Original Research Article

Correlation between glycemic control, lipid profile and C-reactive protein in adults with type 2 diabetes mellitus done in a tertiary care hospital of Nellore, Andhra Pradesh, India

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ABSTRACT

Background: Diabetes mellitus refers to a group of common metabolic disorders that shares the phenotype of hyperglycemia. Complications of diabetes mellitus involve many organ systems only to play an important role in morbidity and mortality. Poor glycemic control is significantly associated with the development of macrovascular complications. Earlier studies have indicated that C-reactive protein (CRP) is an important risk factor for cardiovascular disease as evident from its higher levels in people with diabetes mellitus compared to those without. Not much is known whether CRP is related to the level of glycemic control. The purpose of this study is, to determine the relation between HbA1C, Lipid profile and CRP in individuals with type 2 diabetes mellitus.
Methods: Fifty patients with T2DM reporting to Narayana Medical College and Hospital were included in the study, in whom CRP levels were estimated by using commercially available kits and correlated with HbA1C and other risk factors of coronary artery disease. Follow-up was done on 20 patients who were not on statin therapy with repeat HbA1C and CRP.
Results: This study showed that both HbA1C and CRP levels had reduced significantly in follow-up patients after putting them on treatment (p<0.05). It was also found that lower the HbA1C, lower was the CRP. A positive correlation was found between HbA1C and CRP (p<0.05).
Conclusions: In this study of 50 patients with T2DM, it was found that CRP is significantly correlated with HbA1C level. A positive correlation was found between serum CRP and HbA1C in the initial group and in the follow-up patients, showing that CRP levels lowers with better glycemic control and correlates with dyslipidaemia profile.

Keywords: C-reactive protein, Glycemic control, Hemoglobin A1C, Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus describes a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] Type 2 diabetes mellitus is the most common form of diabetes. The prevalence of type 2 diabetes mellitus is increasing in all populations worldwide. It is a major risk factor for death and numerous nonfatal complications. According to the International diabetes federation (IDF) there are approximately 72 million people with diabetes mellitus in India at present and number is expected to rise more than 134 million by 2045.[2] Factors associated with an increase in mortality rates among those with diabetes mellitus include male gender, longer duration of diabetes, insulin use.[3] It is perceived that chronic low grade inflammation might potentially be a cause underlying the etiology and manifestations of T2DM.[4]

Endothelial dysfunction, subclinical inflammation, and impaired fibrinolysis might contribute to the progression of macrovascular as well as microvascular complications

Pickup and crook analyzed the role of the innate immune system from several studies and found that T2DM is associated with increased blood concentration of markers of acute-phase response including C-reactive protein and cortisol, the main cytokine mediator, interleukin 6.[5]

These cytokines promote the release of acute-phase proteins, which are atherosclerotic risk factors. Cytokines act on liver to produce characteristic dyslipidemia in type 2 diabetes mellitus. TNF-α is a major factor in causing insulin resistance, and long-term hypersecretion of cytokines may impair beta-cell insulin secretion.[6]

Patients with T2DM have a two to four-fold higher risk of cardiovascular events. The progression of coronary artery disease appears faster when compared with non-diabetic patients.[7] Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events.

C-reactive protein is the most reliable marker of inflammation.[8] CRP is produced by hepatocytes largely under the regulatory control of inflammatory cytokines, including IL-6, TNF-α.

Diabetes exposure can be characterized by the level of glycosylated hemoglobin (HbA1C) which is an accurate, precise measure of chronic glycemic levels and correlates well with risk of diabetic complications.

C-reactive protein and glycated hemoglobin (HbA1C) are established risk factors for the development of cardiovascular diseases.

The association of C-reactive protein with blood insulin and glucose may thus help to elucidate the role of inflammation in insulin resistance and development of cardiovascular disease.[9]

CRP levels were found to be related to insulin resistance, obesity, endothelial dysfunction in a cross-sectional study done by Yudkin et al.[10] CRP levels have also been associated with future development hypertension, and are known to play a direct role in atherosclerosis and thrombosis.[11,12]

CRP was also found to be predictive of future cardiovascular events in patients with the metabolic syndrome and to add prognostic information to the ATP-III definition of the metabolic syndrome.[13]

Evidence suggests that CRP might represent a novel biomarker of vascular risk, CRP evaluation might also merit consideration as a method to monitor

pharmacologic interventions used to prevent and treat cardiovascular disease.[14]

The main implication of these findings is that inflammation may not only be implicated in the development of diabetes, but also in ongoing levels of hyperglycemia once diabetes mellitus is established.[15]

CRP is a possible risk factor for the development of type 2 diabetes mellitus. The glycemic control is related to CRP, but the relationship has yet to be elucidated.

