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Study of Correlation Between Highly Sensitive C-Reactive Protein, Serum Triglyceride Level with CIMT In Asymptomatic T2DM Patients with Their Level of Sugar Control

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) patients with uncontrolled sugar are at increased risk of atherosclerosis as compared to diabetic patients with controlled sugar. Detecting atherosclerosis in its subclinical stages can potentially impede or mitigate the development of complications such as coronary artery diseases, stroke, and peripheral vascular diseases. Early identification offers the opportunity to implement interventions that may slow down the progression of the disease and reduce the risk of atherosclerotic-related complications.

Objective: Identification of subclinical atherosclerosis in controlled and uncontrolled diabetic patients and explore various factors [highly sensitive C-reactive protein (hs-CRP) and triglyceride (TG)] that can be associated with a high risk of subclinical atherosclerosis.

Patients and methods: We recruited 60 known case of T2DM patients without any clinically manifested disease and without any past history of a vascular disease. Those patients were divided into two equal groups, well controlled and uncontrolled based on their HbA1c. After complete history and physical examination, investigations including serum triglyceride (TG), hs-CRP, fasting and 2 hours postprandial blood glucose were obtained. All participants underwent for measurement of carotid intima media thickness (CIMT),marker of subclinical atherosclerosis by duplex ultrasonography.

Results: Uncontrolled diabetic patients have increased CIMT (6.9394mm) as compared to controlled diabetic patients (.8181mm). There was highly significant positive correlation between CIMT and hs-CRP in uncontrolled diabetic group (p value .001, r value .469) but no association within controlled diabetic group (p value .074 and r value was .244) . While significant positive correlation with CIMT and TG level in controlled diabetic group (p value <.001 and r value was .689) and no correlation between CIMT and TG level in uncontrolled diabetic group (p = .195 , r = .175).

Conclusion: The risk of subclinical atherosclerosis is more in uncontrolled diabetics as compared to controlled diabetics. In uncontrolled diabetics subclinical atherosclerosis was associated with elevated hs-CRP level and in controlled diabetic CIMT was associated with elevated serum TG levels.

Key Words: *CIMT; T2DM Patients; atherosclerosis*

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INTRODUCTION:

Diabetes mellitus (DM) refers to a collection of prevalent metabolic disorders characterized by the common feature of elevated blood glucose levels, known as hyperglycemia. Depending on etiology it is classified mainly as type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus is identified by significantly diminished insulin levels and primarily impacts individuals in their youth. Type 2 diabetes mellitus is marked by insulin resistance and predominantly affects adults, typically those in their middle years(1).

Diabetes continues to be a significant public ill health, currently affecting 537 million people worldwide. The number is projected to 643 million by 2030. Type 2 DM accounts for 90- 95% of all DM. India has highest number of type 2 DM individuals within cohort of 20- 70 years (2).

Diabetes mellitus is diagnosed by using fasting plasma glucose level, 2 hour postprandial plasma glucose level and by glycatedhaemoglobin (HbA1c). HbA1c is the best available biochemical parameter to diagnose type 2 DM, monitor response to its treatment and risk of developing diabetic complications. The cut off limit of HbA1c to diagnose type 2 DM is 6.5%. It provides information about overall control of glucose within last 3 months (3).

Diabetes mellitus causes both microvascular and macrovascular complications. Macrovascular complications are stroke, cardiovascular diseases, and peripheral vascular disease.Patients with uncontrolled T2DM have 2 to 8 fold increased risk of developing macrovascular complications compared to non-diabetic and controlled diabetic individuals of same age, gender and ethnicity. Macrovascular complications are consequences of atherosclerosis (4).

Atherosclerosis is a chronic, progressive, degenerative, inflammatory disease that is characterized by an increased thickness of inner and middle layer of an arterial wall (CIMT) with subsequent plaque formation in arterial wall (5).

Atherosclerosis has complex pathogenesis, the main components of which are lipid accumulation due to dyslipidemia and chronic inflammation in arterial wall. The main lipidsthat cause atherosclerosis are increased level low density cholesterol (LDL-C), decreased level of high density lipoprotein cholesterol (HDL-C), and high level of triglycerides (TG). Various studies show that hypertriglyceridemia is an independent causative factor for atherosclerosis (6).

