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Research Article

ASSOCIATION OF POSTPRANDIAL HYPERTRIGLYCERIDEMIA AND CAROTID INTIMA MEDIA THICKNESS IN TYPE 2 DIABETES MELLITUS PATIENTS

Fiza Bushra[1*], Mathur Rati[2], Sinha Maheep[1]

[1]Department of Biochemistry, Mahatma Gandhi Medical College & Hospital, Jaipur, India
[2]Department of Biochemistry, SMS Medical College & Hospital, Jaipur, India

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*Corresponding Author: **Bushra Fiza**
Department of Biochemistry,Mahatma Gandhi Medical College & Hospital, Jaipur (Raj), India. Pin-302022

ABSTRACT

The dyslipidemia that accompanies type 2 diabetes plays an important role in the pathogenesis of accelerated atherosclerosis. Elevated triglyceride levels have been suggested as better predictor of Ischemic heart disease (IHD) than elevated LDL cholesterol levels. Although triglyceride levels are generally increased in the postprandial periods, the association between postprandial triglyceride levels and atherosclerosis has not been investigated in diabetic patients. The present study was planned to investigate the association between postprandial triglyceride levels and carotid intima media thickness in type2 Diabetes mellitus patients.

50 patients of type 2 Diabetes mellitus with > 5 year duration of disease, age 30-60 years were included in the present study. Carotid artery Doppler was done by B-mode ultrasound using a 7.5 MHZ transducer with annular array ultrasound imaging system. Blood samples were obtained after an overnight fast and blood samples were taken again 4 hrs after the meal.

All patients were subjected to routine investigations along with fasting and postprandial triglycerides and B mode ultrasound scanning of carotid arteries.

The study population (Type 2 diabetics) was divided into 3 groups based on fasting and postprandial triglyceride levels. **Normo-Normal (NN) Group i.e.** fasting triglyceride level (≤150 mgs/dl) and normal postprandial triglyceride levels (≤200 mgs/dl); **Normo-Hyper (NH) Group i.e.** fasting triglyceride level ≤150 mg/dl and postprandial triglyceride level >200 mgs/dl; **Hyper – Hyper (HH) Group i.e.** fasting triglyceride level (>150mgs/dl) and elevated postprandial triglyceride levels (>200 mgs/dl).

It was observes that postprandial hypertriglyceridemia had a better and more significant association with CIMT and hence, despite normal fasting triglyceride levels it may be an independent risk factor for early atherosclerosis in type 2 diabetes. Hence, evaluating not only FTG level but also PPTG level during clinical assessment of patients with type 2 diabetes is important.

Keywords: Dyslipidemia; Type 2 Diabetes mellitus; Low-density Lipoprotein (LDL); Carotid Intima Media Thickness (CIMT); Fasting triglycerides (FTG); Postprandial hypertriglyceridemia (PPTG)

INTRODUCTION

Diabetes mellitus (DM) comprises of a group of metabolic disorders that share the phenotype of hyperglycemia. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system[1].

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 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[2].

In type 2 DM, insulin resistance in the liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state. Increased hepatic glucose production occurs early in the course of diabetes, though likely after the onset of insulin secretory abnormalities and insulin resistance in skeletal muscle. As a result of insulin resistance in adipose tissue and obesity,

free fatty acid (FFA) flux from adipocytes is increased; leading to increased lipid synthesis, especially very low density lipoprotein (VLDL) and triglyceride (TG) in hepatocytes. This lipid storage or steatosis in the liver may lead to non-alcoholic fatty liver disease and abnormal liver function tests. This is also responsible for the dyslipidemia found in type 2 DM namely elevated TG, reduced HDL, and increased small dense LDL (low density lipoprotein) particles. Both hyperglycemia and hyperlipidemia are important consequences of the disease that can trigger several inflammatory processes to produce larger damage at a later stage[3].

Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. This buildup 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 consistently shown to be associated with a greater risk for atherosclerosis in those with type 2 diabetes. In persons with prolonged increases of plasma triglycerides, either fasting or postprandial, the process of lipid exchange would enrich the triglyceride rich particles in cholesteryl ester and thereby make these particles more atherogenic[4].

