Are triglycerides an Indian risk factor for coronary artery disease?

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Abstract

Triglycerides (TG) are an important barometer of metabolic health. However, the ability of plasma TG levels to predict Coronary Artery Disease (CAD) remains controversial after adjustment for High Density Lipoprotein Cholesterol (HDL-C) and non-HDL-C. TG has an inverse relationship with HDL-C and the adjustment for HDL attenuates the relationship between TG and CAD. However, it is important to realize that TG measurement per se is not that informative as some of the TG rich lipoproteins present in the plasma are not atherogenic like large, Very Low Density Lipoproteins (VLDLs) while others like small dense LDL are highly atherogenic and increased production of small dense LDL in response to hypertiglyceridemia could contribute to atherosclerosis. Most of the available data on TG including ATP-III guidelines show cut off value for TG levels based on fasting TG but in reality it is non-fasting (postprandial) TG which is a predictor of vascular events independent of traditional risk factor, whereas fasting TG has little independent relationship with vascular events. It is also being suggested that the TG prediction of risk should be based on oral TG tolerance test akin to Oral Glucose Test (OGT). Indians often have elevation of TG but at present there is no conclusive data to incriminate it as a risk factor for CAD. However, in future, with more data pouring on postprandial TG and atherogenic small dense LDL commonly elevated in Indians in response to elevated TG, a causal relationship between TG and CAD may become evident.

Key Words

- Triglycerides
- Coronary artery disease
- HDL cholesterol

Introduction

Cardiovascular disease (CVD) has emerged as a major health burden worldwide. CVD contributed to 15.3 million deaths in 1996, of which 5.5 million were from developed countries and 9.77 million from developing countries. A rise in the prevalence of CVD in the early half of 20th century and a subsequent decline in the latter half have been well documented in the industrialized countries. However, the scenario is reversed in developing countries, especially India with a steady escalation in prevalence of CVD.

Dyslipidemia is an important risk factor for coronary artery disease. LDL cholesterol is the primary target and statins is a proven therapy for primary and secondary prevention of CAD. Although, there is a strong inverse relationship between low high density lipoprotein cholesterol (HDL-C) and CAD, the benefits of increasing HDL on top of optimum statin therapy is still under evaluation. Raised TG in blood has also been incriminated as a risk factor for coronary artery diseases (CAD) due to panoply of reasons[1] (Table 1). First of all, it is associated with the accumulation of chylomicron remnants and VLDL remnants which are atherogenic. It also generates atherogenic small, dense LDL and is also the basis for low HDL-C in the general population. It is also associated with increased coagulability and decreased fibrinolysis, as shown by its association with increased levels of plasminogen activator inhibitor 1 (PAI-1) and factor VII and activation of prothrombin to thrombin. Elevated TG is related in large part to lifestyle factors, as well as to diseases such as type 2 diabetes, metabolic syndrome and genetic factors.

Received: 05-03-13; Revised: 17-02-14; Accepted: 19-02-14
Disclosures: This article has not received any funding and has no vested commercial interest
Acknowledgements: None

Table 1: Atherogenic potential of triglycerides[1]

1. Accumulation of chylomicron remnants
2. Accumulation of VLDL remnants
3. Generation of small, dense LDL
4. Association with low HDL-C
5. Increased coagulability
   a. Increased plasminogen activator inhibitor (PAI-1)
   b. Increased factor VIIc
6. Activation of prothrombin to thrombin

Major factors that contribute to hypertriglyceridemia include lifestyle issues, such as obesity/overweight, physical inactivity, cigarette smoking and excess alcohol intake. A high carbohydrate diet, in which 60% or more of energy intake comes from carbohydrates, may also contribute to elevated triglycerides.

Systemic diseases such as type 2 diabetes, hypothyroidism, renal failure and nephrotic syndrome can cause hypertriglyceridemia, as can some drugs, such as corticosteroids and estrogens. Genetic factors also contribute.

In clinical practice, serum TG is most often elevated in metabolic syndrome. Studies[2–7] have provided differing results on the relationship between TG levels and CHD (Table 2). Many epidemiologic and clinical studies have found TG levels to be positively correlated with coronary events. In some studies, the significance of this association may be weakened by the influence of HDL C levels, as well as other CHD risk factors.