Triglyceride rich lipoproteins, their remnant and biomarkers of TG metabolism such as lipoprotein lipase (LPL), and apoC-3 involves in the progression of atherosclerosis by directly and indirectly (7). Direct mechanism is by endothelial dysfunction and indirectly by decreasing HDL and by increasing remnant lipoproteins and small dense lipoproteins which stimulates atherothrombosis (8).

The other important etiology in atherosclerosis is inflammation. And prospective studies of healthy persons have established that circulating levels of inflammatory markers of subclinical atherosclerosis including highly sensitive C-reactive protein (hs-CRP), fibrinogen, leukocytes, and albumin are associated with increased risk of atherosclerotic complications (9) .There are limited studies of cohorts with T2DM and hs-CRP levels. These previous reports studied only mortality or cardiovascular events only in men. So there is a need for studies to evaluate these associations in large cohort of diabetic people. hs-CRP is an acute phase reactant produced by liver , is an extremely sensitive marker of systemic inflammation because it can be found elevated in chronic low grade inflammation produced in T2DM in response of interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF) (10). It exists in two forms monomeric CRP and pentameric CRP. It actively participates by activating the complement system, and inducing apoptosis, vascular cell activation, leukocyte recruitment, lipid accumulation, platelet aggregation, and endothelial dysfunction, plaque instability,increased endothelial cell adhesion molecules and finally thrombosis (11).

Subclinical atherosclerosis can be detected by Carotid intima - media thickness (CIMT), and it is a surrogate marker for presence of atherosclerosis (12).CIMT measurement by ultrasonography is easy, non-invasive,and comparable result with CT angiography. Various previous studies show that CIMT is more in uncontrolled diabetic patients as compared to controlled diabetic or non-diabetic individuals.

METHODS:

Study design:

The present cross sectional, comparative study was conducted on 60 T2DM patients with controlled and uncontrolled sugar from OPD of SawaiMan Singh Medical College and attached group of Hospitals, Jaipur, Rajasthan, India from June 2021 to December 2023. Patients included in this study were type 2 diabetic patients,above 40 years, asymptomatic. Excluded patients in this study were type 1 diabetic, symptomatic individuals i.e. known case of stroke, myocardial infarction, peripheral vascular disease, malignancy, fever, kidney disease. Those 60 T2DM patients were divided into two equal groups according to their sugar control level (HbA1c level). First group include 30,T2DM patients with controlled sugar (HbA1c < 7%) and in second group 30,T2DM patients with uncontrolled sugar (HbA1c > 7%).

Laboratory investigations

All individuals underwent a comprehensive process that involved gathering detailed medical histories, conducting thorough physical examinations, and performing biochemical analyses, including assessments for fasting plasma glucose (FPG), 2-hour postprandial blood glucose (PPG), HbA1c, triglycerides (TG), and hs-CRP.

Each participant provided two venous blood samples following a 12-hour overnight fast. The initial sample was collected in a glass tube with Ethylene diamine tetra acetic acid (EDTA) for HbA1c analysis using the Bio-Rad D-10 high-performance liquid chromatography system (Bio-Rad Laboratories, CA, USA). The second sample, collected in a dry tube without anticoagulant, was promptly centrifuged and stored at minus 80 degrees Celsius. This sample was processed using the automated chemiluminescence method with the IMULITE DPC Medlab system. Serum triglycerides were determined through an enzymatic colorimetric test with lipid clearing factor, employing the Beckman DxC 800 general chemistry analyzer (Beckman Coulter, Fullerton, CA, USA). Measurement of hs-CRP utilized an enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem, San Diego, CA, USA).

On the second day, two venous blood samples were obtained, one following an 8-hour overnight fast for FPG measurement and the other 2 hours after breakfast for PPG measurement. Glucose oxidase and peroxidase methods were employed to measure FPG and PPG, respectively.

Carotid intima-media thickness (CIMT) serves as a marker for detecting subclinical atherosclerotic disease. Its suitability for large-scale population studies is attributed to its simple and non-invasive measurement methodology.

A B-mode Duplex ultrasound (SONO 5500, HP, USA) was utilized for the ultrasound examination of the carotid arteries. The assessment of carotid intima-media thickness (CIMT) was performed 1 cm from the carotid bulb on both the left and right sides. The mean CIMT for each artery was determined by calculating the average measurement from both sides in each individual.

