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Original Research Article.

Study of Carotid Intima Media Thickness (CIMT) In Type 2 Diabetes Mellitus and Its Correlation with Glycaemic Control and Inflammatory Marker HsCRP

Ashok Kumar[1], Abhishek Rathore[2*], Anupam Kumar Singh[3]

[1]Professor & Head, Dept. of Medicine, Santosh Medical College & Hospital, Ghaziabad, Uttar Pradesh, India.
[2]Senior Resident, Dept. of Medicine, IGESI Hospital, Jhilmil, New Delhi, India.
[3]Assistant Professor, Dept. of Medicine, Santosh Medical College & Hospital, Ghaziabad, Uttar Pradesh, India.

ABSTRACT

Background: Carotid Intima Media Thickness (CIMT) and CRP (C Reactive Protein) are have been used for measuring Atherosclerotic Risk in Diabetics. However there is paucity of data regarding their importance in Statin Naïve Diabetics.

Aim: To study Correlation of CIMT with glycaemic control and hsCRP in Statin Naïve Diabetics.

Materials and Methods: 80 Cases (Patient suffering from type 2 Diabetes Mellitus) and 20 controls (non- diabetic health patients) presenting in outpatient department of a tertiary Hospital were included in this observational cross sectional observational study. Complete Blood Count, urine Routine and Microscopy, urine for microalbuminuria, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), glycated haemoglobin (HbA1C), lipid profile, renal function test, hs-CRP and CIMT were evaluated in each individual. Independent samples T-test was used to compare CIMT and hs-CRP both cases and controls. Test of proportion and chi-square test was used for association between categorical variables. Spearman's method was used to assess correlation between hsCRP and CIMT.

Results: 80 cases (Statin naïve and Non-smoker Diabetic patients and 20 healthy controls were included in this study. Average CIMT in cases was significantly higher in Diabetic cases than Control (0.66 $\pm$ 0.14 vs 0.56±0.05, difference = 0.10 mm, 95% C.I. (0.1 - 0.17), p < 0.0001). HsCRP was significantly correlated with average CIMT in Diabetic cases. (r=0.512, 95% C.I. 0.33-0.658, p<0.0001). Fasting Blood Sugar was correlated with average CIMT in Diabetic cases. (r=0.234, 95% C.I. 0.015-0.432, p=0.0366). Post Prandial Blood Sugar was also correlated with average CIMT (r=0.300, 95% C.I. 0.086-0.488, p=0.00677).

Conclusion: Cardiovascular risk factors like glycaemic control and inflammatory markers like hsCRP are significantly associated with CIMT even in non-smoking and statin naïve Diabetics.

Keywords: Carotid Intima Media Thickness (CIMT), Diabetes Mellitus, Glycaemic Control, HsCRP.

***Correspondence to:**

Dr. Abhishek Rathore,
Senior Resident,
Department of Medicine,
IGESI Hospital, Jhilmil, New Delhi, India.

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INTRODUCTION

Diabetes is a metabolic disease whose incidence and prevalence has significantly increased in recent decades, mainly because of an increase in type 2 diabetes, which represents almost 90% of all cases of diabetes. There will be 300 million diabetic patients by 2025 as estimated by WHO (5.4% of the world population).[1] It is an independent risk factor for atherosclerosis and resulting cardiovascular complications.[2]

Carotid intima-media thickness (IMT) is related to cardiovascular risk factors and diseases, and its measurement by ultrasound makes it possible to detect thickening in the initial phases of atherosclerosis.[3,4] For every 0.1-mm increase in carotid IMT, the relative risk of ischemic heart disease increases by 15% and that of cerebrovascular disease by 18%.[5]

In type 2 diabetes mellitus (DM2) patients, the CIMT is 0.13 mm greater than in the controls. This implies an increase in age of 10 years, a circumstance that is related to a 40% higher cardiovascular risk.[6] Major determinants of increased IMT among diabetic patients include obesity, dyslipidaemia and hyperinsulinemia, which constitute the cardinal features of insulin resistance syndrome.[7]

