

# Correlation of Inflammatory Markers and Dyslipidemia with Carotid Intima-Media Thickness in Type 2 Diabetic Subjects

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**Objective:** *C-reactive protein (CRP) and ESR are well-known inflammatory markers. Dyslipidemia are potent risk factors for cardiovascular disease, and carotid intima-medial thickness (CIMT) denotes subclinical atherosclerosis. Our aim was to assess the correlation between them in diabetic subjects.*

**Materials and Methods:** *In this prospective observational study, we selected 78 subjects with type 2 diabetes and dyslipidaemia. The study period was 6 months. Carotid intima-medial thickness of the subjects was measured. The values correlated with the risk markers.*

**Results:** *Mean age of the subjects was 55.1 year with a standard deviation of 12.1. Positive CRP (>6mg/L) was found in 56.41% patients and abnormal CIMT in 46.15%. Mean CIMT was 0.93 with a standard deviation of 0.3. CRP and ESR value positively correlated with CIMT where, p value was significant (<0.05). Subsequently high triglyceride and LDL values was found to be associated mostly with abnormal CIMT with significant correlation with a coefficient of 0.45 and 0.59 respectively with significant p value (<0.05).*

**Conclusion:** *CRP and ESR are well-known markers of inflammation and can also be used as indicators of atherosclerosis as noted by our study. It also establishes that, dyslipidaemia underlies significant atherosclerosis.*

## Introduction

Vascular complications due to atherosclerosis are a major cause of morbidity and mortality in type 2 diabetic patients, more so in India where the number of diabetics is approaching very high levels.<sup>1</sup> Atherosclerosis which is the major risk factor is accelerated in diabetes mellitus. It has

been suggested by the atherosclerotic risk project that the atherosclerotic process occurs at the same time in carotid, cerebral and coronary arteries.<sup>2</sup> The intima media thickness (IMT) of the carotid artery (CIMT) can be measured with a high degree of accuracy and reproducibility by B mode ultrasonography which provides a reliable and valid

estimate of the arterial wall thickness.<sup>3</sup> Of the various non-invasive imaging methods available, arterial intima media thickness measurement obtained by B mode ultrasound is currently recommended by the American Heart Association as being relatively safe, non-invasive and inexpensive method of assessing sub clinical atherosclerosis,<sup>4</sup> and being an independent predictor of atherosclerotic events. Reasonable evidence shows low-grade systemic inflammation plays a significant role in the pathobiology of metabolic syndrome and type 2 diabetes mellitus (T2DM). C - reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are the well- known markers for tissue inflammation. High CRP positively correlated in patients with coronary artery disease (CAD).<sup>5</sup> Small increases in CRP predict the likelihood of developing cardiovascular events both in diabetic and nondiabetic populations. In addition, in apparently healthy subjects, increased levels of CRP predict the risk of developing type 2 diabetes. There is some evidence that CRP, besides its predictive role in determining cardiovascular risk, may represent an active participant in atherogenesis. CRP is expressed in human atherosclerotic plaques and both vascular cells and monocytes/macrophages appear to represent a significant source of CRP in the inflammatory vessel wall. By activating the main cell types present in the atherosclerotic lesions, CRP generated within the coronary plaques, may contribute to the development and progression of atherosclerosis. Data on vascular CRP regulation are scarce. Current evidence suggests that inflammatory and metabolic factors associated with diabetes, such as high glucose, adipokines, modified lipoproteins and free fatty acids ,may trigger CRP production by endothelial cells, smooth muscle cells and monocytes/macrophages. These data suggest that local CRP concentration in diabetic atherosclerotic plaques could be higher than in nondiabetic ones. Given the possible correlation between local CRP production and the degree of severity of coronary artery disease or the nature of the lesion, such alteration may contribute to the accelerated development of vascular disease in patients with type 2 diabetes.

### Aims and Objectives

- To assess the correlation of raised value of inflammatory markers and dyslipidemia with CIMT as cardiovascular associates.
- To identify subjects with subclinical atherosclerotic changes having raised inflammatory markers of coronary artery disease.

### Materials and Methods

The study was carried out in the department of General medicine, Vivekananda Institute of Medical Sciences, Kolkata for a period of 1 year starting from 1st July, 2011. For the study, we selected 78 subjects with type 2 Diabetes and dyslipidaemia.

