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Study of C Reactive Protein in Type 2 Diabetes and its Relation with Various Complications from Eastern India

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ABSTRACT

Diabetes is associated with a pro-inflammatory state and endothelial dysfunction. Various markers of inflammation like C Reactive Protein (CRP) are elevated significantly in diabetic population. The levels of these markers also correlate with the severity of diabetes and presence of various complications. We therefore undertook this study to find the CRP levels in type 2 diabetes and its relation with other parameters. We selected only newly diagnosed drug naïve type 2 diabetes patients. Besides clinical examination, various blood tests including lipid profile and HbA1C were done. CRP levels were done by immunoturbidimetric method and the levels were compared among different subsets of patients. We had total of 80 patients (M: F: 47:33). Dyslipidemia was the commonest complication (n=66) followed by nephropathy. Patients with cardiac and retinal complications had significantly higher levels of CRP. The presence of any 1 diabetic complication was associated with significantly higher CRP levels (1.8± 1.32 mg/dl vs. 0.49± 0.22; p <0.05 by t test). CRP levels showed significant positive correlation with serum triglyceride and HbA1C. CRP was associated with various diabetic complications. It was also related with the severity of glycemic status, as evidenced by HbA1C. Although our study was cross sectional, still, it showed correlation of CRP with many complications of diabetes and thus this can be an effective marker of clinical status in diabetes.

INTRODUCTION

Diabetes is a disease with chronic low grade inflammation. Different studies have shown that inflammatory markers in blood like C Reactive Protein (CRP), IL-6, PAI-1 and fibrinogen are elevated significantly in diabetic population (Kimberly *et al*, 2006). This inflammatory milieu promotes atherosclerosis and gives rise to other complications in diabetes. CRP is not only an associated factor with other established prognostic markers, but promising as an independent risk marker, especially for cardiovascular diseases in diabetes (Sattar *et al*, 2003). High CRP may be a marker of oxidative stress on the endothelium in diabetic patients. In fact, high levels of serum CRP and other inflammatory markers in a normal population is an indicator of future development of diabetes (Pradhan *et al*, 2001). The levels of CRP in blood correlate with the severity of diabetes and degree of control (King *et al*, 2003). In many studies, CRP has been found to vary with blood HbA1C levels, independent of other confounding variables (King *et al*, 2003). Blood levels of CRP also correlate with various complications if diabetes (Kang *et al*, 2005). High CRP levels are found to be associated with the presence of metabolic syndrome, a conglomeration of diabetes with hypertension and other metabolic derangements (Kang *et al*, 2005). A study from India has also found that blood hsCRP levels have strong association with obesity and development of Coronary artery disease in diabetics (Mohan *et al*, 2005). Of these novel inflammatory markers, CRP is the one easily available and can be done in daily clinical practice. The others are mostly of experimental and research value. We therefore undertook this study on CRP levels in type 2 diabetes in a sample Eastern Indian population. We wanted to find out whether the aforesaid data can be applied to our patients and how far CRP correlates with different complications.

AIMS AND OBJECTIVES

1. to study the CRP levels in patients newly diagnosed with type 2 diabetes
2. to analyze any correlation of CRP with various complications of diabetes

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MATERIALS AND METHODS

This was a hospital based cross sectional observational study, conducted from October 2010 to September 2011. Patients with type 2 diabetes, coming to either Medicine or Endocrinology outdoor Departments of Medical College Kolkata were included after proper screening. We included all newly diagnosed patients of Type 2 diabetes as diagnosed by standard ADA criteria (except the HbA1c criteria as it was not present when we started our study) (ADA guidelines, 2012). We included only newly diagnosed i.e. drug naïve diabetes cases as drugs like statins or metformin can alter CRP values. Patients of both sexes, between 18 to 60 years of age were included. Patients with malignancy, any infection, pregnancy, collagen vascular disease, current smoking history and/or history of intake of steroids were excluded.

All patients were first clinically examined, including direct Ophthalmoscopy, Body Mass Index (BMI) and Waist hip ratio (WHR). Then relevant tests were done from central laboratory of our college. The blood tests included complete blood count including ESR, blood glucose (both fasting and post prandial), HbA1C%, urea-creatinine, lipid profile and fasting Insulin and C peptide levels (the last 2 to diagnose type 2 diabetes). Blood CRP was done by immunoturbidimetry with a normal value of <0.8 mg/dl.

