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General Medicine

POSTPRANDIAL HYPERTRIGLYCERIDEMIA AS A RISK FACTOR FOR MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

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ABSTRACT Diabetes mellitus is a common endocrine disorder characterized by chronic hyperglycemia, and disturbances of carbohydrate, fat and protein metabolism. The prevalence of diabetes has been increasing widely in India and worldwide. Diabetes is a cause of significant mortality and morbidity due to macro and micro vascular complications. Dyslipidemia accompanying type 2 Diabetes plays an important role in pathogenesis of atherosclerotic vascular disease. Post prandial hypertriglyceridemia, irrespective of fasting triglyceride levels, has emerged as a significant risk factor for symptomatic and asymptomatic macro vascular disease It is a case control study, conducted for a period of 1 year from November 2020 to October 2021, on patients visiting the Out-patient department of NRI institute of Medical Sciences, Sangivalasa, Visakhapatnam. The cases and controls were subjected to clinical and biochemical evaluation to detect presence of macro vascular complications. The cases were subjected to a high fat meal, and plasma triglycerides were measured two and four hours after a fat challenge. It was observed that post prandial hypertriglyceridemia correlated better than fasting triglycerides in patients with macro vascular complications. Persistent and significant post prandial hypertriglyceridemia was observed in diabetic patients with macro vascular complications; and can be used as a marker for predicting vascular complications in type 2 Diabetes mellitus.

KEYWORDS : hypertriglyceridemia, diabetes mellitus, macrovascular complications

Introduction:

Diabetes mellitus is a common endocrine disorder characterized by chronic hyperglycemia, and disturbances of carbohydrate, fat and protein metabolism. The prevalence of diabetes has been increasing widely in India and worldwide. Diabetes is a cause of significant mortality and morbidity due to macro and micro vascular complications.

Dyslipidemia accompanying type 2 Diabetes plays an important role in pathogenesis of atherosclerotic vascular disease. The most important components of dyslipidemia are an elevated very low density lipoproteins(VLDL), Low density lipoprotein (LDL), triglycerides, and decreased High density lipoproteins(HDL)

The response to injury hypothesis of atherosclerosis states that the initial damage affects the arterial endothelium leading to endothelial dysfunction. It has been hypothesized that hypertriglyceridemia induces endothelial dysfunction through the production of oxidative stress. This process may involve the over generation of superoxide anion, which in turn inactivates nitric oxide (NO).

Post prandial hypertriglyceridemia, irrespective of fasting triglyceride levels, has emerged as a significant risk factor for symptomatic and asymptomatic macro vascular disease Increased serum TGL levels are associated with at least four pathogenic conditions:

- decreased serum HDL cholesterol levels,
- increased remnant lipoproteins,
- increased low-density lipoprotein (LDL), and
- increased thrombogenesis

In the insulin-resistant state the production of VLDL by the liver is inappropriately high. Together with a reduced lipoprotein lipase activity this results in high triglyceride concentrations, especially in the postprandial state.

The large amount of TRLs (triglyceride-rich lipoproteins) and their prolonged residence time in the circulation may lead to increased exchange of the core lipid cholesteryl ester for triglycerides between TRL, LDL and HDL particles mediated by cholesteryl ester transfer protein. This process enriches LDL and HDL with triglyceride, and these particles are subsequently more readily hydrolysed by hepatic lipase resulting in smaller, denser LDL particles and lower concentrations of HDL.

Material and methods:

It is a case control study, conducted for a period of 1 year from November 2020 to October 2021, on 100 patients visiting the Out-patient Department General Medicine, NRI Institute of Medical Sciences,Visakhapatnam.

INCLUSION CRITERIA

- Patients with duration of diabetes mellitus more than 1 year
- Individuals without diabetes or their complications were taken as controls

EXCLUSION CRITERIA

- Patients on lipid lowering agents
- Patients with history of inherited disorders of lipid metabolism
- Patients with history of endocrine disorders affecting lipid levels
- Diagnosis of Diabetes was made on the basis of American Diabetes

Association criteria:

1. Fasting Plasma Glucose ≥126mg/dl
2. 2hr Postprandial Plasma Glucose ≥ 200mg/dl
3. Hemoglobin A1c ≥ 6.5%

The presence or absence of macro vascular complications was made on the basis of the following:

1. Clinical features suggestive of macro vascular events like CAD, stroke, hypertension and peripheral vascular disease.
2. Electrocardiogram
3. Echocardiogram
4. Ankle Brachial Index

After the diagnosis of type 2 diabetes mellitus and its complications, Patients were divided into 3 groups based on the presence or absence of complications as follows-

Group I: Controls (Non-diabetic, healthy individuals)
Group II: Type 2 DM cases without Macro vascular complications
Group III: Type 2 DM cases with Macro vascular complications.

