IMPORTANCE OF HIGH TRIGLYCERIDES AS A CARDIOVASCULAR RISK FACTOR IN INDIAN DIABETIC POPULATION – A REVIEW

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ABSTRACT
Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by a state of chronic hyperglycaemia which may lead to various disabling and life-threatening macrovascular and microvascular complications resulting in reduced quality of life and premature mortality. As per many recent evidences, Cardiovascular disease (CVD) is a major cause of morbidity and mortality in these individuals and is responsible for 70-75% of deaths in diabetes population. India is carrying almost 65 million diabetic populations with almost 77 million populations with pre-diabetes. Majority of diabetes patients suffers from dyslipidaemia. Dyslipidaemia in diabetes is usually a mixed type of hyperlipidaemia, i.e. elevated small dense LDL, high TG and low HDL-C. This pattern of dyslipidaemia is also termed as an Atherogenic Diabetic Dyslipidaemia (ADD). Current evidences suggest that elevated TG is an important independent risk factor for future CV risk.

Key Words: Diabetes; Dyslipidaemia; Triglycerides; Cardiovascular Risk

Introduction
Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by a state of chronic hyperglycaemia which may lead to various disabling and life-threatening macrovascular and microvascular complications resulting in reduced quality of life and premature mortality. As per many recent evidences, cardiovascular disease (CVD) is a major cause of morbidity and mortality in these individuals and is responsible for 70-75% of deaths in diabetes population. India is carrying almost 65 million diabetic populations with almost 77 million populations with pre-diabetes. Majority of diabetes patients suffers from dyslipidaemia. Dyslipidaemia in diabetes is usually a mixed type of hyperlipidaemia, i.e. elevated small dense LDL, high TG and low HDL-C. This pattern of dyslipidaemia is also termed as an Atherogenic Diabetic Dyslipidaemia (ADD). Current evidences suggest that elevated TG is an important independent risk factor for future CV risk.

Epidemiology
According to the International Diabetes Federation (IDF 2013) estimate, India ranks 2nd in the world next to China (Figure 1) with 65.1 million people with diabetes (2013), which is expected to rise beyond 109.0 million by 2035. Approximately 8.3% of adult population globally (i.e. 382 million people) have diabetes and around 80% of them live in low-and middle-income countries. By 2035, 592 million people (10.1% prevalence) will have diabetes with the greatest number of people between 40 and 59 years of age, and this equates to nearly three new cases every 10 seconds or almost 10 million per year. In the year 2013, Diabetes has been associated with 5.1 million deaths and every six seconds a person dies from it, moreover around 175 million people currently remain undiagnosed.[1]

Figure-1: IDF 2013: Top 10 countries for diabetic population (diabetic population in million)

Dyslipidaemia and Diabetes (Atherogenic Diabetic Dyslipidaemia)
Mixed dyslipidaemia is very common in diabetes. Dyslipidaemia associated with diabetes is increased
small dense LDL-C, increased level of triglycerides (TG) and low HDL-C. Such dyslipidaemia is associated with increased progression of atherosclerosis, hence called Atherogenic Diabetic Dyslipidaemia (ADD). In a study done on Indian diabetic population (Figure 2), dyslipidaemia was present in 85.5% males and 97.2% females.[2]

**Factors Contributing to Higher Incidence of Dyslipidaemia in Indian Population**

There are many lifestyle and genetic related factors associated with higher incidence of dyslipidaemia in Indian population[3,4]:

- Physical inactivity
- Dietary habits – Indian diet is rich in carbohydrate and low in omega-3 PUFA exacerbates hypertriglyceridemia.
- Obesity - Indians have excessive body fat and more abdominal adiposity which is harmful even if BMI is under control.
- Excess body fat in relation to body mass index
- Abnormal variants of Apo C3 (causing lipoprotein lipase inhibition) and ApoE3 (formation of VLDL) genes are common in India which can lead to dyslipidemia
- Thrifty gene (“Starvation Gene Theory”)- India suffered droughts for hundreds of years, so the genes were adapted to survive long periods of drought by consuming fats and carbohydrates slowly to make them last longer. Now in spite of adequate supplies of food, these genes are still active. So food continues to be metabolised slowly resulting in the dysfunctional biochemical profile that constitutes Syndrome X.

**Dyslipidemia – Indian vs. Western:** Indians, as compared to the Western counterpart, have a different pattern of dyslipidemia which makes them more prone to atherosclerosis. A study on Asian Indians living in the United States found that 54% of Indian men and 68% of Indian women had relatively lower levels of HDL-C, and 43% of Indian males and 24% of females have relatively higher TG levels (>150 mg/dL).[3]

**Dyslipidemia and CV Risk:** As the INTERHEART study have shown, dyslipidemia is the single most important CV risk factor accounting for almost 50% of first myocardial infarction worldwide[4] and this risk is increased 3-4 times if there is associated diabetes along with dyslipidemia[5].

