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# Association between high sensitive c reactive protein and lipid profile in coronary artery disease with type 2 diabetes mellitus

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## Abstract

**Background:** Diabetes, specifically type 2 diabetes mellitus (T2DM), is one of the most challenging health problems in the 21st century. The cause of higher prevalence of coronary artery disease (CAD) in T2DM is multifactorial. Increased concentrations of acute phase proteins particularly high sensitive high reactive protein (hsCRP) have been reported in patients with T2DM.

**Aim:** To know the association of hsCRP with other risk factors for CAD in T2DM.

**Materials and Methods:** This was a case control study conducted at tertiary care hospital in South India from May 2014 to May 2015. 100 patients (69 males and 31 females) aged between 30-60 years of either sex with type 2 diabetes mellitus and diagnosed for coronary artery disease (clinically and by ECG findings) were selected as cases. 100 controls (64 males and 36 females) without T2DM were chosen. Student 't' test used to test the significance, between cases and controls and P values of <0.05 were considered as statistically significant, P values of <0.01 was considered highly significant. Correlation coefficients (r values) were used to study the association of hsCRP with various risk factors.

**Results:** There was statistically significant difference between the parameters such as BMI, waist circumference, waist hip ratio and family history of CAD and T2DM (P<0.05). Triglycerides and LDL levels were highly significant (P<0.01). Serum hsCRP shows strong positive association with serum total cholesterol, triglycerides and LDL, negative correlation with HDL level. Maximum cases had serum hsCRP levels of more than 3 mg/l.

**Conclusion:** The present study shows that hsCRP levels are increased in CAD patients with T2DM, even with a relatively short disease duration of 2 years. There was a positive correlation of serum hsCRP with other cardiovascular risk factors like BMI, blood glucose and lipid parameters which was highly significant.

**Keywords:** High sensitive C-reactive protein(hs-CRP), Coronary artery disease(CAD), Atherosclerosis, Lipid profile

## Introduction

Diabetes, specifically type 2 diabetes mellitus (T2DM), is one of the most challenging health problems in the 21st century. Its prevalence is increasing worldwide, it was 150 million in 2000, 171 million in 2007, and expected to reach 366 million in 2030[1,2]. In India the estimated prevalence was 41 million in 2006 and is expected to reach 70 million by the year 2025[1,2]. The prevalence of coronary artery disease (CAD) in T2DM is 21.4% as compared to 14.9% in impaired glucose tolerance and 9.1% in persons with normal glucose tolerance[3]. The cause of higher prevalence of CAD in T2DM is multifactorial which includes factors like physical inactivity, obesity, smoking, hypertension and dyslipidemia[4].

Increased concentrations of acute phase proteins particularly high sensitive high reactive protein (hsCRP) have been reported in patients with T2DM[5,6]. An important function of hsCRP is to detoxify toxic substances which are produced due to tissue damage. In addition, hsCRP helps in removal of dead and foreign cells such as microbes by activating the complement system and initiation of opsonization and phagocytosis[7]. It is widely accepted that dyslipidemia such as increase in levels of low density lipoprotein(LDL), very low density lipoprotein (VLDL) total cholesterol (TC), triglycerides (TGs), and decreased levels of high density lipoprotein (HDL) are associated CAD[8,9].

Increased hsCRP level in CAD patients is associated with complex angiographic lesions and the need for revascularization. Also, it has been recently reported that increase in levels of hsCRP is associated with increase in number of vulnerable plaques and patients with high hsCRP levels have increased risk of future CAD[10]. Many studies[11-14] though have shown that both hsCRP and Lipid parameters have role in initiation and progression of atherosclerosis in T2DM. But there are very few studies conducted on association of hsCRP with modifiable and non modifiable risk factors for CAD in T2DM.

## Material and Methods

**Study design:** This was a case control study conducted at tertiary care hospital in South India from May 2014 to May 2015. 100 patients (69 males and 31 females) aged between 30-60 years of either sex with type 2 diabetes mellitus and diagnosed for coronary artery disease (clinically and by ECG findings) were selected as cases. 100 controls (64 males and 36 females) without T2DM were chosen. The study was approved by institutional ethical committee and written informed consent was obtained from all the participants. The following were exclusion criteria.

1. Patients with endocrinal disorders like acromegaly, Cushing's syndrome and with medical disorders like liver, lung and kidney disease or infection.
2. Patients on drugs which may alter the study results (such as oral contraceptive pills, corticosteroids, hormonal replacement therapy) were excluded from the study.
3. Past or present smokers and alcohol addiction.