Other tests included urine for albumin creatinine ratio (ACR), Echocardiography with Doppler study, nerve conduction study (NCV) with quantitative sensory testing and electrocardiography (ECG). The tests were done by the same set of machines. Echocardiography and NCV were done by one examiner for all the patients. Patients were divided into 3 groups according to presenting HbA1C values (A: <6 %; B: 6-8%; C :> 8 %).

The data were first tabulated in Microsoft Excel worksheet. Then they were analyzed using online software like EpiInfo (ver. 3.5.1) and Graphpad. Continuous variables like HbA1C are presented as mean ± S.D. Discreet variables are expressed as absolute number and percentages. Correlation is calculated using Pearson Correlation Coefficient. Data like neuropathy or retinopathy are presented dichotomously (yes/no). Student's T Test is used to find significance of difference of the mean. P value<0.05 is considered significant.

RESULTS

We had a total of 80 patients in our study. Male female ratio was 47:33 with mean age of 47.4± 11.7 years (Table 1). BMI and WHR were comparable between the two sexes. The various study parameters of these patients are shown in table 1. From this table, it is found that blood CRP varied between 0.22 to 4.4 mg/dl. the male patients had significantly greater HbA1C at presentation ($p<0.05$ by students' T Test). There were no gender wise differences in the other parameters. Figure 1 shows the prevalence of different complications of diabetes in our patients. It is seen that dyslipidemia was the commonest (82.5%; n=66) followed by nephropathy, in the form of either overt proteinuria or microalbuminuria. Cardiac involvement, as evidenced by ECG and/or echocardiography and/or symptoms was present in 29 cases. However, coronary angiography was not done due to technical reasons.

Table 2 shows the mean CRP levels according to various complications. It is seen that presence of any complication was associated with significantly higher CRP values. Especially high CRP values are found in cases of cardiac involvement and retinopathy (2.43±1.58 and 2.23±1.45 mg/dl respectively). Patients with any 1 complication had higher CRP values as compared to patients with no diabetic complication (1.8± 1.32 mg/dl vs. 0.49± 0.22; $p<0.05$ by t test). Figure 2 shows the scatter diagram of correlation of CRP with serum triglyceride ($r=0.45$; $p=0.03$) and HbA1C values ($r=0.79$; $p<0.05$). The other study parameters did not show ant statistically significant correlation with CRP.

In table 3 the various parameters in the 3 groups of study subjects is shown. Since 'A' group had only 1 subject, it is not considered for statistical analysis. In between the other 2 groups, CRP levels were significantly high in C group ($p<0.001$ by student's T Test). All other complications of diabetes were also more prevalent in the C group (HbA1c>8%).

Table. 1: Table showing the general characteristics of our patients.

PARAMETER	RANGE	MEANS		
		Male (n=47)	Female (n=33)	All patients together (n=80)
Age (yrs)	22--75	49± 10.7	45.2± 12.8	47.4± 11.7
BMI(kg/m^2)	15.5—26.8	21.45± 3.21	21.39± 3.39	21.43± 3.26
WHR	0.62—1.5	0.92±0.19	0.82±0.15	0.88±0.18
FPG (mg/dl)	94—370	231.13± 72.49	210.27± 73.57	222.53±73.21
PPBG (mg/dl)	168—469	299.43± 80.93	257.79± 68.7	282.25±78.43
TG (mg/dl)	94—374	208.77± 66.12	193.73± 60.67	202.56± 63.97
HDL (mg/dl)	19—64	36.51± 9.45	45.97±9.59	40.41± 10.54
HbA1C (%)	5.8—15.3	9±2	7.91±1.27	8.55±1.82
CRP (mg/dl)	0.22-4.4	2±1.49	1.22±0.84	1.68±1.31

Table. 2: Table showing the CRP levels in mg/dL (mean±S.D.) in the diabetic patients with and without various complications .

