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Mini-Review

Importance of Triglyceride Lowering in Preventing CVD

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Abstract

Type 2 diabetes mellitus is a growing epidemic across globe and in India as well. Due to high prevalence of insulin resistance; elevated triglyceride is usually observed in T2DM, while in India it is observed in ~30% of the diabetes population. TG levels more than 200 mg/dl may be associated with rising cardiovascular risk and according to major guidelines; TG > 200 mg/dl should be treated to avoid future risk of CV diseases. Post statins, various TG-lowering agents are used but Saroglitazar is the only approved molecule as dual PPAR receptor agonists in Indian diabetes patients with elevated TGs. Non Alcoholic Fatty Liver Disease (NAFLD) is another chronic metabolic condition which is more commonly observed in obese, T2DM and patients with elevated TGs. Currently various treatments are under investigation for NAFLD management but Saroglitazar is the only approved molecule by DCGI in India for NAFLD treatment.

Keywords: Diabetes mellitus, Hypertriglyceridemia, Saroglitazar, Atherogenic Diabetic Dyslipidemia, Non Alcoholic Fatty Liver Disease, Cardiovascular disease

Introduction

Cardiovascular disease remains the leading cause of disease burden globally.[1] Amongst abnormal lipids, low density lipoprotein cholesterol (LDL-C) is bad cholesterol and majorly responsible for cardiovascular disease (CVD), but simultaneously elevated triglyceride (TG) is also considered as independent CV risk factor and should be managed accordingly.[2-4] Triglyceride concentrations have high biological variability, which obscures the strength of any association with atherosclerotic cardiovascular disease (ASCVD). Direct association between high-triglyceride (HTG) and ASCVD risk sometimes loses significance after multivariable adjustment including other lipids. For prevention of cardiovascular disease, the primary lipid target is the LDL-C.[5,6] However, despite intensive LDL-lowering therapies, a significant residual risk persists, particularly for patients with elevated triglyceride concentrations. This may be due to a little impact of current cardiovascular medications like statins, PCSK-9 inhibitors on lowering triglycerides. Several recent epidemiological and Mendelian randomization studies have pointed towards a causal role of elevated triglycerides in ASCVD due to an elevation of remnant cholesterol particles.[7] Objective of this article is to provide an insight on triglyceride — is it individually a causal factor for CV risk or Triglyceride Rich Lipoproteins (TGRLs) are the culprit.

Epidemiology of Hypertriglyceridemia in CVD Risk Assessment

Many case-control and cohort-based studies showed non-significant association of triglycerides with CVD after adjustment for either total cholesterol or LDL-C.[4] The first meta-analysis that considered 16 studies, published in 1996 found univariate association of triglyceride for CVD in both men and women after adjustment for HDL-C with more robust association in women.[8] The second meta-analysis among 262000 subjects, found a higher relative risk (1.4) at the upper compared with the lower triglyceride level.[3]

In 2007, the Copenhagen City Heart Study showed that raised non-fasting triglycerides was associated with increased CV events and mortality.[9] The Women's Health Study found non-association between fasting triglycerides and ASCVD among a cohort of healthy women in the USA.[10] In 2009, The Emerging Risk Factors Collaboration analysis analyzed 68 long-term prospective studies and found increased triglyceride concentrations were associated with a 37% increased risk of CHD after adjustment for non-lipid risk factors which was weakened after adjustment for HDL-C, and nullified after adjustment for non-HDL-C.[11] The recent epidemiological data have reinforced the role of TGRLs in CV events. In 2014, The Copenhagen City Heart Study and the Copenhagen General Population Study have shown elevated remnant lipoprotein cholesterol (RLP-C) (total cholesterol – HDL – LDL) was associated with CV events, independent of reduced HDL-C and with all-cause mortality in patients with ischemic heart disease.[12]

