Section: General Medicine

Original Research Article

ASSOCIATION OF TRIGLYCERIDES LEVELS WITH CAROTID INTIMA MEDIA THICKNESS IN TYPE 2 DIABETES MELLETUS PATIENTS

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Abstract

Background: Diabetes mellitus (DM) is marked by chronic hyperglycemia due to insulin resistance and impaired insulin secretion, increasing cardiovascular disease (CVD) risk, especially in type 2 DM. Diabetic dyslipidemia, with high triglycerides and low HDL, promotes atherosclerosis. Carotid intima-media thickness (CIMT), a non-invasive marker, aids in early detection and management of CVD risks in diabetic patients. The aim of this study is to assess association between triglyceride levels and carotid intima media thickness (CIMT) in type 2 diabetes mellitus patients. To quantify CIMT as a reliable marker of atherosclerotic burden in diabetes patients. **Materials and Methods:** This cross-sectional study was conducted from January to June 2022 at Government Rajaji Hospital, Madurai Medical College, among 50 randomly selected patients aged 30-70 years with type II Diabetes Mellitus of more than five years' duration, without hypertension. Institutional Human Ethics Committee approval was obtained, and informed consent was secured from participants. Data collection was done using a questionnaire along with investigations. Carotid intima-media thickness (CIMT) measured by B-mode ultrasound using a 7.5 MHz transducer. Appropriate descriptive and inferential statistics were done, with significance at $p < 0.05$. **Result:** The study found a mean CIMT of 0.8170 ± 0.175 mm among the 50 participants, with 32 individuals having a CIMT ≤ 0.8 mm and 18 with CIMT > 0.8 mm. The mean age of participants was 59.14 ± 6.9 years. Gender, BMI, smoking, and mode of treatment did not show a statistically significant association with CIMT. However, CIMT was significantly correlated with fasting blood sugar (FBS), HbA1c, total cholesterol, triglycerides, and LDL cholesterol levels. Triglycerides and FBS emerged as primary predictors of CIMT, with triglycerides explaining 51% of the variation ($R^2 = 0.514$, $p < 0.001$), and FBS further increasing the model's predictive strength to 55.5% ($R^2 = 0.555$, $p < 0.001$). Elevated CIMT was more prominent in individuals with higher triglycerides and FBS, indicating these factors as key influencers in early atherosclerosis in type II diabetes. **Conclusion:** Carotid intima-media thickness (CIMT) is elevated in individuals with dyslipidemia, especially with high triglycerides and cholesterol, and is also independently influenced by HbA1c levels. CIMT serves as a non-invasive marker for early atherosclerosis in type 2 diabetes, potentially predicting future vascular complications. Larger studies are essential to confirm these associations.

INTRODUCTION

Diabetes mellitus (DM) comprises of a group of metabolic disorders that share the phenotype of hyperglycemia. Hyperglycemia is contributed by factors such as reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic derangements associated with DM causes secondary pathophysiologic changes in many systems that can have a huge impact on the individual with diabetes and on the health care system.

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. In the early stages of the disorder, glucose tolerance

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remains near- normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue.[1]

Type 2 DM is characterized by insulin resistance. It also has a greater propensity to predispose to atherosclerosis. Cardiovascular disease (CVD) is the leading cause of death among diabetic patients. Two-thirds of patients with DM will eventually die of CVD. The macrovascular complications (peripheral arterial disease, congestive heart failure, coronary artery disease, myocardial infarction and sudden death) risk increases up to fivefold in patients with diabetes.[2]

As the prevalence of DM increases, there is also an increase in the global burden of CVD. Some studies have indicated that postprandial derangements like hyperglycemia and hypertriglyceridemia are independent risk factors for CVD as they induce oxidative stress and endothelial dysfunction. Though these are thought as risk factors the mechanism by which they cause the disease is unclear.[3]

