Post Prandial Hypertriglyceridemia As A Risk Factor for Macrovascular Complications In Type 2 Diabetes Mellitus

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Abstract

Context: Apart from the known risk factors for CAD i.e., smoking, hypertension, obesity, and LDL cholesterol, current knowledge suggests the possible role of hypertriglyceridaemia as an important risk factor for atherogenesis in diabetics. Further the role of postprandial triglyceride elevation is recently gaining importance as an early abnormality in type 2 diabetic subjects.

Aim of the study

1. To assess the value of postprandial hypertriglyceridemia as a marker of macro vascular events in type 2 diabetes mellitus.
2. To compare postprandial with fasting triglyceride levels and standard lipid ratios in predicting macro vascular complications.

Settings and design: Analytical Case Control Study.

Materials and methods: The study was conducted on patients attending the outpatient department of Government Rajaji Hospital, Madurai. 68 Patients with new onset diabetes mellitus were included in the study. 22 healthy controls without diabetes or its complications were also included in the study for comparison. Patients on lipid lowering agents, hypertensive’s, smokers, and alcoholics were excluded from the study. All the patients underwent a detailed history elicitation and clinical examination including ankle brachial index. Biochemical analysis of urine albumin, fasting and postprandial plasma glucose, urea, creatinine, ECG, and echocardiogram investigations were done. 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, 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 postprandial state after giving above mentioned high fat meal.

Results: 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±65.1mg/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 even after 4 hours of fat meal in 65.9% (n=29) of patients in group II and 85.3% (n=20) of patients in group III compared to only 18.2% (n=4) of patients in group I. 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). 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. The mean LDL/HDL ratio was 2.91±0.93 in patients with hypertriglyceridemia in comparison with patients without hypertriglyceridemia where the ratio was 2.53±0.73. The correlation was not significant statistically. Thus, postprandial hypertriglyceridemia seems to be more significant and independent risk factor and an early sensitive marker of atherosclerosis in type 2 diabetic subjects.

Keywords: Post Prandial Hypertriglyceridemia, Macrovascular Complications, Type 2 Diabetes Mellitus

I. Introduction

India is frequently referred to as the diabetic capital of the world. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be in the 45–64 years of age. According to the Diabetes Atlas published by the International Diabetes Federation (IDF), there are an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people in 2025 by which time every fifth diabetic subject in the world would be an Indian. The real burden of the disease is
however due to its micro and macro vascular complications which lead to increased morbidity and mortality. This process may involve the over generation of superoxide anion, which in turn inactivates nitric oxide (NO). There is need for a simple investigation which can detect endothelial dysfunction at a much earlier date. Recently, much attention has been paid to the evidence that postprandial hypertriglyceridemia is an important contributing factor for the development of atherosclerosis in diabetes and trials are underway to determine if targeting triglycerides can halt the progress of atherosclerosis in diabetes.

II. Materials And Methods

2.1. Study Population: The study was conducted on patients attending the out patient department of Government Rajaji Hospital, Madurai. Approval from the hospital ethical committee was obtained. The study was a analytical case control study conducted for a period of one year.

2.2. Inclusion Criteria:
Patients with new onset diabetes mellitus were included in the study. Twenty two healthy controls without diabetes or its complications were also included in the study for comparison.

2.3. Exclusion Criteria:
Patients on lipid lowering agents, hypertensive’s, smokers, and alcoholics were excluded from the study.

2.4. Ethical Committee Approval: Obtained.

2.5. Study Protocol:
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

$$\text{LDL-C} = \text{Total Cholesterol} - (\text{HDL + TGL}/5)$$

The enzymatic method was used to estimate serum cholesterol values. Due to the specificity of enzymes, the enzymatic method is the most accurate and reference method for the estimation of Cholesterol. Dyslipidemia was defined by one or more of the following-

1. Total Cholesterol (TC) >200mg/dl
2. HDL Cholesterol <35mg/dl
3. LDL Cholesterol >100mg/dl
4. Triglycerides >150mg/dl

The standard lipid ratios (TC/HDL, LDL/HDL) were also calculated. The information collected regarding all the selected cases were recorded in a Master Chart.

2.6. Statistical Analysis:
Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002). Using this software, 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.

III. Results

Majority of the patients were from in and around Madurai city. The total number of patients included in the study was 68, newly detected type 2 diabetic patients. Twenty two, healthy non-diabetic controls were also included in the study for comparative analysis. Among the total of 68, newly detected Type 2 diabetes mellitus patients, 44 diabetic patients [Female (F)-18; Male (M)-26] had no evidence of macro vascular complications (Group-II), whereas 24 diabetic patients (F-14; M-10) had evidence of macro vascular complications (Group-III).