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) defined elevated triglycerides as 150 mg/dL and higher[5].

The role of elevated triglyceride (TG) levels in the pathogenesis of atherosclerotic cardiovascular disease has remained a controversial issue. TG, the major lipids in chylomicrons, and very-low-density lipoprotein (VLDL) particles, are closely related to the metabolism of other lipoproteins, including high-density lipoprotein (HDL) particles. Increased serum TG levels are associated with at least four pathogenic conditions: decreased serum HDL cholesterol levels, increased remnant lipoproteins, increased small dense low-density lipoprotein (LDL), and increased thrombogenesis, all of which are believed to expedite atherosclerosis. Even though considerable evidence supports the view that elevated TG level is an independent risk factor for coronary artery disease (CAD), adjustment for covariates frequently weakens or eliminates the predictive significance of TG[6].

These abnormalities may explain the characteristic diabetic dyslipidemia, which is now recognized to be very atherogenic[7]. Already in 1959, an association between plasma triglyceride concentrations and incident coronary heart disease was reported by Albrink et al., 1959[8].

In general practice, serum lipid concentrations including triglycerides are measured in the morning after an overnight fast. However, the fasting value should be considered as the result of the 24 hour TG profile and could therefore be misleadingly low. In the past few years several clinical studies have suggested that high postprandial TG may be related to coronary heart and/or carotid artery disease in non-diabetic as well as diabetic subjects[9-11].

Atherosclerosis, unless in a severe form is often asymptomatic, so that a direct examination of the vessel wall is necessary to detect affected individuals in the early stages. High resolution B-mode ultrasound is a non-invasive technique widely used to assess atherosclerosis in superficial arteries. It allows the accurate measurement of the distance between blood–intima and media–adventitia interfaces of the carotid wall, which is defined as carotid intima-media thickness (CIMT)[12]. Several authors have suggested that CIMT is a marker of atherosclerosis in other vascular beds[13]. Indeed, an increased CIMT has been associated with a number of atherosclerosis risk factors[14, 15] with the prevalence and extent of coronary artery disease (CAD)[15] and with the incidence of new coronary and cerebral events[16]. In view of these relationships, carotid IMT has been proposed as a surrogate endpoint to be used in clinical trials as an alternative to coronary atherosclerosis[17, 18].

The present study was planned to assess and compare the association of fasting and post prandial TG levels in Type 2 DM patients with the CIMT and hence with the risk of developing atherosclerosis and CVD.

MATERIALS AND METHODS

50 patients with type 2 diabetes mellitus in the age group of 30-70 years attending Mahatma Gandhi Hospital, Jaipur were included in the present study. The criterion for inclusion was known case of type2 DM for more than one year, having HbA1c <8%. Patients with evidence of CVD, ischemic heart disease (IHD), renal, liver or thyroid disorder and history of antilipidemic drugs were excluded.

Each patient underwent detailed clinical history and physical and systemic examination. The patients were then subjected to investigations viz. Fasting and PP blood sugar, HbA1c, fasting lipid profile and PP TG.

Carotid artery Doppler was done by B-mode ultrasound using a 7.5 MHZ transducer with annular array ultrasound imaging system. Blood samples were obtained after an overnight fast and then the patients ate a standard meal that had a total energy of 9Kcal/Kg with 60-65% of this energy being supplied by carbohydrate, 15-20 % by protein and 20% by fat after taking insulin or oral hypoglycemic agent. Blood samples were taken again 4 hrs after the meal. Total cholesterol, fasting and postprandial triglycerides, HDL were measured by colorimetry using Randox Daytona analyzer. LDL cholesterol was calculated by applying Friedewald's formula.

LDL Cholesterol = Total Cholesterol – (HDL +Triglycerides/5).

Based on fasting & postprandial triglyceride levels, the study population (Type 2 diabetics) was divided into 3 groups

Normo-Normal (NN) Group

This group consists of subjects with normal fasting triglyceride level (≤150 mgs/dl) and normal postprandial triglyceride levels (≤200 mgs/dl).