In Asian population, the cardiovascular disease developed at younger age than other ethnic groups.[13] Review studies in India show a prevalence of dyslipidemia between 10 to 73%.[14] The attributing factors may be urban professionals with sedentary lifestyle who had higher prevalence, less physical activity and high carbohydrate diet with low polyunsaturated fatty acid (PUFA). In 2014, meta-analysis of 26 prospective studies in the Asia-Pacific region concluded TG as an important and independent predictor of CHD and stroke. This meta-analysis done among 96224 individuals during 796671 person-years of follow-up showed persons with highest fifth of triglyceride level had a 70% (95% CI, 47 to 96) greater risk of CHD death, an 80% (95% CI, 49 to 119) higher risk of fatal or nonfatal CHD compared to lowest fifth TG level.[15]

The proportion of cardiovascular death is also higher in younger than 70 years than those aged 70 and older.[16] A study in North India, showed CAD occurs at younger age may be due to a more atherogenic lipid profile (high TG and low HDL in-spite of much lower level of total cholesterol and LDL-C) than older subgroup with Coronary artery disease (CAD).[17] Also, young South Indian females developed CAD at early age due to atherogenic lipid profile.[18]

Pathophysiology

Lipoproteins are macromolecular complexes that carry various lipids and proteins in plasma. Apolipoprotein is the protein part of lipoprotein. Core of lipoprotein is composed of hydrophobic triglyceride and cholesteryl esters (CE) and covered by a unilamellar surface that contains mainly amphipathic phospholipids and smaller amounts of free cholesterol and proteins. Major apoproteins present in lipoproteins are Apo A I, II, IV, Apo B 48, Apo B 100, Apo C I, II, III, Apo D, Apo E. Lipoproteins are classified on the basis of their densities and electrophoretic mobility in the ultracentrifugation. The lipoprotein with highest density will settle down at the bottom. It contains free fatty acid with albumin (> 1.215 g/l), then above that HDL (1.063-1.125 g/l), LDL (1.019-1.063 g/l), IDL (1.006-1.019 g/l), VLDL (0.95-1.006g/l) and Chylomicron (<0.95 g/l), respectively.[19]

Apolipoproteins are present on the surface of the lipoproteins. They participate in solubilizing core lipids and play a critical role in the regulation of plasma lipid and lipoprotein transport. ApoB100 is required for the secretion of hepatic-derived VLDL, IDL and LDL. ApoB48 is required for the secretion of chylomicrons from the small intestine. Apo-B is the major structural protein in TRL. All the Apo-B containing lipoproteins are atherogenic. VLDL formed in the liver, contains apoB100 which is metabolized to VLDL remnants, IDL, and LDL. Chylomicrons are formed in the intestine which contain apoB48. It is also metabolized to remnant particles but not to IDL and LDL.[20]

Hypertriglyceridemia is mainly caused by VLDL1 and VLDL2. Other TG rich lipoproteins are chylomicron, chylomicron remnants, IDL, LDL. Measurement of LDL misses a very substantial part of atherogenic lipoproteins. Although chylomicrons are too large to penetrate the arterial wall, the VLDL, IDL as well as chylomicron remnants are known to have capacity to end up in the subendothelial space and contribute to the accumulation and have been identified in human and animal atherosclerotic plaque. Among the LDL particles, VLDL and IDL particles, 30% of total cholesterol burden of apo-B fraction, are not in the LDL but in the TRL remnants. So, TGs are equally a hidden burden of atherogenic cholesterol within the TG rich fractions.