Dyslipidemia is found to have a direct relation with atherogenesis. Serum triglyceride (TG) levels are found to be an independent risk factor for atherosclerosis.[4,5] Diabetic dyslipidemia contributes to an increased risk in type 2 DM. Diabetic dyslipidemia is a kinetic derangements of the lipoproteins. These contribute to accelerated atherosclerosis. The major quantitative abnormalities include increased TG and decreased high density lipoprotein (HDL) levels. Qualitative abnormalities include an increase in small dense, low density lipoproteins (LDLs) and large, very low density lipoprotein subfraction 1 (VLDL1). Other qualitative lipoprotein derangements include an increase in the TG content of LDL and HDL, glycation of apolipoproteins and heightened susceptibility of LDL to oxidation. The important kinetic lipoprotein abnormalities are characterized by an elevated VLDL1 production, reduced VLDL catabolism, and increased HDL catabolism. LDL-cholesterol (LDL-C) levels may be normal in type 2 diabetics; however, LDL particles exhibit decreased catabolism, which contributes to atherogenesis in type 2 DM.

Insulin resistance in type 2 DM is due to failure of hyperinsulinemia to suppress gluconeogenesis. This results in fasting hyperglycemia and impaired glycogen storage by the liver in the postprandial state. Early in the course of diabetes there will be increased hepatic glucose production. Later there will be the development of insulin secretory abnormalities and insulin resistance in skeletal muscles. Once the patient develops insulin resistance in adipose tissues, there will be increased flux of free fatty acid from adipocytes. This increased flux of free fatty acid leads to derangements in lipoprotein metabolism. This abnormal lipid storage in liver is responsible for diabetic dyslipidemia. The insulin resistance and relative insulin deficiency seen in type 2 DM are believed to be key factors leading to dyslipidemia, as insulin has a major role in regulation of lipid metabolism. Diabetic dyslipidemia is also found to be associated with certain adipocytokines such as retinol-binding protein 4 and adiponectin.[6]

Atherosclerosis is a disease of large and medium sized muscular arteries. It is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. These intravascular alterations results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow and diminished oxygen supply to target organs.

Hypertriglyceridemia has been shown to be associated with a greater risk for atherosclerosis in those with type 2 DM. In persons with prolonged increases of plasma triglycerides, either fasting or postprandial, the process of lipid exchange would enrich the triglyceride rich particles in cholesterol ester and thereby make these particles more atherogenic.[7] Elevated TG according to The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is defined as 150 mg/dL and higher.[8]

Atherosclerosis remains asymptomatic in early stage. In order to detect affected individuals in the early stages direct examination of the vessel wall is necessary. High resolution B-mode ultrasound is a non-invasive technique widely used to assess atherosclerosis in superficial arteries. Carotid intima media thickness (CIMT) is used as a surrogate marker for atherosclerosis.[9] It is the measurement of the distance between blood–intima and media–adventitia interfaces of the carotid wall. This non invasive and quantitative ultrasound measurement can be used to assess early atherosclerosis.[10] There are few studies showing increase in CIMT is associated with increased risk of ischemic heart disease or cerebrovascular accident.[11]

Aims & Objectives

The aim of this study is to assess association between triglyceride levels and carotid intima media thickness (CIMT) in type 2 diabetes mellitus patients. To quantify CIMT as a reliable marker of atherosclerotic burden in diabetes patients.

MATERIALS AND METHODS

This cross sectional study was conducted during January 2022 to June 2022, among 50 randomly selected patients in the age group of 30-70 years with type II Diabetes Mellitus of more than 5 years duration without hypertension, who were admitted in Government Rajaji Hospital, Madurai Medical College, Madurai during the study period of six months.

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Those individuals of age 30 to 70 years, those with duration of diabetes from initial diagnosis more than 5 years were included. The exclusion criteria include patients younger than 30 or older than 70 years, those with a duration of diabetes less than five years from the initial diagnosis, and individuals with a prior history of hypertension, stroke, ischemic heart disease, liver disease, or thyroid disorders. Additionally, alcoholics, patients following a vegetarian diet, and those already on lipid-lowering medications are excluded from the study.