Normo-Hyper (NH) Group

This group consists of subjects with normal fasting triglyceride level (≤150 mgs/dl) and elevated postprandial triglyceride levels (>200 mgs/dl).

Hyper – Hyper (HH) Group

This group consists of subjects with elevated fasting triglyceride level (>150mgs/dl) and elevated postprandial triglyceride levels (>200 mgs/dl).

In order to assess the association of different components of the lipid profile with the carotid intima media thickness, results obtained were subjected to statistical analysis. P< 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Atherosclerosis is a disease of the arterial wall and significant lumen encroachment is apparent only after the artery has experienced tremendous mural changes. Angiography, which measures lumen encroachment, is therefore, an inadequate tool to use in the study of early atherosclerosis. With the capability of measuring the intimal-medial thickness in the arterial wall, B-mode ultrasonography meets these challenges. B-mode ultrasonography is a very useful tool to study early atherosclerosis and the massive mural changes associated with early atherosclerosis. B-mode imaging offers other advantages over angiography, as it is noninvasive, risk free and less expensive. It can also be used to assess progression or regression of atherosclerosis by multiple serial measurements.

Although several studies have shown fasting triglyceride levels to be associated with Coronary artery disease in both diabetic and non-diabetic subjects, relatively little attention has been given to postprandial triglycerides in this regard, especially in diabetic subjects. In the present study, it was observed that carotid intima media thickness (CIMT) was increased in patients with postprandial hypertriglyceridemia despite normal fasting triglyceride levels, and the postprandial triglyceride levels showed the strongest influence on CIMT.

Among the total 50 patients 29 were males (58%) and 21 were females (42%).

The mean serum total cholesterol in the NN, NH and HH group were 148.47±32.60, 174.0±37.63, 181.07±33.79 (mg/dl) respectively (Table 1). Shinichi Teno et al have reported the mean serum total cholesterol in the NN, NH and HH groups in their study as 194.9 ± 28.0, 220.7 ± 23.4 and 228.4 ± 44.2 (mg/dl) respectively.

The mean serum HDL in the NN, NH and HH group were 36.23±5.02, 35.26±5.55 and 36.28±4.39 (mg/dl) respectively. The mean serum LDL in the NN, NH and HH group were 92.23±32.28, 115.47±39.94 and 105.28±29.86 (mg/dl) respectively. The mean serum fasting triglyceride in the NN, NH and HH group were 100.11±21.04, 116.0±20.8 and 197.28±65.76 (mg/dl) respectively. The mean serum postprandial triglycerides in the NN, NH and HH group were 152.52±31.15, 274.26±54.33 and 296.92±65.76 (mg/dl) respectively (Table 1).

Table1: Distribution of analytes in the groups based on fasting and PP Triglyceride levels

Variable	NN group (n=17)	NH group (n=19)	HH group (n=14)	F	P-value
Age	55.12 + 9.77	57.63 + 9.13	48.53 + 10.98	1.03	NS
Cholesterol	148.47 + 32.60	174.0 + 37.63	181.07 + 33.79	3.91	< 0.05
HDL-Chol	36.23 + 5.02	35.26 + 5.55	36.28 + 4.39	0.59	NS
Fasting TG	110.11 + 21.04	116.0 + 20.8	197.28 + 65.76	23.65	<0.001
Post prandial TG	152.52 + 31.15	274.26 + 54.33	296.92 + 65.76	37.21	<0.001
CIMT	0.93 + 0.32	1.48 + 0.54	1.79 + 0.45	5.86	< 0.01

NS – non significant, P-value – as obtained on applying One way ANOVA

Previous studies have suggested that a fat challenge may induce several abnormalities independent of the underlying disorder. Vogel et al demonstrated impaired endothelial function in healthy subjects without risk factors for cardiovascular disease when subjected to a single high fat meal[19].