In healthy middle-aged adults, CIMT values between 0.6 and 0.7 mm have been considered normal, while CIMT of 1 mm or more has been associated with significant increased absolute risk of CHD.[8]

In healthy Indian adults, the average and maximum CIMT values reported were 0.67 and 0.70 mm, respectively. High sensitivity

C- reactive protein (hsCRP) is a biomarker of the low-grade chronic inflammation associated with atherosclerosis. It is a strong independent predictor of cardiovascular risk. It has a role at different phases of atherosclerosis.[9] Adults with hsCRP above 0.3 mg/dL have twice the risk of atherosclerosis compared to those with low levels (< 0.1 mg/dL).[10,11]

HsCRP and CIMT together could help in the diagnosis of CAD, and for predicting coronary events. We support the consensual statements for the assessment of CIMT and hsCRP in individuals who are traditionally considered to be at moderate cardiovascular risk.[12]

However, most of the previous studies including aspirin, statins, ARBs/ ACE inhibitors, while we are looking for changes in CIMT in DM2 patients who are not on these drugs as they are modifier of CIMT. This will help us evaluating independent effect of hsCRP, glycaemic control, dyslipidaemia and anthropometric parameters on structural endothelial dysfunction.

We hypothesized that HsCRP, glycaemic status, lipid abnormality and anthropometric parameters would be associated with carotid atherosclerosis in studied diabetic patients.

AIMS AND OBJECTIVES

- Study of carotid intima media thickness (CIMT) in diabetic population.
- Correlation of CIMT with glycaemic control.
- Correlation of CIMT with inflammatory marker HsCRP.

MATERIALS AND METHODS

80 Cases (Patient suffering from type 2 Diabetes Mellitus) and 20 controls (non- diabetic health patients) were included in this observational cross sectional observational study.

Inclusion Criteria

Cases: Patients with pre-existing / newly diagnosed DMT2

Controls: Patients who are age and sex matched health patients with case group in all variables.

Exclusion Criteria

- Patients with previous history of cardiovascular diseases, peripheral vascular diseases, hypertension or Cerebrovascular events.
- Smokers.
- Patients with renal disease.
- Patients on drugs that might modify the CIMT (statins, aspirin, ACE inhibitors and Angiotensin Receptor Blockers)

Complete general medical and physical examination including history of diabetes, hypertension, smoking and anthropometry.

Laboratory Investigations

CBC, urine R and M, urine for microalbuminuria, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), glycated haemoglobin (HbA1C), lipid profile, renal function test and hs-CRP.

B-mode ultrasound examination done by radiologist with a linear array transducer of 5–10 MHz on the selected subjects in supine position with the head slightly extended and turned to the opposite direction of the CCA being studied. Both sides imaged at three places, i.e. at the proximal part, mid part and distal. Three-maximum right and three maximum left far wall measurements were calculated for each CCA.[13]

In our study, all the six right and left wall values measured, and the average CIMT values were noted and correlated with HsCRP, HBa1c, biochemical markers and anthropometric measurements.

Statistical Analysis

Independent samples T-test was used to compare the numeric variables with parametric distribution in both cases and controls. Test of proportion and chi-square test was used for association between categorical variables. Spearman's method was used to assess correlation between numeric variables.

Table 1: Demographic and biochemical profiles of both groups.