Ethical approval

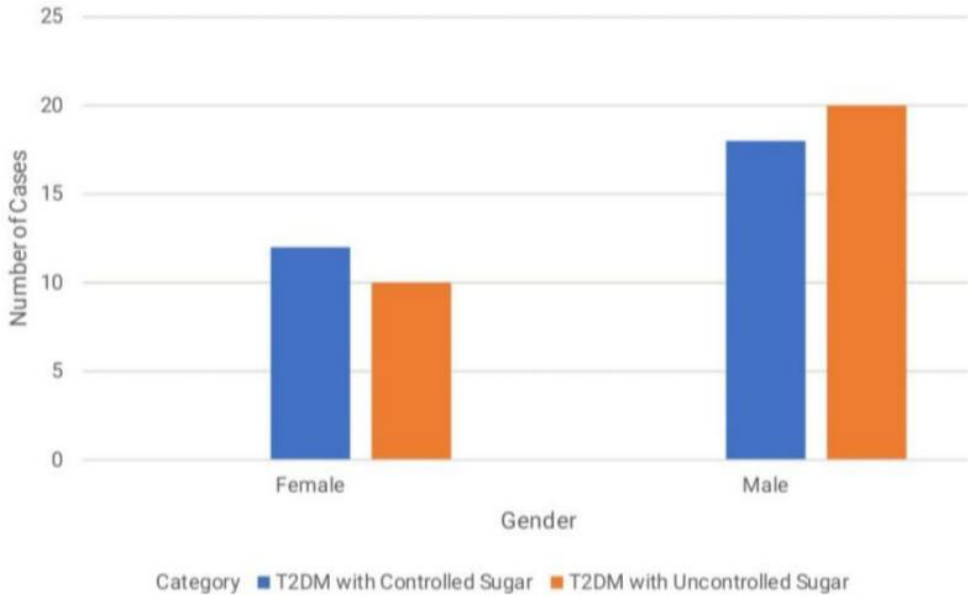
The study is approved by the ethical committee of SMS medical college, Jaipur (Rajasthan).

Statistical analysis

All data were gathered, organized, and subjected to statistical analysis through SPSS 22.0. Categorical data were expressed as percentages, while continuous data were presented as mean ± standard deviation. The Chi-square test ($\chi 2$) was employed to assess the differences between qualitative variables. For comparisons involving more than two dependent groups of normally distributed variables, the one-way analysis of variance (ANOVA) test, along with the Tukey HSD (Honestly Significant Difference) or post hoc test, was utilized. In cases of non-normally distributed variables, Friedman's ranks test was applied. All statistical comparisons were conducted with a two-tailed approach. A P-value ≤ 0.05 was considered statistically significant, and a P-value < 0.001 was regarded as highly statistically significant. Correlations between variables were evaluated using the Pearson correlation coefficient.

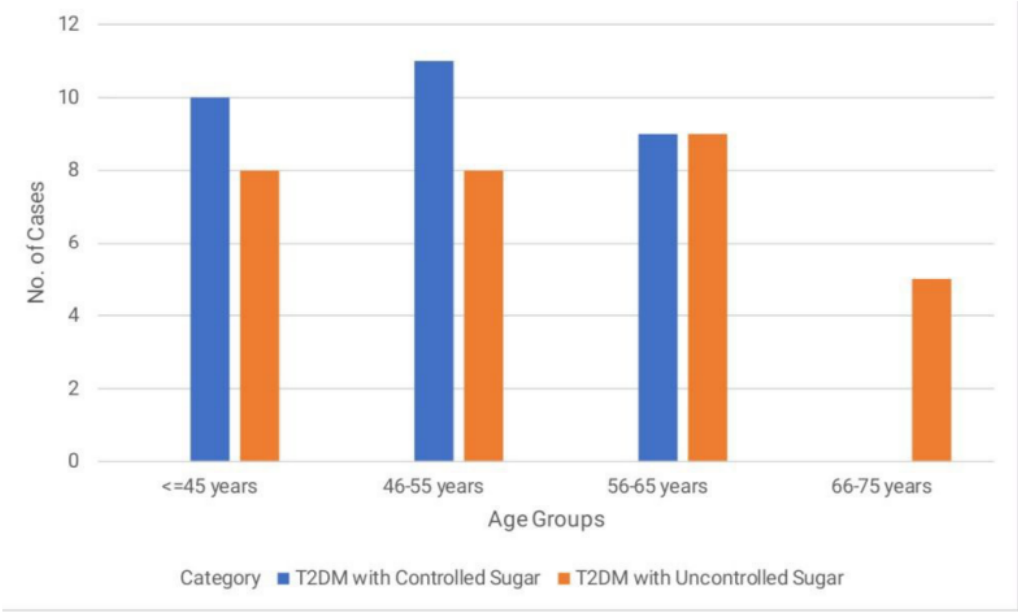
RESULTS

Bar chart 1:



Age wise distribution of cases: In this study 36.7% cases were female and 63.3% cases were male. Half of the cases are T2DM with controlled sugar (group A) and half cases are diabetic with uncontrolled sugar (group B). Out of total

female patients (22), 54.5% in group A and 45.5% in group B. Out of total male patients (38) , 47.4% in group A and 63.3% in group B. Association of glycemic control with sex found statistically insignificant (p value is .592).
Bar chart 2: Age wise distribution of cases.



Total no. Of cases below 45 years are 30% out of which 55.56% in group A and 44.4% in group B. Total no. of cases between 46-55 years were 31.7% out of which 57.89% in group A and 42.11% in group B. Between 56-65 years, total cases were 30%, in which 50% in both group A and group B. Between 66-75 years, total cases were 8.3%, all of them was in group B.

Table 1: Distribution of various parameters in both groups:

Parameters	T2DM with controlled sugar					T2DM with uncontrolled sugar					Total					p-value
	Mean	SD	median	Q1	Q3	mean	SD	median	Q1	Q3	mean	SD	median	Q1	Q3	
Age	52	8	51	45	56	56	10	54	45	65	54	9	53	45	63	126
BMI	23.4	3.3	22.4	21.0	27.1	24.9	3.9	24.1	22.6	26.7	24.1	3.7	23.1	21.4	26.7	.099
Systolic BP	125	5	126	120	128	135	8	135	128	140	130	8	128	25	135	<.001
Diastolic BP	80	4	79	76	84	89	4	90	86	92	84	6	85	79	90	<.001
Duration of DM (years)	6	1	6	5	7	10	2	10	8	11	8	2	8	6	10	<.001
TG	151	15	150	139	165	238	10	235	230	246	195	46	202	150	235	<.001
hs-CRP	7.83	1.01	7.95	6.87	8.86	16.97	1.28	16.93	15.76	17.32	12.40	4.75	12.13	7.95	16.93	<.001
CIMT	.8181	.0831	.8270	.7430	.9120	6.9394	4.20	8.90	1.321	10.10	3.8787	4.2662	1.026	.827	8.90	<.001
FBS	103	4	102	100	107	149	9	149	142	154	126	24	123	102	149	<.001
PPG	156	6	157	150	160	223	12	220	213	231	189	35	188	157	220	<.001

Mean age for group A was 52 ±8 years and for group B was 56±10 years. Here is no significant difference were found among these two studied group regarding age (p = .126). Mean BMI in group A was 23.4 ±3.3 and for group B was 24.9±3.9 kg/ m^2. Here also no significant difference was found among these two group (p= .099). The two groups

had been found significant difference on parameter of hypertension. The mean systolic and diastolic blood pressure values were higher in uncontrolled diabetic group as compared to well controlled diabetic group.

We observed that there was statistically significant difference on TG level, hs-CRP, FBS, PPG and CIMT among these two groups. The mean CIMT for controlled diabetes was found .8181±.0831 and for uncontrolled diabetic group (group B) was 6.93±4.2 mm, with a p value < .001.

We found that CIMT, hs-CRP, TG levels were significantly higher in uncontrolled diabetics (HbA1c >7%) as compared to controlled diabetics (HbA1c < .001 , between well controlled diabetic group (group A) and uncontrolled diabetic group (group B), regarding FBG, PPG, CRP, TG level and CIMT.

Mean age for controlled diabetics was around 52 years and for uncontrolled diabetics was 56 years. But the results of study with age and sugar control level were statistically insignificant. Mean duration of DM in controlled diabetic group was 6 years and in uncontrolled diabetic group was 10 years. And there were statistically significant difference in duration of diabetes between these two groups. The mean BMI for controlled diabetic group was 23.5 kg/m2 and for uncontrolled diabetics group was 25 kg/m2. But study results among two groups with BMI are statistically insignificant.