Patients with previously diagnosed type 2 Diabetes mellitus were randomly selected from among the inpatients of the department. The criteria used for the diagnosis of diabetes was fasting plasma glucose  $\geq 126\text{mg\%}$  or a 2 hour postprandial/OGTT plasma glucose  $\geq 200\text{mg\%}$  or symptoms of hyperglycemia and casual plasma glucose  $\geq 200\text{mg\%}$ .

Type 2 diabetes mellitus was diagnosed on clinical grounds based on the age of presentation, family history of diabetes, external markers of insulin resistance, absence of ketoacidosis, insulin requirements and after ruling out secondary causes. Those with type 1 Diabetes Mellitus, secondary diabetes, urinary tract infection or recent intercurrent illness were excluded from the study.

All patients studied underwent:

- A) In this prospective observational study we selected 78 subjects with Type 2 Diabetes and Dyslipidaemia.
- B) Detailed assessment of history with stress on risk factors and atherosclerotic events.
- C) Thorough general physical examination including anthropometric measurements and system examination for atherosclerotic vascular disease.
- D) Carotid artery intima media thickness was measured by B mode ultrasound having an electric transducer with a mid-frequency of 7.5 MHz. Scans were performed on both the right and left extracranial carotid arteries by trained personnel. The IMT values were measured in six well defined arterial segments- near wall and far wall of distal 6mm of common carotid, the carotid bulb and proximal 6mm of internal carotid artery of both sides. The final IMT considered was the average of the IMT values at the 12 sites examined. Since IMT is considered as a candidate marker of cardiovascular risk, its normal value is interpreted in terms of increased risk rather than in terms of statistic distribution within a population. An upper limit of 0.9mm was chosen for the present study based on epidemiological data currently available.
- E) Routine and special investigations including blood sugar, lipid profile, ECG, urine micro albumin-

creatinine ratio and glycosylated hemoglobin were done. The fasting venous plasma glucose (FBS) and fasting lipid profile (FLP) were obtained after 12 hours of overnight fasting using the Olympus AU-400 Auto Analyzer and the 2 hour post prandial venous plasma glucose (PPBS) estimation was also done. The value of LDL was calculated using Freidewald's formula when the triglyceride was less than 400mg/dl and direct estimation was done when the triglyceride was more than 400mg/dl. Dyslipidemia was defined based on National cholesterol education programme ATP 111 guidelines and the normal cut off values were taken as total cholesterol less than 200mg/dl; LDL less than 100mg/dl; triglyceride less than 150mg/dl and values outside these limits were considered as abnormal. For HDL cholesterol a value less than 40mg/dl was considered low and more than or equal to 60mg/dl was considered high as per the ATP111 guidelines.

F) Qualitative variables were tested using Chi square test and the p values were calculated between

the groups having CIMT less than and more than 0.9 mm. p value of  $<0.05$  was considered statistically significant. Averages were expressed between groups as mean  $\pm$  standard deviation or as percentage.

## Results

A total of 78 patients were studied, of which 68% were males. The bias in the sex was in concordance with the admission statistics of the hospital. Only 20% of the study population had prior hypertension and all had blood pressure in the normal range during the course of study. 17.95% patients were within the age range of 30-45 years, 58.97% patients were within 45-60, 15.38% were within 61-75, 7.69% were within 76-95 years of age group (Fig 1).

Different parameters are shown in Table 1.

AGE	FREQUENCY	PERCENT
30-45	14	17.95
45-60	46	58.97
61-75	12	15.38
76-90	6	7.69

Figure 1. Age Distribution

Table 1. Mean values of different parameters

Variable	N	Mean	Std. Dev.	Minimum	Maximum
AGE	78	56.58	10.08	35	91
DURATION	78	8.38	5.76	1	28
BMI	78	26.04	3.71	20.1	37
WHR	78	0.88	0.17	0.66	1.34
HbA1C	78	8.77	2.49	5.5	19.1
FBS	78	172.76	60.34	53	392
PPBS	78	280.23	94.76	106	532
URICACID	78	6.30	1.51	3.4	11.7
SGPT	78	33.56	13.57	17	96
SGOT	78	36.15	17.88	17	123
U	78	42.58	28.06	14	183
Cr	78	1.55	1.10	0.5	6.7
UACR	78	91.82	92.69	6.8	594.6
Tg	78	191.92	91.39	74	565
TCh	78	215.13	55.00	93	363
LDL	78	139.15	47.61	33	286
HDL	78	45.28	24.92	20	235
CRP	78	8.82	5.12	3.8	28
ESR	78	32.19	11.83	12	70
TC	78	7012.31	2086.35	3200	12930