Variables	Case (n=80) (Mean ±SD)	Control (n=20) (Mean ±SD)	P value
Age (Years)	49.11±9.63	53.70±8.61	0.055
Height (m)	1.63±0.08	1.55±.04	<0.001
Weight (kg)	74.85±9.01	68.10±4.06	0.002
BMI (kg/m^2)	28.18±2.97	28.23±1.81	0.949
Waist Circumference (cm)	89.14±5.84	86.05±5.55	0.035
Hip Circumference (cm)	99.61±6.08	100.75±7.79	0.482
Waist Hip Ratio	0.90±0.04	0.86±0.04	<0.001
Total cholesterol (mg/dl)	199.51±30.41	198.40±11.18	0.873
Triglyceride (mg/dl)	147.66±34.71	118.05±8.37	<0.001
FBS (mg/dl)	176.20±57.69	103.40±5.55	<0.001
PPBS (mg/dl)	229.08±80.22	122.15±6.00	<0.001
HbA1c (%)	7.88±1.85	5.76±0.36	<0.001
Urea (mg/dl)	26.80±5.05	29.80±3.44	0.014
Creatinine (mg/dl)	0.96±0.13	0.88±0.09	0.022

Table 2: Carotid Atherosclerosis

CIMT findings	Case (n=80) (Mean ±SD)	Control (n=20) (Mean ±SD)	P value
Right CIMT (mm)	0.65±0.11	0.55±0.06	<0.001
Left CIMT (mm)	0.73±0.61	0.54±0.05	<0.001
Average CIMT (mm)	0.66±0.14	0.56±0.05	<0.0001

RESULTS

Our Diabetic cohort was middle aged, overweight on an average with moderate hyperglycaemia (HbA1c 7.88±1.85). Twenty Five percent diabetics had abnormal CIMT while 30% had significantly high CRP (>3 mg/dl). All of them were non-smokers and statin-naïve.

Average CIMT in cases was significantly higher in Diabetic cases than Control (0.66 ± 0.14 vs 0.56±0.05, difference = 0.10mm 95% C.I. (0.1-0.17), p<0.0001)

Both Right and left CIMT were correlated.

25% of the Diabetics had abnormal CIMT while none of the control group had abnormal CIMT.

Correlation between Glycaemic Control and CIMT

Fasting Blood Sugar was correlated with average CIMT in Diabetic cases. (r=0.234, 95% C.I. 0.015-0.432, p=0.0366). Post Prandial Blood Sugar was also correlated with average CIMT (r=0.300, 95% C.I. 0.086-0.488, p=0.00677). There was positive correlation between Hba1c and CIMT in cases and controls, but it was not significant. (r=0.209, 95% C.I = -0.110-0.410, p=0.062).

Correlation between Anthropometric parameters and CIMT

There was positive but non-significant correlation between waist hip ratio and CIMT in cases, but it was not significant. (r=0.186, 95%C. I =-0.03-0.39, p=0.09).

Body mass Index was strongly correlated with average CIMT in Diabetic cases. (r=0.492, 95% C.I. 0.30-0.64, p<0.0001).

Correlation between hs-CRP level and CIMT

HsCRP was significantly correlated with average CIMT in Diabetic cases. (r=0.512, 95% C.I. 0.33-0.658, p<0.0001)

Correlation between Dyslipidaemia and CIMT

There was significant association between Triglycerides and average CIMT in our cohort (cases and controls). (r=0.194, 95% C.I. 0.001-0.376, p=0.05).

There was weak non-significant association between LDL and average CIMT in cases. (r=0.133, 95% C.I. -0.08-0.343, p=0.05).

Figure 1: Scatter plot depicting relationship between HbA1c and average CIMT in diabetic and control subgroup.

