blood samples were collected for various biochemical assays.

After clot formation, serum were separated and assayed for estimation of serum total cholesterol (TC), triglycerides (TG), High Density Lipoproteins and hsCRP levels. Blood glucose and lipid profile were assayed using semiautomatic analyzer from Transasia. Blood glucose was estimated by Glucose Oxidase Peroxidase end point method using commercial kits from ERBA Diagnostics.

Quantitative estimation of serum TC was done by Cholesterol Oxidase Peroxidase end point method using kits from RECKON Diagnostics. Serum TG were measured by Lipase/Glycerokinase/Glycerophosphate oxidase end point method using commercial kits from RECKON Diagnostics. Serum HDL was estimated by Phosphotungstic Acid (PTA) end point method using commercial kits from RECKON Diagnostics. Serum Low Density Lipoprotein (LDL) was estimated by Friedewalds formula  $LDL (mg/dl) = Total\ Cholesterol - (HDL + Triglycerides/5)$ .

Serum hsCRP was estimated by chemiluminescence immunoassay using Acculite CLIA microwells with Assay kits from Monobind INC, Lake forest, CA 92630 USA.

Statistical analysis was performed using the SPSS data analysis system. Demographic and biochemical data of all subjects was analyzed as mean $\pm$ S.D. and student 't' test used to demonstrate the significance of different variables. P values less than 0.05 were considered as significant, less than 0.001 as highly significant and more than 0.05 as non significant. Correlation coefficients (r values) were calculated to study association of serum hsCRP with various cardiovascular risk factors in study group.

### 3. Results

Demographic characteristics of cases and controls are represented in table 1.

**Table 1: Demographic characteristics of study population**

Variables	Cases(n=100)	Control(n=100)	pValue
Age(years)	46 $\pm$ 13	43 $\pm$ 9	0.07
Sex	63/37	56/54	0.06
Family H/ODM	63 $\pm$ 15	23 $\pm$ 5	0.02*+
Family H/OCHD	42 $\pm$ 13	13 $\pm$ 4	0.014
SBP(mm HG)	146 $\pm$ 23	116 $\pm$ 12	0.021*
DBP(mmHg)	96 $\pm$ 18	78 $\pm$ 12	0.041*
Smokers	23	3	
Alcoholics	28	10	
BMI(kg/m <sup>2</sup> )	27.3 $\pm$ 3.8	21.7 $\pm$ 2.4	0.0032*
Waist circumference(cm.)	96 $\pm$ 7	82 $\pm$ 6	0.0006*
Waist: Hip	1.3 $\pm$ 0.4	0.7 $\pm$ 0.3	0.0004*

SBP- systolic blood pressure, DBP- diastolic blood pressure, \* - significant p value

The patients of T2DM belonged to age group 33 to 59 years (mean 46 $\pm$ 13 Vs 43 $\pm$ 9 p= 0.07) with no statistically significant difference compared to controls. Among them 63 were males and 37 females out of which 23 males were smokers and 28 were alcoholics. All females were nonsmokers and nonalcoholic. Among diabetics 41 were hypertensive with mean systolic blood pressure 146 $\pm$ 23mmHg and mean diastolic blood pressure 96 $\pm$ mmHg whereas in controls mean systolic blood pressure 116 $\pm$ 12 mmHg and mean diastolic blood pressure 78 $\pm$ 12mmHg with p value 0.021 and 0.041 respectively which are statistically significant

The data showed highly significant difference in mean value of BMI (27.3 $\pm$ 3.8Vs21.7 $\pm$ 2.4 p<0.05), waist circumference (96 $\pm$ 7Vs82 $\pm$ 6 p<0.001) and waist: hip ratio (1.3 $\pm$ 0.4Vs0.7 $\pm$ 0.3 p<0.001) in cases compared to controls.

Table 2 represents data regarding biochemical parameters assayed in cases and controls.