### Comprehensive chart showing mean values of different parameters (Chart 1)

Mean age for this study is 56.58 years with a mean HbA1c of 8.77%. Mean CRP value of 8.82 with a mean ESR of 32.19 (1<sub>ST</sub> hour). Mean Total cholesterol is 215.13 mg/dl with a mean LDL of 139.15 mg/dl.

56.41% cases showed significantly raised CRP value and 46.15% showed abnormal CIMT with a strong correlation ( $r=0.513$ ,  $p=0.001$ ) (Fig 2).

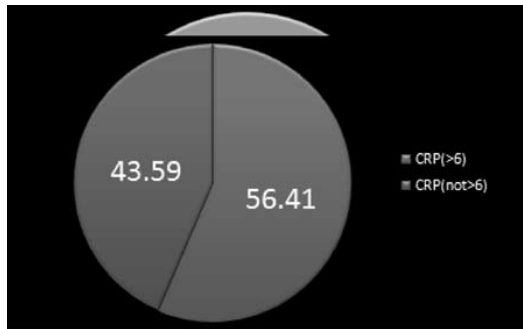


Figure 2. Distribution of Patients with CRP More/Less than 6

Among the cases with CRP positivity, 35.90% patients showed abnormal CIMT, whereas most of the patients with low CRP value (33.33%) showed CIMT below the cut-off (Fig 3).

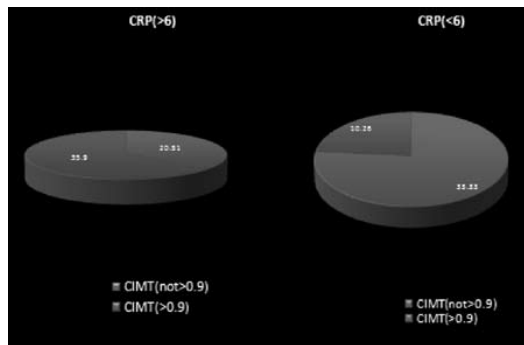


Figure 3. CIMT with CRP

Analysis Variable : CIMT					
SEX	N	Mean	Std.Dev.	Minimum	Maximum
F	36	0.91	0.21	0.4	1.5
M	42	0.98	0.22	0.4	1.7

CIMT according to SEX distribution. (Chart 2)

Maximum value of CIMT for male and female are 1.7 and 1.5 mm respectively with a standard deviation of 0.4 for both.

41.03% cases with raised ESR showed abnormal CIMT whereas only 5.13% cases with low ESR showed abnormal CIMT ( $r=0.34$ ,  $p=0.021$ ) (Fig 4).

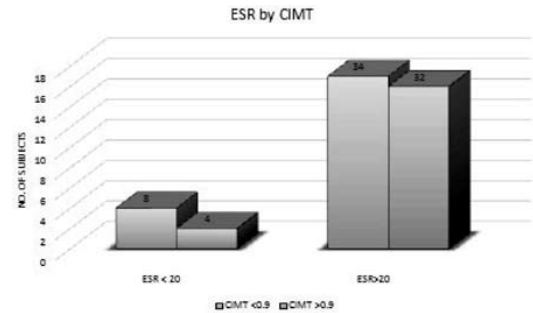


Figure 4. Correlation of ESR with CIMT

Regarding lipid profile, triglyceride (TG), LDL and Total cholesterol (TCL) all correlated with abnormal CIMT values. For TG- $r=0.46$ ,  $p=0.001$ , For LDL- $r=0.59$ ,  $p=0.002$  For TCL- $r=0.37$ ,  $p=0.019$ , HDL values showed strong negative correlation without statistical significance( $r=-0.212$ ,  $p=0.181$ ) (Fig 5).