Similarly, Murphy et al showed that doses of 20 g fat were capable of eliciting an insulin mediated release of lipoprotein lipase, an enzyme that catalyzes plasma triglyceride clearance. Thus there is impaired postprandial clearance of triglycerides in diabetic and prediabetic individuals either due to insulin resistance or decreased insulin secretion[20].

A recently performed meta-analysis including data of 57,000 subjects from 17 studies demonstrated that fasting triglyceride concentrations were an independent risk factor for cardiovascular disease, also when adjusted for HDL cholesterol[21]. An increase in plasma triglyceride by 1 mmol/l was associated with a relative risk of 1.3 for men and 1.8 for women.

In the present study, CIMT exhibited a significant increase in the groups with elevated PP TG levels (Table 1). On applying Pearson's correlation, it was observed that the highest association was observed between PPTG and CIMT (r = 0.429) as compared to that between FTG and CIMT (r = 0.258) (Table 2; Fig 1 - 4).

Table2: Correlation coefficient for CIMT vs components of lipid profile

Variable	(Correlation coefficient) r	P value
Cholesterol	0.105	NS
HDL-Chol	-0.113	NS
Fasting Triglyceride	0.298	0.035
PP Triglyceride	0.429	0.002

NS – non significant, P-value – as obtained on applying Pearson's correlation

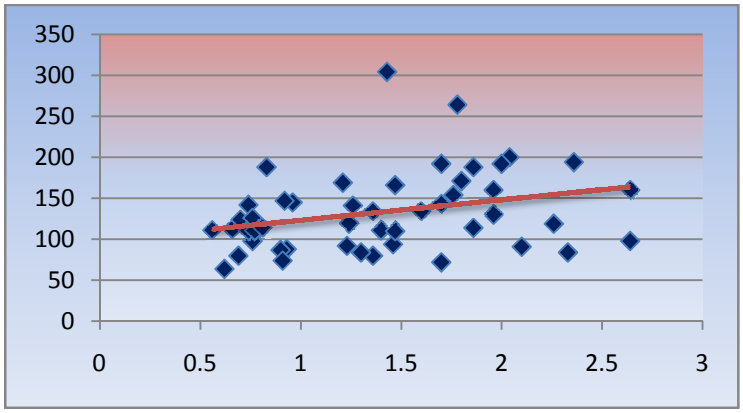

Figure 1: Scatter plot for CIMT (mm) vs FTG (mg/dl)

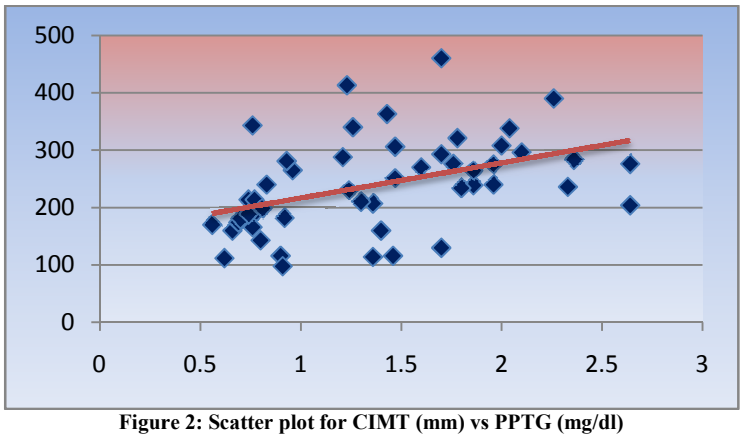

Figure 2: Scatter plot for CIMT (mm) vs PPTG (mg/dl)