The mean Systolic blood pressure for controlled diabetic group was 126 mmHg and for uncontrolled diabetic group was around 136 mmHg. And study results were statistically significant. The mean Diastolic blood pressure for controlled diabetic group was 80 mmHg and for uncontrolled diabetic group was around 90mmHg . And study results are statistically significant.

The mean TG level for controlled diabetic group was 150mg/dl and for uncontrolled diabetic group was around 250mg/dl. And study results are statistically significant. Showing TG levels were much higher in uncontrolled diabetics compared to controlled diabetics. The mean Hs- CRP level for controlled diabetic group was 8 mg/dl and for uncontrolled diabetic group was around 18 mg/dl. And study results were statistically significant. Showing hs-CRP level were much higher in uncontrolled diabetics compared to controlled diabetics. The mean CIMT in controlled diabetic group was 1 mm and in uncontrolled diabetic group was 7 mm. These results show that CIMT was significantly higher in uncontrolled diabetics as compared to controlled diabetic group.

The mean FBS level for controlled diabetic group was 100 mg/dl and for uncontrolled diabetic group was around 150 mg/dl. And study results were statistically significant. Showing FBS was much higher in uncontrolled diabetics compared to controlled diabetics. The mean PPG level for controlled diabetic group was 160mg/dl and for uncontrolled diabetic group was around 230mg/dl. And study results were statistically significant. Showing PPG was much higher in uncontrolled diabetics compared to controlled diabetics.

Table 2: Kendall Tau Correlations of various parameters with CIMT in T2DM.
(Controlled diabetic group' and 'Uncontrolled diabetic group')

Groups	Controlled diabetic group		Uncontrolled diabetic group	
Parameters	Correlation Coefficient	P Value	Correlation Coefficient	P value
Age	.061	.663	.180	.182
BMI	.024	.857	-.270	.044
Systolic BP	-.296	.034	.201	.135
Diastolic BP	.322	.022	.140	.314
Duration of DM (years)	.011	.941	-.100	.466
TG	.689	<.001	.175	.195
hs-CRP	.244	.074	.469	<.001
FBS	.584	<.001	.216	.115
PPG	-.205	.141	.080	.553

We studied the correlation between CIMT and each of age , BMI , systolic BP, diastolic BP , Duration of DM , TG level, hs-CRP , FBS and PPG, in controlled T2DM patients . The significant association found only with TG levels and with FBS. Correlation between CIMT and age, BMI, systolic BP, diastolic BP, duration of DM, TG level, hs-CRP , FBS and PPG in uncontrolled T2DM patients was done. The significant association found only with hs-CRP .

Table 3: Kendall Tau Correlations of various parameters with hs-CRP in 'T2DM'
('Controlled diabetic group' and 'Uncontrolled diabetic group')

	Controlled diabetic group		Uncontrolled diabetic group	
Parameters	Correlation Coefficient	P Value	Correlation Coefficient	P value
Age	.066	.637	-.023	.869
BMI	0	1.00	-.397	.005
Systolic BP	-.159	.252	.442	.002
Diastolic BP	.138	.325	.317	.029
Duration of DM (years)	.132	.355	.321	.026
TG	.289	.035	.504	<.001
cIMT	.244	.074	.469	.001
FBS	.135	.328	.500	<.001
PPG	-.068	.624	.116	.409

DISCUSSION:

Diabetes related atherosclerotic complications are more common in uncontrolled diabetic patients as compared to controlled diabetics. In T2DM patients, cardiovascular atherosclerosis is leading cause of morbidity and mortality (13). Atherosclerosis has a prolonged subclinical stage and there was relatively few studies have been performed in past to formally assess the presence of subclinical atherosclerosis by correlation between serum triglyceride level and hs-CRP with glycemic control in T2DM patients. So a cross sectional study was performed on 60 T2DM patients age > 40 years for presence of subclinical atherosclerosis and explore its correlation with CRP and TG levels. 60 cases of known case of T2DM were divided into two equal groups according to their HbA1c % (controlled diabetic group HbA1c < 7% and uncontrolled diabetic group HbA1c > 7%), subclinical atherosclerosis was measured in term of CIMT measurement. In our study there were statistically significant difference regarding CIMT in those groups; being higher in uncontrolled diabetic group as compared to controlled diabetic group. Age, gender and body mass index(BMI) were confounding factors in our study so excluded. However Alsayed Abdel Aal et al (14) (2021) found significant differences in BMI between uncontrolled diabetic group and controlled diabetic group.