METHODS

This was a hospital-based prospective study comprised of 50 patients with type 2 diabetes mellitus reporting to Narayana Medical College and Hospital from January 2019 to January 2020.

Inclusion criteria

Inclusion criteria were; the patients above 30 years with fasting venous blood glucose value equal or more than 100 mg/dl and postprandial glucose >140 mg/dl were included in the study.

Exclusion criteria

Exclusion criteria were; patients on statins, thiazolidinediones (TZDs), and anti-inflammatory drugs that are known to reduce CRP levels excluded from the study. Patients with heart failure, acute febrile illness, renal, hepatic and malignant disorders, chronic illnesses, asymptomatic infections, type1diabetes, gestational diabetes, alcoholism, pancreatitis, other endocrinal disorders, those on diuretic therapy, amino-glycosides and smokers were also excluded from the study.

Informed consent was taken from the patients. Detailed history, physical examination, which includes height, weight, body mass index (kg/m^2), were measured. Resting pulse rate, blood pressure, body temperature was recorded. FBS and PPBS, CRP (immunoturbidimetric method), and HbA1C (ion exchange chromatography using HPLC) lipid profile samples were drawn at entry and at subsequent follow-up with a minimum gap of 3 months. Patients were put on OHA/insulin for control of blood sugar along with dietary control and exercise.

Statistical analysis

Statistical analysis was done using SPSS package and MS excel. Students 't' test and X^2 test was used. Pearson correlation and p values were calculated. P values <0.05 was considered to be significant.

RESULTS

Fifty T2DM cases were collected from both outpatients and inpatients visiting Narayana Medical College and

Hospital, for estimation of glycemic status, lipid profile and various parameters related to diabetes mellitus were studied, and they were correlated with CRP levels in this study. Cases were followed with a minimum gap of three months, and the parameters were repeated.

Table 1: CRP in males and females.

CRP	Number	Mean
Males	36	1.2514
Females	14	0.9954
Total	50	1.1759

In this study of 50 patients, 36 patients were males, and 14 were females with mean CRP levels of 1.19±1.25 and 1.12±0.99, respectively. There was no significant difference between male and female patients ($p>0.05$) (Table 1).

Table 2: Age distribution and CRP and HbA1C.

Age	Number	HbA1C	CRP
30-40	4	10.43	1.2
40-50	13	10.59	1.8
50-60	22	9.22	1.2
60-70	10	9.20	0.6
>70	1	8.00	0.0

In this study of 50 patients, HbA1C and CRP were correlated with age. Patients between age 30-40 years were 4 with mean HbA1C and CRP of 10.43 and 1.2, respectively. Patients between age 40-50 years were 13 with mean HbA1C and CRP of 10.59 and 1.8, respectively. Patients between age 50-60 years were 22 with mean HbA1C and CRP of 9.22 and 1.2, respectively. Patients between 60-70 years were 10 with mean HbA1C and CRP of 9.2 and 0.6, respectively. Patients above 70 was 1 with mean HbA1C and CRP of 8.0 and 0, respectively. There was no significance between different age groups in this study ($p>0.05$) (Table 2).

Table 3: CRP and BMI.

BMI	Number	CRP
<18	1	1.20
18-23	19	1.12
23-25	21	1.20
25-30	8	1.50
>30	1	1.20

In this study of 50 patients, patients with BMI <18 was 1 with mean CRP of 1.2, BMI between 18 -23 were 19 with mean CRP of 1.2, BMI between 23-25 were 21 with mean CRP of 1.20, BMI 25-30 were 8 with mean CRP of 1.5, with BMI>30 was 1 with mean CRP of 1.2. There was no significant correlation between CRP and BMI in this study (Table 3).