Institutional Human Ethics Committee approval was obtained. After explaining the study purpose to the participants, informed consent was obtained. Then, the investigations conducted alongside a questionnaire include a complete blood count, fasting and postprandial blood sugar levels, lipid profile, and renal function test. Urine microscopy is performed to check for sugar and albumin. Additionally, cardiovascular assessments include an ECG and a 2D transthoracic echocardiogram, as well as the measurement of carotid intima-media thickness (CIMT) for both carotids. Anthropometric measurements—height, weight, and body mass index (BMI)—are also recorded. The CIMT was measured by Doppler Ultrasonogram. Carotid Artery Doppler was done by B-mode ultrasound by using a 7.5 MHZ transducer. Both side CIMT was measured and mean was taken into consideration.

Data were entered in MS Excel and statistical analysis was done using SPSS Software. Numbers and percentages are used in reporting Categorical values. Mean and standard deviation are used while reporting Numerical values. Statistical analysis was done using chi-square test, unpaired T test and Pearsons correlation coefficient. Statistical significance was considered if p value was less than 0.05.

RESULTS

The mean CIMT of the study group was 0.8170 ± 0.175 mg/dL. About 32 of the individuals had CIMT <= 0.8 and 18 of the individuals had CIMT > 0.8. [Figure 1]

The mean age of the study group was 59.14 ± 6.9 years. Among the study population of 50 individuals, 6 of them were in the age group of <= 50. The mean CIMT in this group was 0.741 ± 0.066 mm. 21 of them were in the age group of 51 - 60. The mean CIMT in this group was 0.838 ± 0.17 mm. 23 of them were in the age group of >60. The mean CIMT in this group was 0.817 ± 0.197 mm. There was no statistical significance between the age, gender, mode of treatment, smoking, BMI and CIMT values.

About 27 of them were males and they had mean CIMT of 0.846 ± 0.186 mm. 23 of them were females and they had mean CIMT of 0.782 ± 0.158 mm. About 33 of them were on treatment with oral hypoglycemic agents and they had mean CIMT of 0.813± 0.159 mm. 17 of them were on treatment with oral hypoglycemic agents and they had mean CIMT of 0.823± 0.208 mm. About 18 of them had history of smoking and they had mean CIMT of 0.788± 0.172 mm. 32 of them had no history of smoking and they had mean CIMT of 0.832± 0.177 mm. The mean BMI of the study group was 24.91 ± 2.68 kg/m2. About 28 of them had a BMI of <25 kg/m2, and they had mean CIMT of 0.825± 0.187 mm. 21 of them had a BMI of 25 – 29.9 kg/m2, and they had mean CIMT of 0.809± 0.165 mm. 1 of them had a BMI of >=30 kg/m2. As it is a single individual CIMT is constant.

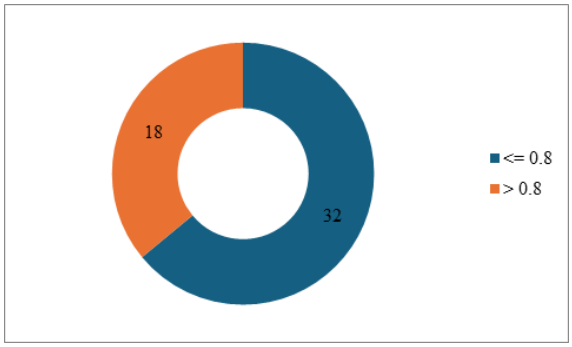

Figure 1: Distribution of study population according to CIMT

The mean FBS of the study group was 138.68 ± 40.82 mg/dL. About 19 of them had FBS of <110 mg/dL, and they had mean CIMT of 0.721± 0.1 mm. 31 of them had FBS of >=110 mg/dL, and they had mean CIMT of 0.875± 0.186 mm. The FBS values showed a positive correlation with CIMT values and it was statistically significant. The mean PPBS of the study group was 160.4 ± 42.35 mg/dL. About 24 of them had PPBS of <140 mg/dL, and they had mean CIMT of 0.82± 0.169 mm. 26 of them had PPBS of >=140 mg/dL, and they had mean CIMT of 0.813± 0.184 mm. There was no statistical significance between PPBS and CIMT values. The mean HBA1C of the study group was 7.25 ± 0.46 %. About 17 of them had a HBA1C value of <=7 %, and they had mean CIMT of 0.764± 0.156 mm. 30 of them had a HBA1C value of 7.1 – 8 %, and they had mean CIMT of 0.845± 0.183 mm. 3 of them had a HBA1C value of >8%, and they had mean CIMT of 0.833± 0.189 mm. There was no statistical significance between BMI and CIMT values.