A classical hyper-triglyceridemic state is insulin resistance which is associated with the diminished activity of adipocyte lipoprotein lipase, leading to free fatty acid mobilization, hepatic VLDL overproduction and up regulation of CETP that facilitates the transfer of TG to LDL and HDL in exchange for CE. TG-enriched LDL particles further acted upon by hepatic lipase, resulting in small, dense LDL particles that are subjected to oxidative modification as compared with larger LDL particles, followed by increased uptake by scavenger receptors on the surface of the arterial wall. Thus, fatty acids released by lipolysis of TRLs elicit proinflammatory responses in endothelial cells.[21]

At optimal fasting TG levels (<100 mg/dL), efficient lipolysis results in limited accumulation of remnant particles, predominantly in the small VLDL and IDL size range. At higher TG levels (≥260 mg/dL), increased secretion and impaired lipolysis result in the substantial accumulation of chylomicron and VLDL remnants. Extreme elevations of plasma TG levels (>880 mg/dL) increase the risk for acute pancreatitis and CV events result from a cluster of metabolic abnormalities that include accumulation of TRL and remnants as well.[22] TRLs are enriched in apo-E which results in accumulation and sticking of these particles to the subendothelial space. These lipoprotein particles become more abundant as TG concentrations increase. VLDL and LDL having apo C-III, stimulate both monocytes and endothelial cells producing adhesion molecules and transcription factors which induce inflammatory mediators TNF-α and IL-1β, responsible for atherogenicity of TRLs.[23] In obese patients with hypertriglyceridemia (HTG) increased levels of prothrombotic (fibrinogen, plasminogen activator inhibitors) as well as proinflammatory molecules (CRP, IL-6, TNF-α) have been seen.

TG in CV risk – Genetic Basis

Previously, most studies showed an association between TGRL and ASCVD but HDL-C was the limiting factor. Recent human genetics studies have not supported HDL-C as a protective CV factor. At least 30 variants have been associated with increase in TGRL, some important ones are – LPL, apo C2, apo C3, apo A5, ANGPTL3, ANGPTL4.[24]

A genetic variant in apo A5 that increased triglyceride concentrations by 16% (0.25 mmol/L) was associated with an increased CHD risk (odds ratio 1.18, 95% confidence interval 1.11–1.26).[26] A doubling in RLP-C concentrations because of mutations in apo A5 was causally associated with a 2.2-fold increase in the risk of myocardial infarction.[24] Loss-of function of apo C3, ANGPTL3 and ANGPTL4 leads to increased LPL activity. Consequently, a reduction in plasma triglycerides happens which translates into a reduction in ASCVD risk.[27] Loss-of-function apo C3 mutations were associated with 39% lower triglyceride concentrations and a 40% lower risk of CHD.[28] Heterozygous carriers of ANGPTL3 loss-of-function mutations had a 12% decrease in LDL-C, a 17% decrease in triglycerides, and a 34% reduction in CHD risk.[28] Currently, there are several ongoing therapeutic trials targeting apo C3 and ANGPTL3 in order to reduce triglycerides and ASCVD risk. Loss-of-function variants in ANGPTL4 are also associated with decreased triglyceride concentrations and CHD risk, but the monoclonal antibodies to ANGPTL4 induce side effects in animals. Recent Mendelian randomization studies suggest HTG is associated with the risk of aortic valve stenosis[29] and abdominal aortic aneurysm. Recent genetic studies suggest, in addition to LDL and lipoprotein(a), remnants of TGRLs are directly causal in ASCVD, with a similar increase in the risk of myocardial infarction for the same cholesterol increment.

Triglyceride Lowering – Does it Help to Reduce ASCVD Risk?

The 2018 AHA/ACC/multi-society cholesterol guidelines recommend that in adults aged 20 years with moderate HTG, first steps for management is the modification of lifestyle factors including overweight/obesity, poor diet quality, sedentary lifestyle, and alcohol. Dietary goals include (i) avoiding highly refined carbohydrate foods; (ii) incorporating seafood, particularly fatty fish; (iii) increasing fiber-rich foods (fruits, vegetables and whole grains); (iv) avoiding excess alcohol; and (v) substituting mono- and poly-unsaturated fat (mostly from plant oils and nuts) for animal fat (meat and dairy).