**Hypertriglyceridemia as a Cardiovascular Risk Factor in Diabetes**

There are plenty of evidence indicating direct relationship between LDL-C and cardiovascular morbidity and mortality. But, there has been more uncertainty regarding the association between high triglyceride (HTG) levels and CVD. One of the important component of metabolic syndrome is high triglyceride level. In recent past, evidences indicating direct relation between high TG and CV risk are mounting. Table 1 demonstrates classification of HTG.[6]

**Table 1: Classification of fasting triglycerides levels**

<table>
<thead>
<tr>
<th>Fasting Triglycerides Levels</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150 mg/dl</td>
<td>Normal</td>
</tr>
<tr>
<td>150-199 mg/dl</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200-499 mg/dl</td>
<td>High</td>
</tr>
<tr>
<td>&gt;500 mg/dl</td>
<td>Very High</td>
</tr>
</tbody>
</table>

Hypertriglyceridemia is usually clinically asymptomatic but patients may present with eruptive xanthoma, hepatosplenomegaly, lidemia retinalis, abdominal pain. When triglyceride levels are very high (≥500 mg/dL), the risk of pancreatitis, peripheral neuropathy, dyspnoea, memory loss and dementia increases.[7]

As per the results of a meta-analysis of 17 prospective studies (> 55,000 patients), for every increase in TG level of 89 mg/dL, CVD risk increases by 32% in men and 76% in women. This suggests that hypertriglyceridemia is an independent risk factor for CVD.[8]

A recent and larger meta-analysis of 29 prospective studies involving 2,62,525 participants reported that there is a strong and highly significant association between triglyceride levels and cardiovascular risk in diabetics even after adjustment for HDL-C. The study yielded an adjusted odds ratio of 1.72 (95% CI, 1.56-
1.90) in a comparison of extreme thirds of usual triglyceride values i.e., individuals with usual log-triglyceride values in the top third of the population compared with those in the bottom third suggesting that patients in highest tertile of serum TG had 72% higher risk of CVD than those in lowest tertile.[9] (Figure 3)

Meta-Analysis of 29 Studies

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>CHD CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>≥10 years</td>
<td>5,902</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4,256</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7,728</td>
</tr>
<tr>
<td>Female</td>
<td>1,984</td>
</tr>
<tr>
<td><strong>Fasting status</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7,484</td>
</tr>
<tr>
<td>Non-fasting</td>
<td>2,674</td>
</tr>
<tr>
<td><strong>Adjusted for HDL</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4,469</td>
</tr>
<tr>
<td>No</td>
<td>5,689</td>
</tr>
</tbody>
</table>

Figure 3: Risk of CHD (coronary heart disease) in individuals in the top vs bottom third of usual log-triglyceride values grouped according to several study characteristics in a meta-analysis of 29 prospective studies

As per an Asian study of diabetic patients who were followed up for 4.6 years, high TGs in diabetes increase cardiovascular risk by 3 times compared to diabetic patients without high TG.[10]

Liu et al carried out a study showing that elevated blood TG levels were dose-dependently associated with higher risks of CVD and all-cause mortality. Compared to the referent (90–149 mg/dL) group, the pooled relative risks ratio of CVD mortality for the lowest (< 90 mg/dL), borderline-high (150–199 mg/dL), and high TG (≥ 200 mg/dL) groups were 0.83, 1.15, and 1.25 respectively. For total mortality they were 0.94, 1.09, and 1.20, respectively. The risks of CVD and all-cause deaths were increased by 13% and 12% (p < 0.001) respectively per 1-mmol/L (89 mg/dL) increase in TG levels.[11]

The Copenhagen City Heart Study also reported that non-fasting TG levels were associated with increased risk of myocardial infarction, ischemic heart disease, and death after adjustment for age, total cholesterol, BMI, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, postmenopausal status, and hormone therapy in women. The levels of non-fasting TG were highly correlated with those of remnant lipoprotein cholesterol. These results may also reflect the effect of postprandial hypertriglyceridemia (independent of and cumulative to the effect of hyperglycemia) on endothelial function.[12]

### Hypertriglyceridemia and Increased CV Risk

Hypertriglyceridemia is associated with increased insulin secretion, suggesting a direct relation of TG with the insulin resistance.[13]

Further, High TG level is directly proportional to increased small dense LDL particle. A threshold appears to exist for a fasting TG concentration above which there is predominance of small dense LDL particles and below which large, more buoyant particles predominate. At a fasting TG concentration of 100 mg/dL, 85% of the population has predominant large buoyant LDL particles (phenotype A), whereas at a fasting TG concentration of 250 mg/dL, 85% have has predominant sd LDL-C particles (phenotype B). Most patients have a threshold for shifting LDL-C subclass pattern within the range of 100 to 250 mg/dL and since sd LDL-C is known to be more atherogenic, therefore keeping TG even at 200-250 may not reduce atherosclerosis completely. A target of TG < 100 mg/dl should therefore be considered.[14]