Table 4: FBS with HbA1C and CRP.

FBS	Number	HbA1C
<100	1	8.00
100-200	22	8.25
200-300	17	10.56
>300	10	11.33

In this study of 50 patients, FBS was correlated to HbA1C and CRP in different groups. Patients with FBS 0f 100 was 1 with HbA1C and CRP were 8.0 and 0.4, between 100-200 were 22, between 200-300 were 17, >300 were 10 had HbA1C of 8.25, 10.56, 11.33 and CRP of 0.6, 1.41, 2.04, respectively. FBS and HbA1C were directly correlated (Table 4).

Table 5: PPBS with HbA1C and CRP.

PPBS	Number	HbA1C	CRP
140-200	9	7.77	0.26
200-300	15	8.85	0.48
300-400	16	10.13	1.65
400-500	8	11.36	2.1
>500	2	13.40	2.4

In this study of 50 patients, PPBS was correlated to HbA1C and CRP. Patients with PPBS between 140-200 were 9, between 200-300 were 15, between 300-400 were 16, between 400-500 were 8, and >500 were 2 had HbA1C 7.77, 8.85, 10.13, 11.63, 13.40 and CRP of 0.26, 0.4, 1.6, 2.1, 2.4, respectively. PPBS showed a direct correlation with both HbA1C and CRP in this study (Table 5).

Table 6: CRP and total cholesterol.

LDL	Number	CRP
<60	7	1.71
60-80	14	0.86
80-100	9	1.70
100-120	13	0.65
120-140	1	1.20
>140	6	2.00

Table 7: CRP and LDL cholesterol.

LDL	Number	CRP
<60	7	1.71
60-80	14	0.86
80-100	9	1.70
100-120	13	0.65
120-140	1	1.20
>140	6	2.00

In this study of 50 patients, total cholesterol was compared to CRP. Number of patients with total cholesterol <100 was 1, between 100-200 were 39 between 200-300 were 10 with mean CRP of 0.0, 0.95,

2.13. There was a significant positive correlation between CRP and total cholesterol (p<0.05) (Table 6).

In this study of 50 patients, LDL cholesterol was compared with CRP. Patients with LDL cholesterol <60 were 7, between 60-80 were 14, between 80-100 were 9, between 100-120 were 13, between 120-140 was 1, >140 were 6 with mean CRP levels of 1.71, 0.86, 1.7, 0.65, 1.2, 2.0. There was no significant correlation between CRP and LDL cholesterol (p>0.05) (Table 7).

Table 8: CRP and HDL cholesterol.

HDL	Number	CRP
0-20	3	2.00
20-40	23	1.25
40-60	22	1.08
>60	2	1.02

Table 9: CRP and triglycerides.

Triglycerides	Number	CRP
100-200	25	0.86
200-300	17	0.98
300-400	4	1.80
400-500	1	2.40
>500	3	2.40

In this study of 50 patients, HDL cholesterol was compared with CRP. Patients with HDL cholesterol between 0-20 were 3, between 20-40 were 23, between 40-60 were 22 and HDL cholesterol >60 were 2 with mean CRP levels of 2.00, 1.25, 1.08, 1.02, respectively. There was a negative correlation between HDL cholesterol and CRP (Table 8).

In this study of 50 patients, triglyceride levels were compared with CRP. Patients with triglyceride levels between 100-200 were 25, between 200-300 were 17, between 300-400 were 4, between 400-500 was 1 and with levels >500 were 3 with mean CRP levels of 0.86, 0.98, 1.8, 2.4, 2.4, respectively. There was significant positive correlation between CRP and triglyceride levels (p<0.05) (Table 9).

Table 10: CRP and HbA1C.

HbA1C	Number	CRP
<7	9	0.40
7-9	14	0.51
9-10	11	1.41
>10	16	2.15

In this study of 50 patients, patients with HbA1C <7 were 9 between 7-9 were 14, between 9-10 were 11, HbA1C >10 were 16 with mean CRP of 0.4, 0.51, 1.41, 2.15, respectively. There was significant correlation between CRP and HbA1C (p<0.05) (Table 10).