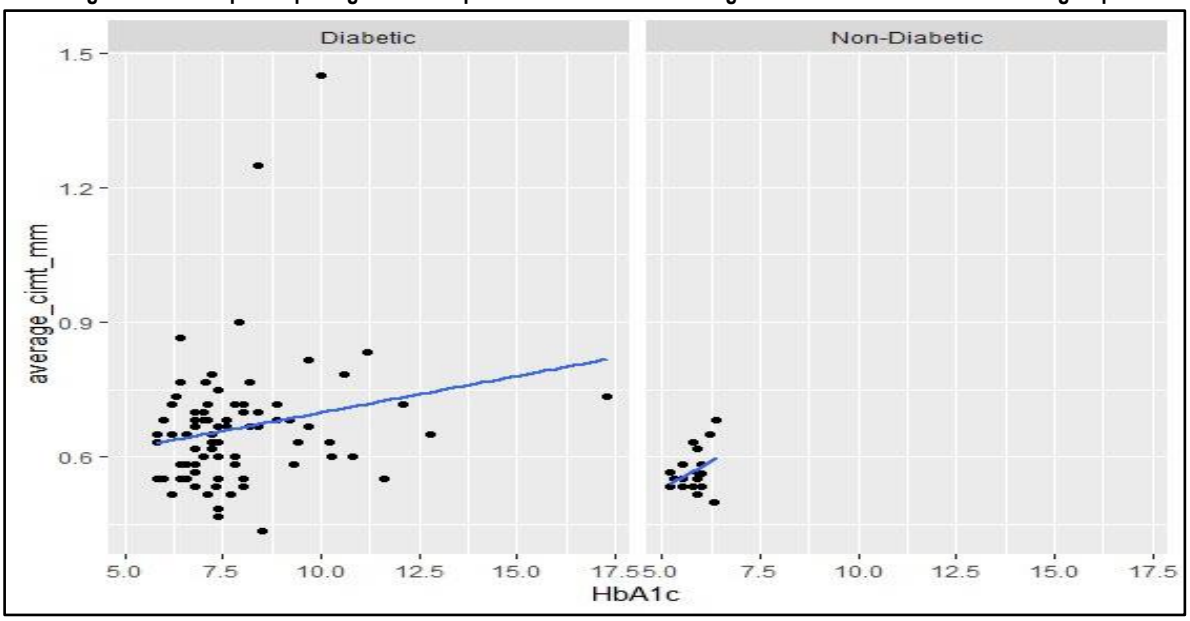


Figure 2: Scatter plot depicting relationship between waist hip ratio and average CIMT.

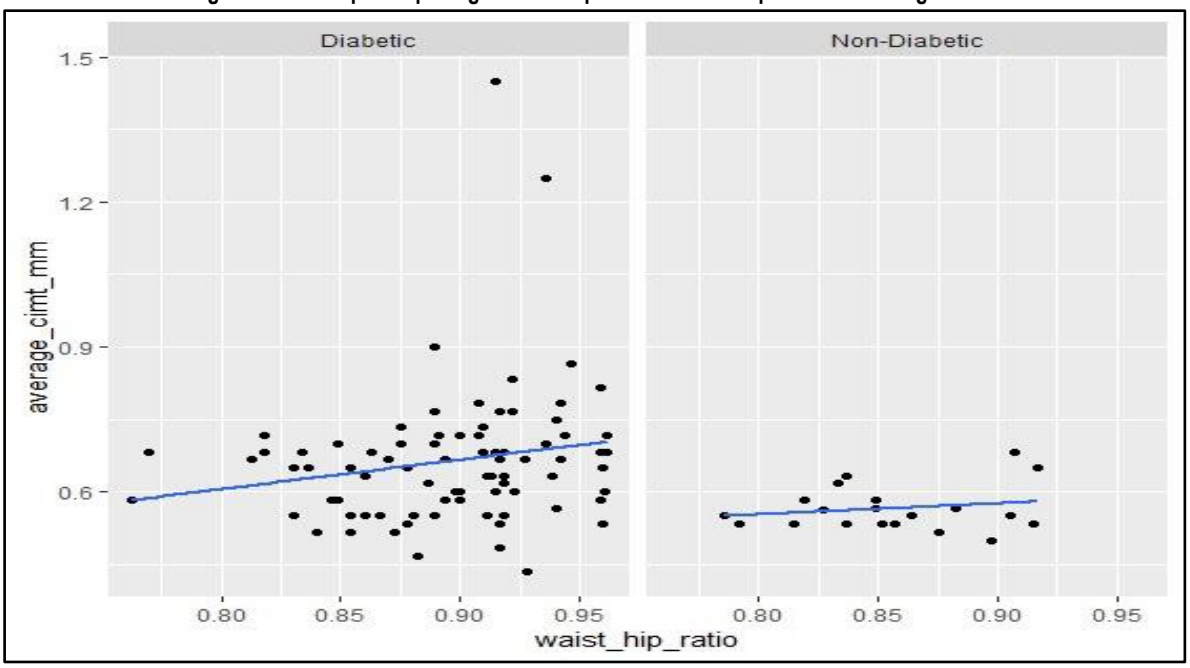


Figure 3: Scatter plot depicting relationship between BMI and average CIMT in diabetic and control group.