Hypertriglyceridemia is also associated with low HDL-C levels and association between reduced HDL cholesterol levels and increased risk of heart disease is well established.[15] Hypertriglyceridemia is usually associated with rise in fibrinogen and plasma plasminogen activator inhibitor leading to a prothrombic state.[16] Hypertriglyceridemia is also associated with Pro-inflammatory state as it is associated with increase in the level of C-reactive protein.[17]

### TG Reduction and Cardiovascular Benefits

**VA-HIT Study:** It was found that gemfibrozil given to 627 diabetic patients resulted in 24% reduction in the expanded end point of death from CHD, nonfatal myocardial infarction (MI), and confirmed stroke which was significant (P = 0.05) as compared to placebo.[18] In a subsequent report, in which the diagnosis of diabetes was modified to include the new criteria of fasting plasma glucose ≥ 126 mg/dL, the total cohort of diabetic patients was increased to 769 and there was a 32% risk reduction of the composite end point of CHD death, stroke, or MI (P = 0.004). This decrease was largely due to a reduction in CHD deaths due to triglyceride reduction.[19]
BIP Study: (Bezafibrate in patients with TG > 200 mg/dl) 3090 CAD patients were followed up for 6.2 years. Bezafibrate use showed a very significant 39.7% reduction in CV events (primary end point was fatal, nonfatal MI/sudden death) as compared to placebo.[18]

In the Diabetes Atherosclerosis Intervention Study (DAIS), 418 T2DM patients were randomized for 3 years to fenofibrate (200 mg/d) or placebo treatment. A significant reduction in triglycerides, LDL-C, and increase in HDL-C were observed in the fenofibrate treated group. There was significantly less coronary angiographic progression in atheroma volume and diameter and percent diameter stenosis, and a decrease in the incidence of microalbuminuria.[19]

**HHS Study:** In the Helsinki Heart Study, treatment with gemfibrozil resulted in a 71% lower incidence of CHD events in the subgroup of patients free of CHD at baseline, with the TG level >200 mg/dl and LDL cholesterol/HDL cholesterol ratio above 5.[20]

**Recent Trials for TG Reduction and CV Outcome (FIELD and ACCORD Trials)**

FIELD and ACCORD trials do not provide benefits in their primary end points but the sub-analyses of the above two trials showed benefit in patients with high baseline TG and low HDL. FIELD Trial comprised of 9795 type 2 diabetes patients of 50-75 years age who were followed for five years with no clear indication for cholesterol-lowering therapy at baseline (total cholesterol 116-251 mg/dL, plus either total cholesterol to HDL ratio ≥4.0 or triglyceride ≥88.6 mg/dL). Fenofibrate reduced total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularisations but the difference in primary outcome was insignificant between the two groups.[21]

However a sub-analysis of the subgroups of more than 2000 patients with high TG (> 200 mg/dl) showed that fenofibrate significantly reduced CV events by 27% concluding that fenofibrate do reduce CV events in T2DM patients when the baseline TG are high.[22]

Similar results were reported in ACCORD trial where 5518 patients with T2DM (HbA1c> 7.5%) were given fenofibrate or placebo. All patients were on simvastatin at baseline and followed up for 4.7 years. The annual rate of the primary outcome was not reduced significantly (p = 0.32).[23]

But when sub-analyzed in 941 patients (out of 5518) with both a high baseline triglyceride level (TG≥204 mg/dl) and a low baseline level of HDL (<34 mg/dl), fenofibrate reduced primary end point significantly by 31%.[24]

Meta-analysis: In a meta-analysis of 5 landmark studies (ACCORD, FIELD, BIP, VA-HIT and HHS) involving 4726 patients, fibrates have been found to reduced CV events significantly by 35% in patients with high TG≥204 mg/dl and low HDL ≤34 mg/dl (atherogenic dyslipidaemia).[25]

**Conclusion**

In India, diabetes and related complications are increasing rapidly. Majority of diabetic patients in India do suffer from dyslipidaemia. Diabetic dyslipidaemia in India is usually a mixed type, i.e. increased small dense LDL, high TG and low HDL. These may be due to different ethnicity and poor lifestyle. High TG is independently associated with increased risk of cardiovascular morbidity and mortality. ACCORD and FIELD study failed to show any CV outcome benefits with TG lowering therapy with fenofibrate. But, we need to remember that baseline TG in both these studies was very close to normal (i.e. around 160 mg/dL). Subgroup analysis of FIELD and ACCORD studies (in patients’ population with high TG and low HDL at baseline) have shown significant CV risk reduction with Fibrates. Meta-analysis of 5 large trials also suggests the same. Indian population is different from Caucasian. High TG and low HDL is important risk factors in Indian. Treatment of high TG improves long term CV outcome.

**References**

Hiren Pandya. High triglycerides as a cardiovascular risk factor in diabetic population


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