Table 2: Relationship between triglycerides and coronary heart disease

Study	Results
PROCAM[2]	High TG levels predict major coronary events *independent* of HDL-C
Copenhagen Male Study[3]	High TG levels predict major coronary events *independent* of HDL-C
Lipid Research Clinics Follow-up Study4	Coronary mortality related to TG levels, but *not independent* of HDL-C and LDL-C
Helsinki Heart Study[5]	The effect of TG levels on CHD is jointly influenced by LDL-C and HDL-C levels
COLTS[6]	"Normal" TG levels (1.1–2.2 mmol/L [100–199 mg/dL]) predict new cardiovascular events *independent* of HDL-C
Framingham Heart Study[7]	TGs were a CHD risk factor only when HDL-C was1.03 mmol/L (≤40 mg/dL)

According to Criqui et al.[8], plasma TG level as a risk factor for CHD has been controversial and evaluation of the TG level as a risk factor is fraught with methodologic difficulties. They, therefore, studied the association between plasma TG levels and the 12 years incidence of death from coronary heart disease in ten North American populations participating in the Lipid Research Clinics follow-up study, while adjusting for the potential confounding effects of other risk factors for CVD including the level of HDL-C. It was concluded that the plasma TG level showed no independent association with coronary mortality. However, in subgroups of persons with lower HDL and LDL cholesterol levels and in younger subjects, an association between the TG level and coronary mortality was observed, although this association was small and was not statistically significant after an adjustment for the plasma glucose level.

According to Gotto[9], the data for an independent association between TG concentration and risk for CAD are equivocal, unlike the data for LDL cholesterol and HDL cholesterol, which show strong consistent and opposing correlation with CAD risk. There is some evidence for TG as an independent risk factor in certain subgroups, for example women in 50–69 years of age (Framingham Study) and in patients with NIDDM. However, the evidence is stronger for TG as a synergistic CAD risk factor. For example patients with "Lipid triad" of elevated LDL cholesterol, low HDL cholesterol and high TG accounted for most of the coronary events reduction with lipid lowering therapy in the Helsinki Heart Study.

A meta-analysis[10] of 17 population-based prospective studies of TG and cardiovascular disease demonstrated that TG level is a significant, independent risk factor for CVD. In univariate analysis (non-adjusted), an increase in TG of 89 mg/dL was associated with a significant 1.32-fold increased CVD risk in men (n = 46,413) and a significant 1.76-fold increased CVD risk in women (n = 10,864). In a multivariate analysis (after adjusting for HDL-C levels), an increase in TG of 89 mg/dL was associated with a significant 1.14-fold increased CVD risk in men (n = 22,293) and a significant 1.37-fold increased CVD risk in women (n = 6345). The important finding from this study is that even after adjustment for HDL-C, a statistically significant increase in the risk of CVD was associated with high TG levels for both men and women corroborating that TG level is an independent risk factor for CVD for both sexes.

A recent metanalysis[11] from emerging risk factor collaboration evaluated 302,430 patients free of known vascular disease at baseline in 68 prospective studies found an association between TG and CAD and stroke, but was

not significant after adjusting for HDL and non-HDL-C levels.

Secondary prevention studies

Post hoc analysis of Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 trial (PROVE IT-TIMI)[12] demonstrated that elevated TG level is a CHD risk factor independent of LDL cholesterol levels. There was significant increase in the CHD risk when the triglyceride level was ≥200 mg/dL in patients with optimal LDL cholesterol (<70 mg/dL) on statins.

Triglyceride in Indians

Several studies have been carried out in India to evaluate the role of TG as a risk factor for CAD.

1. In a large retrospective study on 5748 CAD patients and 8103 healthy normals[13], serum cholesterol levels, LDL cholesterol levels and total cholesterol to HDL ratio were higher among the CAD subjects compared to normal. The study also makes another interesting observation that there is a lack of association of serum TG levels with CAD. Though the study results are of interest, regression analysis to identify the risk factor for CAD would have added more value to the article.