The 2019 ESC/EAS guidelines for dyslipidemia management recognize that ASCVD risk is increased at TG levels >1.7 mmol/L (>150 mg/dL), but only recommend initiating pharmacotherapy in high-risk patients if TG levels >2.3 mmol/L (>200 mg/dL) after excluding secondary causes.[30]

Triglyceride and Statin Therapy

Statin therapy is associated with significant reduction in all CV outcomes, but there is a significant amount of residual risk which persists after optimized statin therapy in HTG patients. There are several studies demonstrating associations between triglycerides and outcomes in selected populations, including those from 4S[31], PROVE-IT[32], IDEAL[33], TNT[34], MIRACL and dal-OUTCOMES[35]. In 4S, patients in the highest triglyceride (> 159 mg/dL) and lowest HDL-C (< 39 mg/dL) quartiles had the highest risk of ASCVD events on placebo. In PROVE IT-TIMI 22 study, elevated TGs ≥150 mg/dl increased the risk of CV events and mortality (HR 0.84) within 30 days to 2 years of follow up compared to those with TG <150 mg/dl (HR 0.72) despite patients having achieved an LDL-C goal of <70 mg/dl with high dose of atorvastatin. The TNT and IDEAL

trials showed similar results. In dal-OUTCOMES, long-term risk increased across quintiles of baseline triglycerides, highest/lowest quintile (>175/≤80 mg/dl) with hazard ratio 1.61 (P <0.001).

Fibrates and non-statin Drugs for TG Lowering

Helsinki Heart Study (HHS) found significant benefits with gemfibrozil for primary prevention. The Veterans Affairs HDL Intervention Trial (VA-HIT) was a secondary prevention trial which also had positive results with gemfibrozil.[36] A meta-analysis of 18 fibrate trials comprising of 45,058 patients with or without atherogenic dyslipidemia found a 13% relative risk reduction of any CV event (p < 0.0001); however, there was no reduction in stroke, CV mortality, and all-cause mortality.[37] In ACCORD trial, fenofibrate used in combination with statin therapy in patients with type 2 diabetes found no further risk reduction, although subgroup analyses in ACCORD-lipid trial, indicated that patients with high triglycerides and low HDL-C may benefit from this combination therapy.[38] Ezetimibe is the only non-statin drug with significant CV lowering effect. The IMPROVE-IT trial showed that there was a 6.4% (95% CI: 1–11%) proportional reduction in major CV events when ezetimibe was combined with simvastatin versus simvastatin monotherapy.[39]

In pre-specified *post hoc* analysis of ACCORD and FIELD study; in subset of patients with hypertriglyceridemia (TG > 204 mg/dl) and low HDL (for men <40mg/dl and for women <50 mg/dl); Fenofibrate showed significant reduction of CV events by 31% and 27%, respectively (p value <0.05).[40]

So, it is evident that, despite optimized statins therapy, a considerable amount of risk still persists. To tackle this, several approaches have been tried such as, niacin, cholesteryl ester transfer protein (CETP) inhibitors, fibrates, ezetimibe, omega-3 fatty acids (FA). Among them, there were no benefits of niacin and CETP inhibitors in RCT despite increase in HDL-C and lowering of TG. Lowering of TG with fibrates has shown mixed results. Only ezetimibe showed positive results.

Role of Omega-3 fatty acid

The omega-3 fatty acids include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and α-linolenic acid (ALA). EPA, DHA, and DPA are found in fish and other sea foods and other foods supplemented with them, whereas ALA is found in walnuts, leafy vegetables, and oils like canola, soy, and flaxseed oil. The omega-3 PUFA, mainly EPA and DHA, plays a wide range of physiological functions in our body including decrease platelet aggregations, reduce inflammations, lower the amount of lipids, inhibit thickening of the arteries by decreasing endothelial cells production of a platelet-derived growth factor and others. Some of these effects appear in a wide range of intake but some appear only when taken in a high dose. It was shown in some experimental studies that EPA modulates the atherosclerotic plaque. Similar to Statin therapy, they reduce plaque atheroma volume, however they do not increase calcifications and do not have a robust LDL-C lowering effects.