The mean total cholesterol of the study group was 206.46 ± 34.82 mg/dL. About 29 of them had total cholesterol of <200 mg/dL, and they had mean CIMT of 0.736± 0.096 mm. 21 of them had total cholesterol of >=200 mg/dL, and they had mean CIMT of 0.928± 0.199 mm. The total cholesterol values showed a positive correlation with CIMT values and it was statistically significant. The mean TGL of the study group was 153.18 ± 27.45 mg/dL. About 32 of them had TGL of <150 mg/dL, and they had mean CIMT of 0.729± 0.08 mm. 13 of them had TGL of 150 - 199 mg/dL, and they had mean CIMT of 0.907± 0.182 mm. 5 of them had TGL of >=200 mg/dL, and they had mean CIMT of 1.14 ± 0.096 mm. The TGL values showed a positive correlation with CIMT

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values and it was statistically significant. The mean HDL of the study group was 45.58 ± 4.03 mg/dL. About 44 of them had HDL of <=50 mg/dL and they had mean CIMT of 0.831± 0.178 mm. 6 of them had HDL of >50 mg/dL and they had mean CIMT of 0.708± 0.102 mm. There was no statistical significance between BMI and CIMT values. The mean LDL of the study group was 130.24 ± 32.7 mg/dL. About 33 of them had LDL of <130 mg/dL, and they had mean CIMT of 0.745± 0.105 mm. 17 of them had LDL of >=130 mg/dL, and they had mean CIMT of 0.955± 0.202 mm. The LDL values showed a positive correlation with CIMT values and it was statistically significant. [Table 1]

A stepwise method of regression was done. The two earlier significant variables TC and LDL were excluded in the first step. This shows that even though the TC and LDL values were correlating with the CIMT, they did not exert a significant influence in the CIMT values when other significant parameters were adjusted for. Two parameters were found to influence the CIMT values in a statistically significant manner - TG and FBS.The model R2 (coefficient of determination) for TG alone was 0.514 which along with p value of <0.001 showed that about 51% of the variation in CIMT can be explained by triglyceride levels. When the other significant parameters were added on, the model R2 for FBS was 0.555, with a p value of <0.001 showing that these values contributed to the variations in the CIMT values in a significant manner. [Table 2] Pearson correlation was done for various other parameters shown in table 3. FBS, HbA1c, Total cholesterol, Triglycerides, HDL and LDL cholesterol showed significant results.

Table 1: Characteristics of study population and its relation with CIMT.

Characteristics	Category	No.	Mean CIMT	SD	p value
Age	<= 50	6	0.741	0.066	0.492
	51 - 60	21	0.838	0.17	
	>60	23	0.817	0.197	
Gender	M	27	0.846	0.186	>0.05
	F	23	0.782	0.158	
Mode of Treatment	OHA	33	0.813	0.159	>0.05
	INSULIN	17	0.823	0.208	
Smoking	YES	18	0.788	0.172	>0.05
	NO	32	0.832	0.177	
BMI	<25	28	0.825	0.187	0.74
	25 - 29.9	21	0.809	0.165	
	>=30	1	-	-	
FBS	<110	19	0.721	0.1	0.003*
	>=110	31	0.875	0.186	
PPBS	<140	24	0.82	0.169	0.832
	>= 140	26	0.813	0.184	
HbA1c	<=7.0	17	0.764	0.156	0.137
	7.1 - 8	30	0.845	0.183	
	>8	3	0.833	0.189	
Total cholesterol	<200	29	0.736	0.096	<0.001*
	>=200	21	0.928	0.199	
TGL	<150	32	0.729	0.08	<0.001*
	150 - 199	13	0.907	0.182	
	>=200	5	1.14	0.096	
HDL	<= 50	44	0.831	0.178	0.293
	>50	6	0.708	0.102	
LDL	<130	33	0.745	0.105	<0.001*
	>= 130	17	0.955	0.202	
*P<0.05 – Statistically significant difference present					