**Table 2: Biochemical characteristics of study population.**

Parameter	Cases	Control	P Values
Blood glucose level mg/dL	137.5+/-32	85.5+/-11	0.0005*
Serum total cholesterol mg/dL	213.5+/-20.2	151.3+/-15.2	0.004*
Serum triglycerides mg/dL	175.4 ± 35.3	92.5+/-23.7	0.0003*
Serum LDL mg/dL	135.4+/-18.5	83.4+/-10.2	0.0003*
Serum HDL mg/dL	35.3+/-5.4	61.5+/-6.5	0.0002*
Serum hsCRP mg/dL	3.89+/-1.5	0.89+/-0.03	0.0001*

\*- statistically significant p value

Fasting blood glucose levels were significantly raised in patients of T2DM with mean 137.5+/-32 compared to controls 85.5+/-11 ( $p<0.001$ ). In the cases we found significantly raised values of fasting serum cholesterol (213.5+/-20.2 Vs 151.3+/-15.2  $p<0.05$ ), serum triglyceride (175.4 ± 35.3 Vs 92.5+/-23.7  $p<0.001$ ), LDL (135.4+/-18.5 Vs 83.4+/-10.2  $p<0.001$ ), and significantly low levels of serum HDL (35.3+/-5.4 Vs 61.5+/-6.5  $p<0.001$ ). Serum hsCRP levels were significantly raised in cases compared to control (mean 3.89+/-1.5 Vs 0.89+/-0.03  $p<0.0001$ ).

To study the correlation of serum hsCRP with other modifiable risk factors in the patients of T2DM we calculated Correlation coefficients (r values) which are represented in table 3.

**Table3: Pearson's correlation analysis of hsCRP and other cardiac risk factors in cases:**

Parameters	r values	P values
BMI (Kg/m <sup>2</sup> )	0.531	< 0.001
Waist: Hip	0.497	< 0.001
Systolic blood pressure(mmHg)	0.362	< 0.001
Diastolic blood pressure(mmHg)	0.312	< 0.001
Total cholesterol(mg/dl)	0.523	< 0.001
Triglycerides(mg/dl)	0.621	< 0.001
HDL(mg/dl)	-0.54	< 0.001
LDL(mg/dl)	0.432	< 0.001

Serum hsCRP shows significant positive correlation with BMI, waist: hip, systolic and diastolic blood pressure, total cholesterol, triglycerides and LDL and TC: HDL, however it correlates negatively with HDL. (r values)

#### 4. Discussion

The present study was aimed to identify multiple coexisting cardiac risk factors in T2DM patients and to study their association with serum hsCRP levels. Our results suggested presence of modifiable multiple cardiac risk factors like smoking, obesity, physical inactivity, dyslipidemia, hypertension and nonmodifiable risk factors like age, family history of T2DM and CVD in first degree relatives in study group.

Serum hsCRP, most actively and commonly studied proinflammatory cardiac risk marker is raised significantly ( $P<0.001$ ) in our patients of T2DM. Our study reaffirms strong positive correlation of serum hsCRP with BMI ( $r= 0.531$ ) and waist: Hip ( $r= 0.497$ ) which are measures of adiposity. Hypertension is observed in 43 cases and also serum hsCRP levels are positively correlated with systolic ( $r= 0.362$ ) and diastolic blood pressure ( $r= 0.312$ )

Diabetic dyslipidemia is characterized by elevated levels of fasting serum triglycerides and reduced serum HDL. In our study group serum total cholesterol, triglycerides and LDL levels are significantly raised ( $p<0.001$ ) and serum HDL

is significantly decreased ( $p < 0.001$ ) Serum hsCRP shows strong positive association with serum total cholesterol ( $r = 0.523$ ), triglycerides ( $r = 0.621$ ), LDL ( $r = 0.432$ ). It is negatively associated with serum HDL level ( $r = -0.54$ ).

In CURES-105 study on south Indian population, subjects with Insulin Resistance and metabolic syndrome had significantly higher levels of inflammatory markers hsCRP, tumor necrosis factor- $\alpha$ , Interleukin-6 and Vascular cell Adhesion molecules compared to the subjects with metabolic syndrome alone.<sup>15</sup> Jennifer K. reported inflammatory markers are associated with biologic and environmental risk factors for CVD including obesity, insulin resistance, T2DM, hypertension, low levels of HDL and lifestyle factors like smoking and physical inactivity.<sup>16</sup> Our findings are consistent with their study which demonstrated role of hsCRP, an atherogenic inflammatory marker in the elevated risk of cardiovascular events associated with T2DM.

