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SIGNIFICANCE OF POST PRANDIAL HYPERTRIGLYCERIDEMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH AND WITHOUT MACROVASCULAR DISEASE

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ABSTRACT

Background: Diabetes Mellitus is one of the largest global health emergencies of this century ranking among the 10 leading causes of mortality together with cardio vascular disease, respiratory disease and cancer. As per the IDF, one in 11 adults has diabetes in India. Postprandial hyperglycemia traditionally considered to be a risk factor for macrovascular events in diabetes, but off late postprandial hypertriglyceridemia is fast emerging as a risk factor for cardiovascular disease Objective. To assess the significance of postprandial hypertriglyceridemia as an early marker of macrovascular complications of Type 2 diabetes mellitus. **Methods**. The study was a case control study conducted for a period of one year between July 2017 and June 2018. Patients were divided into 3 groups: group I, group II, group III, and group III.**Results:** The prevalence of hypercholesterolemia was more in group II and III than controls (56.3% in diabetics compared to 20% in controls) and the difference was statistically significant (p=0.0202). The mean 4-hrspostload total glycerol (TGL) values were 132.6+29.4mg/dl in group I (n=29) compared with 218+96.7mg-dl and 265.1+101.9mg, respectively. The mean TGL values remained persistently elevated in 65.9% and 83.3% of patients in group III and only 18.2% of controls (p0.0001). Postprandial TGL was seen in 81.5% of diabetic patients with macrovascular complication and 61.7% of patients without complications, whereas it was seen only in 20% of controls. **Conclusion**. Persistent and high TGL at four hours post fatty meal was observed in newly detected type 2 DM with complications indicating a marker for predicting vascular events in type 2 diabetes.

Keywords: Postprandial hyperglycemia, postprandial hypertriglyceridemia, Type 2 diabetes mellitus, atherosclerosis, endothelial dysfunction, oxidative stress.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder of carbohydrate, fat and protein metabolism characterized by hyperglycemia, affecting millions of people all over the world. As per the IDF 2017 statistics there were 451 million (age group 18-99 years) people with diabetes worldwide, these were expected to increase to 693 million by 2045. It was estimated that nearly half of all people (49.7%) living with diabetes are undiagnosed. The burden of diabetes is rapidly increasing in developing economies like China and India fueled by high prevalence of overweight/obesity mainly due to unhealthy life styles. The main problem of the disease is mainly due to its vascular complications, microvascular complications like retinopathy, nephropathy and neuropathy, and macrovascular complications like coronary artery disease (CAD), stroke and peripheral arterial diseases which leads to

increase morbidity and mortality. Among the known risk factors for macrovascular complication especially CAD i.e., smoking, hyper tension and obesity, however current research suggests the possible role of hypertriglyceridemia especially postprandial hypertriglyceridemia as an emerging risk factor for atherogenesis in diabetics**(1,2)**. It has been suggested that post prandial hyperglycemia and hypertriglyceridemia induce an endothelial dysfunction through the production of an oxidative stress , causing over generation of super oxide anion (O2-) with decreased nitric oxide(NO) production , suggesting response-to-injury hypothesis of atherogenosis**(3)**.

The aims of the study were to assess the significance of postprandial hypertriglyceridemia as an early marker of macrovascular complications of Type 2 diabetes mellitus and to compare fasting triglyceride with postprandial triglyceride levels and other lipid ratios in predicting macrovascular complications.

MATERIALS AND METHODS

The study was a case control study conducted for a period of one year from July 2017 to June 2018.

Inclusion criteria: Patients with new onset type 2 diabetes mellitus, who were willing to give consent were included in the study. Twenty five healthy controls without diabetes or any complications were also included in the study for comparison.

Exclusion criteria: Patients unwilling to give consent, severe co-morbid conditions and those on lipid lowering agents. Diagnosis of Type 2 diabetes mellitus was made by fasting and postprandinal blood sugar values using WHO criteria.**(2)**The presence or absence of macrovascular complications were made on the basis of the following criteria:

1.Clinical features suggestive of macrovascular events like CAD, stroke, hypertension and peripheral vascular disease(Ankle/brachial index).2.ECG 3.2-D/Echocardiogram.