The mean HbA1C of 50 patients initially was 9.56±1.88, and the mean CRP was 1.152±0.9984. A follow-up of 20 cases was done on patients who were not on statin therapy. On follow-up, the mean HbA1C of 20 cases had reduced to 7.39±1.31 (p<0.05) and mean CRP of those 20 patients reduced to 0.28±0.52 (p<0.05) (Table 11).

Table 11: HbA1C and CRP of 50 initial and 20 follow-up cases.

	HbA1c Initial (50)	HbA1c Follow-up (20)	CRP Initial (50)	CRP Follow-up (20)
Mean	9.6500	7.39	1.1520	0.28
SD	1.8816	1.31	0.9984	0.52
p value		0.0001		0.0004

A comparison was made between initial HbA1C, CRP levels with HbA1C, CRP levels of follow up cases among 20 cases. The initial mean HbA1C of 20 patients was 9.285±1.917, and the mean HbA1C on follow up was 7.39±1.31. The initial mean CRP of 20 patients was 0.78±0.975 and mean CRP on follow up was 0.28±0.52 (Table 12). HbA1C has significantly reduced in patients, after being put on treatment (p<0.05) and CRP levels also reduced (p<0.05).

Table 12: HbA1C and CRP of 20 initial and 20 follow-up cases.

	HbA1c Initial (20)	HbA1c Follow-up (20)	CRP Initial (20)	CRP Follow-up (20)
Mean	9.285	7.39	0.	0.28
SD	1.917	1.31	0.975	0.52
p value		0.0008		0.0421

DISCUSSION

Type 2 diabetes mellitus is a major risk factor for death, and numerous nonfatal complications. C-reactive protein, a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease and has been linked to an increased risk of thrombotic events. CRP levels are higher in people with diabetes compared to those without. Not much is known whether CRP in people with diabetes is related to the level of glycemic control.

This study has therefore gone into the various factors that are related both to CRP and T2DM

HbA1C and CRP

King and others in unadjusted analyses, demonstrated that a higher HbA1C is significantly associated with a higher CRP levels.[15] This study showed that a rise in

HbA1C, higher glycemic levels significantly correlated with increasing values of CRP.

Gender and CRP

Hu et al studied hazard ratios of T2DM for different levels of serum CRP and found that the association between CRP and risk of diabetes was stronger in women than men.[16] In this study, the females had higher CRP levels compared to males, but this difference was not statistically significant (p>0.05); this could be due to a smaller number of the female population in the study.

BMI and CRP

Williams et al showed that obesity was independently related to CRP, an increase in CRP is associated with an increase in BMI.[17] The findings in this study, contrary to others, suggest that CRP was not significantly associated with BMI and that inflammation as a potential mechanism in T2DM may be independent of obesity and leads to increase risk of cardiovascular events.

Total cholesterol and CRP

In this study, it was found that CRP levels significantly increase with an elevation of total cholesterol. Michelle and others stated that CRP levels were significantly related to 10-year Framingham coronary heart disease risk categories.[18]

LDL cholesterol and CRP

Steven et al found that the correlation between the reduction in LDL cholesterol and CRP levels was weak but significant in the group as a whole.[19] In this study, there was no significant correlation between CRP and LDL cholesterol.

HDL cholesterol and CRP

Takiko et al showed that CRP negatively correlated with HDL cholesterol which were similar to the findings observed in this study.[20]

Triglycerides and CRP

Ana et al found that hs-CRP levels were positively correlated with triglycerides.[21] This study also showed a positive correlation similar to other studies.

CONCLUSION

In this study of 50 diabetic patients, a positive correlation between CRP and HbA1C was found. Further, it was found that there exists a positive correlation between CRP and other risk factors of coronary artery disease like total cholesterol, triglycerides. At the same time, HDL showed a negative correlation with CRP. The findings regarding BMI in this study, contrary to others, suggest

CRP was not significantly associated with BMI, and inflammation as a potential mechanism in T2DM may be independent of obesity. Follow-up studies revealed that better glycaemic control resulted in the lowering of CRP, which was significant.

This study, therefore, reveals that CRP is an additional marker of better glycaemic control and also correlates with the dyslipidaemia profile seen in type 2 diabetes mellitus.

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