Complication	Present	Absent	P value
Dyslipidemia	1.89±1.34	0.72±0.58	<0.001
Microalbuminuria	1.63±0.93	0.61±0.29	<0.001
Neuropathy	2.04±1.41	1.18±0.98	<0.05
Retinopathy	2.23±1.45	1.17±0.92	<0.001
Cardiac involvement	2.43±1.58	1.26±0.91	<0.05
Obesity	1.47±0.94	1.73±1.34	0.07

Table. 3: Table showing the different study parameters in different subsets according to glycemic status.

	A(n=1)	B (n=37)	C (n=42)	P value
CRP (mg/dl)	0.22	0.94±0.65	2.38±1.38	<0.001
Dyslipidemia	1 (100%)	24 (64.9%)	41 (97.6%)	0.0001
nephropathy	1 (100%)	23 (62.2%)	37 (88.1%)	0.007
Neuropathy	1 (100%)	17 (45.9%)	29 (69%)	0.037
Retinopathy	0	11 (29.7%)	28 (66.7%)	0.001
Cardiac involvement	0	9 (24.3%)	20 (47.6%)	0.032

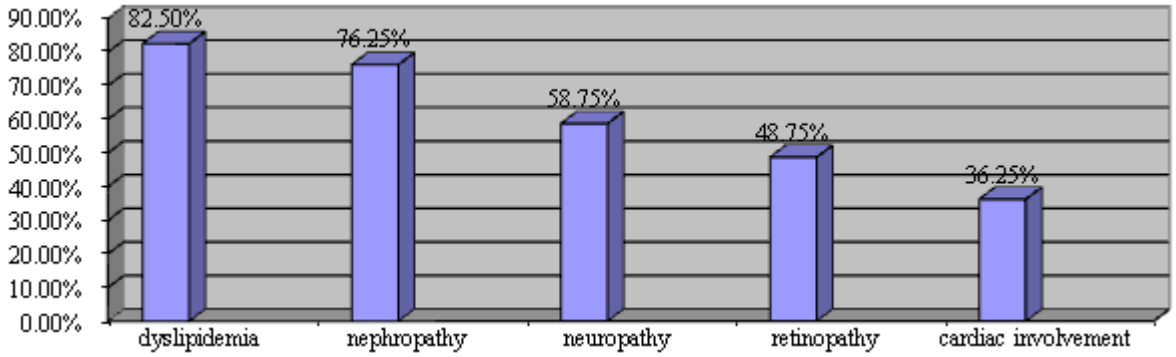

Fig. 1: Figure showing the prevalence of different complications in our patients.

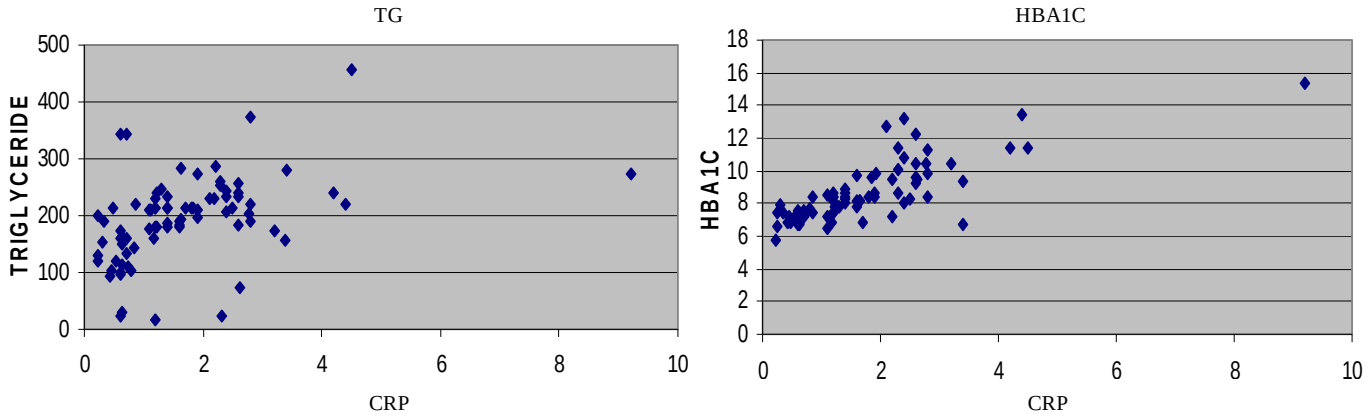

Fig. 2: figure showing the correlation of CRP values with triglyceride (A) and HbA1c (B).