Li Jin Pu and colleagues estimated serum hsCRP levels in the prediction of presence of CAD in patients of T2DM and reported that raised levels of hsCRP  $< 10 \text{ mg/L}$  was associated with a 2.593 fold increased risk for CAD. Also they found increased hsCRP levels were associated with other indicators of diabetes related cardiovascular risk parameters.<sup>17</sup> Rekha Bhagwat and colleagues studied serum hsCRP levels in patients of T2DM alone, T2DM with hypertension and T2 DM with myocardial infarction in Indian subjects. They found levels of serum hsCRP raised 3 times higher in T2 DM and 5 times higher in group of T2 DM with hypertension and 4 times more in T2DM with MI than control.<sup>18</sup> These findings support use of hsCRP as cardiac risk marker for early detection of CHD.

Priya Kalidas *et al* studied coronary risk factors in T2DM and observed significantly increased TGLs, TGL/HDL ratio, BP and the BMI of diabetic patients with metabolic syndrome than those without metabolic syndrome in urban south Indian population.<sup>19</sup> Jaiswal A. *et al* demonstrated strong independent positive relationship of serum hsCRP with measures of adiposity, dyslipidemia and hypertension in patients of prediabetes in Indian subjects.<sup>20</sup>

Hsieh *et al* assessed association between hsCRP and silent MI in Chinese patients of T2DM and found that 24.8% patients with silent MI were missed when the American Diabetes Association guidelines were used alone. So they reported that hsCRP might help to detect silent MI in diabetics who may need aggressive treatment to reduce future cardiovascular morbidity and mortality.<sup>21</sup> Safiullah Amanullah *et al* also showed strong association of hsCRP with age, body weight, BMI and Insulin resistance among individuals with T2DM in Chennai Urban Rural population than without T2DM. But they did not studied association with lipid profile.<sup>22</sup>

Yoshimasa ASO *et al* demonstrated significantly higher values of serum hsCRP in diabetic patients with metabolic syndrome.<sup>23</sup> Our findings confirm the findings of this study. In atherogenesis LDL cholesterol is a main focus of current guidelines to assess cardiac risk. But CVD often occurs in absence of dyslipidemia. So assessment of other modifiable risk factors is desirable along with routine measures. Coexistence of multiple cardiac risk factors accelerates inflammation in these patients.

As T2DM is a state of chronic low grade systemic inflammation, there might a mechanistic connection between T2DM and acute phase response as estimated by measuring hsCRP. The typical dyslipidemia of T2DM as high serum TG and VLDL, low HDL is similar to that appears with experimental induction of acute phase reaction in animals by injecting toxins and in human beings suffering from infection and malignancy. So T2DM may be a maladaptation of normal acute phase response to injury. Environmental threats to person resulting in physical, chemical, infectious or psychological injury triggers release of proinflammatory cytokines from adipocytes and macrophages which induce acute phase response. CRP causes LDL uptake by macrophages, expression of endothelial adhesion molecules and thereby initiates atherogenesis.<sup>24</sup> CRP plays central role in initiation, progression rupture of atheromatous plaque at all stages. Estimation of serum hsCRP complements further evaluation of lipid parameters and cardiovascular risk factors which underscores the pathophysiological link between insulin resistance, inflammation and CVD.<sup>25</sup>

The prevalence of T2DM and related morbidity and mortality is continuously increasing at an alarming rate worldwide. DM is one of the well established strongest risk factor for CHD, although association of these two noncommunicable chronic diseases was recognized as early as the late 1800s, CHD is the infrequent cause of death in patients of DM. About 58 million people die from CVD every year for which DM and HT are major risk factors.<sup>26</sup> This high incidence of CHD in T2DM cannot be explained by hyperglycemia alone, but due to clustering of multiple cardiovascular risk factors.<sup>27</sup>



Over a period of time prevalence of many cardiac risk factors is also likely to increase in developing countries due to socioeconomic advances exerting huge toll on human sufferings and human healthcare system. Aggressive management of cardiac risk factors will be the stitch at a time to avoid further sequels. Patients with established T2DM are having high risk for vascular events with worst prognosis than their counterparts without Type2DM. So accurate risk stratification by measuring biomarker like hsCRP to improve definition of cardiovascular risk profile is needed in the patients of T2DM. So the efforts for prevention and early detection of preclinical atherosclerosis in these high risk individuals remain cornerstone in the management of T2DM.

## 5. Conclusion

Estimation of serum hsCRP levels is useful as an adjunct and not substitutes of traditional risk factors for cardiac risk assessment. India is experiencing rapidly escalating prevalence of DM and CVD. So it is necessary among Indians to screen high risk individuals for the presence of cardiac risk factors and motivate them for lifestyle modification with healthy dietary habits, enhancing physical activity, cessation of smoking and stress management.

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