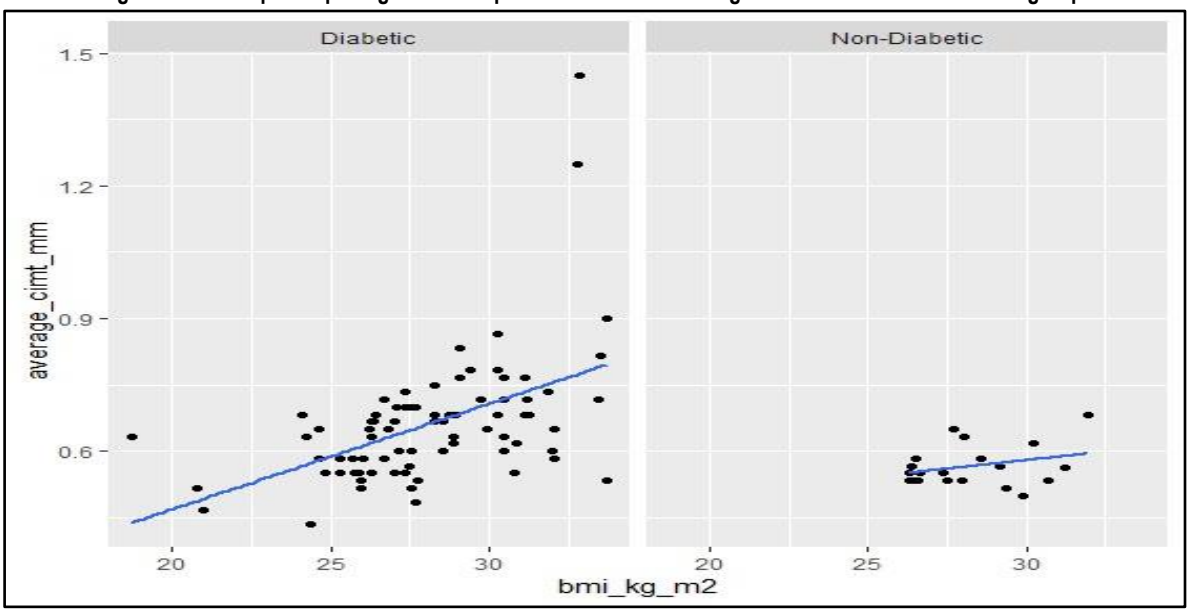


Figure 4: Scatter plot depicting relationship between HsCRP and average CIMT.