DISCUSSION

In our hospital based observational study, we found high serum CRP values in diabetic subjects with various complications. CRP values showed significant correlation with HbA1C and serum triglyceride levels. CRP levels were especially high for cardiac involvement and retinopathy.

CRP is now established as an important risk marker in diabetes. It is associated with the degree of glycemic control and also the different complications of diabetes (Mohan *et al,* 2005). In a study from USA, they have found significant association of CRP and fibrinogen with various diabetic complications (Streja *et al,* 2003). In that study, they also found strong correlation between CRP and fibrinogen. We could not do serum fibrinogen assay due to cost factor. CRP and other inflammatory markers like PAI-1 or IL 6 are markers of endothelial dysfunction and monocyte activation (King, 2008). This inflammatory milieu promotes deregulated lipid metabolism to generate various toxic metabolites which leads to insulin resistance (King, 2008). This also leads to accelerated atherosclerosis and the microvascualr complications (King, 2008). Diabetes is often described as a state of hypercytokinemia along with chronic low grade inflammation and activation of innate immunity (Pickup, 2004). Ours was a cross sectional study that showed increased CRP levels in various complications. In a prospective study from Boston, Schulze et al have shown that increased CRP is indeed associated with higher risk of cardiovascular events (Schulze *et al,* 2004). For the highest quartile of CRP the relative risk was 2.62 and this was after adjusting for factors like smoking, cholesterol and BMI (Schulze *et al,* 2004). In our study, we found significant correlation of CRP levels with serum triglyceride and HbA1C (figure 2). In other studies, similar associations have been recorded (Ladeia *et al,* 2006). In these studies, correlations have been found with both triglycerides (TG) and TG to HDL ratio (Ladeia *et al,* 2006). This association may be due to increased formation of foam cells by increased lipid levels and the subsequent endothelial derangement. However, the association of CRP with serum lipids is controversial. PM Ridker has stated that CRP levels and lipid levels do not always correlate (Ridker, 2003). Thus, CRP levels

cannot supplant lipid level measurement. He proposes inclusion of both these parameters in cardiovascular (CV) risk prediction. Infact, CRP can predict CV risk even in patients with low LDL. Since CRP levels are stable in blood for a long time and not affected by factors like food intake, it is an attractive option for physicians (Ridker, 2003). However, the correlation of CRP with HbA1C is less controversial. It has been shown in different studies that HbA1C correlates positively with CRP levels (Bahceci *et al*, 2005). In a study from Turkey, they have found positive correlation of hsCRP with blood HbA1C, fasting insulin and HOMA-IR (Bahceci *et al*, 2005). King DE et al have also shown that with increasing HbA1C, the CRP levels tend to be higher. In their statistical model, HbA1C>9% was a predictor of high CRP. However, a study from Iran has shown that CRP levels may be high in diabetes even with low HbA1C (Bahrami *et al*, 2007). This proves that only glycemic status does not determine the CRP level in diabetes.

Studies regarding CRP levels in diabetes are scanty from India. However, the few studies that have been done have confirmed this western data regarding CRP for Indian subjects also (Mohan *et al*, 2005). Interestingly, CRP levels are also influenced by environmental factors. A study on Indian community in Britain has depicted higher CRP levels compared to their countrymen staying back (Patel *et al*, 2006). This was also associated with more prevalence of obesity and dietary energy intake in the emigrant Indians of UK (Patel *et al*, 2006). Another study has shown that diabetic Indians have higher mean CRP values that Europeans living in the same environment (Chambers *et al*, 2001). This may be due to increased risk of obesity in Indians and hence the higher chance of adipose tissue cytokinemia.

Our study is limited by small number of subjects, the cross sectional nature of the study, lack of measurement of other markers like fibrinogen and lack of measurement of hsCRP. Still, this study has shown that CRP levels correlate strongly with different diabetic complications. A larger prospective multi center study can actually find the role of CRP in Indian patients and its inclusion in daily clinical practice as a cost effective risk marker.

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