**Measurement of various parameters**

1. For anthropometric measurements, weight (kilograms), height (centimeters), waist circumference (centimeters), hip circumference (centimeters) was recorded. Body mass index (BMI) was calculated as weight (kilograms)/ height (meters) and waist: hip ratio was also assessed. Systolic and diastolic blood pressure was calculated with mercury sphygmomanometer in supine position.
2. Blood samples were drawn from all the subjects with all the aseptic precautions, after overnight fasting and with staple food for two days. Serum total cholesterol (TC) and triglycerides (TG) were measured by an enzymatic method. Serum high density lipo-protein (HDL) levels were estimated by phosphotungstate precipitation, followed by enzymatic colorimetric method. Serum low density lipoprotein (LDL) Cholesterol and very low density lipo-protein (VLDL) Cholesterol levels were calculated by using Friedewald's formula.
3. Commercial kits were used for determination of fasting blood glucose.

**Statistical analysis**

Statistical analysis was performed using the SPSS software (version 16). Demographic and biochemical data were expressed as mean±S.D. Student 't' test used to test the significance, between cases and controls and P values of <0.05 were considered as statistically significant, P values of <0.01 was considered highly significant. Correlation coefficients (r values) were used to study the association of hsCRP with various risk factors.

## Results

The demographic data of the subjects is shown in Table 1.

**Table 1: Demographic data of the subjects**

| Variable | Cases (100) | Controls (100) |
|---|---|---|
| Age | 45.9±7.87 | 47.2±7.11 |
| Male:Female | 69:31 | 64:36 |
| SBP | 136.76±8.64 | 124.32±5.23* |
| DBP | 86.91±4.96 | 81.78±4.12 |
| Family history of diabetes (Yes/No) | 57/43 | 23/77* |
| Family history of CAD (Yes/No) | 42/58 | 19/81* |
| BMI | 28.4±4.1 | 22.6±2.7* |
| Waist circumference | 98.3±7.3 | 84.2±4.7* |
| Waist: Hip ratio | 1.5±0.6 | 0.8±0.2* |

*P <0.05= Significant

SBP = Systolic blood pressure, DBP = Diastolic blood pressure

BMI = Body mass index, CAD = coronary artery disease

The comparison of biochemical parameters among the study groups is shown in Table 2.

**Table 2: Comparison of biochemical parameters among the study groups**

| Parameter | Cases | Controls |
|---|---|---|
| Fasting blood glucose | 142.3±29.9 | 91.65±10.4* |
| hsCRP | 4.46±1.34 | 1.65±0.91* |
| TC | 209.16±44.12 | 159.76±27.87* |
| TGL | 156.24±49.56 | 106.97±31.68** |
| HDL | 34.43±6.43 | 48.65±4.29* |
| LDL | 130.95±29.24 | 92.54±24.92** |
| VLDL | 32.96±7.43 | 23.57±6.78* |

TC = Total Cholesterol, TGL = Triglycerides, HDL = High density Lipoprotein, LDL = Low density Lipoprotein, VLDL = Very low density Lipoprotein cholesterol

*P≤0.05 = Moderately significant

**P≤0.01 = Highly significant

The Pearson's correlation analysis of hsCRP and other cardiac risk factors is shown in Table 3.

**Table 3: Pearson's correlation analysis of hsCRP and other cardiac risk factors**

| Parameter | r value | P value |
|---|---|---|
| BMI | 0.511 | ≤0.01 |
| Waist circumference | 0.472 | ≤0.01 |
| Waist: Hip ratio | 0.510 | ≤0.01 |
| Blood glucose | 0.432 | ≤0.01 |
| TC | 0.592 | ≤0.01 |
| TGL | 0.639 | ≤0.01 |
| HDL | -0.63 | ≤0.01 |
| LDL | 0.464 | ≤0.01 |
| VLDL | 0.479 | ≤0.01 |

*P≤0.01 = Highly significant

TC = Total Cholesterol, TGL = Triglycerides, HDL = High density Lipoprotein, LDL = Low density Lipoprotein, VLDL = Very low density Lipoprotein cholesterol, BMI = Body mas index

Serum hsCRP shows significant positive correlation with BMI, waist circumference, waist: hip, total cholesterol, triglycerides and LDL and TC: and negative correlation with HDL.