METHODS

After the diagnosis of Type 2 diabetes mellitus and its complications, patients were divided into 3 groups.

GroupI: Controls,

Group II: Type 2 DM cases without Macrovascular Complications

Group III: Type 2 DM cases with Macrovascular Complications.

The study groups were also divided into three categories based on the body mass index as follows[1]-**Obesity:** BMI >25kg/m^2,**Overweight:**BMI >23.0-24.9kg/m^2,**Normal weight:** BMI 18.5-22.9kg/m^2,**Underweight:** BMI<=18.4 kg/m^2BMI=Weight (in Kg)/ Height (in meter^2)

All the selected patients were subjected to a high fat meal which consisted of whipped cream (containing 70 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 to 10 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, LDL and triglycerides were estimated separately by using enzymatic colorimetric method.

RESULTS

The total number of patients included in the study was 75. Twenty five controls were included in the study for comparison.

Among the total of 75 Type 2 diabetes mellitus patients, **49 diabetic patients [Female (F)-20; Male (M)-29]** had no evidence of macrovascular complications (**Group-II**), whereas **26 diabetic patients(F-16; M-10)** had evidence of macrovascular complications (**Group-III**).Out of the 25 controls (group I), 11 were female and 14 were male, they had no evidence of diabetes or its complications after clinical and laboratory evaluation. The age of the controls(Group I) ranged from 38 to 62 years with a mean age of 50.9$\pm$8 years. The age of the patients in group II ranged from 34-64 years with a mean of 50.5$\pm$9.5 years, while that of group III ranged from 46-68 years with a mean of 56.5$\pm$6.5 years.

It was observed that the female:Male ratio was almost equal in group I (1:1.27), a slightly higher ratio in group III (1.4:1) and lower in group II (1:1.4).

Patients and controls were classified as overweight, normal weight and underweight according to the body mass index. Out of 25 controls, 16 (64%) were in the normal weight patients as compared to 9 (13.4%) in the overweight patients. In group II, 33 out of 48 (68.75%) were in the normal weight patients as compared to 15 (31.25%) in the overweight patients. In group III, 17 out of 25 (68%) were normal weight patients compared to 10 (32%) overweight patients.

TABLE 1: BODY MASS INDEX

BMI	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Underweight (<=18.4)	6	24	4	8.33	4	14.8
Normal weight (18.5-22.9)	15	60	32	66.6	16	59.7
Overweight(23 to 24.9) /Obese (>25)	4	16	12	25	7	25.9
Range	17-30		18-28		19-31.4	
Mean	22.8		23.9		24.7	
S.D.	3.2		3.1		3.0	
'p'	**0.6126 Not Significant**					

The BMI of the three groups was comparable and there was no statistical difference (p=0.6126).

Biochemical analysis

Analysis of lipid profile was done in relation to the three study groups. The results are summarized in the below tables.

The prevalence of hypercholesterolemia was more in group II and III than controls (56.3% in diabetics compared to 20% in controls) and the difference was statistically significant (p=0.0202). There was no significant difference in HDL or LDL values between the three groups.

TABLE 2 : LIPID PROFILE

Parameter	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Total Cholesterol						
Normal (< 200)	20	80	21	43.7	15	55.5
High (> 200)	5	20	27	56.3	12	45.5
Range	151-266		151-281		161-271	
Mean	189.6		207.9		211.9	
S.D.	27.8		31.9		32	
'p'	**0.0202 Significant**					

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 80.4±12.7 mg/dl compared to 128.6±32.7 mg/dl in group III. On the other hand mean 2 hour PPG values in group I were 125.8±9 mg/dl as opposed to 204.4±45.2 mg/dl in group III.

All the three values were more in the groups II and III. The difference between the three groups was statistically significant (p=0.0001).Fasting TGL levels (0 hr) and post load TGL levels (2 and 4 hours) were analyzed.