A meta-analysis of 10 trials involving 77,917 patients with a randomization to omega-3 fatty acid supplementation for a mean duration of 4.4 years did not have any effect on ASCVD.[41] An open label GISSI trial involving 11,323 patients of recent MI, showed lower major CV events and cardiac death with supplementation of omega-3 FA.[42]

In REDUCED-IT trial, they randomized a total of 8,179 high-risk patients, who are on statin and have high TG levels of 135 to 499 mg/dl and LDL of 41 to 100 mg/dl, receive icosapent-ethyl total daily dose of 4 g + statin vs mineral oil as placebo + optimized statin therapy.[43] The primary end-point event occurred in 17.2% of those in the icosapent-ethyl group vs 22.0% of those in the placebo group (P <0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (P <0.001), respectively. The rates of the primary and secondary composite CVD endpoints were reduced by 25% and 30%, respectively, as well as all individual secondary endpoints except for all-cause mortality in the icosapent-ethyl group. This is one of the first non-LDL-C targeted trials to show a CV benefit. A major adverse effect of atrial fibrillation was seen to be higher in the study group as compared to placebo.

For further explanation, EVAPORATE trial was conducted.[44] This trial looked at the effect of high dose of icosapent ethyl on the progression of coronary atherosclerosis in patients with high triglyceride (200–499 mg/dl) on statin therapy. Patients were evaluated by serial CT angiography. Results showed a significant difference in the change in the primary endpoint of low attenuation plaque volume, which was reduced by IPE by 17%, but increased by 109% in the placebo group (p <0.01). STRENGTH trial showed that a combination of EPA and DHA lowers TGs by up to 31%, however was prematurely

terminated since the combination showed a lower likelihood of benefit. OMEMI trial recently done in 1,014 elderly post myocardial ischemic patients with 1.8 gm of omega-3 fatty acid (930 mg EPA and 660 mg DHA) vs corn oil as placebo. Here again no observed benefit of omega 3 supplementation was seen.

Role of Saroglitazar

Saroglitazar is the first Indian new chemical entity (NCE) having predominant Peroxisome Proliferator Activated Receptor (PPAR) α agonistic with moderate PPAR γ agonistic activity. It is approved by Drug Controller General of India (DCGI) in 2013 for management of HTG in T2DM and diabetes dyslipidemia. In two phase III studies of PRESS V & VI, Saroglitazar 4 mg once daily showed up to 46.7% of TG reduction with 32.5% of non-HDL reduction. Due to PPAR γ agonistic activity, this molecule improves insulin sensitivity in T2DM patients and reduces liver fat content. It is the first approved drug for treatment of NAFLD by DCGI. Based on the available evidences, Saroglitazar is certainly efficacious drug to reduce elevated TG and NAFLD; with better tolerability as well, but yet to provide long-term CV outcome study in Indian patients.[45]

TG-lowering drugs and effect on lipid parameters are listed in Table 1.[46]

Table 1. TG-lowering drugs and effect on lipid parameters.