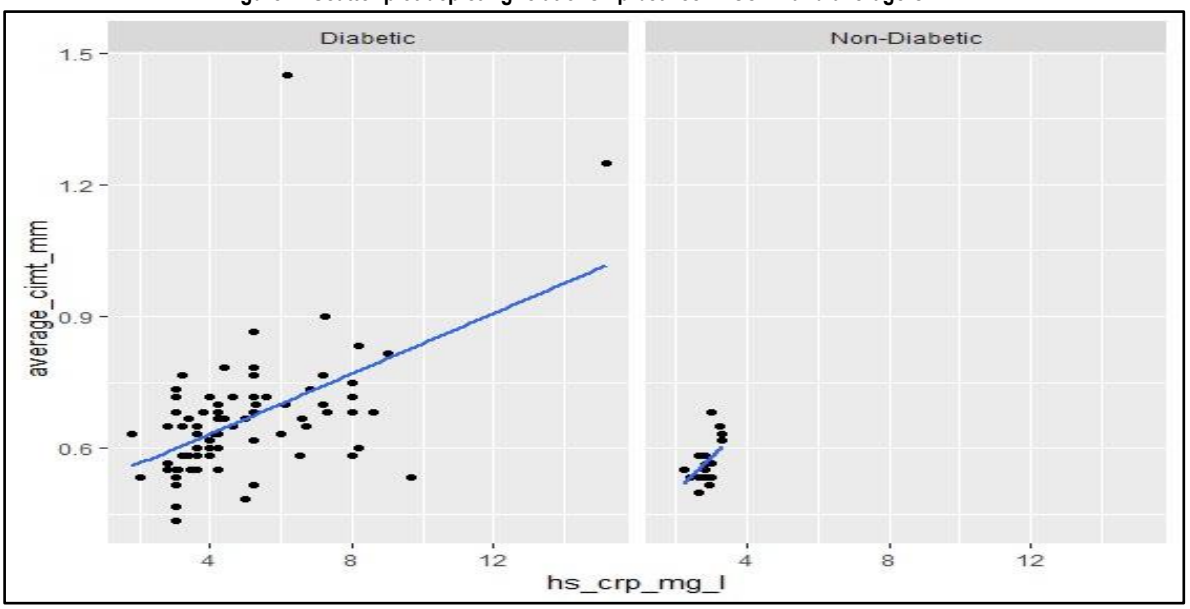
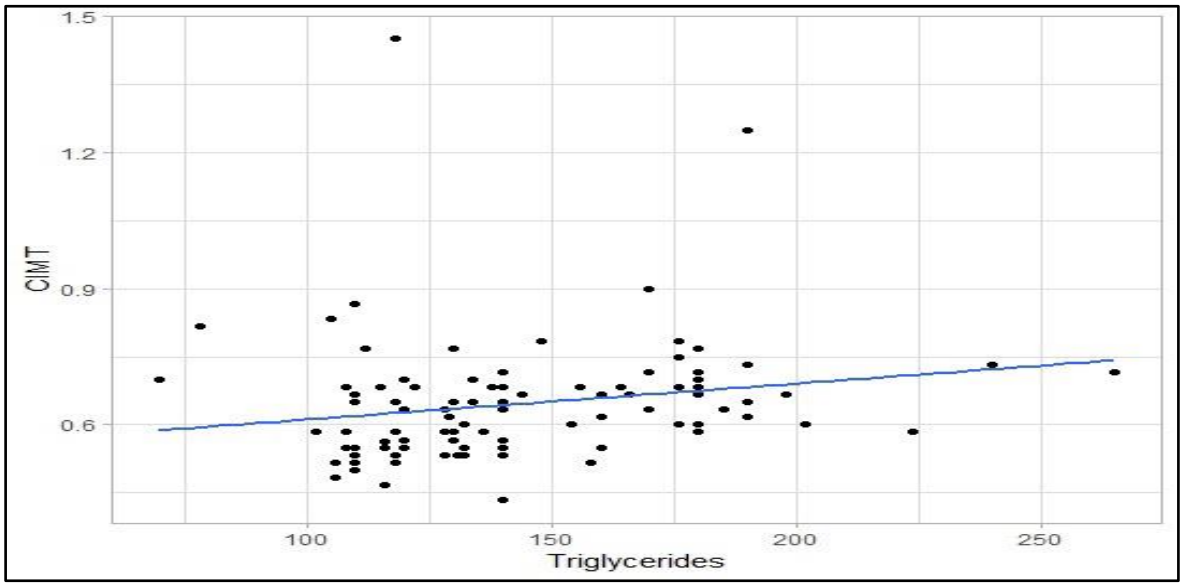


Figure 5: Scatter plot depicting relationship between triglycerides and average CIMT.



DISCUSSION

We found a significant correlation between hsCRP, BMI and Triglycerides and CIMT both in cases and controls. CIMT had weak correlation with LDL and HbA1c.