The mean fasting TGL values were 122±19.7 mg/dl in group I, 157±63.1mg/dl in group II, 183.9±68.3mg/dl in group III. The mean 4-hrs. post load TGL values were 132.6±29.4mg/dl in group I, 218±96.7mg/dl in group II, 265.1±101.9mg/dl in group III. TGL values remained persistently elevated in 65.9% (n=29) of patients in group II and 83.3% (n=20) of patients in group III compared to only 18.2% (n=4) of patients in group I.

TABLE 3: TGL levels at 0, 2 and 4 hours

TGL at	Group I		Group II		Group III		
	No.	%	No.	%	No	%.	
0hour Normal High	25 -	100 -	32 16	66.4 38.4	12 15	44.5 55.5	
2hours Normal High	20 5	80 20	16 32	33.3 66.7	5 22	18.5 81.5	
4 hours Normal high	20 5	80 20	16 32	33.3 66.7	5 22	18.5 81.5	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**'p'**
0 hour	120	19.8	155.9	62.9	183.9	68.8	**0.0027* Significant**
2 hours	141.6	19.8	208.9	86.4	259.1	86.5	**0.0001* Significant**
4 hours	132.6	29.4	218	96.7	265.1	101.9	**0.0001* Significant**

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

TABLE 4: BASELINE CHARACTERISTICS OF PATIENTS

	GROUP I (n=25)	GROUP II (n=48)	GROUP III (n=27)	'P' Value
Age(yrs)	50.9±8	50.5±9.5	56.5±6.5	0.0788(NS)
Male/Female(%)	54.6±45.4	58.9/41.1	42/58	-
BMI(kg/m^2)	22.7±3.2	23.9±3	23.8±3.2	0.6126(NS)
FPG (mg/dl)	80.4±12.7	116.6±29.5	128.6±32.7	**0.0001(S)**
FTGL(mg/dl)	122±19.7	157±63	183.9±68.3	**0.0027(S)**

LDL(mg/dl)	111.3±30.4	122±34	126.9±27.8	0.1311(NS)
HDL(mg/dl)	44.9±8.2	46±11	45.1±10.9	0.5372(NS)
TC(mg/dl)	188.7±26.9	208.1±31.9	212.6±31.3	**0.0202(S)**
V*Values are mean±S.D unless specified. FTGL=fasting triglyceride, NS=not significant; S=significant				

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).**

TABLE 5: HYPERTRIGLYCERIDEMIA IN VARIOUS GROUPS

Hypertriglyceridemia	**Group I(25)**		**Group II(48)**		**Group III(27)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Present (TGL>150)	5	20	32	66.7	22	81.5
Absent (TGL<150)	20	80	16	33.3	5	18.5
TGL at 4 hours						
Range	63-193		89-393		81-297	
Mean	131.6		216		265	
S.D.	29.3		96.2		101.8	
'p' value for						
1. Group I & II	**0.0006 Significant**					
2. Group I & III	**0.0001 Significant**					
3. Group II & III	0.2122 Not Significant					
4. Groups I,II&III	**0.0001 Significant**					

These results indicate that persistent hypertriglyceridemia at four hours post load was seen more in patients with macrovascular complications. Mean cholesterol values were higher in the patients with hypertriglyceridemia (217±34.2mg/dl) than in patients without hypertriglyceridemia (188.2±20.7mg/dl).

High cholesterol values correlated significantly with high TGL values (p=0.0002). Correlation between 4-hr post load hypertriglyceridemia and blood sugar was analyzed. Patients with hypertriglyceridemia had higher mean glucose values (2-hr PPG 186.2±40.6mg/dl, 4-hr PPG 158±41.8mg/dl) than those who did not have

hypertriglyceridemia (2-hr PPG 142±26mg/dl, 4-hr PPG 108±40.6mg.dl).

DISCUSSION

This study was done to emphasize the importance of postprandial hypertriglyceridemia which off late emerging as a significant risk factor for vascular complications of diabetes. Fasting triglycerides represents triglyceride metabolism under basal conditions, have not generally been accepted as an independent risk factor for atherosclerosis including coronary artery disease. Individuals with high fasting triglyceride levels tend to have varying postprandial triglyceride concentrations after normal and especially high fatty meal. Therefore, postprandial dyslipidemia, represents triglyceride metabolism on fat challenge is considered to be more informative for the development of atherosclerosis. Hence, a number of case control studies were done to link prolong hypertriglyceridimia with macrovascular complications of diabetes especially CAD. Many of the observations made in our study correlated well with previous studies as well.