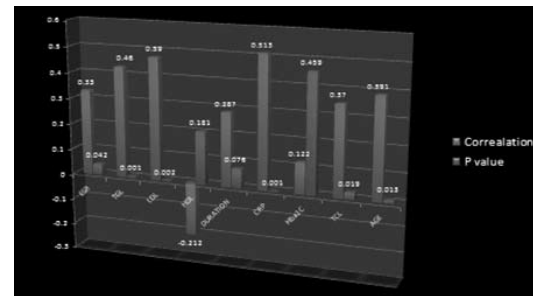


Figure 5. Correlation-coefficient with CIMT

### Discussion

Measurement of carotid artery intima media thickness by non-invasive B mode ultrasonography can detect atherosclerosis at an early preclinical stage and help in the diagnosis of asymptomatic cardiovascular disease<sup>6</sup> and whether increased CIMT is associated with increased risk of atherosclerotic events is of considerable interest. Gayathri R *et al*<sup>7</sup> studied, carotid intima medial thickness in relation with atherosclerotic risk factors in patients with type 2 diabetes mellitus and established vascular complications due to atherosclerosis are major causes of morbidity and mortality in type 2 diabetic patients, more so in India where number of diabetic patients are approaching very high level .

The mean value of carotid artery intima media thickness in this study was 0.93mm. Similar mean value of 0.95 mm was reported earlier in a Chennai based study<sup>8</sup>. Females had a relatively lower value of CIMT as compared to males possibly due to the protective effect of female

hormones and/or male gender being at a higher risk of atherosclerosis. In our series, mean value of CIMT for male is 0.98mm whereas for female it is 0.91mm. Similar results have been reported by Kram L *et al*<sup>9</sup> who also observed significant higher IMT in men than women. In their study, no correlation was observed between age and intima media thickness.

The risk factors for increased carotid artery intima media thickness in diabetic patients seem to be different in various studies. Geroulakos *et al*<sup>10</sup> found that none of the potential risk factors (age, sex, body mass index, and smoking, duration of diabetes, systolic or diastolic blood pressure, and lipid profile and glycosylated hemoglobin) were associated with increased IMT in type 2 diabetics in their study. On the other hand, Temelkova-Kurktschiev *et al*<sup>11</sup> noticed increased intima media thickness in diabetic patients with hyperlipidaemia. Mohan Rema *et al*<sup>12</sup> observed a positive correlation between duration of diabetes and increased intima media thickness. In our study, serum triglyceride, total cholesterol and serum LDL values also positively correlated with raised CIMT with statistical significance. Nishnianidze *et al*<sup>13</sup> observed high total cholesterol, low HDL and high triglyceride levels in their study population, but they failed to show any significant correlation between coronary artery disease severity and lipid profile indices. In our study, on multiple logistic regression analysis HDL level demonstrated a significant negative coefficient (- 0.212) on development of raised CIMT. Normal values of age specific thickness level of CIMT is yet to be standardized in South East Asian population. Definitely CIMT will vary depending on different factors like age, sex, ethnicity, associated diseases like DM, dyslipidaemia, whether patients were taking lipid lowering drugs, oral hypoglycaemic agents or insulin etc. Different studies reported from India showing different values of CIMT and its association with atherosclerotic risk markers<sup>14, 15</sup>.

## Conclusion

Today complications due to atherosclerosis in diabetes are not only the most prevalent, but are the most challenging issue in this era of diabetic management. There has been a steady rise in the prevalence of atherosclerotic events among diabetics, and the problem is more marked in those with type 2 diabetes mellitus. Assessment of carotid artery intima media thickness by B mode ultrasound is a relatively inexpensive means of measuring subclinical atherosclerosis. Age and dyslipidaemia did show association with carotid artery intima media thickness. CRP and ESR are the standard markers of inflammation can also be used as

indicators of atherosclerosis as noted by this study.

Thus the predictive value of this non-invasive investigation, may alert the clinician to the risk of events early enough to intervene, in order to prevent major cardiovascular or cerebrovascular catastrophes. Moreover lifestyle measures and good lipid and glycaemic control can pave the way for drastically reducing such catastrophes. This may make a huge difference in the lives of diabetics, saving them from being between death, dependence or severe restriction in the quality of life, enforced by such events.

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