Carotid Intima media Thickness is an important marker of Atherosclerotic Vascular disease. There was moderate correlation between CIMT and hsCRP. hsCRP is an important marker of inflammation, it implies there is a low grade inflammation in Diabetic patient due to underlying Atherosclerosis which contributes to rise in hsCRP. Similar Significant association between hsCRP and CIMT was also seen in study by Saha et al.[14]

Our patients were statin, aspirin and ACE inhibitor/ARB naïve thus negating the effect of possible CIMT modification due to these drugs which helped up in estimating "true" effect of Diabetes on atherogenesis (as evidenced by CIMT) independent of these confounders as seen in other studies.

Association with Dyslipidaemia

Our study shows a significant association of Triglycerides with CIMT, but a weak non-significant correlation with LDL.

Association with Anthropometric Parameters

CIMT was strongly correlated with BMI in cases while it showed a weak non-significant correlation with Waist-hip ratio, both in cases and controls. It can be explained by young population in our control group and well controlled population in cases (waist hip ratio of 0.9 is borderline high only)

Association with Glycaemic Control

CIMT was positively correlated with fasting and post-prandial sugar in cases. but not with HbA1c.

It might be due to well controlled diabetic patients in case group and smaller variation of HBA1c.

Pathophysiology

C-reactive protein, an acute-phase reactant produced by liver, is an extremely sensitive marker of systemic inflammation. It is perceived that chronic low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein (hs-CRP) might potentially be a cause underlying the aetiology and manifestation of type 2 diabetes (T2DM).

For those individuals especially for those at intermediate risk for cardiovascular diseases according to global risk scores, other markers like high sensitive C-reactive protein (hs-CRP), and carotid intima-media thickness (CIMT) may be useful in predicting the individuals who may benefit from more aggressive preventive therapy. CIMT is considered as a surrogate marker of cardiovascular disease, an independent risk factor, and a tool for early detection of atherosclerosis and also has the ability to determine the management strategy

Proteins are frequently glycated during various enzymatic reactions when the conditions are physiologically favourable. However, in the case of hemoglobin, the glycation occurs by the nonenzymatic reaction between the glucose and the N-terminal end of the β-chain, which forms a Schiff base. During the rearrangement, the Schiff base is converted into Amadori products, of which the best known is HbA1c.

A comparative table of major findings in studies exploring association of CIMT with CV risk factors is shown in Table 3.

Table 3: Comparison of major findings in studies exploring association of CIMT with CV risk factors

Studies	Major Findings	p Value
Present study	HsCRP,BMI and triglycerides were statistically significant with CIMT between cases and controls except LDL and HBA1C	(P<0.05)
Kota SK et al.[15]	Mean CIMT was significantly higher in diabetic subject as compared to healthy subjects	(P<0.05)
Go'mezc Marcos MA et al.[16]	Statistically significant association between BMI and average CIMT thickness	(P<0.05)
Saha et al.[14]	Significant association between age,HsCRP and high CIMT in patients with diabetes	(P<0.05)
Kumar A et al.[17]	Significant association of CIMT among cases and control	(P<0.05)
Jangrozik et al.[18]	Glycemic parameters (FBG,PPPG and HbA1C) and lipid parameters like total cholesterol,LDL and triglycerides were all significantly higher in patients with increased CIMT	(P<0.05)

STRENGTH AND WEAKNESS

Our patients were statin, aspirin and ACE inhibitor/ARB naïve thus negating the effect of possible CIMT modification due to these drugs which helped up in estimating "true" effect of Diabetes on atherogenesis (as evidenced by CIMT) independent of these confounders as seen in other studies.

Our study had smaller sample size and our cohort was young with well controlled Diabetes- this might have led to non-significant association of well-known Cardiovascular risk factors like LDL and HbA1c.

CONCLUSION

CIMT is associated with conventional CV risk factors – glycemic control, Anthropometric parameters and hsCRP.

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