In the present study, majority of our diabetic patients were in the normal weight group (60.1% in complicated diabetes and 71.2% in uncomplicated diabetes). According to Indian data, nearly 70% of type 2 DM patients are normal weight as compared to 60-70% of diabetics from the west. The mean fasting triglyceride levels in our study were 122±19.7mg/dl in the control group, 157±63 mg/dl in un-complicated diabetes and 183.6±68.3mg/dl in complicated diabetes. This is in concordance with other Indian studies. In the current study, the incidence of baseline hypercholesterolemia (p=0.0202) and hypertriglyceridemia (p=0.0027) was more in the diabetic patients than in controls and more so in complicated diabetes. This has been well highlighted in the literature**(4)** and was also observed in studies done by Taskinen MR et al, Ahuja M M et al and Richard J L et al **(5,6,7).** Insulin resistant and hypertriglyceridemia are well co related as high plasma TGL may represent an early step in the insulin action pathway**(8).**

A study conducted by Mohan A et al in South Indian type 2 diabetic showed high prevalence of CAD among patients with isolated high LDL, isolated low HDL and isolated high cholesterol, but not in those patients with high TGL**.(9)** In contrast, Ellis GR et al showed high prevalence of CAD among patients with isolated high TGL.**(10)** In our 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 correlation in the LDL or HDL cholesterol values among the three groups. This could be explained by the fact that diabetic patients may have high small dense LDL (more atherogenic) with normal LDL. **(4,11)**

In our study all patients who had high fasting TGL also had high postprandial TGL. This is in accordance with other studies as well.6 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. The same has been observed by other studies as well. (**2, 12)**

In our study that persistent triglyceridemia at four hours post fat meal was seen in 81.5% of diabetic patients with macrovascular complications and 61.7% of patients without complications, whereas it was seen only in 20% of controls (p=0.0001). It is correlating well with other studies in the past, indicating a definite relationship between macrovascular complications in diabetes and postprandial lipids. Miesenbock G et al.**(13,14,15)**. Golay et al have observed in their study that postprandial dyslipidemia are frequently being neglected as important early marker of coronary events in patients with type 2 diabetes mellitus.**(16)**

It was demonstrated in our study that postprandial (post fatty meal) triglyceridemia(p=0.0027) correlated better than fasting triglyceridemia with vascular events (p=0.0001). It was shown in past studies that there is some evidence for TGL as an independent risk factor in certain subgroups, for example, women 50–69 years of age 47 and men with low total cholesterol levels.**(17)**A meta-analysis of 17 population-based prospective studies, which included 46000 men and 11000 women, revealed a 30%; and 75%; increased risk of CAD, respectively, for TGL

levels.**(18)** In our study as well, women had significantly higher levels of postprandial triglycerides as compared to men, especially in complicated diabetes(p=0.0281).

The above observations indicate a good relationship between postprandial dyslipidemia, mainly postprandial hypertriglycerdemia and atherosclerosis than fasting lipid levels.

CONCLUSIONS

Postprandial dyslipidemia was seen in significant proportions of diabetic patients, especially among patients with macrovascular complications. Persistent and high postprandial TGL was observed in newly detected type 2 DM with complications compared to controls indicating an early marker for predicting vascular events in type 2 DM. Compared to fasting TGL, postprandial TGL is more significant, even so in complicated diabetes. High TGL was observed independent of LDL, HDL and standard lipid ratios in patients with vascular disease. Hence high HDL is an independent risk factor for vascular events.Although the current emphasis in mainly on LDL cholesterol and its reduction, postprandial hypertriglyceridemia may be equally though not more in causing vascular events.Detecting postprandial hypertriglyceridemia and its early correction by life style modification and medication if required could prevent endothelial dysfunction and hence macrovascular complications in diabetes mellitus.

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