The distribution of cases according to their serum concentration of hsCRP is shown in Table 4.

**Table 4: Distribution of cases according to their serum concentration of hsCRP**

| Concentration of serum hsCRP (mg/L) | No. of cases | Percentage |
|---|---|---|
| <1 | 1 | 1 |
| 1-3 | 22 | 22 |
| >3 | 77 | 77 |

Maximum cases had serum hsCRP levels of more than 3 mg/l.

## Discussion

The development of atheroma involves an interaction among factors like the endothelium, inflammatory cytokinines and various blood elements[15]. The inflammatory cell types typically found in the atheroma include monocyte-derived macrophages and lymphocytes. Macrophages present in the atheromas release cytokines and chemokines which in turn increase the plasma concentration of hsCRP which is the cause for inflammatory and procoagulant responses[16,17]. Several studies including Framingham Study have suggested that hsCRP as a risk prediction value for atherosclerosis[18-20].

The demographic data of the subjects is shown in Table 1. There was statistically significant difference in demographic parameters such as BMI, waist circumference, waist hip ratio and family history of CAD and T2DM ($P<0.05$) between cases and controls. The comparison of various biochemical parameters between the cases and controls is shown in Table 2. The triglyceride and LDL levels were higher in cases when compared to controls and the difference was statistically highly significant ($P<0.01$). The levels of FBS, total cholesterol, HDL, VLDL and hsCRP were higher in cases when compared to controls and the difference was statistically significant ($P<0.05$). Serum hsCRP shows strong positive association with serum total cholesterol, triglycerides and LDL, negative correlation with HDL level (Table 3). The distribution of cases according to their serum concentration of hsCRP is shown in Table 4. Maximum cases had serum hsCRP levels of more than 3 mg/l.

Other studies conducted on serum hsCRP levels in CAD with T2DM reported that raised levels of hsCRP and was associated with a 2.593 fold increased risk for CAD[21]. Rekha Bhagwat and colleagues studied serum hsCRP levels in patients of T2DM alone, T2DM with hypertension and T2 DM with myocardial infarction. They found levels of serum hsCRP raised 3 times higher in T2 DM and5 times higher in group of T2 DM with hypertension and 4 times more in T2DM with MI than control[22].

Other studies have also demonstrated strong independent positive relationship of serum hsCRP with measures of adiposity, dyslipedemia and hypertension in metabolic syndrome[23,24]. Some studies have demonstrated that hs-CRP levels were positively correlated with triglycerides and triglyceride-to-HDL ratio but not with the other lipid variables[25,26]. These differences might due to varies demographic characteristics of the case and controls. According to American Heart Association and the Centre for Disease Control and Prevention, hsCRP is an independent marker of CAD and may be useful as a prognostic indicator for recurrent events in patients with acute coronary disease[27-29].

Some authors opine that hsCRP concentration has continuous association not only with CAD but other conditions such as ischemic stroke, vascular mortality and several cancers. hsCRP to such a large discriminates poorly between persons with coronary disease and those without[30,31]. Therefore it repeat testing should be done after persistently elevated hsCRP (>10mg/l) for non-cardiovascular etiologies (Class IIa, Level of Evidence B)[32]. CAD patients who are not under treatment show a significant rise in hsCRP and after treatment a fall in hsCRP level has been observed[33]. Monitoring hsCRP levels at regular intervals will help as a guide to pharmacological and lifestyle intervention[33].

The prevalence of T2DM and related morbidity and mortality is continuously increasing at an alarming rate worldwide. DM is a well-established and one of the strongest risk factor for CAD. About 58 million people die from cardiovascular causes every year for which diabetes mellitus and hypertension are major risk factors[34]. A recent study concludes that estimation of hsCRP can be considered as a better predictor for cardiovascular disease than the serum LDL-cholesterol[35]. Meauring hsCRP levels will improve cardiovascular profile in patients with T2DM.

## Limitations of the study

The present study was done at a single centre and the sample size was small. Future studies should be multi-centric and include a large sample size. More prospective studies are needed to ascertain the role of serum hsCRP level as an independent risk factor.

## Conclusion

The present study shows that hsCRP levels are increased in CAD patients with T2DM, even with a relatively short disease duration of 2 years. There was a positive correlation of serum hsCRP with other cardiovascular risk factors like BMI, blood glucose and lipid parameters which was highly significant.

**Conflict of interest:** None

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