Table 2: Univariate Linear Regression

Dependent variable	Independent variable	R2	p value
CIMT	TG	0.514	<0.001
CIMT	FBS	0.555	<0.001

Table 3: Pearson correlation with CIMT

Parameters	R value	p value	Significant
AGE	-0.052	0.719	NOT SIGNIFICANT
BMI	-0.129	0.373	NOT SIGNIFICANT
FBS	0.487	<0.001	SIGNIFICANT
PPBS	0.034	0.816	NOT SIGNIFICANT
HBA1C	0.3	0.034	SIGNIFICANT
TC	0.694	<0.001	SIGNIFICANT
TG	0.717	<0.001	SIGNIFICANT
HDL	-0.48	<0.001	SIGNIFICANT
LDL	0.675	<0.001	SIGNIFICANT

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DISCUSSION

Diabetic patients are at an increased risk for developing cardiovascular disease. Although there are various reasons for the development of cardiovascular risk, hyperglycemia is an important factor. In recent times the focus has changed to lipids, especially triglycerides. TG levels are being considered as independent risk factors for atherogenesis.

Atherosclerotic changes in vessels can be assessed early by measuring CIMT. In one study it is found that DM patients had a higher CIMT and higher TG values compared with control individuals.[12]

In type 2 DM, due to insulin resistance, the free fatty acid flux increases from the adipocytes. This leads to an increased supply of free fatty acids to liver, and therefore increased lipid (VLDL and TGs) synthesis within the hepatocytes. Together with defective hepatic clearance of lipoproteins, this plays a key role in the causation of dyslipidemia seen in type 2 DM (elevated TGs, low HDL-C, and increased small dense oxidized LDL particles). Diabetic dyslipidemia is an established trigger for atherogenesis and macrovascular disease.[13]

In this study, the results were analyzed in terms of demographic profiles (age and sex), BMI, glycemic status (FBS, PPBS and HBA1C), metabolic parameters (TC, TG, HDL and LDL).

In this study we found out a positive correlation between CIMT and various metabolic parameters – FBS, HBA1C, TC, TG, and LDL. It is also found out that there is negative correlation between CIMT and HDL values. Among the variables except HBA1C (p value 0.034) all other parameters were strongly significant (p value <0.001). Proceeding with regression showed that even though LDL and TC were correlating with CIMT, they didn't exert a significant influence in the CIMT values when other parameters were adjusted for.

The coefficient of determination was higher for TG alone, implying that TG values contributed to the variations in CIMT values in a significant manner.

Limitations: The limitations of this study include a small sample size of only 50 participants, which restricted the ability to draw broader conclusions about potential correlations. Additionally, the CIMT measurements were susceptible to observer variation, which may affect consistency. The study was conducted as a single-center investigation, and there was no clinical follow-up to assess outcomes over time, further limiting the scope of findings.

CONCLUSION

In people with dyslipidemia (especially hypertriglyceridemia and hypercholesterolemia), the carotid intima media thickness is significantly increased. The strongest influence on the variation in the Carotid intima media thickness, among the dylipidemia is hypertiglyceridemia. The HbA1c levels also independently influence the Carotid intima media thickness. Atherosclerosis is a major cause of morbidity and mortality in type 2 DM. CIMT which is an inexpensive and non invasive parameter can be used as a marker of early atherosclerosis. In diabetic individuals, lipid profile may be suggested to predict the future macrovascular complication of diabetes mellitus. However larger studies are needed to confirm these.

Recommendations: Regular monitoring of triglycerides and fasting blood sugar levels is recommended, as these factors significantly influence carotid intima-media thickness (CIMT) and may help predict early atherosclerosis risk in diabetic patients. Additionally, lipid profile screening, especially triglycerides, can be considered a priority in managing cardiovascular risk in diabetes. Larger, multicentric studies are advised to confirm these findings and improve risk stratification.

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