Out of the 22, healthy non-diabetic controls (group I), 10 were female and 12 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±9.4 years, while that of group III ranged from 45-67 years with a mean of 56.4±6.6 years. Twenty two patients in group II (50%) and 11 patients in group III (45.8%) were in the age group of 51-60 years. The age distribution of the patients is shown in the following TABLE 1. The age groups of the cases and controls were comparable and there was no statistical difference (p=0.0788). It was observed that the female: male ratio was almost equal in groups I (1:1.2), 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 22 controls, 14 (63.6%) were normal weight patients as compared to 3 (13.6%) overweight patients. In group II, 31 out of 44 (70.5%) were in the normal weight as compared to 10 (22.7%) overweight patients. In group III, 15 out of 24 (62.5%) were normal weight patients compared to 6 (25%) overweight patients. The BMI of the three groups was comparable and there was no statistical difference (p=0.6126).

<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics Of Patients</th>
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<tr>
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<tr>
<td>Age(yrs)</td>
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<tr>
<td>Male/Female(%)</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
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<tr>
<td>FPG (mg/dl)</td>
</tr>
<tr>
<td>FTGL(mg/dl)</td>
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<td>LDL(mg/dl)</td>
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<tr>
<td>HDL(mg/dl)</td>
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<tr>
<td>TC(mg/dl)</td>
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</tbody>
</table>

Values are mean+S.D unless specified. FTGL=fasting triglyceride NS=not significant; S=significant

The prevalence of hypercholesterolemia (defined as a total cholesterol cut off of 200mg/dl and above) was more in group II and III than controls (57.5% in diabetics compared to 18.2% 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. Above mentioned Table 1 indicates these baseline characteristics of patients. Fasting TGL levels (0 hr) and post load TGL levels after fat meal (2 and 4 hours) were analysed. The mean fasting TGL values were 121±19.8mg/dl in group I, 156.4±63.1mg/dl in group II, 184.8±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 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.

Hypertriglyceridemia at four hours after fat meal was compared between the three groups. There was significant difference in values between groups I and II (p=0.0006), groups I and III (p=0.0001), groups II and III (p=0.0001). TABLE 2 shows the comparative analysis of hypertriglyceridemia in relation to various groups.

<table>
<thead>
<tr>
<th>Table 2: Four Hours Post Fat Meal Load Hypertriglyceridemia In Various Groups</th>
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<tbody>
<tr>
<td>Hypertriglyceridemia Present</td>
</tr>
<tr>
<td>TGL &gt;150</td>
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<tr>
<td>Hypertriglyceridemia Absent</td>
</tr>
<tr>
<td>TGL &lt;150</td>
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<tr>
<td>TGL at 4 hours</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>0.0006 Significant</td>
</tr>
</tbody>
</table>
These results indicate that persistent postprandial hypertriglyceridemia at four hours post load was seen more in patients with macro vascular complications. Mean cholesterol values were higher in the patients with hypertriglyceridemia (215.5±33.2mg/dl) than in patients without hypertriglyceridemia (189.1±21.7mg/dl).

Correlation between 4-hr post load hypertriglyceridemia and blood sugar was analyzed. Patients with hypertriglyceridemia had higher mean glucose values (2-hr PPG 188.2±40.7mg/dl, 4-hr PPG 160±42.6mg/dl) than those who did not have hypertriglyceridemia (2-hr PPG 143±28mg/dl, 4-hr PPG 109±40.5mg/dl). The 4-hr post load hypertriglyceridemia was analyzed in relation to gender. Although the prevalence of hypertriglyceridemia was almost equal among males (49.1%) and females (50.9%), the mean TGL values were higher in females (234.9±107.1) than in males (185.9±84.8). The mean LDL/HDL ratio was 2.91±0.93 in patients with hypertriglyceridemia in comparison with patients without hypertriglyceridemia where the ratio was 2.53±0.73. The correlation was not significant statistically. 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 without it.

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>LDL/HDL RATIO</th>
<th>'p'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Present (TGL &gt;150)(n=53)</td>
<td>41</td>
<td>77.4</td>
</tr>
<tr>
<td>Absent (TGL &lt;150)(n=37)</td>
<td>32</td>
<td>86.5</td>
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</tbody>
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<table>
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<tr>
<th>4 Hours post fat meal load</th>
<th>Hypertriglyceridemia</th>
<th>TC/ HDL ratio</th>
<th>'p'</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Mean</td>
</tr>
<tr>
<td>Present (TGL &gt;150)(n=53)</td>
<td>33</td>
<td>62.3</td>
<td>20</td>
</tr>
<tr>
<td>Absent (TGL &lt;150)(n=37)</td>
<td>23</td>
<td>62.4</td>
<td>14</td>
</tr>
</tbody>
</table>

Table: Hypertriglyceridemia And Ldl/Hdl Ratio

IV. Discussion

Meal absorption is a complex phenomenon and postprandial hyperlipidemia and hyperglycemia are simultaneously present in the post absorptive phase, particularly in patients with type 2 diabetes mellitus and IGT. In non diabetic subjects, there is evidence that postprandial hypertriglyceridemia is a risk factor for CVD, whereas in diabetic subjects, postprandial hyperglycemia has been recently proposed as an independent risk factor for CVD with hypertriglyceridemia as an emerging risk factor. The distinct role and relative importance of these two factors in the pathogenesis of CVD in diabetes is a matter of debate.