All the selected patients were subjected to a high fat meal which consisted of whipped cream (containing 75 grams of fat, five grams of carbohydrate and 6 grams of protein per square meter of body surface area). For lipid analysis, blood samples were collected after 8 hours of

fasting, two hours and four hours of postprandial state after giving high fat meal. Serum was separated and stored in the refrigerator. From the serum, total Cholesterol, HDL and Triglycerides were estimated separately by using ENZYMATIC COLORIMETRIC METHOD.

From the above values, LDL-C was estimated by using FRIEDEWALD formula

LDL-C= Total Cholesterol - (HDL+TGL/5)

The information collected regarding all the selected cases were recorded in a Master Chart and Data analysis was done. Range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship

Results:

The total number of patients included in the study was 75. 25 controls were also included in the study for comparative analysis.

Among the total of 75 Type 2 diabetes mellitus patients, 50 diabetic patients [Female (F)-20; Male (M)-30] had no evidence of macro vascular complications (Group-II), whereas 25 diabetic patients(F-10; M-15) had evidence of macro vascular complications (Group-III).

Out of the 25 controls (group I), 10 were female and 15 were male. They had no evidence of diabetes or its complications after clinical and laboratory evaluation.

The age of the controls ranged from 36 to 60 years with a mean age of 51.2+7.9 years. The age of the patients in group II ranged from 32-62 years with a mean of 50.4+8.4 years, while that of group III ranged from 45-67 years with a mean of 56.4+6.6 years.

Male : Female ratio was 3:2 in all 3 groups

Fasting (0 hr) and postprandial blood sugar values (2 and 4 hours) were analyzed in the three groups. The mean FPG in group I was 81.1+12.7 mg/dl compared to 128.5+32.6 mg/dl in group III. On the other hand mean 2 hour PPG values in group I were 125.3+8.5 mg/dl as opposed to 202.6+45.1 mg/dl in group III

	Group I (controls)	Group II (Diabetes without complications	Group III (Diabetes with complications)
Fasting Plasma Glucose	81.1±12.7mg/dl	118.5±29.4 mg/dl	128.5±32.6mg/dl
2hr Post prandial Glucose	125.3±8.5mg/dl	173.8±30.7mg/dl	202.6±45.1mg/dl
4hr Post Prandial Glucose	86.1±9.6mg/dl	148.9±40.3mg/dl	170.6±39.3mg/dl

The prevalence of hypercholesterolemia was more in group II and III than controls (60% in diabetics compared to 20% in controls) and the difference was statistically significant.

There was no significant difference in HDL or LDL values between the three groups.

	Group I (Controls)	Group II (Diabetes without complications)	Group III (Diabetes with complications)
Total Cholesterol (mg/dl)	188.6+27.7	208.2+31.8	212.5+31
Serum HDL (mg/dl)	44.8+8.1	47±10.7	45.2+10.8
Serum LDL (mg/dl)	112.3+30.3	122.6+33.6	126.8+27.7

Fasting TGL levels (0 hr) and post load TGL levels (2 and 4 hours) were analysed. The mean fasting TGL values were 121+19.8mg/dl in group I, 156+63.1mg/dl in group II, 184+68.7mg/dl in group III.

The mean 4-hrs post load TGL values were 131.5+29.4mg/dl in group I, 217+96.1mg/dl in group II, 264+101.7mg/dl in group III. TGL values remained persistently elevated in 64% (n=32) of patients in group II and 84% (n=21) of patients in group III compared to only 16% (n=4)of patients in group I

	Group I (controls)	Group II (Diabetes without complications)	Group III (Diabetes with complications)
Fasting Triglycerides	121±19.8mg/dl	156.4±63.1 mg/dl	184.8±68.7 mg/dl
2hr Post prandial Triglycerides	140.3±19.8 mg/dl	209.7±86.3mg/dl	258.4±87.4 mg/dl
4hr Post Prandial Triglycerides	131.5±29.4 mg/dl	217±96.1 mg/dl	264.5±101.6 mg/dl

The difference was statistically significant, indicating that postprandial hypertriglyceridemia (p=0.0027), may be more important in macro vascular complications than fasting TGL(p=0.0001).

Hypertriglyceridemia at four hours after fat meal was compared between the three groups. There was significant difference in values between groups I and III (p=0.0001), groups I and II (p=0.0006), groups I, II and III (p=0.0001)

These results indicate that persistent hypertriglyceridemia at four hours post load was seen more in patients with macro vascular complications

Correlation between 4-hr post load hypertriglyceridemia and blood sugar was analyzed. Patients with hypertriglyceridemia had higher mean glucose values than those who did not have hypertriglyceridemia.