2. In the case control study by Burman et al.[14] again LDL cholesterol levels and total cholesterol/HDL cholesterol ratio and Lp (a) levels were higher in CAD patients compared to controls, but there was no significant difference in serum triglyceride levels.

3. In CUPS[15], it was seen that LDL cholesterol and age were risk factors for CAD, but serum TG levels did not come out as an independent variable.

4. Another large clinic based study on 17,855 type 2 diabetic subjects looked at the association of isolated hypercholesterolemia and isolated hypertriglyceridemia with CAD.[16] The prevalence of CAD was significantly higher among patients with isolated hypercholesterolemia, isolated high LDL and isolated low HDL cholesterol compared with normolipidemic individuals, but not in those with isolated hypertriglyceridemia.

5. There appears to be differences in lipid associations with CAD between native and migrant Indians. In migrant Indians, serum TG levels have been consistently found to be associated with CAD.[17] However, in native Indians LDL cholesterol and total cholesterol/HDL cholesterol ratio appears to be more important. One factor which is common to all Indians is a low HDL cholesterol levels. In the face of low HDL cholesterol levels, even moderate elevation of LDL cholesterol appears to be sufficient to produce an atherogenic profile.

Discussion

Triglyceride no doubt is an important barometer of metabolic health; however, the ability of plasma TG levels to predict CVD remains controversial after adjustment for HDL and non-HDL-C (AHA doc. 2011). TG has an inverse relationship with HDL-C and the adjustment for HDL attenuates the relationship between TG and CVD.

The current guidelines for dyslipidemia have, therefore, not recommended a target for TG lowering. Moreover, pharmacological lowering of TG by fibrates on top of statins has not shown any outcome data in the ACCORD lipid trial.[18] The sub group analysis of patients with low HDL and TG did show a trend towards benefit which was not statistically significant (P = 0.6), but this is only hypothesis generating and has to be tested in a large randomized trial which it seems unlikely will ever be conducted in future.

Although we do not have direct data of incrementing TG as a risk for CAD in Indians, the role of triglycerides cannot be completely ruled out as the link between hypertriglyceridemia and CAD has been shown in migrant Indians.[17] Moreover, TG measurement per se is not that informative as some of the TG-rich lipoproteins present in the plasma are not atherogenic like large VLDLs, while others like small dense LDL are highly atherogenic. Increased production of small dense LDL in response to hypertriglyceridemia could contribute to atherosclerosis. This is suggested by the presence of TG-rich lipoproteins in the human atheroma. Moreover, increase in TG levels is associated with low HDL cholesterol and with small dense LDL molecules (Phenotype B). Recently, an increased prevalence of small dense LDL in migrant Asian Indians has been shown in a study conducted in USA.[19]

Most of the available data on TG including ATP-III guidelines show cut-off value for TG levels based on fasting TG, but in reality it is non fasting (postprandial) TG which is a predictor of vascular events independent of traditional risk factor where as fasting TG has little independent relationship with vascular events.[20] This is because postprandial TG rich remnant lipoproteins can penetrate the endothelial cell layer and reside in the sub-endothelial space, where they can contribute to the

formation of atherosclerosis. It is also being realized that the TG prediction of risk should be based on an oral TG tolerance test akin to OGT by administering 15 gm of fat and this will increase postprandial TG by 20%. A normal patient is not expected to have a non fasting TG of >200 mg/dL. The optimum fasting TG level is 100 mg/dL and optimal non-fasting TG is >150 mg/dL.

In future, with more data pouring on post prandial TG and atherogenic small dense LDL commonly elevated in Indians in response to elevated TG, a causal relationship between TG and CAD may become evident.

Conclusion

Triglyceride, despite being an excellent barometer of metabolic health, its status as a risk factor for CAD in Indians remains controversial. However, an analysis of atherogenic small dense LDL, chylomicron remnants and VLDL remnants which are elevated in patients with hypertriglyceridemia and not routinely estimated, may be more contributory rather than mere estimation of TG. Likewise, the atherogenic potential of postprandial TG in future studies require further exploration and in times to come a causal relationship between TG and CAD may emerge out.

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