HbA1c and subclinical atherosclerosis: Most striking finding observed in our study was significant differences in CIMT measurement. The CIMT was significantly higher in uncontrolled diabetic group(6.9394mm) as compared to controlled diabetic group (.8181mm). Same result were found in Alsayed Abdel Aal et al (14) (2021) study. Similarly Baba et al. (15) and Bashir et al. (16) founded that CIMT was more in T2DM patients as compared to non-diabetic individuals. Okeahialam et al. (17) studied CIMT in hypertensive, diabetics and healthy individuals and observed that CIMT was higher in diabetic and hypertensive patients as compared to healthy individuals but the differences were not statistically significant.The discrepancy with our results could be explained on basis of differences in sample sizes, duration of diabetes, differences in demographics, comorbidities, method of measuring CIMT, and levels of glycemic control in participants with our study.

In the present study, TG, hsCRP, HbA1c, FBS and PPG were significantly higher in uncontrolled diabetic patients compared to controlled diabetic patients. Similarly Kotb et al. (18) Hasan et al. (19) andGangadhar et al. (20) in their study found that serum TG level were higher in uncontrolled diabetic group as compared to controlled diabetic group which finding consistent with our results.

CRP and CIMT: Our research identified a noteworthy correlation between hs-CRP and cIMT thickness in the uncontrolled diabetic group, while such an association was not statistically significant in the well-controlled diabetic group. This aligns with the findings of King et al (21), who observed significantly higher hs-CRP levels in uncontrolled diabetics compared to well-controlled diabetics. Consistent with our results, Eldosoky et al (22) and Ali and Hadidi (23) reported a significant positive correlation between CIMT and CRP in their respective studies.

The link between hs-CRP and CIMT may be attributed to ongoing inflammation in the atherosclerotic process. Studies suggest that the level of inflammation, as indicated by specific biomarkers, can serve as an indicator of disease activity and predict the progression of atherosclerosis. Hence, acute-phase reactants such as hs-CRP may serve as an indirect measure of the cytokine-dependent inflammatory processes occurring in the arterial wall.

TG and CIMT: In our study TG level were significantly associated with CIMT in well controlled diabetic group but not significantly associated with CIMT in uncontrolled diabetic group.Fitch et al. (24) found no association between CIMT and TG which was similar to our results. However Touboul et al. (25) in their meta-analysis concluded that, TG levels were positively associated with CIMT.

Blood glucose and CIMT: In our study, we observed a significant association between HbA1c levels and CIMT thickness in the uncontrolled diabetic group. Interestingly, fasting and postprandial blood glucose levels did not show a

significant association with CIMT thickness in the uncontrolled diabetic group. Conversely, in the well-controlled diabetic group, our study revealed a significant association between fasting blood sugar (FBS) levels and CIMT.

However, the findings of Bashir et al. (16) differed from ours, as their study reported no correlation between levels of fasting and postprandial blood glucose or HbA1c and CIMT thickness, presenting an inconsistency with our results. Notably, the DCCT and UKPDS trials suggested that while glycemic control plays a clear role in delaying the onset and progression of micro vascular complications, its impact on atherosclerosis and macro vascular complications remains less evident.

Contrasting with our findings, Alhoussein Alsayed et al. (2021) identified a significant association between FBS and CIMT in the uncontrolled diabetic group (14). These variations highlight the complexity of the relationship between glycemic control measures and CIMT thickness in diabetic individuals.

CRP in DM2 : In our study CRP level were significantly associated with FBS and TG in uncontrolled diabetic group but no significant association was found in controlled diabetic group with any parameters.

CONCLUSION:

From the observation it has been concluded that the risk of subclinical atherosclerosis is more in uncontrolled diabetics as compared to controlled diabetics. And the patients of subclinical atherosclerosis remain asymptomatic for few decades. TG and hs-CRP can be used as markers for subclinical atherosclerosis in patients with T2DM. In uncontrolled diabetics subclinical atherosclerosis was associated with elevated CRP level and in controlled diabetic CIMT was associated with elevated serum TG levels.

Therefore, early detection of subclinical atherosclerosis by these non-invasive and inexpensive parameters (TG level, HbA1C level, hs-CRP, USG guided CIMT) is very helpful in preventing the morbidity and mortality risk in T2DM patients.

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