It was found that hypertriglyceridemia correlated significantly with both fasting and postprandial blood sugar values. The 4-hr PPG correlated better with hypertriglyceridemia (p=0.0001) than fasting blood sugar (p=0.0004).

It is seen that 4-hr post prandial hyperglycemia and hypertriglyceridemia correlated significantly in the presence of macro vascular complications

Mean cholesterol values were higher in the patients with hypertriglyceridemia (215+33.2mg/dl) than in patients without hypertriglyceridemia (189.1+21.7mg/dl).

The 4-hr hypertriglyceridemia was compared with standard lipid ratios. Although there was no significant correlation between triglyceride levels and standard lipid ratios, a slightly higher TC/HDL and LDL/HDL ratios were seen in patients with hypertriglyceridemia than those without it

Discussion:

This study was aimed to identify postprandial hypertriglyceridemia as a significant risk factor for vascular events in type 2 Diabetes mellitus patients.

Individuals with normal fasting triglyceride levels exhibit highly varying postprandial triglyceride concentrations after a fatty test meal. Therefore, postprandial lipemia, representing triglyceride metabolic capacity under challenge, is considered to be more informative for assessing the role of triglyceride metabolism in the development of atherosclerosis.

A study conducted by Rajmohan et al in South Indian type 2 diabetic subjects revealed that the prevalence of CAD was significantlyhigher among patients with isolated hypercholesterolemia, isolated highLDL, and isolated low high-density lipoprotein levels compared to normolipidemic individuals, but not in those with isolatedhypertriglyceridemia[4]. In contrast, Anderson et al showed that CAD was higher in patients with isolated hypertriglyceridemia[5]. In this study, fasting cholesterol levels correlated significantly with triglyceride levels(p=0.0002) and both were high in patients with vascular events. Another observation made in this study was that there was no significant difference in the LDL or HDL cholesterol values between the three groups and triglycerides were elevated even with other lipoprotein measures in the normal range. This can be explained by the fact in thatdiabetic patients, altered morphology of the lipoprotein structure may contribute more to atherogenesis rather than the absolute value (small dense atherogenic LDL)[1,2]

All the patients who had fasting triglyceridemia also had elevated postprandial TGL. This is in accordance with various studies in the past which have made the observations that elevated postprandial TGL levels have been seen in persons with fasting hypertriglyceridemia9.
It was found in our study that postprandial triglyceridemia (p=0.0027) correlated better than fasting triglyceridemia with vascular events (p=0.0001).

There was also good correlation between fasting (p=0.0006) and postprandial blood sugar (p=0.0001) and postprandial triglyceridemia in patients with vascular events, as observed in previous studies, where the independent and cumulative role of postprandial hypertriglyceridemia and hyperglycemia in the causation of endothelial dysfunction in diabetes was proved[3].

It was also observed that while postprandial triglyceride abnormalities occur in type 2 Diabetes Mellitus regardless of presence or absence of macro vascular complication, the magnitude of abnormalities tend to be higher in those with macrovascular diseases suggesting that higher postprandial triglyceride burden was associated with higher macrovascular diseases. Another study done by Patsch et al also demonstrated that postprandial TGL is important for the propensity for atherosclerosis6,7 Golay et al have found in their study that postprandial lipids arefrequently being neglected as important determinants of coronary events in patients with type 2 diabetes mellitus[8]

However, the protocol for measuring postprandial hypertriglyceridemia needs to be formulated, and it is necessary to formulate precise guidelines on the time intervals for measuring postprandial triglyceride levels, and the fat load to be used.

The normal cut-off values for TGL also have to be internationally standardized.

If these guidelines are established, simple measurement of postprandial triglyceride levels and subsequent dietary or pharmacological intervention may help to detect or prevent endothelial dysfunction in diabetes, thus alleviating the mortality and morbidity associated with the disease.

Conclusion:

Persistent and significant post load hypertriglyceridemia was observed in diabetic patients with macro vascular complications compared to controls; hence it is a useful marker for predicting vascular complications in type 2 diabetes mellitus.

Postprandial hypertriglyceridemia was more significant than fasting triglyceridemia in complicated diabetes.

Hypertriglyceridemia was observed independent of LDL, HDL and standard lipid ratios in patients with vascular disease. Hence it may represent an independent risk factor for vascular events in diabetes.

Detecting and correcting early postprandial hypertriglyceridemia with the help of a standardized fat challenge test may be a useful therapeutic option in halting endothelial dysfunction and hence macro vascular complications in diabetes.

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