This study was done to highlight postprandial hypertriglyceridemia as a significant risk factor for vascular events. Fasting triglycerides, representing triglyceride metabolism under relaxation, have not generally been accepted as an independent risk factor for atherosclerosis including coronary artery disease. Individuals with normal fasting triglyceride levels exhibit highly varying postprandial triglyceride concentrations in the postprandial hours of 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. Consequently, a number of case–control studies showed impaired triglyceride metabolic capacity, defined as increased and prolonged postprandial hypertriglyceridemia, to be closely linked to the presence of CAD. Many of the observations made in our study correlated well with previous studies. Most diabetic patients in this study were in the normal weight BMI group (70.5% in uncomplicated diabetes and 60.5% in complicated diabetes). According to Indian data, almost 80% of type 2 DM patients in India are normal weight as compared to 60–80% of diabetics from west. In the present 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 emphasized in literature. Diabetic patients invariably have dyslipidemia sometime in the course of the disease. This was also observed in studies done by Syvanne et al., West et al and Fontbonne et al in patients with diabetes and impaired glucose tolerance. There was good correlation noted between insulin resistance and plasma TGL concentration, as TGL may influence an early step in the insulin action pathway; alternatively, insulin resistance may cause hypertriglyceridemia.

A study conducted by Rajmohan et al in South Indian type 2 diabetic subjects revealed that the prevalence of CAD was significantly higher among patients with isolated hypercholesterolemia, isolated high LDL, and isolated low high-density lipoprotein levels compared to normolipidemic individuals, but not in those with isolated hypertriglyceridemia. In contrast, Anderson et al showed that CAD was higher in patients with...
isolated hypertriglyceridemia. In our study, fasting total 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 that diabetic 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 hypertriglyceridemia 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 hypertriglyceridemia.\(^3\) There was also good correlation between fasting \((p=0.0006)\) and postprandial blood sugar \((p=0.0001)\) and postprandial hypertriglyceridemia in patients with vascular events. This has been noted in the previous study done by Ceriello et al where they proved the independent and cumulative role of postprandial hypertriglyceridemia and hyperglycemia in the causation of endothelial dysfunction in diabetes.\(^9\)

It was seen in our study that persistent hypertriglyceridemia at four hours post fat meal was seen in 83.3\% of diabetic patients with macro vascular complications and 65.9\% of diabetic patients without complications, whereas it was seen only in 18.2\% of healthy Non-diabetic controls \((p=0.0001)\). It is in concordance with various studies in the past which have also proved a consistent relationship between macro vascular complications in diabetes and postprandial lipids. Patsch et al.\(^10\) showed that increased postprandial TGL levels were independently predictive of severe CAD. The Atherosclerosis Risk in Communities (ARIC) trial showed similar observations.\(^1\) Another study done by Patsch et al also demonstrated that postprandial TGL is important for the propensity for atherosclerosis.\(^12\) Golay et al have found in their study that postprandial lipids are frequently being neglected as important determinants of coronary events in patients with type 2 diabetes mellitus.\(^13\)

It was found in our study that postprandial (post load) triglyceridemia \((p=0.0001)\) correlated better that fasting triglyceridemia with vascular events \((p=0.0027)\). Gambhir et al \((1999)\) from Noida, India have shown that there is significant elevation of triglycerides in diabetics in the postprandial state which are further associated with increased oxidative stress. It has been 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\(^7\) and men with low total cholesterol levels.\(^14\) 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.\(^8\) In our study also, women had significantly higher levels of postprandial triglycerides as compared to men, especially in complicated diabetes \((p=0.0281)\).

Some studies have indicated that there is an increased risk of CAD in the presence of TGL levels \(\geq 204\) mg/dl when the ratio of LDL-cholesterol to HDL-cholesterol exceeds five.\(^17\) Though standard lipid ratios did not correlate well with postprandial triglyceride levels in our study, the mean lipid ratios \((TC/HDL, LDL/HDL)\) were found to be higher in patients with hypertriglyceridemia \((4.9, 2.91)\) than those without it \((4.25, 2.53)\). The above observations demonstrate a good relationship between postprandial lipemia and atherosclerosis, and suggest that postprandial TGL levels may be a better indicator of atherogenicity than fasting levels. Therefore, postprandial triglyceride measurements, especially in high risk groups may give important information for risk assessment and planning of treatment strategies for prevention of vascular complications.

However, the protocol for measuring postprandial hypertriglyceridemia has to be formulated, and it is necessary to formulate precise guidelines on the time intervals for measuring postprandial TGL, 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 post load triglyceride and subsequent dietary or pharmacological intervention may help to detect and prevent endothelial dysfunction in diabetes, thus alleviating the mortality and morbidity associated with the disease.

V. Conclusion

Dyslipidemia was seen in significant proportion of diabetic patients, especially those with complications. Persistent and significant post load hypertriglyceridemia was observed in new 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. Although the emphasis in recent times is mainly on LDL cholesterol in type 2 diabetes and metabolic syndrome, postprandial TGL increase may be equally or more important than LDL cholesterol in causation of vascular events. 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.
There is no conflict of interest, Pertaining to this artical.

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