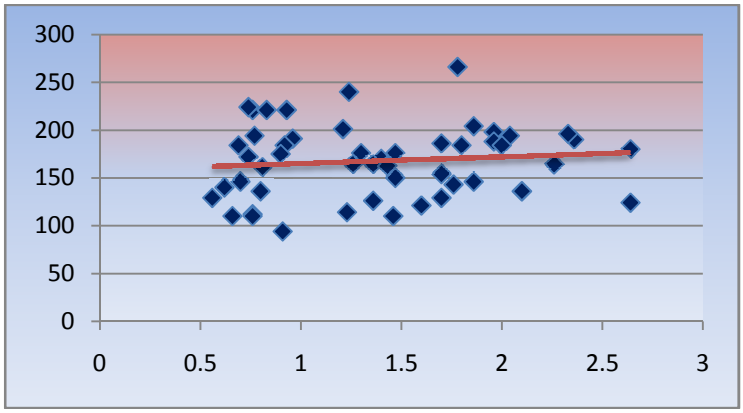

Figure 3: Scatter plot for CIMT (mm) vs CHOL (mg/dl)

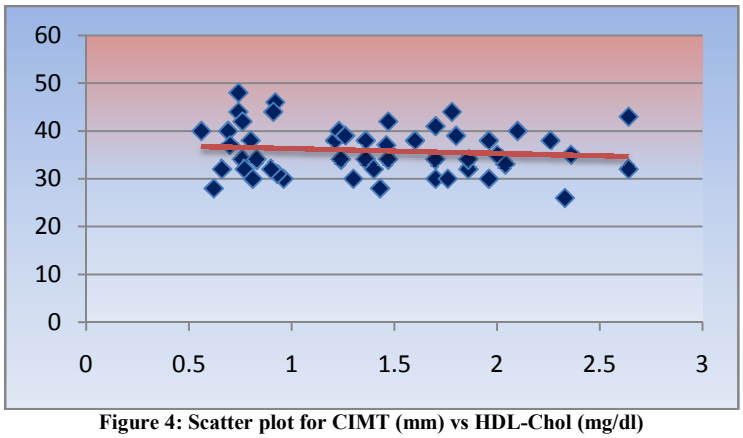

Figure 4: Scatter plot for CIMT (mm) vs HDL-Chol (mg/dl)

These findings were similar to those of Xiang C, 2003 who observed that CIMT in patients with postprandial hypertriglyceridemia was significantly greater than that in patients with normal PPTG levels (0.90 mm vs 0.81 mm, $p < 0.05$), which remained significant after adjustment for FTG and HDL levels[22].

In a recent study by Ahmad J et. al., 2005, the mean CIMT in the NN, NH and HH group were 0.59 ± 0.09, 0.79 ± 0.09 ($p < 0.001$ versus NN group) and 0.82 ± 0.06 mm ($p < 0.001$ versus NN group) respectively. So, it was observed that CIMT was increased in patients with postprandial hypertriglyceridemia despite normal FTG levels, and the PPTG levels showed the strongest influence on CIMT[23]. These results were similar to our study.

In a previous study by Boquist S et. al., 1999, it was observed that in the postprandial state, the plasma triglycerides, total triglyceride area under curve, incremental triglyceride area under curve were significantly associated with CIMT ($p < 0.05$)[24].

In a study done by Mohan V et. al., 2000[24] on intimal-medial thickness of carotid artery in the south Indian diabetic and non-diabetic, it was shown that the mean intimal-medial thickness of the diabetic subjects 0.95 ± 0.31 mm were significantly higher than those of nondiabetic subject 0.74 ± 0.14 mm with $P< 0.001$.

The present study therefore suggests that postprandial hypertriglyceridemia is an independent risk factor for development of early atherosclerosis in patients with type 2 diabetes mellitus. The evaluation of postprandial triglyceride levels can therefore serve as markers for screening of diabetic patients for risk of atherosclerosis and other related complication.

CONCLUSION

The chief observation in the present study was that elevated fasting triglyceride level was significantly correlated with carotid intima media thickness, but higher correlation was found in this study between elevated postprandial triglyceride level and carotid intima media thickness. So, postprandial hypertriglyceridemia, despite normal fasting triglyceride levels, may be an independent risk factor for early atherosclerosis in type 2 diabetes. Hence, evaluating not only FTG level but also PPTG level during clinical assessment of patients with type 2 diabetes is important. Further, the study proposes that extensive research is necessary to assess the correlation of other CVD risk factors with CIMT so as to improve patient management and minimize the risk of such disorders.

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