Drug	Lipid effects	Outcomes data
Bezafibrate	LDL decrease: 9.6-25% (400 mg) HDL increase: 15-24% (400 mg) Triglyceride decrease: 25-43% (400 mg)	Secondary prevention: Prevents composite endpoint of MI and sudden death in a subgroup with triglycerides of 200 mg/dL or higher. No increase in non-CV death
Fenofibrate	LDL decrease: 20.6% (145 mg) HDL increase: 11% (145 mg) Triglyceride decrease: 23.5-50.6% (greatest drop in patients with highest triglycerides) (145 mg)	Prevention of CV events in type 2 diabetes: Did not reduce primary composite outcome (nonfatal MI or CV death). Improved outcomes included nonfatal MI (24% decrease), coronary revascularization (21% decrease), progression to albuminuria, and reduced laser treatments for retinopathy. Nonsignificant increase in risk of CV death. But in a pre-specified subgroup analysis, participants with triglyceride levels of greater than 2.30 mmol/l (>204 mg/dl) and HDL-C levels of less than 0.88 mmol/l (<34 mg/dl; HTG/low HDL-C) experienced a 31% reduction in events with fenofibrate therapy (nominal p = 0.032) versus no effect in the remaining participants (all others).[40] In *post hoc* analyses of FIELD study, a subset (21%) of participants with the baseline characteristic of combined low HDLC levels of less than 1.04 mmol/l in men and less than 1.30 mmol/l in women (<40 and <50 mg/dl respectively and hypertriglyceridemia (>2.3 mmol/l or >204 mg/dl) experienced 27% fewer cardiovascular events with fenofibrate therapy.[40]
Gemfibrozil	LDL: No effect HDL increase: 6% (1200 mg/day) Triglyceride decrease: 33-50% (greatest drop in patients with highest triglycerides) (1200 mg/day)	Primary prevention of coronary heart disease Secondary prevention of cardiac events in men with low HDL
Icosapent ethyl	LDL decrease: 5% HDL decrease: 4% Triglyceride decrease: 27%	Secondary CV risk prevention; REDUCE-IT trial showed primary endpoint (major CV events) occurred in 24.7% of placebo compared with 18.2% of icosapent ethyl treated patients (p = 0.000001)
Niacin	LDL decrease: 14-17% (2 g/day); 12% (niacin immediate-release 1.5 g/day) HDL increase: 22-26% (2 g/day); 17% (niacin immediate release 1.5 g/day) Triglyceride decrease: 20-50%	Secondary MI prevention; in combination with a resin, slows progression or promotes regression of atherosclerosis; reduces mortality

Saroglitazar	LDL decrease: 31.3% (4 mg/day) Triglyceride decrease: 45.0% - 46.7% (4 mg/day) Non-HDL decrease: 32.5% (4 mg/day)	First dual PPAR α/γ agonist, approved for hypertriglyceridemia in T2DM patients uncontrolled with statin in India Currently, this molecule has not been investigated for CV outcome data

Guideline Recommendations on High TG Management

Evidence supports a potential role of TG as vascular risk factors, owing in part to the accompanying burden of atherogenic remnant particles, sdLDL-C, reduced HDL-C and a high frequency of accompanying insulin resistance.

Recently, international guidelines by European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) recommended that hypertriglyceridemia in high-risk patients should be managed with TG lowering agents. ESC/EAS 2019 guideline on the management of dyslipidemia recommends no goal for TG level, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. In high-risk (or above) patients with TG levels between 1.5-5.6 mmol/L (135-499 mg/dL) despite statin treatment, TG lowering drugs should be considered in combination with statin.[47]

A recently published consensus statement by Research Society for the Study of Diabetes in India/Endocrine Society of India (RSSDI-ESI) has also endorsed treatment of high TG (> 150 mg/dl) in high-risk ASCVD patients through fibrates, saroglitazar, omega 3 fatty acid etc.[48]

Conclusion

Although elevated LDL-C is well established, major predictor of CV risk, itS has been a primary target for the lipid lowering strategy, many epidemiological, genetic and other recent Mendelian studies have shown despite optimal LDL-C reduction, there is a high residual risk for recurrent CV events and that is associated with high triglyceride level. Recent genetic studies support TG as individually or as TGRLs causally related to ASCVD and also demonstrated TGRLs have more potent proatherogenic properties than LDL-C. In recent trial, high dose of icosapent-ethyl along with statin therapy showed significant cardiovascular benefit in high-risk patients with hypertriglyceridemia. So, there is substantial evidence that triglyceride rich lipoproteins play a causative role in cardiovascular disease. TG levels remain a significant predictor of residual risk and it is recommended to focus on non-HDL-C after addressing and control of LDL-C levels associated cardiovascular risk in ASCVD.

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